Continuous Functional Magnetic Resonance Imaging Reveals Dynamic Nonlinearities of "Dose–Response" Curves for Finger Opposition

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Linear experimental designs have dominated the field of functional neuroimaging, but although successful at mapping regions of relative brain activation, the technique assumes that both cognition and brain activation are linear processes. To test these assumptions, we performed a continuous functional magnetic resonance imaging (MRI) experiment of finger opposition. Subjects performed a visually paced bimanual finger-tapping task. The frequency of finger tapping was continuously varied between 1 and 5 Hz, without any rest blocks. After continuous acquisition of fMRI images, the task-related brain regions were identified with independent components analysis (ICA). When the time courses of the task-related components were plotted against tapping frequency, nonlinear "dose–response" curves were obtained for most subjects. Nonlinearities appeared in both the static and dynamic sense, with hysteresis being prominent in several subjects. The ICA decomposition also demonstrated the spatial dynamics with different components active at different times. These results suggest that the brain response to tapping frequency does not scale linearly, and that it is history-dependent even after accounting for the hemodynamic response function. This implies that finger tapping, as measured with fMRI, is a nonstationary process. When analyzed with a conventional general linear model, a strong correlation to tapping frequency was identified, but the spatiotemporal dynamics were not apparent.

Key words: fMRI; nonlinear; dynamics; motor function; individual differences; cortex; cerebellum; ICA

The majority of functional neuroimaging studies have been based on the assumption of fixed experimental effects. Under this model, an experiment is designed so that a variable, or set of variables, is explicitly controlled by the experimenter. The resulting data are then analyzed in terms of these explanatory variables, typically using a form of the general linear model (GLM). Although this is a powerful approach for both the design and analysis of functional neuroimaging experiments, it places stringent constraints on the types of experiments that can be performed. Because this type of analysis is hypothesis-driven, it can only yield answers specific to those questions that are asked. Often this results in a set of static activation maps that reach some threshold of significance regarding a particular null hypothesis. In this report, we describe the use of an alternative analysis (McKeown et al., 1998a,b) that reveals the complex spatiotemporal dynamics of a finger-tapping task.

One aspect of the GLM that may be problematic for brain imaging is the requirement of linearity. By definition, the GLM is a linear combination of explanatory variables, which can be added to or taken away from a given model in a modular manner. Although "nonlinear" terms can be added to these models by specifying higher-order effects (e.g., x^2, or xy in the case of two variables), the hypothesized shape of these effects must be specified in advance. This can make it difficult to test a hypothesized relationship between brain activation and an experimental variable if the nature of the relationship is not already known. A second aspect of the GLM that can be troublesome for brain imaging is the assumption of stationarity. To gain statistical power, most GLMs are designed around repetitions of observations, but this assumes that repetitions of an experimental condition are true replicates. It can be argued that because of both neuronal and cognitive adaptations, no observation is truly a replicate of a previous one (Vazquez and Noll, 1998). Subjects continually adapt to a particular task, resulting in at least subtle changes in brain activation with time. Although one can assume stationarity in the GLM, these adaptive processes add to the within-subject variance, thereby weakening statistical power.

The GLM approach to neuroimaging has been used to great success during the past 10 years. The simplest method is to design a blocked, or "boxcar" experiment in which subjects perform a task for a period of time, typically 30–60 sec, and then compare

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the average brain response during these blocks. Single-trial or event-related functional magnetic resonance imaging (fMRI) has demonstrated the potential for fine temporal resolution (Buckner et al., 1996; Rosen et al., 1998). This approach can be considered similar to blocked designs, except with very small blocks.

An extension of event-related fMRI would be to do away with event interleaving and simply to let the measured signal stand on its own. "Continuous fMRI" might have a subject perform a task, perhaps with some slow variation in a task parameter, and continuously acquire functional images without any prespecified comparison condition. A major impediment to this approach is the presence of low-frequency "noise." Multiple sources, both physiological and artifactual, contribute to what are usually referred to as low-frequency noise. At long scan repetition times (TRs), both cardiac and respiratory signals can be aliased back into the sampled interval and appear as low-frequency signals. Beyond this, a number of other sources contribute to the baseline drift commonly observed in fMRI time series, some of which may be correlated with the task (Biswal et al., 1997). The easiest, and most common, method for dealing with this is to simply high-pass filter the data so that all low-frequency components are removed (Frackowiak et al., 1997).

