
Research Article: New Research | Disorders of the Nervous System

Brain Dynamics of Aging: Multiscale Variability of EEG Signals at Rest and during an Auditory Oddball Task

Brain Dynamics of Aging.

Rita Sleimen-Malkoun^{1,2,*}, Dionysios Perdikis^{1,3,*}, Viktor Müller³, Jean-Luc Blanc^{1,4}, Raoul Huys^{1,4}, Jean-Jacques Temprado² and Viktor K Jirsa^{1,4}

¹Aix-Marseille Université, Inserm, Institut de Neurosciences des Systèmes UMR_S 1106, 13385, Marseille, France

²Aix-Marseille Université, CNRS, Institut des Sciences du Mouvement UMR 7287, 13288, Marseille, France

³Max Planck Institute for Human Development, Center for Lifespan Psychology, Berlin, Germany

⁴CNRS, Marseille, France

DOI: 10.1523/ENEURO.0067-14.2015

Received: 1 December 2014

Revised: 2 February 2015

Accepted: 16 March 2015

Published: 11 May 2015

Author contributions: RSM, DP, VM and VKJ designed research; RSM, DP, VM and VKJ performed research; RSM, DP and JLB analyzed data; RSM, DP, VM, RH, JLB, JJT and VKJ wrote the paper.

Funding: Aix-Marseille Foundation A*Midex; Max Planck Society;

Conflict of Interest: Authors report no conflict of interest.

This work was supported by the Aix-Marseille Université foundation A*Midex - CoordAge project, and Max Planck Society.

*R.S.M. and D.P. contributed equally to this work

Address correspondence to Viktor Jirsa, Aix-Marseille Université, Inserm, Institut de Neurosciences des Systèmes UMR_S 1106, 13385, Marseille, France. E-mail: viktor.jirsa@univ-amu.fr.

Cite as: eNeuro 2015; 10.1523/ENEURO.0067-14.2015

Alerts: Sign up at eneuro.org/alerts to receive customized email alerts when the fully formatted version of this article is published.

Accepted manuscripts are peer-reviewed but have not been through the copyediting, formatting, or proofreading process.

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution and reproduction in any medium provided that the original work is properly attributed.

eNeuro

<http://eneuro.msubmit.net>

eN-NWR-0067-14R1

Brain Dynamics of Aging: Multiscale Variability of EEG Signals at Rest and during an Auditory Oddball Task

1 **1. Title**

2 Brain Dynamics of Aging: Multiscale Variability of EEG Signals at Rest and during an
3 Auditory Oddball Task.

4 **2. Abbreviated title**

5 Brain Dynamics of Aging.

6 **3. Authors and affiliations**

7 Rita Sleimen-Malkoun^{1,2*}, Dionysios Perdakis^{1,3*}, Viktor Müller³, Jean-Luc Blanc^{1,4}, Raoul
8 Huys^{1,4}, Jean-Jacques Temprado², Viktor K Jirsa^{1,4}

9 ¹Aix-Marseille Université, Inserm, Institut de Neurosciences des Systèmes UMR_S 1106, 13385,
10 Marseille, France

11 ²Aix-Marseille Université, CNRS, Institut des Sciences du Mouvement UMR 7287, 13288,
12 Marseille, France

13 ³Max Planck Institute for Human Development, Center for Lifespan Psychology, Berlin, Germany

14 ⁴CNRS, Marseille, France

15 *These authors contributed equally to this work

16 **4. Authors Contributions:**

17 RSM, DP, VM and VKJ designed research; RSM, DP, VM and VKJ performed research;
18 RSM, DP and JLB analyzed data; RSM, DP, VM, RH, JLB, JJT and VKJ wrote the paper.

19 **5. Correspondence:**

20 Address correspondence to Viktor Jirsa, Aix-Marseille Université, Inserm, Institut de
21 Neurosciences des Systèmes UMR_S 1106, 13385, Marseille, France. E-mail:
22 viktor.jirsa@univ-amu.fr.

23 **6. Number of Figures:** 11.

24 **7. Number of Tables:** 2.

25 **8. Number of Multimedia:** 0.

26 **9. Number of words for Abstract:** 244.

27 **10. Number of words for Significance Statement:** 120.

28 **11. Number of words for Introduction:** 748.

29 **12. Number of words for Discussion:** 2976.

30 **13. Acknowledgements:** NA.

31 **14. Conflict of interest:** Authors report no conflict of interest.

32 **15. Funding sources:** This work was supported by the Aix-Marseille Université foundation
33 A*Midex - CoordAge project, and Max Planck Society.

34 Abstract

35 The present work focused on the study of fluctuations of cortical activity across time-scales in young
36 and older healthy adults. The main objective was to offer a comprehensive characterization of the
37 changes of brain (cortical) signals variability during aging and make the link with known underlying
38 structural, neurophysiological and functional modifications, as well as aging theories. We analyzed
39 EEG data of young and elderly adults, which were collected at resting state and during an auditory
40 odd-ball task. We used a wide battery of metrics that typically are separately applied in the
41 literature, and we compared them to more specific ones that address their limits. Our procedure
42 aimed to overcome some of the methodological limitations of earlier studies and verify whether
43 previous findings can be reproduced and extended to different experimental conditions. In both rest
44 and task conditions, our results mainly revealed that EEG signals presented systematic age-related
45 changes that were time-scale dependent with regard to the structure of fluctuations (complexity) but
46 not with regard to their magnitude. Namely, compared to young adults, the cortical fluctuations of
47 the elderly were more complex at shorter time-scales, but less complex at longer scales, while always
48 showing a lower variance. Additionally, the elderly showed signs of spatial as well as between
49 experimental conditions dedifferentiation. By integrating these so far isolated findings across time
50 scales, metrics and conditions, the present study offers an overview of age-related changes in the
51 fluctuations electrocortical activity while making the link with underlying brain dynamics.

52

53 Significance Statement

54 Recently, the study of brain signals fluctuations is widely put forward as a promising entry point to
55 characterize brain dynamics in health and disease. While interesting results have been reported
56 regarding how variability of brain activations can serve as an indicator of performance and
57 adaptability in elderly, many uncertainties and controversies remain with regard to the
58 comparability, reproducibility and generality of the described findings, as well as the ensuing
59 interpretations. Following a systematic investigation of these issues by using a large set of metrics
60 and different experimental conditions, our results draw an overview of age-related changes of the
61 magnitude and structure of brain fluctuations, which integrate well with known structural and
62 functional alterations as well as the main aging theories.

63

64 Introduction

65 The view that variability in brain activity serves a functional role is gaining increasing support (Ghosh
66 et al., 2008; Deco et al., 2009, 2011, 2013; Garrett et al., 2011; Hong and Rebec, 2012). The
67 characteristics of brain signals fluctuations are considered to capture the underlying complex
68 interactions between neuronal structures and ensembles.

69 At rest, the brain displays a complex though spatiotemporally structured dynamics, where brain
70 states known as resting state networks are intermittently activated. These states are considered to
71 be functionally meaningful because several of them have been known from task paradigms (Deco et
72 al., 2013). As underlying mechanisms, within deterministic frameworks, heteroclinic cycles have been
73 proposed to generate sequential transitions from one unstable equilibrium point (saddle) to another.
74 Other deterministic approaches soften the requirement of unstable states and require linked
75 attractive subspaces (see Huys et al 2014). These approaches are subject to noise, which seems to be
76 pervasive at different levels of the central nervous system (Faisal et al., 2008). However, they do not
77 necessarily require the latter as a generative element as do those considering that the continually
78 fluctuating background activity, random or not, drives the multistable system through a cascade of
79 epochs of invariant, but distinct, coordinated network activities (Hansen et al., 2014). McIntosh et al
80 (2010) argued that noise is linked to an increased number of functional network configurations that
81 can be occupied in stochastic systems. This suggests that maturational changes in brain noise
82 represent an enhancement of the functional network potential, the brain's dynamic repertoire
83 (Ghosh et al., 2008). Conversely, the natural process of aging, as well as disease, has been associated
84 with an evolution towards a poorer dynamics, more local interactions and more regular fluctuations
85 in brain and behavior (see Garrett et al., 2013; Sleimen-Malkoun et al., 2014, for reviews).

86 In the ergodic theory framework, entropy has been theoretically demonstrated to be an non-
87 redundant measure of dynamical systems (see Adler and Weiss, 1967; Ornstein and Weiss, 1991). In
88 empirical data, neuro-behavioral variability is characterized through the magnitude (variance-derived
89 measures) and the time structure (long-range correlations and entropy-derived metrics, see Bravi, et
90 al., 2011) of fluctuations. The main operational principle is that the healthy system exhibits complex
91 fluctuations somewhere at a sweet spot between randomness and regularity. Such resonance-like
92 phenomena are known as stochastic resonance and have been observed in biological systems
93 including brain networks (Gammaitoni et al., 1998; Deco et al., 2009; McDonnell and Abbott, 2009;
94 McDonnell and Ward, 2011). Nevertheless, most of the widely used measures cannot distinguish
95 between deterministic and stochastic components of the dynamics. Entropy measures, for instance,
96 are relevant for comparisons between different conditions (e.g., resting vs. task) or systems (e.g.,
97 young vs. old), assuming conventionally that more entropy corresponds to more complexity
98 (Feldman and Crutchfield, 1998). *Sensu stricto*, this latter assumption is not always correct, at least
99 not with single-scale measures (Costa et al., 2002, 2005).

100 In fMRI studies, variance based measures (Grady and Garrett, 2014) as well as entropy measures (Liu
101 et al., 2013; Sokunbi, 2014) have been shown to be relevant to characterize and understand the
102 dynamics of the aging brain. In this context, multiscale analyses have also been used (Yang et al.,
103 2013; Smith et al., 2014), although, their contribution is restricted due to the limited range of
104 functionally meaningful scales that can be covered. Such measures are of more interest in signals
105 with higher time resolution, as EEG and MEG recordings, where time-scale dependence of aging

106 effects can be revealed (McIntosh et al., 2013). Nevertheless, notwithstanding a number of
107 converging findings showing that aging does affect the variability of brain activity, no final
108 conclusions can be made yet concerning the nature of such changes or their link with functional and
109 adaptive capabilities. The present study makes a helpful step in this direction by offering a consistent
110 and coherent characterization of EEG signals in young and older adults through a multiplicity of
111 metrics applied to both resting and task conditions. Specifically, it investigates the following: i) the
112 type of information that can (or cannot) be captured by the (univariate) metrics that are
113 conventionally used to characterize brain signals; ii) the distinction between multiscale changes in
114 the magnitude of fluctuations and their structure in time; iii) the correspondences between different
115 classes of metrics with regard to age-related modifications in brain activity; iv) the comparability
116 between aging effects on resting and task-evoked brain fluctuations; v) the extent to which changes
117 in brain fluctuations can be linked to structural and functional changes occurring in the aging brain.

118

119 **Methods**

120 *Participants*

121 Participants were recruited through announcements at schools in Saarland and at the Saarland
122 University. They received a compensation of 7.5 Euro per hour. All the participants were right-
123 handed, had no reported history of head or neurological disorders, and none were on medication.
124 The studied sample consisted of 31 young ('Y', mean age = 22.7, SD = 1.6, age range = 18.8–25.1
125 years, 14 females), and 28 old adults ('O', mean age = 67.8, SD = 3.0, age range = 63.9–74.5 years, 14
126 females). Participants of all ages were able to sustain their attention for the entire duration of the
127 experiment, and they all underwent a psychological and audiological assessment prior to their
128 enrollment. The used protocol was in accordance with the regulation of local ethic committee. All
129 participants volunteered for this experiment and gave their written informed consent prior to their
130 inclusion in the study.

