

Decoding the functional reorganization of the aging brain

By

Christian Johannes Gölz

A thesis presented for the degree of
Doctor rerum naturalium
(Dr. rer. nat)

Paderborn University
Faculty of natural sciences

2022

Contents

Acknowledgement	III
Abstract	II
List of Figures	III
List of Tables	IV
List of Abbreviations	V
Publications and other scientific contributions	VII
1 General Introduction	1
1.1 Motivation	1
1.2 Outline	2
1.3 Aging	3
1.3.1 Age-related Reorganization of the Brain	3
1.3.2 Studying Brain Aging by Electroencephalography	6
1.4 Machine learning	9
1.4.1 Forms of Machine Learning	10
1.4.2 State of the Art Approaches to Electroencephalographic Data	13
1.4.3 Applications in the Context of Aging Research	14
2 Aims and scope	16
3 General methodology	19
3.1 Datasets	19
3.1.1 Dataset I	19
3.1.2 Dataset II	21
3.1.3 Dataset III	21
3.1.4 Electroencephalography: Recording and Preprocessing	23
3.2 Machine learning procedures	23
3.2.1 Dimensionality reduction	25

3.2.2 Classification	27
4 Summary of the Main Results	30
4.1 Research Article I	30
4.2 Research Article II	32
4.3 Research Article III	34
4.4 Research Article IV	36
5 General discussion	38
References	39
Published Research Articles	51
Published Research Article I	52
Published Research Article II	52
Published Research Article III	52
Published Research Article IV	52

Acknowledgement

Danke.

Abstract

Aim: Apply data science methods to questions in aging Neuroscience

Methods: Supervised and unsupervised methods in different settings

Results: Novel Data Driven insights

Conclusion: ML rocks!

List of Figures

1.1	The computational model of dedifferentiation.	5
1.2	The three main forms of machine learning.	10
3.1	Schematic presentation of the force-tracking task conducted in dataset I.	20
3.2	Schematic presentation of the flanker task conducted in Dataset II.	22
3.3	Schematic presentation of the motor, sensory and cognitive tasks conducted in Dataset III.	23
3.4	Machine learning approach used in this thesis	25
3.5	Exemplary nested cross-validation procedure.	27
4.1	Main results of Published Research Article I.	31
4.2	Main results of Published Research Article II.	33
4.3	Main results of Published Research Article III	35
4.4	Main results of Published Research Article IV	37

List of Tables

3.1	Overview of datasets and participants in each research article.	24
3.2	Dimensionality reduction and classification methods utilized in each research article	24
3.3	Confusion Matrix	28
3.4	Summary of metrics to evaluate model performance	29

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
FBCSP	filter based common spatial patterns
fMRI	functional magnetic resonance imaging
FN	false negative
FP	false positive
HAROLD	hemispheric asymmetry reduction in older adults
ICA	independent component analysis
LDA	linear discriminant analysis
MLE	maximum likelihood estimation
MRI	magnet resonance imaging
MVC	maximum voluntary contraction
MVPA	multivariate pattern analysis
PASA	posterior–anterior shift in aging
PCA	principal component analysis
STAC	scaffolding theory of cognitive aging
SVD	singular value decomposition
SVM	support vector machine
t-SNE	t-distributed stochastic neighbor embedding
TN	true negative
TP	true positive
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,
2020

One of Western society's most significant societal challenges is the demographic shift towards an older population, which poses enormous demands for society, 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 these goals, 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 life to years* [1].

An essential part of promoting healthy aging and enabling participation in society includes the early identification and treatment of pathological conditions, developing and evaluating targeted interventions for prevention and therapy, or designing assistive technologies for older adults. These efforts require a deep understanding of the dynamics of aging in the context of individual trajectories and general patterns. Since many of the mechanisms leading to cognitive and physical decline are related to changes in the brain, it is of great interest to understand and quantify the aging process at this level.

Not only is aging a highly complex phenomenon, but also the brain is a complex system that is nonlinear, dynamic, and multi-scale in space and time [2]. Machine learning offers valuable data-driven methods to unravel this complexity and gain insights by uncovering complex relationships and identifying predictive markers related to the aging process and associated health status.

In general, progress in science is more and more characterized by applying methods from artificial

intelligence (AI), including machine learning algorithms, which make it possible to systematically analyze large and complex amounts of data [3]. This development has led to proclamations of an "AI revolution in science" [4] or promoting science has entered a new area characterized by *data-intensive computing* [5]. Moreover, these methods serve as the foundations 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 [6], the medical sector, e.g., diagnostic imaging [7], or social interaction, e.g., tools for communicative interaction [8], and are thus one of the basic building blocks for assistive technology facilitating the participation of older people with disabilities in society. AI and machine learning as a key technology have become a hope for solving societal challenges, including the shift towards an older population.

However, the implementation of machine learning approaches in aging research is still at an early stage compared to the rapid development in the commercial sector, and the most effective applications and integration into the traditional scientific system have yet to be evaluated, despite the potential to better understand the aging brain.

This is the starting point of this work which aims to investigate brain aging using machine learning techniques. The focus is on using these methods to better understand the neurophysiological factors contributing to age-related sensory, motor, and cognitive alterations. To this end, existing hypotheses about the aging brain will be tested and validated while new hypotheses will be generated. The results may inform the development assistive technologies to facilitate participation of older adults in society, the early detection of pathological conditions or the development of targeted interventions to counteract age-related decline.

1.2 Outline

This thesis is separated into five main chapters. This chapter describes the thesis's theoretical framework. In chapter 1.3, a description of aging at the level of the brain focuses on the most relevant concepts for the context of this work and forms the starting point for introducing the added value of applying machine learning in the context of studying the reorganization of the aging brain. Next, machine learning is introduced in chapter 1.4 to provide the methodological framework. The general terminology and 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 2. The following chapter 3 includes a description of the general methodological approaches of this work. In the subsequent chapter 4, the main results of the published research articles underlying this thesis will be presented. These include:

- Research Article I:

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)

- Research Article II:

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)

- Research Article III:

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

- Research Article IV:

Gaidai, R., Goelz, C., *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 overarching discussion in which the results are evaluated in the light of the current scientific discourse highlighting consequences and future research topics (chapter 5).

1.3 Aging

Biologically aging is "the time-dependent functional decline that affects most living organisms" [13]. It can be observed in the reorganization of multiple interacting physiological systems operating at different spatial and temporal scales [14]. 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 [14–16]. At the same time, however, overarching, generalizable patterns can be identified [17]. The most recognizable consequences of aging are alterations in cognitive, sensory, and motor abilities that challenge the daily lives of older adults [18]. However, not all abilities are equally affected by declines, and the alterations are highly individual. While sensory, motor, and cognitive abilities, such as memory and processing speed, are generally declining, abilities in the context of acquired knowledge, such as verbal abilities, tend to be stable or even improve with age [19]. One factor that plays a crucial role in these alterations is reorganization at the level of the brain [20]. A profound understanding is, therefore, of particular interest to research efforts as this is a prerequisite to identifying unfavorable trajectories and developing prevention and therapy concepts. It is important to note that the reorganization of the brain can be viewed from many perspectives, so in the following, only the aspects and concepts essential for the understanding of this work will be presented.

1.3.1 Age-related Reorganization of the Brain

Reorganization in the brain's structure includes, among others, atrophy of the gray and white matter and 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 behavioral 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 the performance in various tasks with sensory, cognitive as well as motor demands [20, 23]. Regarding activation dynamics, brain activity in response to a stimulus is often slower or delayed. Moreover, the frequency distribution of oscillatory neural activity changes to a slowing of the primary rhythms and altered temporal dynamics, which is interpreted as changes in neural communication [24].

By emphasizing neural communication and information flow, rather than viewing the brain as functionally separate, it can be conceptualized as a complex system whose functional units, i.e., neurons, areas, and subsystems, are interconnected structurally and functionally [25, 26]. In this concept, functional connectivity reflects coherent activation patterns within and between these units. Several distinct but interconnected functional networks were identified [27]. The dynamic interplay between and within these networks is characterized by segregation and integration at different levels, indicating the flow of information in the brain [28]. Older adults' information flow tends to 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 [23, 26, 29]. However, studies on sensorimotor and visual networks seem very heterogeneous, which could indicate individual reorganization patterns [26].

Dedifferentiation

The functional reorganization patterns described in the previous section have been attributed to dedifferentiation [30]. Dedifferentiation refers to the loss of neural specialization or reduced distinctiveness of neural responses resulting in diffuse, nonspecific 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 [18, 32]. To explain this behavioral dedifferentiation Li and colleagues [18, 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 [18, 22] (see Figure 1.1 for an overview on the computational model). In several computational simulations, the authors demonstrated that the proposed model could explain behavioral co-variation and several other phenomena, such as decreased average behavioral performance or increased behavioral intra- and inter-person variability [18, 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]. Additionally, research has indicated that the degree of dedifferentiation might predict the behavioral performance in cognitive

tasks [31].

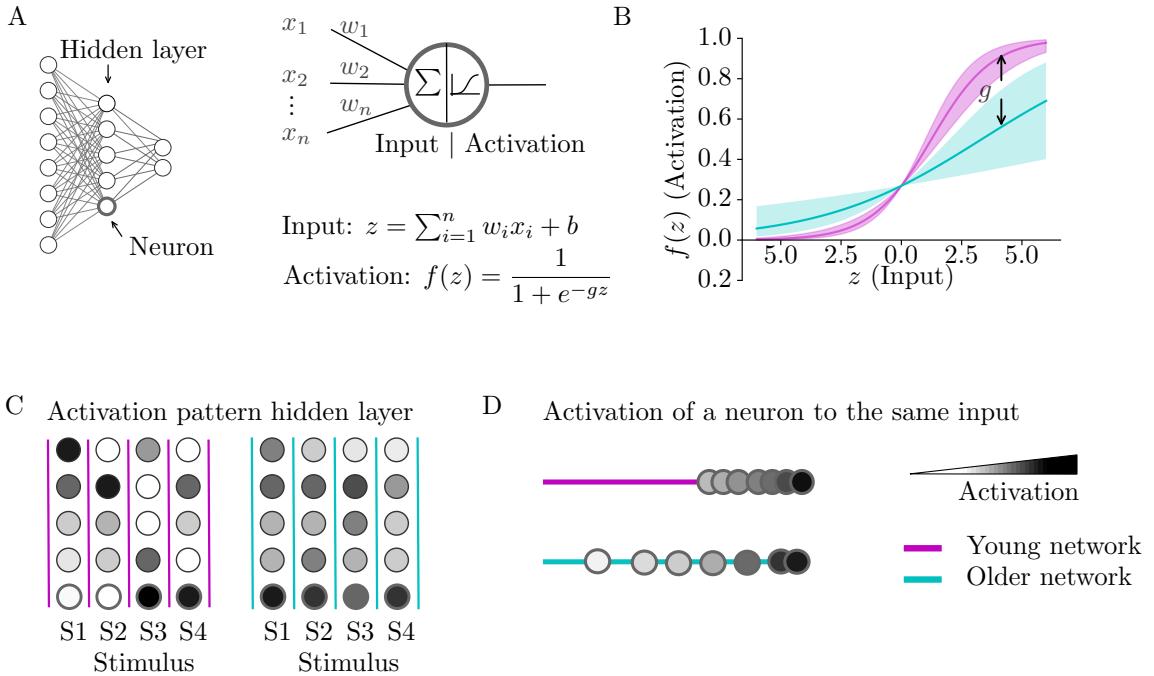


Figure 1.1: The computational model of dedifferentiation. Li and colleagues [18, 22] used a feedforward backpropagation neural network model with logistic activation function $f(z)$ and simulated altered neuromodulation by varying the gain parameter g in $f(z)$ of each neuron (A). Lower g values represent deficient neuromodulation and responsiveness due to aging, resulting in a damped neuron activation (B). Simulations showed that the activation pattern of simulated neurons differs less for different stimuli, i.e., the network’s hidden layer shows a less distinctive representation of the stimulus (C). The activation of a single neuron is more variable in networks with lower g value, i.e., older networks, for multiple stimulations with the same stimulus (D). Adapted from Li *et al.* [22] with permission.

The aforementioned reorganization of functional networks characterized by a less segmented and modular and less specialized network organization in older adults, has also been referred to as dedifferentiation [23, 26, 31]. Fornito *et al.* [36] describe dedifferentiation as a fundamental maladaptive mechanism of brain networks that requires compensation. This view is consistent with the argument that dedifferentiation and compensation are complementary mechanisms [20]. However, dedifferentiation could also 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 to maintain cognitive or behavioral functioning [20, 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 frequently 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 [15, 31, 40]. In this context, the reserve hypothesis defines *reserve* as the accumulated capacity of neural resources over the lifespan that can withstand decline or pathology [37, 41]. Although the concept was initially based on observations that the degree of pathological changes in the brain does not necessarily mean clinical manifestation, it has also been applied to explain the individuality of non-pathological aging [37, 41, 42].

Reserve can be both anatomically quantifiable, referred to as brain reserve, and more functional in nature, referred to as cognitive reserve [37]. At the functional level, compensatory activation, as well as more efficient utilization (less activation of neural resources), and 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, 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]. Essential elements 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]. Since reserve is not directly measurable, proxies are often used to compare individuals with high or low scores for a particular proxy value (e.g., physical fitness or occupational history) [41].

Other complementary concepts, such as the maintenance or the scaffolding theory of cognitive aging (STAC) model, highlight these influencing factors additionally. The concept of maintenance emphasizes the ability of the brain to repair. STAC postulates that lifelong positive and negative plasticity defines 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 factors mentioned above leading to the dynamics of age-related reorganization of the brain is highly complex. Understanding these dynamics regarding individual trajectories and overarching patterns is a prerequisite to differentiating healthy from pathological changes and developing and verifying treatments and 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 brain's 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 sections [20]. However, its use in the public health system is mainly limited to cases with a clear indication, making early detection of unfavorable aging trajectories challenging. 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 simple use, mobility, and relative cost-effectiveness. Although it has a lower spatial resolution than MRI based methods, EEG measures neuronal activity directly with a 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 particular interest to understand age-related changes of the brain and their relation to behavior [24].

