INVESTIGATING CORRELATIONS OF RESTING-STATE FRACTAL BRAIN CONNECTIVITY AND COGNITIVE PERFORMANCE IN HEALTHY AGING

PhD thesis

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1. Introduction

The human brain is one of the most intricate systems in nature, composed of billions of neurons connected through trillions of synapses. This vast network enables perception, cognition, and behavior through interactions that span a wide range of spatial and temporal scales. A key concept in capturing these interactions is functional connectivity (FC), which refers to statistical dependencies between distant brain regions and is typically inferred from time series data such as EEG, fMRI, or MEG. Research into FC has greatly advanced our understanding of the neural underpinnings of attention, memory, language, and other cognitive functions. Aging is often accompanied by a gradual decline in cognitive abilities, even in the absence of overt neurological disease. This decline reflects a range of structural and functional changes in the brain, including reduced cortical thickness, diminished white matter integrity, and alterations in synaptic functioning. On a systems level, these changes are mirrored by shifts in FC, which becomes less modular and more locally segregated with age. While these general patterns are well established, the specific nature of age-related connectivity changes, and how they relate to cognitive performance, remains a topic of ongoing investigation.

In recent years, interest has grown in studying the brain through the framework of complexity science. One promising direction involves analyzing the fractal properties of neural signals. Fractal processes exhibit self-similarity across scales and are characterized by long-range temporal correlations—features found throughout nature, from ecological systems to heart rhythms. In neuroscience, fractal measures such as the Hurst exponent and the spectral exponent have been used to assess the temporal structure of brain activity. These metrics offer a way to probe intrinsic neural dynamics and have been associated with both cognitive function and clinical conditions.

Building on these ideas, a new concept known as fractal connectivity (FrC) has emerged. FrC extends the notion of scale-free structure to inter-regional interactions, combining traditional connectivity analysis with the mathematical principles of fractals. This approach holds particular promise for characterizing how brain regions maintain enduring, non-random relationships over time. Yet there are significant methodological challenges. In EEG data, signals typically comprise both broadband fractal and narrowband oscillatory components. Standard connectivity methods often conflate these elements, which can obscure meaningful patterns and lead to misleading interpretations.

This thesis addresses this issue by introducing Multiple-Resampling Cross-Spectral Analysis (MRCSA), a novel method designed to estimate fractal connectivity from EEG signals while minimizing contamination

from oscillatory components. MRCSA builds on the mathematical invariance of fractal signals under non-integer resampling, which allows for their separation from more transient oscillations. The goal of this method is to provide a more accurate and interpretable measure of long-range dependencies between brain regions. In doing so, it offers a new tool for exploring the complexity of neural communication, especially in cases where subtle alterations are expected, such as during healthy aging.

Studying FrC is not only methodologically innovative but also conceptually important. It ties into the theory of brain criticality, which posits that the brain operates near a critical state—between order and chaos—that optimizes its capacity for flexible, efficient information processing. Fractal dynamics are thought to reflect this critical regime. If aging disrupts these dynamics, then changes in FrC could serve as indicators of a shift away from this optimal state. This insight may ultimately help distinguish normal aging from early stages of neurodegenerative diseases, providing a noninvasive biomarker with clinical relevance.

Fractal analysis also complements and expands traditional approaches to FC. Conventional metrics such as coherence or correlation are typically confined to fixed frequencies or timescales, which may limit their ecological validity. By contrast, fractal metrics capture persistent patterns across scales, reflecting the continuous and dynamic nature of brain activity. This is especially relevant for EEG, where neural signals

span a broad frequency spectrum and exhibit complex, nonstationary behavior. Through the lens of fractal connectivity, we can obtain a richer and more physiologically grounded view of brain network dynamics.

While previous studies of FC have largely focused on oscillatory coupling—particularly in frequency bands like alpha or theta—such interactions are known to be transient and task-specific. Although oscillations are crucial for certain cognitive processes, they may not capture the underlying, ongoing interactions that sustain baseline function. FrC, by contrast, reflects a more intrinsic property of the neural system. It captures long-term dependencies that may be especially important for maintaining cognitive performance over time. Investigating these properties in both young and older adults can help clarify whether age-related cognitive decline is linked to a disruption in the brain's scale-free network organization.

The broader significance of this work lies in its convergence of multiple research aims: to refine the tools available for EEG analysis, to investigate the neurophysiological correlates of cognitive aging, and to contribute to a theoretical framework that situates brain function within the principles of complex systems. As the global population continues to age, the need for sensitive and theoretically grounded biomarkers of brain function becomes more urgent. Fractal connectivity may offer one such biomarker, and this thesis explores its potential through both methodological innovation and empirical application.