131 *Procedure*

132 The EEG measurement began with a 3-minute resting state recording (1.5 minutes with eyes closed,
133 and 1.5 minutes with eyes open) and was followed by the auditory oddball task. During the task,
134 participants were seated comfortably on a chair in an electrically shielded room, with their eyes
135 closed. They heard two different tone beeps: a frequent 1000 Hz tone as a standard stimulus and a
136 rare 800 Hz tone as a deviant stimulus. The standard and deviant stimuli were presented binaurally
137 (with a probability of 0.8 and 0.2 for standard and deviant, respectively) through headphones (Sony
138 DJMDR-V300) at 70 dB SPL with duration of 70 ms (including 10-ms rise and fall time). Stimuli were
139 generated with the software Audacity 1.2.4. The inter-stimulus interval ranged from 1200 to 1500
140 ms. There were two different experimental conditions: passive listening (unattended) and active
141 counting (attended). In the first condition, participants merely listened to the tone beeps without any
142 response, whereas in the second condition, they had to attend to stimuli and to count the deviant
143 tones. After the session, they were asked to report their counting results. Each experimental
144 condition contained 152 standard tones and 38 deviant tones presented in a pseudo-random order
145 fixed for all participants. The order of the conditions was always the same, with the active counting
146 condition following the passive listening condition. For this study we considered three conditions, all

147 with eyes closed: resting state ('R'), auditory oddball task without counting ('OnC') and auditory
 148 oddball with counting ('OC'). The condition of resting state with eyes open was not included since it
 149 differed largely in its frequency content compared to all other conditions, which interfered with tasks
 150 contrasts. Instead, we focused on studying differences under comparable conditions along the axis of
 151 increasing attentional and task demands.

152 *EEG recordings and preprocessing*

153 The electroencephalogram (EEG) was recorded from 58 Ag/AgCl electrodes using an elastic cap
 154 (Electrocap International), with a sampling rate of 500 Hz in a frequency band ranging from 0.5 to
 155 100 Hz. The left mastoid was used as a reference and the right mastoid was recorded as an active
 156 channel. The data were re-referenced off-line to an average of the left and right mastoids for further
 157 analysis. The electrodes were placed according to the international 10–10 system. Vertical and
 158 horizontal electrooculogram (EOG) was recorded for control of eye blinks and eye movements. Eye
 159 movement correction was accomplished by independent component analysis (Vigario, 1977).
 160 Thereafter, artifacts from head and body movements were rejected by visual inspection. Finally, data
 161 were downsampled to a sampling rate of 250 Hz, segmented in artifact free 10 s segments (i.e.,
 162 comprising $N_t = 2500$ data points each), and mean centered within segments before further analysis.
 163 Accordingly, we insured to have continuous time-series of equal length for all three experimental
 164 conditions, on which multiscale analyses can be reliably applied. For the two task conditions,
 165 segments corresponded to time intervals containing a comparable number of stimuli (7-8). **Table I**
 166 shows the statistics of the resulting number of segments included in the analysis for each condition
 167 and group.

168 *Metrics*

169 Multiple metrics were applied to all data segments using MATLAB (The Mathworks Inc.) or Python
 170 scripts for all calculations. We computed: the power spectrum, the spectral degrees of freedom, the
 171 detrended fluctuation analysis, the variogram and several measures related to multiscale entropy. In
 172 general, all of these metrics relate in some way to the autocorrelation properties of the signals.
 173 However, it should be noted that neither a straightforward relationship amongst metrics, nor a direct
 174 correspondence between time scales and frequencies exist. On the one hand, the entropic measures
 175 and detrended fluctuation analysis capture nonlinear correlations in addition to linear ones, but it is
 176 not the case for the variogram and the power spectrum. On the other hand, the detrending and the
 177 coarse graining procedures (for entropic measures) transform the data in ways that make such direct
 178 correspondence impossible. In the following, we present the different metrics.

179 **Power spectrum (P).** For the calculation of the *power spectrum*, we applied a Hanning window of $N_t =$
 180 2500 points to each data segment. Then, after padding with trailing zeros, a 4096 point Fast Fourier
 181 Transform (using the MATLAB function *fft.m*) resulted in the complex signal in the frequency domain

$$182 \quad X(k) = \sum_{j=1}^{N_p} \left(x(j) e^{(-2\pi i/N_p)(j-1)(k-1)} \right),$$

183 where x is the signal in the time domain, $N_p = 4096$ and
 184 indices j and k run through points in the time and frequency domain, respectively. Then, the *power*
 185 *spectrum* was calculated for positive frequencies as $P(k) = X(k)X(k)^*$, where the operator $*$
 signifies the conjugate complex number.

186 **Degrees of freedom (DoF).** Spectral *DoF* is a statistic that evaluates the uniformity of spectral density
 187 (Vaillancourt and Newell, 2003). It is calculated as $DoF = \left(\sum_k^{N_f} P(k) \right)^2 / \frac{1}{N_f} \sum_k^{N_f} P(k)^2$, where P and
 188 k are as above and N_f is the number of positive frequencies. *DoF* ranges from $\frac{1}{N_f}$ for a single peak
 189 spectral density to 1 for a completely flat one, i.e., for white noise.

190 **Detrended fluctuation analysis (DFA) and generalized Hurst exponent (H).** *Detrended fluctuation*
 191 *analysis* was introduced in (Peng et al., 1994) in order to extend Hurst's *Rescaled Range Analysis*
 192 (Hurst, 1951) for the evaluation of long-range time correlations in non-stationary signals. Its
 193 suitability for non-stationary signals has been questioned recently (Bryce and Sprague, 2012).
 194 However, it is widely used in different domains and has found many applications in biology (see
 195 Hardstone et al., 2012 for applications in EEG). We calculated *DFA* along the following steps:

- 196 1. We calculated the cumulative sum of each segment's time series after removal of its mean:
 197 $y(j) = \sum_1^j (x(j) - \sum_k^{N_t} x(j) / N_t)$, where all symbols follow the above presented notation.
- 198 2. For a particular time-scale $T(s)$, with scale $s = 4...50$, and $T = 16...200$ ms in steps of 4 ms, we
 199 segmented the time series into adjacent (non-overlapping) windows y_{ws} of a length of $N_w(s)$
 200 samples. Thus, the number of windows $W(s)$ ranged as $W = 625...50$, and the number of
 201 samples per window as $N_w = 4...50$, respectively.
- 202 3. For each scale s we calculated the average fluctuation across all windows as the average
 203 root-mean-square error of a polynomial fit of second order (i.e., it corresponds to removal of
 204 linear trends):

$$205 F(s) = \left(\sum_s^{W(s)} \sqrt{1/N_w(s) \left(\sum_m^{N_w(s)} (y_{ws}(m) - (a_2 m^2 + a_1 m + a_0))^2 \right)} \right) / W(s),$$

206 where a_0, a_1, a_2 are the coefficients of the polynomial fit, and m is the index of all samples within a
 207 window. We used the MATLAB functions `polyfit.m` and `polyval.m` for the calculations of the
 208 polynomial coefficients and fitting, respectively.

- 209 4. Fluctuations were plotted against time-scales in a $\ln T(s) - \ln F(s)$ plot and a generalization
 210 of the *Hurst exponent*, H , was calculated as the slope of the linear fit (using `polyfit`
 211 in MATLAB) of the resulting curve for time scales T in the range 24 – 124 msec. This range was
 212 chosen after visual inspection for linear scaling of randomly chosen data segments as well as
 213 of the groups' mean curves for each condition. Finally, we compared both $\ln F(s)$ and H
 214 across groups and conditions.

215 H is indicative of the autocorrelation structure of a signal as follows: (a) for $0 < H < 0.5$, negative
 216 correlation (anti-correlation), (b) for $H \approx 0.5$, lack of any correlation, i.e., white noise, (c) for $0.5 < H < 1$,
 217 positive correlation, (d) for $H \approx 1$, $1/f$ or pink noise, (e) for $1 < H < 2$, non-stationarity, (f) for $H \approx 1.5$,
 218 brown noise. The *Hurst exponent* is equal to H for $H < 1$ and to $H - 1$ for $H > 1$ (Hardstone et al., 2012).

219 **Variogram (V).** The *variogram* is an alternative way to evaluate how the magnitude of variability of a
 220 signal varies for different time-scales (Cressie, 1993). However, until present its use has been limited
 221 in neurosciences (see Conte et al., 2009, for an example). It has the advantage over *variance* in that it
 222 can be calculated for stochastic processes for which the mean is either undefined, i.e., when the
 223 related probability distribution function decays according to a power law with an exponent lower or
 224 equal to 1, or when it is hard to empirically observe, i.e., in the cases of a very large autocorrelation
 225 time. It was calculated as: $V(s) = \frac{1}{N_s} \left(\sum_j^{N_s} (x(j) - x(j+s))^2 \right)$, where N_s is the number of distinct
 226 pairs of time points $x(j)$ and $x(j+s)$ of a distance of s samples, in the range $s = 1...50$, which

227 corresponds to time-scales $T(s)$ in the range of 4-200 msec. Finally, we compared $\ln V(s)$ among
228 groups and conditions.

229 **Multiscale entropy measures.** We calculated multiscale entropy using two different estimators:
230 *sample entropy* (*SampEn*, Richman and Moorman, 2000), giving multiscale sample entropy (*MSE*),
231 and *Lempel-Ziv complexity* (LZ, Lempel and Ziv, 1976), yielding multiscale *Lempel-Ziv entropy* (*MLZ*).
232 In order to improve the interpretability of our results, we also estimated a normalized version of
233 each, i.e., *MSEn* and *MLZn* (see below).

234 Multiscale sample entropy (*MSE*) was introduced by Costa *et al.* (2002, 2005) to evaluate the
235 complexity of physio-biological signals such as heart rate, i.e., the degree to which long-range
236 correlations exist in such signals. The *MSE* algorithm combines the calculation of *SampEn* with a
237 coarse graining procedure, acting similar, albeit not identical, to a low pass filter, thereby precluding
238 a one-to-one comparison between time-scales and frequency content of the signal. *SampEn* is an
239 improved version of the *approximate entropy* algorithm (Pincus, 1991), which have been designed
240 to approximate the so called *Kolmogorov-Sinai* entropy of dynamical systems (that quantifies the
241 global temporal organization of time series and provides a meaningful index for discriminating
242 between various dynamic systems), or the *metric entropy* or *mean entropy rate* of stochastic
243 processes (that is the rate with which such processes create new information), for time series of
244 relatively short length, as it is usually the case in biology. In short, we calculated *MSE* along the
245 following steps:

- 246 1. For a particular time-scale $T(s)$, with scale $s = 1 \dots 50$, and $T = 4 \dots 200$ ms in steps of 4 ms, we
247 segmented the time series $x(j)$ into adjacent (non-overlapping) windows y_{ws} of a length of
248 $N_w(s)$ samples. Thus the number of windows $W(s)$ ranged as $W = 2500 \dots 50$, and the number
249 of samples per window as $N_w = 1 \dots 50$, respectively.
- 250 2. We averaged all points within each window y_{ws} to generate new time series $z_{ws} =$
251 $1/N_w(s) \sum_{j=1}^{N_w(s)} y_{ws}(j)$ for each scale s .
- 252 3. Then, *SampEn* was calculated for each of the z_{ws} time series, resulting in a *SampEn* value for
253 each scale, as $MSE(s) = -\ln(N(m+1)/N(m))$, where $N(m)$ is the number of all possible
254 sequences of m points in z_{ws} that are closer to each other than a distance r , i.e., where
255 $(|z_{ws}(i) - z_{ws}(j)| < r) \cap (|z_{ws}(i+1) - z_{ws}(j+1)| < r) \cap \dots \cap (|z_{ws}(i+m-1) -$
256 $z_{ws}(j+m-1)| < r)$ and $i < j$ (no self-matches are counted). Thus, *SampEn* evaluates the
257 percentage of similar sequences of m points that are still similar (in terms of distance) when
258 the next point, i.e., the $m+1$, is added to the sequence. In all our calculations we set $m=2$ and
259 r as 50% of the standard deviation of the original signal $x(j)$, i.e., at scale 1.

