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Reporting of Resting-State Functional Magnetic Resonance Imaging Preprocessing Methodologies

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Abstract

There has been a rapid increase in resting-state functional magnetic resonance imaging (rs-fMRI) literature in the past few years. We aim to highlight the variability in the current reporting practices of rs-fMRI acquisition and preprocessing parameters. The PubMed database was searched for the selection of appropriate articles in the rs-fMRI literature and the most recent 100 articles were selected based on our criteria. These articles were evaluated based on a checklist for reporting of certain preprocessing steps. All of the studies reported the temporal resolution for the scan and the software used for the analysis. Less than half of the studies reported physiologic monitoring, despiking, global signal regression, framewise displacement, and volume censoring. A majority of the studies mentioned the scanning duration, eye status, and smoothing kernel. Overall, we demonstrate the wide variability in reporting of preprocessing methods in rs-fMRI studies. Although there might be potential variability in reporting across studies due to individual requirements for a study, we suggest the need for standardizing reporting guidelines to ensure reproducibility.

Keywords: analysis; preprocessing; reporting; resting-state fMRI; techniques; variability

Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as a popular method of assessing intrinsic brain connectivity (Birn, 2012). The majority of the rs-fMRI studies to date use seed-based correlation analysis (SBA) or independent component analysis (ICA). In a seed-based approach, time courses of one or more regions of interest (ROIs) may be correlated with other ROIs, or on a voxel level, to the whole brain (Biswal et al., 1995; Greicius et al., 2003; Raichle et al., 2001). Using ICA, the blood oxygenation level-dependent (BOLD) time courses may be partitioned into maximally independent components (Beckmann et al., 2005; Kiviniemi et al., 2003; McKeown et al., 1998), generating spatial (or temporal) maps of well-known intrinsic brain networks, such as the widely studied default mode network (DMN) (Damoiseaux et al., 2006; Greicius et al., 2003).

Rs-fMRI has multiple advantages over task-fMRI. Rs-fMRI obviates the necessity of constructing a specific task designed to elicit a particular neurobehavioral response. In addition to eliminating resources necessary to design and implement such tasks (including software and hardware for stimulus presentation, MRI technologists who are adequately trained to run the fMRI examinations, and experienced professionals who can design appropriate paradigms, train subjects to perform tasks properly, and monitor such task performance during the image acquisitions), rs-fMRI has a distinct advantage in populations where task compliance may be compromised due to physical or cognitive impairment or language difficulties (Fox and Greicius, 2010). Furthermore, rs-fMRI potentially may provide similar or increased information (i.e., simultaneously evaluating multiple networks) about brain function compared to task-fMRI (Fox et al., 2006) in a shorter period of time (Van Dijk et al., 2010), which is beneficial when attempting to implement rs-fMRI at a clinical level.

There are, however, certain challenges that are currently greater in rs-fMRI compared to task-fMRI, primarily the selection of appropriate preprocessing measures to counter the effects of nuisance signals (Hallquist et al., 2013). Well known is the effect of motion on causing artifactual changes in connectivity measures, which necessitates additional processing steps to mitigate this confound (Power et al., 2012; Van Dijk et al.,

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2012). As preprocessing steps for rs-fMRI continue to evolve, we may eventually see a convergence of these approaches to a recommended consensus. Currently, however, there is ongoing debate about the pros and cons of many steps of rs-fMRI preprocessing, for example, the inclusion of global signal regression, which is advocated (Fox et al., 2009) by some and discouraged (Murphy et al., 2009) by others.

Detailed reporting of preprocessing measures in rs-fMRI therefore becomes paramount in adequately evaluating comparison studies and ensuring reproducibility. Our aim in this article was twofold: first, to demonstrate the variability in rs-fMRI processing across studies, and second, to measure the level of detail of methods reporting in rs-fMRI studies, following guidelines previously described for task-fMRI studies (Poldrack et al., 2008).

