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Variability in heart and brain activity across the adult lifespan

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Deniz Kumral

aus Istanbul, Türkei

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Table of Contents

1. SUMMARY 1
1.1 ABSTRACT (ENGLISH) 1
1.2 ABSTRACT (DEUTSCH) 3
1.3 INTRODUCTION 5
1.4 OBJECTIVES 9
1.5 METHODS 10
1.6 RESULTS 14
1.7 DISCUSSION 16
1.8 BIBLIOGRAPHY 19
2. STATUTORY DECLARATION 23
3. DECLARATION OF CONTRIBUTION TO THE PUBLICATIONS 24
4. PRINT VERSIONS OF THE SELECTED PUBLICATIONS 27
4.1 PUBLICATION 1 27
4.2 PUBLICATION 2 41
4.3 PUBLICATION 3 58
4.4 PUBLICATION 4 (DATASET 1) 71
4.5 PUBLICATION 5 (DATASET 2) 93
5. CURRICULUM VITAE 113
6. COMPLETE LIST OF PUBLICATIONS 115
7. ACKNOWLEDGEMENTS 117

Introductory remarks

Structure and extent of this synopsis follow the doctorate regulations ("Promotionsordnung") of the Charité – Universitätsmedizin Berlin. It summarizes five peer-reviewed publications underlying this dissertation which are abbreviated as **Study 1** (Kumral et al., 2019), **Study 2** (Koenig et al., 2020), **Study 3** (Kumral et al., 2020), **Dataset 1** (Babayan et al., 2019), and **Dataset 2** (Mendes et al., 2019). For more detailed information about background, methods, results, and discussions of these studies, please see the respective publications which are inserted in their complete form in the section 'Print versions of the selected publications', starting on page 27.

1. Summary

1.1 Abstract (English)

Introduction

The world population is rapidly aging. In Germany for example, the percentage of individuals 60 years and older is projected to be 38% in 2050[1]. Longer lifetimes entail more progressive impairment of brain and body. It is therefore a crucial question how to assess and quantify these frequently occurring alterations associated with aging. In order to address this question, the overarching goal of this dissertation is to explore and characterize bodily and neural signals which reflect effects of aging across the adult lifespan. To this end, I performed two studies as lead investigator and contributed to three more large-scale collaborative studies.

Methods

In **Study 1** (Kumral et al., 2019), I investigated the relationship of heart rate variability (HRV) to brain structure (gray matter) and resting state (rs) brain activity (functional connectivity) in a well-characterized sample of healthy subjects across the adult lifespan (N=388). For **Study 2** (Koenig et al., 2020), I contributed to a mega analysis testing the association between cortical thickness and heart-rate variability (HRV) at rest, also across the lifespan (N=1218). In **Study 3** (Kumral et al., 2020), I examined whether different measures of brain signal variability – identified with hemodynamic (functional magnetic resonance imaging; fMRI) or electrophysiological (EEG) methods – reflect the same underlying physiology in healthy younger and older adults (N=189). Lastly, during my dissertation work, I was part of the Mind-Body-Emotion group in Leipzig, which established two publicly available – and now widely used – datasets (**Datasets 1** and **2**; Babayan et al., 2019, Mendes et al., 2019), which include structural and functional MRI, EEG data as well as a range of physiological and behavioral measures.

Results

In **Study 1**, I showed that age-related decreases in resting HRV are accompanied by age-dependent and age-invariant alterations in brain function, particularly located along cortical midline structures. In **Study 2,** we found that the age-related decrease of resting HRV was associated with cortical thinning in prefrontal brain structures. In **Study 3**, I demonstrated age differences in brain signal variability obtained with rs-fMRI and rs-EEG, respectively. Surprisingly, the two measures of neural variability showed no significant correlation, but rather seemed to provide complementary information on the state of the aging brain.

Conclusions

The present dissertation provides evidence that measures of cardiovascular and neural signal variability may be useful biomarkers for neurocognitive health (and disease) in aging. With these measures, we can further specify the dynamic interplay of the human body and the brain in relation to individual health-related factors.

1.2 Abstract (Deutsch)

Einführung

Die Weltbevölkerung wird immer älter. In Deutschland wird der Anteil der Personen, die 60 Jahre und älter sind, bis zum Jahr 2050 voraussichtlich auf 38 Prozent ansteigen[1]. Eine längere Lebensdauer bedeutet auch eine fortschreitende Beeinträchtigung des Gehirns und des Körpers. Es ist daher eine entscheidende Frage, wie diese häufigen alterungsbedingten Veränderungen festgestellt und quantifiziert werden können. Das Ziel dieser Dissertation bestand daher darin, Körper- und Gehirnsignale zu untersuchen und zu charakterisieren, welche die Auswirkungen des Alterns über die gesamte Lebensspanne widerspiegeln. Für dieses Ziel führte ich in meiner Dissertation zwei Studien als „lead investigator" durch, darüber hinaus habe ich mich an drei weiteren Kooperations-Projekten beteiligt.

Methoden

In **Studie 1** (Kumral et al., 2019) habe ich die Beziehung zwischen der Herzfrequenzvariabilität in Ruhe (HFV), dem Gehirnvolumen (graue Substanz) und der Gehirnaktivität (bzw. Konnektivität) im Ruhezustand anhand einer gut charakterisierten Stichprobe gesunder Probanden über die gesamte Lebensspanne (N=388) untersucht. **Studie 2** (Koenig et al., 2020) ist eine Mega Analyse des Zusammenhangs zwischen der kortikalen Dichte und der HFV im Ruhezustand über die gesamte Lebensdauer (N=1218), zu der ich wesentlich beigetragen habe. Im Mittelpunkt von **Studie 3** (Kumral et al., 2020) stand die Frage, ob verschiedene Messungen der Variabilität des Gehirnsignals – erhoben mit hämodynamischen (funktionelle Magnetresonanztomografie; fMRT) oder elektrophysiologischen (EEG) Methoden – die gleichen physiologischen Grundlagen bei gesunden jüngeren und älteren Menschen widerspiegeln (N=189). Als Teil der Mind-Body-Emotion-Gruppe in Leipzig war ich an der Erstellung von zwei großen – öffentlich zugänglichen und weltweit genutzten – Datensätzen aktiv beteiligt (**Datensätze 1** und **2**; Babayan et al., 2019, Mendes et al., 2019), die neben strukturellen und funktionellen MRT- sowie EEG-Daten auch physiologische und Verhaltensmaße umfassen.