260 However, the *SampEn* algorithm has not been analytically proven to converge towards metric
261 entropy and requires a preliminary setting of the parameter m that could lead to an under-
262 estimation if set inappropriately. We therefore also tested the Lempel-Ziv (*LZ*) complexity, which is
263 an adaptive entropy estimator. In addition of being parameter-free, it was shown to be reliable even
264 for short sequences of a few hundreds of symbols (Lesne *et al.*, 2009). We used the same procedure
265 as described above but, at step 3, we calculated *LZ* instead of *SampEn*. In the *LZ* compression
266 algorithm, a symbolic sequence of length N_s is parsed recursively into words, considering as a new
267 word the shortest one that has not yet been encountered. For instance, in a binary example the
268 sequence 100110111001010001011 ... is parsed according to 1 . 0 . 01 . 10 . 11 . 100 . 101 . 00 . 010 .
269 11 One then computes $LZ = N_w(1 + \log_k N_w)/N_s$, where N_w is the number of words used and k

270 is the number of symbols in the ‘alphabet’. Under the assumption that the source is stationary and
271 ergodic (assumptions that apply to the *SampEn* estimator as well), Lempel-Ziv theorems ensure that
272 *LZ* coincides with the entropy rate up to a factor $\log k$ with $\lim_{N \rightarrow \infty} LZ = h/\log k$, where h
273 corresponds to metric entropy. We used an equi-quantization procedure (Hlavackovaschindler et al.,
274 2007) to convert signals into symbolic sequences by partitioning them into 4 bins ($k=4$). The bin size
275 was inversely proportional to the distribution of the amplitude values of EEG, such that the number
276 of values was the same in all bins.

277 MSE curves have been shown to be highly influenced by the effect of the coarse graining procedure
278 on the *standard deviation* at each scale (see Nikulin and Brismar, 2004). Therefore, we also
279 calculated the standard deviation across scales ($SD(s)$) (i.e., after coarse graining) as well as $MSEn(s)$,
280 for which we set a different threshold $r(s)$ for each scale that was equal to 50% of $SD(s)$ (i.e., relative
281 to the *standard deviation* of the coarse grained signal z_{ws}). This normalization was also applied to
282 MLZ by applying at each scale a new grid, adjusted to the variance of the coarse-grained signal.

283

284 *Partial Least Squares (PLS) statistical analysis*

285 We used ‘*contrast*’ or ‘*non-rotated task PLS*’ (as implemented in MATLAB by McIntosh and Lobaugh,
286 2004; see also Krishnan et al., 2011 for updated information) to test the main effects of groups and
287 conditions differences. In a nutshell, *contrast task PLS* is a multivariate statistical method that is
288 suitable for testing hypotheses about spatial and/or time distributed signal changes by combining
289 information across the different signal dimensions (in our case channels and time-scales or
290 frequencies). *PLS* addresses both the problem of multiple comparisons for statistical significance and
291 of that of element-wise reliability via a permutation test and a bootstrap resampling test,
292 respectively. A task *PLS* analysis with N_g groups and N_c conditions starts with a *data matrix* for each
293 group and a *contrast matrix* of maximally $N_g * N_c - 1$ (as many as the degrees of freedom) *orthonormal*
294 *contrasts* that represent the hypotheses to be tested. The rows of each *data matrix* contain a
295 metric’s data points or *elements* of participants within conditions, which in our case were a metric’s
296 values for all channel and time-scale or frequency combinations. From those two matrices, a
297 *covariance matrix* is calculated that contains the covariance of each *orthonormal contrast* with each
298 *element* across participants. This matrix is subjected to singular value decomposition (SVD) resulting
299 in three matrices: i) the orthonormal matrix of the *saliences of the contrasts* (as determined by the
300 initial *contrast matrix*) i.e., it contains the *task (or design) latent variables* that describe the relations
301 among the conditions and groups of our design; ii) the orthonormal *matrix of element saliencies* that
302 are proportional to the covariance of each metrics’ *element* with each one of the *task contrasts*, i.e.,
303 it describes the so-called *brain latent variables*; and iii) the diagonal matrix of *singular values* that are
304 indicative of the variance explained by each contrast. Then, a permutation test on the *singular*
305 *values*, with resampling of the initial *data matrices*, results in a *p*-value for each contrast tested.
306 Finally, a bootstrap test with resampling of the initial *data matrices*, with replacement within
307 conditions and groups, results in statistical reliability estimations of each *element* of both the *task*
308 and the *brain latent variables* within a chosen level of confidence. Thus, the bootstrap test controls
309 for the robustness of the results among participants. For the *task latent variables*, we plotted
310 intervals of 95% confidence. Conditions with non-overlapping intervals are robustly distinguished by
311 the respective contrast. For the *brain latent variables*, we calculated bootstrap ratios by dividing each

312 *element* with its standard error as calculated by the corresponding bootstrap sample distribution.
313 Bootstrap ratios greater than 2.5758 approximate the 99th two-tailed percentile for a particular
314 *element*. Regarding the Statistical Table (**Table II**), we calculated the Agresti-Coull 95% confidence
315 intervals for the p -value of all permutation tests, assuming a binomial distribution for the probability
316 that a permutation sample will lead to a larger eigenvalue than the observed one (Brown et al.,
317 2001), whereas for the bootstrap tests we direct the reader to the corresponding figures, where the
318 confidence intervals of the task latent variables and the bootstrap ratios of the brain latent variables
319 are depicted.

320 In our design, we had two groups (i.e., $N_g = 2$), namely young ('Y') and old ('O') participants, and three
321 conditions ($N_c = 3$), i.e., 'R', 'OnC' and 'OC' as explained above. We tested two orthogonal contrasts.
322 The weights for the first one before normalization were set to 1 for 'Y-'Rest', 'Y-'OnC' and 'Y-'OC'
323 and to -1 for 'O-'R', 'O-'OnC' and 'O-'OC', i.e., the main group effect ('Y' - 'O'). Similarly, the weights
324 for the second contrast were set to 1 for 'Y-'R' and 'O-'Rest', 0 for 'Y-'OnC' and 'O-'OnC' and -1 for
325 'Y-'OC' and 'O-'OC', i.e., the main effect of conditions that orders them from the task requiring the
326 least attention and effort ('Rest') to the one demanding the most ('OC'). Our choices for these
327 contrasts were hypotheses driven, and as such they have clear interpretations. However, they were
328 also justified to a large degree in terms of the amount of variance in our data that they actually
329 explain. We confirmed this by running an alternative explorative version of *task PLS*, namely a '*mean-*
330 *centering task PLS*'. Following this version of the method, not only the *brain latent variables* but also
331 the *task* ones are allowed to "rotate" during the SVD of the mean-centered and concatenated auto-
332 covariance matrix of the initial group *data matrices*, in order to explain as much variance of the data
333 as possible (always under the constraint of orthogonality; see (McIntosh and Lobaugh, 2004) for a
334 detailed description of the method). For all metrics, the first two *latent variables* of the *mean-*
335 *centering task PLS* corresponded to contrasts similar (albeit not identical) to the ones we tested
336 (group and condition main effects), and explained approximately 77-99% and 1-15% of the total
337 variance, respectively, and 88-99% in sum.

338 **Results**

339 To give the reader an intuition on the metrics and their comparability, as well as some guidance in
340 the interpretation of the results, we illustrate in Figure 1 and 2 representative EEG traces and their
341 respective metrics curves. *Figure 1*, left column, depicts randomly selected data segments from two
342 participants, one young and one old, for the resting state – requiring the least attention – and the
343 Oddball counting – requiring the most attention – conditions. In the right column of *Figure 1*, the
344 corresponding power spectra (P) and the associated *DoF* are shown. The results of the respective
345 multiscale metrics are presented in *Figure 2*. In the following we report the observed effects with
346 respect to aging and experimental conditions for all the different metrics.

347 *Between group differences: aging effects*

348 We first investigated group differences between young and old participants by performing a separate
349 *contrast task PLS* analysis for each metric for the main effect "Y" – "O". Group differences can be
350 inspected in Figures 3 and 4, where the mean values with standard error intervals are depicted. The
351 Cz electrode was chosen to visualize mean differences since oddball responses are well represented
352 by the central electrodes (see for instance Müller et al., 2008, 2009), and generally Cz is less affected

353 by muscle artifacts. The permutation tests showed that the contrast was significant for all metrics (p
354 < 0.001 , except for MSE , for which $p = 0.002$). These effects were to a large degree homogeneous
355 among conditions (albeit not identical), and statistically reliable according to the bootstrap tests as
356 shown in *Figure 3*. In the following we describe the main patterns of the results via the mean and
357 standard error intervals (*Figures 3 and 4*), and the bootstrap ratios of the *brain latent variables*
358 (*Figures 6-8*). As regards the magnitude of variability metrics (see *Figures 3 and 6*), it can be seen that
359 the young participants had reliably more *power* (P) at frequencies below 12 Hz (with the exception of
360 a narrow band around 8 Hz), as well as a larger magnitude of *detrended fluctuations* ($\ln(F)$), *variance*
361 ($\ln(V)$) and *standard deviation* (SD). The effects of the last 3 metrics were generally reliable across
362 channels and scales, although they were the strongest for the parieto-occipital channels and longer
363 time-scales. As for the metrics that evaluate the structure of EEG variability across time-scales
364 (*Figures 4, 7 and 8*), the elderly's *degrees of freedom* of all channels' *power spectra* were larger than
365 that of the young participants, i.e., the former's *spectra* were flatter. Moreover, the *DoFs* were the
366 highest for the anterior channels as well as for the lateral ones, which were also noisier (see *Figure*
367 *4*). *Figures 4 and 7* also show that the magnitude of the *detrended fluctuations* coincided with a
368 larger *Hurst exponent* for young participants than for the older. On average, H was around 1.5 for
369 older participants and 1.7 for the young one (*Figure 3*). In both groups, H values were the highest for
370 more posterior as well as midline (and also less noisy) channels. With respect to the entropic metrics
371 (*Figure 8*), relative to the young participants, *entropy* was higher for the older participants at time-
372 scales shorter than 24 ms, and lower at longer scales from this point on. Exemplified in *Figure 4*, the
373 MSE curves of channel Cz across all conditions show a crossing point. The effect below the crossing
374 point (i.e., higher *entropy* for the old participants for short time-scales) was slightly stronger at the
375 parieto-occipital channels, whereas the effect above the crossing point (i.e., higher *entropy* for the
376 young participants for long time-scales) was stronger at the fronto-central channels, and was present
377 at least up to the scale of 80 ms (*Figure 8*). After normalizing for the *standard deviation* at each scale
378 after coarse graining, the resulting $MSEn$ also showed group differences, but in this case mainly so for
379 time-scales lower than 32 ms, where $SampEn$ was higher for old participants. In contrast, the
380 differences between groups for longer time-scales were not as strong. Results were similar for the
381 *Lempel-Ziv entropy* metrics (MLZ and $MLZn$) shown in *Figures 4 and 8*. However, effects were
382 statistically weaker than for MSE , and the crossing point tended to be one scale shorter for MLZ , i.e.,
383 at 20 ms, and one scale longer for $MLZn$, i.e., at 36 ms.