2. Objectives

The overarching goal of this dissertation was to advance our understanding of how aging affects brain network communication by introducing and applying a novel framework for measuring scale-free neural interactions. This entailed both methodological innovation and empirical application. Specifically, the work focused on two primary objectives that guided the research.

Our first goal was to fill a methodological gap in neural time series analysis by developing a tool for estimating FrC from EEG data. Existing methods like are limited to univariate analysis and cannot capture inter-regional interactions. To overcome this, we developed MRCSA, which isolates the fractal component of cross-spectral power between EEG signal pairs by exploiting the invariance of fractal signals under non-integer resampling. MRCSA was validated on simulations with known ground truth, showing accurate estimation of FrC even under noise and overlapping oscillatory activity. It was then applied to a public EEG dataset recorded during a cognitive task, revealing increased FrC in frontoparietal regions with mental workload, supporting its sensitivity to cognitive state changes.

The second goal was to apply MRCSA to investigate age-related differences in resting-state FrC and their relationship to cognition. EEG was recorded from healthy young and elderly participants in an eyes-closed condition. We examined whether aging alters FrC patterns and identified regions most affected. Participants also completed the CANTAB cognitive battery to assess

memory, attention, and reaction time. By correlating FrC metrics with behavioral performance, we aimed to link neural complexity to cognitive aging.

3. Methods

The methodological framework of this dissertation involved both theoretical modeling and empirical experimentation. The study was executed in two major phases. The first phase focused on the development and technical validation of the MRCSA method, and the second phase applied this tool to investigate age-related changes in FrC and their cognitive correlates.

3.1. Mathematical Foundation of Fractal Processes

Fractal processes are characterized by self-affinity, meaning their statistical properties remain consistent across different scales of observation. This property can be captured in the frequency domain by analyzing the spectral power distribution of a signal. In a log-log plot, fractal signals typically follow a straight line, and the slope of this line indicates the degree of long-range temporal correlation. Such scale-free properties are important in neurophysiology because they reflect the brain's ability to maintain structured variability and dynamic balance.

However, neurophysiological signals are composed not only of fractal components but also of oscillatory elements such as alpha, theta, and beta waves. These narrowband oscillations can distort the estimation of

fractal exponents, especially in bivariate settings such as functional connectivity analysis. To address this, the MRCSA method was developed as an extension of the Irregular Resampling Auto-Spectral Analysis (IRASA), enabling robust estimation of fractal cross-spectral power.

3.2. Development of Multiple-Resampling Cross-Spectral Analysis

MRCSA works by resampling a pair of time series using multiple non-integer scaling factors and then computing the cross-spectrum for each resampled pair. By taking the geometric mean of these resampled cross-spectra and aggregating them using the median, the method effectively filters out oscillatory peaks that shift under resampling, isolating the fractal component. The final output is a measure of fractal cross-spectral power, from which a scaling exponent can be derived. This exponent reflects the scale-invariance of connectivity between two neural regions.

The algorithm also computes the percentage contribution of fractal power to total cross-spectral power, providing an index of how dominant the fractal structure is within the observed connectivity. This measure is useful in identifying whether age or task conditions affect the overall complexity of network dynamics.

3.3. Technical Validation

To ensure that MRCSA produces accurate and unbiased results, it was

validated using synthetic datasets with predefined fractal and oscillatory components. The validation showed that MRCSA could estimate cross-spectral slopes within 5% error margins, even at signal-to-noise ratios as low as 10. In contrast to conventional cross-spectral analysis, MRCSA was resilient to interference from overlapping oscillatory activity, making it suitable for analyzing real-world EEG data.

3.4. Empirical Study Design

After technical validation, MRCSA was applied in two empirical studies. The first was a reanalysis of a publicly available EEG dataset from 26 healthy young adults who performed a cognitive word generation task. EEG data were recorded using a 28-channel setup and preprocessed to remove artifacts using Independent Component Analysis (ICA). MRCSA was then used to compute cross-spectral slopes for each channel pair in both baseline and task conditions. The results showed significant increases in FrC during the task, validating the method's sensitivity to cognitive load.