Ergebnisse

In **Studie 1** fand ich, dass die altersbedingte Abnahme der Ruhe-HFV von altersabhängigen und altersinvarianten Veränderungen der Gehirnfunktion begleitet war, insbesondere entlang der kortikalen Mittellinie. In **Studie 2** berichteten wir, dass die altersbedingte Abnahme der Ruhe-HFV mit einer kortikalen Verdünnung präfrontaler Hirnstrukturen verbunden war. In **Studie 3**

beobachtete ich Altersunterschiede in der Variabilität des Gehirnsignals, das mit Ruhe-fMRT und Ruhe-EEG gemessen wurde. Überraschenderweise zeigten die zwei Messmethoden der neuronalen Variabilität keine signifikante Korrelation, sondern lieferten ergänzende Informationen über den Zustand des alternden Gehirns.

Schlussfolgerungen

Die vorliegende Dissertation erbringt den Nachweis, dass die Messungen der kardiovaskulären und neuronalen Signalvariabilität nützliche Biomarker für die neurokognitive Gesundheit (und Krankheit) während des Alterns sein können. Mit diesen Markern können wir das dynamische Zusammenspiel des menschlichen Körpers und des Gehirns im Verhältnis zu individuellen, gesundheitsbezogenen Faktoren weiter spezifizieren.

1.3 Introduction

Aging is a complex biological process associated with progressive changes in the human body and brain. It is a major risk factor and contributor to almost all cardiovascular morbidities and mortalities. A major goal in aging research is to achieve what has been termed "successful aging" or "healthy aging", i.e., aging without the appearance of concurrent physical and mental diseases[2]. It is evidently important to understand the factors contributing to healthy aging as, in doing so, we could sustain a better quality of life across the lifespan.

How is healthy aging characterized in the human body and brain? To address this question, different biomarkers reflecting different aspects of aging must be established. Currently, however, there is no consensus on optimal biomarkers and their validity regarding the aging process. In this dissertation, I will discuss potential cardiovascular and neural biomarkers for measuring key aspects of healthy aging (outlined individually below).

1.3.1 Heart Rate Variability (HRV) as a biomarker for health

Advancing age leads to alterations in structural and functional systems (e.g., perturbed autonomic balance). One cardiovascular health marker for investigating such age-related autonomic changes is heart rate variability (HRV). HRV describes variations of the cardiac beat-to-beat (or RR) interval. Phasic modulation of the heart rate arises from the influences of the two branches of the autonomic nervous system (ANS): the sympathetic and parasympathetic nervous system. Autonomic afferents at the heart's sinoatrial node originate from brainstem nuclei, which also receive input from cortical brain regions including anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and also subcortical brain regions like the insula, amygdala, and hypothalamus[3]. These brain regions are part of the central autonomic network (CAN)[3] which is implicated in the maintenance of homeostasis. While vagal influences on the heart act rapidly (milliseconds), sympathetic activity increases the heart rate relatively slowly (seconds). Therefore, analyzing rapid changes in heart rate allows for the extraction of the parasympathetic (vagal) component of cardioregulation.

HRV can be quantified from a standard electrocardiogram (ECG), acquired during a task or in the absence of stimulation (i.e., "at rest"). It has been used, for example, to quantify individual differences in parasympathetic cardioregulation – with higher HRV generally indicating higher bodily integrity or health and maintenance, but also better cognitive performance and greater well-

being[4]. It is also linked to age-related attenuated vagal control that could capture longevity[5]. Thus, HRV offers a measure of autonomic responsiveness which might be clinically useful as a biomarker of cardiovascular autonomic (ab)normalities during aging.

1.3.2 Structural and functional neural biomarkers of aging

The brain is known to be strongly affected by aging, however, there is pronounced inter-individual variability. Recent advances in magnetic resonance imaging (MRI) now permit noninvasive exploration of brain structure and function in relation to these age-associated changes and inter-individual variations. In the last two decades, to assess the *brain structure* quantitively, based on high-resolution anatomical images (e.g., T1-weighted MRI), several methods have been established. The two most widely used techniques are voxel-based morphometry[6] (VBM) and the measurement of cortical thickness (CT)[7]. While VBM is a classical quantitative method based purely on a volumetric representation of the brain[6], CT is based on the estimation of an absolute measure of thickness across the cortical surface[7]. Both methods have been used successfully to characterize age-dependent structural degenerations including shrinkage of gray matter volume (GMV)[8,9] as well as widespread reductions in CT[9,10]. To further investigate inter-individual variability during aging, these methods are utilized (**Study 1** and **2**), as discussed in detail below.

In addition to changes in brain structure, it is also well-established that *brain function* alters with age. Contemporary functional neuroimaging techniques provide excellent opportunities for investigating the aging brain *in vivo*[11,12]. Using T2*-weighted echo planar imaging (EPI), it is possible to study brain activity, acquired with or without an experimental task or stimulation, the latter being called resting state fMRI (rs-fMRI)[13]. The mostly widely used fMRI method is blood oxygenation level dependent (BOLD) fMRI. BOLD fMRI is based on local concentration changes in deoxygenated hemoglobin (Δ[deoxy-Hb]) during functional activation with a concomitant increase of cerebral blood flow (CBF). This is caused by vascular (blood velocity and volume: "neurovascular coupling") and metabolic (oxygen consumption: "neurometabolic coupling") changes[14,15].

While fMRI is ideal for studying age-related functional changes with superb spatial resolution, a major disadvantage is its dependence on vascular reactions to the brain activity. This concern is especially relevant for studies involving an aging population in which structural changes are known to occur in the cerebral vasculature, a notable example of which would be arteriosclerosis.

These changes can reduce vessel elasticity and may alter the BOLD fMRI signal due to their effect on neurovascular coupling[14].