384 In summary, the metrics that primarily evaluate the magnitude of variability across scales (the *power*
385 *spectrum*, the *detrended fluctuations'* amplitude, the *variogram* and the *standard deviation*),
386 indicated that the young participants exhibited larger fluctuations, mainly so for low frequencies,
387 long time-scales, and for the posterior channels. Inversely, entropy differences between groups
388 reversed at the scale of 20-24 ms, and showed higher entropy for old (young) participants at shorter
389 (longer) time-scales, mainly so for posterior (anterior) channels, respectively. Normalizing for the
390 standard deviation after coarse graining substantially weakened the effect at the long time-scales.
391 The *generalized Hurst exponent*, as a metric of complexity (or structure in the variability), was in
392 accordance with the $SampEn$ at long-scales, which was higher for the young participants, whereas
393 the more *DoF* of the old participants was to be expected given their "flatter" power spectrum,
394 especially for the lower frequencies below 12 Hz.

395 *Effects of experimental conditions*

396 We next tested for the main effect of condition, mainly contrasting resting state ('R') and oddball
397 counting ('OC'), as the oddball no-counting ('OnC') was placed in the middle. The permutation test
398 showed that the contrast was significant with $p < 0.001$ for P , $\ln(V)$, SD , $\ln(F)$, and MSE , and with $p =$
399 0.002 for $MSEn$, $p = 0.069$ for MLZ , and $p = 0.005$ for $MLZn$. The contrast was not significant for DoF
400 and H ($p > 0.1$). Notably, the contrast for condition explained much less variance in our data than that
401 for group, which was revealed by comparing the singular values of the condition contrast for each
402 metric in *Figure 8* with the corresponding ones for the group contrast in *Figure 5* (the latter were
403 much larger). As further illustrated in *Figure 8*, the bootstrap test showed that for P , $\ln(V)$, SD , and
404 $\ln(F)$ the three conditions could not be separated reliably with a confidence of 95% (the respective
405 confidence intervals around the weights of the *task latent variables* were largely overlapping).
406 Instead, for the entropic metrics (MSE , $MSEn$, MLZ , and $MLZn$) 'R' was generally reliably separated
407 from the task conditions ('OC' and 'OnC'), which was more clearly so for young participants. In order
408 to evaluate the statistically reliable effects as well as the statistically un- or less reliable tendencies,
409 we here present the *brain latent variables* for all metrics (*Figures 10 and 11*). As for the metrics of
410 the magnitude of variability, $\ln(V)$ and $\ln(F)$ were generally higher for the resting condition across all
411 scales and channels, but particularly so for parieto-occipital channels. The SD was higher also for 'R'
412 at time scales up to 100 ms, also particularly for the posterior channels. Regarding P , 'R' had more
413 power in the 5-10 Hz and 15-30 Hz frequency intervals than the task conditions, whereas 'OC' had
414 more power in the delta band (i.e., 1-4 Hz), particularly so for fronto-central channels. Regarding the
415 entropic metrics shown in *Figure 11*, MSE was higher (lower) for 'R' than for 'OC' for time-scales
416 shorter (longer) than 44-48 ms, respectively. The effect below those scales was stronger for the
417 fronto-central channels. The result for MLZ was very similar for short-scales, but was statistically
418 weaker, and with the crossing point moving at shorter scales (32-36 ms). However, above the
419 crossing point, i.e., for long time-scales, the effect was practically lost. In addition, $MSEn$ and $MLZn$
420 were generally higher for 'R' across all scales, mainly so for the fronto-central channels. This effect
421 was statistically much stronger for the time-scales lower than 56 ms and, more generally, for $MSEn$
422 as compared to $MLZn$.

423 In summary, the resting state resulted generally in larger fluctuations (except for the *standard*
424 *deviation* at long time scales and *power* at the delta band at the frontal channels). Moreover, the
425 resting condition exhibited higher (lower) *entropy* than the task condition with counting ('OC') at
426 short (long) time-scales, respectively. However, after normalizing for the standard deviation at each
427 scale after coarse graining, this effect tended to reverse for long time-scales. It is worth noticing that
428 the patterns of results for P and MSE , as well as for $MSEn$, MLZ , and $MLZn$, at short scales only for the
429 last 3, were to a large degree inverse to those of the group main effect, i.e., the results for the
430 attentive task (rest) condition followed the ones for the young (old) participants. This rough
431 correspondence, however, reversed for the rest of the metrics, i.e., $\ln(V)$, SD , and $\ln(F)$.

432

433 Discussion

434 The present study investigates the changes of cortical dynamics with aging through the use of a
435 battery of multiscale metrics, which allows that characterize the structure and the magnitude of EEG
436 fluctuations.

437 Age-related differences in the magnitude of EEG signals variability across time-scales

438 Our results show that the cortical activity of older participants displayed smaller fluctuations than
439 young participants in a (close to) scale-independent manner. Consistent with previous studies (e.g.,
440 Dustman et al., 1993, 1999; Gaal et al., 2010; Müller and Lindenberger, 2012), EEG signals of the
441 elderly generally contained less spectral power than that of the young adults. Similarly, the *DFA*, *SD*,
442 and *Variogram* results also indicated a decrease in the fluctuations' magnitude with aging. While, to
443 our knowledge, this aspect of brain signal variability has never been explicitly addressed before in
444 EEG recordings, it is in line with recent fMRI studies (Garrett et al., 2012, 2013), where older adults
445 were found to display a reduction of *SD* BOLD signals in most brain areas (especially cortical) in both
446 resting and task-driven states (Garrett et al., 2011, 2012). Our study extends these observations to
447 scalp EEG and shows that it is indeed a pervasive characteristic of the aging brain across time-scales.

448 Effects of aging on the organization of cortical fluctuations across time-scales

449 In the frequency domain, older adults showed flatter power spectra with a lower alpha peak, and
450 more spectral *DoF*, suggestive of increased 'broadband' noisiness of the cortical activity. Further,
451 long range autocorrelations were less present in older participants' data (higher *H* exponent). The
452 multiscale entropy metrics revealed a time-scale dependence of aging effects regardless of the used
453 estimator (*SampEn* or *LZ*) with the elderly's EEG signals being more irregular at fine/shorter-scales,
454 and less complex at coarser/longer scales. Thus, young and old brains appear to operate at different
455 time constants making them, under the effect of coarse graining, reach maximal entropy at different
456 time-scales. After reaching their respective peak, both young and older adults' *MSE/MLZ* curves
457 decreased; however, those of the young remained significantly higher. This loss of complexity across
458 the long scales may be indicative of a diminished global information integration with aging, since
459 these scales relate mostly to low frequency oscillations mediating long-range interactions. Mind,
460 however, that the inverse does not directly apply, because the short scales enclose information
461 about both high and low frequency oscillations. Furthermore, it is known also that (multiscale)
462 entropy-based measures reflect both variance and correlation properties of time series (Costa et al.,
463 2002, 2005). To extract variance-related changes, we compared the multiscale entropy curves (*MSE*,
464 *MLZ*) with their normalized versions (*MSEn*, *MLZn*) and the *SD* curves. A crossing-over was present
465 for the entropy metrics (regardless of the normalization), but not for *SD*, for which young and
466 elderly's curves were parallel. It is notable however, that, although the age-groups differences in
467 entropy remained mostly significant after normalization, they were substantially weakened. The
468 normalization affected essentially the part of *MSE/MLZ* curves after the peak that contains the scales
469 accounting for the auto-correlated (low frequencies) content of the signal, which actually contain the
470 most power (roughly below 20Hz).

471 The above results are in accordance with the current literature, and extend it with several new
472 findings. First, we reproduced McIntosh et al.'s (2013) results and extended them to longer time-
473 scales, as well as to resting state activity. For the first time-scale, our findings (i.e., more irregularity
474 for older adults) are consistent with those of other EEG studies using single-scale measures of
475 complexity (Anokhin et al. 1996; Pierce et al. 2000, 2003; Müller and Lindenberger 2012). Conversely,
476 our observations at longer scales approximate the observations of fMRI studies, in which the time
477 resolution is much lower than in EEG. Indeed, fMRI investigations at resting state have also shown a
478 loss of entropy with aging (Yang et al., 2013; Smith et al., 2014; Sokunbi, 2014).

479 Overall, we show that aging effects on cortical fluctuations are time-scale dependent with regard to
480 structure (i.e., less regular fluctuations at shorter scales and less complex fluctuations at longer
481 scales), but not in terms of magnitude (i.e., a systematic reduction regardless of the time-scale).

482 **Spatial patterns of variability changes with aging**

483 The observed aging effects on EEG variability were rather robust for almost all channels.
484 Nevertheless, some spatial patterns showing stronger effects for certain electrodes were
485 distinguishable over the scalp. Notably, the posterior channels were found to display the highest
486 young-old differences in terms of variability magnitude (across all scales), with the younger adults
487 being furthermore variable than the elderly for these regions. This was also the case for the *power*
488 *spectrum*, the *variogram*, and the *DFA* analyses. This spatial pattern of age-related differences in
489 terms of fluctuations magnitude is consistent with the observation that young adults have more
490 power in most of the frequency bands at the posterior areas (seen in our results, and previously
491 reported in Gaal et al., 2010). Conversely, entropy-wise, young-old differences for the longer/coarser
492 scales were stronger at the fronto-central channels, because EEG signals of the younger participants
493 were more complex for these channels than for the occipital ones.

494 These results suggest that the detected antero-posterior difference in the magnitude of group
495 effects stems from a fronto-occipital differentiation expressed only in the younger adults' brains. This
496 interpretation corroborates the view of spatial dedifferentiation in the aged brain, as shown for
497 instance in Garrett et al.'s (2012, 2013) studies, wherein older adults were found to exhibit low and
498 nearly indistinguishable levels of variability across brain structures in both resting and task-driven
499 states.

