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Development and validation of retrospective spinal cord motion time-course estimates (RESPITE) for spin-echo spinal fMRI: Improved sensitivity and specificity by means of a motion-compensating general linear model analysis

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ABSTRACT

Cervical spinal cord displacements have recently been measured in relation to the cardiac cycle, substantiating that cord motion in this region reduces both the sensitivity and reproducibility of functional magnetic resonance imaging of the spinal cord (spinal fMRI). Given the ubiquitous and complex nature of this motion, cardiac gating alone is not expected to sufficiently remove these errors, whereas current modeling approaches for spin-echo methods are not specific to motion artifacts, potentially eliminating function-related data along with components of motion-related noise. As such, we have developed an alternative approach to spinal cord motion-compensation, using retrospective spinal cord motion time-course estimates (RESPITE) to forecast a small number of physiological noise regressors. These are generated from the principal components of spinal cord motion, as well as subject-specific cardiac data, and are subsequently included in a general linear model (GLM) analysis. With this approach, the components of motion-related signal fluctuation are modeled, along with functionally-relevant signal changes (i.e., those components fitting the stimulus paradigm), to account for the effects of spinal cord and cerebrospinal fluid (CSF) motion in a thorough, yet discerning, manner. By analyzing 100 previously acquired half-Fourier turbo spin-echo (HASTE) spinal fMRI data sets, along with a collection of null-task data, we show that the implementation of RESPITE reduces the occurrence of both type I (false-positive) and type II (false negative) errors, effectively increasing the specificity (5–6%) and sensitivity (15–20%) to neuronal activity.

Introduction

Given its small cross-sectional area, substantial length, and proximity to vertebrae, functional magnetic resonance imaging of the spinal cord (spinal fMRI) presents many unique challenges in addition to those routinely encountered during fMRI of the brain (Brooks et al., 2008; Maieron et al., 2007; Stroman, 2005). In addition, spinal cord (SC) motion and the flow of cerebrospinal fluid (CSF) are thought to further confound the analysis, and therefore the interpretation of functional data (Brooks et al., 2008; Madi et al., 2001; Stroman, 2006). For these reasons, spin-echo (SE) spinal fMRI methods have adapted and evolved to maximize spatial and temporal resolution, as well as scanning efficiency (volume versus time), while minimizing magnetic susceptibility-related image artifacts resulting from the vertebrae and inter-vertebral discs (Stroman et al., 2005). On the other hand, the effects of motion have yet to be addressed with comparable rigor — no doubt owing to our prior lack of knowledge regarding the normal, periodic motion occurring within the human spinal canal.

It is likely that all fMRI time-course data contain, to some degree, the desired task-dependent signal changes (related to neuronal activity), as well as superimposed perturbations owing to various components of noise, physiological or otherwise (Biswal et al., 1996). Unfortunately, physiological changes are often aliased into similar frequency regions as the functional paradigm, thereby mimicking, and reducing the statistical significance of actual task-related signal changes (Biswal et al., 1996; Glover et al., 2000; Lund et al., 2006). For spinal fMRI studies, it has long been suspected, but not confirmed, that this type of low-frequency noise – resulting from SC and CSF motion – comprises the largest source of systematic error, contributing to both type I (false-positive) and type II (false negative) errors (Brooks et al., 2004; Figley and Stroman, 2006; Moffitt et al., 2005). It has already been observed that SC motion produces time-dependent partial volume effects along the cord/CSF interface (Figley and Stroman, 2007); and the movement of tissues between adjacent slices may also change the effective repetition time (TR), depending on the direction of motion and the slice orientation. For these reasons,

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deficits in our understanding of normal SC movements (direction, magnitude, and timing) have made it difficult to estimate, let alone correct for such errors.

Previous efforts to prospectively address the effects of physiological motion have been made for both gradient-echo (GRE) and SE spinal fMRI techniques, although to date, these have not yielded definitive (and simultaneous) gains in sensitivity *and* specificity. For example, early attempts showed that cardiac gating yielded modest improvements in the sensitivity of GRE spinal fMRI (Brooks et al., 2004); however, given the persistent and complex nature of CSF and SC motion, it is unlikely that cardiac gating alone is sufficient to fully eliminate motion-related noise (Figley and Stroman, 2007). Alternatively, implementation of a SE fluid-attenuated inversion recovery (FLAIR) sequence – to reduce CSF inflow artifacts – did not show consistent task-related signal changes (Moffitt et al., 2005), perhaps because of the inherent T_1-weighting added as a result of the inversion recovery sequence.

