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Endogenous multifractal brain dynamics are modulated by age, cholinergic blockade and cognitive performance

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Abstract

The intuitive notion that a healthy organism is characterised by regular, mechanistic function has been challenged by observations that a loss complexity is, in fact, indicative of ill-health. Monofractals succinctly describe complex processes, and are controlled by a single time-invariant scaling exponent, H , simply related to the fractal dimension. A previous analysis of resting fMRI time-series demonstrated that ageing and scopolamine administration were both associated with increases in H and that faster response in a prior encoding task was also associated with increased H . We revisit this experiment with a novel regional, multifractal approach in which fractal dynamics are assumed non-stationary and defined by a spectrum of local singularity exponents. Parameterisation of this spectrum was capable of refracting the effects of age, scopolamine and task performance as well as a refining a description of the associated signal changes. Using the same imaging data, we also explored turbulence as a possible mechanism underlying multifractal dynamics. Evidence is provided that Carstang's model of turbulent information flow from high to low scales has only limited validity, and that invariance of energy dissipation is better explained by critical-phase phenomena, supporting the proposition that the brain maintains a state of self-organised criticality.

Keywords

fractal; multifractal; ageing; scopolamine; recognition; self-organised; critical phase

1. Introduction

Fractals - signals that display scale-invariant or self-similar behaviour - are ubiquitous in nature and result from a wide variety of physical processes, including diffusion, erosion, turbulence and criticality. The traditional view that the healthy state of an organism is represented by homeostatic, regular, steady-state behaviour has been challenged by the observation that many physiological signals are, in fact, non-linear, inhomogeneous and fractal (Ivanov et al, 1999;

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Goldberger et al, 2002). From this viewpoint, healthy function is regarded as the capacity to adapt to a wide variety of exogenous or endogenous stimuli, which is compatible with chaotic physiological dynamics. In contrast, the emergence of simpler dynamics, such as white noise or a purely periodic oscillation, can be seen as a degradation of fractal complexity and an indication of ill-health or maladaptivity (Ivanov et al, 2001).

Fractals are quantified by decomposing a signal into a hierarchy of temporal or spatial scales: from a coarse-scale representation of long-term variations through to high-frequency fluctuations at fine scales. The high and low frequency limits of the scale range are determined ultimately by the resolution of the measuring device and the total length of the time series, respectively. If the property of interest, e.g., the spectral density of a time series at a particular frequency, shows a simple relationship to change of scale, e.g., the spectral density is related to frequency by a power law, then the process is said to be a *monofractal*. The appearance of monofractal signals may well be irregular and include a number of singularities (points at which it is non-differentiable). However, the properties of these singularities are constant in time and the entire process can be adequately characterised by a single scaling exponent, the Hurst exponent, H , which is simply related to the fractal dimension or the spectral exponent of the process (Schroeder, 1991).

Although monofractal analysis of physiological signals has yielded a number of interesting observations in health and disease (Bullmore et al, 2004; Beckers et al, 2006), it has become clear that a fuller description of physiological dynamics is required to better capture their inhomogeneity and non-stationarity (Goldberger et al, 2002). For example, we can allow that the scaling behaviour of the process will not be governed by a single, stationary parameter but instead by a number of local scaling exponents. Such a *multifractal* signal is characterised by the histogram of Hölder exponents h , known as the singularity spectrum (Muzy et al, 1991; Muzy et al 1993; Turiel et al 2006), that generally spans $0 < h < 1.5$. Values of the spectrum $h < 0.5$ correspond to anti-persistent or negatively correlated behaviour and $h > 0.5$ to persistent or positively correlated behaviour. Singularity spectra with non-zero widths, indicative of multifractal dynamics, have been measured in electrocardiographic (ECG) signals (Ivanov et al, 1999, 2001; Chiu et al, 2007; Wang et al, 2007; Pavlov et al, 2005), human gait recordings (West and Latka, 2005), electroencephalographic (EEG) signals (Song et al, 2005), and functional magnetic resonance imaging (fMRI) time series (Shimizu et al, 2004). Studies of multifractal properties of ECG signals especially have shown that the maximum (peak) value and width of the singularity spectrum are affected by disease (cardiac failure) and ageing, confirming that these parameters are sensitive to dynamic departures from health.

Turbulent energy transfer is a well-known physical process that results in multifractal dynamics (Arneodo et al, 1996; Chevillard et al, 2006). In fully-developed turbulent flow, kinetic energy injected into a liquid via a stirrer, for example, generates vortices at scales similar to that of the stirrer. The generation of smaller vortices from a cascade of the energy occurs increasingly rapidly as scale decreases, until energy is ultimately dissipated at the molecular level through viscous interactions. The local velocity differences measured during turbulent flow have magnitude and directional changes that are non-differentiable (i.e. singular) over a range of temporal scales. Criticality, or the state of a system close to a phase transition, is another physical phenomenon that has been associated with multifractal dynamics. For example, multifractal signals are observed in the flow of information through a computational network as the volume of traffic approaches the critical point of transition to a congested state (Li and Shang, 2005; Takayasu et al, 2000). Empirical evidence to suggest the preferential adoption of either mechanism as an explanatory model for neuroimaging data would be beneficial for interpretation at a systems level.

