Age-Dependent Spatial Patterns of Brain Noise in fMRI Series

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***Abstract*— Functional Magnetic Resonance Imaging (fMRI) serves as a unique non-invasive tool for investigating brain function by analyzing blood oxygenation level-dependent (BOLD) series. These signals result from the complex interplay between deterministic and stochastic components underpinning biological brain activity. In this context, the quantification of the stochastic component, here defined as brain noise, is challenging without making assumptions on the deterministic dynamics. Leveraging on Approximate Entropy, in this study we present a methodological framework aimed to estimate intrinsic stochastic brain dynamics through fMRI data analysis without making assumption on the deterministic model. We estimated brain noise from fMRI series of 200 participants from the publicly available Cam-CAN dataset, aiming to quantify the amount of stochastic dynamics in different brain regions. Moreover, we hypothesize that a functional relationship exists between intrinsic brain noise and subject's age. Results indicate that a significant part - approximately 18% to 60% - of the fMRI signal power can be attributed to the intrinsic stochastic dynamics within the brain, and a linear augmentation is reported in association with the maturation process. These findings underscore the physiological importance of characterizing neural noise and its unique distributions across various brain regions.**

I. Introduction

Blood oxygenation level-dependent (BOLD) signals detected through functional magnetic resonance imaging (fMRI) is a powerful tool for capturing functional brain activity. However, these signals are susceptible to contamination from diverse noise sources, broadly categorized as measurement noise and intrinsic brain noise [1], [2]. Measurement noise, also referred to as additive or output noise, primarily arises from factors related to the scanner (e.g., thermal noise, magnetic field instability, coil imperfections) [1], or to physiological processes (e.g., subject movement, cardiac and respiratory cycles) [2].

Intrinsic stochastic components in brain dynamics stem from neuronal interactions and the inherent variability and randomness of neuronal activity [3], [4]. Recent studies have emphasized the crucial role of stochastic neural network states [5], emphasizing the necessity for theoretical frameworks and experimental paradigms aimed to understand noise dynamics at the brain network level. Stochastic changes in synaptic activities are thought to improve neural network performance, potentially contributing to learning [6]. Furthermore, the stochastic nature of information transfer at chemical synapses, where vesicles fuse with the plasma membrane and release neurotransmitter, plays a vital role in regulating signal propagation within neuronal networks [7]. Finally, stochastic resonance has been observed to enhance processing in both experimental and theoretical models of neural systems [8].

Inherent brain noise is dynamical, influencing brain activity over time. Generally, it can be expressed as $y_n = T(y_{n-1}, y_{n-2}, \dots, y_0) + \varepsilon_n$, where y_n represents the fMRI signal at time t_n, and $\{\varepsilon_n\}_n$ denotes intrinsic brain noise. Characterizing $\{\varepsilon_n\}_n$ is essential for ensuring the reliability and validity of fMRI-based inferences regarding brain function [9]. However, recognizing a component as deterministic or stochastic relies on the understanding of the underlying physiology and biophysics. Notably, components initially categorized as noise later gained significance as signals of interest [2]. Reasonably, this is due to the estimation of dynamical brain noise $\{\varepsilon_n\}_n$ being contingent on the precise definition of the deterministic component T.

Recent studies have investigated brain activity stochastic component through waveform regularity [10]. However, it is crucial to note that such approach assumes brain dynamics to be entirely random, disregarding the potential presence of complex and chaotic deterministic components in brain functioning. In the last few years, attempts have been made trying to estimate stochastic components of dynamic series, particularly regarding physiological signals [11], but these were not applied on fMRI series yet.

In this study, for the first time we try to quantify the intrinsic stochastic component in brain dynamics recorded through fMRI series without making assumptions on the deterministic part, thus making our approach suitable for any continuous and differentiable function associated with fMRI signals. The study hypothesis is that the presented estimation of fMRI-based brain noise is not a measurement noise, but a measure of physiological noise that change according to brain regions or physiological conditions (e.g., aging). To test the proposed approach, we employ the publicly-available Cambridge centre for ageing and neuroscience (Cam-CAN) dataset [12], gathered from a cohort of over healthy individuals aged from 18 to 87 years.

