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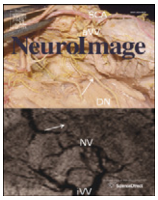

An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data

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ABSTRACT

Several recent reports in large, independent samples have demonstrated the influence of motion artifact on resting-state functional connectivity MRI (rsfc-MRI). Standard rsfc-MRI preprocessing typically includes regression of confounding signals and band-pass filtering. However, substantial heterogeneity exists in how these techniques are implemented across studies, and no prior study has examined the effect of differing approaches for the control of motion-induced artifacts. To better understand how in-scanner head motion affects rsfc-MRI data, we describe the spatial, temporal, and spectral characteristics of motion artifacts in a sample of 348 adolescents. Analyses utilize a novel approach for describing head motion on a voxelwise basis. Next, we systematically evaluate the efficacy of a range of confound regression and filtering techniques for the control of motion-induced artifacts. Results reveal that the effectiveness of preprocessing procedures on the control of motion is heterogeneous, and that improved preprocessing provides a substantial benefit beyond typical procedures. These results demonstrate that the effect of motion on rsfc-MRI can be substantially attenuated through improved preprocessing procedures, but not completely removed.

Introduction

Although it has long been known that in-scanner head motion can have profound effects on fMRI timeseries data (Bullmore et al., 1999; Friston et al., 1996), the specific importance of this artifact for the analysis of resting state functional connectivity MRI (rsfc-MRI; Biswal et al., 1995; Fox and Raichle, 2007) has only recently been appreciated. In particular, it has been demonstrated in three large independent samples (Power et al., 2011a, 2011b; Satterthwaite et al., 2012a; Van Dijk et al., 2011) that even relatively small amounts of in-scanner head motion represent a substantial confound for rsfc-MRI data. All three studies concluded that motion in general tends to enhance short-range connectivity and diminish long-distance connectivity among network nodes. As rsfc-MRI has evolved to become an important tool for examining brain networks in health and disease (Biswal et al., 2010; Fox and Greicius, 2010; Glahn et al., 2010; Seeley et al., 2009; Yeo et al., 2011; Zhou et al., 2010), it is of critical importance to understand how best to model and account for this artifact.

Power et al. (2011a, 2011b) recently introduced a novel method, called "scrubbing," that identifies motion-induced spikes in the rsfc-MRI timeseries and excises these data with a temporal mask; adjacent timepoints are then temporally concatenated. Subsequently, Carp (2011) proposed a modification of scrubbing where data were removed and interpolated prior to band-pass filtering in order to avoid propagation of the motion artifact during the application of the band-pass filter. Using simulated data, he demonstrated that this modified scrubbing procedure was able to recover the "ground truth" connectivity in this timeseries (Carp, 2011). In a reply to Carp, Power et al. (2012) note that this procedure may be of marginal benefit given the fact that motion often occurs in long epochs, and that the effect of motion may occur beyond one isolated volume.

Scrubbing is a preprocessing technique that can be implemented after (Power et al., 2011a, 2011b) or as part of (Power et al., 2012) standard rsfc-MRI preprocessing, which usually includes image re-alignment, spatial smoothing, filtering, and confound regression (Van Dijk et al., 2010). Notably, no prior report has investigated

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whether these standard rsfc-MRI preprocessing steps can themselves be improved to control the artifacts induced by in-scanner head motion. Here, we focus on two of these steps – confound regression and filtering – and investigate whether improved methods can produce better control of motion artifact.

There is substantial variation regarding how motion is modeled during confound regression (Auer, 2008; Johnstone et al., 2006): some studies include only the six motion parameters themselves, while others include the temporal derivatives, or even the quadratic of both the raw parameters and derivatives (zu Eulenburg et al., 2012). Yet other studies have modeled motion-induced spikes in the timeseries data with individual regressors, effectively removing the effect of these data points on any subsequent analysis of the residual timeseries (Lemieux et al., 2007). Furthermore, while most studies apply a band-pass filter with a high-pass cutoff in the range of 0.008–0.01 Hz and a low-pass threshold of 0.08–0.1 Hz (Cordes et al., 2001; Niazy et al., 2011), it has not yet been specifically demonstrated how motion affects the magnitude spectra of rsfc-MRI data, nor is it known whether band-pass filtering can be tailored for better control of motion artifact.

This study investigates the effect of motion and the improvement of preprocessing procedures in a large sample of adolescents ($n=348$) who completed an rsfc-MRI study of typical duration (6 minutes). We had two primary goals. First, we sought to describe the spatial, temporal, and spectral characteristics of motion artifact, and evaluated how typical preprocessing steps alter the manifestations of this artifact. Second, we systematically evaluated whether confound regression and filtering could be improved to provide better control of motion artifact. Results reveal that the effectiveness of preprocessing procedures on the control of motion artifact are quite variable, and that improved preprocessing provides a substantial benefit beyond typical procedures, allowing the attenuation but not complete removal of motion artifact from rsfc-MRI data.