While fMRI BOLD is only partially and indirectly related to neural activity[15], different electrophysiological methods such as electroencephalography (EEG) provide a more direct assessment of neural activity. EEG measures the currents resulting from the synchronization of dendritic postsynaptic potentials across the cortical neural population and offers a direct measure of neuronal activity with high temporal (at milliseconds scale)[16], but at low spatial resolution. Interestingly, the combination of EEG with fMRI-based techniques can complement, to some extent, the inherent limitations within each individual modality. For example, EEG has been used to separate neural from vascular components of the BOLD signal[17], while fMRI can be used to improve the spatial resolution of EEG signals[18]. Therefore, to overcome distinct limitations of these imaging methods, we employed both fMRI and EEG in **Study 3**.

While the above-mentioned cardiovascular neural biomarkers have been widely used in studies on aging, several important questions are still open. For example, given that HRV reflects the interaction of the brain and the heart, little is known about the specific brain regions underlying this interaction and – more relevant for this dissertation – whether (and how) this interaction alters with age. Furthermore, regarding the above-mentioned functional brain measures, there is still an active search for understanding age-related brain alterations, given that both fMRI and EEG have significant shortcomings. To address these issues, this dissertation firstly outlines the interaction between HRV and the brain across the lifespan and secondly, explores different neural biomarkers in aging, for which subsequently some background is given:

1.3.3 HRV and the Brain

The relation of spontaneous, intrinsic brain activity to different cardiovascular biomarkers (e.g., HRV) is relevant for understanding how the brain integrates and regulates internal changes during aging. Accordingly, the neurovisceral integration model[19,20] highlights the role of vagally-mediated HRV in cognition and bodily homeostasis. Evidence in favor of this model comes from a meta-analysis reporting different cortical and subcortical brain structures and functions to be associated with HRV[20]. Given this close relationship between functional and structural features of the brain and HRV, it is tempting to further speculate that age-related attenuations in HRV might go along with specific neural alterations as well. To address this hypothesis, the first section of

this dissertation (**Study 1** and **2**) investigates structural (CT and GMV) and functional (functional connectivity) correlates of resting HRV across the adult lifespan.

1.3.4 Brain signal variability as potential new neural biomarkers

To quantify age-related alterations in the brain, researchers typically compute within-subject average signals across a given time course to capture what is conceived as the most task-relevant brain activity. However, the evaluation of mean changes in each variable over time ignores the dynamic nature of physiological processes. Recently, examining moment-to-moment signal variability using fMRI or EEG has provided new insights into the dynamic aspects of the aging brain[21]. For instance, in several neuroimaging studies, age-related changes in BOLD and EEG signal variability have been observed[22,23]. However, it remains unclear whether these alterations are dominated by joint signal sources of fMRI and EEG, or by potentially different signal contributions. Given the potentially large non-neuronal signal contribution, this issue is particularly relevant for BOLD fMRI studies. In **Study 3** of this dissertation, I addressed this question by analyzing rs-fMRI and EEG measures of variability in healthy young and old participants.

1.4 Objectives

The main goals of this dissertation were to (i) investigate potential links between a cardiac biomarker of healthy aging (e.g., heart-rate variability) and brain structure (ii) and function, and (iii) to compare two potential neural biomarkers of healthy (brain) aging, i.e., variability of BOLD fMRI signal and of EEG. As a groundwork for achieving these goals, I was also involved in establishing two large datasets on which the brain-body interactions have been studied, not only by myself, but also by other groups world-wide given that these data are now publicly available.

The specific objectives of this dissertation were as follows:

- **Study 1** (Kumral et al., 2019): To investigate resting HRV in relation to brain structure (GMV) and resting state functional connectivity in a well-characterized healthy sample with different age groups across the adult lifespan.
- **Study 2** (Koenig et al., 2020): Data contribution into the cross-sectional pooled mega analysis exploring the association between brain structure using CT and resting HRV across the lifespan from 12 to 87 years of age.
- **Study 3** (Kumral et al., 2020): To explore whether different measures of brain signal variability – identified with either hemodynamic or electrophysiological methods – reflect the same underlying physiology in healthy younger and older adults.
- **Datasets** (Babayan et al., 2019, Mendes et al., 2019): To establish a framework for the study of mind, brain, and body interaction, e.g., the interaction between the heart (ECG) and the brain (fMRI, EEG). These datasets are now publicly available and include raw and preprocessed structural and functional MRI as well as EEG data and a range of other health and behavioral measures.

1.5 Methods

The specific methodologies of each study, including study design, participant selection criteria, image preprocessing, and statistical analysis are described in the methods section of the respective publications.

1.5.1 Subjects and Study Design

In **Study 1,** I combined two datasets, (i) the "Leipzig Research Centre for Civilization Diseases" (LIFE[24]; N=278) and (ii) the Leipzig Study for Mind-Body-Emotion Interactions (LEMON[25]; N=110), totaling 388 healthy young (N=140, 26.0±4.2 years, range: 20–35, 38 female), middle-aged (N=119, 46.3±6.2 years, range: 35–60, 36 female), and older (N=119, 66.9±4.7 years, range: 60–80, 50 female) adults.

In **Study 2**, I contributed structural MRI and ECG data (N=110) collected under similar protocols to be pooled in a mega analysis (N=1218, 36.7±14.9 years, range: 12–87, 615 female). Preregistration and a full preprint/manuscript detailing the hypotheses, strategies for pooling of data, and analyses of the project have been posted on the Open Science Framework (https://osf.io/btjpw/).

In **Study 3**, I also used the LEMON dataset, consisting of 135 healthy younger (25.10±3.70 years, 42 females) and 54 older subjects (67.15±4.52 years, 27 females). Lastly, as part of the Mind-Body-Emotion group at MPI in Leipzig, we made an extended version of the data used in our empirical studies publicly available, containing raw and preprocessed structural, functional MRI and EEG data as well as a range of behavioral, physiological and phenotypic measures[25,26].

All subjects were healthy and gave written informed consent according to the declaration of Helsinki prior to investigation. All studies were conducted in compliance with the relevant laws and institutional guidelines and approved by the local ethics committee at the Medical Faculty of the University of Leipzig.