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 signal expressions are in the range of a few micro-volts and are much lower than other biological and non-biological electrical generators, e.g., muscular activity or line noise, so the EEG signal is often affected by a low signal-to-noise ratio [50].

One of the EEG's most striking signal characteristics is the rhythmic voltage fluctuations that define the signal and are summarized under the term oscillation. Commonly, the EEG signal is analyzed based on the frequency composition of oscillatory activity in loosely defined frequency ranges, i.e., δ (<4 Hz), θ ($\sim 4\text{-}8$ Hz), α ($\sim 8\text{-}12$ Hz), β ($\sim 12\text{-}30$ 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 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 provide information on the direct processing of stimuli. The analysis of ERPs involves time-locking the EEG data to the onset of a specific stimulus and averaging the EEG signal across hundreds of trials to extract a reliable signal 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 [24, 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]. These changes have been interpreted as reflecting changes in brain function and connectivity associated with healthy aging. Variations in these have shown potential utility in the diagnosis of pathological conditions such as, Alzheimer's disease [56]. However, assessing preclinical or mild stages such as mild cognitive impairment poses additional challenges, and researchers have proposed the potential benefits of incorporating task-related EEG measures for a more effective evaluation [57, 58]. However, this requires a deep understanding of the changes in task-related information processing and reorganization that occur in healthy aging.

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 [59]. In contrast, attention tasks may demonstrate enhanced frontal network involvement and power in the θ frequency band [60]. In addition, the neural response to stimuli may exhibit a temporal slowing and altered spatial expression. These alterations 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 [61, 62].

Often these changes are discussed concerning 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 needs to be clarified. As such, other EEG findings may point in the opposite direction than described above. Hübner *et al.* [63], 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 on the task context considered. Age-related changes in decreased ERP latency and lower or increased functional connectivity of the examined networks depending on the task context are also reported [24]. 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 and 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 challenging and needs to be clarified. EEG signals are temporally and spatially highly dimensional, i.e., large amounts of data points contain intricate patterns of electrical activity. However, the signals often have a low signal-to-noise ratio, making it difficult to detect and visualize age-related brain reorganization and its dynamics. As such, analysis of EEG signals requires advanced signal analysis methods. In this context, methods from the field of machine learning could be of particular interest. By leveraging machine learning techniques, it is possible to extract meaningful patterns from the high-dimensional EEG data and uncover subtle age-related changes that may not be evident through traditional analysis methods.

1.4 Machine learning

Machine learning emerged in the 1950s to enable computers to learn without being explicitly programmed [64]. 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 [65]. The notion of *learning* therein describes the automated inference of general rules based on the observation of examples using algorithms to solve a specific task or problem [66]. In its basic form, these tasks often involve making predictions based on learned relationships or extracting 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 advancements in generative AI systems. Examples can be found in numerous areas, such as predicting stock prices, personalized advertising, or autonomous driving [67].

In science, machine learning is increasingly used as a complementary method to classical statistical analyses because of the ability to make predictions and deal with the multidimensional structure and non-linearity in real-world datasets for drawing inference [68]. Especially in areas where high-dimensional data is prevalent, such as in neuroscience, machine learning methods offer insight by extracting complex patterns purely data-driven [3]. In terms of EEG, machine learning can help identify subtle patterns and nonlinear relationships from the complex multidimensional 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 based on various properties.

1.4.1 Forms of Machine Learning

The three main forms of machine learning are supervised, unsupervised, and reinforcement learning. These forms are defined by the type of feedback a machine learning algorithm has access to during learning [69].

Supervised machine learning aims to learn a generalizable relationship between data and associated information, so-called labels or targets. The learned model can then be used to predict the label of new data not used during the learning process. If the labels are categorical, the prediction task is called classification; for continuous labels, the term is regression. Unsupervised machine learning aims to find hidden structures in data without considering 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*[70]. Reinforcement learning describes the task of learning optimal actions to solve a particular problem by maximizing the reward linked to that action. See Figure 1.2 for an overview.

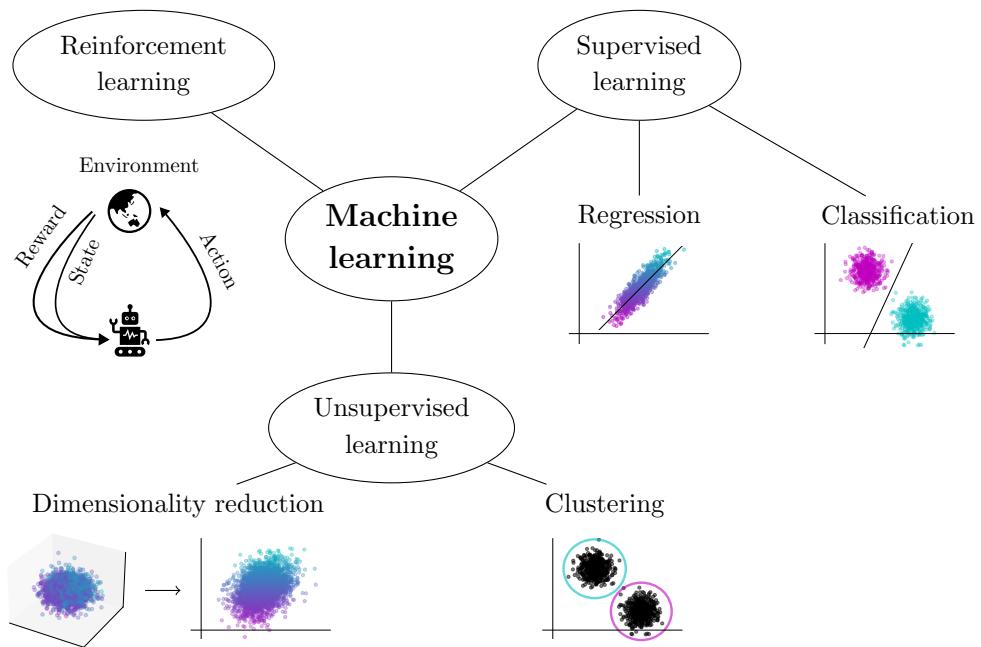


Figure 1.2: The three main forms of machine learning.

In practice, however, a clear separation is often impossible. As such, dimensionality reduction can also be supervised, i.e., labels are provided to learn a new representation of the data [71]. Besides, in semi-supervised learning, the goal is the same as in supervised learning. However, the data set used to learn the relationship contains labeled and unlabeled examples. The hope is to build a stronger representation by providing more information in the form of data [72].

In addition, traditional machine learning is often contrasted with 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 the input data is used without any form of pre-processing. Usually, they require a vast amount of data and computational power. In the context of this thesis, the tasks considered involve the processing of EEG from experiments with mid to small sample sizes to learn meaningful patterns and relationships in data. In the following state of the art approaches in the application to EEG data are presented.

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 ” [73]. 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. Some basic building blocks can be defined, which can be used to describe computational learning formally. In the following description, the view of statistical learning theory is considered, and notation is adapted from Shalev-Shwartz & Ben-David [69], von Luxburg & Schölkopf [66].

Learning is always based on data, i.e., measurable information about some phenomenon, consisting of attributes of the phenomenon, so-called features, and an associated label in supervised learning. It is mathematically defined as an open bounded set $\mathcal{Z} \subset \mathbb{R}^n$ of dimension n . Typically there is only a set of examples or training data $S = \{z_i, \dots, z_m\} \subset \mathcal{Z}^m$ 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 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.,

$$f : \mathcal{X} \rightarrow \mathcal{Y}, \quad (1.1)$$

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.,

$$f : \mathcal{X} \rightarrow \mathcal{W}. \quad (1.2)$$

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 priori. Thus, learning can be thought of as selecting a hypothesis h from a space of potential solutions \mathcal{H} with $\mathcal{H} = \{h : \mathcal{X} \rightarrow \mathcal{Y}\}$ in supervised learning and $\mathcal{H} = \{h : \mathcal{X} \rightarrow \mathcal{W}\}$ 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, $\ell : \mathcal{H} \times \mathcal{Z} \rightarrow \mathbb{R}_+$. In other words, it measures how well a specific hypothesis is doing.

The expected risk is a 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

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

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

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

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

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

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 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 structures in data. This is known as empirical risk minimization (ERM).

Upon ERM, more complex learning paradigms can be used to address common problems such as overfitting, in which the learned hypothesis too 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 be 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.,

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

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

1.4.2 State of the Art Approaches to Electroencephalographic Data

Various established supervised and unsupervised algorithms have been utilized in the analysis of EEG data, and the selection is usually based on the goal of the analysis. Unsupervised learning aims to highlight specific information in the data, so the selection is made based on the information one aims to highlight [69]. This is to highlight group structure in EEG data when using clustering or to highlight EEG inherent characteristics in dimensionality reduction. In contrast, the selection of a suitable supervised learning algorithm is more guided by its performance, i.e., its ability to derive generalizable rules that allow predictions from the available data. Typically this involves an iterative approach that divides the available data into training and testing sets, trains and validates various models within the training portion (cross-validation), and finally tests the best-performing model on the testing portion to estimate its ability to generalize [65]. Thereby, recent work highlights deep neural networks that can be used for unsupervised and supervised machine learning applications to EEG [74]. However, their advantage comes into play with large data resources, which are often expensive to acquire in the case of EEG [75]. Traditional learning approaches can be more efficient with good performance and promise better interpretability, especially for comparatively smaller data sets and limited computational resources [76].

Due to the low signal-to-noise ratio and high complexity of EEG data, the inputs in these approaches are often represented by well-known EEG characteristics or features that are believed to be related to the problem being learned. Typical features include time, frequency, time-frequency, connectivity, and theoretical information parameters extracted for each sensor (see [76] 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 [77].

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 [78, 79]. However, they require a head model based on MRI, which is often unavailable individually or merely estimated. 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. In contrast, 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 [80]. Additionally, supervised methods such as common spatial patterns (CSP) [81] or xDAWN [82] extract signal components that correlate with the labels to be predicted.

While the aforementioned supervised and unsupervised methods offer 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 [71]. These methods can be beneficial for exploring the relationships between different EEG features or 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.

1.4.3 Applications in the Context of Aging Research

Traditionally, the previously presented machine learning approaches have been the core building block for developing intelligent systems that can automate tasks or enhance and assist humans in performing their tasks. Such systems are critical in terms of assistive technology, for example, to support older adults with disabilities to live their daily lives, but are also relevant in the medical field. 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 treatment responses [83]. 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 promoting a healthy aging trajectory [56, 84]. An application is to estimate biological age based on regression models trained based on neural data, e.g., EEG data, recorded in extensive population studies [85]. Using data from an individual person, a regression model can predict that person's age. If the brain appears older than it would chronologically, this can be an early indication of an unfavorable state of health [86]. Another highly relevant application in the context of aging is the development of devices 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 [87, 88]. Decoding refers to learning a classification or regression model that predicts 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 [89]. 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 understanding age-related reorganization are mostly limited to fMRI studies. A common approach is to measure dedifferentiation at the individual level, i.e., the loss of neural specificity. Since dedifferentiation, by definition, results in more similar brain activation patterns for different tasks or stimuli, a poorer performance of classifiers trained to discriminate between them based on neural recordings is indicative of a less distinctive neural representation [31, 90]. Furthermore, classifying 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 [91].

In addition to typical statistically motivated analysis methods that calculate bivariate connectivity between sensors based on the phase difference or coherence of the EEG signals, dimensionality reduction techniques, such as the aforementioned DMD, provide a data-driven way to capture dynamic network characteristics. This has already been used to map age- or expertise-related changes at the network level [45]. Further, unsupervised methods, such as nonlinear dimensionality reduction techniques, were frequently used to describe the structure of data sets with respect to age-related changes. [75, 92].

In summary, 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 studying 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 predict a particular 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 to visualize high-dimensional data.

Chapter 2

Aims and scope

The main goal of this dissertation is to study age-related brain reorganization, considering both global patterns and individual trajectories, by applying established methods from supervised and unsupervised machine learning to EEG signals. The focus is on studying age-related phenomena, such as dedifferentiation, and investigating the replicability of hypotheses, such as reserve.

As described in the previous chapter 1.3, the reorganization of the brain of older adults is described in terms of dedifferentiated activation. According to Koen & Rugg, the evidence of dedifferentiation is quite robust if operationalized based on the original model of Li and colleagues [18, 22] as loss of neural selectivity to different stimuli or on the network level as decreased segregation and modularity of brain networks. However, the findings are based primarily on fMRI studies. Often machine learning, more precisely classification techniques, are used in these studies to quantify dedifferentiation (see chapter 1.4.3). An application to EEG data is pending and would allow more direct detection of age-related reorganization processes at the individual level while offering several advantages in terms of practical availability, low cost, ease of use, and the possibility to capture the dynamics of reorganization processes of the aging brain. Consequently, the idea is to train classifiers to test the differentiability of task-related EEG signals to draw conclusions about dedifferentiation. Especially in combination with dimension reduction methods, this approach could provide novel insights into the aging brain. Furthermore, training classifiers at the group level to discriminate EEG signals from different age groups with different lifestyle backgrounds will help verify factors contributing to healthy aging trajectories and identify corresponding EEG markers. This approach expands the understanding of dedifferentiation in aging. It provides valuable information about the effects of lifestyle choices on brain function across the lifespan, contributing to the understanding and testing the reserve hypothesis.

To achieve this, four empirical studies use datasets with participants from different life stages and lifestyles, including work experience and physical fitness. These datasets include experiments covering sensory, motor, and cognitive domains. Results from the analysis are presented in the following research articles that focus on specific sub-questions.

In **Research Article I** we investigated the difference in the classification performance of visuo-motor tracking tasks between younger and older participants in order to draw conclusions about the reorganization of the motor system and extend a previous publication that found differences between younger and older adults in EEG markers of sensorimotor processing during visuomotor tracking tasks [45].