To assess the feasibility of using a continuous fMRI paradigm, we conducted experiments using visually paced finger tapping. Although finger tapping has been extensively studied with both PET and fMRI (Blinkenberg et al., 1996; Rao et al., 1996; Sadato et al., 1996, 1997; Schlaug et al., 1996; Jancke et al., 1998; Kansaku et al., 1998; Ramsey et al., 1998), the fundamental question of how the brain performs finger tapping is still unanswered. The primary sensorimotor cortex is consistently activated during finger tapping, and the magnitude of both regional cerebral blood flow and blood oxygenation level-dependent (BOLD) changes appears to be linearly related to the frequency of finger tapping. If these regions are truly linear, then only the frequency of tapping should be related to the magnitude of response. If not, then any number of nonlinearities will be apparent. The goals of this study were two-fold: (1) to assess the signal-to-noise ratio in the absence of a "base condition," and (2) to characterize both the static and dynamic linearity of the BOLD response to finger tapping frequency.

MATERIALS AND METHODS

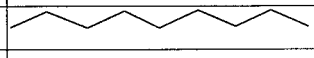
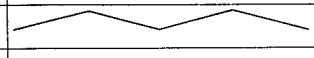
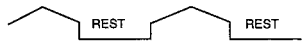
Subjects. Nine normal volunteers were studied (five male, four female). All subjects provided informed consent after the potential risks of MRI were explained. The study was approved by the Emory University Human Investigations Committee.

Behavioral task. A personal computer connected to an LCD projector was used to administer the task. The behavioral program was written in Visual Basic. The visual stimuli consisted of a black background with the outlines of two boxes on the screen. The boxes were alternately filled in white, and the box that was filled in was simply switched back and forth between the left and the right. This was the visual cue for the subject. Subjects were instructed to tap their index finger to their thumb on both hands and to keep pace with the visual cue. The frequency of tapping was continuously varied by ramping the frequency up and down, ranging from 1 to 5 Hz. Each functional scan lasted 4 min, and a total of six scans were performed on each subject (Table 1). The first two scans consisted of four 60 sec up–down cycles; the second two scans each had two 120 sec up–down cycles; and the last two scans were the same as the first, except that a red X appeared on the screen during the second and fourth cycles, indicating that the subject should not finger tap. This was done for comparison with the conventional task–rest paradigm.

Imaging. All imaging was performed at Emory University Hospital on a Philips 1.5 T ACS/NT scanner equipped with a PowerTrak gradient system (23 mT/m). Each imaging session consisted of a scout image, a T1-weighted structural scan [spin-echo; echo time (TE), 20 msec; TR, 500 msec; flip angle, 90°), and the six functional scans described above. The structural scan consisted of 10 8-mm-thick slices (0 mm gap), 256 × 256 matrix, and field of view of 24 cm. The scan planes were oriented obliquely, pitched up 45° to the anterior commissure–posterior commissure (AC–PC) line (Fig. 1). This imaged a region of the brain extending from the premotor cortex down to the cerebellum, at the loss of prefrontal and orbitofrontal regions. Functional scans were obtained with gradient-recalled echo-planar imaging (EPI) for T2* weighting of the BOLD effect (TR, 1000 msec; TE, 40 msec; flip angle, 81°; 64 × 64 matrix; 8-mm-thick slices; 10 slices) (Kwong et al., 1992; Ogawa et al., 1992). Because high-temporal resolution was desirable for the functional scans, this limited the number of planes to ~10. Each run consisted of 240 acquisitions. Head motion was minimized with lateral padding and a Velcro strap across the forehead. No motion correction was performed on the images.

Analysis. Because it was hypothesized that nonlinear effects would play a significant role in the brain response, it was not clear what the appropriate reference waveform should be. For example, the brain response may be either linear or nonlinear in terms of the driving frequency, but this may be different whether the subject is speeding up or slowing down. The data-driven method used was an independent components analysis (ICA) as developed by Sejnowksi and colleagues (Bell and Sejnowski, 1995; Makeig et al., 1997; McKeown et al., 1998b). The ICA algorithm is

Table 1. Design of continuous fMRI finger tapping experiment.

