

Research Paper: Effect of Physiological Noise on Thoracolumbar Spinal Cord Functional Magnetic Resonance Imaging in 3T Magnetic Field



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ABSTRACT

Introduction: Functional Magnetic Resonance Imaging (fMRI) methods have been used to study sensorimotor processing in the spinal cord. However, these techniques confront unwanted noises to the measured signal from the physiological fluctuations. In the spinal cord imaging, most of the challenges are consequences of cardiac and respiratory movement artifacts that are considered as significant sources of noise, especially in the thoracolumbar region. In this study, we investigated the effect of each source of physiological noise and their contribution to the outcome of the analysis of the blood-oxygen-level-dependent signal in the human thoracolumbar spinal cord.

Methods: Fifteen young healthy male volunteers participated in the study, and pain stimuli were delivered on the L5 dermatome between the two malleoli. Respiratory and cardiac signals were recorded during the imaging session, and the generated respiration and cardiac regressors were included in the general linear model for quantification of the effect of each of them on the task-analysis results. The sum of active voxels of the clusters was calculated in the spinal cord in three correction states (respiration correction only, cardiac correction only, and respiration and cardiac noise corrections) and analyzed with analysis of variance statistical test and receiver operating characteristic curve.

Results: The results illustrated that cardiac noise correction had an effective role in increasing the active voxels (Mean±SD = 23.46±9.46) compared to other noise correction methods. Cardiac effects were higher than other physiological noise sources

Conclusion: In summary, our results indicate great respiration effects on the lumbar and thoracolumbar spinal cord fMRI, and its contribution to the heartbeat effect can be a significant variable in the individual fMRI data analysis. Displacement of the spinal cord and the effects of this noise in the thoracolumbar and lumbar spinal cord fMRI results are significant and cannot be ignored.

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Highlights

- Respiration and heartbeat as physiological functions affect the spinal cord functional Magnetic Resonance Imaging (fMRI) data.
- Physiological noise correction in spinal fMRI increases the activated voxels in the spinal cord as true positive, and decreases the activated voxels in cerebrospinal fluid and surrounded tissues.
- Respiration function correction has a significant role in the reduction of physiological noise in thoracolumbar spinal cord fMRI, compared to cardiac function effect correction.

Plain Language Summary

During the last decades, functional MRI has become a powerful tool in discovering complicated cognitive functions and diagnosing neurological problems. Recently, spinal cord fMRI is introduced to investigate sensory and motor pathways to detect functions of the central nervous system. As it has several confounding factors, including the physiological noise, spinal cord fMRI is encountered as a challenging methodology. Two of the main sources of noise in spinal cord fMRI, which affect the activation map, are respiration and heartbeat. In this study, we assessed the effects of each of these noise sources, separately. We also integrated them in thoracolumbar and lumbar regions, where most of the noise effects exist. Our results suggest that correction of the heartbeat would result in a greater effect on the activated voxels in the spinal cord, comparing with respiration noise correction. Also, we have shown that integration between these two corrections may increase the precision of fMRI activation maps. It is worth mentioning that this study is the first of its kind to investigate the effect of different noises in thoracolumbar and lumbar regions.

1. Introduction

Functional Magnetic Resonance Imaging (fMRI) methods have been used to study sensorimotor processing in the brain and the spinal cord. Nowadays, spinal cord fMRI studies have investigated spinal cord in several pathologic conditions such as spinal cord injury (Alexander, Kozyrev, Figley & Richards, 2017; Cadotte et al., 2012; Chen, Mishra, Yang, Wang, & Gore, 2015; Chen, Kong, Wang, Xie, & Wu, 2007; Choe, 2017; Stroman et al., 2004; Stroman et al., 2016; Zhong et al., 2017), multiple sclerosis (Agošta et al., 2009; Agošta, Valsasina, Caputo, Stroman, & Filippi, 2008; Agošta et al., 2008; Kearney, Miller, & Ciccarelli, 2015; Rocca et al., 2012; Valsasina et al., 2010; Valsasina et al., 2012), chronic and neuropathic pain (Bosma et al., 2016; Leitch, Cahill, Ghazni, Figley, & Stroman, 2009), all of which need consistent and sensitive clinical results. However, there are numerous challenges for spinal cord fMRI which arises from the nature of spinal cord: bony structure of the vertebral canal; movement of the cord and adjacent tissues due to physiological processes such as swallowing, breathing, and so on; the CSF flux in the subarachnoid space circumambient the spinal cord; small cross-sectional dimensions of the spinal cord and; changing in