Retrospective motion-compensation techniques, on the other hand, have shown greater promise. A recent study by Brooks et al. (2008) has determined an optimal retrospective motion-compensating method for gradient-echo echo-planar imaging (GRE-EPI) spinal fMRI. This approach is based on the RETROICOR method (Glover et al., 2000), and uses a series of 37 sinusoidal (sine and cosine) motion regressors – derived primarily from cardiac, respiratory, and interaction (cardiac and respiratory) terms – to model physiological noise. However, because this approach has been optimized for GRE-EPI acquisition parameters, it is unlikely to have similar efficacy for single-shot fast spin-echo (SSFSE) or half-Fourier single-shot turbo spin-echo (HASTE) spinal fMRI acquisition parameters, which have been used in more than half of the reported spinal fMRI studies to date (Giove et al., 2004; Stroman, 2005). Because the SSFSE and HASTE sequences are more robust to magnetic susceptibility artifacts and global phase shifts owing to changes in lung volume, respiratory effects are not as significant compared to data acquired with GRE-EPI readouts; hence, the main sources of physiological noise are expected to be cardiac-related (Stroman, 2006). This is due not only to the differences between proton-density-, T2-, and T2*-weightings, but will also result from the differences between the spatial encoding schemes (fast spin-echo versus EPI), with respect to their signal-to-noise and vulnerability to spatial distortions. However, the long TRs of these non-EPI SE sequences will cause more severe aliasing of higher frequency physiological parameters (such as cardiac pulsations) compared to GRE-EPI and other faster imaging sequences. Therefore, given the differences between GRE-EPI and SSFSE or HASTE, and the resultant trade-offs between speed and susceptibility artifacts, it is important to develop an optimized motion-compensating method for these single-shot spin-echo spinal fMRI techniques.

Historically, attempts to model physiological noise in SE spinal fMRI have suffered from an inability to precisely model the confounding physiological processes. Including resampled cardiac traces in a retrospective general linear model (GLM) analysis has been shown to produce fewer false-positive activations and better voxel-wise reproducibility across subjects (Stroman, 2006). However, because this approach uses a large (and potentially non-specific) GLM basis set, it is prone to overfitting physiological noise, thereby reducing the sensitivity to neuronal activity by removing components of task-related signal change along with motion-related noise. Therefore, while modeling structured noise has shown great promise for functional brain imaging (Deckers et al., 2006; Glover et al., 2000; Lund et al., 2006) and GRE-EPI spinal fMRI methods, a similar approach has not yet been developed for SE spinal fMRI.

Fortunately, recent studies of pulsatile CSF and SC motion have revealed significant temporal consistencies between their velocity/displacement and cardiac phase, allowing accurate estimates of CSF and SC motion time-courses from cardiac pulse recordings. It has been established that peak CSF flow in the spinal canal occurs synchronously with systole in the carotid artery (Enzmann and Pelc, 1991), and that maximum SC velocities occur slightly after the peripheral pulse (Feinberg and Mark, 1987; Figley and Stroman, 2007; Levy et al., 1988). Furthermore, the principal components (PCs) of anterior-posterior SC motion (i.e., the largest directional component) have also been calculated relative to the peripheral pulse, and it has been shown that linear combinations of as few as three PCs are sufficient to accurately model cardiac-related cord motion on a subject-by-subject basis (Figley and Stroman, 2007).

With the ability to record the cardiac pulse during fMRI experiments and the new-found capacity to model SC motion from three cardiac-related PCs (Figley and Stroman, 2007), we believe that it is now possible to remove motion-related noise from single-shot SE spinal fMRI by means of a highly selective modeling approach, ultimately improving the sensitivity and specificity of spinal fMRI to neuronal activity. Thus, we have developed a method to generate retrospective spinal cord motion time-course estimates (RESPITE), and incorporate these into an automated general linear model (GLM) analysis, creating subject- and slice-specific models of SC motion to reduce the prevalence of physiological noise. Herein, we describe the development and implementation of RESPITE, and demonstrate the efficacy of this method in reducing motion-related errors in SE spinal fMRI data.

Materials and methods

Method development: general

All software was written in MatLab® (The Mathworks Inc., Natick, MA) on Windows®-based PC workstations (Sun Microsystems Inc., Santa Clara, CA). The new analysis program was written and integrated into an existing suite of spinal fMRI analysis software (Stroman et al., 2005; Stroman, 2006), which is based on statistical parametric mapping (SPM) methods described by Friston et al. (2006). The required inputs for the proposed method include recordings of the peripheral pulse data, the relative timing of each slice acquisition, and the time-course of the functional paradigm.

In order to achieve large volume coverage in a reasonably short time, HASTE spinal fMRI data are typically acquired in sagittal slices, which are subsequently reformatted into transverse segments to facilitate anterior–posterior and medial–lateral SC alignment (Stroman et al., 2005). With this in mind, the method described herein has been developed specifically for the analysis of sagittal image data, performing a slice-by-slice GLM analysis (using the sagittal image data) before reformatting, aligning, and normalizing the data to a standard SC reference volume (Stroman et al., 2008a). Thus, cardiac-related SC motion is modeled before reformatting the sagittal data into transverse slices and, in so doing, mixing data acquired at different cardiac phases (i.e., different phases of cord motion).