Scan	Description	Frequency Waveform
1	4 60-sec up/down cycles	
2	"	
3	2 120-sec up/down cycles	
4	"	
5	4 60-sec up/down cycles, with cycles 2 and 4 being "rest"	
6	"	

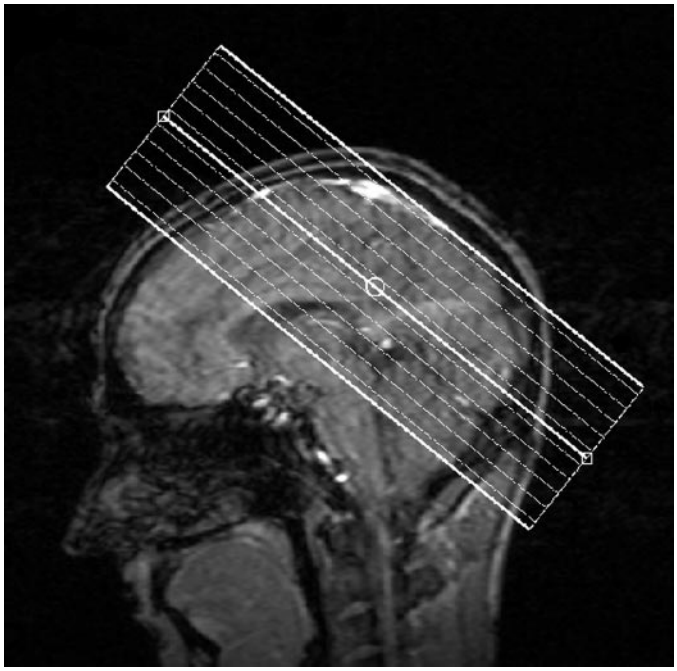


Figure 1. Sagittal image showing oblique orientation of both structural and functional scans. Ten 8-mm-thick slices were oriented 45° to the AC–PC line.

similar to principal components analysis (PCA) in that it decomposes a data set into discrete components. PCA orients the first component in the direction of maximal variance in the data set with subsequent components oriented orthogonally. This is often poorly suited to functional imaging data sets in which the cognitive effect is small and contributes relatively little to the overall variance. The ICA algorithm also decomposes the data set, but under the principle of minimizing the mutual information between components. This means that although the resultant spatial maps are independent, the corresponding time courses are not constrained to be independent. ICA may be better at identifying task-related signals in the brain, signals that typically contribute relatively little to the overall variance. It is particularly useful in paradigms in which the time course of the brain response is unknown.

The ICA analysis was performed on an individual basis and was limited to those voxels within the brain (based on the structural image). Each subject's structural image was edited to exclude nonbrain structures, and this was used to spatially transform each brain into the space of the first subject, using the automated image registration program (AIR 3.08) of Woods et al. (1998). The transformations for motion correction, EPI to structural, and structural to template were computed with AIR, and each EPI image was resliced only once using the combined transformation matrix. The two repetitions of each run were concatenated in time, creating a large matrix with each row representing the brain voxels for a given time point. To eliminate transient magnetization effects, the first nine and the last scan were discarded, creating a single matrix of 460 rows (two runs of 230) $\times$ ~9000 columns (the approximate number of brain voxels). Correction for the delay between slice acquisitions was not performed, because this was relatively small compared with the TR of 1000 msec. The ICA algorithm was then applied after reducing the data set to 70 components with PCA (McKeown et al., 1998b). The PCA decomposition was used purely as a means of dimensional reduction, because the number of components must be less than the number of time points. This number of components was empirically derived so that the reduced data set contained at least 99.95% of the variance of the original data set.