1.5.2 Data Acquisition

Electrocardiography. In **Study 1**, ten seconds of a standard medical 12-lead resting ECG was acquired using a Page-Writer TC50 ECG system in the supine position (LIFE, N=278) in the LIFE study, while in the LEMON study (N=110), four minutes of resting ECG were acquired using a Biopac MP35 amplifier with three disposable electrodes on the thorax.

Structural and Functional Magnetic Resonance Imaging. In all studies, MRI data were acquired using a whole-body 3T scanner (Magnetom Verio, Siemens, Germany) equipped with a 32-channel head coil. In **Study 1, 2**, and **3**, the MRI data for each participant comprised a structural scan acquired using a three-dimensional Magnetization-Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) sequence, and rs-fMRI scans acquired using a multiband gradient EPI sequence.

Electroencephalography. In **Study 3**, Rs-EEG was recorded with a BrainAmp MR plus amplifier with 62-channel active ActiCAP electrodes attached according to the international standard 10–20 localization system. Rs-EEG session comprised a total of 16 blocks, each 60 s long, 8 with eyes-closed and 8 with eyes-open.

1.5.3 Data Analysis

Electrocardiography. In **Studies 1** and **2**, the time series of heart rate consisting of beat-to-beat intervals (RR-intervals) were detected automatically and inspected visually. As a HRV measure, I calculated the root mean square of successive differences (RMSSD) of adjacent RR intervals from the ECG time series (Figure 1).

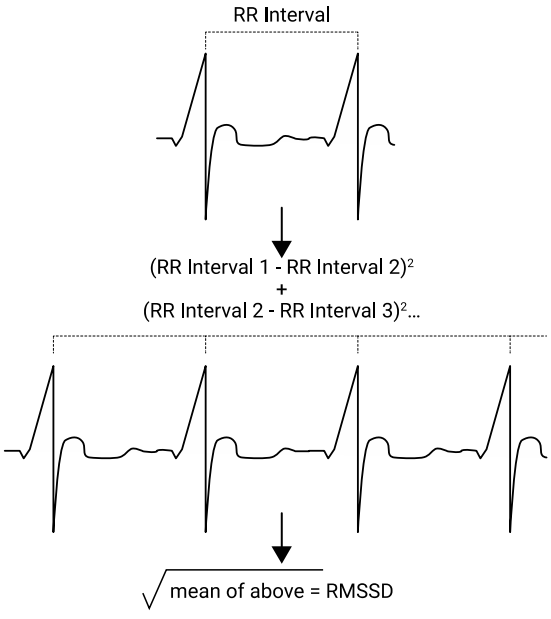

Figure 1. The Root Mean Square of Successive Differences (RMSSD) between each heartbeat (R peak). RMSSD is a common time-domain measurement to assess mainly vagally-mediated heart rate variability (HRV), the successive differences being neighboring RR intervals.

Structural and Functional Magnetic Resonance Imaging. MRI preprocessing pipelines were implemented using Nipype, and all code is available in a Github repository (https://github.com/NeuroanatomyAndConnectivity/pipelines/). I thereby ensure that our entire research process is transparent to other researchers for reproduction and critical discussion. A detailed description of the preprocessing steps and all employed tools can be found in the publications on the two **Datasets**[25,26].

In **Study 1,** I analyzed structural brain alterations (GMV) on the T1-weighted 3D images using VBM implemented in the Computational Anatomy Toolbox[6]. Based on spontaneous modulations of the rs-fMRI BOLD signal, it is further possible to quantify temporal properties such as resting state functional connectivity[27]. For rs-fMRI data, I used whole-brain functional connectivity analysis with graph theory metrics, called Eigenvector Centrality Mapping (ECM) that attributes a value to each voxel in the brain such that it receives a larger centrality value if it is strongly correlated with many other voxels that are themselves central in the brain[28]. To further explore the functional connectivity patterns of identified centrality changes across the whole brain, ECM was complemented by an exploratory seed-based connectivity analysis (SBCA), in which correlations between the time series of the seed and every other voxel in the whole brain were computed for each subject.

In **Study 2,** FreeSurfer software was used to generate models of the cortical surface and to model CT from the T1-weighted images. CT was quantified for a total of 68 regions of interest (ROIs). A series of multiple regression models using frequency and Bayesian statistics were used to predict the association between resting HRV and brain structure (CT).

In **Study 3**, I computed brain signal variability as the standard deviation (SD) of BOLD fMRI signal that quantifies the amount of variation or dispersion across the whole time-series (Figure 2). Essentially, I calculated SD_{BOLD} across the whole time series for each voxel and subsequently within 96 boundaries of preselected ROIs.