The functional and structural evolution of the brain in healthy aging is a topic that is attracting progressively in-

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creasing attention [13]–[15]. Specifically, diminished BOLD activation has been reported among older adults in the prefrontal cortex and hippocampus in cognitive tasks [16], [17], as well as in fronto-parietal regions in resting state [18], and further cerebrovascular changes have been detected associated with age [19]–[21]. This paper presents preliminary results on age-dependent spatial patterns of brain noise in fMRI series. Further findings are detailed in [22].

II. Data and Methods

A. Cam-CAN data set description

The Cam-CAN dataset comprises fMRI series gathered from a large population of healthy subjects, with ages spanning from 18 to 87, recorded during different experimental conditions. In this study, we considered data from 200 subjects, randomly chosen among the entire cohort, and we limited the analysis to the resting state (with a repetition time, TR, of 1970*ms*) for 8*min* and 40*s*. The fMRI data underwent standard preprocessing, and the obtained brain volume was partitioned into 116 regions of interest (ROI) based on the automated anatomical labeling (AAL) atlas [23]. Additional details regarding data collection and preprocessing can be found in [12].

B. Brain Intrinsic Noise and Numerical Estimation

Consider the signal observed in a brain ROI as a measurable outcome generated by an unknown, discrete metric dynamical system denoted as (Y,μ,T). In this model, Y represents a compact subset of $\mathbb{R}$, while T denotes a differentiable mapping function with a bounded derivative, preserving the probability measure μ. Conceptually, the collected signal is produced by a deterministic, unknown, and smooth function or map whose values are confined to a limited interval of real numbers. In this context, we posit that a noise-free fMRI series from a ROI can be formulated as $w_n = T(w_{n-1}, w_{n-2}, \ldots, w_0)$, where w_i belongs to Y for all positive integers i.

We define the *intrinsic brain noise* as the *dynamical noise*, or rather a sequence of independent and identically distributed random variables $\{\varepsilon_n\}_n$, where the samples ε_n interact with the brain dynamics according to equation

$$y_n = T(y_{n-1}, ..., y_0) + \varepsilon_n. \tag{1}$$

Under the hypothesis that any fMRI recording is driven by the effects of dynamical or brain noise, we can estimate the power of such distortion. The approach we follow is fully described in [24]. Here we recall the main features: first that the method does not require any knowledge about the analytic dynamics described by the map T in presence of the dynamical noise; and second that it exploits the geometric behavior of the approximate entropy (ApEn) quantifier [25], which diverges under noisy perturbations if one of its parameter is small enough. Consequently, assuming that a perturbed series of the form $z(\sigma) = (z_0, T(z_0) + \varepsilon_1, T(T(z_0) + \varepsilon_1) + \varepsilon_2, \ldots)$ is corrupted by the dynamical noise ε_n having a Gaussian distribution $\mathcal{N}(0,\sigma)$, then the proposed algorithm finds the dynamical noise standard deviation σ by searching for the radius r where the curves $\mathrm{ApEn}(z(\sigma), m, r)$ and $-\log[r/(\sigma\sqrt{\pi})]$ approximately converge, leading to the following quantification

$$\log(\sigma) \approx \mathrm{ApEn}(z(\sigma), m, r) + \log(r/\sqrt{\pi}) \tag{2}$$

for any embedding dimension m when $r \leq \sigma$. In this work we apply the estimation procedure for embedding dimension $m = 2$ and for the tolerance resolution $\Delta r = 0.001 \times \{\text{time series range}\}$. An interested reader can find a comprehensive description of the methodology, its derivation and mathematical foundation in [11], [24].

C. Statistical analysis

After quantifying the intrinsic brain noise for each fMRI series, thus meaning for each subject and each brain volume ROI, a basic functional relation between the brain noise and the subject age has been quantified using the nonparametric Spearman correlation coefficient. To statistically assess significance of the correlation coefficients the associated p-values were calculated through large sample approximation, due to the large sample size. The significance threshold was fixed at 0.05, and p-value correction for multiple comparisons was accounted for using the Bonferroni correction, thus meaning that the corrected significance threshold was fixed at $0.05/116 = 4.31 * 10^{-4}$ (where 116 is the number of ROI).

To qualitatively compare the difference between the experimental results in terms of estimated brain noise obtained through the presented method, and a basic statistical estimator of variability, we performed the same analysis using the standard deviation of each ROI fMRI series and calculating its correlation to subjects' ages, again through Spearman's coefficient.