The time course of each ICA component was examined individually, and a "dose–response" curve for finger tapping was obtained by plotting the magnitude of this ICA component against the tapping frequency (after convolution with a hemodynamic response function). An average curve was obtained using a periodic average of points on the ICA curve, with the period equal to 60 sec, which corresponded to the period of the experiment. The ICA spatial map was interpolated to a 256 $\times$ 256 matrix using the inverse AIR transformation and overlaid on the oblique T1-weighted structural image. Many subjects had more than one component that was related to the task, either consistently or transiently. The results reported here are limited to three consistently task-related components in each subject, and these were coded red, green, and blue before overlaying on the structural image. Transiently task-related components are not reported here because of the difficulty in identifying them in a continuously varying task. All ICA analyses were performed on an individual basis and without motion correction (motion was not considered significant enough to affect the task-related spatial maps).

For comparison to the GLM, a group analysis using the Statistical Parametric Mapping (SPM96) package was performed. Using the spatially normalized data, a fixed effects model was specified with the convolved tapping rate waveform as the main covariate. Global intensity differences were removed with an ANCOVA model.

All analyses were run on a 350 MHz personal computer running FreeBSD (a Linux-like operating system) using MatLab 5.2. A typical ICA analysis required ~15 min to process.

RESULTS

The SPM analysis identified several brain regions that were significantly correlated with tapping frequency (Fig. 2). Bilateral motor cortex activity was strongly correlated with tapping frequency, but the dose–response curve of the maximally correlated voxel was obviously nonlinear. Because the data were spatially normalized into a common space, and global intensity effects were removed, these represent mean cohort effects. Similar correlations were found in a medial frontal region, most likely supplementary motor area (SMA).

The ICA component time courses displayed more variability between subjects than the SPM analysis suggested, and all subjects showed varying types of nonlinear relationships between tapping frequency and magnitude of response (Fig. 3). At least one approximately linear ICA component was identified in each subject (Fig. 3, *red*), but the amount of hysteresis varied dramatically between subjects. Hysteresis refers to the property of time dependence and in this experiment was apparent as different curves for acceleration and deceleration (subjects A and C). Other ICA components were identified that were related to tapping frequency, but these components had strikingly nonlinear dose–response curves (Fig. 3, *green* and *blue*). Whereas the more linear ICA component (*red*) showed spatial distributions closely overlapping with primary motor cortex, these other ICA components had spatial distributions that localized more medially. Higher tapping frequency did not simply result in more activity in certain areas, but it changed the overall pattern of activity. Thus the activity patterns were nonlinear in both the spatial and temporal domains.

ICA decomposition of the runs obtained with rest blocks showed substantial spatial overlap with the components obtained during the continuous runs. All subjects showed a similar spatial map of activity, but the magnitude of response, compared with rest, was at least threefold greater in most subjects. In some subjects there was no evidence of a parametric relationship to tapping frequency during these blocked runs, because the magnitude of response was dominated by tapping versus rest. This was seen primarily in those subjects whose continuous time course showed a saturating effect.

DISCUSSION

Finger tapping has been one of the most studied paradigms in functional neuroimaging, yet the results shown here offer new insights into how the brain accomplishes this relatively simple task. The use of a continuously varying task without a baseline allows for a more precise characterization of the mapping from brain state to cognitive state. These results go beyond the parametric comparison to a rest condition. "Rest" is notoriously difficult to control, and performing discrete analyses of one state versus another inherently assumes that a state, rest or otherwise, is stationary and can be maintained for a period of time. The maps obtained in such experiments have been helpful in localizing patterns of activation and deactivation, but they are static maps and do not capture the complex spatiotemporal patterns that must be the hallmark of brain activity.

Several studies have already reported BOLD signal changes during prolonged task blocks, which under some circumstances suggest the feasibility of continuous fMRI. Bandettini et al. (1997) reported on the stability of the BOLD signal during a variety of stimulation paradigms and noted that finger opposition resulted in no signal attenuation even after 20 min of continuous tapping. The issue is unresolved, because several prolonged activation studies of visual cortex have yielded conflicting findings about signal stability and possible neuronal habituation or recoupling of blood flow and metabolism (Hathout et al., 1994; Kruger et al., 1996, 1998; Fransson et al., 1997; Howseman et al., 1998). Our results lend further support to continuous paradigms in at least the motor domain. Relatively little dose response was observed in the visual cortex, which would be expected to show signs of activation at higher frequencies because of the higher frequency of visual stimulation.