Method development: modeling and removing motion-related noise

As a first approach, high-frequency signal fluctuations in the time-course image data are removed with a low-pass filter. For all analyses reported herein, the cutoff frequency and transition bandwidth were set to one-half and one-quarter of the Nyquist frequency (i.e., one-quarter and one-eighth of the sampling frequency), respectively.

Retrospective spinal cord motion time-course estimate (RESPITE) terms are generated from the previously reported principal components (PCs) of cardiac-related cord motion (Figley and Stroman, 2007) sampled appropriately to account for cardiac phase and interleaved slice timing. First, SC motion is modeled throughout the entire experiment with proper phase alignment during each inter-systolic interval (Fig. 1A). This is achieved by temporally scaling and then replicating each of the three PCs between systolic periods (from peak-to-peak) in the peripheral pulse trace. As Fig. 1A shows, the three PCs

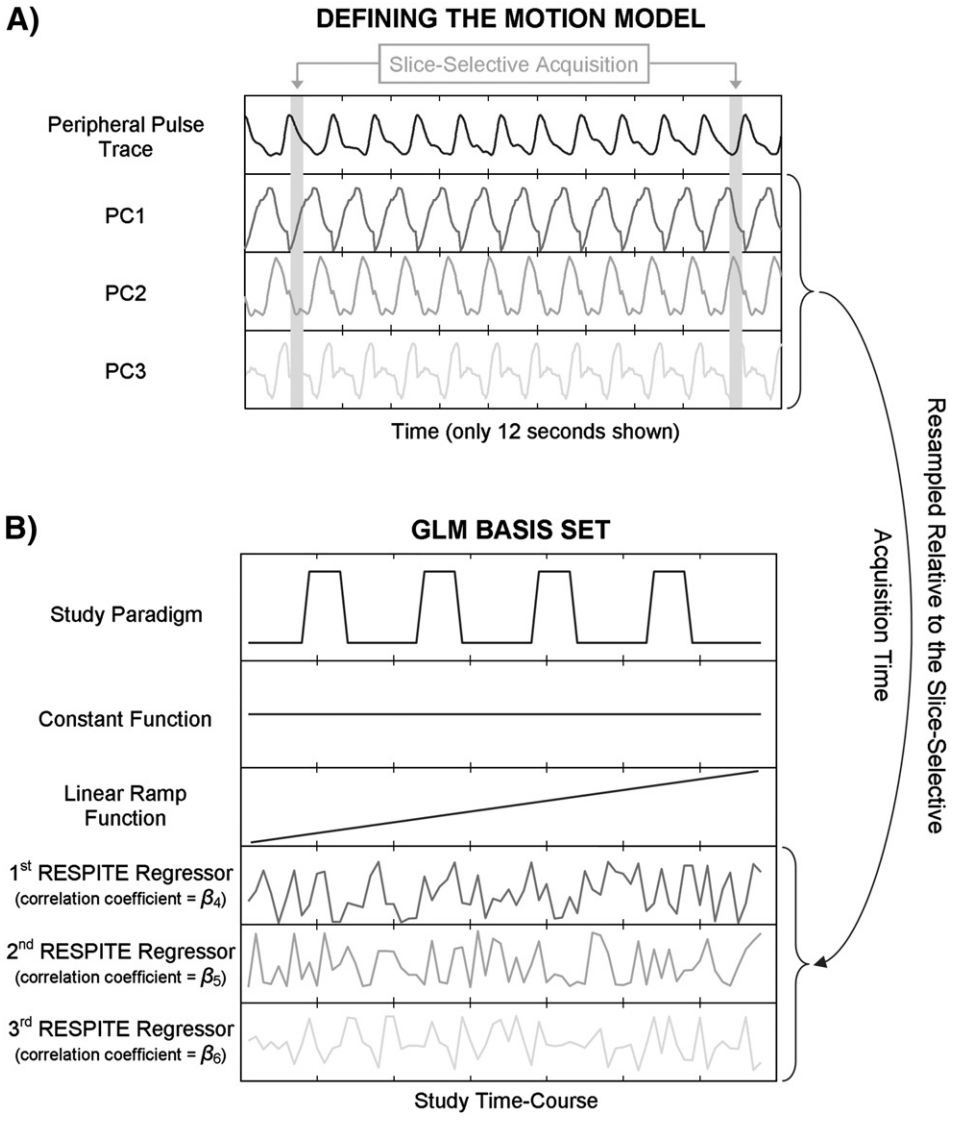

Fig. 1. Motion-compensation is achieved by including three RESPITE terms in the GLM basis set. A) The RESPITE terms are custom-generated by first modeling the principal components (PCs) of cardiac-related spinal cord motion between systolic onsets in the cardiac time-course, and then resampling each of these on a slice-by-slice basis to account for phase shifts between the resultant cord motion model and the slice acquisition timing. B) An example of a motion-compensating (MC) basis set. Note that RESPITE terms are custom-generated for each sagittal slice within the imaging volume, and thus, each slice is analyzed by means of a unique GLM basis set.

