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Spontaneous BOLD event triggered averages for estimating functional connectivity at resting state

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Abstract

Recent neuroimaging studies have demonstrated that the spontaneous brain activity reflects, to a large extent, the same activation patterns measured in response to cognitive and behavioral tasks. This correspondence between activation and rest has been explored with a large repertoire of computational methods, ranging from analysis of pairwise interactions between areas of the brain to the global brain networks yielded by independent component analysis. In this paper we describe an alternative method based on the averaging of the BOLD signal at a region of interest (target) triggered by spontaneous increments in activity at another brain area (seed). The resting BOLD event triggered averages (“rBeta”) can be used to estimate functional connectivity at resting state. Using two simple examples, here we illustrate how the analysis of the average response triggered by spontaneous increases/decreases in the BOLD signal is sufficient to capture the aforementioned correspondence in a variety of circumstances. The computation of the non linear response during rest here described allows for a direct comparison with results obtained during task performance, providing an alternative measure of functional interaction between brain areas.

Keywords

Functional Magnetic Resonance Imaging; Resting State; Triggered Averages; Functional Connectivity

1. INTRODUCTION

Since the first observations of correlations in the spontaneous fluctuations of brain blood oxygen level-dependent (BOLD) signals, a wide array of methodologies was introduced to

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quantify the strength of functional interactions and extract spatial networks of brain coordinated activity. Current methods include the assessment of pairwise interactions using seed based correlation analysis [7,10,14,21] and frequency domain [1?, 26,27,30,33]. Other methods involve the use of probabilistic independent component analysis (PICA), which, being data driven, do not require a priori selection of seed regions [6,18,22,29].

The output of the above cited methods is either a single numerical value or spatial maps of statistical significance. Additionally, important temporal changes at the onset of activity can be detected in block design fMRI experiments, by the analysis of the averaged BOLD response [8,13,23]. However, in brain resting data the absence of a task difficulties the definition of appropriate trigger points, thus preventing until now the computation of similar averages. Here we propose a simple method that resolves this issue, allowing the calculation of the average BOLD response at a given brain region (target) after spontaneous increases in the signal at another region (seed). The resulting averages capture the temporal patterns of BOLD signal after peaks of activity in regions of interest, as well as both the strength and the variability of the interaction, thus extending the usual pairwise similarity measures both in information and interpretability.

To demonstrate the method, (dubbed “rBeta” for resting BOLD event triggered average) we compare the functional connectivity between regions under task and rest conditions. The correspondence between these two conditions has already been explored and validated with many of the methods introduced in the first paragraph [10,14,29].

Two cases were analyzed: the first is used to introduce the method and involves the functional connectivity during a simple motor task (finger tapping) and during rest. The second case studies the resting functional connectivity of key regions in a group of healthy controls compared with chronic back pain (CBP) patients. The latter study has recently been shown to discriminate between both groups through different dynamics of the nucleus accumbens during stimulation [4]; in the present paper we apply triggered averages to demonstrate a similar effect during rest.

2. MATERIALS AND METHODS

Subjects and fMRI data acquisition

Two different data sets were analyzed. The first one corresponds to a single 37 years right handed female, (studied in [9]), executing a finger tapping task. The second set belongs to the cohort reported recently ([31]) which includes 12 chronic low back pain patients (CBP) (29–67 years old, avg=51.2) and 12 healthy controls (HC) (21–60 years old, avg=38.4), all right-handed. As already reported [9,31], all subjects gave informed consent to procedures approved by Northwestern Univ. IRB committee.

For the motor task study the participant was instructed to lay still in the scanner and tap her right finger at intervals of 25 sec interleaved with intervals of 25 sec of rest. Three scans were performed under this condition and another one during rest (participant was instructed to lay still in the scanner, keep her mind blank, eyes closed and avoid falling asleep [11]). For the second comparison participants were similarly instructed to rest in the scanner avoiding falling asleep.

