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A Linear/Nonlinear Characterization of Resting State Brain Networks in fMRI Time Series

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Abstract

Resting state functional connectivity studies in fMRI have been used to demonstrate that the human brain is organized into inherent functional networks in the absence of stimuli. The basis for this activity is based on the spontaneous fluctuations observed during rest. In the present study, the time series generated from these fluctuations were characterized as either being linear or nonlinear based on the Delay Vector Variance method, applied through an examination of the local predictability of the signal. It was found that the default mode resting state network is composed of relatively more linear signals compared to the visual, task positive visuospatial, motor, and auditory resting state network time series. Also, it was shown that the visual cortex resting state network is more nonlinear relative to these aforementioned networks. Furthermore, using a histogram map of the nonlinearly characterized voxels for all the subjects, the histogram map was able to retrieve the peak intensity in four out of six resting state networks. Thus, the findings may provide the basis for a novel way to explore spontaneous fluctuations in the resting state brain.

Keywords

Functional connectivity; Resting state network; Nonlinear; fMRI; Default mode; Visual cortex

Introduction

Blood oxygen level dependent (BOLD) contrast functional MRI (fMRI) studies of the resting state brain have garnered great attention in the past decade due to their potential to elucidate the inherent functional organization of the human brain. It is known that the human brain contributes only 2 % to the total body mass, but consumes 20 % of the total energy which is mostly used for continual neuronal signaling (Attwell and Laughlin 2001; Ames 2000; Lennie 2003; Raichle and Mintun 2006; Shulman et al. 2004). Accordingly, a task related increase of less than 5 % is observed as described in Shulman et al. (2004), demonstrating the significance of characterizing the ongoing neuronal activity. This fact is in line with studies showing that the brain is an internal dynamical system modulated by external stimuli (Gusnard and Raichle 2001; Kenet et al. 2003; Raichle and Gusnard 2005).

Correlation analysis of slow spontaneous fluctuations (<0.1 Hz) during rest in the BOLD signal has been found to give inherently functional networks (Biswal et al. 1995; Fransson 2005; Greicius et al. 2003; Fox et al. 2005). Initially, this correlation was first reported in fMRI spontaneous fluctuations between left and right motor cortices when the brain was at

rest, wherein it was suggested that these fluctuations may underlie spontaneous neuronal activity (Biswal et al. 1995). Elsewhere it has been shown that resting networks were found to exist in the motor (Biswal et al. 1995; Damoiseaux et al. 2006; De Luca et al. 2006; Cordes et al. 2000; Beckmann et al. 2005; Lowe et al. 1998) visual (Damoiseaux et al. 2006; De Luca et al. 2006; Cordes et al. 2000; Beckmann et al. 2005), auditory (Damoiseaux et al. 2006; De Luca et al. 2006; Cordes et al. 2000; Beckmann et al. 2005; Lowe et al. 1998), visuospatial attention (Fox et al. 2005; Damoiseaux et al. 2006; De Luca et al. 2006), and default mode networks (Fransson 2005; Greicius et al. 2003; Fox et al. 2005; Damoiseaux et al. 2006; De Luca et al. 2006; Raichle et al. 2001).

Given the importance and prevalence of resting state in functional studies, the impetus for this study was to analyze whether the time series of the resting state fMRI exhibits any nonlinearities, which may further delineate the underlying neuronal mechanisms.

Typically, a linear model of the hemodynamic response is used for the fMRI time series, with which the neuronal activity is convoluted with a hemodynamic response function (Friston et al. 1994). The neuronal activity is estimated from the presented stimuli or requisite task. As an extension of this model, the nonlinear effects were incorporated using a Volterra series expansion (Friston et al. 1998). The Volterra series can model any dynamical input-state-output system and is model-independent, thus providing a representation of any nonlinear time-invariant system through empirical characterization. In Friston et al. (2000), the Volterra based model was combined with the mechanistic Balloon model proposed by Buxton et al. (1998), using physiological based parameters. Using the model given in Friston et al. (2000), it has been postulated that the nonlinear effects observed in event-related fMRI can be generated through interactions of repetitive signal presentation (Mechelli et al. 2001).

With the possibility that the fMRI time series can be generated through nonlinear mechanisms, in this study, the linearity/nonlinearity of the signal itself was characterized by the Delay Vector Variance (DVV) method (Gautama et al. 2004a, b; Mandic et al. 2008). The DVV method characterizes time series with respect to its predictability and compares it to its surrogates, which are linearized versions of the original time series (Mandic et al. 2008). The deviation of the original time series from the surrogate data is used for statistical testing of the time series, where an increasing deviation signifies the presence of nonlinearity (see Methods).