are replicated and automatically stretched or compressed (temporally) so as to fit between each of the systolic peaks in the peripheral pulse time-course. The three resultant traces – comprising a model of cardiac-related SC motion – are then resampled (to account for the phase of motion) at the acquisition times of each slice. For example, resampling the cardiac-aligned PCs with respect to the acquisition times of a single slice (i.e., the locations of the vertical bars in Fig. 1A) produces the RESPITE terms for that particular slice (i.e., the lower three elements of Fig. 1B). Note, however, that each slice in the image volume will yield slightly different RESPITE terms, owing to differences in acquisition timing. Therefore, compensation for SC and CSF motion is achieved by means of an automated GLM analysis, which employs a customized basis set and performs the subsequent statistical analysis on a subject-by-subject and slice-by-slice basis. In all, each GLM employs six basis functions: the stimulation paradigm, a constant term, a linear ramp, and the three additional RESPITE regressors that depend on the slice acquisition timing (Fig. 1B).

Following the slice-specific analysis, the motion-compensated spinal fMRI results are then aligned in the anterior-posterior direction before reformatting the sagittal images into cubic voxels and transverse segments, as previously described (Stroman et al., 2005). These data are then spatially normalized and co-registered to a spinal cord reference volume (Stroman et al., 2008a), allowing region-of-interest (ROI) analysis, and enabling comparisons across a group (or groups) of subjects. By means of an ROI mask, the software also permits data from different regions of the cord, brainstem, and/or surrounding anatomy (i.e., CSF, vertebrae, etc.) to be included or excluded from further analysis.

Method validation

Previous reports have used task-dependent and 'resting state' fMRI to quantify the sensitivity and specificity of fMRI analysis methods (Biswal et al., 1996; Brooks et al., 2008). Therefore, to validate the RESPITE method, a database of 100 spinal fMRI datasets were analyzed with, and then without SC motion regressors in the GLM basis set. All spinal fMRI data were collected using a 3 T whole-body system (Siemens Magnetom Tim Trio, Erlangen, Germany), with subjects lying supine. Each of the experimental protocols had been fully approved by the Institutional Research Ethics Board, and all subjects provided informed consent prior to study enrollment. Time-series image data were collected in accordance with previously reported spinal fMRI

parameters based on signal enhancement by extravascular water protons (SEEP) (Stroman et al., 2007, 2008b). Each protocol consisted of either 9 or 14 contiguous sagittal slices, each with 200×100 mm^2 field of view (spanning the entire cervical spinal cord, brainstem, and thalamus); TE=38 ms; TR=1000 ms/slice; flip angle=90° (with 150° refocusing pulses); slice thickness=2.00 mm. Thus, partial *k*-space data were acquired in 192×96 matrices (phase oversampling=11 lines; total phase-encoding lines acquired=59; echo spacing≈3.2 ms; readout time≈189 ms), yielding predominantly proton-density weighted images with 1.02×1.02 mm^2 in-plane resolution. Cardiac data were recorded continuously throughout each study using a peripheral pulse oximeter (sampling rate of 50 Hz) attached to the subject's index finger, while TTL trigger pulses, at the time of each slice acquisition, were recorded (sampling rate of 200 Hz). These traces were sampled synchronously by the Siemens MRI console.

The 100 sets of spinal fMRI data were selected from a large archive of previously acquired data. Of these, 44 were acquired from eleven subjects undergoing periods of 15 °C thermal stimulation during an audio-visual attention/distraction task, 24 were acquired from eight subjects undergoing periods of 42 °C, 46 °C, and again 42 °C thermal stimulation (without an attention/distraction task), and 32 were acquired from eight subjects undergoing somatosensory stimulation with 2 gram and 15 gram von Frey filaments, and two artist's brushes of different stiffness (all on-going studies, unpublished data). The complete experimental details, results, and discussion of these studies – hereafter referred to as 'Attention', 'Thermal', and 'Touch', respectively – are beyond the scope of this manuscript, and will therefore be published separately. Their purpose here is to serve as a sufficiently large and diverse sampling of spinal fMRI data which can be used to evaluate the performance of our proposed motion-compensating GLM. To this end, data from each study type were characterized with, and then without including RESPITE terms in the GLM basis set – referred to as MC (motion-compensated) and UC (uncompensated) analysis, respectively – allowing a comparative analysis on the effects of the motion regressors across a number of statistical thresholds (specifically $p=0.0001$, $p=0.0005$, $p=0.001$, $p=0.003$, and $p=0.005$).

Data from the MC analysis were also analyzed to determine where, anatomically, the motion model had the largest effects. To this end, the root-mean-squared power (RMS) of the RESPITE correlation coefficients (β_4, β_5, and β_6, respectively) was calculated across all of the 'Attention', 'Thermal', and 'Touch' data sets ($n=100$):

$$RMS = \frac{\sum_{i=1}^{n} \sqrt{\beta_4^2 + \beta_5^2 + \beta_6^2}}{n}. \quad (1)$$

The voxel-wise RMS was then assigned a color scale and plotted to show the magnitude and spatial distribution of anatomical regions that contained components of the modeled SC motion (Fig. 2).