500 **Differences between experimental conditions**

501 The differences between resting and the auditory stimuli conditions (with and without counting)
502 followed a similar pattern across metrics, with the contrast driven mainly by the difference between
503 resting state and the cognitively most demanding oddball counting task. However, this distinction
504 could only be made reliably through *MSE*, and more consistently so for young participants. The
505 limited change between rest and task situations might be related to the fact that in all experimental
506 conditions participants were instructed to keep their eyes closed. Eyes opening was indeed shown to
507 significantly affect brain signals complexity elsewhere (see Hogan et al., 2012; Müller and
508 Lindenberger, 2012), as was also found in our preliminary analysis including the eyes-open condition.
509 In addition, the cognitive task we used is not very demanding. With respect to *MSE*, the pattern of
510 difference between the resting (least demanding) and oddball counting (most demanding) condition
511 resembled the one differentiating the age groups (old vs. young): the EEG of the less demanding task
512 was more complex at shorter scales. A stronger difference was found for the fronto-central channels,
513 most likely due to the attentional load imposed by the task. This difference was reversed at longer
514 scales where the 'Odc' condition yielded the most entropic signals. To our best knowledge, this is the
515 first time a specific *MSE* pattern with obvious time-scale dependence is shown to differentiate
516 between brain states at different cognitive loads. Nevertheless, the low differentiability between
517 conditions in elderly has been reported earlier and seems to be one of the general signatures
518 characterizing the senescent brain (cf., Garrett et al. 2012). This lack of specificity in the aged brain
519 manifests itself thus, both through a spatial (within experimental condition, as shown in the section
520 before) and a 'states' (between conditions) dedifferentiation.

521 **Convergence of aging theories and empirical findings**

522 The *dedifferentiation* hypothesis initially introduced by Baltes and Lindenberger (1997) is repeatedly
523 referred to in the literature to describe and explain cognitive declines with advanced age (see Park
524 and Reuter-Lorenz, 2009, for a review). Notwithstanding its initial framework (i.e., correlations
525 between sensory and cognitive functions), *dedifferentiation* can be used to account for several facets
526 of age-related changes in brain and behavior (see Sleimen-Malkoun et al., 2014). In the brain, it can
527 be seen through increased interdependence between functional domains (e.g., cognition and motor
528 control, Schäfer et al., 2006, 2010), decreased specialization of brain regions (Dennis and Cabeza
529 2011; Park et al., 2004), and more widespread activations (Reuter-Lorenz et al., 2000; Heuninckx et
530 al., 2005, 2008). Nevertheless, neuro-behavioral variability is not an outcome measure in the
531 dedifferentiation approach and its extensions. In this regard, for a long time, the aging literature
532 essentially focused on behavioral variability (e.g., response times) in relation to changes in patterns
533 of brain activations (Hultsch et al., 2008; MacDonald et al., 2009), rather than on characterizing brain
534 signals fluctuations themselves. The *neural noise hypothesis* (Li et al., 2000; Li and Sikstrom, 2002) is
535 one of the first and most established approaches dealing with this aspect. It argues in favor of an
536 increased random background activity in the aged CNS (referred to as neural noise), resulting in a
537 higher intra-individual variability in performance (Li et al., 2000, 2001; Li and Sikstrom, 2002; Hultsch
538 et al., 2002). Currently, it is widely recognized that the variability of brain activations in space and
539 time is of high relevance to understand brain functioning in health (e.g., development, Vakorin et al.,
540 2011, and normal aging, McIntosh et al., 2013) and disease (e.g., autism, Bosl et al., 2011, and
541 Alzheimer disease, Mizuno et al., 2010). This rather recent interest succeeds a more established view
542 in the domains of physiology and motor behavior where the *loss of complexity hypothesis* (LOCH) was
543 developed (Lipsitz and Goldberger, 1992; Lipsitz, 2002, 2004). In this framework, the structure of
544 fluctuations is considered to reflect the complexity of the underlying functional organization and
545 interactions within and between different subsystems. The LOCH stipulates that during aging, as well
546 as disease, there is a generic tendency towards less complex (behavioral and physiological) outputs
547 that could be in the direction of an increased regularity or an increased randomness (Goldberger,
548 1996; Vaillancourt and Newell, 2002, 2003), both supposedly indicative of a breakdown of functional
549 synergies and a decoupling of components. The LOCH can be connected to dedifferentiation of brain
550 activations by looking at the spatial distribution of variability and linking time-scales of fluctuations to
551 information processing in the brain. A more uniform spatial representation of variability across
552 cortical and subcortical structures expresses the characteristic spatial dedifferentiation of the aging
553 brain (Garrett et al., 2011). Conversely, the time-scales view presumes that complexity at finer scales
554 characterizes local processing, and may thus be related to short neural connections, whereas the
555 coarser scales (by filtering out higher frequencies) reflect the more long-range (i.e., global)
556 interactions, and therefore depend on longer neuronal fibers (Mizuno et al., 2010; Vakorin et al.,
557 2011; McIntosh et al. 2013). McIntosh et al. (2013) argued in favor of this assumption and showed
558 that scale differences observed with *MSE* follow closely those that can be quantified through other
559 entropy measures that distinguish local and distributed informational exchanges (i.e., *conditional*
560 *entropy* and *mutual information*).

561 All the aforementioned aging hypotheses could be linked to underlying alterations of neural
562 structures and interactions, as well as dysregulation of neurotransmission, together leading to a less
563 rich and flexible repertoire of functional synergies. Structurally and physiologically, the aging brain is
564 known to incur changes characterized by a marginal neuronal loss (Bishop et al., 2010; Morrisson and

565 Hof, 1997; Wickelgre, 1996), but a substantial decline in the integrity of white matter (Madden et al.,
566 2012; Sullivan et al., 2010), as well as a disruption in the synthesis of some neuro-transmitters
567 (dopamine, norepinephrine, acetylcholine). These modifications greatly affect large-scale brain
568 networks by disturbing inter-hemispheric functional connections and interactions (Duffy et al., 1996;
569 Kikuchi et al., 2000; Langan et al., 2010), as well as somatosensory cortical inhibition (Cheng and Lin,
570 2013). Impaired dopaminergic neurotransmission further compromises the modulation of neural
571 noise, which is an additional cause of inflexibility of brain activity and behavior (Hong and Rebec,
572 2012). The conjunction of all these alteration is most likely responsible for the observed changes in
573 multiscale variability and activation patterns, which nicely merges with the predictions stemming
574 from main aging theories. Indeed, although these theories were developed to cover different
575 domains and mechanisms, they converge to describe systemic modifications characterizing the
576 senescence process(es) in the neuro-behavioral system (Sleimen-Malkoun et al., 2014). An essential
577 current debate that needs to be settled is the relative importance of local (i.e., grey matter and
578 neurotransmission degradation) and global (i.e., white matter degradation and demyelination)
579 network changes, as well as the beneficial or detrimental role of stochastic components of brain
580 dynamics (i.e., noise), and how these factors affect functional connectivity, brain signal variability,
581 and performance. In the framework of *dedifferentiation* the degradation of neurotransmission is
582 thought to reduce the signal-to-noise ratio in local networks leading to less distinct cortical
583 representations, and potentially to less specific functional connectivity (Li and Lindenberger, 1999; Li
584 et al. 2001; Li, 2002; Li and Sikström, 2002). Functional connectivity and complexity are considered to
585 entertain an inverse relationship, according to which higher entropy is found when connectivity is
586 poor, and vice versa (Friston, 1996; Müller and Lindenberger, 2012; Ghanbari et al., 2013). However,
587 from a different perspective, the reverse is commonly suggested (cf. Vakorin et al., 2011) based on
588 the assumption that information processing and (neural) complexity go hand in hand (Tononi et al.,
589 1994, 1998; Slifkin and Newell, 1999). Conversely, following the finding that neural information
590 transmission is determined by both the degree and time-scale of synchrony (Baptista and Kurths,
591 2008), a different view can be suggested. Accordingly, neural processing would be maximized when
592 synchronization is high at coarse time-scales (strong connectivity requiring complexity to be low) and
593 low at fine-scales (weak connectivity allowing the expression of greater complexity). Evidence for
594 such time-scale dependence, with a negative connectivity-complexity association at fine-scales and
595 the reverse at coarser scales was found in resting-state fMRI data (McDonagh and Nashiro, 2014),
596 as well as in mean field model and BOLD simulations (Jirsa et al. 2010; Nakagawa et al., 2013).
597 Therefore, it could be concluded that entropic and variability changes convey different information
598 depending on the time-scale under scrutiny. More precision should be gained in the future by
599 accounting for the recently uncovered non-stationarity of the dynamics of resting state fMRI (Allen
600 et al., 2012), which is expressed through different functional connectivity measures for different time
601 windows and moments in time. Hansen et al. (2014) demonstrated that the non-stationarity of the
602 resting state dynamics is evident in rapid changes in functional connectivity patterns, which are
603 otherwise relatively invariant during epochs lasting one to two minutes. These transitions are
604 reminiscent of phase transitions as known from statistical physics and were referred to as Functional
605 Connectivity Dynamics (FCD, Hansen et al., 2014). A successful quantification of FCD promises to
606 provide a more profound understanding of variability- and complexity-related phenomena in brain
607 networks and thus ageing-related changes in brain and behavior.

608 Overall, it appears that while the aging brain displays more widespread activations, in terms of
609 information processing, it is characterized by an increased spatial clustering with a shift towards a
610 lesser contribution of long-range connections (cf., Meunier et al., 2009). However, the contribution
611 of changes in connectivity and non-stationaries remains to be unraveled.

612 **Conclusion**

613 Our findings provide support to the importance of multiscale brain signal variability as a means to
614 assess the effects of aging on brain functioning. Even though no absolute value or a single metric can
615 currently be offered as a biomarker of brain age, the contribution of a systematic study of variability
616 through multiple measures and scales rests in the link that can be established with functional and
617 structural connectivity, as well as the richness of activation patterns. Nevertheless, we argue that any
618 expected or discussed effect of aging should meet the complexity of the functional organization
619 within the human neurophysiological and neurobehavioral system, which makes simple, strict and
620 irrevocably generalizable correspondences unlikely to be found. It would be misleading, for instance,
621 to expect that aging is a process of “loss”, and that what is observed in term of behavior mirrors
622 *sensu stricto* changes in brain activations. In the brain, what counts most to insure a rich adaptable
623 behavior is the interplay between multiple factors, namely, local and global neuro-anatomical
624 connectivity, noise levels and interaction delays (cf., Ghosh et al., 2008; Jirsa et al., 2010; Deco et al.,
625 2011). Accordingly, the healthy brain expresses critical magnitudes and structures of variability that
626 undergo significant changes with development, aging, and disease. Regarding aging, some general
627 features can be extracted. Mainly, a pervasive reduced level of variability, in terms of magnitude, an
628 increased irregularity at shorter time-scale, a decrease complexity at long scales, and finally a spatial
629 dedifferentiation in activations and between brain states (e.g., rest vs. task). The meaning of these
630 changes and their link with structure, function and dynamics can be significantly furthered and made
631 more explicit through theoretical and simulation studies and empirical investigations. Systematic
632 investigation of how aging-relevant functional and structural modifications affect the outcome of
633 multiscale variability and complexity metrics would offer a major contribution. A wider set of entropy
634 estimators (e.g., *epsilon entropy*) and metrics can also be covered (*multivariate measures*,
635 *synchronization measures*, *Lyapunov exponents*, etc.). However, it is to be expected that these
636 supplementary methods will provide converging evidence in terms of global effects, as it has been
637 found in the present study for the measures quantifying fluctuations’ magnitude and those
638 quantifying their structure. Therefore, based on our findings we contend that adding more metrics
639 would not profoundly advance our current understanding of aging. Conversely, a novel and more
640 promising direction would be appropriately taking into account the non-stationary nature of brain
641 processes, which seem to be an inherent property of brain functioning and to occur on various scales
642 of organization (cf., Hansen et al., 2014). Finally, combining different modalities of brain imaging and
643 investigating different brain states in a single aging experiment would make it possible to irrefutably
644 relate the different phenomena that have been separately shown to characterize aging (e.g.,
645 dedifferentiation, loss of complexity, variability changes), as well as integrate newly uncovered ones
646 (e.g., non-stationaries in functional connectivity; Allen et al., 2012; Hansen et al., 2014) while
647 establishing the link with performance and behavior.