Materials and Methods

Selection of articles

The PubMed database was searched in January 2016 using the terms *(fMRI OR functional MRI OR functional magnetic) AND (functional connectivity OR resting state OR resting-state)*. Only articles written in English and those involving human subjects were selected. Any editorials, reviews, meta-analyses, conference proceedings, or case reports were excluded from our selected list. We also excluded any rs-fMRI methods/technical improvement studies to limit our focus to studies of rs-fMRI application. We first evaluated the abstract of each article to determine whether our criteria were met, and if so, then the full texts were evaluated. We excluded studies for which we were unable to access the full-text articles. The most recent 100 articles that met our above-described criteria were selected from the search.

Evaluation of articles

A checklist, described below and shown in Table 1, was devised for the evaluation of articles. The aim of the checklist was to investigate whether the studies used certain preprocessing steps and to check for the reporting of said items in the studies. After the selection of the articles, each article was manually inspected by a single rater for extraction of information pertaining to the items of the checklist. A second rater confirmed the accuracy of the information, and in cases where there was a definite or possible discrepancy, a consensus was determined by a third rater.

Table 1. Parameter Checklist for the Evaluation of Articles

Acquisition/Preprocessing parameters
Acquisition information
1. Length of scan acquisition
2. Temporal resolution
3. Physiological monitoring (cardiac/respiratory)
4. Eye status (closed/open with fixation/open without fixation)
Preprocessing information
1. Software used
2. Removal of initial volumes before reaching steady state
3. Despiking
4. Temporal filtering
5. Compartment-based nuisance removal (CSF/WM noise removal)
6. Head motion regression
7. Global signal regression
8. Motion characterization and group differences
9. Volume censoring
10. Spatial smoothing

CSF, cerebrospinal fluid; WM, white matter.

Checklist items

Publication date and journal name were recorded for each article and scanner characteristics for the study (MR vendor and field strength) logged. Then, each item on the acquisition/preprocessing checklist was recorded. Acquisition information included the following: (1) length of scan acquisition, (2) temporal resolution (MR repetition time TR), (3) physiological (i.e., cardiac/respiratory) monitoring, and (4) eye status (closed, open with fixation, open without fixation) during acquisition. Preprocessing information included the following: (1) software used, (2) removal of initial rs-fMRI volumes before reaching steady state, (3) despiking, (4) temporal filtering and its parameters, (5) indication of compartment-based nuisance regression (i.e., CSF/WM nuisance removal), (6) head motion regression, (7) global signal regression, (8) motion characterization and group differences, (9) volume censoring (scrubbing), and (10) spatial smoothing.

For each item in the checklist mentioned above, we checked whether or not that item was reported. If multiple software were used, then all were counted.

It is important to note that articles were assessed according to the procedures and techniques that were explicitly stated. We also evaluated any supplementary data if available.

Results

A summary of processing reporting is presented in Figure 1.

Scanning characteristics

The majority of the studies mentioned the manufacturer of the MR scanner (97%) and the field strength (99%). All of the studies were performed using either a 1.5 T or 3 T magnet. The temporal resolution (TR) for the scan was reported by 100% of the studies. The TR ranged from 0.7 to 3.5 sec with a median of 2 sec. The most commonly used TR was 2 sec (59%) followed by 3 sec (14%). Sixty-nine percent of the studies reported the total length of acquisition. Twenty-seven percent of the studies did not mention the scanning time but did provide the number of volumes acquired, so that total length time could be calculated. We calculated the scanning time for such studies. Four percent of the studies failed to mention both the scan duration and the number of volumes acquired; hence, the scanning time for such studies could not be calculated. The scanning time ranged from 3 min 20 sec to 26 min 42 sec. The median scanning time was 7 min, and the most commonly used scanning time was 8 min (22.9%, 22/96) followed by 6 min (16.7%, 16/96) and 5 min (11.5%, 11/96).