the susceptibility of tissues due to breathing and bulk motion (Brooks et al., 2008; Fratini, Moraschi, Maraviglia, & Giove, 2014; Stroman et al., 2014; Verma & Cohen-Adad, 2014). Some of these challenges can be addressed by improving the pulse sequence (Bosma & Stroman, 2014; Bouwman, Wilmink, Mess, & Backes, 2008; Cohen-Adad, 2017; Nash et al., 2013; Weber, Chen, Wang, Kahnt, & Parrish, 2016; Xie et al., 2009), utilizing relevant MR imaging equipment (Bodurka, Ledden, & Bandettini, 2008; Cohen-Adad, Mareyam, Keil, Polimeni, & Wald, 2011; Topfer, Foias, Stikov, & Cohen-Adad, 2017; Topfer et al., 2016; Zhang, Seifert, Kim, Borrello, & Xu, 2017), correction of B0-related distortions (Finsterbusch, Eippert, & Büchel, 2012; Finsterbusch, Sprenger, & Büchel, 2013; Ryan et al., 2016; Topfer et al., 2016; Van Gelderen, De Zwart, Starewicz, Hinks, & Duyn, 2007), k-space sampling and Fourier image reconstruction (Agošta et al., 2008; Fruehwald-Pallamar et al., 2012; Glover, 2012; Griswold et al., 2002; Li, Yu, Griffin, Levine, & Ji, 2015; Moeller et al., 2010; Nash et al., 2013), acquisition-based k- and image-space corrections (Bollmann et al., 2017; Brooks, 2014; Xie et al., 2012), and raw-data processing in the form of signal and image (Brooks et al., 2008; Brooks, 2014; Cohen-Adad, Rossignol, & Hoge, 2009; Kong, Jenkinson, Andersson, Tracey, & Brooks, 2012; Piché et al., 2009; Stroman, 2006; Xie et al., 2012). Although these

solutions help improve the signal quality, ultimately the effect of physiological fluctuations' contribution to the measured signal is still controversial (Caballero-Gaudes & Reynolds, 2017; Kong et al., 2012). Several sources of physiological noises have been described in the fMRI literature, including those associated with cardiac and respiratory processes which were recognized as the most significant ones (Brooks, 2014; Fratini et al., 2014; Kong et al., 2014). Spinal cord in thoracolumbar is close to the lungs and the diaphragm, that influence cerebrospinal fluid-filled spaces and cause changes in the susceptibility due to the changes in the amount of air in the lung (Tillieux et al., 2018; Verma & Cohen-Adad, 2014). Cardiac physiological noise is produced as a result of changes in Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV), arterial pulsatility, and effect of those on the CSF flow (Fratini et al., 2014; Parrish, Gitelman, LaBar, & Mesulam, 2000). On the other hand, spinal cord in thoracolumbar is close to the lungs and the diaphragm, that influences cerebrospinal fluid-filled spaces and causes changes in the susceptibility due to the changes in the amount of air in the lung (Verma & Cohen-Adad, 2014).

Solutions for the effect of physiological noise in the spinal cord fMRI data series are categorized into three: strategies of image acquisition, preprocessing strategies, and physiological noise modeling in the general linear model (GLM) analysis for the first level data processing (Brooks, 2014). There are two main strategies for the acquisition of spinal cord fMRI data. First, imaging in axial orientation with Gradient Recall Echo-Echo Planar Imaging (GRE-EPI) sequence that has a high in-plane resolution to make difference between white matter and gray matter. GRE-EPI sequence combining double-shot spiral in/out trajectories can reduce physiological noise in spinal cord fMRI by diminishing susceptibility-induced B0 field variations. Second, imaging in sagittal orientation to cover the considerable part of the spinal cord for the mapping based on the segments which remove susceptibility artifact which is necessary to suppress the effect of respiration using Fast Spin-Echo pulse (FSE) sequence and has a high contrast to noise ratio (Cohen-Adad, 2017; Leitch, Figley, & Stroman, 2010). In some previous studies, researchers used cardiac and respiratory gating to suppress the effect of respiration and heartbeat in the image acquisition strategies (Backes, Mess, & Wilmink, 2001; Mainero, Zhang, Kumar, Rosen, & Sorensen, 2007; Stroman & Ryner, 2000; Stroman & Ryner, 2001), but the cardiac and respiration gating alone is suggested not being sufficient in eliminating the noise. Alternative solutions for detecting and mitigating physiological noise are

based on recommendations for pre-processing spinal cord fMRI data. These recommendations include combining pre-whitening with high-pass filtering (Eippert, Kong, Jenkinson, Tracey, & Brooks, 2017; Xie et al., 2012) and identifying and scrubbing noise components which are obtained from spatiotemporal decomposition of fMRI signal by Independent Component Analysis (ICA)- and principal component analysis (PCA)-based methods (Hu, Jin, Li, Luk, & Wu, 2018; Xie et al., 2012). Furthermore, the main solution for spinal cord fMRI analysis is the methods based on GLM fitting of noise regressors. These methods are generated from the principal components of spinal cord physiological motion-related signal fluctuation, along with functionally-relevant signal changes. These regressors will be given from subject-specific cardiac and respiration recorded data during the imaging session (Brooks, 2014; Figley & Stroman, 2009; Kong et al., 2014). The toolboxes which can be used in fMRI data analysis are summarized in Table 1.