To further support method validation, a set of 'Null-Task' data sets ($n=4$; 2 male, 2 female) were also acquired, during which no time-variant stimuli or tasks were imposed. These studies employed the same imaging protocol as used in the 'Attention', 'Thermal', and 'Touch' studies (described above). As with the 100 previously acquired spinal fMRI data sets, these 'Null-Task' data were then analyzed with the MC and UC analysis methods at the same statistical thresholds (*p*-values). However, because a model study time-course is required for GLM analyses, a hypothetical block-designed paradigm, similar to the 'Attention', 'Thermal', and 'Touch' studies, was imposed over the 42 acquired volumes. Because there is no reason for structured motor or stimulus-induced neuronal activity to correlate with this paradigm, the number of 'activated' voxels in this analysis is expected to provide a relative estimate of the false-positive rate, thereby providing a relative estimate of the specificity to neuronal activity (Biswal et al., 1996). As such, the results were normalized and fit to a SC reference volume and ROI mask (Stroman et al., 2008a) to facilitate group analyses. With the results broken down by study type ('Attention', 'Thermal', 'Touch', and 'Null-Task'), analysis type (MC or UC), and statistical threshold, the number of positively correlated (i.e., 'active') voxels within the cervical cord were identified, and the signal characteristics (mean and standard deviation) of these voxels were determined.

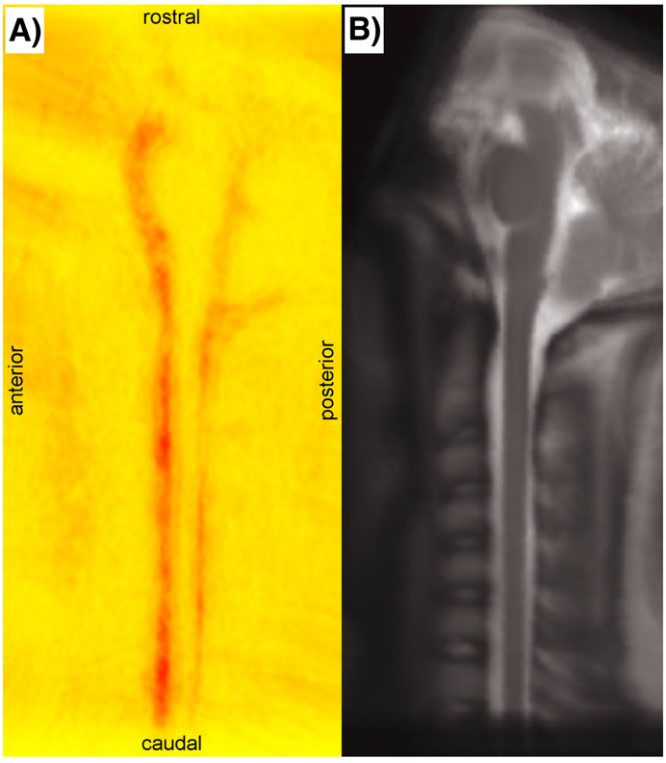

Fig. 2. A) A midsagittal color map depicting the voxel-wise root-mean-squared power (RMS) of the RESPITE coefficients across 100 motion-compensated spinal fMRI studies ('Attention', 'Thermal', and 'Touch'), and B) a midsagittal spinal cord reference volume. Regions of high, intermediate, and low RMS are shown in red, orange, and yellow (respectively). Outlines of the cervical spinal cord, midbrain, pons, and cerebellum are clearly visible, indicating that the motion-compensating RESPITE terms have the largest effect in the cerebrospinal fluid (CSF) and along the spinal cord/CSF interface.

Results and discussion

After developing and incorporating RESPITE terms into a motion-compensating GLM, HASTE spinal fMRI data were analyzed to validate and quantify any improvement(s) in specificity and/or sensitivity resulting from the inclusion of these motion-specific models. The anatomical locations most affected were identified by calculating the RMS power of the RESPITE correlation coefficients (i.e., the β-values) across the 'Attention', 'Thermal', and 'Touch' studies ($n=100$). Fig. 2 shows a midsagittal color map of the RMS power on a voxel-by-voxel basis, averaged across all 100 studies. The largest components of modeled motion (red) appear throughout the paraspinal subarachnoid space, indicating that the motion regressors – although modeled from the resampled PCs of SC motion – simultaneously account for the temporally correlated flow of CSF. Moreover, intermediate (orange) regions along the anterior and posterior SC/CSF interfaces, demonstrate that components of structured noise in the cord tend to be localized along the edge, similar to previous accounts of cardiac-related noise in the brain (Deckers et al., 2006; Glover et al., 2000; Lund et al., 2006). It also appears that the motion-compensating GLM reduces artifacts in regions beyond the spinal canal, as evidenced by the clear edge definition (between yellow and red regions) observed around the midbrain, pons, and cerebellum. This suggests that CSF-related artifacts in these regions are also correlated with the RESPITE terms, and implies that SC motion is driven by CSF flow.