Continuing this approach, **Research Article II** aimed to investigate whether the cortical representation of inhibitory control differs across different age groups. Again, previously published findings, in which distinct mechanisms of selective attention in older adults and children were detected using classical ERP analyses, should be extended [93]. To this end, performance on the classification of two stimulus types of a flanker task, i.e., one with high demands on inhibitory control and one with low demands on inhibitory control, was compared between different age groups. Furthermore, it was investigated whether we can train a classifier that can determine to which age group a participant belongs based on the EEG data. The idea was to identify relevant markers and gain insight into the dataset's structure to capture overarching patterns of the aging brain.

Research Article III aimed to examine the potential influence of cardiorespiratory fitness, a lifestyle factor, on patterns of dedifferentiation extracted through dimensionality reduction applied to EEG. This investigation was motivated by the reserve hypothesis, which postulates that cardiorespiratory fitness could impact age-related brain reorganization and the observed patterns of dedifferentiation. While this has already been shown in fMRI studies mainly concerning resting-state brain networks [94], it is not clear whether the differentiability of task-related information processing is affected as well and whether this is reflected in the EEG.

In addition to cardiorespiratory fitness, another significant lifestyle factor is professional expertise. Therefore, the subsequent **Research Article IV** aimed to characterize middle-aged experts using supervised and unsupervised machine learning techniques. In doing so, machine learning methods should be applied as a complement to previous studies in which expertise-related differences were investigated utilizing classical statistical methods [45, 95] in order to detect the influence of expertise on the dedifferentiation of fine motor tasks and to better understand the phenomenon of expertise employing group classifications.

Applying machine learning methods, both on individual and group levels, will allow concluding markers of brain reorganization and help identify the individual status and overreaching trajectories. The information gained from these tools could be used to determine and evaluate intervention programs, on-the-job-trainings, and support diagnosis. It may have applications in the development of assistive technological systems by providing insights in the performance of decoding behavior in

different age groups.

Chapter 3

General methodology

This chapter introduces the overarching methods of the published research articles on which this thesis is based. The focus is rather on an overall description of the methods, which is crucial for the following summary of the main results than on details in terms of reproducibility. For this, reference is made to the original description as it can be found in the published research articles.

3.1 Datasets

The datasets were selected from experiments in published projects in which different study paradigms were used to investigate age-related differences between age groups and groups with different lifestyle backgrounds. The following is a brief description of the datasets. All included participants gave their written informed consent. For children, guardians gave their written informed consent and children agreed to participate. Table 3.1 gives an overview of which datasets were used in the respective Research Article I to IV.

3.1.1 Dataset I

Dataset I was collected in one of the experiments conducted in the context of the Bremen Hand Study@Jacobs, which investigated the influence of age and expertise on manual dexterity over the working life [96]. This study was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the German Psychological Society. The dataset was analyzed in Research Article I and IV.

Participants

There are recordings of 59 participants in the dataset. The dataset represents a subset of the Bremen Hand Study@Jacobs and considers only participants with EEG measurements in the respective experiment. Based on their age and occupation, each participant is labeled as a young novice, middle-aged novice, middle-aged expert, late middle-aged novice, or late middle-aged expert. The group of novices comprised occupational profiles whose daily routine did not require

fine motor control of the hands, such as service workers, insurance agents, office workers, and students. Experts, on the other hand, referred to persons with more than ten years of professional experience in a job with pronounced fine motor requirements for hand control, such as opticians, goldsmiths, dentists, dental technicians, or hearing aid technicians [97]. In Research Article I, only the young ($N=13$, age: 18 to 25 years) and late middle-aged ($N=13$, age: 55 to 65 years) novices were considered. In Research Article IV all middle-aged and late middle-aged experts ($N=22$, age: 34 to 65 years), as well as all middle-aged and late middle-aged novices ($N=21$, age: 35 to 64), were included in the analyses¹.

Experimental Procedures

The experiment conducted was a force-tracking experiment (see Figure 3.1 and Published Research Article I and II for experimental details). Participants held a force transducer between the thumb and index finger of their respective right and left hands. The task was to apply the correct force to track a target force line displayed on a screen as accurately as possible. A total of 160 trials were conducted. For the first 40 trials, a steady line and the following 40 trials, a sinusoidal line had to be followed both with the right hand. This sequence, i.e., 40 times steady and 40 times sinusoidal force tracking, was then repeated with the left hand.

Grip force and EEG were recorded. Before the experiments resting EEGs with eyes open and eyes closed were recorded for 30 s each while participants sat comfortably on a chair.

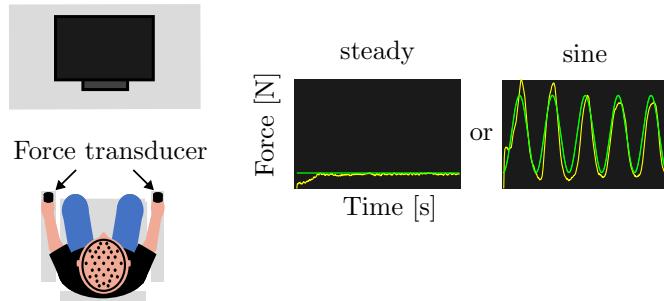


Figure 3.1: Schematic presentation of the force-tracking task conducted in dataset I. The task was to apply the correct force to a force transducer using a precision grip with the right or left hand to track a target force level (green line) as precisely as possible. Participants received feedback, i.e., they saw their applied force (yellow line).

¹Due to incorrect trigger position and insufficient data quality five participants of the initial sample were excluded

3.1.2 Dataset II

Dataset II contains recordings from three experimental studies, each focusing on a different age group and referred to below as Study 1, Study 2, and Study 3.

Study 1 is the Bremen-Hand-Study@Jacobs presented above. Study 2, the Re-LOAD project, investigated the relationship between motor learning and cognitive function in older adults [63, 98]. Study 3, the CEBRIS project, investigated the influence of physical training on the cognitive functions of children [99]. The German Psychological Society granted ethical approval for Study 1 and 2 and the Ethics Committee of the Faculty of Humanities of the Saarland University, Germany, for Study 3. The dataset is described detailed in [93] and was analyzed in Research Article II

Participants

The full dataset contains recordings from 222 participants, including 92 participants recorded in Study 1, 81 in Study 2, and 49 in Study 3. Participants are separated into the following age categories [93]: children ($N = 46$, age: 8 to 10 years), young adults ($N = 39$, age: 20 to 29 years), early middle-aged adults ($N = 21$, age: 36 to 48 years), late middle-aged adults ($N = 25$, age: 55 to 64 years), old adults <75 ($N = 40$, age: 66 to 75 years), very old adults >75 ($N = 38$, age: 76 to 83 years)².

Experimental Procedures

All participants performed a modified version of the Flanker task previously reported in Reuter *et al.* [62], Winneke *et al.* [100, 101], and summarized in Reuter *et al.* [93] (see Figure 3.2 and Published Research Article II). The task was to press the correct key corresponding to a central target stimulus surrounded by distracting flanker stimuli as quickly as possible. In Study 1 and Study 3, participants performed 300 trials (approx. 100 trials per stimulus), whereas, in Study 2, they performed 150 trials (approx. 50 trials per stimulus) in randomized order. Other than this, the same experimental procedures were used in all studies, including the EEG measurements system.

3.1.3 Dataset III

Dataset III was collected during an intervention study at Paderborn University in which the feasibility of learning to play golf, as well as its impact on cognitive performance and on (neuro-)biological markers, was investigated [102–104]. This intervention study was registered at the German Clinical Trials Register (DRKS00014921) and approved by the Ethics Committee of the University of Muenster. The dataset is described in detail in Published Research Article III.

²In the sample used here 13 participants were excluded due to insufficient data quality.

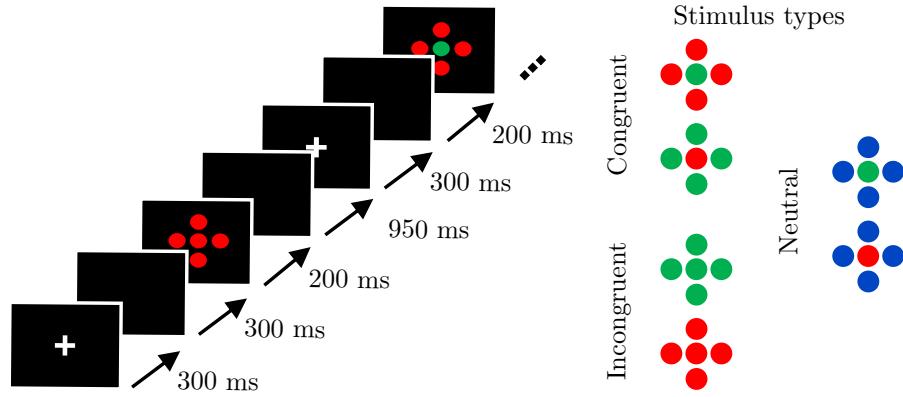


Figure 3.2: Schematic presentation of the flanker task conducted in Dataset II. The task was to press the correct key corresponding to a central target stimulus surrounded by distracting flanker stimuli as quickly as possible. Adapted from Winneke *et al.* [101] with permission.

Participants

The dataset contains recordings from 41 elderly participants. Based on their performance on a 6 min walking test participants' cardiorespiratory fitness was assessed in preceding appointments and two groups were formed, a less fit ($N=16$, age: 63 to 77 years) and a fit group ($N=15$, age: 60 to 66 years).

Experimental Procedures

Participants performed sensory, motor, and cognitive tasks each lasting 90 s during which EEG was recorded (see Figure 3.3) Prior to the tasks, EEG was recorded for four minutes in a rest condition in a supine position with eyes closed.

Sensory task The index fingertips of the participant's left hand were stimulated with the pins of a braille device presenting two pin configurations in random order.

Motor task The motor task corresponded to the force tracking experiment as described in chapter 3.1.1. Here, the target was a line that moved from the right to the left on the screen for 90 s and changed level every 3 s in randomized order between heights representing 10%, 20% and 30% of participants' individual maximum voluntary contraction (MVC). The task was to apply the appropriate force to the force transducer to move a cursor so that it followed the target force level presented on a screen as closely as possible.

Cognitive task The cognitive task was an auditory n-back task. Participants were asked to listen to a sequence of letters presented via two speakers behind them and press the foot switch with the right foot if a letter appeared again two letters later (2-back).

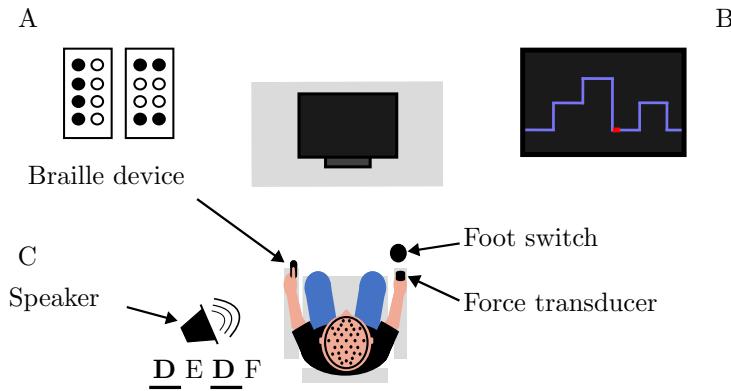


Figure 3.3: Schematic presentation of the motor, sensory and cognitive tasks conducted in Dataset III. The sensory task involved the stimulation of the index finger with two pin patterns of a braille device (A). The motor task was to apply the correct force to a force transducer using a precision grip with the right hand to track a target force level (blue line) as precisely as possible. Participants received feedback, i.e., they saw their applied force (red bar) (B). The cognitive task involved listening to a sequence of letters presented via two speakers behind them (C) and pressing the foot switch with the right foot if a letter appeared again two letters later (2-back).

3.1.4 Electroencephalography: Recording and Preprocessing

The EEGs in Dataset chapter 3.1.1 and chapter 3.1.2 were recorded with a 32-channel Biosemi active electrode system (ActiveTwo, BioSemi, Amsterdam, Netherlands). In chapter 3.1.3 EEG measurements were recorded with a 128-channel actiCap active electrode system (BrainProducts, Munich, Germany).

Based on the different analysis methods, objectives, and EEG systems used, the preprocessing differed slightly between the research articles. In each case, the data were down-sampled, re-referenced, and filtered. In Research Article I, III and IV, ICA was used to reduce ocular and muscle artifacts. In Research Article I and IV, trials containing large artifacts were excluded using the *autoreject pipeline* [105]. Due to the high number of electrodes used in Dataset III, bridges were detected and interpolated based on coherence measurements and electrical distance [106]. The exact pipelines are described in the published research articles.

3.2 Machine learning procedures

Following state of the art approaches (see chapter 1.4.3) we used a combination of dimensionality reduction methods and classification. Dimensionality reduction was used at the first level to extract a suitable representation of the EEG data for the following classification, i.e. for feature extraction (see Figure 3.4 1a), and at the second level to detect and visualize patterns in the data sets (see Figure 3.4 1b). Classification procedures were used both at the individual level as well as at the

Table 3.1: Overview of datasets and participants in each research article.

Research Article	Dataset	EEG-System	Paradigm	Participants	
I	I	Biosemi: 32-channels	Force Control	Late m-a adults	N=13, age: 55 to 65 years
				Young adults	N=13, age: 18 to 25 years
II	II	Biosemi 32-channels	Flanker	Children	N=46, age: 8 to 10 years
				Young adults	N=39, age: 20 to 29 years
				Early m-a adults	N=21, age: 36 to 48 years
				Late m-a adults	N=25, age: 55 to 64
				Old adults >75	N=40, age: 66 to 75 years
III	III	actiCap: 128-channels	Nback Tactile Oddball Force Control	Low fit	N=16, age: 63 to 77 years
				Fit	N=15, age: 60 to 66 years
IV	I	Biosemi: 32-channels	Force Control	Experts	N=22, age: 34 to 65 years
				Novices	N=21, age: 35 to 64

group level (see Figure 3.4.2). The former means that one model per participant was trained, which represents the cortical representation of an experimental condition, e.g., a task, and finally allows conclusions, e.g., about the dedifferentiation of cortical processes at the individual level. The latter means that a model was trained for the whole group to detect general overlapping patterns in the group structure. The selection of a suitable method was based on the dataset, i.e. data structure and experimental conditions, and the aim of the analysis. Table 3.2 summarizes the used methods for each research article. In the following, the methods will be briefly described.