Eye status

Eighty-two percent of the studies provided information about the eye status during the scan. The majority of the studies mentioned that the subjects were instructed to keep their eyes closed (60.9%, 50/82). Other eye status information

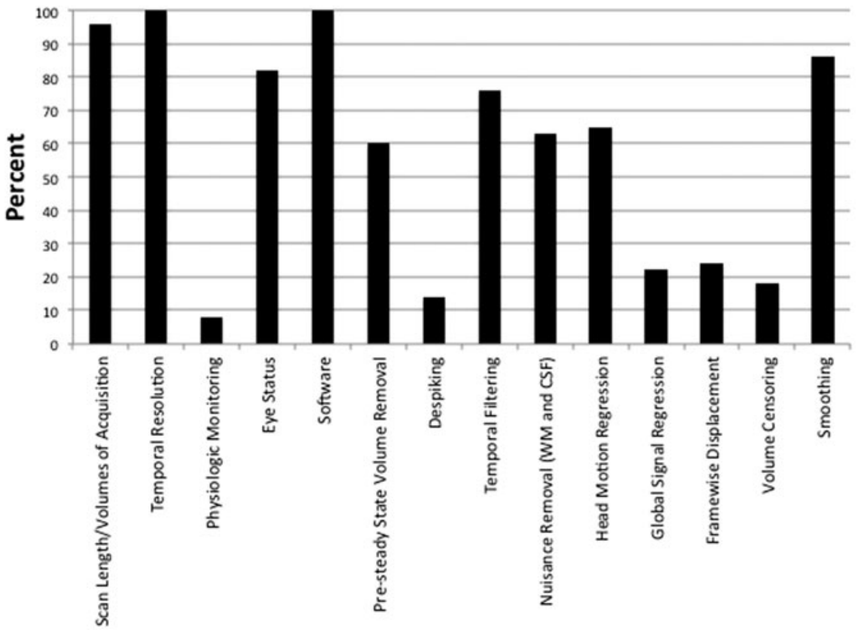

FIG. 1. Reporting of specific processing steps utilized in resting-state functional magnetic resonance imaging studies.

reported was eyes open without fixation (17.1%, 14/82) and eyes open with fixation (14.6%, 12/82) during the scan, while 21.9% (18/82) of the studies provided no information about the eye status. The remaining studies used subjects who were anesthetized, sedated, or asleep.

Software used

Twelve different software packages were used in the 100 studies. Many articles utilized the use of multiple software for analysis. The most commonly used software was SPM (56%) followed by DPARSF (29%) and FSL (25%). Other less commonly used software included AFNI and various MATLAB toolboxes, such as the GIFT toolbox and the Conn toolbox.

Type of analysis

Forty-five percent of the studies performed an SBA of the data, whereas 32% of the studies used the ICA approach. Graph Theory was used by 9% and amplitude of low-frequency fluctuations (ALFF) was used by 8% of the studies. Twelve percent of the studies used multiple techniques for analysis. Other techniques used included data-driven global connectivity approach, dual regression, dynamic analysis, entropy connectivity, functional connectivity density mapping, functional connectivity strength analysis, intrinsic connectivity contrast analysis, ReHo, semimetric analysis, and voxel-mirrored homotopic connectivity.

Volumes removed

Sixty percent of the articles mentioned the number of volumes removed at the onset of imaging before reaching steady state. The range of volumes removed was 2–10, with median of 6 and a mode of 10.

Temporal filtering

Seventy-six percent of the studies mentioned performing temporal filtering. Band-pass filtering of the signal was performed by 76.3% (58/76), high-pass filtering by 22.4% (17/76), and low-pass filtering by 1.3% (1/76) of the studies. The most commonly used filters for band-pass filtering were 0.01–0.08 Hz (44.8%, 26/58), 0.01–0.1 Hz (22.4%, 13/58), and 0.008–0.09 Hz (12.1%, 7/58). The high-pass filtering cutoff ranged from 50 to 150 sec with a median and mode of 100 sec. The low-pass filter cutoff used by one of the study was 12.5 sec.

Nuisance removal

Sixty-three percent of the studies mentioned performing white matter (WM) noise removal, while 67% of the studies mentioned regressing out cerebrospinal fluid (CSF) noise. Sixty-three percent of the studies mentioned regressing out both WM and CSF signals. Seven percent of the studies mentioned using the CompCor method for noise removal. Eight percent of the studies mentioned using the ICA-based Xnoiseifier for noise removal. Two percent of the studies mentioned using the RETROICOR method for noise removal.

