Technical Note

Reduction of physiological noise with independent component analysis improves the detection of nociceptive responses with fMRI of the human spinal cord

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The evaluation of spinal cord neuronal activity in humans with functional magnetic resonance imaging (fMRI) is technically challenging. Major difficulties arise from cardiac and respiratory movement artifacts that constitute significant sources of noise. In this paper we assessed the Correction of Structured noise using spatial Independent Component Analysis (CORSICA). fMRI data of the cervical spinal cord were acquired in 14 healthy subjects using gradient-echo EPI. Nociceptive electrical stimuli were applied to the thumb. Additional data with short TR (250 ms, to prevent aliasing) were acquired to generate a spatial map of physiological noise derived from Independent Component Analysis (ICA). Physiological noise was subsequently removed from the long-TR data after selecting independent components based on the generated noise map. Stimulus-evoked responses were analyzed using the general linear model, with and without CORSICA and with a regressor generated from the cerebrospinal fluid region. Results showed higher sensitivity to detect stimulus-related activation in the targeted dorsal segment of the cord after CORSICA. Furthermore, fewer voxels showed stimulus-related signal changes in the CSF and outside the spinal region, suggesting an increase in specificity. ICA can be used to effectively reduce physiological noise in spinal cord fMRI time series.

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Introduction

Following the success of functional magnetic resonance imaging (fMRI) in the investigation of brain function, fMRI of the spinal cord was shown to be technically feasible in both humans (Backes et al., 2001; Bouwman et al., 2008; Brooks et al., 2008; Cohen-Adad et al., 2010; Eippert et al., 2009; Guy et al., 2008; Govers et al., 2007; Madi et al., 2001; Maieron et al., 2007; Majcher et al., 2007; Stracke et al., 2005; Stroman et al., 2004; Summers et al., 2010; Valsasina et al., 2008; Yoshizawa et al., 1996) and animals (Cohen-Adad et al., 2009; Givo et al., 2004). Because of the relatively small cross-sectional size of the spinal cord grey matter, even very little motion can contaminate the signal. Spinal cord motion and in-flow effects from the surrounding cerebrospinal fluid (CSF) along with cardiac and respiratory cycles greatly degrade the quality of fMRI data by adding unwanted variance in the time series (Figu et al. and Stroman, 2007; Givo et al., 2004; Kong et al., 2012; Stroman, 2006; Stroman et al., 2005). Non-invasive acquisition of functional images of the spinal cord is very challenging but remains much needed even though there is currently no methodological consensus on the adequate means to address this challenge.

Several methods exist to minimize physiological-related noise. Respiratory-gated acquisition and breath-hold have been employed to reduce the effect of respiratory activity (Stroman and Ryner, 2001; Stroman et al., 1999), although with moderate success (Stroman, 2005). Cardiac gating has also been used in the brain (Guimaraes et al., 1998) and spinal cord (Backes et al., 2001) but this requires substantially longer acquisition time. Moreover, variable TR can introduce additional signal variance due to T₁-effects, which are difficult to correct in the spinal cord due to the necessity of acquiring a robust T₁ map. Additionally, heart rate can correlate with the experimental paradigm — especially for painful stimuli, therefore spurious activations can appear...
in the statistical map as TR would also correlate with heart rate (Tousignant-Lafaye et al., 2005).