III. Results

Experimental results are graphically represented in terms of topographical distribution of Spearman correlation coefficients across brain ROIs in Fig. 1, where the figure portrays external ROIs for graphical reasons, thus excluding more subcortical regions such as limbic system, cerebellum, and vermis. In detail, the figure shows the right hemisphere in the first row (the left hemisphere is in the second row), for both the lateral (left column) and medial (right column) views. Graphical representations of brain volume and ROIs were visualized using R-Studio[1] software and the ggseg[2] package.

In Fig. 1, red areas represent significant positive correlation, white areas stand for not significant correlations, whereas blue represent significant negative correlation. It is reminded that significance threshold is set at $\alpha = 0.05/116 = 4.31 * 10^{-4}$. A darker color is used for higher Spearman coefficient in terms of absolute value.

It is possible to notice that most of the brain ROIs have a significant correlation coefficient (53 out of 116), which appears stronger on lateral view of the left hemisphere, reaching a maximum value of ≈ 0.38 in a central ROI and

[1] 1https://posit.co/download/rstudio-desktop/

[2] https://github.com/ggseg

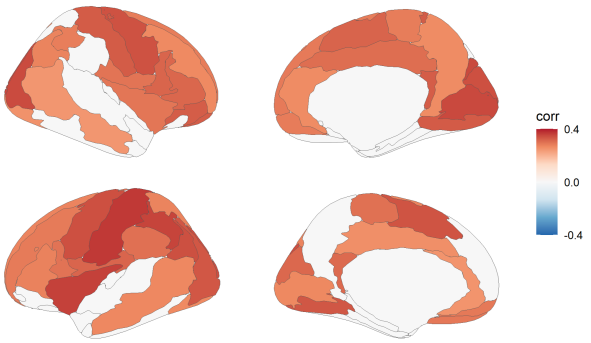

Fig. 1: **Regions of interest (ROIs) in the brain exhibit notable correlations between functional brain noise and age.** These images showcase significant Spearman correlation coefficients reflecting the relationship between noise and aging. Darker red areas represent more robust positive correlation, white areas stand for not significant correlations, whereas blue represent significant negative correlation. The first row is the right hemisphere, the second row represents the left hemisphere, whereas left column is the lateral view and the right column represents the medial view.

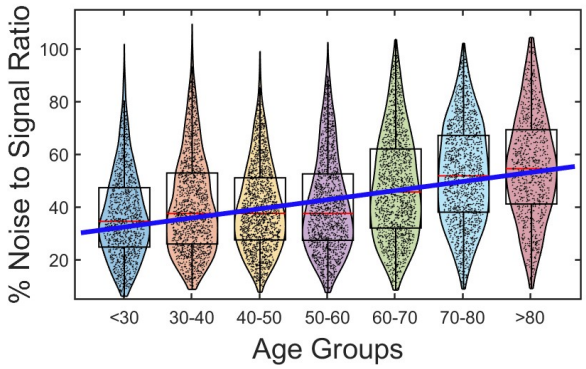

Fig. 2: **Variation in fMRI Noise associated with age.** Violin boxplots depict the noise-to-signal ratio, calculated as the variance of encountered noise divided by the power of the signal, across all significant brain ROIs in 7 different age groups spanning the entire age range (i.e., 18 to 87 years). Individual subject noise estimations are denoted by black crosses. The thick blue line represents the least-square linear regression of group-wise median noise levels.

a temporal ROI. More specifically, a higher correlation (ρ in $(0.35, 0.38)$) was found in the ROIs #57, #29 and #50 (Postcentral Gyrus L, Insula L, and the Superior Occipital Gyrus R, respectively).

Figure 2 depicts the overall trends between estimated brain noise and age across all significant ROIs. Please note that the estimated intrinsic brain noise is represented as the ratio between noise and signal power, to quantitatively appreciate how the intrinsic noise can substantially contribute to the overall signal power. Violin boxplots in figure 2 depict such noise-to-signal ratio across all significant brain ROIs in 7 different age groups spanning the entire age range (i.e., 18 to 87 years). The age groups are categorized as follows: $<$30, 30-40, 40-50, 50-60, 60-70, 70-80, and $>$80. Each black dot denotes an individual subject noise estimation. A noticeable positive trend is evident in median noise levels with increasing age, indicated by a Spearman coefficient $\rho = 0.9643$ (p-value$= 0.0028$), here highlighted by the thick blue line. A qualitative comparison has been performed by analyzing fMRI signal standard deviation throughout age groups. Results are illustrated in Figure 3, where topographical and colorful notation are the same as used in figure 1. When the Spearman correlation coefficient was calculated between fMRI signal standard deviation and subject age, only 9 ROIs showed significant correlations with no accordance in sign (i.e., 5 ROIs had positive correlation coefficients, and the remaining 4 were anticorrelated with age). Also the absolute values of the significant coefficients were largely lower than those reported in figure 1.