Table 3.2: Dimensionality reduction and classification methods utilized in each research article

	Dimensionality Reduction		Classification	
	level 1a	level 1b	Task	Group
Research Article I	DMD	CSP	LDA	SVM
Research Article II	xDAWN	-	SVM	SVM
Research Article III	DMD	PCA	-	-
Research Article IV	DMD	CSP, UMAP	LDA	SVM

DMD: dynamic mode decomposition, CSP: common spatial patterns, LDA: linear discriminant analysis, SVM: support vector machine, PCA: principal component analysis

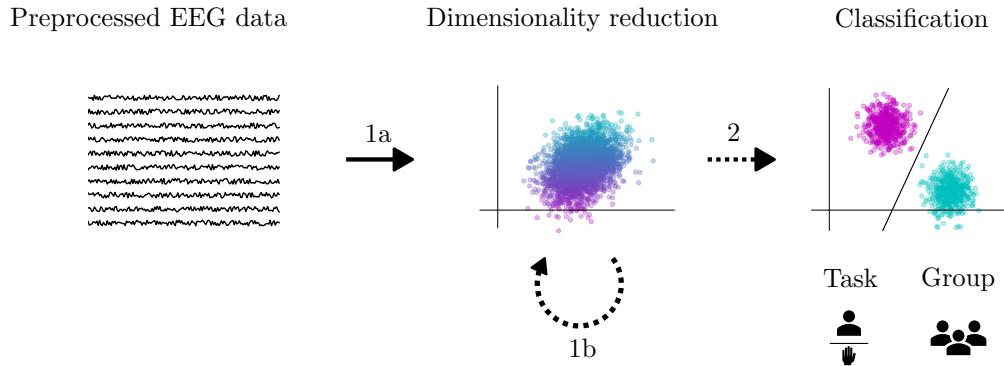


Figure 3.4: Machine learning approach used in this thesis. Dimensionality reduction was used to produce a suitable representation of the EEG data (1a). Optionally a second level dimensionality reduction was applied to extract patterns and for visualization (1b). Finally, Classification was used to classify either the task at the individual level or the group membership (2) using either the results of 1a or 1b.

3.2.1 Dimensionality reduction

As described above, different dimensionality reductions were performed with the aim to extract a suitable representation of the EEG on the first level and to further investigate this representation on the second level. In the following, the methods listed in Table 3.2 are briefly introduced. 

Dynamic mode decomposition

To extract a relevant representation of the continuous EEG activity, we chose DMD because it is able to decompose the signals into spatial activation patterns that are dynamically coherent, reflecting the network nature of the underlying brain activity [80]. DMD was developed in the field of fluid mechanics and was applied to various fields to model time-varying dynamical systems, including neuroscience proving to extract physiological valid signal patterns [80, 107–109]. The activation patterns (modes) extracted from DMD analysis can reveal key features such as the spatial distribution of coherent dynamics in relation to oscillation frequencies and rates of growth or decay. This provides a deeper understanding of the functional reorganization of the brain and can serve as a starting point for further analysis [80].

For the computation of DMD, we used the *exact DMD* algorithm introduced by Tu *et al.* [110] and described in [80] as applied to electrophysiological data. The analysis was based on the preprocessed and windowed EEG data and DMD modes associated with the frequency ranges θ (4 to < 7 Hz), α (7 to < 12 Hz), β_1 (12 to < 16 Hz), and β_2 (16 to < 30 Hz) were considered. We calculated the DMD mode magnitude (absolute value) to obtain the influence of each electrode in a DMD mode representing spatially coherent activation [80].

Common spatial patterns

To extract the information from the DMD modes that would allow the best possible differentiation between the tasks, we leveraged supervised dimensionality reduction (see chapter 1.4.2). This approach is based on filter based common spatial patterns (FBCSP), a widely used algorithm for the classification of continuous tasks that extracts a weighting for each EEG channel that maximizes the class discriminative energy for selected frequency bands [111]. By multiplying these weights with the channel values, meaningful features are generated. The weightings were calculated based on DMD magnitudes in each frequency band (see Publisshed Research Article I for details on the implementation).

Principal component analysis

PCA aims at extracting the statistically most descriptive components from highly dimensional data [112]. We used the singular value decomposition (SVD) algorithm and reduced the dimension of the DMD modes of all time windows to their main features. We therefore calculated a SVD over all frequency-specific modes over all time windows per participant and extracted the singular vectors and singular values. The singular vectors represent the principal components and capture the most significant or dominant DMD patterns, while the singular values capture the proportion of variance accounted for by this pattern. Higher singular values indicate that the associated dominant pattern captures more variation among all DMD modes during task completion and can be considered representative of the stability or prominence of this pattern.

Uniform manifold matrix approximation and projection

While PCA was used to explain patterns of variation within a participant, we relied on UMAP to capture the structure both on a local level, i.e., within a participant, and on a global level, i.e., between participants. UMAP constructs a low-dimensional representation by modeling the data as a topological manifold, considering both the distances between data points and the local density and is particularly effective in visualizing and exploring complex data patterns and meaningful relationships in the data [71]. For this, we first calculated the arithmetic mean over the DMD modes of all windows per frequency band, trial, and participant and then applied UMAP to obtain a lower-dimensional representation that captures underlying patterns and meaningful relationships in the data, facilitating visualization and exploration of DMD patterns.

xDAWN

To process the event-related EEG data, we utilized the xDAWN algorithm [82]. By applying the xDAWN algorithm, it is possible to obtain a set of weights that emphasize the relevant EEG activity while suppressing noise and artifacts, leading to improved signal quality for further analysis or classification tasks. In this way, it is possible to induce activation patterns, i.e., neural responses to external stimuli at the level of individual trials. In contrast to the previous methods, we did

not use DMD first but applied xDAWN to the preprocessed trials as originally described to ensure comparability to previous ERP analyses [93].

3.2.2 Classification

The classification was performed on a trial-by-trial basis, i.e., models were learned that can predict for each participant to which task a given trial belongs or cross-participant to which group the performing participant belongs. Typically, different classification algorithms and their parameters are selected, trained on one portion of the data, the so-called training data, and then tested for their performance on data not used for training, the so-called testing data [113]. The training data can further be divided into a training and validation portion to compare different model types or user-defined learning algorithm settings, so-called hyperparameters. Finally, the best model configuration is tested for its predictive performance on the test data and reported. However, this three-time division may drastically reduce the data size usable for training and may result in flawed generalization evaluation due to the randomness of the split [114]. Therefore several procedures can be applied. In simple k-fold cross-validation, for example, the training data is divided k-times. Thus each time, a different subset of the data is used for validation while the rest is used for training. Usually, this is repeated for a range of models and subsequent hyperparameters, and the model and hyperparameter performing best on average are selected for final testing. We used a more advanced method denoted nested cross-validation, which adds a second cross-validation loop for the final model evaluation (see Figure 3.5 for a visual representation of the procedure).

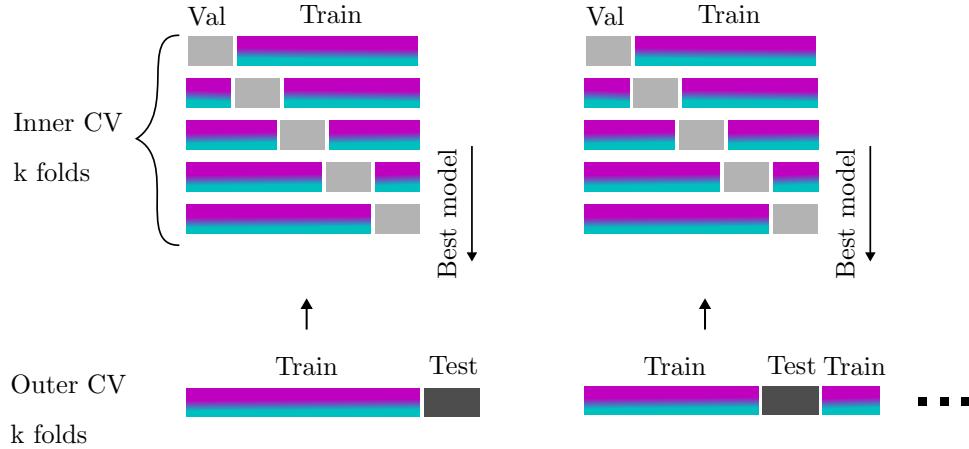


Figure 3.5: Exemplary nested cross-validation procedure. K-fold cross-validation is used in an outer loop for testing the best configuration tuned in an inner cross-validation loop. CV: cross-validation, Val: Validation

For all datasets, ten splits were used in the inner and outer cross-validation loops, keeping 80 % of the dataset for training and 20 % for testing. In the inner loop, hyperparameters were tuned according to a grid search procedure in which a given parameter space is provided to select the

best-fitting parameters [114] comprehensively. Consequently, one model was tested for each of the ten outer splits. The final metrics are the average over the outer splits and represent the performance of the classification algorithm. For classifiers, these can be derived using a so-called confusion matrix (Table 3.3), which summarizes all correct and false predicted instances of the test set [115].

Table 3.3: Confusion Matrix

		Predicted Class	
		Positive	Negative
Actual Class	Positive	True Positive (TP)	False Negative (FN)
	Negative	False Positive (FP)	True Negative (TN)

If an actual value is positive and is classified as positive, it is a true positive (TP) result. If the positive instance is classified as negative, it is a false negative (FN) result. If an instance is actually negative and classified as negative, it is called true negative (TN). Consequently, if an instance is negative and classified as positive, it is a false positive (FP) [115]. This forms the basis for various metrics reported in the research articles. Table 3.4 summarizes the metrics and their meaning.

These values, can be related to the theoretical chance level of the values that would occur if the class labels were randomly assigned. However, since this gives a biased estimate of the significance of model performance when the distribution is uneven and the data sets are small, the random level of the values can be determined by permutation procedures, in which the labels are randomly shuffled repeatedly (e.g., 1000 times) to produce a null distribution against which the significance of a model can be tested. This analytical approach is computationally expensive. An alternative is to empirically determine a model's significance by computing a binomial cumulative distribution to estimate the significance threshold [116]. To evaluate the validity of the trained models in the present work, the appropriate method was chosen individually depending on the data set, model objective, and distribution of classes. The results consequently mark the reference values as theoretical, analytical, or empirical chance level. A detailed justification of the chosen methods is described in the published research articles.

In the research articles, we experimented with multiple algorithms based on recent literature to find the most suitable models for the respective tasks [117]. In doing so, we used support vector machine (SVM) and linear discriminant analysis (LDA), which both have a comprehensive application history to neuroscience data and are well suited to our specific problems. SVMs is one of the most commonly used algorithms for neuroscience data [114]. The algorithm generates optimal decision boundaries, called hyperplanes. It can thus handle both linearly separable and non-linearly separable data by using kernel functions to map the input space into a higher-dimensional feature space [117]. LDA is specifically used in the context of BCI and has proven to be successful in

Table 3.4: Summary of metrics to evaluate model performance

Metric	Formula	Description
Accuracy	$\frac{TP + TN}{TP + TN + FP + FN}$	Measures the overall correctness of the model's predictions.
Precision	$\frac{TP}{TP + FP}$	Measures the proportion of true positive predictions among all positive predictions.
Recall (Sensitivity)	$\frac{TP}{TP + FN}$	Measures the proportion of true positive predictions among all actual positive samples.
Specificity	$\frac{TN}{TN + FP}$	Measures the proportion of true negative predictions among all actual negative samples.
F1 Score	$\frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}$	Harmonic mean of precision and recall, providing a balanced measure between the two.
AUC	-	Area under the receiver operating characteristic curve, which measures the performance of a binary classification model across various threshold settings.

TP: true positive, TN: true negative, FP: false positive, FN: false negative, AUC: area under the receiver operating characteristic curve

task decoding [81]. This algorithm aims to find a linear combination of features that maximizes the separation between different classes, making it particularly effective when the classes are well-separated [117].

All machine learning pipelines were implemented following the framework of the Python package scikit-learn [118]. If the methods were not implemented, they were implemented by using custom scripts implemented in Python or Matlab. A detailed description of the complete analysis pipelines and details of the respective implementation can be found in the published research articles.

Chapter 4

Summary of the Main Results

In the following, the main results of the published research articles will be briefly presented. The style of the illustrations published in the respective articles has been adapted from the original publication. The Authors' contributions are indicated as published in the articles and reviewed and agreed to by all authors.



4.1 Research Article I

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)

This research article aimed to investigate differences in the classification performance between younger and older adults of visuomotor tracking tasks to infer age-related dedifferentiation of the motor system.



To describe the classifier input, we used classical statistical methods first. Next, we trained a classifier for each participant to output the appropriate task label based on the EEG data recorded during a trial. That is, the classifier should be able to identify, given the EEG data, whether the participant was tracking a sinusoidal target force with the left or right hand or whether the task was to track a steady target force with the right or left hand. To gain deeper insight into classification performance, we trained classifiers to predict only the hand side or only the task characteristic individually. We compared the DMD derived brain activity patterns between the groups and tasks with permutation t-tests and the classification performance between the groups with Man-Whitney-U tests.