In this article we revisit functional MRI datasets that we have previously analysed using a wavelet-based algorithm that assumed the endogenous brain dynamics were monofractal and could be appropriately summarised by the Hurst exponent (Wink et al, 2006; Wink et al 2008). On this basis, we reported that healthy ageing and cholinergic receptor blockade by scopolamine were both associated with significant increase in H , implying that increased H might be a marker of suboptimal neurophysiological dynamics (Wink et al, 2006). However, we also reported that faster processing speed in a fame decision/facial encoding task was associated with increased H , implying that increased H might be associated with faster cognitive performance (Wink et al, 2008). To investigate this apparent discrepancy we here apply multifractal analysis to time series extracted from brain regions demonstrating these various effects on the Hurst exponent to address the question: are there subtle differences in the dynamics associated with ageing, scopolamine and faster cognitive processing that are better differentiated by a multifractal analysis than by monofractal analysis? Additionally we investigate turbulence as one possible physical mechanism for multifractal dynamics and ask the question: is there evidence for turbulence in endogenous brain dynamics measured using fMRI?

2. Methods

2.1 Study sample

Twenty-three, right-handed, healthy participants took part in the study. Data from one participant was omitted due to a scanner malfunction leaving 22 participants for analysis: 11 young (6 female, 5 male; mean age = 22.4 years, range = 20-25 years), 11 older (6 female, 5 male; mean age = 65.3 years, range = 60-70 years). The groups were matched for education ($t = 1.48$, $df = 20$, $p = 0.15$). All participants had a normal clinical examination to exclude any medical, neurological, or psychiatric disorder, or any contraindication to MRI.

In order to exclude possible non-clinical dementia cases in the older group, older participants were screened using the mini-mental state examination (MMSE; maximum score = 30): mean = 29.6, range 29-30. Additionally all participants were screened radiologically for brain structural lesions. Within the older group, one participant was currently medicated with thyroxine and one participant was undergoing hormone replacement therapy.

All participants gave informed consent in writing. The protocol was approved by the Addenbrooke's NHS Trust Local Research Ethics Committee.

2.2 Study design

We used a randomized, double blind, placebo-controlled design. Participants were scanned using functional MRI in two separate sessions scheduled at least 1 week apart. Sixty minutes before each fMRI session, participants received one of two treatments: (1) scopolamine hydrochloride 0.3 mg (0.75 ml) subcutaneously; or (2) saline placebo (0.75 ml) subcutaneously. The order of treatments was counterbalanced across participants. A more detailed description is given in Wink et al (2006).

2.3 Session design

During each session there were four sets of fMRI data acquisition: (1) during a fame decision/facial encoding task (8 minutes 15 seconds); (2) during a serial reaction time task (9 minutes 44 seconds); (3) during two recognition tasks (one with famous faces, the other with non-famous faces; total of 16 minutes and 30 seconds); (4) whilst participants lay quietly at rest (9 minutes and 36 seconds). The order of the four acquisitions was maintained across participants, although the order of famous and non-famous face presentations during the recognition task

was counterbalanced. Tasks were separated by a few minutes in order to make preparations for the next acquisition.

2.3.1 Fame decision/facial encoding task—The stimuli for the episodic memory task consisted of viewing 40 famous faces, 40 unfamiliar faces and 40 fixation crosses in a randomised order with each presented for 4 seconds. Participants were instructed to press one of two response buttons to indicate whether a face was famous or not, as well as at the presentation of each fixation cross (either button). Participants were also instructed to try to encode the faces so that they would recognize them in a subsequent recognition task. Due to technical failure, data from two participants (one from the young group and one from the older group) were unavailable, leaving 20 participants used in the subsequent analysis involving this paradigm.

2.3.2 Resting acquisition—During data acquisition participants were instructed to lie quietly with their eyes closed.

2.4 FMRI data acquisition

Data depicting BOLD contrast were acquired using a Bruker Medspec scanner (Ettlingen, Germany) operating at 3T in the Wolfson Brain Imaging Centre, Cambridge UK. For each echo-planar imaging (EPI) acquisition 21 slices of data parallel to the intercommissural (AC-PC) line were specified with the following parameters: TE = 30 ms, TR = 1100 ms, flip angle = 65°, slice thickness = 4 mm plus 1 mm interslice gap, in-plane resolution = 3.75 mm.

During the fame decision/facial encoding task 450 EPI data volumes were acquired, the first 6 of which were discarded leaving 444 volumes for analysis. During the resting state acquisition 524 volumes were acquired of which the first 12 were discarded.

2.5 FMRI data analysis

2.5.1 Analysis of the fame decision/facial encoding task—Following temporal and spatial motion correction of the imaging data, regression analysis modeled the contrast of famous and non-famous decision trials against cross-hair fixation trials, whilst participants were under the explicit instruction to encode the faces for later recall. Group median responses were statistically tested in the standard anatomical space of the Montreal Neurological Institute (MNI) against the two-tailed null-hypothesis of no stimulus related activation based on permutation of the original time-series that preserves their spectral properties (Bullmore et al, 2001). Probabilistic thresholding was performed at a three-dimensional cluster level at a threshold such that the expected number of false positive tests was less than one. Full details of the methodology are given elsewhere (Bullmore et al, 1999; Suckling et al, 2006).

2.5.2 Estimation of H from resting state acquisition—Following temporal and spatial motion correction, maps of H in acquisition space for each individual were estimated by maximum likelihood in the wavelet domain (Maxim et al, 2005) and registered into MNI standard space with an affine spatial transformation.