In order to quantify the sensitivity and specificity of the RESPITE GLM (MC) compared to the uncompensated analysis (UC), the numbers of active voxels were compared at a number of statistical thresholds: $p=0.0001$, $p=0.0005$, $p=0.001$, $p=0.003$, and $p=0.005$. The solid (MC) and dashed (UC) black lines in Fig. 3 show that motion-compensation not only increased the total number of active voxels identified in the 'Attention', 'Thermal', and 'Touch' studies, but also reduced the total number of active voxels identified in the 'Null-Task' studies. Across the three task-related studies, the RESPITE analysis increased the number of positively correlated voxels by 14.8±1.6% and 20.7±2.9% (mean±SD at p-values of 0.001 and 0.0001, respectively), suggesting that the MC analysis improved the overall sensitivity, with an increasing effect at higher statistical thresholds (i.e., lower p-values). On the other hand, the total number of 'Null-Task' (i.e., false-positive) activations was decreased 6.1% and 4.5% (at p-values of 0.001 and 0.0001, respectively) as a result of the RESPITE terms, showing a decreasing, though noticeable effect, even at the lower p-values (see inset of 'Null-Task' panel in Fig. 3). The concurrent reduction of type I and type II errors is likely a result of the large regressor correlations throughout CSF-filled regions, and along the cord edge (resulting from SC motion and partial volume averaging with CSF). By reducing the residual variance estimates (compared to the uncompensated analysis), the RESPITE regressors serve to increase the statistical significance of the study paradigm — *ergo*, increasing the sensitivity to neuronal activity.

The number of exclusively active voxels – i.e., those that were identified as active with one *or* the other, but not both, GLMs at a given statistical significance – are also shown for each group analysis in Fig. 3. Here, the solid (MC) and dashed (UC) gray lines exhibit similar trends to the corresponding number of total active voxels (black lines), with increased task-related activity and decreased resting state activity resulting from the MC analysis. However, while it seems that RESPITE increased the sensitivity and specificity to neuronal function, the relatively low numbers of exclusively active voxels (compared to the total numbers) affirms that task-related activity is not completely dominated by motion errors, even in UC spinal fMRI analyses. Therefore, this serves to validate previous SE spinal fMRI findings, revealing that earlier analyses (without motion-compensation) have probably suffered more from type II (false negative) than from type I (false-positive) errors. In this case, regions of apparent activity are likely to have been accurately reported, although other areas may have been erroneously overlooked due to cord motion and the resultant decrease in sensitivity.

Comparisons of the signal properties among active voxels in the cervical SC did not reveal any significant differences between the MC and UC analyses (Fig. 4). That is, for each experimental type, the