648

649 **References**

- 650 Adler, R.L., and Weiss, B. (1967). Entropy, a complete metric invariant for automorphisms of the
651 torus. *Proc Natl Acad Sci USA* 57, 1573-1576.
- 652 Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., and Calhoun, V.D. (2012). Tracking
653 whole-brain connectivity dynamics in the resting state. *Cereb Cortex*. 2014 Mar;24(3):663-76.
- 654 Anokhin, A.P., Birbaumer, N., Lutzenberger, W., Nikolaev, A., and Vogel, F. (1996). Age increases
655 brain complexity. *Electroencephalogr Clin Neurophysiol* 99, 63-68.
- 656 Baltes, P.B., and Lindenberger, U. (1997). Emergence of a powerful connection between sensory and
657 cognitive functions across the adult life span: a new window to the study of cognitive aging?
658 *Psychol Aging* 12, 12-21.
- 659 Baptista, M.S., and Kurths, J. (2008). Transmission of information in active networks. *Phys Rev E Stat*
660 *Nonlin Soft Matter Phys* 77, 026205.
- 661 Bishop, N.A., Lu, T., and Yankner, B.A. (2010). Neural mechanisms of ageing and cognitive decline.
662 *Nature* 464, 529-535.
- 663 Bosl, W., Tierney, A., Tager-Flusberg, H., and Nelson, C. (2011). EEG complexity as a biomarker for
664 autism spectrum disorder risk. *BMC Med* 9, 18.
- 665 Bravi, A., Longtin, A., and Seely, A. (2011). Review and classification of variability analysis techniques
666 with clinical applications. *BioMed Eng OnLine* 10, 90.
- 667 Brown, L.D., Cai, T.T., and DasGupta, A. (2001). Interval Estimation for a Binomial Proportion. *Statist*
668 *Sci*, 16(2), 101–133.
- 669 Bryce, R.M., and Sprague, K.B. (2012). Revisiting detrended fluctuation analysis. *Sci Rep* 2, 315.
- 670 Cheng, C.H., and Lin, Y.Y. (2013). Aging-related decline in somatosensory inhibition of the human
671 cerebral cortex. *Exp Brain Res* 226, 145-152.
- 672 Conte, E., Khrennikov, A., Federici, A., and Zbilut, J.P. (2009). Fractal fluctuations and quantum-like
673 chaos in the brain by analysis of variability of brain waves: A new method based on a fractal
674 variance function and random matrix theory: A link with El Naschie fractal Cantorian space-
675 time and V. Weiss and H. Weiss golden ratio in brain. *Chaos Solitons Fract* 41, 2790-2800.
- 676 Costa, M., Goldberger, A.L., and Peng, C.-K. (2005). Multiscale entropy analysis of biological signals.
677 *Phys Rev E Stat Nonlin Soft Matter Phys* 71, 021906.
- 678 Costa, M., Goldberger, A.L., and Peng, C.K. (2002). Multiscale entropy analysis of complex physiologic
679 time series. *Phys Rev Lett* 89, 068102.
- 680 Cressie, N.A.C. (1993). *Statistics for Spatial Data*. New York: Wiley.
- 681 Deco, G., Jirsa, V., McIntosh, A.R., Sporns, O., and Kötter, R. (2009). Key role of coupling, delay, and
682 noise in resting brain fluctuations. *Proc Natl Acad Sci USA* 106, 10302-10307.
- 683 Deco, G., Jirsa, V.K., and McIntosh, A.R. (2011). Emerging concepts for the dynamical organization of
684 resting-state activity in the brain. *Nat Rev Neurosci* 12, 43-56.
- 685 Deco, G., Jirsa, V.K., and McIntosh, A.R. (2013). Resting brains never rest: computational insights into
686 potential cognitive architectures. *Trends Neurosci* 36, 268-274.
- 687 Dennis, N.A., and Cabeza, R. (2011). Age-related dedifferentiation of learning systems: an fMRI study
688 of implicit and explicit learning. *Neurobiol Aging* 32, 2318 e2317-2330.
- 689 Duffy, F.H., Mcanulty, G.B., and Albert, M.S. (1996). Effects of age upon interhemispheric EEG
690 coherence in normal adults. *Neurobiol Aging* 17, 587-599.
- 691 Dustman, R.E., Shearer, D.E., and Emmerson, R.Y. (1993). EEG and event-related potentials in normal
692 aging. *Prog Neurobiol* 41, 369-401.
- 693 Dustman, R.E., Shearer, D.E., and Emmerson, R.Y. (1999). Life-span changes in EEG spectral
694 amplitude, amplitude variability and mean frequency. *Clin Neurophysiol* 110, 1399-1409.
- 695 Faisal, A.A., Selen, L.P.J., and Wolpert, D.M. (2008). Noise in the nervous system. *Nat Rev Neurosci* 9,
696 292-303.
- 697 Feldman, D.P., and Crutchfield, J.P. (1998). Measures of statistical complexity: Why? *Physics Letters A*
698 238, 244-252.

- 699 Friston, K.J. (1996). Theoretical neurobiology and schizophrenia. *British Medical Bulletin* 52, 644-655.
- 700 Gaal, Z.A., Boha, R., Stam, C.J., and Molnar, M. (2010). Age-dependent features of EEG-reactivity--
701 spectral, complexity, and network characteristics. *Neurosci Lett* 479, 79-84.
- 702 Gammaitoni, L., Hanggi, P., Jung, P., and Marchesoni, F. (1998). Stochastic resonance. *Rev Mod Phys*
703 70, 223-287.
- 704 Garrett, D., Kovacevic, N., McIntosh, A.R., and Grady, C. (2011). The Importance of Being Variable. *J*
705 *Neurosci* 31(12), 4496-4503.
- 706 Garrett, D.D., Kovacevic, N., McIntosh, A.R., and Grady, C.L. (2012). The Modulation of BOLD
707 Variability between Cognitive States Varies by Age and Processing Speed. *Cereb Cortex* 2013
708 Mar;23(3):684-93.
- 709 Garrett, D.D., Samanez-Larkin, G.R., MacDonald, S.W., Lindenberger, U., McIntosh, A.R., and Grady,
710 C.L. (2013). Moment-to-moment brain signal variability: a next frontier in human brain
711 mapping? *Neurosci Biobehav Rev* 37, 610-624.
- 712 Ghanbari, Y., Bloy, L., Christopher Edgar, J., Blaskey, L., Verma, R., and Roberts, T.L. (2013). Joint
713 Analysis of Band-Specific Functional Connectivity and Signal Complexity in Autism. *J Autism*
714 *Dev Disord*, 1-17.
- 715 Ghosh, A., Rho, Y., McIntosh, A.R., Kötter, R., and Jirsa, V.K. (2008). Noise during Rest Enables the
716 Exploration of the Brain's Dynamic Repertoire. *PLoS Comput Biol* 4, e1000196.
- 717 Goldberger, A.L. (1996). Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at
718 the bedside. *Lancet* 347, 1312-1314.
- 719 Grady, C.L., and Garrett, D.D. (2014). Understanding variability in the BOLD signal and why it matters
720 for aging. *Brain Imaging Behav* 8, 274-283. doi: 10.1007/s11682-013-9253-0.
- 721 Gratton, G., Coles, M.G.H., and Donchin, E. (1983). A New Method for Off-Line Removal of Ocular
722 Artifact. *J Autism Dev Disord* 55, 468-484.
- 723 Hansen, E.C., Battaglia, D., Spiegler, A., Deco, G., and Jirsa, V.K. (2014). Functional Connectivity
724 Dynamics: Modeling the switching behavior of the resting state. *Neuroimage In Press*.
- 725 Hardstone, R., Poil, S.-S., Schiavone, G., Jansen, R., Nikulin, V.V., Mansvelder, H.D., and Linkenkaer-
726 Hansen, K. (2012). Detrended fluctuation analysis: a scale-free view on neuronal oscillations.
727 *Front Physiol* 3, 450.
- 728 Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., and Swinnen, S.P. (2005). Neural basis of
729 aging: the penetration of cognition into action control. *J Neurosci* 25, 6787-6796.
- 730 Heuninckx, S., Wenderoth, N., and Swinnen, S.P. (2008). Systems neuroplasticity in the aging brain:
731 recruiting additional neural resources for successful motor performance in elderly persons. *J*
732 *Neurosci* 28, 91-99.
- 733 Hlaváčková-Schindler, K. (2009). "Causality in Time Series: Its Detection and Quantification by Means
734 of Information Theory," in *Information Theory and Statistical Learning*, eds. F. Emmert-Streib
735 & M. Dehmer. Springer (US), 183-207.
- 736 Hogan, M.J., Kilmartin, L., Keane, M., Collins, P., Staff, R.T., Kaiser, J., Lai, R., and Upton, N. (2012).
737 Electrophysiological entropy in younger adults, older controls and older cognitively declined
738 adults. *Brain Res* 1445, 1-10.
- 739 Hong, S.L., and Rebec, G.V. (2012). Biological sources of inflexibility in brain and behavior with aging
740 and neurodegenerative diseases. *Front Syst Neurosci* 6, 77.
- 741 Hultsch, D.F., Strauss, E., Hunter, M.A., and Macdonald, S.W. (2008). "Intraindividual variability,
742 cognition, and aging," in *The handbook of aging and cognition*, eds. F.I.M. Craik & T.A.
743 Salthouse. 3rd ed (NY: Psychology Press), 491-556.
- 744 Hurst, H.E. (1951). Long-term storage capacity of reservoirs. *Trans Amer Soc Civ Eng* 116, 770-808.
- 745 Huys, R., Perdikis, D., and Jirsa, V.K. (2014). Functional architectures and structured flows on
746 manifolds: a dynamical framework for motor behavior. *Psychol Rev* 121, 302-336.
- 747 Jirsa, V.K., Sporns, O., Breakspear, M., Deco, G., and McIntosh, A.R. (2010). Towards the virtual brain:
748 network modeling of the intact and the damaged brain. *Arch Ital Biol* 148, 189-205.
- 749 Kikuchi, M., Wada, Y., Takeda, T., Oe, H., Hashimoto, T., and Koshino, Y. (2002). EEG harmonic
750 responses to photic stimulation in normal aging and Alzheimer's disease: differences in