We found significant differences in the expression of DMD patterns between the tasks and groups focusing mainly on central and posterior electrodes, most pronounced in the β frequency bands but also in the α and θ frequency ranges (see Figures 2 to 4 in Published Research Article I for the

statistical values per electrode). In addition, there were group differences in the spatial distribution concerning a more bilateral and frontal expression of the patterns in the late middle-aged adults. Overall the classifiers' performance was above chance level within all participants (accuracy: $M = 0.66$, $SD = 0.11$; theoretical chance level: 0.25) and yielded distinct misclassification patterns between younger and late middle-aged adults (see Figure 4.1). The classification of the hand side in the late middle-aged participants performed significantly worse compared to young adults, i.e., the classifier misclassified trials performed with the right hand as left-handed trials and vice versa (accuracy late middle-aged adults: $M = 0.70$, $SD = 0.08$; accuracy young adults: $M = 0.82$, $SD = 0.09$; $U = 39.5$, $p = 0.02$, $r = 0.45$). On the other hand, the classification of which target force was followed, i.e., steady vs. sinusoidal, worked significantly better in the late middle-aged adults (accuracy late middle-aged adults: $M = 0.86$, $SD = 0.09$; accuracy young adults: $M = 0.75$, $SD = 0.09$; $U = 40.00$, $p = 0.02$, $r = 0.45$). Consequently, fewer steady trials were classified as sinusoidal trials in the late middle-aged compared to the younger participants or vice versa.

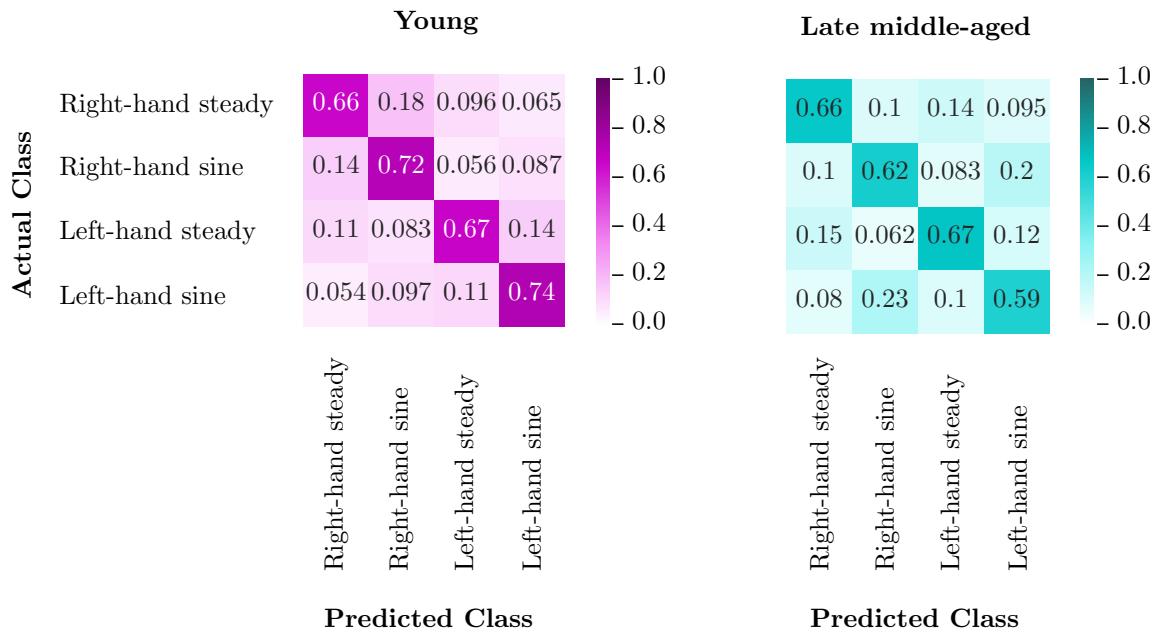


Figure 4.1: Main results of Published Research Article I. The misclassification rate of the hand side (left vs. right) was higher, and the misclassification rate of task type (sinusoidal vs. steady) was lower in late middle-aged compared to young adults.

The lower classification performance in the classification of the body side, i.e., left vs. right-handed task execution in late middle-aged adults, points to a less segregated brain network activation of the motor system. In contrast, the higher classification performance with respect to the task characteristic sinusoidal vs. steady force tracking might indicate a higher level of compensatory involvement when the task gets more demanding.

Author Contributions

C. Goelz: Analyzed data, design, and implementation of the work, including interpretation of the results, drafting parts of the work. **K. Mora:** Analyzed data, design, and implementation of the work, including interpretation of the results, drafting parts of the work. **J. Rudisch:** Design and implementation of the work, including interpretation of the results, drafting parts of the work. R. Gaidai: Analyzed data, design, and implementation of the work, including interpretation of the results, drafting parts of the work. **E. Reuter:** Conceived and planned the experiments, design, and implementation of the work, including interpretation of the results, drafting parts of the work. **B. Godde:** Conceived and planned the experiments, design, and implementation of the work, including interpretation of the results, drafting parts of the work. **C. Reinsberger:** Design and implementation of the work, including interpretation of the results, drafting parts of the work. **C. Voelcker-Rehage:** Conceived and planned the experiments, design, and implementation of the work, including interpretation of the results, drafting parts of the work. **S. Vieluf:** Conceived and planned the experiments, design, and implementation of the work, including interpretation of the results, drafting parts of the work.

4.2 Research Article II

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)

Following the previous approach, the discriminability of inhibitory and non-inhibitory stimuli within a subject should be investigated using classification techniques. The intention was to study differences in the neural representation of inhibitory control across age groups and extend previous findings on the same data.

In this study, we trained a classifier for each participant that could predict which stimulus, i.e., congruent (requires no inhibitory control) or incongruent (requires inhibitory control), was presented based on the EEG data (see chapter 3.1.3). We also examined how well classification worked over time after stimulus presentation, extracting the time points at which the most accurate classification was possible and the level of performance at that time. We compared the classification trajectories recorded in this manner between the different age groups using one-way ANOVAs, or Kruskal-Wallis tests, followed by t-tests or Dunn tests for post-hoc comparisons.

To further investigate the group structure, we also trained a group-level classifier to predict which age group the performing participant belongs to based on the EEG recording of a trial.

The maximum classification performance of the model trained to predict which stimulus was presented within a participant was above the chance level in over 95 % of the participants (AUC:

$M = 0.72$, $SD = 0.06$, analytical chance level: 0.61). The classification performance was further dependent on the group [$F(5,206) = 4.805$, $p < 0.001$], with classification performance lower in the children's group compared to the other groups ($p < 0.05$). When comparing the trajectories, we found that this also differed between the groups ($H(5) = 35.575$, $p < 0.001$) with later performance peaks in the children and the two oldest age groups ($p < 0.05$) (see Figure 4.2 A).

The classification of group membership was overall above chance level (accuracy: 0.55%, empirical chance level: 0.17), and a characteristic pattern of misclassifications emerged (see Figure 4.2 B). The classification of children was the most accurate. An increasing number of misclassifications were observed in the other age groups, where the classifier incorrectly assigned trials to a neighboring age group. This resulted in clusters of adjacent age groups within which this misclassification accumulated. The first cluster ranged from young adults to late middle-aged adults, and the second cluster included the two oldest age groups. There were higher misclassification rates within these clusters but fewer misclassifications between clusters, especially between the two oldest groups and the adjacent group of late middle-aged adults.

We also studied the time points for which the classification performance of the group model was highest and found a 10 % performance increase after stimulus onset compared to before, with a peak at 100 ms to 200 ms.

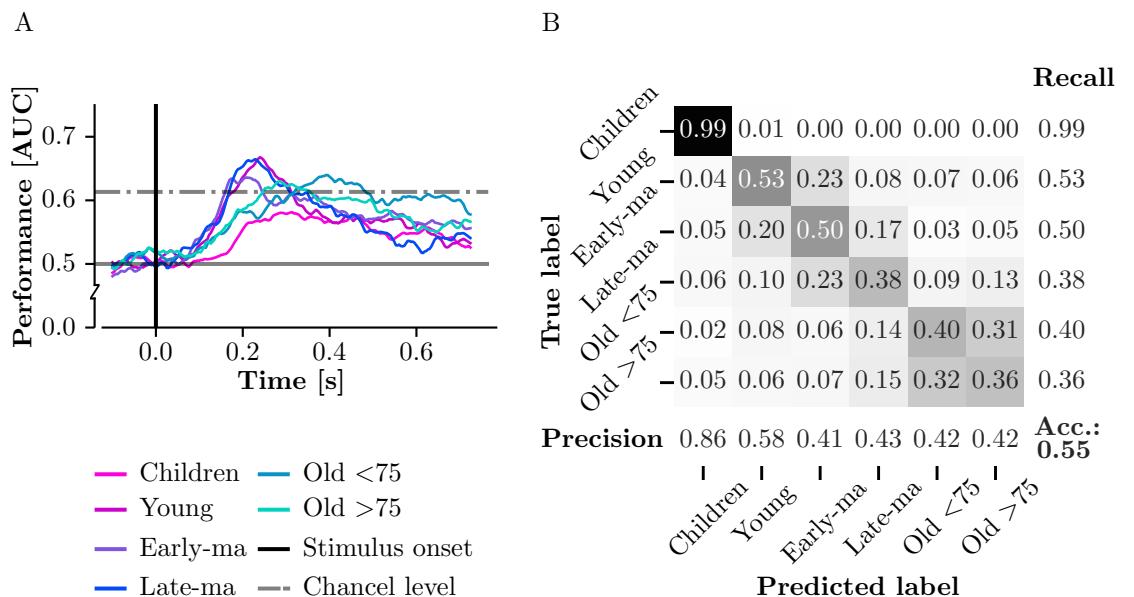


Figure 4.2: Main results of Published Research Article II. The evolution of classification performance of models trained to discriminate between congruent and incongruent trials differed between age groups. Mean trajectories per age group are shown here (A). Classifying between these age groups revealed clusters of groups in which misclassifications happened predominately (B). Acc.: accuracy, AUC: area under the receiver operating characteristic curve, ma: middle-aged.

The results of the task classification suggest that the distinctiveness of the cortical representation of inhibitory control does not differ with older age but that different time windows and, therefore, different processes are important for selective attention at different ages. The higher classification performance during the task than before stimulus onset underscores the added value of task-related EEG. The grouped structure of misclassifications, especially the comparable fewer misclassifications between the oldest group and the late middle-aged groups, could reflect gross changes, e.g., after retirement.

Author Contributions

C. Goelz: Conceptualization, software, formal analysis, writing — original draft. **E. Reuter:** Conceptualization, investigation, data curation, writing — review, and editing. **S. Froehlich:** Writing — review and editing. **J. Rudisch:** Writing — review and editing. **B. Godde:** Conceptualization, writing — review and editing. **S. Vieluf:** Conceptualization, investigation, supervision, writing — review, and editing. **C. Voelcker-Rehage:** Conceptualization, investigation, supervision, project administration, writing — review, and editing. All authors read and approved the final manuscript.

4.3 Research Article III

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

This study aimed to study the influence of cardiorespiratory fitness on the dedifferentiation of task-related brain network activation patterns by assessing coherent spatio-temporal patterns of EEG in rest and tasks representing the sensory, motor, and cognitive domains, respectively.

We compared the dominant DMD patterns derived by SVD per frequency band between the tasks using permutation t-test to infer the differentiability of task-related DMD modes in fit and less fit participants. For a statistical evaluation of group differences, we compared the multivariate distribution of obtained t-values with Cramér tests between the groups. We further compared the singular values associated with the dominant pattern to infer the prominence of that pattern throughout task execution between the groups using repeated measures ANOVAs.

The comparison of t-distributions with Cramér tests between the groups revealed higher differentiability of dominant DMD modes in the fit compared to the less fit participants in all frequency bands (all $p < 0.05$, see Figure 3 and Table 2 in Published Research Article III for exact statistical values). However, the difference in the differentiability was most pronounced in the θ and β_2 frequency bands (see Figure 4.3). Furthermore, a significantly lower proportion of total variance could be explained by the dominant pattern in the β_2 frequency range for the less fit compared

to the fit group [$F(1,29) = 12.572$, $p = 0.001$, partial $\eta^2 = 0.300$] in the motor (fit: $M = 80.5\%$ $SD = 0.60\%$, less fit: $M = 79.95\%$ $SD = 0.52\%$), the sensory (fit: $M = 80.8\%$ $SD = 0.76\%$, less fit: $M = 80.05\%$ $SD = 0.53\%$) and the cognitive task (fit: $M = 81.07\%$ $SD = 0.78\%$, less fit: $M = 80.21\%$ $SD = 0.54\%$).

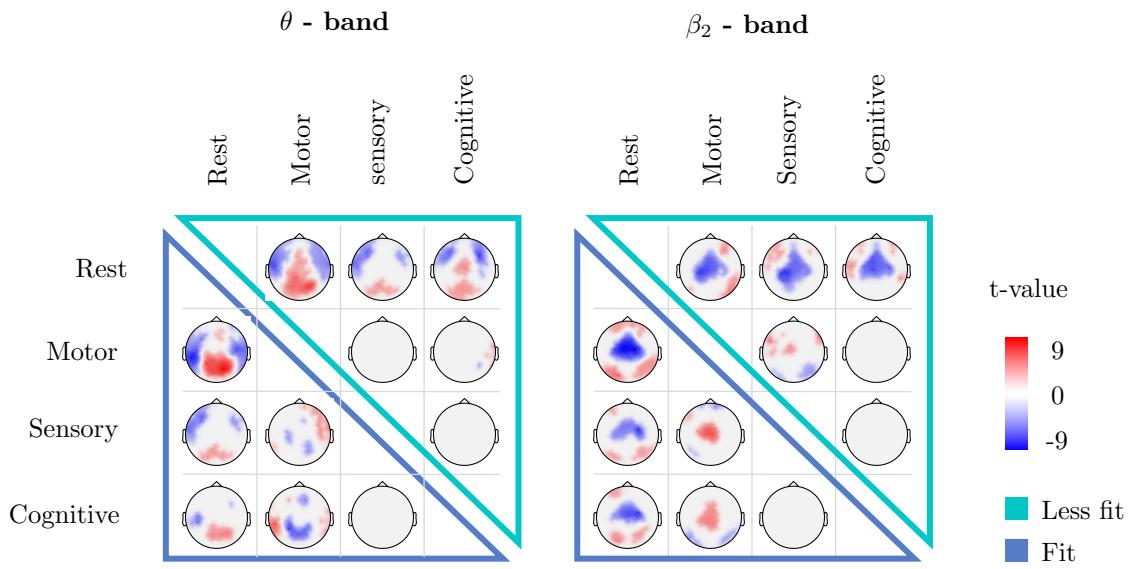


Figure 4.3: Main results of Published Research Article III. Statistical t-maps of significant differences of dominant DMD mode patterns in the θ and β_2 frequency bands between the tasks. Fit participants (blue) showed higher specificity of task-related patterns than less fit participants (turquoise), indicated by higher pronounced differences between the tasks.