Previous research suggested that the lumbar spinal cord is motionless and the noise fitting can be ignored (Figley, Yau, & Stroman, 2008). Others only considered the cardiac motion-related effects on the spinal cord and CSF (Alexander et al., 2017; Alexander et al., 2016; R. Bosma & Stroman, 2015; Figley & Stroman, 2009; Kozzyrev et al., 2012), and both these approaches may lead to biased information due to ignoring the respiration noise as one of the main sources of noise production. In this study, we investigated the effect of each source of physiological noise and their contributions to the outcome of the analysis of the Blood-Oxygen-Level-Dependent (BOLD) signal by recording the changes in the heart-beat and respiration during fMRI experiments. We determined the quota of respiration and heartbeat physiological noise in thoracolumbar spinal cord neural activity detected by fMRI and evaluated the impact of this physiological noise on false-positive rates.

2. Methods

2.1. Study participants

The participants included 15 right-handed healthy adults (14 males, Mean±SD age=25.88±4.44 years). None of the participants had any history or evidence of spinal cord/vertebral injury or dysmorphology. The participants provided informed consent before enrollment in the study, and the Ethics Review Board at Tehran University of Medical Sciences approved this study [Code: IR.TUMS.REC.1395.2616].

Table 1. Tools which have been already used in physiological noise modeling in fMRI data analysis

Toolbox	Reference Paper	Software Package Integration	User Interface	Using in the spinal fMRI	Additional Information
RETROICOR	Glover et al., 2000	AFNI	MATLAB scripting; Command line	*	Utilizing Fourier analysis to model and create physiological noise
RVHRCOR	Chang et al., 2009	SPM	MATLAB scripting	–	A convolution model comprise respiratory volumes and heartbeat rate
GLMdenoise	Kay et al., 2013	SPM	MATLAB scripting	–	Automatically generate nuisance regressors and determines the optimal number of them
PhLEM	Verstynen et al., 2011	SPM	MATLAB scripting	–	Automatically create multiple models of physiological noise to applying in the GLM model
DRIFTER	Särkkä et al., 2012	SPM	MATLAB scripting	–	A nonlinear Bayesian model of physiological noise
PhysIO	Bollmann et al., 2017	SPM; TAPAS	MATLAB scripting	–	Toolbox integrates preprocessing of physiological data and fMRI noise modeling.
PART	Decker et al., 2006	SPM; FSL	GUI; command line	–	Toolbox conducts a complicated form of retrospective correction (like RETROICOR)
RESPITE	Figley et al., 2009	SPM; Spinal fMRI	MATLAB scripting	*	Cardiac motion-related noise modeling for spin-echo spinal fMRI
PNM	Brooks et al., 2008	FSL	GUI; command line	*	Toolbox models the MRI signal via a series of sinusoidal basis functions (like RETROICOR)

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2.2. Data acquisition procedure

All subjects were scanned while lying supine in a 3T whole-body MRI system (Siemens Magnetom Prisma; Siemens, Erlangen, Germany). Uniform radiofrequency (RF) pulses were transmitted with a body coil, while a matrix coil and the elements of a spine phased-array coil were used as receivers. Initial localizer images

were acquired in three planes to provide a reference position for subsequent imaging.

Subjects were carefully positioned in the scanner and a pain paradigm was performed. The pain stimulation intensity was regulated to 120% of the calculated pressure pain threshold (Mean±SD: 4.691±0.577 kg) in the form of 60 monotonic pressure pain stimuli delivered

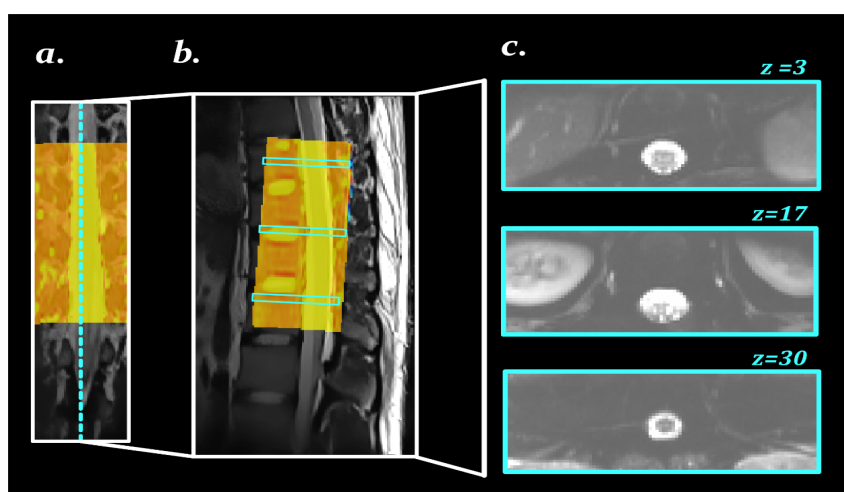


Figure 1. Example of our GRE-EPI images

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A: Coronal; and B: Sagittal views of the spine, with the yellow box illustrating the field of view of imaging; part c of the image shows the axial view of three sample slices

GRE-EPI: Gradient Recall Echo-Echo Planar Imaging.

on the L5 dermatome between the two malleoli in 6 blocks of 60 seconds during one run of 540 seconds.