Functional magnetic resonance data was acquired as described previously [9,31] using a 3T Siemens Trio whole-body scanner (see scanning parameters in Suppl. Information). A total of 400 images (spaced by 2.5 sec) were obtained in the first experiment and 300 (same TR=2.5 s.) in the second, in which the brain oxygen level dependent (BOLD) signal was recorded for each one of the $64 \times 64 \times 49$ sites (voxels dimension $3.44 \text{ mm} \times 3.44 \text{ mm} \times 3$

mm). Standard preprocessing (see details in [9,31] and Suppl. Information) of BOLD signal was performed using FMRIB Expert Analysis Tool [17]. In the dataset corresponding to the second experiment an independent component analysis (ICA) denoising procedure [5] was applied, consisting of edge removal and high frequency artifacts by linear regression.

Activation maps Activation maps in the finger tapping experiment follows a general linear model (GLM) and were generated using FEAT (FMRI Expert Analysis Tool), part of FSL [29]. Time-series statistical analysis was carried out using FILM with local autocorrelation correction. Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P=0.05$.

Seed based correlation analysis

Correlation maps were constructed by first extracting the BOLD time course from a given seed region ($3 \times 3 \times 3$ voxels cube) and then computing the correlation coefficient between its time course and the time course of all other grey matter voxels (see for example [3,10]). Linear correlation is computed as follows,

$$r = \frac{\langle (x - \langle x \rangle)(y - \langle y \rangle) \rangle}{\sigma_x \sigma_y} \quad (1)$$

where $\langle x \rangle$ represents the time average and σ_x the standard deviation of signal x . Individual maps were then averaged and converted to Z scores.

Triggered BOLD averages

The spontaneous event triggered averages procedure is outlined in Figure 1. The data set used for this analysis corresponds to either a brain resting state condition or to the performance of a task, as discussed further in the results section. In both cases, the triggered BOLD average at a *target area* is computed for a window of time started when the BOLD signal in another area (*seed*) crosses an arbitrary threshold (Figure 1, panels A and B). This average time courses follow a typical pattern, although exhibit variability (see Figure 1C and D), for both the seed and targets temporal patterns. Finally, panel D in the same figure shows the temporal patterns of the triggered events observed in a co-activated region as well as in a non co-activated region.

A comparison between this method and linear correlations approaches usually computed in functional connectivity studies admits a few possibilities (see Fig. 1A and B). For instance, one can compute the correlations between signals (from seed and targets) obtained by concatenating successive supra-threshold events, giving $r_{conc}^1 = 0.50$ and $r_{conc}^2 = -0.31$.

Alternatively, the correlations between the averages of the events themselves give $r_{avg}^1 = 0.99$ and $r_{avg}^2 = -0.62$. On the other hand, the linear correlation between the whole time series of seed and targets gives $r_{lin}^1 = 0.37$ and $r_{lin}^2 = -0.11$ respectively. However, one should be careful in attempting to simplify the rBeta into a single number, because relevant information is lost, including the shape and timing of the triggered events. Further discussion can be found in Fig. S4, S5 and S6 of the Supp. Info.

As an additional control, rBeta were also computed between the BOLD time series with randomized phases, to test the null hypothesis that similar averages may be obtained by chance (see Supplementary Material). Phase randomization was performed first by Fourier transforming the time series, followed by a random shuffle of the phases and finally applying an inverse Fourier transform to bring the data back to the temporal domain.

3. RESULTS

To highlight the main features of the rBeta approach we describe the results of two comparisons. In the first, the spatial activation pattern and temporal course at key areas are described for the finger tapping task. Regions of interest are defined using a GLM approach and functional connectivity between this regions is compared with the BOLD event triggered averages. In the second we use rBeta to compare resting functional connectivity in two population of subjects, one of healthy controls and other of chronic low back pain patients.

Finger tapping task

Activation maps and task triggered averages using linear and rBeta correlations were obtained for a single subject performing a finger tapping task. As seen in Figure 2A peaks of activation include, as expected, regions in the left primary motor and somatosensory cortices, namely, postcentral gyrus (PoCG.L) and precentral gyrus (PreCG.L) respectively and the supplementary motor area (SMA) - abbreviations are as in [26]. Four spatial maps are presented, from top to bottom: the task activation computed using GLM, the task seed correlation, the rest seed correlation and the rest rBeta correlation which are all qualitatively similar, despite their different origin and methods of calculation. In particular, note that the rBeta map (bottom panel), computed from a few dozen events, successfully highlight the functional network comprised by both primary motor cortex, the SMA, PreCG.R and regions from the cerebellum. Despite these gross similarities, it need to be noted that the application of the rBeta to construct functional connectivity maps deserves further work, in particular to define robust statistical tests.