2.5.3 Relationship between H and fame decision/facial encoding task reaction time—To identify regions that showed a significant relationship between H and the mean reaction time of all correct decision tasks, a between-subjects linear model was regressed at each intracerebral voxel in standard space using subject data under the placebo condition only. The observed regression coefficient, normalized by its standard error, was tested for significance against a two-tailed null-distribution generated following permutation of the reaction times across participants to simulate conditions under the null-hypothesis of no linear relationship. In the same way as the analysis of group median activation during the fame

decision/facial encoding task, significant effects were identified at the cluster-level (Bullmore et al, 1999). Again, the cluster-wise threshold for significance was such that the expected number of false positive tests was less than one across the entire volume.

2.5.4 Two-way ANOVA of H—A mixed effects analysis of variance (ANOVA) model, with age as the between-subject factor and drug as the within-subject factor was estimated with the 22 estimates of H at each voxel as the dependent variable; statistical significance of the main effects and interaction was tested by a permutation test on local voxel clusters of large F statistics (Wink et al, 2006; Suckling and Bullmore, 2004). The threshold for cluster-level significance was set such that we expect less than one false positive test.

2.5.5 Calculation of the regional singularity spectrum—The formalism for multifractals has its origins in the work of Kolmogorov (1941) on fluid turbulence, but has been successful in accounting for a wide range of phenomena with varying underlying physical processes (Mandelbrot, 1982). In fully developed three-dimensional turbulence the energy cascade from large to small scales occurs in the inertial range. Over these spatial scales the q -order moments of the mean velocity changes between two points a distance r apart, $\langle |\Delta v(r)|^q \rangle = \langle |v(x+r) - v(x)|^q \rangle$, and the energy dissipation averaged over a sphere of radius r , $\langle \varepsilon(r) \rangle$, both have a power law dependence on r ; that is, $\langle |\Delta v(r)|^q \rangle \propto r^{\rho(q)}$ and $\langle \varepsilon(r) \rangle \propto r^{\tau(q)}$, where $\rho(q)$ and $\tau(q)$ are the velocity and the energy dissipation scaling exponents respectively.

The dependence in r of the q -order moment is given by the power-law: $\langle \varepsilon(r)^q \rangle \propto r^{\tau(q)}$. $\tau(q)$ is a non-linear function of q and thus the exponent of the scaling law is restricted to a given locality in time:

$$\varepsilon_r(x) \propto r^{h(x)} \quad \text{as } r \rightarrow 0 \quad (1)$$

where the exponent, $h(x) \equiv h$, is also known as the singularity or Hölder exponent.

A partition function describes the energy (information) of a system at each of its states (scales) and is important for deducing the macroscopic properties of the system. The information contained within a signal is completely and efficiently represented by the set of lines - the skeleton - where the modulus of the wavelet transform of the signal is locally a maximum (Muzy et al, 1991; Turiel et al, 2006). Formally, the partition function, $Z(r, q)$ of order q is:

$$Z(r, q) \equiv \sum_{\{x(r)\}} |T_g(r, x_i(r))|^{qr^{\tau(q)}} \quad (2)$$

where $T_g(r, x_i(r))$ is the convolution of the original signal with the wavelet basis function g dilated to scale r , and $\{x_i(r)\}$ are the set of modulus maxima of the wavelet transform. Note that the skeleton formed by the maxima is connected across scale space in terms of its nearest neighbours, with unconnected lines deleted (Goldberger et al, 2000; Turiel et al, 2006).

Operationally, the continuous wavelet transform of a BOLD time-series was computed using the Gaussian derivative as the basis function from which the modulus maxima skeleton of the signal was calculated. For given q , the exponent $\tau(q)$ is the slope of the line regressed onto the log-log plot of the partition function and scale, r (Eqn. 2). Averaging the values of $\tau(q)$ across all voxels of a region-of-interest yields the regional relationship between q and $\tau(q)$. Finally, the regional singularity spectrum, $D(h)$, was obtained via a Legendre transform:

$$D(h) = q \frac{d\tau(q)}{dq} - \tau(q) \quad (3)$$

Two parameters were derived from this distribution: the value of h at which the distribution is a maximum, h_{max} , and the negative and positive half-width at half-height, W_- and W_+ .

respectively (Wink et al, 2008). Regional mean values: $\bar{h}_{\max}$, $\bar{W}_-$ and $\bar{W}_+$, were subsequently calculated for each participant.

These values were entered as the dependent variables into multivariate general linear models that paralleled the image-based analysis described above. Namely, with task reaction time as the independent variable and as a two-way repeated-measures factorial design with main effects of age and drug.

2.5.6 Regional probability density functions for cascade models—Experimentally, as r approaches the larger scales, where energy is injected into the system, the probability density function (PDF) of $\Delta v(r)$ is Gaussian, while in the inertial range, intermittent large fluctuations lead to a non-Gaussian PDF with heavy-tails (Naert et al, 1994).

The theoretical model of the PDF of $\Delta v(r)$ (Castaing et al, 1990) makes the distinction between two levels of fluctuations. First, for a fixed value of $\varepsilon(r)$ the PDF for $\Delta v(r)$ is a Gaussian, determined by its variance σ . Second, the fluctuations of $\varepsilon(r)$ are postulated as having a log-normal distribution determined by λ , the variance of $\ln \sigma$. The distribution of $\Delta v(r)$ is then:

$$P(\Delta v(r)) = \frac{1}{2\pi\lambda} \int \frac{1}{\sigma^2} \exp\left(-\frac{\Delta v(r)^2}{2\sigma^2}\right) \exp\left(-\frac{\ln^2 \sigma}{2\lambda^2}\right) d\sigma \quad (4)$$

Empirical PDFs of the differences in BOLD signal (analogous to $\Delta v(r)$) at *temporal* distances $r = 2, 4, 8, 16, 32, 48, 64$ and 80 time-points were obtained from mean zero and unit variance voxelwise time-series constituting the regions identified as significant through a univariate test of H , as described above. The theoretical PDF (Eqn. 4) was then regressed onto the data to using Simpson's rule for the integration over σ and a Golden Search to obtain the value of λ^2 corresponding to a least-squares minimum between data and model (Fig. 1).