MRI images were acquired in an axial orientation and were sampled in an ascending, interleaved order between the ninth thoracic and the second lumbar vertebrae with high-order shimming, optimized over the vertebral canal. We performed fMRI which was optimized to minimize the unwanted artifacts, as well as the susceptibility-induced signal drop-out. High-resolution functional images of the thoracic and lumbar spinal cord were acquired with a T2*-weighted GRE-EPI sequence using ZOOMit selective field-of-view imaging EPI (TR = 3000 ms; TE = 30 ms; FA = 80°; FOV = 160 × 160 mm; matrix size = 64 × 64; slice thickness = 4 mm; in-plane resolution = 2.5×2.5 mm; spectral attenuated inversion recovery [SPAIR]). Figure 1 shows some GRE-EPI images for the thoracolumbar spinal cord are shown in.

Cardiovascular and respiratory procedures were monitored utilizing the scanner's photoplethysmograph, located on a finger of the left hand, and a pneumatic belt tied around and under the chest region, respectively. Heart and respiratory data were both inspected at 400 Hz on the Magnetom Prisma physiological monitoring unit. A record containing heartbeat trigger times and respiratory waveforms were produced for each scanning session. Quantities in the respiratory waveform were transformed to a level of the full scale (the distinction between the most extreme and least belt positions measured during imaging).

2.3. fMRI data preprocessing

Preprocessing steps were performed using the Oxford Center for fMRI of the Brain's FMRIB software library (FSL) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004), and Spinal Cord Toolbox (SCT) (De Leener et al., 2017). In the motion correction step, the effect of non-rigid motion of tissues outer on the vertebral column was decreased. This step was performed in two steps; I) 3D-realignment was performed using FMRIB's linear image registration tool (Jenkinson, Bannister, Brady, & Smith, 2002) and II) the output of the previous step was entered into the 2D slice-wise realignment procedure by SliceReg, which estimates the slice-by-slice translations and regularization qualifications in the Z-axis direction (Cohen-Adad, Levy, & Avants, 2015; De Leener et al., 2017). In the motion correction level, we utilized a drawn binary cylindrical mask to cover the spinal cord and exclude other organs in the axial slices. The output

of each motion correction level was visually and quantitatively (by calculating temporal SNR) inspected over the spinal cord and CSF, for quality control.

Then slice-timing correction and image intensity normalization procedures were applied. Advanced spatial smoothing was performed next with a Gaussian kernel of 2 mm full width half maximum (FWHM) in the straight spinal cord, and a high pass temporal filtering (sigma = 90 s). It is clear that the motion correction step does not remove all motion-related impacts and therefore, to complete this step, motion outlier volumes were identified with FSL's motion outlier detection tool, and using the intensity-based DVARS (root mean square variance of intensity difference of volume N to volume N+1) metric and the default threshold calculated as follows: boxplot cutoff = 75th percentile + 1.5 × interquartile range (IQR) (Afyouni & Nichols, 2018; Power et al., 2014).

Spatial ICA categorizes signal components into either neural activity, unwanted impacts of artifacts, or physiological changes outside of the vertebral column. This step was performed in two levels, visual and quantitative characterization of the independent components. In the first step, activated clusters outside of the vertebral column were considered as a structure of non-physiological patterns such as the activated voxels in kidneys that are usually correlated to physiological noise (respiration, pulsation) (Griffanti et al., 2017). In the second step, components were obtained for each data set, and specified criteria were determined as noise: (a) the power of the spatial component's time series at high frequencies were larger than 0.08 Hz (b) more than 50% of significantly activated voxels [$Z > 2.3$] was seen out of the manually drawn spinal cord and CSF mask in the component's spatial map (Kelly Jr et al., 2010; Vahdat et al., 2015).