The second empirical study was conducted using data collected from a custom participant cohort. The sample included 24 healthy young adults (mean age: 25.7, 12 females) and 19 healthy elderly participants (mean age: 66.2 and 8 females), all without known neurological or psychiatric disorders. EEG recordings were performed during a resting-state eyes-closed condition using a 14-channel wireless system. Data were filtered and cleaned using manual inspection and ICA, ensuring high-quality

segments of 72 seconds per subject. These were split into 8-second epochs, each analyzed using MRCSA.

3.5. Cognitive Assessment Protocol

To evaluate cognitive performance, participants completed the Cambridge Neuropsychological Test Automated Battery (CANTAB). This included seven tasks: Delayed Matching to Sample (DMS), Paired Associates Learning (PAL), Pattern Recognition Memory (PRM), Reaction Time (RTI), Rapid Visual Processing (RVP), Spatial Working Memory (SWM), and the Motor Screening Task (MOT). These tasks assess a range of cognitive functions that are sensitive to aging, including attention, learning, working memory, and reaction speed.

Each test provided multiple performance metrics, such as accuracy, reaction time, variability, and strategic effectiveness. The objective was to correlate these behavioral outcomes with MRCSA-derived measures of FrC. This allowed for a multidimensional understanding of how neurophysiological complexity relates to behavioral performance in aging.

3.6. Statistical Analyses

Statistical comparisons between young and elderly groups were conducted using two-sample t-tests or Mann-Whitney U tests depending on normality (verified by the Lilliefors test). To address the issue of multiple comparisons, particularly in connection-wise analyses,

Bonferroni and False Discovery Rate (FDR) corrections were applied. Correlation analyses were calculated using Spearman's cross-correlation coefficient, focusing on connections and cognitive metrics that showed significant group differences.

4. Results

4.1. Validation of MRCSA and its Cognitive Relevance

The validation studies demonstrated that MRCSA can reliably detect changes in FrC in response to increased mental workload. In the word generation task, participants exhibited widespread increases in cross-spectral slope values, particularly in frontoparietal circuits. This result is consistent with previous literature suggesting that greater network complexity is associated with heightened cognitive engagement. Importantly, these findings validate MRCSA not only as a mathematically sound technique but also as a neurophysiologically meaningful tool.

4.2. Fractal Connectivity and Healthy Aging

The central aim of the study was supported by several key findings. Compared to younger adults, elderly participants exhibited lower values of cross-spectral slope in several connections, especially those involving frontal and temporal lobes. This suggests a reduction in the scale-

invariance of connectivity with age, which may reflect a loss of dynamical flexibility or robustness within brain networks.

Interestingly, these changes were not uniformly distributed across the cortex. Instead, they appeared localized to areas known to be vulnerable to aging-related decline, such as the prefrontal cortex and medial temporal structures. These regions are involved in executive control, working memory, and episodic memory, all functions that tend to deteriorate with age. This anatomical specificity supports the idea that MRCSA is capturing functionally relevant aspects of brain organization.

4.3. Cognitive Correlates of Fractal Connectivity

The cognitive assessments provided additional evidence for the link between network complexity and behavioral performance. Elderly participants performed significantly worse than younger ones on most tasks, including those involving memory (PAL, PRM), sustained attention (RVP), and reaction time (RTI). These deficits were accompanied by reductions in FrC in relevant brain regions. For example, lower connectivity between temporal and prefrontal regions was associated with poorer memory performance in the elderly cohort.

Interestingly, while younger participants also exhibited some variability in FrC, these patterns were less predictive of cognitive scores. This could indicate that in healthy young brains, network complexity is more uniformly distributed or less critical for baseline cognitive performance.

In contrast, older adults may rely more heavily on preserved network complexity to maintain cognitive function, making FrC a more sensitive marker in this population.

5. Conclusions

5.1. Physiological Interpretation and Broader Implications

The physiological basis of FrC is not yet fully understood. However, it likely reflects the influence of multiscale regulatory mechanisms in the brain, including neuronal adaptation, synaptic plasticity, and neuromodulatory input. From this perspective, reduced FrC in aging might reflect a shift away from criticality, leading to more stereotyped or less adaptable neural responses.

The broader implications of these findings are significant. If FrC can reliably indicate cognitive decline before overt symptoms appear, it could serve as a non-invasive biomarker for early intervention. This is particularly important in aging populations, where timely detection of cognitive impairment can inform preventive strategies and improve quality of life. Moreover, the method could be applied to other clinical populations, such as patients with neurodegenerative diseases, psychiatric conditions, or traumatic brain injury.