Post-hoc correction can be used to reduce physiological noise in fMRI time series, as shown in the brain (Behzadi et al., 2007; Deckers et al., 2006; Glover et al., 2000; Hu et al., 2005; Lund et al., 2006; Thomas et al., 2002; Tohka et al., 2008) and spinal cord (Brooks et al., 2008; Figley and Stroman, 2007; Kong et al., 2012; Stroman, 2006). One method based on the RETROSpective Image CORRection (RETROICOR) algorithm (Glover et al., 2000) consists in estimating a set of regressors based on external physiological recordings (pulse oxymeter and respiration trace) to be included in the general linear model (GLM). Although it has shown great success in capturing the variance of physiological noise in several fMRI studies, this approach might inaccurately model the shape of physiological-related signal by a combination of sine and cosine functions. Alternatively, data-driven methods aim at extracting the physiological noise part of the fMRI data from the data itself. One such method performs CORrection of structured noise using Spatial Independent Component Analysis (CORSICA) (Perlbarg et al., 2007). The principle of CORSICA is to estimate a noise map via the spatial independent component analysis (ICA) and to remove the corresponding components from the functional data before testing for the effect of interest. The noise components can be identified using anatomical priors, as in (Perlbarg et al., 2007), or based on separate data acquisition using a short TR to assess the spatial distribution of noise at rest. Short-TR data are used to avoid aliasing, particularly for cardiac signal, whose main spectrum typically ranges from 0.8 to 1.4 Hz. Therefore a sampling frequency of at least 2 × 1.4 Hz (or TR<350 ms) is required to satisfy the Nyquist condition. CORSICA proved to be useful in reducing physiological noise in brain fMRI time series (Schrouff et al., 2011; Vanhaudenhuyse et al., 2010). The main assumption of CORSICA is that physiological noise is spatially structured. Our recent investigation on the spatial distribution of physiological noise in spinal cord fMRI demonstrated that cardiac-related noise — one major source of signal variance in spinal cord fMRI — is spatially structured and stable within each individual (Piché et al., 2009). Brooks et al. performed ICA on spinal cord fMRI data acquired with short TR (200 ms) to allow exploration of the physiological noise spectra (Brooks et al., 2008). They showed that cardiac and respiratory effects are easily extracted by the ICA decomposition. The cardiac-related signal was mostly located in the CSF region and in the carotid and vertebral vessels, while the respiratory-related signal usually appeared at the interface between connective tissues (neck, muscles). The interaction between cardiac and respiratory signal (amplitude modulation) also appeared in the ICA. In addition, a low-frequency component (<0.1 Hz) was robustly identified in multiple subjects. All these observations suggest that a map of physiological noise can be computed for each subject and subsequently used within the same subject in various experiments.

In this paper we assessed whether CORSICA can improve the sensitivity and specificity of BOLD responses to nociceptor stimuli in the cervical spinal cord.

Materials and methods

Acquisitions

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of our institution ("Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie Québec: CMERNQ). All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice, and received compensation for their travel expenses, time and commitment. FMRI acquisitions were carried out in 14 healthy volunteers with a 3 Tesla Siemens Trio system (Siemens Healthcare, Germany). RF reception was achieved by combining the product neck coil (4-channel) with the spine matrix (the 6 most rostral elements were used). Coils were sensitive from about C1 to T5. Subjects were between 20 and 49 years old (mean: 34), and had no history of neurological conditions, including degenerative disorder or spinal trauma.

Subjects were carefully positioned to limit head movement and neck lordosis and were requested not to move. An anatomical scan was performed using a T1-weighted sequence (3D MPRAGE, sagittal orientation, 208 slices, TR=2250 ms; TE=3.4 ms; flip angle=9°; field of view=256 mm, 1 mm isotropic). Three functional scans were performed in each subject using a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence. Sagittal slices were positioned to cover the vertebral body of C3 to T1, with the middle slice centered on the mid-sagittal plane. Parameters were: TR=2 s, TE=20 ms, flip angle=82°, 9 sagittal slices, thickness=3 mm, no gap, in-plane resolution=1.6×1.6 mm², 315 volumes. In addition, one short-TR run of 120 s was performed without stimulation (TR=250 ms, TE=20 ms, flip angle=40°, 5 sagittal slices, thickness=3 mm, gap=1.5 mm, in-plane resolution=1.6×1.6 mm², 480 volumes). The short-TR data were used to generate a map of physiological noise for each subject.

Functional paradigm

Nociceptive transcutaneous electrical stimuli (trains of 1-ms pulses at 5 Hz) were delivered to the subject’s right thumb by a pair of custom-made surface electrodes (1 cm²; 2 cm inter-electrode distance) and using a custom-made optically isolated constant current stimulator triggered by a Grass S48 train generator (Grass Medical Instruments, Quincy, MA, USA). Stimuli were synchronized with fMRI acquisitions using a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). Before scanning, subjects were familiarized with the electrical stimuli and pain threshold was determined individually using the ascending method of limit. Series of supra-threshold stimuli were then administered to determine the stimulus intensity required to produce moderate to strong painful sensations while insuring that the subject could tolerate it for 60 s (i.e. rated 50–70 on a 0–100 numerical rating scale with 0 defined as no pain and 100 as worst pain imaginable). The functional paradigm consisted of alternating blocks of stimuli (S) and rest (R) as follows: R S R S R S R S R S R. Each block was 60 s long (except for the first block, which lasted 30 s). Total acquisition time for each run was 10 min 30 s. Each subject had three functional runs. BOLD responses to nociceptive stimuli of the thumb were expected to occur mostly in the spinal cord at around C5 vertebral level, which roughly corresponds to spinal level C6.