Note that in proceeding analysis, the inherent mechanism of signal generation is not analyzed, but rather the output, that is the signal itself, since the generation process may still be classified as linear (Gautama et al. 2004a). Therefore, even though a signal may be classified as nonlinear, the system generating that signal may not necessarily be nonlinear. For instance, if the input into the system is nonlinear and the mechanism is linear, the output signal would be considered nonlinear. Due to this fact, it is not possible to unequivocally characterize the generation mechanism, but it does allow for the comparison of different systems using the same inputs (Gautama et al. 2003a). This paradigm has been previously used with the DVV tool in the characterization of BOLD and mono-crystalline iron oxide particle (MION) fMRI in macaque monkey that were trained for motion processing experiments (Gautama et al. 2003a). However, the relationship between the functional connectivity and the nonlinear characterization was not analyzed.

In this study, we analyze the interaction of the functional connectivity with the nonlinearly characterized voxels in the resting state. To this end, several resting state networks (RSNs) are considered to investigate this relationship. First, we use the DVV method to characterize regions in the brain that exhibit linear and nonlinear time series in the resting state. Second,

a functional connectivity analysis using cross-correlation analysis of the RSN for the default mode, task positive visuospatial, visual, auditory, and motor networks are performed. Additionally, functional connectivity is also performed on a network defined by the nonlinear characterization scheme to investigate whether a new functional connectivity map is discovered. Finally, the overlapping voxels between the functional connectivity maps and the nonlinear histogram map are analyzed to provide a means for understanding the nature of the time series that can be used for investigating the physiological behavior of the system.

Materials and Methods

The proposed data processing framework for the subjects is given in Fig. 1. There are two streams of processing: (1) standard functional connectivity analysis and (2) nonlinear characterization of fMRI time series, both which use the same preprocessed fMRI dataset.

Subjects

Seventeen healthy subjects (nine females), aged 21–39, taken from the Newark dataset (TR = 2; # slices = 32; # time points = 135; closed eyes) from the publicly available 1,000 Functional Connectomes project at www.nitrc.org/projects/fcon_1000/, were used for this study. The two subjects, sub71402 and sub46570, were not included in this study because the former had stretching in the anatomical scan (as indicated in the dataset's readme file), and the latter did not have available the anonymized T1 MPRAGE with the skull included. For the normalization step in the preprocessing of the functional images, only the MPRAGE images including the skull were used to minimize user and system dependent processing effects.

Preprocessing of Functional Data

For the functional images of each subject, the following steps were performed in Matlab (Mathworks, Natick, MA) by using Data Processing Assistant for Resting-State fMRI (DPARSF) (<http://www.restfmri.net>) which is based on Statistical Parametric Mapping (SPM8) (<http://www.fil.ion.ucl.ac.uk/spm>) and Resting State fMRI Data Analysis Toolkit (<http://www.restfmri.net>) (Yan and Zang 2010; Song et al. 2011):

1. The first five time points were removed to account for T1 stabilization effects.
2. Slice timing correction was performed to correct for the timing difference that arise from an interleaved MRI acquisition.
3. Motion and distortion corrections were applied using the realign procedure. The six realignment parameters generated here were later used as regressors in the functional connectivity analysis.
4. Coregistration was applied to the structural image.
5. Segmentation of the cerebrospinal fluid (CSF), gray matter, and white matter components of the structural image were obtained to provide the normalization parameters.
6. Normalization of the functional images to the MNI template brain at voxel size of $3 \times 3 \times 3 \text{ mm}^3$ using the parameters provided in the segmentation procedure.
7. Spatial smoothing at 6 mm full width half maximum was performed.
8. The functional images were detrended for linear drift effects and temporally band-pass filtered between 0.01 Hz and 0.08 Hz.

Linear/Nonlinear Characterization of fMRI Time Series

Using the DVV method (Gautama et al. 2004a, b; Mandic et al. 2008), the functional time series for each of the subjects were determined to either be linear or nonlinear. Consequently, the result is a binary map signifying that the voxel is linear or nonlinear. The following is an overview of the concepts and steps that are used in producing this characterization; for a more detailed review please refer to Gautama et al. (2004a, b) and Mandic et al. (2008).