Standard task triggered BOLD averages (averages over all cycles of tapping) show that the signal slowly increases and finally drops to the baseline, following the stereotypical shape of a square signal convoluted with the hemodynamic response function (see Figure 2B).

Figure 2C corresponds to the BOLD averages triggered by increases (threshold of 1, 0.5 and 0 s.d. over the mean) in the BOLD signal of PreCG.L itself. In all cases, the BOLD signal increases during a period ranging from 2.5 s. to 5 s. and then drops below the baseline before reaching the mean again. The intensity of the response is the greatest when the seed (PreCG.L) and the target are the same, less significant increases are found in SMA, PreCG.R and cerebellum. In all cases, the response is significantly different from zero ($p < 0.05$, Hotelling multivariate test).

When an analogous analysis is conducted over resting state activity (i.e. rBeta) very similar responses are found, both in BOLD amplitude and in the average time course (see Figure 2C). In particular, the order of the peak intensity is the same as during the task. The main difference between panels in Figure 2C is the fact that for times longer than about 6–8 sec. the BOLD signal returns to baseline values. When the phases of the time series were randomly shuffled, rBeta values were not different from zero, as expected (see Supp. Information).

Functional connectivity of nucleus accumbens in healthy and CBP subjects

The BOLD signal was extracted from bilateral nucleus accumbens (nAC) and its linear correlation coefficient with all grey matter voxels was computed (as described in the Materials & Methods section) for the population of CBP patients and healthy controls (HC). The result of this analysis is shown in Figure 3A. Notice that these spatial maps resemble much those presented in previous work during noxious thermal stimulation [4]. The main differences between both networks is the recruitment of regions in the middle prefrontal

cortex in CBP patients, and the decrease of connectivity with regions in the dorsal & anterior cingulate cortex.

Figure 3b shows the results of computing $r\text{Beta}$ to different brain regions (targets) known to exhibit altered connectivity with nAC during stimulation in CBP patients [4]. In all cases, the seed time course was extracted from bilateral nAC. First, notice that the responses in the seeds of both groups are identical. The group differences include an increased BOLD hemodynamic response in CBP of regions of the orbital part of the frontal cortex (ORBmid) and thalamus while the response is diminished in the anterior cingulate cortex (ACC) and Insula (Ins). These results match those previously reported during noxious thermal stimulation, except for the alterations detected here for the thalamus and cingulate cortex connectivity. In particular, thalamic connectivity alteration shows the larger effect since its response is significantly weaker in HC patients. Finally, the results in Figure 3C show alteration of the Insula L functional connectivity with a number of key regions, including Tha, ORBmid and ACC. Another feature of the average response is the fact that it can be asymmetric, as it is seen here for nAc and Insula. In addition, note that the alterations are time dependent, consistent with the findings under noxious thermal stimulation [4]. A comparison with linear correlations reveals the same tendencies commented for Fig. 1 (see Supp. Information).

4. DISCUSSION

In this paper a method is presented to study functional interactions between regions of the human brain computing averages of spontaneous large BOLD events. The results show that the approach provides compelling information not only about the strength of the interaction, but also about its temporal length, directionality and overall shape of the response to spontaneous (or induced) increases in a seed region. The approach is straightforward, it is easily interpretable and the information it provides goes beyond the single numerical linear correlation measure between time courses commonly utilized in functional connectivity studies. A few simple approaches to collapse the triggered averages into single numerical values in order to allow the comparison with linear correlation measures are shown in Figures S4, S5 and S6 of the Supp. Information. With all the caveats and limitations of reducing a nonlinear method to a linear one, this analysis indicates that the peak value of the $r\text{Beta}$ is the best proxy candidate of coherence between two sites, better than the linear correlations between them but, of course, losing the information about general shape and timing that characterize the full $r\text{Beta}$ measure.