We found that only 4% of the studies mentioned using physiological monitoring of both cardiac and respiratory traces, while another 4% of the studies only used monitoring of cardiac traces. Of these 8% of the studies mentioning physiological monitoring, three studies (37.5%, 3/8) used the monitoring for physiological artifact removal.

Sixty-five percent of the studies mentioned performing head motion regression. 43.1% (28/65) of such studies mentioned head motion regression based on 6 motion parameters, 20% (13/65) based on 12 motion parameters (with derivative), and 12.3% (8/65) based on 24 motion parameters. 1.5% (1/65) of the studies mentioned using 18 motion parameters for head motion regression. Meanwhile, 23.1% (15/65) of the studies provided no detail about the parameters used for head motion regression. We also found that 84.4% (38/45) of the seed-based analysis studies performed head motion regression, while only 12.5% (4/32) of the ICA-based studies performed head motion regression.

Twenty-two percent of the studies mentioned performing global signal regression. 13.6% (3/22) of such studies mentioned results both with and without global signal regression.

Motion characteristics

Forty-two percent of the studies mentioned a technical exclusion criterion for subjects based upon maximum displacement, with 95.2% (40/42) specifying the threshold value for maximum displacement. The threshold value for maximum displacement ranged from 1 to 6 mm with a median of 2 mm. The most commonly used threshold value for maximum displacement was 3 mm (30.9%, 13/42) followed by 2 mm (23.8%, 10/42). Framewise displacement (FD) was calculated by 24% of the studies. Ten percent of the studies computed the root-mean-square (RMS) of the translation parameters. Only 10% of the articles provided a table of motion. Eighty-one percent of the studies involved group-level comparisons. Overall, 29% of the studies calculated motion statistics between groups.

Only 18% of the studies performed scrubbing or censoring of volumes based on head micromovements, however, 27.8% (5/18) of such studies provided no cutoff value for the scrubbing of volumes. The scrubbing cutoff ranged from 0.2 to 0.5 mm with a median of 0.3 mm. The most commonly used scrubbing cutoff value was FD >0.5 mm (33.3%, 6/18). DVARS (D = temporal Derivative of timecourses, VARS = RMS variance of voxels) was reported in 8% of the studies; of those, half reported using DVARS for scrubbing, with parameters reported in three total studies with cutoff values reported as ">5," ">8," and ">0.6%" of BOLD.

Others

Only 14% of the articles mentioned despiking the signal. Furthermore, 34% of the articles mentioned detrending the signal for either linear or quadratic trends. Two percent of the studies provided no information about the initial voxel size. Eight-six percent of the studies used a smoothing kernel. For 12% of the studies, we had to access the supplementary data provided to complete the checklist.

Discussion

Our findings confirm the widespread variability of processing strategies for rs-fMRI analysis, as well as reporting of specific techniques used. We highlight some key findings and discuss possible rationales for this variability, emphasizing the necessity of accurate reporting of methodologies.

Scan duration, either directly reported or easily calculated from data provided, was reported in nearly all studies. However, 4% of studies failed to provide directly the length of acquisition or indirect information (volumes acquired) for calculation. In addition to TR, this probably represents the most critical piece of information in rs-fMRI studies. Based on Van Dijk and colleagues (2010), the majority of rs-fMRI studies appear to acquire data for 5–8 min, following the observation that estimates of connectivity strengths stabilize after 5–6 min of scan time. Acquisition length of a similar duration has also been shown to enable identification of unique individuals (subject-level fingerprinting) using rs-fMRI (Airan et al., 2016). More recent reports indicate, however, that reliability of connectivity measures may be improved by further increasing scan time to 13 min (Birn et al., 2013).

On the contrary, the length of acquisition is also dependent upon the exact measure of connectivity that is assessed; for example, some graph theoretic metrics of brain connectivity may be computed accurately from as little as 1.5–2 min of acquisition (Whitlow et al., 2011). The optimum length of acquisition, therefore, may be heavily influenced by the analysis method used.