Linear Signal and Surrogate Time Series

A linear signal is defined to be generated by an autoregressive model driven by normally distributed white noise wherein the phase spectrum is inconsequential to characterizing a linear signal, i.e., the amplitude is sufficient to characterize the signal. This guideline is used as a basis for creating surrogate time series. The purpose of generating a surrogate time series are to have linear signals with which to compare the original time series, i.e., in a statistical test where the null hypothesis is assumed to be a linear signal. The surrogates are produced using the iterative Amplitude Adjusted Fourier Transform (iAAFT) method, which produces a time series with amplitude same as the original, but the phase is randomized in the frequency spectrum (Gautama et al. 2004a, b; Mandic et al. 2008). The DVV analysis is computed for the original time series and the surrogates.

DVV Analysis

To perform DVV analysis, the embedding dimension needs to be determined; wherein our analysis it is determined using the differential entropy approach (Gautama et al. 2003b). For an embedding dimension, a time series is decomposed into a set of delay vectors (DVs), which is denoted as $\mathbf{x}(k)$. Every DV $\mathbf{x}(k)$ has the target $\mathbf{x}(k+1)$, thus for a given embedding dimension m , DVV calculates the mean target variance σ^{*2} over all sets Ω_k , which is a set of DVs bounded by a specific distance r_d from $\mathbf{x}(k)$. For a given embedding dimension the following steps are performed in DVV:

1. The mean μ_d and standard deviation σ_d are computed over all pairwise distances between DVs.
2. Generate $\Omega_k(r_d)$ where r_d is defined by interval $[\max\{0, \mu_d - n_d\sigma_d\}, \mu_d + n_d\sigma_d]$, where n_d is the span to perform DVV analysis.
3. For every set $\Omega_k(r_d)$ the measure of unpredictability, $\sigma^{*2}(r_d)$, is computed by normalizing the mean of the variances of the targets, σ_x^2 , by the variance of the time series, σ_x^2 .

Statistical Testing

The DVV analysis is applied to the original and the surrogate time series, thus using a test statistic computed as the root-mean-square error between the σ^{*2} s of the original time series and the average of σ^{*2} s of the surrogate time series can be used in hypothesis testing. The surrogate time series satisfy the null hypothesis, consequently, if the original time series is significantly different from the surrogates, the null hypothesis is rejected. More specifically, the null hypothesis is defined as a linear time series generated from a linear and stationary process driven by the input of Gaussian white noise that produces an output where the amplitude is transformed by a zero-memory observation function (Gautama et al. 2004b). An example of linear time series generated in such a manner is an autoregressive model driven by normally distributed white noise. The alternate hypothesis is essentially denoted as the absence of linearity since it is not fundamentally possible to define a single measure of nonlinearity (Gautama et al. 2004a; Mandic et al. 2008).

A non-parametric rank test is used for the hypothesis testing because the distribution of test-statistic is unknown. Thus, the test statistic for the original and surrogate are sorted in increasing order in which the rank of the original time series is determined. If it exceeds the significance level, then the null hypothesis is rejected. Multiple comparison correction was not applied in characterizing the nonlinearity of the time series. The DVV calculations have been used and applied without multiple comparisons correction (Gautama et al. 2003a, c, 2004a; Mandic et al. 2008). It is also known that correcting for multiple comparisons to reduce type 1 error, the false positive error, will increase type 2 error, i.e., the false negative error (Rothman 1990). Thus, a multiple comparisons correction may cause a loss of sensitivity in our detection of nonlinear voxels.

Parameters Used

The estimation of the embedding dimension and the DVV computation are both time consuming computations. One way to decrease computation time is to keep the embedding dimension at a constant value that is sufficiently large enough to construct the delay vectors. In our analysis the embedding dimension was determined to be $m = 2$. This was justified by randomly choosing two subjects for which the embedding dimension was computed for all time series within the brain mask. For the first subject, all of the 70,831 voxels were found to have embedding dimension of 2, and in the second subject all but three voxels were found to have $m = 2$.

For the DVV analysis, the following input parameters were used:

1. Embedding dimension, $m = 2$.
2. Maximal span, $n_d = 3$.
3. Number of reference DVs, $N_{\text{sub}} = 100$.
4. Number of surrogates was 39, given by $N_s = 1/\alpha - 1$, for a right-tailed test where α is the 0.025 significance level.

The toolboxes for estimating the embedding dimension and performing the DVV analysis are available at <http://simone.neuro.kuleuven.ac.be/temu/>. To demonstrate the reproducibility of the DVV experiments, using the same parameters as the initial calculation of the linear/nonlinear characterization, the DVV computation was repeated a second time to demonstrate the stability of the calculations. Since the phase of the original time series is randomized in the frequency spectrum to generate the surrogate data (Gautama et al. 2004a, b; Mandic et al. 2008), the significance level should be set high enough to mitigate chance results due to the randomization effects of the surrogate data. By comparing original and repeated linear/nonlinear maps of each subject, it was confirmed that the same maps were reproduced.