Physiological monitoring

A pulse oximeter probe was attached to the subject’s left index finger. A respiratory belt was attached around the subject’s chest. Physiological data were sampled at 1000 Hz and recorded on a MP150 system (Biopac Systems, Inc., Goleta, CA, USA).

Data analysis

Data analysis was performed with Matlab® (The Mathworks Inc., Natick, MA, USA) using the sICA toolbox© (2007 Inserm U678 V. Perlbarg), the CORSICA toolbox (Perlbarg et al., 2007) and SPM2 (www.fil.ion.ucl.ac.uk/spm/spm2.html). EPI data were corrected for slice timing differences and motion-corrected using a rigid body alignment. The mean of the whole functional data set was calculated to obtain a target volume for registration to the individual’s T1-weighted anatomical volume. No smoothing was applied to the data.

Generation of noise maps from short-TR data

Spatial ICA was performed on short-TR data to retrieve physiological-related signal. A principal component analysis was first performed to whiten the data without reducing the data dimension, then spatial ICA was run (INFOMAX algorithm). Number of independent components was set to 30, which is enough to explain most
physiological noise variance (Brooks et al., 2008; Piché et al., 2009). The power spectrum of each component was examined to identify three components showing the highest coherence with the power spectra of cardio-respiratory data recorded in the corresponding run. Namely, we identified one component having the highest coherence with the cardiac trace, one component having the highest coherence with the respiratory trace, and one component with the highest coherence with both respiratory and cardiac spectra. Mean peak frequencies of cardiac and respiratory fluctuations were 1.2 Hz and 0.33 Hz, respectively (Fig. 1a).

The time course of the three selected components was regressed out from the short-TR fMRI time-series on a voxel-by-voxel basis to obtain a spatial distribution of physiological noise components. The resulting T-maps indicated that most of the physiological noise variance was located in the cerebrospinal fluid (CSF) and along the spinal cord/CSF interface, overlapping partly with spinal tissue (Fig. 2). T-maps were then converted into a binary mask using an upper threshold of $T = 3.12$ ($P$-uncorrected = 0.001). Masks were not blurred.

**Removal of physiological-related components from long-TR data**

Spatial ICA was conducted on the long-TR data to generate 60 independent components. The noisy components were then identified on the basis of the similarity between the spatial maps of each component and the noise map. To prevent us from selecting components related to functional activity, only the components that shared the highest similarity with the noise map were selected. Then, the components selection was achieved by a stepwise regression procedure. This procedure iteratively selects a subset of components that explain each noise characteristic signal. These noise characteristic signals were extracted from the noise map by using a k-means clustering. Then, the frequency of selection of each component ($F_q$) was calculated from the stepwise regression procedure (one selection by noise characteristic signal). $F_q$ represents the spatial similarity between each component and the noise map (Fig. 1b). The full procedure is detailed in (Perlbarg et al., 2007). $F_q$ was then thresholded based on the Otsu’s approach (Otsu, 1979). The Otsu’s approach consists in finding an adaptive threshold of the histogram of $F_q$ scores. This algorithm supposes that the histogram is bimodal (i.e. there are two classes of components, the noise components and the other ones) and finds the optimal threshold by minimizes the intraclass variance.

Finally, data were reconstructed by combining all ICA components without the “noisy” components, i.e., components with $F_q$ score higher than the threshold.

**Analysis of stimulus-evoked responses**

Statistical analysis was conducted on the long-TR data, using the standard GLM implemented in SPM2, with high-pass filtering at 128 s cut-off and motion regressors. Blocks of nociceptive stimuli were convolved with the default canonical hemodynamic response function. For each subject, data from all three runs were combined using a fixed-effect analysis (i.e., intra-subject analysis). To assess the benefit of CORSICA, the GLM was conducted with and without noise correction. We also compared CORSICA with the GLM that includes a CSF regressor (Kong et al., 2012). We used the CSF masks (see next section) to reconstruct the averaged time course of the CSF signal for each run and each subjects, and subsequently applied it as a regressor in the GLM for further comparison with the CORSICA method.