- 751 interhemispheric coherence. *Clin Neurophysiol* 113, 1045-1051.
- 752 Krishnan, A., Williams, L.J., McIntosh, A.R., and Abdi, H. (2011). Partial Least Squares (PLS) methods
753 for neuroimaging: a tutorial and review. *Neuroimage* 56, 455-475.
- 754 Langan, J., Peltier, S.J., Bo, J., Fling, B.W., Welsh, R.C., and Seidler, R.D. (2010). Functional implications
755 of age differences in motor system connectivity. *Front Syst Neurosci* 4, 17.
- 756 Lempel, A., and Ziv, J. (1976). On the Complexity of Finite Sequences. *Information Theory, IEEE*
757 *Transactions on* 22, 75-81.
- 758 Lesne, A., Blanc, J.-L., and Pezard, L. (2009). Entropy estimation of very short symbolic sequences.
759 *Phys Rev E Stat Nonlin Soft Matter Phys* 79, 046208.
- 760 Li, S., Lindenberger, U., and Sikström, S. (2001). Aging cognition: from neuromodulation to
761 representation. *Trends Cogn Sci* 5, 479-486.
- 762 Li, S.C., Lindenberger, U., and Frensch, P.A. (2000). Unifying cognitive aging: from neuromodulation
763 to representation to cognition. *Neurocomputing* 32-33, 879-890.
- 764 Li, S.C., and Sikstrom, S. (2002). Integrative neurocomputational perspectives on cognitive aging,
765 neuromodulation, and representation. *Neurosci Biobehav Rev* 26, 795-808.
- 766 Lipsitz, L.A. (2002). Dynamics of stability: the physiologic basis of functional health and frailty. *J*
767 *Gerontol A Biol Sci Med Sci* 57, B115-B125.
- 768 Lipsitz, L.A. (2004). Physiological complexity, aging, and the path to frailty. *Sci Aging Knowledge*
769 *Environ* 2004, pe16.
- 770 Lipsitz, L.A., and Goldberger, A.L. (1992). Loss of complexity and aging. Potential applications of
771 fractals and chaos theory to senescence. *JAMA* 267, 1806-1809.
- 772 Liu, C.Y., Krishnan, A.P., Yan, L., Smith, R.X., Kilroy, E., Alger, J.R., Ringman, J.M., and Wang, D.J.
773 (2013). Complexity and synchronicity of resting state blood oxygenation level-dependent
774 (BOLD) functional MRI in normal aging and cognitive decline. *J Magn Reson Imaging* 38, 36-
775 45.
- 776 MacDonald, S.W.S., Li, S.-C., and Bäckman, L. (2009). Neural underpinnings of within-person
777 variability in cognitive functioning. *Psychol Aging* 24, 792-808.
- 778 Madden, D.J., Bennett, I.J., Burzynska, A., Potter, G.G., Chen, N.-K., and Song, A.W. (2012). Diffusion
779 tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica et Biophysica*
780 *Acta (BBA) - Molecular Basis of Disease* 1822, 386-400.
- 781 McDonnell, M.D., and Abbott, D. (2009). What is stochastic resonance? Definitions, misconceptions,
782 debates, and its relevance to biology. *PLoS computational biology* 5, e1000348.
- 783 McDonnell, M.D., and Ward, L.M. (2011). The benefits of noise in neural systems: bridging theory and
784 experiment. *Nat Rev Neurosci* 12, 415-426.
- 785 McDonough, I.M., and Nashiro, K. (2014). Network complexity as a measure of information
786 processing across resting-state networks: evidence from the Human Connectome Project.
787 *Front Hum Neurosci* 8, 409.
- 788 McIntosh, A.R., Kovacevic, N., Lippe, S., Garrett, D., Grady, C., and Jirsa, V. (2010). The development
789 of a noisy brain. *Arch Ital Biol* 148, 323-337.
- 790 McIntosh, A.R., and Lobaugh, N.J. (2004). Partial least squares analysis of neuroimaging data:
791 applications and advances. *Neuroimage* 23 Suppl 1, S250-263.
- 792 McIntosh, A.R., Vakorin, V., Kovacevic, N., Wang, H., Diaconescu, A., and Protzner, A.B. (2013).
793 Spatiotemporal Dependency of Age-Related Changes in Brain Signal Variability. *Cereb Cortex*
794 2014 Jul;24(7):1806-17.
- 795 Meunier, D., Achard, S., Morcom, A., and Bullmore, E. (2009). Age-related changes in modular
796 organization of human brain functional networks. *Neuroimage* 44, 715-723.
- 797 Mizuno, T., Takahashi, T., Cho, R.Y., Kikuchi, M., Murata, T., Takahashi, K., and Wada, Y. (2010).
798 Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy.
799 *Clin Neurophysiol* 121, 1438-1446.
- 800 Morrison, J.H., and Hof, P.R. (1997). Life and death of neurons in the aging brain. *Science* 278, 412-
801 419.
- 802 Mueller, V., Brehmer, Y., Von Oertzen, T., Li, S.C., and Lindenberger, U. (2008). Electrophysiological

- 803 correlates of selective attention: a lifespan comparison. *BMC Neurosci* 9, 18.
- 804 Müller, V., Gruber, W., Klimesch, W., and Lindenberger, U. (2009). Lifespan differences in cortical
805 dynamics of auditory perception. *Dev Sci* 12, 839-853.
- 806 Müller, V., and Lindenberger, U. (2012). Lifespan differences in nonlinear dynamics during rest and
807 auditory oddball performance. *Dev Sci* 15, 540-556.
- 808 Nakagawa, T.T., Jirsa, V.K., Spiegler, A., McIntosh, A.R., and Deco, G. (2013). Bottom up modeling of
809 the connectome: linking structure and function in the resting brain and their changes in
810 aging. *Neuroimage* 80, 318-329.
- 811 Nikulin, V.V., and Brismar, T. (2004). Comment on "Multiscale entropy analysis of complex
812 physiologic time series". *Phys Rev Lett* 92, 089803.
- 813 Ornstein, D.S., and Weiss, B. (1991). Statistical Properties of Chaotic Systems. *Bull. Amer Math Soc*
814 24, 11-116.
- 815 Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., and Smith, M.R. (2004). Aging reduces neural
816 specialization in ventral visual cortex. *Proc Natl Acad Sci U S A* 101, 13091-13095.
- 817 Park, D.C., and Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding.
818 *Annu Rev Psychol* 60, 173-196.
- 819 Peng, C.K., Buldyrev, S.V., Havlin, S., Simons, M., Stanley, H.E., and Goldberger, A.L. (1994). Mosaic
820 Organization of DNA Nucleotides. *Phys Rev E* 49, 1685-1689.
- 821 Pierce, T.W., Kelly, S.P., Watson, T.D., Replogle, D., King, J.S., and Pribram, K.H. (2000). Age
822 differences in dynamic measures of EEG. *Brain Topogr* 13, 127-134.
- 823 Pierce, T.W., Watson, T.D., King, J.S., Kelly, S.P., and Pribram, K.H. (2003). Age differences in factor
824 analysis of EEG. *Brain Topogr* 16, 19-27.
- 825 Pincus, S.M. (1991). Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci USA*
826 88, 2297-2301.
- 827 Reuter-Lorenz, P.A., Jonides, J., Smith, E.E., Hartley, A., Miller, A., Marshuetz, C., and Koeppel, R.A.
828 (2000). Age differences in the frontal lateralization of verbal and spatial working memory
829 revealed by PET. *J Cogn Neurosci* 12, 174-187.
- 830 Richman, J.S., and Moorman, J.R. (2000). Physiological time-series analysis using approximate
831 entropy and sample entropy. *Am J Physiol Heart Circ Physiol* 278, H2039-H2049.
- 832 Schaefer, S., and Schumacher, V. (2010). The interplay between cognitive and motor functioning in
833 healthy older adults: findings from dual-task studies and suggestions for intervention.
834 *Gerontology* 57, 239-246.
- 835 Schäfer, S., Huxhold, O., and Lindenberger, U. (2006). Healthy mind in healthy body? A review of
836 sensorimotor-cognitive interdependencies in old age. *Eur Rev Aging Phys Act* 3, 45-54.
- 837 Sleimen-Malkoun, R., Temprado, J.J., and Hong, S.L. (2014). Aging induced loss of complexity and
838 dedifferentiation: consequences for coordination dynamics within and between brain,
839 muscular and behavioral levels. *Front Aging Neurosci* 6, 140.
- 840 Slifkin, A.B., and Newell, K.M. (1999). Noise, information transmission, and force variability. *J Exp*
841 *Psychol Hum Percept Perform* 25, 837-851.
- 842 Smith, R.X., Yan, L., and Wang, D.J. (2014). Multiple time scale complexity analysis of resting state
843 fMRI. *Brain Imaging Behav* 8, 284-291.
- 844 Sokunbi, M.O. (2014). Sample entropy reveals high discriminative power between young and elderly
845 adults in short fMRI data sets. *Front Neuroinform* 8, 69.
- 846 Sullivan, E.V., Rohlfing, T., and Pfefferbaum, A. (2010). Quantitative fiber tracking of lateral and
847 interhemispheric white matter systems in normal aging: relations to timed performance.
848 *Neurobiol Aging* 31, 464-481.
- 849 Tononi, G., Edelman, G.M., and Sporns, O. (1998). Complexity and coherency: integrating information
850 in the brain. *Trends Cogn Sci* 2, 474-484.
- 851 Tononi, G., Sporns, O., and Edelman, G.M. (1994). A measure for brain complexity: relating functional
852 segregation and integration in the nervous system. *Proc Natl Acad Sci USA* 91, 5033-5037.
- 853 Vaillancourt, D.E., and Newell, K.M. (2002). Changing complexity in human behavior and physiology
854 through aging and disease. *Neurobiol Aging* 23, 1-11.

- 855 Vaillancourt, D.E., and Newell, K.M. (2003). Aging and the time and frequency structure of force
856 output variability. *J Appl Physiol* 94, 903-912.
- 857 Vakorin, V.A., Lippe, S., and McIntosh, A.R. (2011). Variability of brain signals processed locally
858 transforms into higher connectivity with brain development. *J Neurosci* 31, 6405-6413.
- 859 Vigário, R.N. (1997). Extraction of ocular artefacts from EEG using independent component analysis.
860 *Electroencephalogr. Clin. Neurophysiol.*, 395-404.
- 861 Wickelgren, I. (1996). For the cortex, neuron loss may be less than thought. *Science* 273, 48-50.
- 862 Yang, A.C., Huang, C.C., Yeh, H.L., Liu, M.E., Hong, C.J., Tu, P.C., Chen, J.F., Huang, N.E., Peng, C.K., Lin,
863 C.P., and Tsai, S.J. (2013). Complexity of spontaneous BOLD activity in default mode network
864 is correlated with cognitive function in normal male elderly: a multiscale entropy analysis.
865 *Neurobiol Aging* 34, 428-438.

866 **Legends**

867 **Figure 1. EEG time series and power spectra of randomly chosen data segments.** Time series (left column) and
 868 power spectra (right column) of randomly chosen data segments for channel Cz of two participants, one young
 869 and one old, are shown. Resting state 'R' condition is presented in blueish colors, and oddball counting 'OC'
 870 in reddish colors. From top to bottom, the two conditions for the young participant, and then similarly for the
 871 old one. The corresponding *DoF* is reported with each power spectrum. A peak close to 10 Hz is apparent in all
 872 cases but for the 'OC' condition of the old participant.