The higher degree of task differentiability in the fit group compared to the unfit group supports the idea that physical fitness manifests in task-related brain activation patterns consistent with lower dedifferentiation in older adults. The higher proportion of explained variance in the fit participants can be interpreted as higher prominence of the patterns in this group due to lower noise levels, which is consistent with the predictions by the model of dedifferentiation.

Author Contributions

C. Goelz, J.K. Stroehlein, F.K. Haase, C. Reinsberger, and S. Vieluf contributed to the study conception and design. **C. Goelz and F. K. Haase** set up the experiments. Data collection was performed by **C. Goelz, J. K. Stroehlein and F. K. Haase**. **C. Goelz and K. Moora** analyzed data. All authors interpreted results, drafted parts of the work, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

4.4 Research Article IV

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

Professional expertise is another factor influencing age-related reorganization. This study aimed to characterize middle-aged fine motor experts and novices by using classification at task and group levels.

As described previously, we used class-level statistical methods first to compare the inputs to the classification algorithms. Analogous to chapter 4.1, we trained a classifier for each participant that outputs the type of task, i.e., uniform or sinusoidal force tracking with the left and right hands. We compared the classification performance, i.e. the differentiability of the tasks, between the groups. In addition, we trained a group-level classifier to predict whether the participant performing the force tracking is a fine motor expert or a novice. We used EEG and the force tracking data as input to the classification pipelines

To further examine the EEG patterns at the trial level, we transformed the DMD modes of all subjects via UMAP. We quantified the clustering structure of the UMAP embedding by calculating the Euclidean distance of each trial within each participant. We also computed the centroids of all trials per participant and determined the Euclidean distance between these centroids.

Although the groups differed at the behavioral level in left-handed force tracking, we found no statistical differences in DMD modes. Classification of task levels for all subjects performed better than chance (accuracy: $M = 0.68$, $SD = 0.13$, theoretical chance level: 0.25). There were no differences in classification performance between experts (accuracy: $M = 0.66$, $SD = 0.16$) and novices (accuracy: $M = 0.70$, $SD = 0.10$) [$t(41) = 0.96$, $p = 0.35$].

Classification of group membership was not possibly better than chance (theoretical chance level: 0.5), neither based on the EEG ($M = 0.53$, $SD = 0.07$) nor based on the force tracking data ($M = 0.43$, $SD = 0.16$).

Visualization of the EEG feature space revealed patterns of individuality in both groups (see Figure 4.4). This is expressed in a structure of small clusters, with each cluster assigned to one participant. Our comparison of the distances showed a more considerable distance between the individual clusters of the experts ($M = 7.26$, $SD = 2.25$) than between those of the novices ($M = 3.92$, $SD = 1.33$) with more compact clusters for the experts ($M = 1.03$, $SD = 0.55$) compared to the novices ($M = 1.34$, $SD = 0.48$).

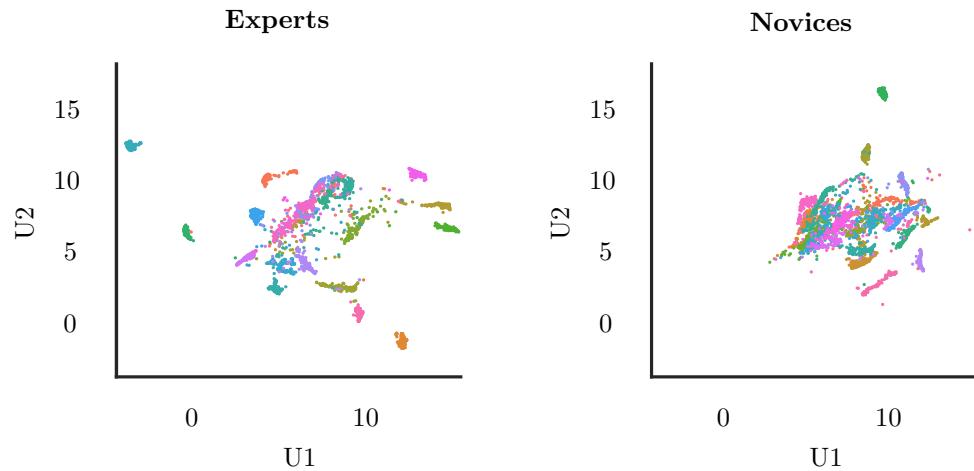


Figure 4.4: Main results of Published Research Article IV. UMAP embedding of EEG feature space of fine motor experts and novices. Each color corresponds to one participant; each dot corresponds to one trial. The experts’ data clustered structure is more dispersed, and clusters are more compact.

The results of task classification suggest that contrary to what was predicted by the reserve hypothesis, expertise does not influence the differentiation of task representations. Also, we could not classify between experts and novices. However, the analysis of the group structure indicates a higher individuality of task-related brain activation patterns in experts compared to novices.

Author Contributions

R. Gaidai: Software, formal analysis, writing – original draft. **C. Goelz:** Software, formal analysis, writing – original draft. **K. Mora:** Software, formal analysis, writing – review, and editing. **J. Rudisch:** Writing – review, and editing. **E. Reuter:** Conceptualization, Investigation, writing – review, and editing. **B. Godde:** Conceptualization, Supervision, writing – review, and editing. **C. Reinsberger:** Writing – review and editing. **C. Voelcker-Rehage:** Conceptualization, supervision, writing – review and editing. **S. Vieluf:** Conceptualization, investigation, supervision, project administration, writing – review and editing.

Chapter 5

General discussion

References

1. *Ageing* <https://www.who.int/health-topics/ageing>.
2. Betzel, R. F. & Bassett, D. S. Multi-scale brain networks. *NeuroImage* **160**. Functional Architecture of the Brain, 73–83. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S1053811916306152> (2017).
3. Brunton, B. W. & Beyeler, M. Data-driven models in human neuroscience and neuroengineering. *Current Opinion in Neurobiology* **58**. Computational Neuroscience, 21–29. ISSN: 0959-4388. <https://www.sciencedirect.com/science/article/pii/S0959438818302502> (2019).
4. Appenzeller, T. *The AI revolution in science: How deep learning is helping scientists cope with a data deluge* 2017. <https://www.science.org/content/article/ai-revolution-science>.
5. Hey, T., Tansley, S., Tolle, K. & Gray, J. *The Fourth Paradigm: Data-Intensive Scientific Discovery* ISBN: 978-0-9825442-0-4. <https://www.microsoft.com/en-us/research/publication/fourth-paradigm-data-intensive-scientific-discovery/> (Microsoft Research, Oct. 2009).
6. Leonard, J. J., Mindell, D. A. & Stayton, E. L. Autonomous vehicles, mobility, and employment policy: the roads ahead. *Massachusetts Inst. Technol., Cambridge, MA, Rep. RB02-2020* (2020).
7. Liu, Y., Jain, A., Eng, C., Way, D. H., Lee, K., Bui, P., Kanada, K., de Oliveira Marinho, G., Gallegos, J., Gabriele, S., Gupta, V., Singh, N., Natarajan, V., Hofmann-Wellenhof, R., Corrado, G. S., Peng, L. H., Webster, D. R., Ai, D., Huang, S. J., Liu, Y., Dunn, R. C. & Coz, D. A deep learning system for differential diagnosis of skin diseases. *Nature Medicine* **26**, 900–908. ISSN: 1546-170X. <https://doi.org/10.1038/s41591-020-0842-3> (June 2020).
8. Adamopoulou, E. & Moussiades, L. *An Overview of Chatbot Technology in Artificial Intelligence Applications and Innovations* (eds Maglogiannis, I., Iliadis, L. & Pimenidis, E.) (Springer International Publishing, Cham, 2020), 373–383. ISBN: 978-3-030-49186-4. https://doi.org/10.1007/978-3-030-49186-4_31.

9. Goelz, C., Mora, K., Rudisch, J., Gaidai, R., Reuter, E.-M., Godde, B., Reinsberger, C., Voelcker-Rehage, C. & Vieluf, S. Classification of visuomotor tasks based on electroencephalographic data depends on age-related differences in brain activity patterns. *Neural Networks* **142**, 363–374 (2021).
10. Goelz, C., Reuter, E.-M., Fröhlich, S., Rudisch, J., Godde, B., Vieluf, S. & Voelcker-Rehage, C. 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).
11. Goelz, C., Mora, K., Stroehlein, J., Haase, F., Dellnitz, M., Reinsberger, C. & Vieluf, S. Electrophysiological signatures of dedifferentiation differ between fit and less fit older adults. *Cognitive Neurodynamics* **15**, 1–13 (2021).
12. Gaidai, R., Goelz, C., Mora, K., Rudisch, J., Reuter, E.-M., Godde, B., Reinsberger, C., Voelcker-Rehage, C. & Vieluf, S. Classification characteristics of fine motor experts based on electroencephalographic and force tracking data. *Brain Research* **1792**, 148001 (2022).
13. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The Hallmarks of Aging. *Cell* **153**, 1194–1217. ISSN: 0092-8674. <https://doi.org/10.1016/j.cell.2013.05.039> (2013).
14. Mooney, K. M., Morgan, A. E. & McAuley, M. T. Aging and computational systems biology. *WIREs Systems Biology and Medicine* **8**, 123–139. eprint: <https://wires.onlinelibrary.wiley.com/doi/pdf/10.1002/wsbm.1328>. <https://wires.onlinelibrary.wiley.com/doi/abs/10.1002/wsbm.1328> (2016).
15. Smith, S. M., Elliott, L. T., Alfaro-Almagro, F., McCarthy, P., Nichols, T. E., Douaud, G. & Miller, K. L. Brain aging comprises many modes of structural and functional change with distinct genetic and biophysical associations. *eLife* **9** (eds Peelle, J. E., de Lange, F. P., Madan, C. & Nyberg, L.) e52677. ISSN: 2050-084X. <https://doi.org/10.7554/eLife.52677> (2020).
16. Cohen, A. A., Ferrucci, L., Fülop, T., Gravel, D., Hao, N., Kriete, A., Levine, M. E., Lipsitz, L. A., Olde Rikkert, M. G. M., Rutenberg, A., Stroustrup, N. & Varadhan, R. A complex systems approach to aging biology. *Nature Aging* **2**, 580–591. ISSN: 2662-8465. <https://doi.org/10.1038/s43587-022-00252-6> (2022).
17. Salthouse, T. A. Trajectories of normal cognitive aging. *Psychol. Aging* **34**, 17–24 (Feb. 2019).
18. Li, K. Z. & Lindenberger, U. Relations between aging sensory/sensorimotor and cognitive functions. *Neuroscience & Biobehavioral Reviews* **26**, 777–783. ISSN: 0149-7634. <https://www.sciencedirect.com/science/article/pii/S0149763402000738> (2002).

19. Park, D. C. & Reuter-Lorenz, P. The Adaptive Brain: Aging and Neurocognitive Scaffolding. *Annual Review of Psychology* **60**. PMID: 19035823, 173–196. eprint: <https://doi.org/10.1146/annurev.psych.59.103006.093656> (2009).
20. Reuter-Lorenz, P. A. & Park, D. C. Human Neuroscience and the Aging Mind: A New Look at Old Problems. *The Journals of Gerontology: Series B* **65B**, 405–415. ISSN: 1079-5014. <https://doi.org/10.1093/geronb/gbq035> (May 2010).
21. Fjell, A. M. & Walhovd, K. B. Structural Brain Changes in Aging: Courses, Causes and Cognitive Consequences. *Reviews in the Neurosciences* **21**, 187–222. <https://doi.org/10.1515/REVNEURO.2010.21.3.187> (2010).
22. Li, S.-C., Lindenberger, U. & Sikström, S. Aging cognition: from neuromodulation to representation. *Trends in Cognitive Sciences* **5**, 479–486. ISSN: 1364-6613. <https://www.sciencedirect.com/science/article/pii/S1364661300017691> (2001).
23. Sala-Llonch, R., Bartrés-Faz, D. & Junqué, C. Reorganization of brain networks in aging: a review of functional connectivity studies. *Frontiers in Psychology* **6**. ISSN: 1664-1078. <https://www.frontiersin.org/articles/10.3389/fpsyg.2015.00663> (2015).
24. Courtney, S. & Hinault, T. When the time is right: Temporal dynamics of brain activity in healthy aging and dementia. *Progress in Neurobiology* **203**, 102076. ISSN: 0301-0082. <https://www.sciencedirect.com/science/article/pii/S0301008221000903> (2021).
25. Friston, K. J. Functional and Effective Connectivity: A Review. *Brain Connectivity* **1**. PMID: 22432952, 13–36. eprint: <https://doi.org/10.1089/brain.2011.0008>. <https://doi.org/10.1089/brain.2011.0008> (2011).
26. Deery, H. A., Di Paolo, R., Moran, C., Egan, G. F. & Jamadar, S. D. The older adult brain is less modular, more integrated, and less efficient at rest: A systematic review of large-scale resting-state functional brain networks in aging. *Psychophysiology* **60**. e14159 PsyP-2022-0050.R2, e14159. eprint: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/psyp.14159>. <https://onlinelibrary.wiley.com/doi/abs/10.1111/psyp.14159> (2023).
27. Uddin, L. Q., Yeo, B. T. T. & Spreng, R. N. Towards a Universal Taxonomy of Macroscale Functional Human Brain Networks. *Brain Topography* **32**, 926–942. ISSN: 1573-6792. <https://doi.org/10.1007/s10548-019-00744-6> (2019).
28. Sporns, O. Network attributes for segregation and integration in the human brain. *Current Opinion in Neurobiology* **23**. Macrocircuits, 162–171. ISSN: 0959-4388. <https://www.sciencedirect.com/science/article/pii/S0959438812001894> (2013).
29. Betzel, R. F., Byrge, L., He, Y., Goñi, J., Zuo, X.-N. & Sporns, O. Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage* **102**, 345–357. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S1053811914006508> (2014).