If the underlying process is turbulent information flow then the relationship between $\ln \lambda^2$ and $\ln r$ will be linear. Alternatively, scale invariance of λ^2 is associated with critical phase phenomena (Mehta et al, 2002).

3. Results

3.1 Fame decision/ facial encoding task analysis

Under the placebo condition, the overall accuracy for correct recognition of famous faces was 0.79 +/- 0.16 with mean reaction time 1.091 +/- 0.220 seconds, and for correctly rejecting non-famous faces accuracy was 0.94 +/- 0.07 with mean reaction time for these events of 1.228 +/- 0.211 seconds. Participants were significantly more accurate with non-famous than famous decisions ($t(df = 19) = 2.586, p = 0.018$), and reaction times were significantly faster for famous than non-famous decisions ($t(df = 19) = 3.500, p = 0.002$). Reaction time and accuracy were correlated for both famous ($R = -0.689, p = 0.001$) and non-famous ($R = -0.439, p = 0.050$). A regression of age on reaction time was not significant ($F(1,19) = 1.434, p = 0.247$).

Activated regions from a comparison of face trials > cross-hair fixation are shown in Fig. 2b as yellow regions. The regions identified included bilateral cerebellum, bilateral visual cortex, hippocampus, fusiform and lingual gyri, as well as right inferior and middle frontal gyrus located at MNI standard space coordinates: $x = -40\text{mm}$, $y = +22\text{mm}$, $z = +2\text{mm}$. Regions of deactivation (face trials < cross-hair fixation) are displayed in blue on Fig. 2b and describe a pattern consistent with the default mode network (Grecius et al, 2003; Gusnard and Raichle, 2001) including anterior and posterior cingulate cortex and large areas of parietal lobe.

A focal region in the right middle and inferior frontal gyrus (located at MNI standard space coordinates: $x = -42\text{mm}$, $y = +22\text{mm}$, $z = -10\text{mm}$ and including the right inferior frontal

(triangular part); Fig. 2a) demonstrated a significant linear relationship of H , calculated from resting state time-series, and the mean reaction time across all famous and non-famous decisions in the fame decision/facial encoding task. This region and the regions of task activation (Fig. 2b) are very similar to those reported previously using half this sample; that is, young subjects only (Wink et al, 2008).

The results from the two-way analysis of variance of H are described in detail in Wink et al (2006) and shown in Fig. 3. In summary, there was a significant main effect of age in bilateral medial temporal lobe structures, including hippocampus, amygdala and parahippocampal gyrus. In all these regions, H was increased in older participants. There was a significant main effect of drug on H in right medial temporal lobe structures including hippocampus, amygdala and parahippocampal gyrus. In these regions, H was increased by scopolamine compared to placebo.

3.2 Can multifractal analysis further differentiate effects of ageing, scopolamine and faster cognitive performance on fMRI dynamics?

Within the single region of significant linear relationship between H calculated from the resting acquisition and fame decision reaction time, univariate regression analysis was non-significant for each parameter derived from the regional singularity spectrum (Table 1), and non-significant for the multivariate test ($F(1,18) = 1.738$, $p = 0.204$).

Two regions of significant main effect of age on resting acquisition H were identified in the left- and right- hemispheres of the neocortex. Within the left-hemispheric region the multivariate GLM was significant: $F(19,2) = 3.785$, $p = 0.041$. The univariate test was significant for $\bar{h}_{\max}$ and $\bar{W}_{-}$ but not for $\bar{W}_{+}$ (Table 1). For the right-hemispheric region, the multivariate GLM was significant: $F(19,2) = 4.144$, $p = 0.032$. The univariate tests were significant for $\bar{h}_{\max}$ (larger for older participants), at trend for $\bar{W}_{-}$ (larger for older participants), but non-significant for $\bar{W}_{+}$ (Table 1). To illustrate graphically these differences, singularity spectra for participants with the highest and lowest values of H are shown in Fig. 4a and boxplots of the regional means for each of the parameters in Fig. 5a.

Within the single region of significant main effect of drug on resting acquisition H , the multivariate GLM was significant: $F(19,2) = 5.384$, $p = 0.014$. Univariate tests were also significant for $\bar{h}_{\max}$, $\bar{W}_{-}$ and $\bar{W}_{+}$ (Table 1), with scopolamine generating larger values of these parameters in comparison to placebo. Singularity spectra for participants with the highest and lowest values of H are shown in Figs. 4b (right) and 4c (left) with boxplots for the regional mean parameters extracted from right (Fig. 5b) and left (Fig. 5c) regions of effect.