Histogram Map

After calculating the subject specific binary maps signifying the voxel based characterization of linearity or nonlinearity, the map for each subject was summed to create an overall histogram map of the voxel counts of all the binary values. Before the summation was performed, the individual binary maps were processed to eliminate voxels of noninterest, such as lone voxels or characterizations based on noisy voxels. To accomplish this, the binary map of each subject was thresholded cluster-wise at a voxel volume of 44, which was determined using the AlphaSim tool (parameters: p -value = 0.01, FWHM = 6 mm, with brain mask) from Analysis of Functional NeuroImages (AFNI) software (Ward 1997).

Functional Connectivity Analysis

The functional connectivity of each RSN was calculated using the standard ROI-based functional connectivity analysis (Biswal et al. 1995). Recently, there have been opposing views regarding the existence of anti-correlated networks being introduced due to global signal removal as a regressor of noninterest in the general linear model (Fox et al. 2009; Murphy et al. 2009). In light of this development, we have only analyzed the positive correlations in the RSNs. Using the DPARSF toolbox, the functional connectivity for the default mode, task positive, visual, auditory, motor, and nonlinear-seed based networks were calculated for each subject; wherein the regressors of noninterest, specifically, the extracted time series for white matter, CSF, whole brain, and the movement parameters were removed, and a Fisher *r*-to-*z* transformation was performed. This was followed by random effects group-level one sample *t* test for each RSN. The following are the seed ROI (7.5 mm radius) anatomical locations in MNI space, used for the functional connectivity:

1. Default mode RSN: the precuneus/posterior cingulate cortex (PCC) at (−5, 49, 40) given in Fox et al. (2005) was used.
2. Task positive RSN: is defined by the middle temporal region (MT+) at (−45, −69, −2) according to Fox et al. (2005) which was determined by the activity increases in working memory and attention in Corbetta et al. (2002).
3. Visual RSN: (−10, −75, 10) in the left calcarine fissure, Brodmann area (BA) 17.
4. Auditory RSN: (−42, −40, 18) in left superior temporal gyrus, BA 41.
5. Motor RSN: (−40, −12, 50) in left precentral gyrus, BA 4/6.
6. Nonlinear RSN: (66, −9, 0) right superior temporal gyrus, BA 22. This seed point was defined by locating the voxel in the nonlinear histogram map where the count was the highest.

To correct for multiple comparisons in the functional connectivity maps, they were thresholded voxel-wise at a *p*-value of 0.05, 0.01, 0.005, and 0.001, and were corrected cluster-wise at a voxel volume of 148, 44, 27, and 13, respectively, which were determined using the AlphaSim tool (parameters: *p*-value = 0.05, 0.01, 0.005, and 0.001, FWHM = 6 mm, with brain mask) from AFNI software (Ward 1997). This range of thresholds was used to demonstrate the varying amount of overlap between the histogram and functional connectivity maps. The resulting functional connectivity images thresholded at the *p*-value of 0.01 were displayed using MRICroN (<http://www.mricro.com>).

Overlap Maps

To determine a relationship between the histogram map and the functional connectivity maps of the RSNs, the overlap of the common voxels in the two types of map were determined. The overlap calculation was performed for each of the four thresholding levels in functional connectivity maps. Furthermore, the number of overlapping voxels for each RSN was calculated, which were used to calculate the connectivity map fraction (CMF = # voxels overlapped/# significant voxels in functional connectivity) and the histogram map fraction (HMF = # voxels overlapped/# nonlinear voxels in nonlinear histogram). CMF defines the ratio between the overlap and the total number of significantly activated voxels in functional connectivity RSN maps. HMF is the ratio between the overlap and the total number of nonlinearly characterized voxels in histogram map. The CMF and HMF are used to demonstrate the magnitude of overlaps within the connectivity and histogram maps, respectively.

Results

Resting State Network

For the default mode, task positive, visual, auditory, motor, and nonlinear-seed RSNs, the regions most significantly activated in the function connectivity maps, demonstrated using the map thresholded at the p -value of 0.01, are summarized in Table 1. The following is a list of the regions showing the largest activations for each network: default mode, $T = 36.25$ in the Precuneus; task positive, $T = 25.05$ in the left middle occipital gyrus; visual, $T = 26.73$ in the left calcarine sulcus; auditory, $T = 23.74$ in the left superior gyrus; motor $T = 28.5$ in the left precentral gyrus; nonlinear-seed, $T = 26.95$ in the right superior temporal gyrus. Figures 2 and 3 show the functional connectivity maps for each RSN overlaid with the histogram map, highlighting the overlaps of the two maps in additive coloring, i.e., red and green produces yellow for the overlaps.