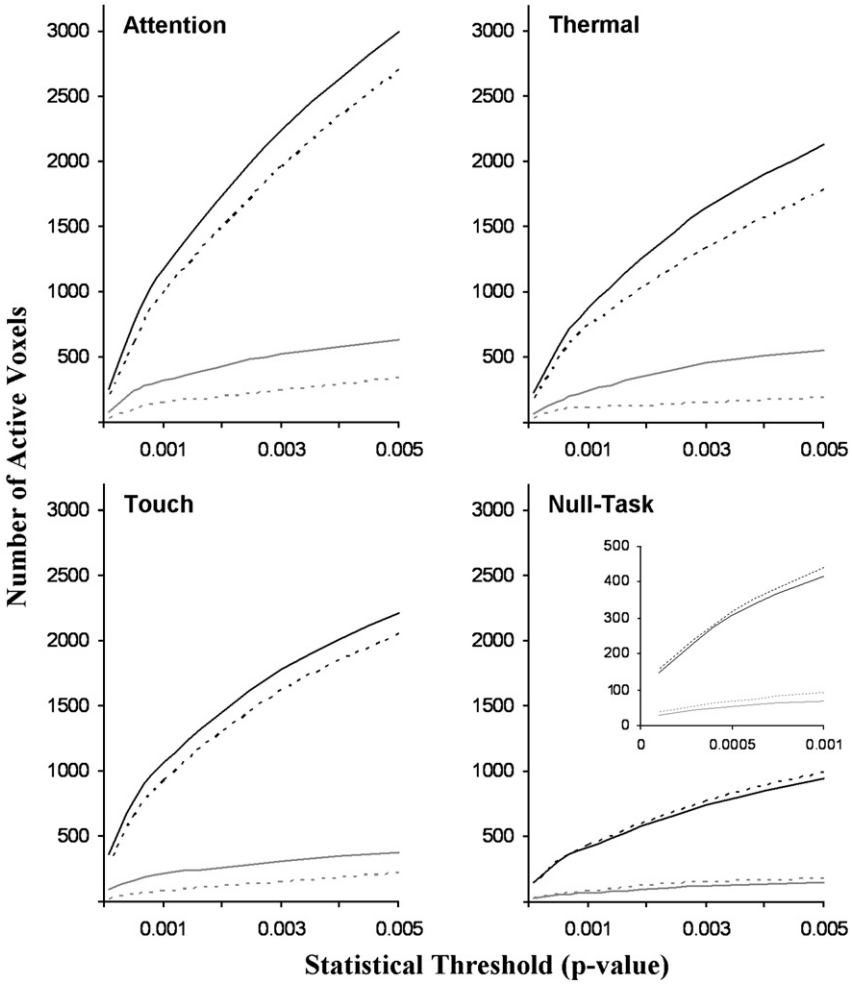

Fig. 3. Sensitivity curves showing the number of positively correlated voxels identified over a range of statistical thresholds (p-values). The total number of active voxels (black lines) and the number of exclusively active voxels (i.e., those identified *only with* or *only without* motion-compensated analysis; gray lines) are shown for each study type. Motion-compensated (MC) values are depicted with solid lines, whereas uncompensated (UC) values are depicted with dashed lines. Based on the proportion of exclusively active voxels (compared to the respective totals) in the 'Attention', 'Thermal', and 'Touch' studies, it is clear that motion-related noise reduces the sensitivity, but does not completely obscure task-related signal changes. By increasing the number of active and exclusively active voxels in the 'Attention', 'Thermal', and 'Touch' studies – and decreasing the number of active and exclusively active (i.e., false-positive) voxels in the 'Null-Task' data – it is apparent that RESPITE analysis increases both the sensitivity and specificity to neuronal activity.

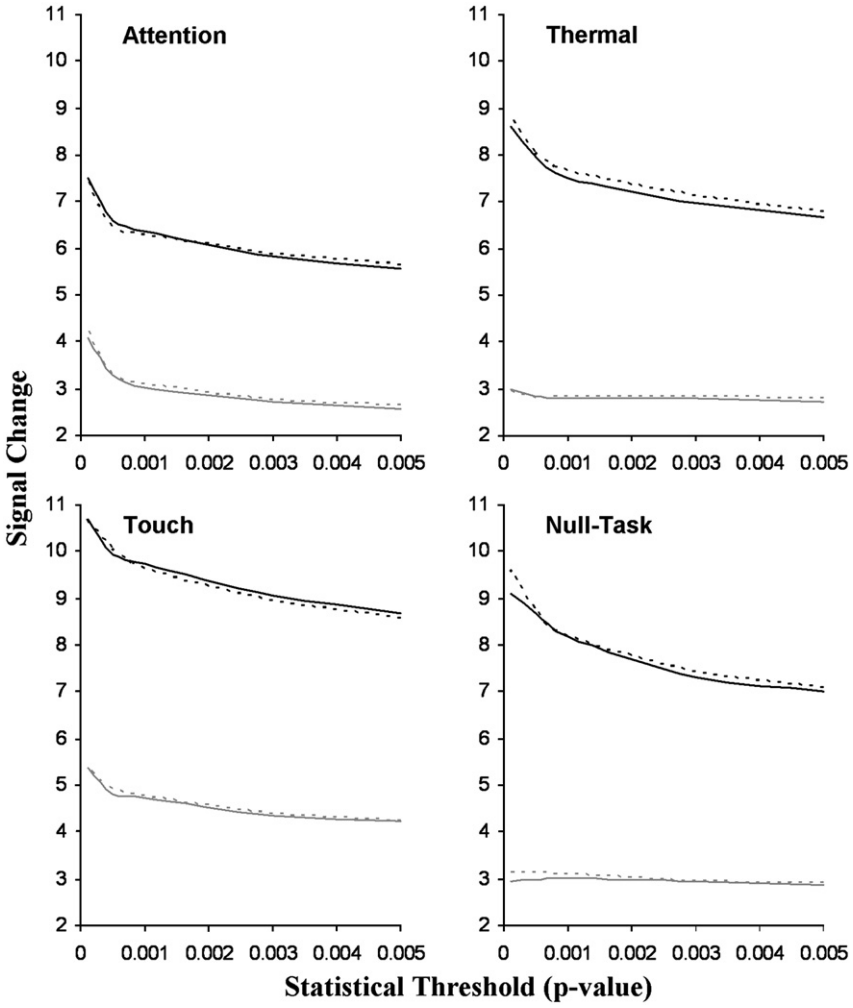

Fig. 4. Signal properties among positively correlated voxels within the cervical spinal cord. The average magnitude (black lines) and standard deviation (gray lines) are shown for each study type, with motion-compensated (MC) values depicted by solid lines and uncompensated (UC) values depicted by dashed lines across the range of statistical thresholds (*p*-values). Note that the magnitude and variability of signal changes are quite similar between MC and UC analyses, and across the 'Attention', 'Thermal', and 'Null-Task' studies, indicating that motion-related signal changes closely mimic activity-related signal changes. Elevated magnitude and standard deviation within the 'Touch' study can likely be attributed to the different stimuli (2 g and 15 g von Frey filaments, as well as soft and stiff artist's brushes) used to elicit activity.