3.3 Are fMRI dynamics turbulent?

The behaviour of λ^2 estimated as a function of separation in time of the difference in BOLD measurements, r , is shown in Fig. 6 for each of the regions identified by the univariate analyses of H (Fig. 3). Decreasing values of λ^2 correspond to increasingly Gaussian-like distribution of the PDF. Relatively low values of λ^2 observed for small r , likely reflecting the white noise component of the signal. For $r > 8$, values of λ^2 are constant and of a similar magnitude across all regions, suggesting an underlying non-turbulent process. However, λ^2 is not correlated with H and is unable to distinguish the effects of ageing (Figs. 6a and 6b), scopolamine administration (Fig. 6c) or correlation with task performance (Fig. 6d).

4. Discussion

4.1 Can multifractal analysis further differentiate effects of ageing, scopolamine and faster cognitive performance on fMRI dynamics?

We have previously reported (Wink et al, 2006) that the Hurst exponent is a measure sensitive to both age and scopolamine administration. From that initial study the conclusion was drawn that the BOLD signal contains information on the dynamics of the brain that can be influenced by long-term trends (age) and short-term perturbations (psychoactive drug). However, the monofractal assumptions that lead to the calculation of H yield a measurement that is limited in its ability to fully characterize the dynamic responses to such physiological challenges.

The Holder exponent, h , at a given point in time represents contributions from the temporal hierarchy of singularities. High values of h correspond to those points at which the dominant contribution is from (slowly decaying) singularities at lower frequencies and vice versa. The parameterisation of the singularity spectra derived from fMRI time-series has been capable of refracting the effects of age and scopolamine that have previously demonstrated both a similar directional and magnitudinal change in H (Wink et al, 2006). Relative to placebo, scopolamine significantly increased both upper, $\bar{W}_+$, and lower, $\bar{W}_-$, ranges of the spectrum as well as positively shifting the location of the spectral maxima, $h_{\max}$ (Table 1, Figs. 4c and 5c). However, ageing did not significantly change $\bar{W}_+$, but increased both $\bar{W}_-$ (although the right medial temporal region only at trend levels) and $h_{\max}$ (Table 1, Figs. 4a and 4b, 5a and 5b).

Distinct from both these effects is the correlation seen between the mean reaction time during the fame decision/facial encoding task and H calculated from resting state data acquired some 30 minutes later (Fig. 2). For signals that are multifractal, the Hurst exponent measures the overall, 'average' behaviour of the singularities and is generally correlated with $h_{\max}$: main effect of drug, $R = 0.748$, $p < 10^{-6}$; main effect of age, $R = 0.700$, $p < 10^{-6}$ (right) and $R = 0.738$, $p < 10^{-6}$ (left); correlation with reaction time, $R = 0.851$, $p < 10^{-6}$. Nevertheless, the parameterisation of the singularity spectra adopted did not yield variables that demonstrated any significant relationship with reaction time.

The analysis introduced in this article has been able to resolve the apparently paradoxical situation in which increases in H were positively correlated with increased age and administration of an antimuscarinic agent known to reduce performance on memory tasks (Everitt and Robbins, 1997) in medial temporal regions, as well as faster reaction times for recognition of faces in inferior frontal regions. In fact, they each exert distinct influences on the neural networks that are active during unconstrained (resting) wakefulness, which are apparent in the spectral properties of the corresponding fMRI time-series. The description of scopolamine as a mimic of ageing effects (Wink et al, 2006) can now be refined; low frequency singularities are promoted by both factors and the distribution is generally shifted to positive values of h , in agreement with the increase in persistence observed by increases in H . However, rapidly decaying singularities appear unchanged by age, but are significantly increased by scopolamine.

Analysis of singularity spectra has been applied to a wide-variety of biological signals, although the overall literature is not extensive. Corroborative evidence for the effects observed in this fMRI study can be found in the multifractal analysis of electrocardiograms, which was able to distinguish between abnormal rhythms (Wang et al, 2007), disease and ageing (Goldberger et al, 2002; Ivanov et al, 2001; Ivanov et al, 1999). In particular, patients with severe heart failure demonstrated a loss of multifractality and a tendency for signals to be purely monofractal, yet ageing effects were in the opposite direction when compared with healthy young participants. In contrast to the report of cardiological disease states, singularity spectra calculated from

electroencephalographic (EEG) recordings were increased in width during epileptic seizures (Song et al, 2005). Drug effects also have had a measurable effect on cardiograms with the administration of beta-blockers to patients with congestive heart failure restoring the multifractal properties of the signal (Chiu et al, 2007) and normal controls where administration resulted in a loss of multifractality (Amaral et al, 2001).

4.2 Relationship of the resting state dynamics to task performance

We have previously reported on half this sample (younger participants only) that the Hurst exponent calculated from the resting state time-series was significantly correlated with reaction time of a fame decision/facial encoding task conducted during a separate acquisition some 30 minutes previously (Wink et al, 2008). We have confirmed this result with a larger sample, including the older participants (Fig. 2a). As previously, this result coincides as the region of the right inferior frontal gyrus identified is close in location and size to a region that is active during the task (Fig. 2b). The design of the experimental sessions does not permit us to draw any conclusions on causality; that is, whether H is modified by the task or if it is a regional signature that might predict performance. For this a specific experimental design would be required.

As far as we know this is there are no existing examples of a relationship between resting state and prior task performance. However, an increase in the width of singularity spectrum calculated from the texture extracted from the frontal region of anatomical T2-weighted MRI images was associated with older compared to younger healthy volunteers. Within the older group, the width of the spectrum from the same region was positively correlated with a reduction in executive performance. These results were not repeated in a parieto-occipital region (Takahashi et al, 2004). Whilst there are a number of differences between this experiment and that reported in this article in terms of cognitive task and the cohort involved, it illustrates the broad applicability of multifractals to characterise both temporal and spatial patterns, and specifically that a parameterisation of the singularity spectrum is related to task performance and ageing.