Materials, methods, and results

Overall approach

Reflecting the two main goals of this study, the methods and results of this paper are described in two parts. In the first section we further describe how in-scanner motion affects rsfc-MRI data through use of both real data and simulations, and how different preprocessing strategies may alter the way motion artifact manifests. In order to evaluate the spatial distribution of motion artifact, we introduce a novel procedure for estimating motion on a voxelwise basis. In the second section, we investigate strategies for improving preprocessing through different techniques of confound regression and filtering. However, we begin by detailing the general methods that are common to both parts.

General methods

Subjects and sub-samples

The present study is a collaboration between the Center for Applied Genomics (CAG) at Children's Hospital of Philadelphia (CHOP) and the Brain Behavior Laboratory at the University of Pennsylvania (Penn); full study design and procedures are described elsewhere (Gur et al., 2012; Satterthwaite et al., 2012a; Satterthwaite et al., 2012b). For the purposes of this report, we compared preprocessing techniques among a subsample of 348 adolescents (ages 8–23) previously examined in Satterthwaite et al. (2012a), who were selected through a manual process so that age and in-scanner motion were uncorrelated. As described in Satterthwaite et al. (2012a) subjects with gross motion (>0.55 mm mean relative displacement) were initially excluded from analysis. Furthermore, in the age/motion matching process several additional high-motion subjects were excluded; thus, the highest mean relative displacement of any subject in the present sample was 0.20 mm. Because age and motion were uncorrelated, this sample thus avoids any confounding influence of subject age on estimated effects of in-scanner motion, as younger subjects move substantially more during image acquisition. All subjects or their parent or guardian provided informed consent (or assent if <18 years old); study procedures were approved by the Institutional Review Boards of both Penn and CHOP.

Throughout this report, we compare two sub-samples of these 348 subjects. These sub-samples consisted of two groups of 100 subjects each: the "low-motion" group comprised the 100 lowest-motion subjects, whereas the "high-motion" group included 100 high-motion subjects who were matched for age and sex on a 1:1 basis with the low-motion group using a matching algorithm implemented in MATLAB (The Mathworks; Natick, MA). This algorithm (code available upon request) started with the 100 lowest-motion subjects in the sample, and then iteratively found subjects of the same gender and most-similar age from the remaining pool of 248 higher-motion participants. Therefore, the "low-motion" group comprises the subjects the lowest movement in this sample, whereas the "high-motion" group includes age and gender matched subjects with higher motion. Note, however, that this "high-motion" group is not simply comprised of the highest-motion subjects in the overall sample, as that would have lead to substantial differences in age between the low motion and the high motion groups, with the high-motion group being significantly younger. Subject demographics for the complete sample and matched sub-samples are detailed in Table 1.

Image acquisition

All imaging data in this report are the same as the data from our initial report on the effect of in-scanner motion on functional connectivity (Satterthwaite et al., 2012a). All subject data were acquired on the same scanner (Siemens Tim Trio 3 Tesla, Erlangen, Germany; 32 channel head coil) using the same imaging sequences. Blood oxygen level dependent (BOLD) fMRI was acquired using a whole-brain, single-shot, multi-slice, gradient-echo (GE) echoplanar (EPI) sequence of 124 volumes with the following parameters: TR/TE = 3000/32 ms, flip angle = 90 degrees, FOV = 192 × 192 mm, matrix = 64 × 64, 46 slices, slice thickness/gap = 3 mm/0 mm, interleaved acquisition. The resulting nominal voxel size was 3.0 × 3.0 × 3.0 mm. A fixation cross was displayed as images were acquired. Subjects were instructed to stay awake, keep their eyes open, fixate on the displayed crosshair, and remain still. Prior to timeseries acquisition, a magnetization-prepared, rapid acquisition gradient-echo T1-weighted (MPRAGE) image (TR 1810 ms, TE 3.51 ms, FOV 180 × 240 mm, matrix 256 × 192, 160 slices, TI 1100 ms, flip angle 9 degrees, effective voxel resolution of 1 × 1 × 1 mm) was acquired to aid spatial normalization to standard atlas space. In order to acclimate subjects to the MRI environment, a mock scanning session was conducted prior to image acquisition for each individual using a decommissioned MRI scanner and head coil. Mock-scanning was accompanied by acoustic recordings of the noise produced by gradient coils for each scanning pulse sequence. During these sessions, feedback regarding head movement was provided to the subjects using the MoTrack (Psychology Software Tools, Inc, Sharpsburg, PA) motion tracking system. Motion feedback was only given during the mock scanning session. In order to further minimize

Table 1
Sample characteristics.

Sample	*n*	Mean age, year (S.D.)	No. of male	MRD, mm (S.D.)	DVARS, % (S.D.)
Complete sample	348	16.64 (3.01)	146	0.062 (0.039)	0.74 (0.16)
Low-motion subsample	100	16.99 (2.74)	37	0.029 (0.004)	0.63 (0.10)
High-motion subsample	100	17.10 (2.72)	37	0.097 (0.043)	0.83 (0.18)