Using finger tapping as a test of several new techniques, we have begun to identify the temporal evolution of spatial patterns of activity and how these correlate with at least one behavioral

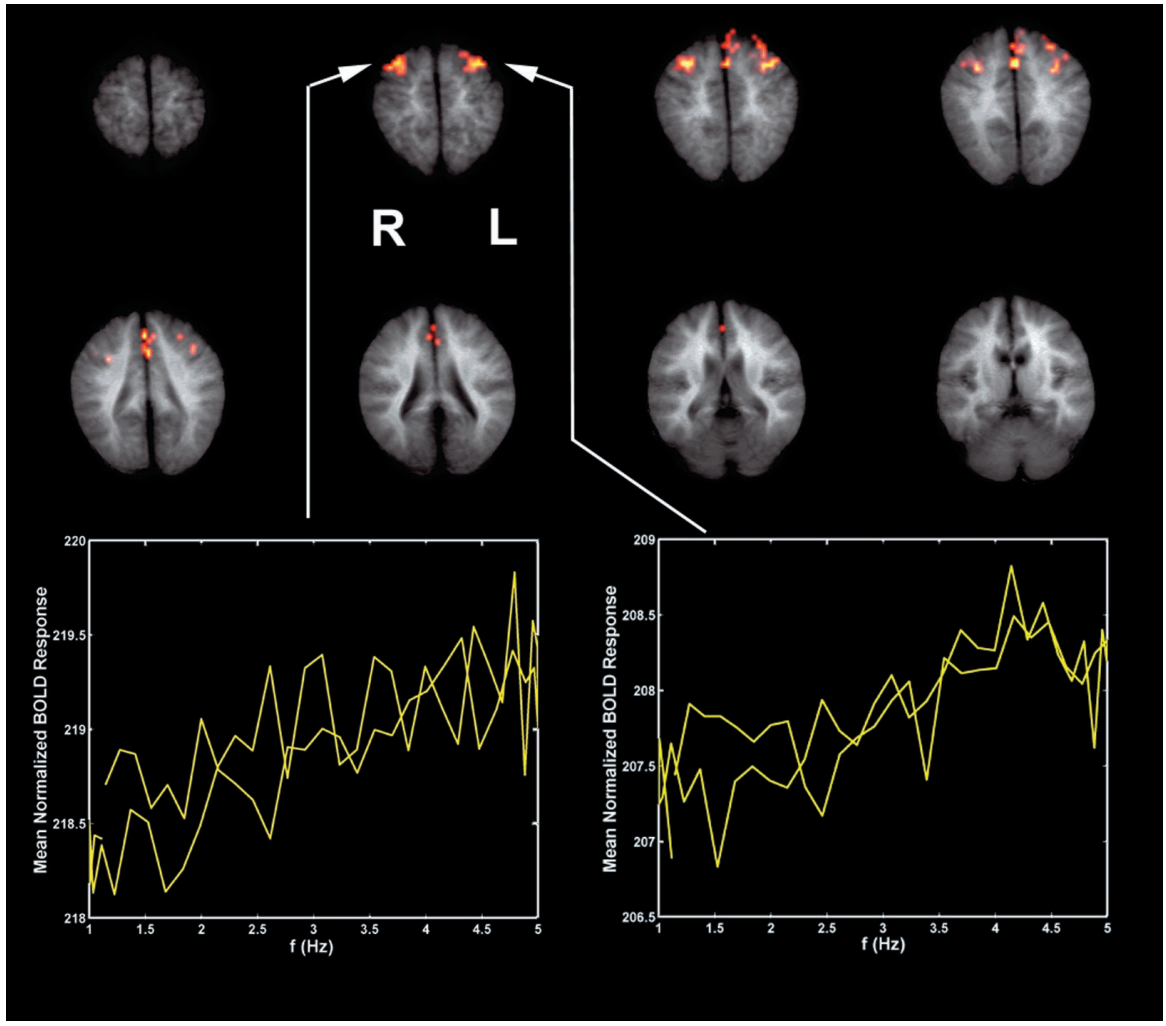


Figure 2. Results from a linear correlational analysis across subjects. Areas of significant linear correlation with tapping frequency were thresholded at $p < 0.001$ (corrected for spatial extent at $p < 0.05$) and overlaid on the mean MRI of all subjects (after spatial normalization). The top and bottom image planes are not shown, because there was no significant effect observed in these regions. The waveform of tapping frequency was convolved with a hemodynamic response function before correlation. A mean dose–response curve for both the left and right motor region demonstrates this correlation but shows that this is a nonlinear relationship.