IV. Discussion

In this study, we employed a novel mathematical framework to estimate intrinsic brain noise by considering it as the stochastic component of an unknown dynamical system that encapsulates functional brain activity gathered as fMRI BOLD series. We also considered the differences between measurement noise and intrinsic brain noise within the observed dynamics. Indeed, measurement noise emerges from external sources during the data acquisition process with respect to the actual brain functioning, such as sensor fluctuations, environmental interference, background noise, or subjects movements. This type of noise may significantly affect the recorded signal, often concealing the genuine underlying biological phenomena. Conversely, intrinsic brain noise, or dynamical noise, is an intrinsic characteristic of biological systems, arising from the stochastic nature of various brain processes like gene expression, cellular activity, or neural fluctuations. The quantification of this dynamical noise poses a challenge, as it relies on the specific modeling attributed to deterministic brain activity.

To address the challenge of quantifying intrinsic brain noise, we introduced an estimation framework without making assumption on the dynamical feature of the deterministic component of the overall underlying brain activity. Our method leverages the nonlinear quantifier (ApEn) [25] and explores its differential behavior in noisy series when the quantifier is considered as a function of one of its parameters [11], [24]. Note that our proposed noise estimation framework can be applied to any time series, making it potentially valuable in fields beyond computational physiology and neuroscience. Here, we investigated stochastic brain components across different stages of brain maturation. Assuming that measurement noise is uncorrelated with aging due to its distribution across data acquisition from various subjects and MRI machines, we uncovered a modulation of intrinsic brain noise with age progression in healthy individuals. Our findings, based on 200 subjects from the Cam-CAN dataset, underscore the distinct distribution of

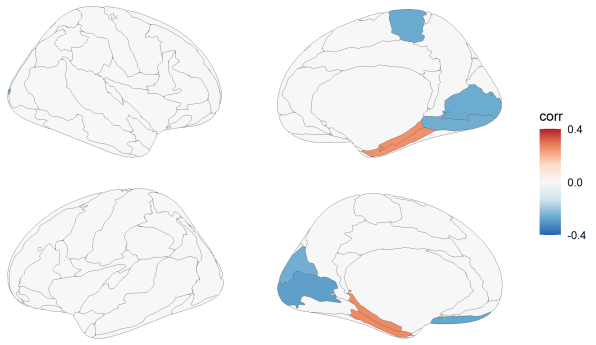

Fig. 3: **Regions of interest (ROIs) in the brain do not exhibit notable correlations between signal standard deviation and age.** These images showcase significant Spearman correlation coefficients reflecting the relationship between signals standard deviation and aging. Darker red areas represent more robust positive correlation, white areas stand for not significant correlations, whereas blue represent significant negative correlation. The first row is the right hemisphere, the second row represents the left hemisphere, whereas left column is the lateral view and the right column represents the medial view.

stochastic brain activity components during the resting state, as well as their modulation during maturation.

Specifically, all the trends demonstrate a statistically significant increase along with aging across various brain regions, particularly in regions such as the precentral and frontal areas, Rolandic Operculum, medial Cingulum, occipital areas, and others. In addition, our examination indicates that in cases where the variability of the fMRI series shows partial or no distinct patterns with aging [26], our approach unveils that the intrinsic stochastic component predominantly influences the variability series of elderly subjects. Simultaneously, this noise has minimal impact on the overall dynamics of the young cohort.

The presence of noise can differentially influence biomarker definition and estimation across distinct brain regions, potentially resulting in inaccuracies in pinpointing and characterizing reliable indicators for specific conditions. Consequently, these inaccuracies may give rise to misinterpretations and incorrect clinical decisions, particularly when comparing biomarker levels among different brain areas. Therefore, precise estimation of biological noise is crucial for evaluating psychological function and associated pathophysiology. Limitations of this study concern the reduced number of subjects and the choice of only one dataset. Further developments will be devoted to extending the noise analysis to a larger cohort from different datasets and for different pathophysiological conditions, investigating physiological correlates of intrinsic brain noise.

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