Scrubbing, or motion-censoring, of rs-fMRI data sets is commonly used to minimize motion-related aberrancies in functional connectivity estimates (Power et al., 2012). In our sample, almost one-fifth of the studies used data scrubbing. The criteria for scrubbing typically involve a threshold of FD and/or DVARS, both of which may have variations across sites due to inclusion of assumed estimates that are used, for example, the assumed spherical estimate of a standard head size to calculate FD or the varying methods of intensity normalization to calculate DVARS.

There is ongoing debate on whether it is better to keep eyes closed or open, with or without fixation, for reproducible estimates of connectivity. Eighteen percent of the studies did not indicate eye status, which can significantly affect connectivity.

Yan and colleagues (2009) demonstrated that ALFF was greater for eyes closed when compared to both eyes open and eyes fixated. They also reported that functional connectivity maps of DMN appear similar across different resting conditions; however, the strength of connectivity was lower for eyes closed when compared with eyes fixated. Van Dijk and colleagues (2010) yielded some consistent results showing that functional connectivity strength within the default and attention networks was significantly diminished for eyes closed when compared with eyes fixated. Zou and colleagues (2009) demonstrated negative correlations between the thalamus and visual cortex, and positive correlations between the bilateral thalamus in eyes closed and eyes open. However, these correlations were stronger under the eyes closed condition than the eyes open condition.

Patriat and colleagues (2013) showed that only the auditory network displays significantly higher connectivity in the eyes closed condition compared to the other two conditions. For the other networks, there were no significant between-condition differences in connectivity strength. As far as reliability and consistency were concerned, they found that primary visual network connectivity was most reliable when subjects had their eyes open, while for all within-network connections and within default-mode, attention, and auditory networks, statistically significantly greater reliability was found when the subjects were lying with their eyes fixated on a cross, a finding replicated in a subsequent study (Zou et al., 2015). Marx and colleagues (2004) showed that activation of the ocular motor system and the deactivation of multiple sensory areas can go undetected with eyes open as rest condition.

These findings on different resting states and how they may affect functional MRI findings show that each study may need to tailor their eye status, depending on which network properties are of interest.

WM and CSF noise removal is a commonly used step in seed-based correlation and sometimes ICA-based, rs-fMRI analysis to mitigate nuisance signal from cardiac and respiratory sources (Dagli et al., 1999; Lund et al., 2006). We find that approximately two-thirds of the studies described nuisance removal methods. More controversial is the inclusion of global signal regression (Yeh et al., 2015), which was utilized in approximately one-fifth of the studies. The inclusion of global signal regression has been theorized to recenter or rescale the estimates of connectivity, introducing or enhancing anticorrelations by decreasing the mean of these estimates (Anderson et al., 2011; Chai et al., 2012; Fox et al., 2009; Murphy et al., 2009; Van Dijk et al., 2010; Weissenbacher et al., 2009).

While an earlier study indicated that global signal regression suppresses false correlations and increases the specificity of functional connectivity results (Weissenbacher et al., 2009), more recent studies argue against the use of global signal regression, which decreases both intra- and intersession reliability of regional homogeneity measures (Zuo et al., 2013), and introduces distortion of correlations (Gotts et al., 2013).

Reporting every detail can be onerous and may not be convenient according to journal guidelines and considering reader interest. Accordingly, we suggest the need to accurately report parameters that have practical value. We suggest that the following parameters be adequately described in future rs-fMRI studies: TR (in seconds), length of scan (based on time or number of volumes), eye status (closed/open/open with fixation to cross/etc), number of initial rs-fMRI volumes removed, physiological monitoring, group-level head motion in millimeter with exclusion criteria and group-level statistics if appropriate, nuisance regression (e.g., motion/WM/CSF/global signal regression), temporal filtering (including detrending) and range, despiking, smoothing kernel, and software utilized with version.

Conclusion

With ongoing data-sharing initiatives, such as the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org), efforts are underway to streamline processing and analysis methods for typical rs-fMRI studies. However, as variability in methods will continue to exist due to specific needs of particular studies, we highlight in this study the necessity of accurate reporting of techniques to ensure reproducibility for the end goal of utilizing rs-fMRI as a widespread clinically viable tool.

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Author Disclosure Statement

No competing financial interests exist.

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