Elucidating the impulse response function of SEEP contrast in the human spinal cord by means of event-related spin-echo spinal fMRI

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Introduction

Event-related fMRI has demonstrated considerable utility for discerning between brief changes in brain states, and is now commonly used in both systems and cognitive neuroscience.[1] However, as of yet, there have been no reports of event-related spinal fMRI in the literature, likely because of the difficulties associated with imaging a suitable length of cord (with adequate spatial resolution), while achieving sufficient signal- and contrast-to-noise ratios in the presence of cardiac-related spinal cord motion.[2] However, with recent methods to reduce motion-related confounds, the sensitivity and specificity of proton-density weighted spin-echo spinal fMRI – based on signal enhancement by extravascular water protons (SEEP) – has been dramatically improved.[3]

The purpose of this experiment was to exploit the improved sensitivity of these new motion-compensating spinal fMRI techniques to detect and map peristimulus signal intensity changes induced by brief periods of cold thermal stimulation. Therefore, by achieving these objectives, this study has refined our understanding of the SEEP impulse response function in the healthy human spinal cord, and in so doing, also represents the first successful demonstration of event-related spinal fMRI.

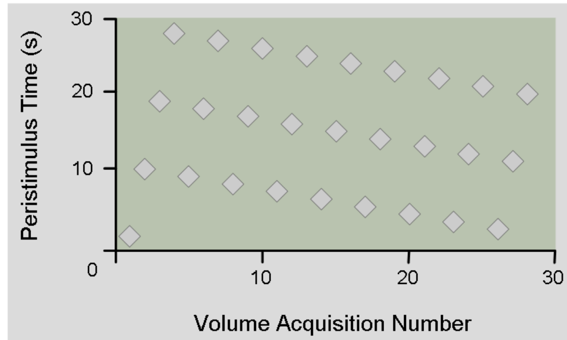

Figure 1: Event-related thermal stimulation versus acquisition timing for a given slice. For example, images acquired in the 1st, 2nd, 3rd, and 4th volume occur 1, 10, 19, and 28 seconds following the stimulus epoch (respectively). The entire peristimulus time-course can therefore be sampled at 1 Hz by acquiring 28 volumes (252 seconds).

Methods

Block-designed functional localizer: Before acquiring any event-related spinal fMRI data, each experiment began with a block-designed paradigm to investigate applications of 22 °C thermal stimulation to the palm of the right hand, approximately at the level of the C6 dermatome. This was achieved by applying 45 second epochs of 22 °C, interleaved with 63 second periods of 32 °C (i.e., skin temperature) baseline conditions. Functional MRI data were acquired using a spin-echo spinal fMRI protocol with 9 contiguous sagittal slices (TE = 38 ms; TR = 1000 ms/slice; FOV = 200 × 100 mm^2 spanning the entire cervical spinal cord, brainstem, and thalamus; flip angle = 90° with 150° refocusing pulses; slice thickness = 2.00 mm; in-plane resolution = 1.02 × 1.02 mm^2). The spinal fMRI data were then analyzed using a RESPITE general linear model (p = 0.001), as previously described,[3,4] so that the peristimulus time-course of activated voxels could be closely studied in the subsequent event-related experiments.

Event-related spinal fMRI protocol: To establish the time-course of the SEEP response, spinal cord proton-density weighted signal changes were then measured during brief periods of cold thermal stimulation. The event-related paradigm consisted of 1 second intervals of 22 °C, with an interstimulus interval of 28 seconds, in order to avoid convolving sequential impulse responses associated with the periodic thermal stimuli. Therefore, due to the 9 second effective TR, a unique peristimulus time was acquired during each imaging volume, as illustrated in Figure 1, and for each of the 9 slices, the complete impulse response function (from 1-28 seconds) was able to be acquired – with a sampling frequency of 1 Hz – in 28 volumes (252 seconds). In this manner, an impulse response time-course was extracted, on a subject-by-subject basis, for every active voxel identified in the block-designed portion of the study.

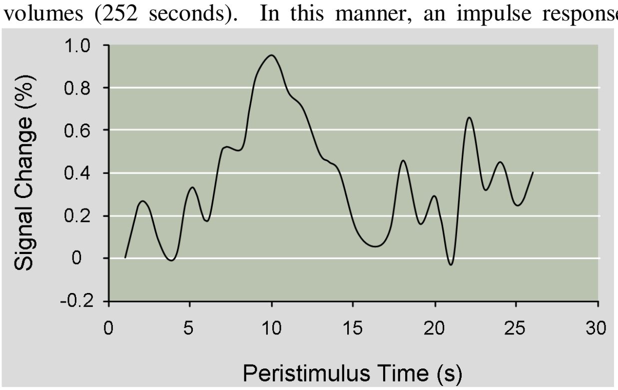

Figure 2: Experimental data showing the SEEP impulse response function in the healthy human spinal cord. Data are plotted as the average signal intensity change (across all experiments and all subjects) as a function of peristimulus time. Note that the maximum signal change (~ 1%) occurs approximately 10 seconds following the stimulus.

Results and Conclusions

By using a block-designed functional localizer, and then acquiring event-related spinal fMRI data, we were able to map the SEEP impulse response function in the healthy, intact human spinal cord. Figure 2 shows the peristimulus signal intensity averaged across all voxels, all experiments, and all subjects. Although previous reports have suggested that the SEEP response is slower than blood-oxygen-level-dependant (BOLD) signal changes, estimating a maximum peristimulus response at approximately 6 or 7 seconds,[5] our data indicate that the peak SEEP response may, in fact, lag the stimulus by as much as ~10 seconds in the cervical spinal cord.

By virtue of the fact that an event-related response was clearly observed, and moreover, that the peristimulus signal time-course was able to be measured, this is the first clear demonstration of event-related spinal fMRI. What is more, by improving our understanding of the SEEP impulse response function in spinal cord tissue, future spinal fMRI studies can implement this to more accurately model event-related signal changes: a factor that is critically important for the sensitivity of event-related fMRI studies.

References

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