parameter, tapping rate. The fact that brain regions were identified in individual subjects that showed time courses highly correlated with the driving frequency is significant in the context of a continuous paradigm. There is ample evidence for a monotonic relationship of cortical activation to tapping frequency in blocked paradigms (Blinkenberg et al., 1996; Rao et al., 1996; Sadato et al., 1996, 1997; Schlaug et al., 1996; Jancke et al., 1998; Ramsey et al., 1998), but the nonlinearity of this relationship has been difficult to demonstrate because of intersubject averaging. The time courses shown in Figure 3 are all nonlinear in different ways. The ICA decomposition showed that nonlinearities can also appear in the spatial domain, as evidenced by the appearance of different spatial activity maps at different frequencies (Thickbroom et al., 1998).

A nonlinear dose–response curve for finger tapping frequency has already been suggested (Sadato et al., 1996, 1997; Ramsey et al., 1998), but equally interesting was the demonstration of hysteresis (Fig. 3). Speeding up was not the same as slowing down, even at a specific frequency. This raises the question of whether this is a property of the tissue itself, or whether speeding up and slowing down are different cognitive states. Behavioral responses were not acquired during this task, so neither reaction times nor error rates were available for correlation, but the observation is sufficient to state that history effects are important and that assumptions about stationarity are potentially suspect.

The subjective perception of the task gives some insight into the cognitive state. Most subjects reported that slowing down was more difficult than speeding up. Considering this as a simple stimulus–response task, during the acceleration phase, the stimulus always arrives slightly earlier than expected, and thus triggers a response. During the deceleration phase, each stimulus is delayed, and the subject must actively inhibit their tendency to respond until the stimulus arrives. It is tempting to postulate attentional effects, but alternatively one can simply allow the data themselves to define what constitutes a cognitive state. Although subjects were all apparently doing the same task, finger tapping, the hysteresis of the brain activity patterns differentiated between the parts of the task. The appearance of other spatial modes at different frequencies also supports the notion that different cognitive processes may be involved at higher tapping frequencies.

New analytic methods, such as ICA, have made it possible to identify task-related components of brain activity even when one