Histogram Map

The group histogram map of the subjects contains a total of 36,449 nonlinearly characterized voxels within the total brain volume of 70,831 voxels. The maximum count recorded in the histogram map was eight, which was contained in only two voxels. This means that for all of the 17 subjects, eight of the subjects characterized the same voxel as being nonlinear. 35.6 % of the nonlinear characterized voxels contained subject count between two and eight. Furthermore, the maximum count of 8 occurs at about (66, -9, 0) in the right superior temporal gyrus, BA 22. This nonlinear-seed point was defined by locating the voxel in the nonlinear histogram map where the count was the highest.

Overlap Maps

For the connectivity map fractions (CMF), the lowest percentage was computed with the default mode network for each of the connectivity maps thresholded at $p < 0.05$, 0.01, and 0.005 with values of 48.1, 49.0, and 49.9 %, respectively (Table 2). At the threshold of $p < 0.001$, the CMF was lowest in the auditory network (49.8 %); however, the default mode network was very close in value (50.0 %).

The highest CMF was found with the visual RSN for all of the threshold levels (Table 2). Furthermore, since the distribution of the CMF values is a small sample size, using the Student's t -distribution with $\alpha = 0.05$, it was found that the CMF values for the visual and default mode networks were, respectively, statistically higher (for all threshold levels) and lower (except for the $p < 0.001$ threshold) than the mean of the CMF group values (Table 2). The following is a ranking of the CMFs for each RSN in ascending order for the thresholds at $p < 0.01$ and 0.005: (1) default mode, (2) auditory, (3) nonlinear-seed, (4) motor, (5) task positive, and (6) visual. In the threshold at $p < 0.05$, the motor and nonlinear RSNs are ranked the same, and for the $p < 0.001$ threshold the default mode and auditory RSN are switched. At the $p < 0.001$ threshold, the default mode RSN is only slightly similar to the mean of CMFs with a probability of 0.0505, which is just below the significance level.

In the HMF results, the lowest and highest percentages observed were with the auditory and motor RSNs, respectively, in the connectivity maps thresholded at $p < 0.01$, 0.005, and 0.001 (Table 2). With the $p < 0.05$ thresholding, the HMF was lowest in the nonlinear map and highest in the task positive and motor maps. As in the previous case, using the t -distribution with $\alpha = 0.05$, it was found that the HMF values for the motor and auditory RSNs were also statistically higher and lower, respectively, than the mean of the HMF group values (for maps thresholded at $p < 0.01$, 0.005, and 0.001). A ranking of the HMFs, in ascending order for each RSN at $p < 0.01$ and 0.005, is given as such: (1) auditory, (2)

nonlinear-seed, (3) visual, (4) default mode, (5) task positive, and (6) motor. The results for CMF and HMF are summarized in Table 2.

In Table 1, it is also seen that the histogram map overlapped with the peak intensity in the functional connectivity maps, demonstrated using the maps thresholded at $p < 0.01$, in four out of the six RSNs, which are the task positive, visual, motor, and nonlinear-seed RSNs. The overlap of the peak intensity in the functional connectivity RSN maps with the nonlinear histogram map was determined irrespective of the peak counts in the histogram map. Also, these networks have the top four CMF values, but no such relationship is found with the HMF.

Discussion

Using the DVV method (Gautama et al. 2004a, b; Mandic et al. 2008), it has been shown that the default mode resting state network time series are relatively more linear than time series in the task positive, visual, auditory, motor, nonlinear-seed RSNs. This was determined by the lack of overlap between the nonlinear histogram and functional connectivity maps. This finding follows the simulation results in Mechelli et al. (2001) in which the stimuli presented with insufficient stimulus onset asynchrony does not allow for the reorganization of hemodynamic processes; in other words, a recovery from the hemodynamic refractory period. Following this idea, it may be postulated that, since the default mode network is given by a mechanism involving slow spontaneous neuronal fluctuations, the underlying neuronal mechanism may be classified as a linear system. The reason is that the spontaneous neuronal fluctuations may be time invariant signals by virtue of their intrinsic independence in the phase spectrum.