**Regions of interest (ROI)**

Masks were created from the mean functional mask to avoid mismatch between the $T_1$-weighted anatomical image and the EPI due to susceptibility distortions. A mask of the spinal canal (CSF + spinal cord) and spinal cord was manually drawn on the mean functional image (Fig. 3). The spinal cord mask was then split to a ventral and a

Fig. 1. a: The power spectrum of one component that exhibits both cardiac and respiratory signals. This is the first of the 30 independent components extracted by sICA from a raw time-series acquired using a short-TR. The cardiac and respiratory components were identified based on the coherence with the cardiac and respiratory activity in the power spectrum. b: Selection of the noise-related components in long-TR. The score $F_q$ is plotted against all 60 components of long-TR data in one subject. An adaptive threshold of $F_q$ was automatically determined by CORSICA to select noise-related components (horizontal red line).
dorsal mask for quantifying BOLD responses in the ventral and dorsal segments. Masks were then divided into six parts corresponding to vertebral levels, i.e., from C3 to T1. A mask of the CSF was created by subtracting the spinal cord mask from the spinal canal mask.

The mean T-scores and the total voxel counts above threshold were extracted within each ROI at the following thresholds: $P = 0.01$, $P = 0.001$ (uncorrected for multiple comparisons) and $P = 0.05$ (corrected for multiple comparisons using Bonferroni). Results were compared across methods using two-sample Student's $t$-test paired for subject, with a threshold of $P = 0.01$ (corrected for comparisons between the three conditions, i.e., no correction, CSF regressor and CORSICA).

**Results**

Fig. 4 shows T-maps of responses to nociceptive stimuli in four representative subjects, without and with physiological noise correction using CORSICA. Overall, higher peak T-score (subjects #1, #3, #4) and higher voxel count (subjects #3, #4) of stimulus-related responses was detected in the cord with CORSICA. Fewer stimulus-related responses were observed outside the spinal cord with CORSICA, suggesting an increase in spatial specificity. Similar results were obtained in the 10 other subjects. The time course of data after CORSICA exhibited lower high frequency variations, as illustrated by Fig. 5.

Mean T-score and voxel count of significant ($P < 0.01$) responses to nociceptive stimuli in all 14 subjects across vertebral levels in the spinal cord were compared without correction, with the CSF regressor and with CORSICA (Fig. 6). The voxel count and mean T-scores were significantly increased with CORSICA at levels C4 and C6 (for voxel count) and at C4 and C7 (for the mean T-score). Note that the T-maps shown in Fig. 4 suggest a different interpretation on the distribution of positive responses across vertebral levels, compared to the one described in Fig. 6. However, the four subjects in Fig. 4 were presented only for illustrating the effect of T-score distribution before and after CORSICA. Fig. 6 should be considered the most reliable measure of the distribution of responses across vertebral levels, as it includes all 14 subjects.

Fig. 7 shows significant voxel counts in the ventral spinal cord, dorsal spinal cord and CSF. After CORSICA, the number of “active” voxels was significantly higher in the ventral and dorsal spinal cord ($P < 0.05$). No significant change was detected in the CSF region.

**Discussion**

This study assessed the efficiency of the CORSICA method to correct physiological noise fluctuation in spinal cord fMRI time series. This method utilizes ICA from short-TR data to derive subject-dependent spatial map of physiological noise and subsequently used to remove physiological-noise-related components from long-TR fMRI data based on the similarity criterion. CORSICA showed an increase in sensitivity and specificity for the detection of BOLD responses to noxious stimuli in the spinal cord.
Efficiency of physiological noise correction

Although our main focus was the application of the CORSICA method, we also evaluated the use of a CSF regressor for modeling major cardiac-related fluctuations, as reported elsewhere to be one of the main source of signal variance in the cord (Kong et al., 2012). We were not able to compare our method with the RETROICOR method because some of the physiological traces recorded for the long-TR data contained artifacts. Evaluation criteria were based on the spatial specificity of the responses by comparing number of “activated” voxels (i.e., passing a certain T-threshold) and mean T-score at different levels of the spinal cord and in the CSF area. Our results showed that the CSF regressors and the CORSICA produced higher T-score, indicating that the residual variance is decreased when modeling the physiological noise in the fMRI time series, as confirmed by the time course (Fig. 5). Test–retest repeatability will be performed in future studies to assess the robustness of the detected activations across sessions.