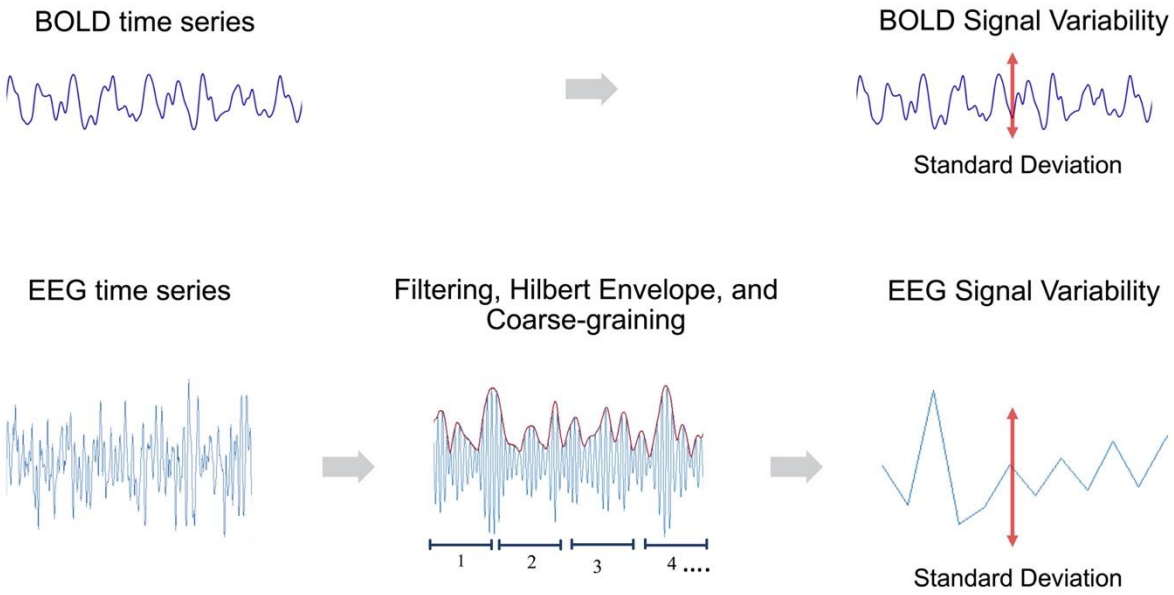

Figure 2. Brain signal variability from the preprocessed resting state functional MRI and EEG signal. Standard deviations of the blood oxygen level-dependent (BOLD) signal and of the coarse-grained amplitude envelope of EEG time series for a number of standard frequency bands at the source space were calculated. Each sample of coarse-grained amplitude envelope of -EEG (represented in numbers) was generated by averaging the samples in non-overlapping windows of length 0.5 s.

Electroencephalography. Rs-EEG preprocessing and analyses were performed with custom Matlab (The MathWorks, USA) scripts using functions from the EEGLAB environment. Firstly, the continuous EEG data were down-sampled to 250 Hz, band-pass filtered within 1–45 Hz. Artefactual channels and data segments were removed after visual inspection. Principal component analysis was used to reduce data dimensionality. Next, I applied Infomax independent component analysis to manually remove components representing eye-movement, eye-blinks, muscle activity, and residual ballistocardiography artifacts. For all subjects, the "New York Head", a standard highly-detailed forward model was used. Source activity was estimated using exact low-resolution tomography and then the data were filtered into several frequency bands. The amplitude envelope of filtered oscillations was extracted using the Hilbert transform. I then applied temporal coarse-graining by averaging data points in non-overlapping windows of length 0.5 s (Figure 2). Finally, I calculated the variability of amplitude envelope of band-pass filtered oscillations on the coarse-grained signal (SD_{EEG}) in each of 96 ROIs.

1.6 Results

In **Study 1**, I examined the relationship between parasympathetic cardioregulation indexed by resting HRV and brain structure (gray matter) as well as whole-brain functional connectivity across the adult lifespan. In structural brain analyses (VBM), there was no significant association between HRV and GMV across all subjects, in either younger or older adults. However, there was a significant HRV-related increase of GMV in the left cerebellum in the middle-aged group. In whole-brain graph-based analysis (ECM) on rs-fMRI, a higher HRV was linked to stronger network centrality in several brain regions, particularly along the cortical midline structures. More precisely, there was a significant interaction between age group and resting HRV in the bilateral vmPFC and an increased centrality in the bilateral posterior cingulate cortex (PCC) across all age groups. In the connectivity analysis (SBCA), I found a significant effect of age on the relation between resting HRV and whole-brain bilateral vmPFC connectivity in the bilateral cerebellum, right superior parietal lobe, left middle and inferior occipital gyrus, and left superior frontal gyrus. Furthermore, there was an increased functional connectivity with the left middle frontal gyrus extending to the dorsolateral prefrontal cortex in the overall sample (N=388). All statistical 3D maps are available at *NeuroVault* for detailed inspection in 3D (http://neurovault.org/collections/TELEUIIY).

In the cross-sectional study (**Study 2**), I contributed data (N=110) collected under similar protocols of CT assessment and HRV recording to be pooled in a mega analysis. Previous findings were confirmed by illustrating that resting HRV and CT decline with increasing age. Further, frequentist analyses revealed a significant relationship between CT in the left lateral OFC and HRV accounting for all potential confounds. However, regression analyses for 68 ROIs did not yield significant associations between RMSSD and CT. Finally, Bayesian analyses showed moderate evidence for the association of resting HRV with CT in left lateral OFC and left inferior temporal gyrus thickness.

The primary aim of **Study 3** was to investigate the effects of age differences on the variability in brain activity, as measured by rs-fMRI and rs-EEG. After controlling for different confounding factors such as head size and head motion, nonparametric ANCOVAs with BOLD signal variability (SD_{BOLD}) as a dependent variable demonstrated a significant main effect of age in 72 ROIs including frontal, temporal, and occipital brain regions. Similarly, I showed age group differences for EEG signal variability (SD_{EEG}) in all frequency bands: SD_{DELTA} in 14 ROIs in

occipital, SD_{THETA} in 16 ROIs in frontal and parietal, SD_{ALPHA} in 20 ROIs in occipital, and SD_{BETA} in 19 ROIs in central and temporal brain regions. As a secondary aim, I also explored sex differences in both brain signal variability measures. There was no significant main effect of sex on SD_{BOLD}. However, a main effect of sex was found in all EEG frequency bands: SD_{DELTA} in 21 ROIs in temporal and occipital, SD_{THETA} in 74 ROIs including frontal, occipital, and temporal, SD_{ALPHA} in 4 ROIs in frontal, and SD_{BETA} in 69 ROIs in temporal, occipital, and central brain areas. The details of the topographic distribution (3D images) of age and sex group differences are available at *Neurovault* (https://neurovault.org/collections/WWOKVUDV/). Lastly, correlations between two measurements of signal variability were examined: Both univariate and exploratory confirmatory multivariate analyses showed that none of the pairwise associations between SD_{BOLD} and SD_{EEG} were significant.

1.7 Discussion

The empirical studies presented in this dissertation aimed to explore and characterize the signal variability measured in the heart and brain across the lifespan. Crucially, multi-modal and integrative approaches (e.g., ECG, fMRI, and EEG) were used to understand normal aging on a more sophisticated level, as different physiological properties do not function in isolation.

Throughout the literature, variability is often conceived as neural "noise" despite the longstanding knowledge that it is instead a central feature of a well-functioning nervous system[29]. Accordingly, the dynamics of a healthy organism produce an apparently irregular and highly complex type of variability at multiple scales (e.g., in time and space) and adapt themselves in response to adverse conditions[30]. In contrast, aged and diseased systems are often associated with more regularity and less complexity, i.e., they lose the capability to adapt.