Since the CMF of the default mode network was statistically less than the mean of the all the RSNs for three out of the four thresholding levels, this may suggest that the default mode network may function with fewer physiological parameters than the other analyzed RSNs; and the converse may be true of the visual RSN, which was statistically larger (Table 2). An increase in input parameters tends to drive a system towards nonlinearity due to the possibility of an increase of interactions. Furthermore, the task positive RSN contains the MT+, which is involved in higher level visual processing. Considering this with the fact that the visual and task positive RSN had the two highest CMF percentages for all threshold levels (Table 2), it may be the case that the visual network tends to be more nonlinear than the other RSN networks. The ranking of the CMFs indicates that the visual networks are more nonlinear relative to the motor and auditory systems. This may suggest that despite the absence of external stimuli to the visual systems, the baseline activity of the visual cortex may be more complex than the motor and auditory systems, which still receive tactile and aural input, despite, however minimal it may be.

The HMF is an indicator of the number voxels contributed by the functional connectivity maps to the histogram map. The motor RSN had the greatest contribution to HMF for connectivity at all threshold levels, whereas the auditory contribution was the smallest for $p < 0.01$, 0.005, and 0.001 (Table 2). The HMFs of the visual and default mode RSNs were not significantly different than the mean HMF, which indicates that the CMF is not a predictor of HMF. Also, the performance of the nonlinear-seed based RSN was similar to the auditory RSN for both the CMF and HMF (typically less than 10 % difference), which indicates that the nonlinear seed may be able to identify a relevant functional connectivity network.

Interestingly, the histogram map overlapped with the functional connectivity maps was able to retrieve the peak intensity in four out of six cases. This was possible in the visual, task

positive, motor, and nonlinear-seed RSNs. However, these four networks had the top four highest CMF values, which indicates that as the proportion of the nonlinearly characterized voxels in the functional connectivity map increase, so does the ability to identify the peak intensity by the histogram map. Furthermore, this demonstrates that the nonlinear characterization of fMRI time series may help to identify brain regions where the activity is the strongest in a functional connectivity network.

In Gautama et al. (2003a), a task based study using macaque BOLD and MION signals was used in the application of DVV, as a result, the recruitment of physiological inputs such as cerebral blood volume, flow, and metabolic rate of oxygen into these two systems may be increased compared to a resting state study where there is no task. Furthermore, it was found that the embedding dimension of a pair of BOLD signals in the left and right regions of the MT+/V5 were 21 and 16, respectively, whereas for a pair of MION signals in the left and right regions were 15 and 11, respectively. This may reflect their conclusion that the BOLD signal is more nonlinear relative to the MION signal, which depends on fewer physiological parameters. The lower embedding dimension in our estimation may be indicative of the lower complexity of resting-state systems within the brain; it is necessary to choose the dimensions high enough to capture the phase space of the dynamical system (Gautama et al. 2004a).

Also, in our study we estimated the embedding dimension using the differential entropy method in which the optimal embedding dimension and time lag are determined simultaneously (Gautama et al. 2003b) while in Gautama et al. (2003a) it was estimated using Cao's method (Cao 1997) where the time lag is determined prior to the embedding dimension. Simultaneous estimation of the embedding dimension and time lag was shown to give better performance (Gautama et al. 2003b).

In the same study of Gautama et al. (2003a), it is assumed that both the BOLD and MION signals are driven by the same underlying cerebral activity, as the same two foci of activity for each type of signal in the left and right MT+/V5 are compared. In our comparison of the six different RSNs, if we consider the whole brain as our foci of interest, which is valid since there is no a prior constriction on the extent of the networks, we can assume that each network has the same underlying cerebral activity. However, this fact is inconsequential to our results since we do not have any task based experiments.

Although it may be counterintuitive to have a nonlinear time series provide strong correlation values in a linear regression analysis, this result is plausible because linear regression determines the linear fit between a dependent and independent time series and not an analysis of the signal itself. Thus, this is the reason why a target linear time series may have a weak or no linear correlation with a time series of interest, whereas nonlinear time series may have strong linear correlation.