5.2. Future Directions

There are several avenues for future research. First, the EEG recordings

were limited to a modest number of channels (14) in the aging study, which may have constrained spatial resolution. Future studies could incorporate high-density EEG or multimodal imaging to refine topographical analyses. Second, the cross-sectional design does not allow for causal conclusions about the trajectory of aging-related changes. Longitudinal studies are needed to confirm whether reductions in FrC precede cognitive decline.

One promising direction is to explore task-based FrC in aging, which may reveal whether older adults can dynamically modulate network complexity in response to cognitive demands. Another direction is to examine the effects of interventions, such as cognitive training, physical exercise, or pharmacological treatments, on FrC. Such work could inform targeted therapies aimed at preserving brain network integrity.

Finally, the generalizability of these findings should be tested in more diverse populations and clinical settings.

In conclusion, my thesis contributes to a growing body of literature that emphasizes the importance of network complexity in brain function. By developing a robust new method and applying it to the study of healthy aging, this work underscores the value of FC as a sensitive, meaningful, and potentially transformative marker of cognitive health.

Furthermore, the findings underscore the importance of examining neural activity beyond traditional frequency bands and localized

measurements. FrC encourages a network-centric perspective, emphasizing the importance of long-term dependencies across distributed regions of the brain.

Another point of reflection lies in the possible clinical applications of this work. With the growing availability of wearable EEG devices and advances in mobile brain-computer interface technologies, there is real potential for MRCSA and similar algorithms to be deployed in ambulatory settings. This could allow routine monitoring of FrC metrics in older adults, providing real-time insights into brain health and responses to interventions. If validated in larger cohorts, such tools might even support personalized cognitive training programs by identifying which domains of function are most vulnerable to decline.

Finally, the concept of FrC as explored in this work adds to the broader understanding of how the brain manages complexity. In the same way that fractal structures are found in nature, in tree branches, river networks, and coastlines, the brain's architecture may also rely on recursive patterns that support scalability and resilience. This opens up philosophical and scientific questions about the nature of intelligence, aging, and the mathematical order that underpins living systems. By contributing empirical evidence and computational methods, my thesis aims to serve as a stepping stone in this multidisciplinary exploration.

6. Bibliography

6.1 Publications forming the basis of the thesis

1. Czoch A, Kaposzta Z, Mukli P, Stylianou O, Eke A, Racz FS. Resting-state fractal brain connectivity is associated with impaired cognitive performance in healthy aging. GeroScience. 2024;46(1):473-489.

2. Racz FS, Czoch A, Kaposzta Z, Stylianou O, Mukli P, Eke A. Multiple-Resampling Cross-Spectral Analysis: An Unbiased Tool for Estimating Fractal Connectivity With an Application to Neurophysiological Signals. Front Physiol. 2022;13.

6.2. Additional publications from the candidate

3. Racz FS, Farkas K, Stylianou O, Kaposzta Z, Czoch A, Mukli P, Csukly G, Eke A. Separating scale-free and oscillatory components of neural activity in schizophrenia. Brain Behav. 2021;11(5):e02047.

4. Stylianou O, Kaposzta Z, Czoch A, Stefanovski L, Yabluchanskiy A, Racz FS, Ritter P, Eke A, Mukli P. Scale-Free Functional Brain Networks Exhibit Increased Connectivity, Are More Integrated and Less Segregated in Patients with Parkinson's Disease following Dopaminergic Treatment. Fractal Fract. 2022;6(12).

5. Kaposzta Z, Czoch A, Stylianou O, Kim K, Mukli P, Eke A, Racz FS. Real-Time Algorithm for Detrended Cross-Correlation Analysis of Long-Range Coupled Processes. Front Physiol. 2022;13.

6. Stylianou O, Racz FS, Kim K, Kaposzta Z, Czoch A, Yabluchanskiy A, Eke A, Mukli P. Multifractal Functional Connectivity Analysis of Electroencephalogram Reveals Reorganization of Brain Networks in a Visual Pattern Recognition Paradigm. Front Hum Neurosci. 2021;15:740225.

7. Kaposzta Z, Czoch A, Mukli P, Stylianou O, Liu DH, Eke A, Racz FS. Fingerprints of decreased cognitive performance on fractal connectivity dynamics in healthy aging. GeroScience. 2024;46(1):713-736.

8. Racz FS, Kumar S, Kaposzta Z, Alawieh H, Liu DH, Liu R, Czoch A, Mukli P, Millán JdR. Combining detrended cross-correlation analysis with Riemannian geometry-based classification for improved brain-computer interface performance. Front Neurosci. 2024;Volume 18 - 2024.