4.3 Evidence for a critical-phase model for brain function

From the time-series contained within the regions of significant change of H (Fig. 3) the PDF of differences of BOLD measurement are invariant to the temporal distance, r . This is evidence that a turbulent model of information flow from high to low scales has only limited validity, and the invariance of the energy dissipation over temporal distances, $r > 8$ time-points (that is, constant λ^2 above ~ 9 seconds of separation) is better explained by critical-phase phenomena in which competing or opposing 'forces' maintain the system in a dynamic equilibrium. Strong scale invariance is encountered in diverse circumstances, including the changing polarisation of magnetic domains in materials experiencing a continuously increasing external magnetic field (Mehta et al, 2002) and time-series of inter-beat intervals of the heart (Kiyono et al, 2004; Kiyono et al, 2006), which exhibit multifractal behaviour (Amaral et al, 2001).

Systems operating at a phase transition are metastable with respect to a set of control parameters, and capable of rapid qualitative change in response to external stimuli. Behavioural phase changes from syncopated to synchronised finger tapping in response to a tone of increasing frequency are matched by corresponding neurophysiological fluctuations (Kelso et al, 1992; Wallenstein et al, 1995). Moreover, these transitions occur over short and long spatial and temporal scales (Freeman, 2003) lending credence to the proposition that the brain is maintained in a state of self-organised criticality (Bak et al, 1987). Under these circumstances, the critical point of the system is not approached by the systematic tuning of a parameter, rather it is a minimally stable state reached irrespective of the initial conditions and to which it returns following a perturbation. Emergent properties of this type are also observed in

neurocomputational models where the number of long-range connections (axons) within a random network of cellular automata controls the robustness of the criticality to internal noise (Kozma et al, 2005). Whilst these models are incomplete in their description of the cortex, they draw interesting parallels with the scale-invariant, small-world topologies observed from resting state fMRI and MEG data (Achard et al, 2006; Achard et al, 2008). From these observations and the results presented in this study, self-organised criticality appears to offer a tractable association between the spatial and temporal behaviours of the brain.

4.4 Methodological issues

Calculating the singularity spectrum can be undertaken via a number of distinct algorithms. The wavelet transform maximum modulus method (Muzy et al, 1993) was chosen as it has been used in a number of previous studies that provide a precedent for the results reported in this article (Goldberger et al, 2001; Ivanov et al, 1999; Song et al, 2005; Chiu et al, 2007; Shimizu et al, 2004). However, recent comparative testing with synthetic signals (Turiel et al, 2006) has demonstrated that the WTMM method has a tendency towards linearization of the tail of the singularity spectrum towards higher values of h . Whilst this may have consequences on the accuracy of the measurement of W_+ , it seems reasonable to assume that under the consistent spectral conditions of the BOLD time-series any bias will be equally present in all participants and will not unduly influence subsequent statistical inferences. Moreover, the methods compared each had their own limitations and performance characteristics and further work is indicated in the comparative testing of algorithms for obtaining the singularity spectrum with synthetic signals that adequately simulate time-series from resting state fMRI.

4.5 Conclusion

BOLD signal dynamics acquired during resting wakefulness demonstrate properties consistent with critical-phase systems. These systems are known to produce multifractal behaviour, the analysis of which is capable of distinguishing between the effects of ageing, drug administration and correlation with task performance unavailable with a univariate, monofractal approach. Nevertheless, the Hurst exponent is sensitive to changes in multifractality and is adequate for exploratory statistical testing.

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References

- Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 2006;26:63–72. [PubMed: 16399673]
- Achard S, Bassett DS, Meyer-Lindenberg A, Bullmore ET. Fractal connectivity of long memory networks. *Phys Rev E*. 2008in press
- Amaral LAN, Ivanov PCh, Aoyagi N, Hidaka I, Tomono S, Goldberger AL, Stanley HE, Yamamoto Y. Behaviour-independent features of complex heartbeat dynamics. *Phys. Rev. Letts* 2001;86:6026. [PubMed: 11415420]
- Arneodo A, Baudet C, Belin F, Benzi R, Castaing B, Chabaud B, Chavarria R, Ciliberto S, Camussi R, Chilla F, Dubrulle B, Gagne Y, Hebral B, Herweijer J, Marchand M, Maurer J, Muzy JF, Naert A, Noullez A, Peinke J, Roux F, Tabeling P, vandeWater W, Willaime H. Structure functions in turbulence, in various flow configurations, at Reynolds number between 30 and 5000, using extended self-similarity. *Europhys. Lett* 1996;34:411–416.