In previous studies, it has been shown that the primary visual cortex (V1) was involved in visual recall and imagery (Kosslyn et al. 1993, 1995, 1999; Le Bihan et al. 1993). Also, there has been optical imaging with voltage-sensitive dyes showing that the V1 of anesthetized animals have spontaneous activity in the absence of visual stimuli (Kenet et al. 2003; Arieli et al. 1995, 1996; Tsodyks et al. 1999). In a previous application of DVV to macaque BOLD and MION fMRI time series from the MT+/V5, it was also found that the BOLD and MION time series both contain nonlinear voxels (Gautama et al. 2003a) which is in line with the result presented here that the human visual cortex may contain nonlinear BOLD time series. Therefore, understanding the ongoing spontaneous activity within the visual cortex could provide a better understanding of the mental process in visual imagery and recall. Using the linear/nonlinear characterization provided by the DVV scheme, areas

assumed not to have neuronal activity may be found in the visual cortex. As a possible extension to our proposed characterization scheme, a possible next step may be to determine the functional clusters contained within the areas by measuring the nonlinear interdependence between the fMRI time series, as demonstrated in EEG (Dimitriadis et al. 2009).

In other studies, it has been demonstrated that in the resting state EEG recordings, that spontaneous alpha (8–12 Hz) activity bursts switch between high and low amplitude activity, rather than following a Gaussian amplitude distribution (Freyer et al. 2009). Later the same group had shown through biophysical model using delay differential equations with physiological parameters that the spontaneous alpha activated can be generated through nonlinear mechanisms (Freyer et al. 2011). This finding in the EEG alpha fluctuations may be complementary to the fMRI nonlinear characterizations of resting state fluctuations presented in the present study. Furthermore, the switch observed in the alpha EEG may be an indication of neural synchrony, which provides a means to organize the neuronal information within the brain. Therefore, future investigations looking at the correlation between EEG and fMRI nonlinear responses may provide interesting insight into the mechanisms involved. Recently, using simulated EEG-fMRI measurements for epileptic spikes, it was shown that there is a nonlinear decoupling of the neurovascular hemodynamic response and spiking activity (Voges et al. 2012).

From the histogram map, the maximum observed count of nonlinear characterization was 8, while the number of subjects was 17, which gives a 47.1 % occurrence rate. Also, only 35.6 % of the observed counts in histogram map were equal to two or higher. This indicates that not all subjects contributed to the frequency count. Despite the fact that only about half the subjects contributed to the maximal count of 8 in the histogram map, the largest *T*-score was retrieved in four out of the six resting state functional connectivity maps (Table 1). This demonstrates that it is not necessary for the all the subjects to contain a nonlinear characterization at the same voxel to capture a meaningful characterization of the time series. It may be the case that not all subjects have nonlinear voxel and in general, it is only present in approximately half of the subjects. This may be demonstrated with multiple datasets; however, there is the significant drawback of processing time. Even with the current subject dataset, maximum *T*-score retrieval was performed, which holds promise that this methodology can translate to other datasets.

For future work, it would be interesting to further characterize the fMRI time series in the resting state as either being stochastic or deterministic in nature. This may highlight some of the ongoing neuronal mechanisms in the resting state. This type of characterization may provide a finer classification of the signals generated. Other future characterizations can be performed on stimuli based functional studies to determine whether the linear/nonlinear characterization can capture regions with the strongest linear correlation.

The nonlinear/linear characterization of the resting state fMRI time series analysis has provided a new method of analyzing areas of activity within the resting state brain. The DVV method is able characterize regions of interest that may provide functional connectivity in the resting state. Furthermore, it is shown that the time series of the resting state default mode network are more linear in nature relative to that of the visual, task positive, auditory, and sensory system. Also, it was demonstrated that the visual cortex RSNs were more nonlinear relative to these other networks. Therefore, the methodology presented in this study provides a novel way to explore spontaneous fluctuations in the resting state brain and possibly to study task based paradigms.

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Fig. 1.

The fundamental steps in the processing of resting state fMRI data to produce the overlap maps that quantify the amount of nonlinearity in the functional connectivity maps. *Step 1:* Preprocess the fMRI dataset. *Step 2:* Calculate the nonlinear/linear characterizations of the preprocessed fMRI time series and create the group histogram map. *Step 3:* Calculate the functional connectivity. *Step 4:* Determine the overlap between the functional connectivity and the histogram map

Fig. 2.

Overlap maps of the nonlinear histogram map with the most linear functional connectivity map: **a** Default mode, and the two most nonlinear functional connectivity maps, the **b** Task positive, and **c** Visual RSNs. The functional connectivity map shows positive correlation (*red*) overlaid with the histogram map of the nonlinear characterization (*green*). The *cluster colors* are additive, i.e., *green* and *red* produces *yellow*, showing overlap between the two maps. Connectivity maps are thresholded at $p > 0.01$ and cluster-wise at a voxel volume of 44 (Color figure online)

Fig. 3.