30. Grady, C. The cognitive neuroscience of ageing. *Nature Reviews Neuroscience* **13**, 491–505. ISSN: 1471-0048. <https://doi.org/10.1038/nrn3256> (2012).
31. Koen, J. D. & Rugg, M. D. Neural Dedifferentiation in the Aging Brain. *Trends in Cognitive Sciences* **23**, 547–559. ISSN: 1364-6613. <https://www.sciencedirect.com/science/article/pii/S1364661319301044> (2019).
32. Baltes, P. B. & Lindenberger, U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging* **12**, 12–21 (1997).
33. Li, S.-C., Lindenberger, U. & Frensch, P. A. Unifying cognitive aging: From neuromodulation to representation to cognition. *Neurocomputing* **32-33**, 879–890. ISSN: 0925-2312. <https://www.sciencedirect.com/science/article/pii/S0925231200002563> (2000).
34. Tucker-Drob, E. M., Brandmaier, A. M. & Lindenberger, U. Coupled cognitive changes in adulthood: A meta-analysis. *Psychological Bulletin* **145**, 273–301. <https://doi.org/10.1037/bul0000179> (2019).
35. Carp, J., Park, J., Hebrank, A., Park, D. C. & Polk, T. A. Age-Related Neural Dedifferentiation in the Motor System. *PLOS ONE* **6**, 1–6. <https://doi.org/10.1371/journal.pone.0029411> (Dec. 2011).
36. Fornito, A., Zalesky, A. & Breakspear, M. The connectomics of brain disorders. *Nature Reviews Neuroscience* **16**, 159–172. ISSN: 1471-0048. <https://doi.org/10.1038/nrn3901> (2015).
37. Stern, Y. Cognitive reserve. *Neuropsychologia* **47**, 2015–2028. ISSN: 0028-3932. <https://www.sciencedirect.com/science/article/pii/S0028393209001237> (2009).
38. Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S. & Cabeza, R. Qué PASA? The Posterior–Anterior Shift in Aging. *Cerebral Cortex* **18**, 1201–1209. ISSN: 1047-3211. eprint: <https://academic.oup.com/cercor/article-pdf/18/5/1201/1002115/bhm155.pdf>. <https://doi.org/10.1093/cercor/bhm155> (Oct. 2007).
39. Cabeza, R. Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and aging* **17**, 85–100 (Apr. 2002).
40. Douw, L., Nieboer, D., van Dijk, B. W., Stam, C. J. & Twisk, J. W. R. A Healthy Brain in a Healthy Body: Brain Network Correlates of Physical and Mental Fitness. *PLOS ONE* **9**, 1–8. <https://doi.org/10.1371/journal.pone.0088202> (Feb. 2014).
41. Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J. & Rajah, M. N. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience* **19**, 701–710. ISSN: 1471-0048. <https://doi.org/10.1038/s41583-018-0068-2> (2018).

42. Esiri, M., Matthews, F., Brayne, C., Ince, P., Matthews, F., Xuereb, J., Broome, J., McKenzie, J., Rossi, M., McKeith, I., Lowe, J. & Morris, J. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *The Lancet* **357**, 169–175 (Jan. 2001).
43. Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., Flynn, J., Sackheim, H. & van Heertum, R. Brain Networks Associated with Cognitive Reserve in Healthy Young and Old Adults. *Cerebral Cortex* **15**, 394–402. ISSN: 1047-3211. eprint: <https://academic.oup.com/cercor/article-pdf/15/4/394/1005032/bhh142.pdf>. <https://doi.org/10.1093/cercor/bhh142> (Aug. 2004).
44. Fabel, K., Wolf, S., Ehninger, D., Babu, H., Galicia, P. & Kempermann, G. Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Frontiers in Neuroscience* **3**. ISSN: 1662-453X. <https://www.frontiersin.org/articles/10.3389/neuro.22.002.2009> (2009).
45. Vieluf, S., Mora, K., Gölz, C., Reuter, E.-M., Godde, B., Dellnitz, M., Reinsberger, C. & Voelcker-Rehage, C. Age-and expertise-related differences of sensorimotor network dynamics during force control. *Neuroscience* **388**, 203–213 (2018).
46. Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., Fanning, J., Awick, E., Gothe, N. P., Olson, E. A., McAuley, E. & Kramer, A. F. Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage* **131**. Effects of Physical and Cognitive activity on brain structure and function, 113–125. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S1053811915009556> (2016).
47. Soldan, A., Pettigrew, C., Zhu, Y., Wang, M.-C., Bilgel, M., Hou, X., Lu, H., Miller, M. I., Albert, M. & Team, T. B. R. Association of Lifestyle Activities with Functional Brain Connectivity and Relationship to Cognitive Decline among Older Adults. *Cerebral Cortex* **31**, 5637–5651. ISSN: 1047-3211. eprint: https://academic.oup.com/cercor/article-pdf/31/12/5637/40812786/rsfmri\champs\pib_cognition_supplement_06_02_2021\bhab187.pdf. <https://doi.org/10.1093/cercor/bhab187> (June 2021).
48. Reuter-Lorenz, P. A. & Park, D. C. How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition. *Neuropsychology Review* **24**, 355–370. ISSN: 1573-6660. <https://doi.org/10.1007/s11065-014-9270-9> (2014).
49. Jackson, A. F. & Bolger, D. J. The neurophysiological bases of EEG and EEC measurement: A review for the rest of us. *Psychophysiology* **51**, 1061–1071. eprint: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/psyp.12283>. <https://onlinelibrary.wiley.com/doi/abs/10.1111/psyp.12283> (2014).
50. Cohen, M. X. Where Does EEG Come From and What Does It Mean? *Trends in Neurosciences* **40**, 208–218. ISSN: 0166-2236. <https://www.sciencedirect.com/science/article/pii/S0166223617300243> (2017).

51. Siegel, M., Donner, T. H. & Engel, A. K. Spectral fingerprints of large-scale neuronal interactions. *Nature Reviews Neuroscience* **13**, 121–134. ISSN: 1471-0048. <https://doi.org/10.1038/nrn3137> (2012).
52. Rossini, P. M., Rossi, S., Babiloni, C. & Polich, J. Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Progress in Neurobiology* **83**, 375–400. ISSN: 0301-0082. <https://www.sciencedirect.com/science/article/pii/S0301008207001451> (2007).
53. Ishii, R., Canuet, L., Aoki, Y., Hata, M., Iwase, M., Ikeda, S., Nishida, K. & Ikeda, M. Healthy and pathological brain aging: from the perspective of oscillations, functional connectivity, and signal complexity. *Neuropsychobiology* **75**, 151–161 (2017).
54. Smit, D. J. A., Boersma, M., Schnack, H. G., Micheloyannis, S., Boomsma, D. I., Hulshoff Pol, H. E., Stam, C. J. & de Geus, E. J. C. The Brain Matures with Stronger Functional Connectivity and Decreased Randomness of Its Network. *PLOS ONE* **7**, 1–11. <https://doi.org/10.1371/journal.pone.0036896> (May 2012).
55. Samogin, J., Rueda Delgado, L., Taberna, G. A., Swinnen, S. P. & Mantini, D. Age-Related Differences of Frequency-Dependent Functional Connectivity in Brain Networks and Their Link to Motor Performance. *Brain Connectivity* **12**. PMID: 35152734, 686–698. eprint: <https://doi.org/10.1089/brain.2021.0135>. <https://doi.org/10.1089/brain.2021.0135> (2022).
56. Babiloni, C., Arakaki, X., Azami, H., Bennys, K., Blinowska, K., Bonanni, L., Bujan, A., Carrillo, M. C., Cichocki, A., de Frutos-Lucas, J., Del Percio, C., Dubois, B., Edelmayer, R., Egan, G., Epelbaum, S., Escudero, J., Evans, A., Farina, F., Fargo, K., Fernández, A., Ferri, R., Frisoni, G., Hampel, H., Harrington, M. G., Jelic, V., Jeong, J., Jiang, Y., Kaminski, M., Kavcic, V., Kilborn, K., Kumar, S., Lam, A., Lim, L., Lizio, R., Lopez, D., Lopez, S., Lucey, B., Maestú, F., McGeown, W. J., McKeith, I., Moretti, D. V., Nobili, F., Noce, G., Olichney, J., Onofrij, M., Osorio, R., Parra-Rodriguez, M., Rajji, T., Ritter, P., Soricelli, A., Stocchi, F., Tarnanas, I., Taylor, J. P., Teipel, S., Tucci, F., Valdes-Sosa, M., Valdes-Sosa, P., Weiergräber, M., Yener, G. & Guntekin, B. Measures of resting state EEG rhythms for clinical trials in Alzheimer's disease: Recommendations of an expert panel. *Alzheimer's & Dementia* **17**, 1528–1553. eprint: <https://alz-journals.onlinelibrary.wiley.com/doi/pdf/10.1002/alz.12311>. <https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1002/alz.12311> (2021).
57. Fröhlich, S., Kutz, D. F., Müller, K. & Voelcker-Rehage, C. Characteristics of Resting State EEG Power in 80+-Year-Olds of Different Cognitive Status. *Frontiers in Aging Neuroscience* **13**. ISSN: 1663-4365. <https://www.frontiersin.org/articles/10.3389/fnagi.2021.675689> (2021).

58. Farina, F., Emek-Savaş, D., Rueda-Delgado, L., Boyle, R., Kiiski, H., Yener, G. & Whelan, R. A comparison of resting state EEG and structural MRI for classifying Alzheimer's disease and mild cognitive impairment. *NeuroImage* **215**, 116795. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S1053811920302822> (2020).
59. Quandt, F., Bönstrup, M., Schulz, R., Timmermann, J. E., Zimmerman, M., Nolte, G. & Hummel, F. C. Spectral Variability in the Aged Brain during Fine Motor Control. *Frontiers in Aging Neuroscience* **8**. ISSN: 1663-4365. <https://www.frontiersin.org/articles/10.3389/fnagi.2016.00305> (2016).
60. Hong, X., Liu, Y., Sun, J. & Tong, S. Age-Related Differences in the Modulation of Small-World Brain Networks during a Go/NoGo Task. *Frontiers in Aging Neuroscience* **8**. ISSN: 1663-4365. <https://www.frontiersin.org/articles/10.3389/fnagi.2016.00100> (2016).
61. Li, L., Gratton, C., Fabiani, M. & Knight, R. T. Age-related frontoparietal changes during the control of bottom-up and top-down attention: an ERP study. *Neurobiology of Aging* **34**, 477–488. ISSN: 0197-4580. <https://www.sciencedirect.com/science/article/pii/S0197458012001741> (2013).
62. Reuter, E.-M., Voelcker-Rehage, C., Vieluf, S., Parianen Lesemann, F. & Godde, B. The P3 Parietal-To-Frontal Shift Relates to Age-Related Slowing in a Selective Attention Task. *Journal of Psychophysiology* **31**, 49–66. eprint: <https://doi.org/10.1027/0269-8803/a000167>. <https://doi.org/10.1027/0269-8803/a000167> (2017).
63. Hübner, L., Godde, B. & Voelcker-Rehage, C. Older adults reveal enhanced task-related beta power decreases during a force modulation task. *Behavioural Brain Research* **345**, 104–113. ISSN: 0166-4328. <https://www.sciencedirect.com/science/article/pii/S016643281731687X> (2018).
64. Samuel, A. L. Some Studies in Machine Learning Using the Game of Checkers. *IBM Journal of Research and Development* **3**, 210–229 (1959).
65. Hastie, T., Tibshirani, R. & Friedman, J. *The Elements of Statistical Learning. Data Mining, Inference, and Prediction, Second Edition* Second. ISBN: 978-0-387-84857-0. <https://link.springer.com/book/10.1007/978-0-387-84858-7> (Springer-Verlag, New York, 2009).
66. Von Luxburg, U. & Schölkopf, B. in *Handbook of the History of Logic, Vol. 10: Inductive Logic* 651–706 (Elsevier North Holland, Amsterdam, Netherlands, May 2011).
67. Rudin, C. & Wagstaff, K. L. Machine learning for science and society. *Machine Learning* **95**, 1–9. ISSN: 1573-0565. <https://doi.org/10.1007/s10994-013-5425-9> (2014).
68. Bzdok, D., Altman, N. & Krzywinski, M. Statistics versus machine learning. *Nature Methods* **15**, 233–234. ISSN: 1548-7105. <https://doi.org/10.1038/nmeth.4642> (2018).