- Bak P, Tang C, Wiesenfeld K. Self-organised criticality: an explanation of $1/f$ noise. *Phys. Rev. Letts* 1987;59:381–384. [PubMed: 10035754]
- Beckers F, Verheyden B, Aubert AE. Aging and nonlinear heart-rate control in a healthy population. *Am. J. Physiol. Heart Circ. Physiol* 2006;290:H2560–H2570.
- Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ. Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Trans. Med. Imaging* 1999;18:32–42. [PubMed: 10193695]
- Bullmore E, Long C, Suckling J, Fadili J, Calvert G, Zelaya F, Carpenter TA, Brammer M. Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. *Human Brain Mapping* 2001;12:61–78. [PubMed: 11169871]
- Bullmore ET, Fadili MJ, Maxim V, Sendur L, Whitcher B, Suckling J, Brammer M, Breakspear M. Wavelets and functional magnetic resonance imaging of the human brain. *NeuroImage* 2004;23:S234–S249. [PubMed: 15501094]
- Castaing B, Gagne Y, Hopfinger EJ. Velocity probability density functions of high Reynolds number turbulence. *Physica D* 1990;46:177–200.
- Chevillard L, Castaing B, Leveque E, Arneodo A. Unified multifractal description of velocity increments statistics in turbulence: intermittency and skewness. *Physica D* 2006;218:77–62.
- Chiu K-M, Chan H-L, Chu S-H, Lin T-Y. Carvedilol can restore the multifractal properties of heart beat dynamics in patients with advanced congestive heart failure. *Autonomic Neurosci. Basic and Clinical* 2007;132:76–80.
- Everitt BJ, Robbins TW. Central cholinergic systems and cognition. *Annu. Rev. Psychol* 1997;48:649–684. [PubMed: 9046571]
- Freeman WJ. Evidence from human scalp electroencephalograms of global chaotic itinerancy. *Chaos* 2003;13:1067–1077. [PubMed: 12946200]
- Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov P Ch, Peng C-K, Stanley HE. Fractal dynamics in physiology: Alterations with disease and ageing. *PNAS* 2002;99:2466–2472. [PubMed: 11875196]
- Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the U. S. A* 2003;100:253–258.
- Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience* 2001;2:685–694.
- Ivanov, P Ch; Amaral, LAN.; Goldberger, AL.; Havlin, S.; Rosenblum, MG.; Struzik, ZR.; Stanley, HE. Multifractality in healthy heartbeat dynamics. *Nature* 1999;333:461–465. [PubMed: 10365957]
- Ivanov, P Ch; Amaral, LAN.; Goldberger, AL.; Havlin, S.; Rosenblum, MG.; Stanley, HE.; Struzik, ZR. From $1/f$ noise to multifractal cascades in heartbeat dynamics. *Chaos* 2001;11:641–652. [PubMed: 12779503]
- Kelso JAS, Bressler SL, Buchanan S, DeGuzman GC, Ding M, Fuchs A, Holroyd T. A phase transition in human brain and behavior. *Physics Letters A* 1992;169:134–144.
- Kiyono K, Struzik ZR, Aoyagi N, Sakata S, Hayano J, Yamamoto Y. Critical scale invariance in a healthy human heart rate. *Phys. Rev. Lett* 2004;93:178103. [PubMed: 15525130]
- Kiyono K, Struzik ZR, Aoyagi N, Yamamoto Y. Multiscale probability density function analysis: non-Gaussian and scale-invariant fluctuations of healthy human heart rate. *IEE Trans. Biomedical Engineering* 2006;53:95–102.
- Kolmogorov AN. Dissipation of energy in a locally isotropic turbulence *Doklady Akad. Nauk SSSR* 1941;32:141–149. English translation in *Proc. Roy. Soc. London A* 1991; 434: 15-17
- Kozma R, Puljic M, Balister P, Bollobas B, Freeman WJ. Phase transitions in the neuropercolation model of neural populations with mixed local and non-local interactions. *Biol. Cybern* 2005;92:367–379. [PubMed: 15920663]
- Li X, Shang P. Multifractal classification of road traffic flows. *Chaos, solitons and fractals* 2005;31:1089–1094.
- Mandelbrot, BB. *The fractal geometry of nature*. Freeman; San Francisco: 1982.