The functional connectivity maps of the **a** Auditory, **b** Motor, and **c** Nonlinear-seed RSNs are overlapped with the nonlinear histogram map are shown. These three RSNs contain an intermediate number of nonlinear characterized voxels. Functional connectivity map shows positive correlation (*red*) overlaid with the histogram map of the nonlinear characterization (*green*). The *cluster colors* are additive, i.e., *green* and *red* produces *yellow*, showing overlap between the two maps. Connectivity maps are thresholded at $p > 0.01$ and cluster-wise at a voxel volume of 44 (Color figure online)

Table 1

Regions show activation in the resting state networks thresholded at $p < 0.01$ and retrieval of peak intensity in the overlap regions

RSN	Brain region	BA	MNI coords.	Max T-score	Retrieval ^a
Default mode	Precuneus, cingulate gyrus	31	(-9, -42, 39)	36.25	
	Superior frontal gyrus	10	(-15, 63, 12)	10.33	
	Middle temporal gyrus	20	(-54, -24, -15)	8.44	Yes
	Right cerebellum crus		(24, -84, -36)	7.68	Yes
	Right angular gyrus	40	(48, -60, 36)	6.69	Yes
	Cerebellar tonsil		(12, -51, -48)	5.85	
	Right inferior temporal		(54, 0, -39)	5.20	
Task positive	Right middle temporal gyrus	21	(63, -12, -15)	5.18	Yes
	Cuneus	19	(-27, -84 -33)	4.53	
	Left middle occipital gyrus	37	(-48, -69, 0)	25.05	Yes
	Right middle occipital gyrus	37	(45, -69, 0)	10.62	
	Right inferior frontal gyrus	9	(42, 9, 18)	5.91	Yes
	Left middle frontal gyrus	6	(-24, 3, 45)	5.81	
	Right middle frontal gyrus	6	(30, 0, 51)	5.56	Yes
	Left cerebellum crus		(-12, -75, -42)	5.24	
	Left inferior frontal gyrus	9	(-51, 6, 27)	5.22	
	Left calcarine Sulcus	18	(-6, 75, 9)	26.73	Yes
Visual	Left superior gyrus	13	(-42, -39, 18)	23.74	
	Right superior gyrus	13	(36, -33, 9)	9.33	
	Cingulate gyrus	24	(-15, -6, 48)	6.47	Yes
	Left amygdala		(-21, -6, -15)	5.26	
Auditory	Left postcentral gyrus	3	(-21, -33, 51)	4.63	
	Right postcentral gyrus	3	(21, -30, 57)	4.23	
	Left precentral gyrus	6	(-39, -9, 54)	28.5	Yes
	Right culmen		(12, -51, -18)	7.53	
Motor	Left thalamus		(-12, -24, -3)	7.26	
	Right thalamus		(18, -21, 0)	7.05	
	Right superior temporal gyrus	22	(63, -12, 3)	26.95	Yes

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RSN	Brain region	BA	MNI coords.	Max <i>T</i> -score	Retrieval ^a
	Left superior temporal gyrus	42	(-66, -30, 12)	11.23	
	Left middle temporal gyrus	19	(-54, -75, 18)	5.84	Yes
	Cingulate gyrus	24	(6, 0, 39)	4.42	Yes

RSN resting state network; *MNI*/Montreal Neurological Institute coordinates in mm; *BA* Brodmann's areas

^aRetrieval indicates whether the score was contained in the overlap between the functional connectivity and histogram map; *blank cell*/indicates no retrieval

Table 2

A comparison of voxels that are in both the RSNs and histogram map

RSN	<i>P</i> -value threshold in FC map					
	0.05		0.01		0.005	
	HMF	CMF	HMF	CMF	HMF	CMF
Default mode	15.1	48.1 [*]	10.9	49.0 [*]	9.4	49.9 [*]
Task positive	17.9 [*]	60.0	13.1	63.0	11.6	64.2
Visual	12.4	65.4 [*]	9.5	67.7 [*]	8.3	67.9 [*]
Auditory	13.7	52.5	7.6 [*]	52.1	5.8 [*]	52.8
Motor	17.9 [*]	54.3	14 [*]	57.6	12.4 [*]	58.9
Nonlinear	12.7	54.3	8.2	56.3	6.9	56.2
Mean value	14.9±2.6	55.8±6.4	10.6±2.7	57.6±7.2	9.1±2.7	58.3±7.2
					6.5±2.3	58.3±8.4

HMF histogram map fraction; *CMF* connectivity map fraction; *FC* functional connectivity^aThe probability for the default mode network was 0.0505^b*p* < 0.05