The applicability of the method has been illustrated in two different experimental situations which are of interests in their own. In the first one, strong similarities were found between the interactions of the primary motor cortex (a seed located in the precentral gyrus) and other components of a motor related network both during task and in complete resting state. This kind of correspondence between task and rest has been demonstrated for a wide range of experiments including adaptive motor learning [2,19], recovery from working memory overload [24,32], and individual differences between subjects [11,15,16,25]. We have demonstrated in the present paper a striking correspondence between the hemodynamic response of cerebellum, supplementary motor area and bilateral primary motor cortices to spontaneous peaks of activity in a seed located in the precentral gyrus. Even if the task performed was very simple and a similarity of this kind was expected in the light of previous findings, the application of the triggered averages method to demonstrate task-rest correspondence in more subtle situation remains an open and interesting possibility.

Regarding the second experiment, both the generation of seed based correlation maps and the application of triggered averages confirm a close similarity between the functional

connectivity at rest and during noxious thermal stimulation, both for a group of CBP patients and healthy controls. Furthermore, these similarities allow discrimination between both groups based in the functional connectivity of the nAC in an analogous fashion to that performed in previous work during thermal stimulation [4]. Correspondence between task and resting state during pathological conditions has been rarely explored, an exception being recent work linking altered default mode network dynamics in CBP patients during rest and a simple visual tracking task [3,31]. Since resting state scans of diseased subjects are easier to obtain and in many cases more straightforward to analyze progress along this line remains an interesting topic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A) Procedure to construct triggered averages: when the BOLD signal at the seed's region crosses an arbitrary threshold (here set to 1 s.d.), events at both (seed and target/s) regions are defined. B) The BOLD signal is extracted over a time window including the event onset time from all regions of interest and then is averaged. C) Typical diversity of event's shapes identified by K-mean clustering of the BOLD signal time course after onset of events, for seed region located in right supramarginal gyrus (SMG.R) and targets at precuneus (PCUN) and orbital part of the middlefrontal gyrus (ORBmid). D) Variability of events in seed region (SMG.R - first row), events in a coactivated region (PCUN - second row) and events in a non coactivated region (ORBmid). MNI coordinates for SMG.R are 58, -38, 28; PCUN 10, -42, 60 and for ORBmid 2, 62, -8.

Figure 2.

A) Functional maps constructed from a single subject using four different paradigms. Task activation: Activation map for a finger tapping task obtained using GLM. Task seed correlation: PreCG.L seed correlation map for the same finger tapping task data in the top. Rest seed correlation: PreCG.L seed correlation map during resting state. Rest rBeta correlation: Spatial map, for resting conditions, of correlations between the average rBeta of a seed (in PreCG.L) and the average rBeta computed for each of the voxels (using a threshold of 1 S.D.). B) BOLD averages triggered by the task for regions PreCG.R, SMA, PreCG.L and Cer. L during the finger tapping task. Left data corresponds to one full rest/activity cycle lasting 50 sec.; middle and right panels show in more details the same data for the rest and tapping respectively. C) BOLD averages triggered by increments in PreCG.L computed at PreCG.L, SMA, PreCG.L and Cer. L during finger tapping (top panels) and during resting state (lower panels) for three different triggering thresholds. Vertical bars indicate the onset time of the event. Data points are mean $\pm$ SEM. Approximately 140 events during task and 30 for resting state were averaged. MNI coordinates for PreCG.L are $-38, -20, 56$; SMA $2, -6, 52$; Cer. L. $-18, -50, -20$; and for PreCG. R $50, -10, 52$.

Figure 3.

A) nAC seed correlation maps for healthy control subjects (HC) and chronic low back pain patients (CBP). B) BOLD averages triggered by increases (1 s.d.) in bilateral nAC computed at nAC, Tha, ORBmid, ACC, Insula.L and Insula R (HC, continuous blue line; CBP, dashed red lines). C) Same analysis performed with the seed located at Insula. L. Vertical bars signal the onset time of the event. Data points are mean $\pm$ SEM. MNI coordinates for right and left nAC are 10, 2, -4 and -10, 2, -4; right and left Tha are 6, -16, 6 and -6, -16, 6; ORBmid 2, 62, -8; ACC -2, 38, 0; Insula. L -42, -6, 0 and for Insula R 42, -6, 0.