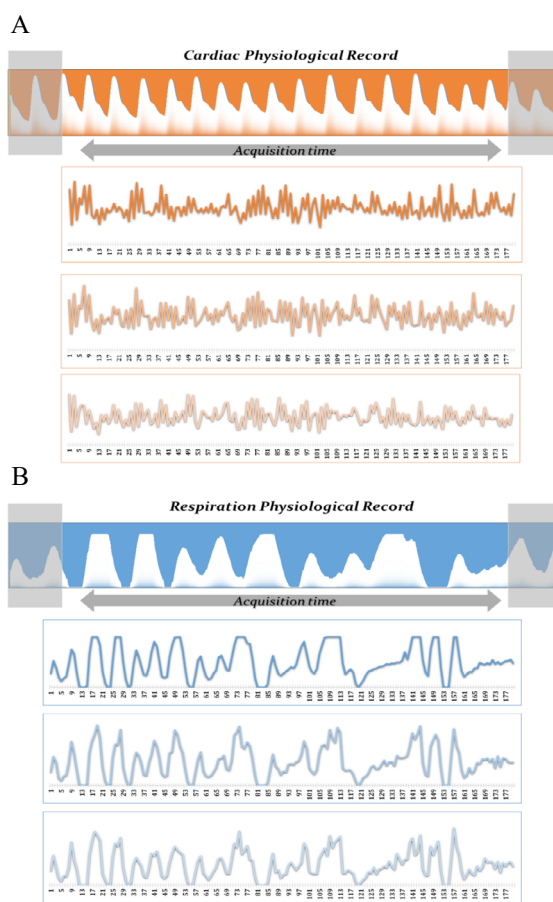
2.4. Physiological noise modelling

To remove the respiratory and cardiovascular effects, and to evaluate each source of physiological noise, slice-specific regressors were generated by MATLAB and using a custom-made algorithm, based on a model similar to the retrospective image correction (RETROICOR) and FSL's physiological noise modeling tool (PNM) (Brooks et al., 2008; Glover, Li, & Ress; Glover, Li, & Ress, 2000). After distinction of the recorded physiological signal, a cardiac and respiratory phase was defined for each slice, and next the respiratory and cardiac signals were modeled using a Fourier series (sine and cosine terms), using the principal frequency

and the next three harmonics (Glover et al., 2000). Figure 2 illustrates the example of respiration and cardiac noise regressors for GLM analysis.

2.4.1. General Linear Model analysis

FMRIB's Improved Linear Model (FILM) with pre-whitening was used to create statistical maps of the filtered data-sets (Woolrich, Ripley, Brady, & Smith, 2001; Worsley et al., 2002). The generated design matrix was included as the hemodynamic response function (gamma, phase 0 s, standard deviation 3 s, average lag 6 s) convolved pain paradigm vectors. In this design matrix, the voxel-wise cardiac and respiration effects vectors, and the temporal masks of outlier time points were also included. Voxels with a $P < 0.05$ (uncorrected) were considered as active, separately in the spinal cord and the CSF.



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Figure 2. Sample cardiac and respiration physiological records

A: A sample record of cardiac; and B: respiration pulsations, along with their three harmonics

2.5. Statistical evaluation

The activated voxels of the clusters were obtained from each data set in four levels: 1) without any physiological noise correction, 2) with respiration noise correction, 3) with cardiac noise correction, and 4) with cardiac along with respiration physiological effects correction. The mean value of each parameter was computed and the analysis was performed using SPSS (Version 16.0, The SPSS, Inc., Chicago, IL, USA) and MATLAB (Version R2016a, The MathWorks, Inc., Natick, MA, USA). Normal distribution of the active voxels in different correction levels was assessed with the Kolmogorov-Smirnov test. The average value of the active voxels in the spinal cord and CSF were processed with 1-way ANOVA with repeated measures in a within-subject comparison.

For each Z-score map, sensitivity and specificity were determined by comparing the spatial locations of activated voxels. Sensitivity was estimated as the percentage of active voxels in the physiological corrected data-sets via respiration + cardiac effect modeling that was correctly detected as activated, and specificity was described as the percentage of voxels correctly detected as non-activated.

Comparisons between different source noise effects and noise modeling methods were assessed by using receiver operating characteristic (ROC) curves (Constable, Skudlarski, & Gore, 1995; Skudlarski, Constable, & Gore, 1999; Sorenson & Wang, 1996). ROC curves have been utilized extensively as a tool for objective comparisons of various methods in fMRI studies (Bowring, Maumet, & Nichols, 2018; Wang, Wang, Aguirre, & Detre, 2005; Zhong, Zheng, Liu, & Lu, 2014). The attributes of the distribution of the probability of the signals and noise, and the degree to which they overlap, affect the accurate state of the ROC curve but do not make a hypothesis about these distributions (Sorenson & Wang, 1996).

3. Results

Comparison of the sum of active voxels in the spinal cord and share of each in the activated clusters are illustrated in Figures 3 and 4 and explained in Table 2. Also, in Table 2, the results of descriptive statistical data analysis are presented. One-way within-subjects or repeated-measures ANOVA was utilized to evaluate the effect of physiological functions on spinal cord fMRI datasets, in the 4 correction levels. There was a statistically significant effect of physiological noise correction on the number of active voxels in the spinal cord ($F_{3,42} = 21.314$, $P < 0.001$, 0.21), and in CSF

Table 2. The results of the ANOVA test on the active voxels (df=3)