Spatial distribution of physiological noise

Here we utilized the information from short-TR data to identify the spatial distribution of physiological noise. The main assumption of CORSICA is that physiological noise is spatially structured, i.e., some areas should exhibit spatially organized patterns of physiological

Fig. 4. T-statistic maps of stimulus-evoked responses without (top) and with (bottom) physiological noise correction using CORSICA in four representative subjects. Statistical maps are overlaid on the mid-sagittal slice of the individual anatomical image. Overall, higher number of stimulus-related responses is detected in the cord with CORSICA (e.g. subjects #3, #4) with fewer false-positive responses outside spinal cord (e.g. subjects #1, #2, #4). Data were smoothed with a 3×3×6 mm³ kernel for clarity purpose.

Fig. 5. Time course of fMRI data before (blue) and after CORSICA (red) in one subject (single run). Motion-corrected and detrended data were selected out of a cluster at C6 of 13 voxels passing the P=0.01 threshold (regressor of interest from the GLM statistics), then averaged. The location of this cluster was chosen at the C6 vertebral level. The stimulation paradigm is displayed in gray.
noise. Our previous investigation on the spatial distribution of physiological noise in spinal cord fMRI demonstrated that cardiac-related noise — one major source of signal variance in spinal cord fMRI — is spatially structured and stable across successive runs within individual (Piché et al., 2009). Most cardiac-related variance was detected in the CSF area as well as within large vessels. In addition, a recent study demonstrated that the physiological noise was higher in the CSF and along the spinal cord/CSF interface (Figley and Stroman, 2009). In the present study, noise masks derived from short-TR data also showed that physiological-related noise was mainly present within the CSF and along the spinal cord/CSF interface (Figley and Stroman, 2009). In the present study, noise maps were qualitatively different between individuals, as clearly evidenced in Fig. 2. This suggests that a template of noise map for the spinal cord is not advisable yet, and that noise map should be estimated for each individual for maximum accuracy in the removal of physiological noise-related components.

External recording of physiological signals

Cardiac and respiratory traces were recorded using external probes to identify three independent components from the short-TR data. Although CORSICA has originally been introduced as a method that does not necessarily require external physiological recording — as opposed to RETROICOR-based methods — physiological recording has been conducted for the sole purpose of validating the method for spinal cord fMRI. In the future it is conceivable to use an algorithm that would identify cardiac and respiratory frequency peaks based on a template of the expected physiological spectra computed from a population.

Habituation effects

Previous studies have reported a habituation effect during repeated nociceptive stimulations, characterized by a decrease of the BOLD responses (Becerra et al., 1999). To address the potential presence of habituation effect in our data, we inspected the time courses of fMRI signals within significant voxels in several subjects (see Fig. 5). We could notice a decrease in the signal amplitude after a certain time (~30 s), which could correspond to a decrease of the BOLD response associated with a habituation effect. Although this habituation effect may have somewhat decreased the sensitivity to detect BOLD responses in the cord, the main purpose of this study was to assess the efficiency of CORSICA to model physiological noise in fMRI time series.

Sagittal acquisition

Here we chose to acquire the long-TR and short-TR data in sagittal orientation at relatively large thickness (3 mm). This resulted in partial volume effect in the lateral direction. To extract cardiac-related variance on the short-TR data, this scheme of acquisition appears appropriate, given that most of the cardiac-related noise occurs in the large blood vessels distributed at the periphery of the spinal cord (in the spinal venous plexus). We have shown that the distribution of cardiac-related noise is relatively smooth in space (Piché et al., 2009), therefore partial volume effect is likely of minimum concern for extracting cardiac-related noise. However, given that the spinal cord grey matter anatomy is arranged in laminae in the cross-sectional plane, axial acquisition is often preferred for extracting the neuronal responses to a given stimulus with high spatial accuracy (Backes et al., 2001; Brooks et al., 2008; Cohen-Adad et al., 2010; Giulietti et al., 2008; Maieron et al., 2007; Stroman and Ryner, 2001; Summers et al., 2010). Here, the reason for acquiring the short-TR and long-TR data in sagittal orientation was to match the FOV between the two acquisitions, in order to apply the estimated noise mask without further registration, which could have resulted into mis-registration and re-interpolation errors. However, overcoming the latter issues would make it possible to acquire the...
short-TR data in sagittal orientation, and the long-TR data in axial orientation.