average signal changes (solid and dashed black lines) are similar for both MC and UC analyses. In addition, the magnitude of 'Null-Task' signal changes are within the range of the other study types, confirming that motion-related artifacts are capable of closely resembling task-related signal changes. As a result of motion-compensation, however, there does appear to be an overall trend toward lower standard deviations (solid versus dashed gray lines). Unlike the task-related data, both gray lines (SD) in the 'Null-Task' panel of Fig. 4 are linear, implying that the SD of false-positive signal changes is approximately 3% regardless of statistical threshold. Consistent with Biswal et al. (1996), we also found that task-related signal changes often exhibit higher standard deviations than the physiological noise, particularly at lower *p*-values. The higher signal variability, especially in the 'Attention' (attending versus not attending to a thermal stimulus) and 'Touch' (tactile stimulation with 2 different von Frey filaments and 2 different artist's brushes) studies can likely in-part be attributed to the different stimuli presented within each broadly defined experimental type.

As previously stated in the Materials and methods section, both analysis methods (MC and UC) made use of a low-pass filter to remove signal fluctuations greater than one-half of the Nyquist frequency (i.e., one-quarter of the sampling frequency). Therefore, given that the effective TR=9 s for the 'Attention' and 'Thermal' experiments, and TR=14 s for the 'Touch' experiments (nine or fourteen slices at 1000 ms/slice), the cutoff frequency was either 0.028 Hz or 0.018 Hz. Cardiac-related fluctuations – ranging from 0.6 Hz to 1.5 Hz (Lund et al., 2006) – are not critically sampled given our imaging parameters, which means that they will be aliased between −0.056 Hz and 0.056 Hz. It is therefore possible that some components of physiological noise could have been removed by the low-pass filter, even before using the RESPITE GLM. Thus, in a sense, it is inaccurate to refer to the UC analysis as "uncompensated", as it may in fact have removed some cardiac-, SC- and CSF-related noise. As a result, the utility of RESPITE is likely even higher than reported herein.

Methodological limitations: considerations for data acquisition

1. The proposed method is specifically suited for analysis of single-shot spin-echo (SSFSE or HASTE) sagittal time-series data, although the same motion-modeling principles should apply equally to other image orientations.
2. It is assumed that motion-related noise is dependent on the relative timing between physiological motion and image acquisition, such that a unique phase of motion can be assigned to each image. As Glover et al. (2000) point out, this assumption holds for single-shot methods, but not for multi-shot pulse sequences (or even single-shot methods with exceptionally long readout times) due to the likelihood that multiple phases of motion will be encoded within

each image. Therefore, as in other retrospective motion-compensation methods (Brooks et al., 2008; Deckers et al., 2006; Glover et al., 2000; Lund et al., 2006), the current approach requires single-shot data acquisition with a reasonably short readout time to the centre of *k*-space (where most of contrast-to-noise is encoded).

3. Previous studies have shown that the magnitude of SC motion varies considerably across individuals, approximately half of whom exhibit little or no motion at all (Figley and Stroman, 2007; Matsuzaki et al., 1996). In such cases, the motion regressors in the MC analysis are expected to have little effect whatsoever, and as long as the RESPITE terms are orthogonal to the study paradigm (i.e., the motion regressors remain linearly independent of the study paradigm) there should be no consequence as a result of their inclusion in the GLM. In fact, because the comparisons in the present study were carried out on such a large and diverse sample set (with data from many individuals), it is expected that much larger improvements (than the average) would be observed for specific individuals; namely those exhibiting significant cord motion.

Conclusions

Given the recent advances in our ability to model SC motion as a function of the cardiac cycle, we have developed and reported a novel method to automatically generate retrospective spinal cord motion time-course estimates (RESPITE). Moreover, we have demonstrated that RESPITE can be integrated into an automated, subject- and slice-specific GLM analysis to effectively remove motion-related noise from SSFSE and HASTE spinal fMRI data. Thus, using only three physiological noise regressors, we have established that SC- and CSF-related artifacts can be modeled to improve, simultaneously, the sensitivity and specificity of spinal fMRI. Furthermore, using RESPITE, we also characterized the anatomical locations of motion-related signal changes, which appear to be most prevalent along the edge of the cord (near the cord/CSF interface) and in the subarachnoid space: throughout the spinal canal, and regions surrounding the midbrain, pons, and cerebellum. Finally, based on comparative analyses of both task-related and 'Null-Task' spinal fMRI data sets, we have shown that REPITE terms improve the detection of neuronal activity by approximately 15–20% (on average), while reducing the probability of false-positive activations by approximately 5–6%, depending on the level of statistical significance. However, since motion-related errors were not found to dominate task-related signal changes, previous single-shot SE spinal fMRI findings – although less sensitive than what is now possible with RESPITE – remain valid.

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