Subset for Alpha = 0.05				
	Parameters	Mean	F	P
Cerebrospinal fluid	No correction	15.8	63.2	= 0.002743
	Only respiratory noise correction	14.6		
	Only cardiac noise correction	16.9		
	Both corrections	12.6		
Spinal cord	No correction	15.6	21.31	< 0.00001
	Only respiratory noise correction	17.6		
	Only cardiac noise correction	23.4		
	Both corrections	20.8		

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Table 3. Receiver operating characteristic analysis on the active voxels in the spinal cord

Type of Map	Sensitivity	Specificity	AUC	P
No correction	0.616	0.649	0.577	0.128
Only cardiac noise correction	0.808	0.765	0.859	0.003*
Only respiration noise correction	0.861	0.843	0.936	0.001*

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The activation map with both cardiac and respiration correction was selected as the ground truth, and the three other maps were compared against it; AUC: Area under the curve;

* Demonstrates significant value (P<0.05).

($F_{3,42} = 63.2, P < 0.05, \eta^2 = 0.28$). The Bonferroni post hoc test results indicate that cardiac noise correction had an effective role in the increased number of active voxels in both the spinal cord (Mean±SD = 23.46±9.46) and CSF (Mean±SD = 16.99±7.43) compared to other noise correction methods.

The results of ROC analysis of spinal cord and CSF GLM results in the different physiological noise correction levels are illustrated in Figures 5 and 6, and summarized in Table 3 and 4.

Table 4. Receiver operating characteristic analysis of the active voxels in CSF areas

Type of Map	Sensitivity	Specificity	AUC	P
No correction	0.626	0.622	0.659	0.0717
Only cardiac noise correction	0.748	0.715	0.751	0.0321*
Only respiration noise correction	0.811	0.754	0.864	0.0151*

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The activation map with both cardiac and respiration correction was selected as the ground truth, and the three other maps were compared against it; AUC: Area under the curve.

* Demonstrates significant value (P<0.05).

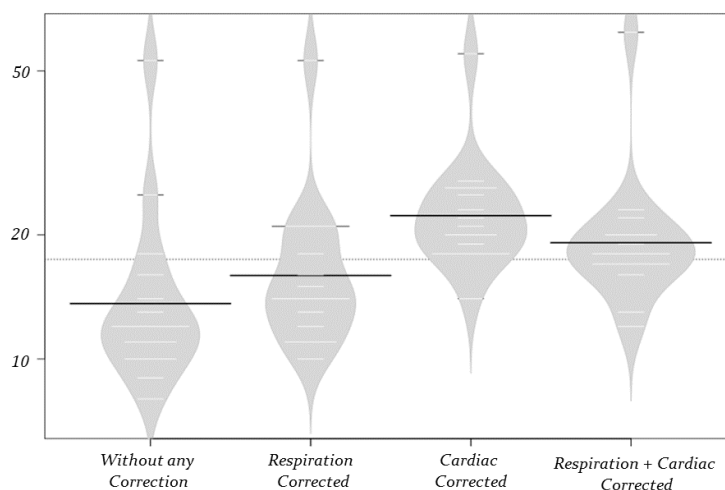


Figure 3. The influence of correction steps on the number of active voxels

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The graphs show how the type of correction step influences the number of active voxels in the spinal cord areas

Overall performance of the correction method was rated as the area under the ROC curve (AUC), considering both uncorrected fMRI analysis results and alternative physiological effects. In the evaluation of physiological noise of both corrected and uncorrected spinal cord fMRI results, the AUC corresponding to the cardiac effect correction was 0.856 ($P < 0.05$), and it was 0.936 ($P < 0.05$) for the respiration effect correction. In the CSF, the AUC corresponding to the cardiac effect correction was 0.751 ($P < 0.05$), and 0.864 ($P < 0.05$) for the respiration effect (Figure 7). Table 4 summarizes the results of the ROC analysis.

4. Discussion

The heartbeat- and respiration-related movements are the main sources of physiological noise in the spine. Because of the concurrency between movements and tasks, correction of this movement can influence the observed effects of stimulations. Respiration effect is suggested to be the most important source, and its effects on the results are higher than the other sources of noise in the thoracolumbar and lumbar GRE-EPI fMRI. In this study, the effect of respiration physiological noise was strongly observed in the cardiac noise-corrected datasets, and ROC analysis demonstrated that the sensitivity and specificity of the respiration effect correction were increased. This result can be ex-