873 **Figure 2. Multiscale metrics of randomly chosen data segments.** The multiscale metrics of the same data
 874 segments of *Figure 1* are shown, the metrics being arranged from top to bottom ('*ln(V)*' and '*ln(F)*' – also
 875 depicting the value of '*H*' – in logarithmic scale, then, '*SD*', '*MSE*' (solid line) and '*MLZ*' (dotted line) and, finally,
 876 '*MSEn*' (solid line) and '*MLZn*' (dotted line), in linear scale), and data segments arranged from left to right
 877 column, in the same colors as in *Figure 1*. The frequency peaks close to 10 Hz correspond to local minima of
 878 '*ln(V)*' at the time scale of 100 ms. The peaks of MSE and MLZ, as well as the first peaks of the '*ln(V)*', close to
 879 the time scale of 40 ms, are related to the fact that most of the power of the signals lies below 50 Hz.
 880 Accordingly, the instances where '*ln(V)*' reduces again after the time scale of 148 ms correspond to additional
 881 power peaks in the low theta and delta frequencies. However, in general, there is no straightforward
 882 relationship between frequencies of the power spectra and time-scales of the metrics that undergo either
 883 detrending ('*ln(F)*' of *DFA*) or coarse graining ('*SD*', '*MSE*', '*MLZ*', '*MSEn*', and '*MLZn*').

884 **Figure 3. Group means and standard error intervals of the metrics of the variability magnitude across**
 885 **conditions.** From top to bottom: *power spectra (P)*, logarithmic plots of *variograms (ln(V))*, *standard deviation*
 886 *(SD)*, and logarithmic plots of *detrended fluctuations (ln(F))* are shown for channel Cz, for all conditions ('R' –
 887 bluish colors, 'OnC' –greenish colors, and 'OC' –reddish colors, from left to right columns), with darker colors
 888 for old participants (lighter for young). Thick lines and areas of faded colors represent the means and the
 889 standard error intervals, respectively. Horizontal axes depict frequency for *P*, and time-scale logarithmically for
 890 *ln(F)* and *ln(V)*, and linearly for *SD*. Please note the group differences, which are similar (but not identical)
 891 among conditions. The magnitude of variability is generally higher for young participants than old participants
 892 across scales, particularly so for longer time scales and lower frequencies (except for a small interval around 8
 893 Hz).

894 **Figure 4. Group means and standard error intervals of the metrics of the of variability structure across**
 895 **conditions.** From top to bottom: *degrees of freedom (DoF)*, *generalized Hurst exponent (H)*, *multiscale sample*
 896 *entropy (MSE)*, *normalized multiscale entropy (MSEn)*, *multiscale Lempel-Ziv entropy (MLZ)*, and *normalized*
 897 *multiscale Lempel-Ziv entropy (MLZn)* for all conditions. The arrangement of columns, as well as the color and
 898 line conventions, are similar to *Figure 1*, except for *DoF* and *H*, where error bars are used to depict the standard
 899 error intervals. For *DoF* and *H*, all channels are shown along the horizontal axis (from frontal to occipital and
 900 left to right hemisphere ones), whereas channel Cz is shown for the rest of the metrics. Thus, the horizontal
 901 axes for those metrics depict time-scale in a linear scale. Please note the group differences, which are similar
 902 (but not identical) among conditions. In particular, *DoF* are more and *H* is lower for the old participants than
 903 the young participants across all channels, *MSE* and *MLZ* are higher for old participants for short time-scales,
 904 below 24 and 20 ms, respectively, and the inverse for longer scales. *MSEn* and *MLZn* are also higher for old
 905 participants for scales below 32 ms, but the effect for longer time-scales is weaker.

906 **Figure 5. Task latent variables for the group main effect.** Each panel shows the weights of the *task latent*
 907 *variables* of the contrast that corresponds to the group main effect 'Y'-'O'. Each bar corresponds to a group-
 908 condition combination, with groups being arranged in increasing age from left to right, and conditions arranged
 909 in an order of increasing attention and/or task demands (i.e., from 'R' to 'OC'), also from left to right. Color
 910 conventions are identical to previous figures. The name of each metric together with the corresponding *p*-value
 911 (as derived from the parametric test for significance) and the singular value *s* of the SVD (proportional to the

912 variance explained by the contrast) are shown on top of the respective panel. Non-overlapping confidence
 913 intervals signify that conditions and/or groups are separated reliably by the contrast. Thus, the contrast is
 914 significant and reliably separates the two groups.

915 **Figure 6. Brain latent variables for the group main effect of the magnitude of variability metrics.** The panels
 916 show how much each data *element*, i.e., a metric's data point, covaries with the contrast that corresponds to
 917 the group main effect (see *Figure 3*), in terms of bootstrap ratios, from left to right: $\ln(V)$, SD , and $\ln(F)$.
 918 Absolute values larger than 2.5758 approximate the 99th two-tailed percentile. The vertical axis for all panels
 919 depicts channels arranged from top to bottom, starting from frontal and left hemisphere channels, to occipital
 920 and right hemisphere ones. The horizontal axes depict frequency for P and time-scale in a logarithmic scale for
 921 $\ln(V)$ and $\ln(F)$, and in a linear one for SD . Since the contrast is 'Y'-'O', positive values in reddish colors signify
 922 points where young (old) participants had higher values, and the inverse for negative/bluish values. All metrics
 923 are higher for young participants: P for frequencies below 12 Hz with the exception of a short band around 8
 924 Hz, $\ln(F)$ for time-scales longer than 20-32 ms, $\ln(V)$ for almost all time-scales, and SD for all time-scales. In
 925 general, the effect is statistically stronger for parieto-occipital channels, and for longer time-scales and lower
 926 frequencies.

927 **Figure 7. Brain latent variables for groups' main effect for DoF and H.** The two panels depict the bootstrap
 928 ratios of the group main effect for DoF and H (left and right, respectively) across a whole brain with the nose at
 929 the top. Interpretations are the same as in *Figure 4*. The old participants showed reliably more DoF and lower H
 930 for (almost) all channels than the young participants.

931 **Figure 8. Brain latent variables for groups' main effect of metrics of the structure of variability.** The panels
 932 depict the bootstrap ratios of the group main effect for MSE , $MSEn$, MLZ and $MLZn$, from left to right.
 933 Interpretations, vertical axes and color conventions are the same as in *Figure 4*. The horizontal axes depict
 934 time-scale in a linear scale. All metrics are higher for old participants below some scale (approximately 24, 32,
 935 20, and 36 ms, respectively); this effect is statistically stronger for parieto-occipital channels. Above these
 936 scales MSE and MLZ are higher for young participants than for the old participants up to at least the scale of
 937 80ms. This effect is marginally reliable for $MSEn$ and $MLZn$ and stronger for fronto-central channels.

938 **Figure 9. Task latent variables for condition main effect.** This figure has an identical arrangement and
 939 conventions as *Figure 3* (DoF and H are omitted because they were not significant). This latent variable
 940 contrasts 'R' versus 'OdC' with 'OnC' being in the middle, i.e., it arranges conditions in an order of increasing
 941 attention and/or task demands. It is significant for almost all metrics with a $p < 0.001$, except for $MSEn$ and
 942 $MLZn$ that have slightly higher values ($p = 0.002$ and $p = 0.005$, respectively), whereas MLZ is significant only to
 943 a value of $p = 0.069$. However, confidence intervals are largely overlapping, i.e., conditions are not separated
 944 reliably, except for the entropic measures (MSE , $MSEn$, MLZ , and $MLZn$), where 'R' is generally separated
 945 reliably from the task conditions, mainly so for young participants.

946 **Figure 10. Brain latent variables for the condition main effect of the variability magnitude metrics.** The panels
 947 depict the bootstrap ratios of the condition main effect for P , $\ln(V)$, SD , and $\ln(F)$, from left to right.
 948 Interpretations, axes and color conventions are the same as in *Figure 4*, only now positive (negative) values in
 949 reddish (bluish) colors signify values that were higher for condition 'R' ('OC'). $\ln(V)$, and $\ln(F)$ where generally
 950 higher for the resting condition across all scales and channels, but mainly so for parieto-occipital channels. SD
 951 was higher also for 'R' for shorter time scales up to 100 ms, also mainly for posterior channels. Regarding P , 'R'
 952 had more power in the 5-10 Hz and 15-30 Hz frequency intervals, whereas 'OC' had more power in the delta
 953 band, mainly so for fronto-central channels. Notice that P has almost an inverse pattern with the groups' main
 954 effect in *Figure 4*.

955 **Figure 11. Brain latent variables for conditions' main effect for the structure of variability metrics.** The panels
 956 depict the bootstrap ratios of the condition main effect for MSE , $MSEn$, MLZ and $MLZn$ from left to right.

957 Interpretations, axes and color conventions are the same as in *Figure 6*, only now positive values in reddish
958 colors signify values that were higher for condition 'R' ('OC'), and the inverse for negative (bluish) values. All
959 metrics are higher for 'Rest' below some scale (approximately 48, 56, 36, and 56 ms, respectively) for fronto-
960 central channels. *MSE* is higher for 'OC' for scales above 48 ms for all channels, as well, whereas *MSEn* and
961 *MLZn* showed a statistically weaker tendency to be higher for 'R' for scales further than the points mentioned
962 above and for almost all channels. Notice that the pattern of the results is to a large degree inverse to the
963 results of the group main effect, mainly so for *MSE* and for short scales.

964

965 **Tables**

966 **Table I.** Mean, standard deviation, minimum and maximum numbers of EEG segments per group and
 967 condition included in the analysis

		Mean	SD	Min	Max
	<i>Rest</i>	7.8	0.6	5	8
<i>Young</i>	<i>OnC</i>	23.9	2.0	15	25
	<i>OC</i>	23.0	3.1	11	25
<i>Old</i>	<i>Rest</i>	7.4	1.1	4	8
	<i>OnC</i>	22.3	3.4	12	25
	<i>OC</i>	21.6	3.1	15	25

968

969 **Table II.** Statistical table

Effect	Metric	Data Structure	Type of test	Confidence intervals
Group main effect	<i>P</i>	empirical	<i>permutation</i>	[-0.0008, 0.0046]
			<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 6 for the Brain LV bootstrap ratios
	<i>ln(V)</i>		<i>permutation</i>	[-0.0008, 0.0046]
			<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 6 for the Brain LV bootstrap ratios
	<i>SD</i>		<i>permutation</i>	[-0.0008, 0.0046]
			<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 6 for the Brain LV bootstrap ratios
	<i>ln(F)</i>		<i>permutation</i>	[-0.0008, 0.0046]
			<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 6 for the Brain LV bootstrap ratios
	<i>DoF</i>		<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 7 for the Brain LV bootstrap ratios
	<i>H</i>		<i>permutation</i>	[-0.0008, 0.0046]

	MSE	<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 7 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[0.0000, 0.0078]	
	MSEn	<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 8 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	
	MLZ	<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 8 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	
	MLZn	<i>bootstrap</i>	see Figure 5 for Task LV confidence intervals and Figure 8 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	
	Condition main effect	P	<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 10 for the Brain LV bootstrap ratios
			<i>permutation</i>	[-0.0008, 0.0046]
n(V)		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 10 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	
SD		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 10 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	
ln(F)		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 10 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	
MSE		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 11 for the Brain LV bootstrap ratios	
		<i>permutation</i>	[-0.0008, 0.0046]	

	MSEn	<i>permutation</i>	[0.0000, 0.0078]
		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 11 for the Brain LV bootstrap ratios
	MLZ	<i>permutation</i>	[0.0548, 0.0865]
		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 11 for the Brain LV bootstrap ratios
	MLZn	<i>permutation</i>	[0.0018, 0.0120]
		<i>bootstrap</i>	see Figure 9 for Task LV confidence intervals and Figure 11 for the Brain LV bootstrap ratios

970

971





