Localization of BOLD signal in response to nociceptive stimuli

BOLD responses were stronger in the dorsal versus in the ventral aspect of the spinal cord (see Fig. 7), which is consistent with the termination of nociceptive peripheral afferent fibers in the ipsilateral dorsal (posterior) horn of the spinal cord (Porro et al., 1991). Regarding the laterality of the responses, we attempted to separate right and left sides of the cord in order to assess stronger BOLD responses ipsilaterally. However, the right–left curvature of the cord associated with relatively large slice thickness which (3 mm) resulted in un-balanced partial volume effect between the right and the left side, prevented us to pursue such analysis in a robust manner. According to previous studies, BOLD signal responses can be present ipsi- and contralaterally during sensory and painful stimulations (Giove et al., 2004; Summers et al., 2010). Contralateral activations could be the result of activity in reflex arcs, intraspinal and projection systems (Coghill et al., 1991) or could be false positives.

BOLD responses were mostly detected at C3–C4 vertebral levels, which is consistent with two previous studies employing nociceptive stimuli of the thumb (Stracke et al., 2005; Stroman, 2006). Stracke et al. found the strongest activation at C3–C4 levels and Stroman et al. found strongest activation at C2–C3 levels. BOLD responses to nociceptive stimuli of the thumb were expected to occur mostly in the spinal cord at around C5 vertebral level, which roughly corresponds to the position of spinal level C6. Possible factors contributing to such discrepancy between C3 and C6 dermatome may lead to activation of dorsal horn neurons distributed across segments since axons in the lateral division of the dorsal-root fibers split to form Lissauer's tract. These axons may ascend or descend in Lissauer's tract for at least two spinal segments before entering into the lateral portion of the dorsal horn to synapse on cells in the dorsal horn (Murray, 2003). This implies that activation of nociceptive fibers from C6 dermatome may lead to activation of dorsal horn neurons distributed in spinal segments C4 to C8, extending roughly from vertebral levels C3 to C7. This argument however does not by itself account for the fact that there is such a discrepancy in the activated levels between C3–C4 instead of –C5). Secondly, the stimulus at dermatome C6 can yield synaptic relays via interneurons, thereby spreading BOLD responses across levels (Stracke et al., 2005) (as clearly seen in Fig. 4). Moreover, the extension of the activation depends on the intensity of the nociceptive stimulus (Coghill et al., 1991). Thirdly, the identification of spinal levels based on vertebral levels may not be accurate (Stroman et al., in press). Fourthly, the signal-to-noise ratio (SNR) is likely variable across vertebral levels, due to the uneven distribution of coil arrays elements. As a result, the sensitivity to detect BOLD responses in lower segments can be decreased. The use of highly sensitive coils for fMRI of the spinal cord can alleviate this limitation (Cohen-Adad et al., 2011). This argument also raises concerns about the physiological noise to thermal image noise ratio, which directly relates to the sensitivity to detect BOLD responses (Triantafyllou et al., 2011). Decreasing the thermal noise via more sensitive coils would in turn increase the contribution of physiological noise, in which case post-processing methods such as CORSICA may be even more useful in increasing the sensitivity to detect fMRI activations.

Conclusion

One of the most challenging aspects of spinal cord fMRI is the effect of physiological noise on the detection of the BOLD signal. As the fMRI community has moved to higher field strengths, physiological noise has become an increasingly important confound limiting the sensitivity and the specificity of fMRI studies (Liu et al., 2006). It is therefore even more important to limit this confound via post-processing techniques such as the one presented here. While several approaches are being proposed to correct physiological noise, we recommend that these developments be based on a careful assessment of the spatio-temporal dynamics of the noise (Piché et al., 2009), an explicit model of the physiological signal to be removed (e.g. here based on spectral coherence), a confirmation of the assumptions of the applied correction model (e.g. here CORSICA assumes spatial stability of physiological noise, a condition that has been verified by Piché et al.), and a convincing demonstration that the proposed method improves sensitivity, specificity, or both. Further developments and in depth validation of this correction method appear indispensable before spinal fMRI can be applied more generally as a clinical assessment tool.

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References