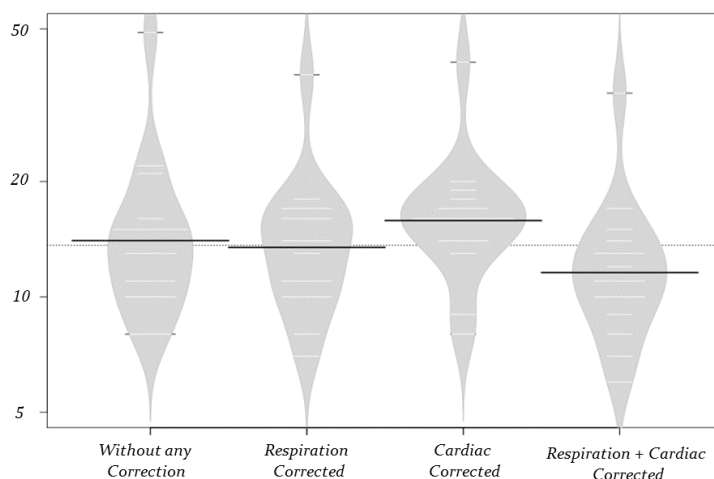
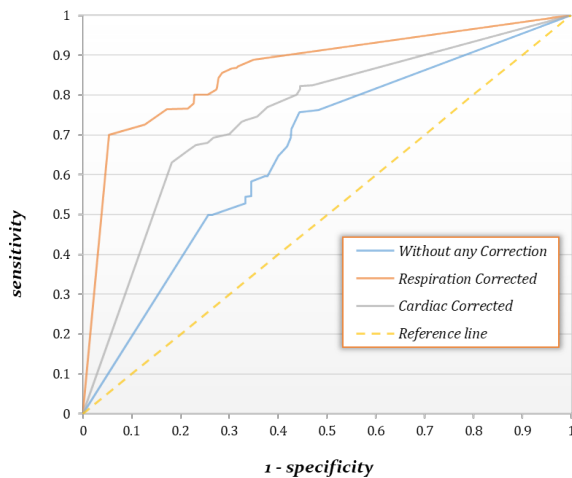


Figure 4. The influence of correction steps on the number of active voxels

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The graphs show how the type of correction step influences the number of active voxels in the CSF areas



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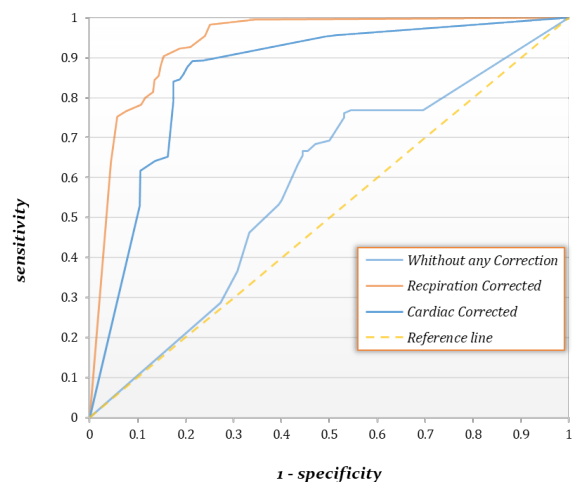
Figure 5. The Receiver Operating Characteristic (ROC) curves for different noise correction methods in CSF areas

Plots are the mean ROC curves of the 15th thoracolumbar spinal cord fMRI data-sets in the CSF areas. For respiration noise correction, the area under the ROC curve (AUC) is 0.864, and for the cardiac noise correction it is 0.751, showing the superiority of the respiration noise correction method

plained by considering the bulk magnetic susceptibility changes and the associated B0 shifts in the spinal cord by respiration and the changes in the volume of lungs (Tillieux et al., 2018; Verma, 2014). B0 field shifting is reported to affect the pre-processing and GLM analysis of the spinal cord fMRI data (Durand, van de Moortele, Pachot-Clouard, & Le Bihan, 2001; Parkes, Fulcher, Yu, & Fornitod, 2018; Raj, Anderson, & Gore, 2001; Yeo, Fessler, & Kim, 2008).

The other source of noise is the physiological motion of the spinal cord by the respiration effects. The differences between the respiration and heartbeat noises were assessed in this study, and the results showed that the effects of respiration on lumbar and thoracolumbar spinal cord physiological movements, as well as on the CSF flow, are significantly greater than the effects of the heartbeat. The impact of cardiac and respiration effects on spinal cord movements has been illustrated in previous studies as well (Figley et al., 2008; Winklhofer et al., 2014; Yildiz et al., 2017). The effect of respiration is more frequently studied than the heartbeat (Winklhofer et al., 2014; Yildiz et al., 2017), and these effects were reported to be reduced in the lower parts of the vertebral column (Yildiz et al., 2017).

For spinal fMRI acquisition, researchers mostly use two MR imaging pulse sequences: HASTE/SS-FSE and GRE-EPI MR (Bouwman et al., 2008; Stroman et al., 2014). The effects of respiration on B0 bulk suscep-



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Figure 6. The Receiver Operating Characteristic (ROC) curves for different noise correction methods in spinal cord areas

Plots are the mean ROC curves of the 15th thoracolumbar spinal cord fMRI data-sets in the spinal cord areas. For respiration noise correction, the area under the ROC curve (AUC) is 0.936, and for the cardiac noise correction, it is 0.856, showing the superiority of the respiration noise correction method.

tibility are greater than the heartbeat in the GRE-EPI sequence. The HASTE/SS-FSE is not sensitive to the susceptibilities in the vertebral column, the intervertebral disks, and the air-filled lung (Poser & Norris, 2007; Stroman et al., 2014; Ye, Zhuo, Xue, & Zhou, 2010).