In my dissertation, I aimed to improve the physiological understanding of potentially important biomarkers of healthy aging. In **Study 1,** I demonstrated the frequently observed age-related decrease in resting HRV to be accompanied by age-dependent and age-invariant alterations in brain functional connectivity, particularly along the cortical midline structures. As discussed in more detail in Kumral et al.,[31], changes in the network architecture in the anterior default mode network (DMN) regions may represent altered cardiovascular control with advancing age and concomitant network reorganization. Age-invariant patterns in posterior DMN (e.g., PCC) might reflect the "internal milieu" throughout the lifespan, that is, monitoring and regulating bodily signals (e.g., the parasympathetic "rest-and-digest"). Importantly, these brain regions also form the central autonomic network (CAN) that has the connections to the sinoatrial node of the heart via the stellate ganglia and the vagus nerve[20]. CAN is critical for tonic background excitation in autonomic and respiratory motoneurons but also for integrated autonomic, neuroendocrine, and behavioral responses to maintained homeostasis[3]. In the mega analysis (**Study 2)**[32]**,** we found an association between resting HRV and thinning in the prefrontal cortex (e.g., lateral OFC) with aging. This finding provides evidence for global autonomy from a neurovisceral perspective throughout aging and highlights the crucial role of the prefrontal cortex in maintaining parasympathetic vagal activity. Overall, the findings in these two studies are consistent with the notion that brain structure and function in frontal areas are related to autonomic cardiac function as indexed by HRV across the adult lifespan. **Studies 1** and **2** thus provide a comprehensive picture of heart-brain interactions and also highlight the importance of inter-individual differences on

parasympathetic outflow at the neural level. Crucially, understanding which brain areas are associated with autonomic function may lead to better focused clinical interventions targeting specific autonomic pathways, thereby improving well-being and promoting adaptive psychophysiological flexibility in aging.

Age-related alterations in the vascular system are known to impact neurovascular coupling. Since the most widely used method to study brain function, BOLD fMRI, depends on neurovascular coupling, one can never be certain whether findings on aging obtained with BOLD fMRI mainly reflect neuronal or vascular or a combination of both components. One approach to estimate the neuronal contributions to the BOLD fMRI signal is to use independent measures of neural function, such as EEG. To achieve this goal, in **Study 3**, brain variability measures based on rs-fMRI and rs-EEG were compared in healthy younger and older adults. Replicating previous findings, it was firstly demonstrated that BOLD signal variability decreases with age in DMN and fronto-parietal network (FPN) regions[22,33] in which cognitive performance (e.g., speed of cognitive processing) were also correlated[34]. As discussed earlier, DMN is an intrinsically correlated network of brain regions and associated with self-referential thought and integration of cognitive processing[35]. The FPN is involved in cognitive control[36]. In this study, I thus suggest that reduced BOLD signal variability in both networks might be an index for age-related neural processing deficits and impaired cognitive functioning.

Regarding rs-EEG, in **Study 3** it was demonstrated that age-related signal variability alterations within the same network was associated with more than one frequency band. More precisely, age-related reductions in SD_{DELTA} and SD_{ALPHA} were mainly found in a visual network, SD_{THETA} in posterior DMN, while an enhancement of SD_{BETA} was mainly seen in the fronto-temporal and sensorimotor networks. Alpha rhythm is the most salient rs-EEG oscillatory phenomenon that originates from thalamo-cortical and cortico-cortical interactions[37,38]. Accordingly, decreased alpha variability in occipital regions might be associated with the cholinergic basal forebrain functioning, affecting thalamo-cortical and cortico-cortical processing. Further, healthy aging has been previously associated with an increase in movement-related beta-band attenuation, suggesting an enhanced GABAergic inhibitory activity in elderly individuals[39]. Therefore, greater beta-band variability in sensorimotor brain regions could be interpreted as a compensatory mechanism to account for a decline in motor performance. It is further important to note that these observed age effects might be due to localized or global disturbances of brain anatomy leading to deviations in the EEG sources and resulting in EEG amplitude changes. This further motivated us

to explore inter-subject variability of EEG signals (amplitude, peak frequency, and temporal dynamics) on the basis of individual neuroanatomical characteristics (white-matter hyperintensities) in a large sample of healthy elderly individuals (N=907, https://osf.io/mdwc6/).

Finally, in **Study 3** - somewhat surprisingly - there were no significant associations between the two measures of signal variability based on the BOLD signal and EEG, respectively. This finding was supported by the distinct anatomical distributions of age-dependent changes in both measures, that scarcely showed spatial overlap. As discussed in more detail in Kumral et al.,[34] neuronal activity is the main signal source for EEG recordings and consequently for EEG-based variability measures. On the other hand, BOLD signal variability can reflect both vascular and neural processes. As mentioned in the introduction, changes of the ultrastructural integrity of the cerebral vasculature in aging (e.g., decrease in the elasticity and compliancy of affected vessels) are likely to influence neurovascular coupling[14], consequently the BOLD variability. Given different underlying physiology of both methods, findings in **Study 3** emphasize that joint EEG and fMRI variability measures may provide complementary information about aging.

The scientific community is evolving towards a more transparent and collaborative endeavor[40]. Aligned with this idea, one of my main aims (as part of the Mind-Body-Emotion group at the MPI in Leipzig) was to publish a large dataset combining high-quality structural and functional MRI and EEG measures with health markers (e.g., blood markers, anthropometric measures), and also several broad state and trait phenotypic variables (e.g., emotion, personality). Since our datasets have become publicly available as of January 2019[25,26], a multitude of studies around the world have started to explore brain structure and function and its potential relationship to higher-order cognitive faculties, personality features, and health-related factors using these data.

In conclusion, this dissertation provides further evidence, that cardiovascular and neural signal variability are not just “meaningless noise”, but rather can provide important information about the dynamic interplay between body and brain throughout the lifespan. Such techniques might be valuable biomarkers for neurocognitive health (and disease) in aging, and may also impact clinical outcomes.