69. Shalev-Shwartz, S. & Ben-David, S. *Understanding Machine Learning: From Theory to Algorithms* ISBN: 9781107057135. <https://books.google.de/books?id=ttJkAwAAQBAJ> (Cambridge University Press, 2014).
70. Murphy, K. P. *Machine learning: a probabilistic perspective* (Cambridge, MA, 2012).
71. McInnes, L., Healy, J. & Melville, J. Umap: Uniform manifold approximation and projection for dimension reduction. *arXiv preprint arXiv:1802.03426* (2018).
72. Burkov, A. *The Hundred-Page Machine Learning Book* ISBN: 9781999579517. <https://books.google.de/books?id=0jbxwQEACAAJ> (Andriy Burkov, 2019).
73. Mitchell, T. *Machine Learning* ISBN: 9780071154673. <https://books.google.de/books?id=EoYBngEACAAJ> (McGraw-Hill, 1997).
74. Roy, Y., Banville, H., Albuquerque, I., Gramfort, A., Falk, T. H. & Faubert, J. Deep learning-based electroencephalography analysis: a systematic review. *Journal of Neural Engineering* **16**, 051001. <https://dx.doi.org/10.1088/1741-2552/ab260c> (2019).
75. Banville, H., Chehab, O., Hyvärinen, A., Engemann, D.-A. & Gramfort, A. Uncovering the structure of clinical EEG signals with self-supervised learning. *Journal of Neural Engineering* **18**, 046020. <https://dx.doi.org/10.1088/1741-2552/abca18> (2021).
76. Gemein, L. A., Schirrmeyer, R. T., Chrabaszcz, P., Wilson, D., Boedecker, J., Schulze-Bonhage, A., Hutter, F. & Ball, T. Machine-learning-based diagnostics of EEG pathology. *NeuroImage* **220**, 117021. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S1053811920305073> (2020).
77. Saeidi, M., Karwowski, W., Farahani, F. V., Fiok, K., Taiar, R., Hancock, P. A. & Al-Juaid, A. Neural Decoding of EEG Signals with Machine Learning: A Systematic Review. *Brain Sciences* **11**. ISSN: 2076-3425. <https://www.mdpi.com/2076-3425/11/11/1525> (2021).
78. Khan, S., Hashmi, J. A., Mamashli, F., Michmizos, K., Kitzbichler, M. G., Bharadwaj, H., Bekhti, Y., Ganesan, S., Garel, K.-L. A., Whitfield-Gabrieli, S., Gollub, R. L., Kong, J., Vaina, L. M., Rana, K. D., Stufflebeam, S. M., Hämäläinen, M. S. & Kenet, T. Maturation trajectories of cortical resting-state networks depend on the mediating frequency band. *NeuroImage* **174**, 57–68. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S105381191830106X> (2018).
79. Westner, B. U., Dalal, S. S., Hanslmayr, S. & Staudigl, T. Across-subjects classification of stimulus modality from human MEG high frequency activity. *PLOS Computational Biology* **14**, 1–14. <https://doi.org/10.1371/journal.pcbi.1005938> (Mar. 2018).
80. Brunton, B. W., Johnson, L. A., Ojemann, J. G. & Kutz, J. N. Extracting spatial-temporal coherent patterns in large-scale neural recordings using dynamic mode decomposition. *Journal of Neuroscience Methods* **258**, 1–15. ISSN: 0165-0270. <https://www.sciencedirect.com/science/article/pii/S0165027015003829> (2016).

81. Blankertz, B., Tomioka, R., Lemm, S., Kawanabe, M. & Muller, K.-r. Optimizing Spatial filters for Robust EEG Single-Trial Analysis. *IEEE Signal Processing Magazine* **25**, 41–56 (2008).
82. Rivet, B., Souloumiac, A., Attina, V. & Gibert, G. xDAWN algorithm to enhance evoked potentials: application to brain–computer interface. *IEEE Transactions on Biomedical Engineering* **56**, 2035–2043 (2009).
83. Woo, C.-W., Chang, L. J., Lindquist, M. A. & Wager, T. D. Building better biomarkers: brain models in translational neuroimaging. *Nature Neuroscience* **20**, 365–377. <https://doi.org/10.1038/nn.4478> (2017).
84. Mei, J., Desrosiers, C. & Frasnelli, J. Machine Learning for the Diagnosis of Parkinson’s Disease: A Review of Literature. *Frontiers in Aging Neuroscience* **13**. ISSN: 1663-4365. <https://www.frontiersin.org/articles/10.3389/fnagi.2021.633752> (2021).
85. Engemann, D. A., Mellot, A., Höchenberger, R., Banville, H., Sabbagh, D., Gemein, L., Ball, T. & Gramfort, A. A reusable benchmark of brain-age prediction from M/EEG resting-state signals. *NeuroImage* **262**, 119521. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S105381192200636X> (2022).
86. Gonzeaud, J. *et al.* Accelerated functional brain aging in pre-clinical familial Alzheimer’s disease. *Nature Communications* **12**, 5346. ISSN: 2041-1723. <https://doi.org/10.1038/s41467-021-25492-9> (2021).
87. Saha, S., Mamun, K. A., Ahmed, K., Mostafa, R., Naik, G. R., Darvishi, S., Khandoker, A. H. & Baumert, M. Progress in Brain Computer Interface: Challenges and Opportunities. *Frontiers in Systems Neuroscience* **15**. ISSN: 1662-5137. <https://www.frontiersin.org/articles/10.3389/fnsys.2021.578875> (2021).
88. Anumanchipalli, G. K., Chartier, J. & Chang, E. F. Speech synthesis from neural decoding of spoken sentences. *Nature* **568**, 493–498. ISSN: 1476-4687. <https://doi.org/10.1038/s41586-019-1119-1> (2019).
89. Holdgraf, C. R., Rieger, J. W., Micheli, C., Martin, S., Knight, R. T. & Theunissen, F. E. Encoding and Decoding Models in Cognitive Electrophysiology. *Frontiers in Systems Neuroscience* **11**. ISSN: 1662-5137. <https://www.frontiersin.org/articles/10.3389/fnsys.2017.00061> (2017).
90. Park, J., Carp, J., Hebrank, A., Park, D. C. & Polk, T. A. Neural Specificity Predicts Fluid Processing Ability in Older Adults. *Journal of Neuroscience* **30**, 9253–9259. ISSN: 0270-6474. eprint: <https://www.jneurosci.org/content/30/27/9253.full.pdf>. <https://www.jneurosci.org/content/30/27/9253> (2010).

91. Petti, M., Toppi, J., Babiloni, F., Cincotti, F., Mattia, D. & Astolfi, L. EEG Resting-State Brain Topological Reorganization as a Function of Age. *Computational Intelligence and Neuroscience* **2016**, 6243694. ISSN: 1687-5265. <https://doi.org/10.1155/2016/6243694> (2016).
92. Kottlarz, I., Berg, S., Toscano-Tejeida, D., Steinmann, I., Bähr, M., Luther, S., Wilke, M., Parlitz, U. & Schlemmer, A. Extracting Robust Biomarkers From Multichannel EEG Time Series Using Nonlinear Dimensionality Reduction Applied to Ordinal Pattern Statistics and Spectral Quantities. *Frontiers in Physiology* **11**. ISSN: 1664-042X. <https://www.frontiersin.org/articles/10.3389/fphys.2020.614565> (2021).
93. Reuter, E.-M., Vieluf, S., Koutsandreou, F., Hübner, L., Budde, H., Godde, B. & Voelcker-Rehage, C. A Non-linear Relationship Between Selective Attention and Associated ERP Markers Across the Lifespan. *Frontiers in Psychology* **10**. ISSN: 1664-1078. <https://www.frontiersin.org/articles/10.3389/fpsyg.2019.00030> (2019).
94. Stillman, C., Donofry, S. & Erickson, K. Exercise, Fitness and the Aging Brain: A Review of Functional Connectivity in Aging. *Archives of Psychology* **3**. ISSN: 2573-7902. <https://www.archivesofpsychology.org/index.php/aop/article/view/98> (2019).
95. Gölz, C., Voelcker-Rehage, C., Mora, K., Reuter, E.-M., Godde, B., Dellnitz, M., Reinsberger, C. & Vieluf, S. Improved Neural Control of Movements Manifests in Expertise-Related Differences in Force Output and Brain Network Dynamics. *Frontiers in Physiology* **9**. ISSN: 1664-042X. <https://www.frontiersin.org/articles/10.3389/fphys.2018.01540> (2018).
96. Voelcker-Rehage, C., Reuter, E.-M., Vieluf, S. & Godde, B. in *Age-Differentiated Work Systems* (eds Schlick, C. M., Frieling, E. & Wegge, J.) 391–415 (Springer Berlin Heidelberg, Berlin, Heidelberg, 2013). ISBN: 978-3-642-35057-3. https://doi.org/10.1007/978-3-642-35057-3_17.
97. Ericsson, K. A. & Smith, J. *Toward a general theory of expertise: Prospects and limits* (Cambridge University Press, 1991).
98. Hübner, L., Godde, B. & Voelcker-Rehage, C. Acute Exercise as an Intervention to Trigger Motor Performance and EEG Beta Activity in Older Adults. *Neural Plasticity* **2018**, 4756785. ISSN: 2090-5904. <https://doi.org/10.1155/2018/4756785> (2018).
99. Koutsandréou, F., Wegner, M., Niemann, C. & Budde, H. Effects of Motor versus Cardiovascular Exercise Training on Children's Working Memory. *Medicine & Science in Sports & Exercise* **48**. ISSN: 0195-9131. https://journals.lww.com/acsm-msse/Fulltext/2016/06000/Effects_of_Motor_versus_Cardiovascular_Exercise.21.aspx (2016).
100. Winneke, A. H., Godde, B., Reuter, E.-M., Vieluf, S. & Voelcker-Rehage, C. The Association Between Physical Activity and Attentional Control in Younger and Older Middle-Aged Adults. *GeroPsych* **25**, 207–221. <https://doi.org/10.1024/1662-9647/a000072> (2012).

101. Winneke, A. H., Hübner, L., Godde, B. & Voelcker-Rehage, C. Moderate Cardiovascular Exercise Speeds Up Neural Markers of Stimulus Evaluation During Attentional Control Processes. *Journal of Clinical Medicine* **8**. ISSN: 2077-0383. <https://www.mdpi.com/2077-0383/8/9/1348> (2019).
102. Ströhlein, J. K., Vieluf, S., van den Bongard, Franziska, Götz, C. & Reinsberger, C. Golf spielen gegen die Vergesslichkeit: Effekte des Erlernens der Sportart auf das Default Mode Netzwerk des Gehirns. DE. *B&G Bewegungstherapie und Gesundheitssport* **36**, 65–72. ISSN: 1613-0863. <http://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-1120-7002> (2020).
103. Stroehlein, J. K., Vieluf, S., Zimmer, P., Schenk, A., Oberste, M., Goetz, C., van den Bongard, F. & Reinsberger, C. Learning to play golf for elderly people with subjective memory complaints: feasibility of a single-blinded randomized pilot trial. *BMC Neurology* **21**, 200. ISSN: 1471-2377. <https://doi.org/10.1186/s12883-021-02186-9> (2021).
104. Gowik, J. K., Goetz, C., Vieluf, S., van den Bongard, F. & Reinsberger, C. Source connectivity patterns in the default mode network differ between elderly golf-novices and non-golfers. *Scientific Reports* **13**, 6215. ISSN: 2045-2322. <https://doi.org/10.1038/s41598-023-31893-1> (2023).
105. Jas, M., Engemann, D. A., Bekhti, Y., Raimondo, F. & Gramfort, A. Autoreject: Automated artifact rejection for MEG and EEG data. *NeuroImage* **159**, 417–429. ISSN: 1053-8119. <https://www.sciencedirect.com/science/article/pii/S1053811917305013> (2017).
106. Alschuler, D. M., Tenke, C. E., Bruder, G. E. & Kayser, J. Identifying electrode bridging from electrical distance distributions: A survey of publicly-available EEG data using a new method. *Clinical Neurophysiology* **125**, 484–490. ISSN: 1388-2457. <https://www.sciencedirect.com/science/article/pii/S1388245713010158> (2014).
107. Kunert-Graf, J. M., Eschenburg, K. M., Galas, D. J., Kutz, J. N., Rane, S. D. & Brunton, B. W. Extracting Reproducible Time-Resolved Resting State Networks Using Dynamic Mode Decomposition. *Frontiers in Computational Neuroscience* **13**. ISSN: 1662-5188. <https://www.frontiersin.org/articles/10.3389/fncom.2019.00075> (2019).
108. Schmid, P. J. Dynamic mode decomposition of numerical and experimental data. *Journal of Fluid Mechanics* **656**, 5–28. ISSN: 0022-1120 (2010).
109. Schmid, P. J. & Sesterhenn, J. L. *Dynamic mode decomposition of numerical and experimental data* in *Bulletin of the American Physical Society, 61st APS meeting* (San Antonio, 2008), 208.
110. Tu, J. H., Rowley, C. W., Luchtenburg, D. M., Brunton, S. L. & Kutz, J. N. On dynamic mode decomposition: Theory and applications. *Journal of Computational Dynamics* **1**, 391–421. ISSN: 2158-2491. [/article/id/1dfefbc20-876d-4da7-8034-7cd3c7ae1161](https://doi.org/10.1137/1409567) (2014).

111. Ang, K. K., Chin, Z. Y., Wang, C., Guan, C. & Zhang, H. Filter bank common spatial pattern algorithm on BCI competition IV datasets 2a and 2b. *Frontiers in neuroscience* **6**, 39 (2012).
112. Brunton, S. L. & Kutz, J. N. in *Data-Driven Science and Engineering: Machine Learning, Dynamical Systems, and Control* 154–194 (Cambridge University Press, 2019).
113. Daumé, H. *A Course in Machine Learning* <https://books.google.de/books?id=27NQzgEACAAJ> (Hal Daumé III, 2017).
114. Varoquaux, G., Raamana, P. R., Engemann, D. A., Hoyos-Idrobo, A., Schwartz, Y. & Thirion, B. Assessing and tuning brain decoders: Cross-validation, caveats, and guidelines. *NeuroImage* **145**. Individual Subject Prediction, 166 –179. ISSN: 1053-8119. <http://www.sciencedirect.com/science/article/pii/S105381191630595X> (2017).
115. Fawcett, T. An introduction to ROC analysis. *Pattern Recognition Letters* **27**. ROC Analysis in Pattern Recognition, 861–874. ISSN: 0167-8655. <https://www.sciencedirect.com/science/article/pii/S016786550500303X> (2006).
116. Combrisson, E. & Jerbi, K. Exceeding chance level by chance: The caveat of theoretical chance levels in brain signal classification and statistical assessment of decoding accuracy. *Journal of Neuroscience Methods* **250**. Cutting-edge EEG Methods, 126–136. ISSN: 0165-0270. <https://www.sciencedirect.com/science/article/pii/S0165027015000114> (2015).
117. Shoorangiz, R., Weddell, S. J. & Jones, R. D. in *Handbook of Neuroengineering* 1–39 (Springer, 2021).
118. Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M. & Édouard Duchesnay. Scikit-learn: Machine Learning in Python. *Journal of Machine Learning Research* **12**, 2825–2830. <http://jmlr.org/papers/v12/pedregosa11a.html> (2011).

Published Research Articles

Published Research Article I

Published Research Article II

Published Research Article III

Published Research Article IV