As mentioned previously, the lumbar and sacral spinal cord are motionless in the three directions, suggesting that the spinal cord physiological motion can be ignored as a confounding factor for fMRI (Figley et al., 2008). This was observed in the HASTE/SS-FSE lumbar and thoracolumbar spinal cord fMRI as well (Alexander et al., 2017; Alexander et al., 2016; Kornelsen, Smith, & McIver, 2014; Kornelsen et al., 2013; Kozyrev et al., 2012), by using RESPITE to remove residual cardiac noise effects (Figley & Stroman, 2009). Previous studies have shown the lumbar spinal cord (L1, L2) movements to be greater than lower thoracic spinal cord (T7, T8, T9, T10) movements due to breathing (Winklhofer et al., 2014; Yildiz et al., 2017), and therefore our study suggests that the effect of respiration on physiological noise should be considered in the spinal cord fMRI analysis.

In older spinal fMRI studies, the physiological noise correction was rarely performed, and therefore in some of those studies, the activation voxels in the spinal cord were correlated with the motion caused by physiologi-

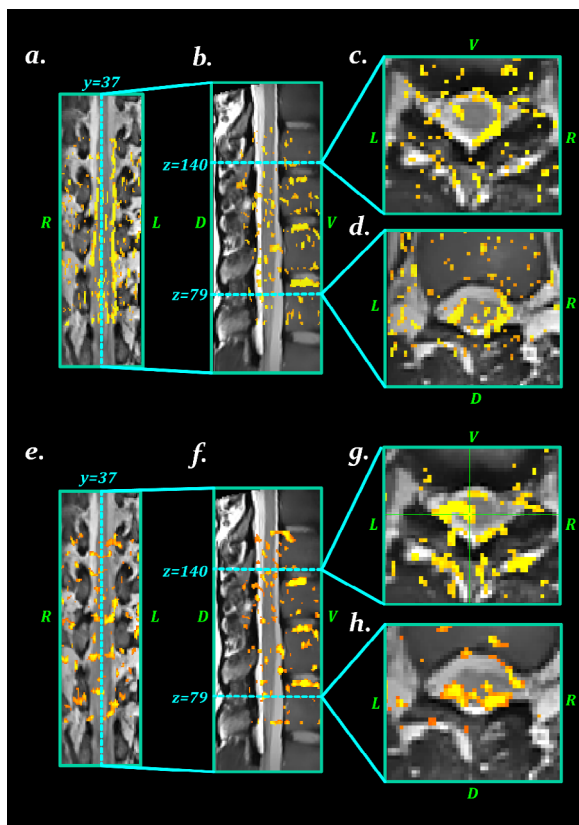


Figure 7. The influence of noise correction methods on the activation maps

A-D: The activation maps with no noise correction; E-H: The activations map after cardiac and respiration noise correction; This figure illustrates that physiological noise correction decreases the active voxels in the CSF (false positives) and increases active voxels in the spinal cord.

cal functions (Chen et al., 2007; Komisaruk et al., 2002; Madi, Flanders, Vinitiski, Herbison, & Nissanov, 2001; Maieron et al., 2007; Ng et al., 2008; Yoshizawa, Nose, Moore, & Sillerud, 1996). As an example, Kashkouli Nejad et al. investigated the impacts of interoceptive attention/awareness training on spinal cord neural activity (Kashkouli Nejad et al., 2014), which is an interesting finding; however, this study was limited by not recording the physiological measurements to correct the fMRI signal, which shows the need for replication of the results of this study.

4.1. Study limitations

Despite the interesting findings of this study, some limitations should be considered. The interaction between respiration and heartbeat is important, which is ignored here. Also, the ICA-based motion and artifact corrections are better to be applied only to the tissue

of interest, which was not considered here. And finally, this study only used a GRE-EPI optimized pulse sequence, and for more reliable results, this procedure should be replicated for a HASTE/SS-FSE protocol in the sagittal orientation.

This study is novel research on physiological noise sources and their impacts on the spinal cord fMRI in the lumbar and thoracolumbar regions and illustrated that the respiration effects along with the heartbeat have much influence on the individual fMRI data and the outcomes of the analysis. These results show that correcting the fMRI data of the lower parts of the spinal cord for such effects is very essential. These physiological noise corrections can help obtain pure physiological reactions related to neural activities. For future studies, the k-space motion correction and detecting motions during the MRI acquisition can be suggested to decrease the effect of physiological noise sources, especially the respiration.

Ethical Considerations

Compliance with ethical guidelines

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, revised in 2008. Informed consent was obtained from all subjects to be included in the study.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

All authors confirm that they have no conflicts of interest.

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