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2. Statutory Declaration

I, *Deniz Kumral*, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic *Variability in heart and brain activity across the adult lifespan* independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts, and tables) are exclusively my responsibility. My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.

Date _____ Signature _____

3. Declaration of contribution to the publications

Deniz Kumral contributed as follows to these publications:

- Publication 1: **Kumral D**, Schaare HL, Beyer F, Reinelt J, Uhlig M, Liem F, Lampe L, Babayan A, Reiter A, Erbey M, Roebbig J, Loeffler M, Schroeter ML, Husser D, Witte AV, Villringer A, Gaebler M. The age-dependent relationship between resting heart rate variability and functional brain connectivity. *Neuroimage*. 2019;185:521-533.
    - Impact Factor (2018) = **5.812**
    - Contribution in detail: Deniz Kumral contributed to the study design, assessed the quality of the structural MRI, resting state (rs) functional (f)MRI, and ECG data, preprocessed them, and computed secondary analyses (gray matter volume, connectivity matrix, and heart rate variability measures) using various programs including FSL, AFNI, SPM, and Kubios. She performed the statistical analysis using R and matlab. She visualized all figures, created all tables including in the Supplementary Materials. She uploaded the statistical brain maps into the *NeuroVault* (open data repository). She further interpreted the results and wrote all (first and subsequent) drafts of the manuscript and coordinated the journal submission process.
- Publication 2: Koenig J, Abler B, Agartz I, Åkerstedt T, Andreassen OA, Anthony M, Bär K, Bertsch K, Brown RC, Brunner R, Carnevali L, Critchley HD, Cullen KR, De Geus EJC, de la Cruz Monte de Oca F, Dziobek I, Ferger MD, Fischer H, Flor H, Gaebler M, Gianaros PJ, Giummarra MJ, Greening SG, Guendelman S, Heathers JAJ, Herpertz SC, Hu MX, Jentschke S, Kaess M, Kaufmann T, Klimes-Dougan B, Koelsch S, Krauch M, **Kumral D**, Lamers F, Lee T, Lekander M, Lin F, Lotze M, Makovac E, Mancini M, Mancke F, Månsson KNT, Manuck SB, Mather M, Meeten F, Min J, Mueller B, Muench V, Nees F, Nga L, Nilsonne G, Ordonez Acuna D, Osnes B, Ottaviani C, Penninx BWJH, Ponzio A, Poudel GR, Reinelt J, Ren P, Sakaki M, Schumann A, Sørensen L, Specht K, Straub J, Tamm S, Thai M, Thayer JF, Ubani B, van der Mee DJ, van Velzen LS, Ventura-Bort C, Villringer A, Watson DR, Wei L, Wendt J, Westlund Schreiner M, Westlye LT, Weymar M, Winkelmann T, Wu G, Yoo HJ, Quintana DS. Cortical Thickness and Resting State Cardiac Function Across the Lifespan: A Cross-Sectional Pooled Mega Analysis. *Psychophysiology*, 2020;11-16.
    - Impact Factor (2018) = **3.378**

- Contribution in detail: Deniz Kumral assessed the quality of the data ECG and structural MRI data, preprocessed them using various programs (e.g., Freesurfer), computed cortical thickness and heart rate variability measures, and curated these data for sharing. She further coordinated the communication during the mega analysis process. She interpreted the results and contributed the writing process of (first and subsequent) drafts of the manuscript.

- Publication 3: **Kumral D**, Sansal F, Cesnaite E, Mahjoory K, Al E, Gaebler M, Nikulin VV, Villringer A. BOLD and EEG signal variability at rest differently relate to aging in the human brain. *Neuroimage*. 2020; 207:116373.

    - Impact Factor (2018) = **5.812**

    - Contribution in detail: Deniz Kumral contributed to the study design, assessed the quality of the data, preprocessed the resting state functional MRI, performed source-reconstruction of EEG, computed the signal variability measures of both EEG and functional MRI, and performed the statistical analysis using matlab and R. She visualized all figures, created all tables including in the Supplementary Materials. She uploaded the statistical brain maps into the *NeuroVault* (open data repository). She further interpreted the results and wrote all (first and subsequent) drafts of the manuscript and coordinated the journal submission process.

- Publication 4: Babayan A, Erbey M, **Kumral D**, Reinelt JD, Reiter AMF, Röbbig J, Schaare HL, Uhlig M, Anwander A, Bazin PL, Horstmann A, Lampe L, Nikulin VV, Okon-Singer H, Preusser S, Pampel A, Rohr CS, Sacher J, Thöne-Otto A, Trapp S, Nierhaus T, Altmann D, Arelin K, Blöchl M, Bongartz E, Breig P, Cesnaite E, Chen S, Cozatl R, Czerwonatis S, Dambrauskaite G, Dreyer M, Enders J, Engelhardt M, Fischer MM, Forschack N, Golchert J, Golz L, Guran CA, Hedrich S, Hentschel N, Hoffmann DI, Huntenburg JM, Jost R, Kosatschek A, Kunzendorf S, Lammers H, Lauckner ME, Mahjoory K, Kanaan AS, Mendes N, Menger R, Morino E, Näthe K, Neubauer J, Noyan H, Oligschläger S, Panczyszyn-Trzewik P, Poehlchen D, Putzke N, Roski S, Schaller MC, Schieferbein A, Schlaak B, Schmidt R, Gorgolewski KJ, Schmidt HM, Schrimpf A, Stasch S, Voss M, Wiedemann A, Margulies DS, Gaebler M, Villringer A. Data descriptor: A mind-brain-body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults. *Scientific Data*. 2019;6:180308.

    - Impact Factor (2018) = **5.929**

- Contribution in detail: Deniz Kumral contributed to the study design, recruited participants and was responsible for MRI and EEG data acquisition, assessed the quality of the raw MRI data, preprocessed the resting state functional MRI. She created the Table 4, visualized Figure 1 and Figure 2 in the manuscript. She wrote the neuroimaging parts of the manuscript and revised the all drafts of the manuscript before the submission and after the review.