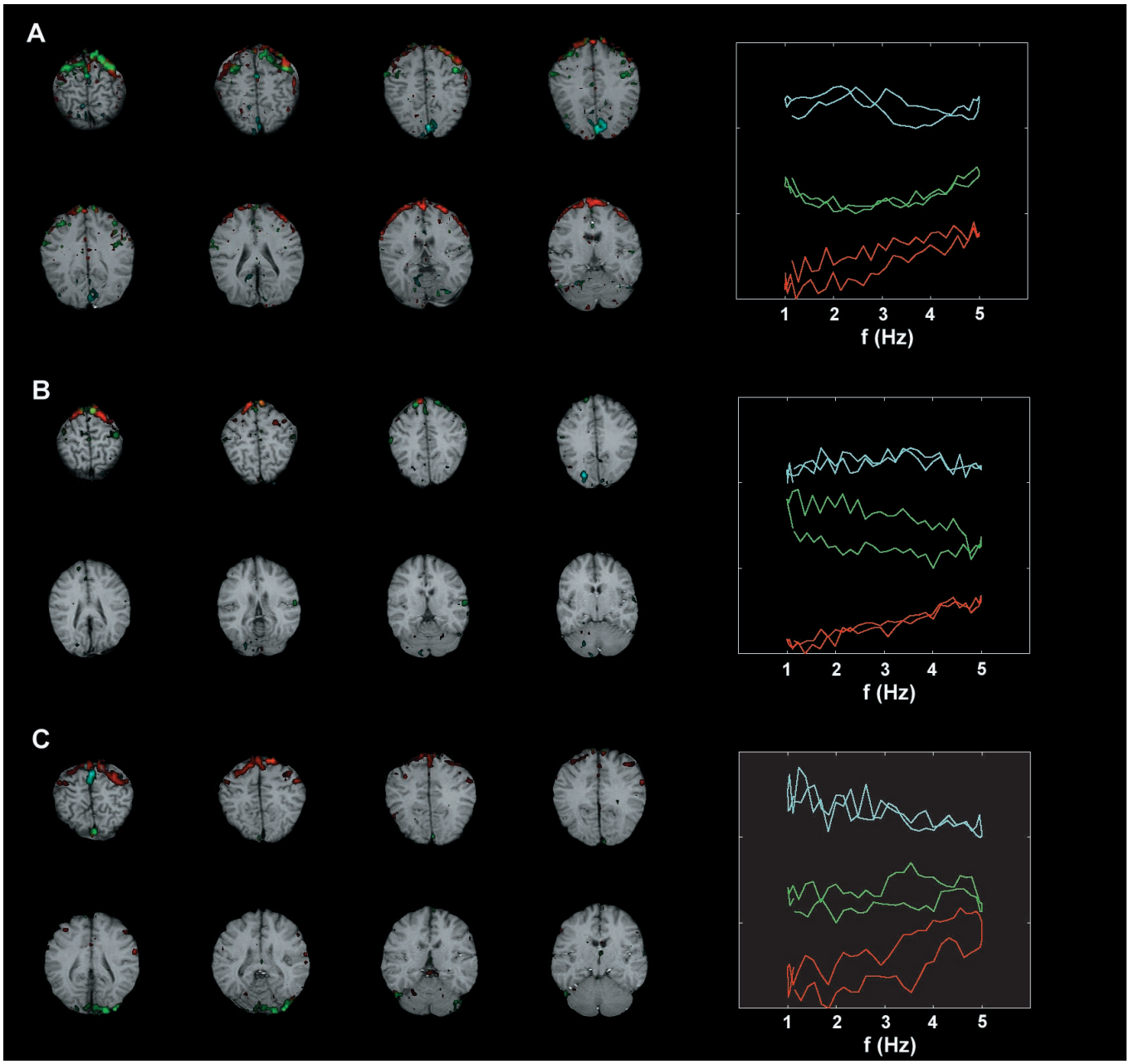


Figure 3. Spatial maps and dose–response curves of ICA components related to tapping frequency in three subjects. The three components (*red*, *green*, *blue*) showing the strongest relationship to tapping frequency are displayed for each subject. The spatial maps were interpolated to 256 × 256 resolution and overlaid on each subject's structural image. To improve localization, the spatial maps were thresholded to exclude any pixels with magnitude <10% of the maximal pixel value. The dose–response curve for each of these components is shown to the *right* (placed above each other for visualization purposes only). Most subjects displayed at least one linear component (*red*), but this had different amounts of hysteresis between subjects. Other components showed nonlinear relationships to tapping frequency and with varying amounts of hysteresis (*green, blue*). There was a tendency for more medial components (*A, B, green*; *C*, *blue*) to display a relationship opposite to the motor cortex. This region was situated close to the SMA. Animation (linked to this figure) of the first slice from subject B demonstrates the full spatiotemporal dynamics. The animation was created by modulating each spatial component by the corresponding time course. The *slider bar* indicates the instantaneous tapping frequency and cycles between 1 and 5 Hz. The *red* component was linearly related to tapping frequency, independent of history effects, but the *green* component showed substantial hysteresis. It was relatively inactive during the acceleration phase but became increasingly active during deceleration.

does not know the shape of the relationship beforehand (McKeown et al., 1998a,b). This is a powerful approach, because it allows one to design experiments in the absence of fixed effects, which are necessary for conventional ANOVA-type models. It also demonstrates the possibilities of continuous fMRI. Comparison conditions are notoriously difficult to design, because one must hypothesize about the relevant cognitive dimension to the task and then design an appropriate control condition along this dimension. Even parametric, but discrete, tasks, such as working memory tasks in which the number of items retained in memory is varied (Cohen et al., 1997; Callicott et al., 1998; Courtney et al., 1998), do not allow for the possibility that dramatic alterations in both brain state and cognitive strategy occur between levels in the task. Continuously varying tasks afford the opportunity to see

whether there are smoothly varying brain regions or whether they go through discrete jumps to different states and whether these transitions are history-dependent.

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