- Maxim VT, Sendur LS, Fadili J, Suckling J, Gould R, Howard R, Bullmore ET. Fractional Gaussian noise, functional MRI and Alzheimer's disease. *NeuroImage* 2005;25:141–158. [PubMed: 15734351]
- Mehta AP, Mills AC, Dahmen KA, Sethna JP. Universal pulse shape scaling function and exponents: critical test for avalanche models applied to Berkhausen noise. *Phys. Rev. E* 2002;64:046139.
- Muzy JF, Bacry E, Arneodo A. Wavelets and multifractal formalism for singular signals: Application to turbulence data. *Phys. Rev. Letts* 1991;2:3515–3518. [PubMed: 10044755]
- Muzy JF, Bacry E, Arneodo A. Mutlifractal formalism for fractal signals: The structure-function approach versus the wavelet-transform modulus-maxima method. *Phys. Rev. E* 1993;47:875–884.
- Naert A, Puech L, Chabaud B, Peinke J, Castaing B, Hebral B. Velocity intermittency in turbulence: how to objectively characterize it? *J. Phys. II France* 1994;4:215–224.
- Pavlov AN, Ziganshin AR, Klimova OA. Multifractal characterization of blood pressure dynamics: stress-induced phenomena. *Chaos, Solitons and Fractals* 2005;24:57–63.
- Schroeder, M. *Fractals, chaos, power laws: Minutes from an infinite paradise*. W.H. Freeman and Co; New York: 1991.
- Shimizu Y, Barth M, Windischberger C, Moser E, Thurner S. Wavelet-based multifractal analysis of fMRI time series. *Neuroimage* 2004;22:1195–202. [PubMed: 15219591]
- Song, I-H.; Lee, S-M.; Kim, I-Y.; Lee, D-S.; Kim, SI. *Lecture Notes in Computer Science*. Springer-Verlag; Berlin: 2005. *Mutifractal Analysis of Electroencephalogram Time Series in Humans*; p. 921-926. IWANN
- Suckling J, Bullmore ET. Permutation tests for factorially designed neuroimaging experiments. *Human Brain Mapping* 2004;22:193–205. [PubMed: 15195286]
- Suckling J, Davis MH, Ooi C, Wink AM, Fadili JI, Salvador R, Welchew D, Sendur L, Maxim V, Bullmore ET. Permutation testing of orthogonal factorial effects in a language-processing experiment using fMRI. *Human Brain Mapping* 2006;27:425–433. [PubMed: 16596618]
- Takahashi T, Murata T, Omori M, Kosaka H, Takahashi K, Tonekura T, Wada Y. Quantitative evaluation of age-related white matter microstructural changes on MRI by multifractal analysis. *J. Neurological Sciences* 2004;225:33–37.
- Takayasu M, Takayasu H, Fukuda K. Dynamic phase transistion observed in the internet traffic flow. *Physica A* 2000;277:248–255.
- Turiel A, Pérez-Vincente CJ, Grazzini J. Numerical methods for the estimation of multifractal singularity spectra on sampled data: A comparative study. *J. Comp. Phys* 2006;216:362–290.
- Wallenstein GV, Kelso JAS, Bressler SL. Phase transitions in spatiotemporal patterns of brain activity and behavior. *Physica D* 1995;84:626–634.
- Wang G, Huang H, Hongbo X, Wang Z, Hu X. Multifractal analysis of ventricular fibrillation and ventricular tachycardia. *Medical Engineering and Physics* 2007;29:375–379. [PubMed: 16839796]
- West BJ, Latka M. Fractional Langevin model of gait variability. *J. NeuroEngineering and Rehabilitation* 2005;2:24–33.
- Wink AM, Bernard F, Salvador R, Bullmore ET, Suckling J. Age and cholinergic effects on hemodynamics and functional coherence of human hippocampus. *Neurobiology of Aging* 2006;27:1395–1404. [PubMed: 16202481]
- Wink AM, Bullmore ET, Barnes A, Bernard F, Suckling J. Monofractal and multifractal dynamics of low frequency endogenous brain oscillations in functional MRI. *Human Brain Mapping*. 2008in press

Figure 1. Probability density of function, $P(\Delta v(r))$ of the difference in BOLD signal measurements, $\Delta v(r)$, separated in time by r . Data points represents values of (top to bottom) $r = 2, 4, 8, 16, 32$ and 64 time-points (vertically offset for clarity) and the solid line is the regressed fit of the turbulence model.

Figure 2.

Coronal ($y = +22$ mm), sagittal ($x = -42$ mm) and axial ($z = -10$ mm) views of the MNI template with, (a) top row: significant negative correlation between mean reaction during the fame decision/facial encoding task and estimates of the Hurst exponent from subsequent resting time series; (b) bottom row: activation elicited by the contrast of all faces against cross-hair fixation during the fame decision/facial encoding task. Yellow corresponds to activated regions, blue to deactivated regions. Left of the image corresponds to the right-hand of the brain. R = right and L = left hand-sides of the brain.

Figure 3. Regions of significant main effects of (a) age and (b) drug on the Hurst exponent of resting fMRI time series. For all maps, the right side of the brain is represented by the right side of the image; the origin of the x and y dimensions of Talairach space is indicated by the cross-hair; the z coordinate of each section, i.e., mm below the intercommissural plane, is indicated by numbers adjacent to each section. Reproduced in part (with permission) from Wink et al (2006).

Figure 4.

Singularity spectra extracted from regions demonstrating: (a) main effect of age in right hemisphere; (b) main effect of age in left hemisphere; (c) main effect of drug, based on a univariate voxelwise test of H . In each plot the hashed line is the spectrum extracted from the participant with the lowest value of H , and the solid line for the highest value of H in the labelled groups (drug or age).

Figure 5.

Boxplots of regional mean parameters $\bar{h}_{max}$, $\bar{W}_+$ and $\bar{W}_-$ extracted from regions demonstrating significant: (a) main effect of age in right hemisphere; (b) main effect of age in left hemisphere; (c) main effect of drug, based on a univariate, voxelwise test of H .

Figure 6. Regional relationship between $\ln \lambda^2$ and r for each of the regions identified in the univariate analyses of H . (a) main effect of age (left and right regions); (b) main effect of drug; (c) correlation with mean reaction time of fame decision/facial encoding task

Table 1

Results from statistical testing of multifractal parameters ($\bar{h}_{\max}$, $\bar{W}_-$ and $\bar{W}_+$) extracted from within regions of the brain identified by prior whole brain analysis using as the dependent variable the Hurst exponent

		$\bar{h}_{\max}$	$\bar{W}_-$	$\bar{W}_+$
Correlation with encode decision reaction time.		$F(18,1) = 1.738$ $p=0.204$	$F(18,1) = 0.025$ $p=0.877$	$F(18,1) = 0.012$ $p=0.913$
Main effect of drug		$F(20,1) = 10.459$ $p=0.004^*$	$F(20,1) = 8.632$ $p=0.008^*$	$F(20,1) = 7.588$ $p=0.012^*$
Main effect of age	Left region	$F(20,1) = 6.156$ $p=0.022^*$	$F(20,1) = 4.756$ $p=0.041^*$	$F(20,1) = 1.453$ $p=0.242$
	Right region	$F(20,1) = 6.671$ $p=0.018^*$	$F(20,1) = 3.894$ $p=0.062$	$F(20,1) = 1.273$ $p=0.272$

* denotes significant at $p < 0.05$.