- Publication 5: Mendes N, Oligschläger S, Lauckner ME, Golchert J, Huntenburg JM, Falkiewicz M, Ellamil M, Krause S, Baczkowski BM, Cozatl R, Osoianu A, **Kumral D**, Pool J, Golz L, Dreyer M, Haueis P, Jost R, Kramarenko Y, Engen H, Ohrnberger K, Gorgolewski KJ, Farrugia N, Babayan A, Reiter A, Schaare HL, Reinelt J, Röbbig J, Uhlig M, Erbey M, Gaebler M, Smallwood J, Villringer A, Margulies DS. Data descriptor: A functional connectome phenotyping dataset including cognitive state and personality measures. *Scientific Data*. 2019;6:180307.

    - Impact Factor (2018) = **5.929**
    - Contribution in detail: Deniz Kumral contributed to the study design, recruited participants and was responsible for MRI data acquisition, assessed the quality of the raw MRI data, preprocessed the resting state functional MRI. She revised the all drafts of the manuscript before the submission and after the review.

Signature, date and stamp of the supervising University teacher

Signature of the doctoral candidate

4. Print versions of the selected publications

4.1 Publication 1

Kumral D, Schaare HL, Beyer F, Reinelt J, Uhlig M, Liem F, Lampe L, Babayan A, Reiter A, Erbey M, Roebbig J, Loeffler M, Schroeter ML, Husser D, Witte AV, Villringer A, Gaebler M. The age-dependent relationship between resting heart rate variability and functional brain connectivity. *Neuroimage*. 2019;185:521-533.
https://doi.org/10.1016/j.neuroimage.2018.10.027

4.2 Publication 2

Koenig J, Abler B, Agartz I, Åkerstedt T, Andreassen OA, Anthony M, Bär K, Bertsch K, Brown RC, Brunner R, Carnevali L, Critchley HD, Cullen KR, De Geus EJC, de la Cruz Monte de Oca F, Dziobek I, Ferger MD, Fischer H, Flor H, Gaebler M, Gianaros PJ, Giummarra MJ, Greening SG, Guendelman S, Heathers JAJ, Herpertz SC, Hu MX, Jentschke S, Kaess M, Kaufmann T, Klimes-Dougan B, Koelsch S, Krauch M, **Kumral D**, Lamers F, Lee T, Lekander M, Lin F, Lotze M, Makovac E, Mancini M, Mancke F, Månsson KNT, Manuck SB, Mather M, Meeten F, Min J, Mueller B, Muench V, Nees F, Nga L, Nilsonne G, Ordonez Acuna D, Osnes B, Ottaviani C, Penninx BWJH, Ponzio A, Poudel GR, Reinelt J, Ren P, Sakaki M, Schumann A, Sørensen L, Specht K, Straub J, Tamm S, Thai M, Thayer JF, Ubani B, van der Mee DJ, van Velzen LS, Ventura-Bort C, Villringer A, Watson DR, Wei L, Wendt J, Westlund Schreiner M, Westlye LT, Weymar M, Winkelmann T, Wu G, Yoo HJ, Quintana DS. Cortical Thickness and Resting State Cardiac Function Across the Lifespan: A Cross-Sectional Pooled Mega Analysis. *Psychophysiology*, 2020;11-16.

https://doi.org/10.1111/psyp.13688

4.3 Publication 3

Kumral D, Şansal F, Cesnaite E, Mahjoory K, Al E, Gaebler M, Nikulin VV, Villringer A. BOLD and EEG signal variability at rest differently relate to aging in the human brain. *Neuroimage*. 2020;207:116373.
https://doi.org/10.1016/j.neuroimage.2019.116373

4.4 Publication 4 (Dataset 1)

Babayan A, Erbey M, **Kumral D**, Reinelt JD, Reiter AMF, Röbbig J, Lina Schaare H, Uhlig M, Anwander A, Bazin PL, Horstmann A, Lampe L, Nikulin VV, Okon-Singer H, Preusser S, Pampel A, Rohr CS, Sacher J, Thöne-Otto A, Trapp S, Nierhaus T, Altmann D, Arelin K, Blöchl M, Bongartz E, Breig P, Cesnaite E, Chen S, Cozatl R, Czerwonatis S, Dambrauskaite G, Dreyer M, Enders J, Engelhardt M, Fischer MM, Forschack N, Golchert J, Golz L, Guran CA, Hedrich S, Hentschel N, Hoffmann DI, Huntenburg JM, Jost R, Kosatschek A, Kunzendorf S, Lammers H, Lauckner ME, Mahjoory K, Kanaan AS, Mendes N, Menger R, Morino E, Näthe K, Neubauer J, Noyan H, Oligschläger S, Panczyszyn-Trzewik P, Poehlchen D, Putzke N, Roski S, Schaller MC, Schieferbein A, Schlaak B, Schmidt R, Gorgolewski KJ, Schmidt HM, Schrimpf A, Stasch S, Voss M, Wiedemann A, Margulies DS, Gaebler M, Villringer A. Data descriptor: A mind-brain-body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults. *Scientific Data*. 2019;6:180308.
https://doi.org/10.1038/sdata.2018.308

4.5 Publication 5 (Dataset 2)

Mendes N, Oligschläger S, Lauckner ME, Golchert J, Huntenburg JM, Falkiewicz M, Ellamil M, Krause S, Baczkowski BM, Cozatl R, Osoianu A, **Kumral D**, Pool J, Golz L, Dreyer M, Haueis P, Jost R, Kramarenko Y, Engen H, Ohrnberger K, Gorgolewski KJ, Farrugia N, Babayan A, Reiter A, Schaare HL, Reinelt J, Röbbig J, Uhlig M, Erbey M, Gaebler M, Smallwood J, Villringer A, Margulies DS. Data descriptor: A functional connectome phenotyping dataset including cognitive state and personality measures. *Scientific Data*. 2019;6:180307. https://doi.org/10.1038/sdata.2018.307

5. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

My curriculum vitae is not published in the electronic version of my dissertation for data protection reasons.

6. Complete List of Publications

An up-to-date list is available here: https://orcid.org/0000-0001-6584-7948

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[4]Selected publication for PhD thesis: Dataset 2

[5]Selected publication for PhD thesis: Study 1

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