Title

Motion and morphometry in clinical populations

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Abstract

Introduction

The relationship between participant motion, demographic variables and MRI-derived morphometric estimates was investigated in autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and schizophrenia. Participant motion was estimated using resting state fMRI and used as a proxy measure for motion during T1w MRI acquired in the same session. Analyses were carried out in scans qualitatively assessed as free from motion-related artifact.

Methods

Whole brain T1-weighted MRI and resting state fMRI acquisitions from the ABIDE, ADHD-200 and COBRE databases were included in our analyses. Motion was estimated using coregistration of sequential resting state volumes. Morphometric estimates were obtained using Freesurfer v5.3. We investigated if motion is related to diagnosis, age and gender, and scanning site. We further determined if there is a relationship between participant motion and cortical thickness, contrast, and volumetric estimates.

Results

2131 participants were included in our analyses. Participant motion was higher in all clinical groups compared with healthy controls. Younger (age < 20 years) and older (age > 40 years) people move more than individuals aged 20 – 40 years. Increased motion is associated with reduced average cortical thickness (-0.02 mm thickness per mm motion, $p = 4.03\times10^{-5}$) and cortical contrast (0.95% contrast reduction per mm motion, $p = 5.25\times10^{-11}$) in scans that have been qualitatively assessed as free from motion artifact.

Conclusions

Participant motion is increased in clinical groups and is systematically associated with morphometric estimates. These findings indicate that accounting for participant motion may be important for improving the statistical validity of morphometric studies.

1. Introduction

Movement artifact is a potential source of error for morphometric analysis of structural MRI. In this study we quantitatively assessed the relationship between participant motion during MRI acquisition and morphometric estimates in clinical populations, comprising autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia. MRI data for each of these disorders was obtained from the ABIDE, ADHD-200, COBRE databases respectively. Participant motion was estimated using resting state fMRI (rsfMRI) data acquired in the same session as the whole brain T1-weighted MRI acquisition. After determining the validity of rsfMRI-based motion as a proxy measure of motion during the structural MRI scan, we investigated if participant motion was related to diagnosis, participant age, gender and scanning site. We then investigated the effect of motion on cortical thickness, contrast between white and cortical gray matter, and subcortical volume. In order to determine if a visual quality assurance rating can adequately control for motion effects, analyses were carried out on scans that had been qualitatively assessed as free from motion-related artifact.

If motion has a systematic effect on morphometric estimates, and also varies between subject groups, then participant motion may be a source of bias in morphometric brain analyses, and a potential source of false positive findings. A recent prospective study in which participants were instructed to move during MRI acquisition demonstrated that participant motion is correlated with reduced cortical thickness and volume [1]. Our study extends this analysis to investigating participant movement in a ‘natural’ setting in which participants were not instructed to move, as well as investigating how motion varies in clinical groups and with demographic variables.

Motion was quantified using resting state fMRI (rsfMRI) that was acquired in the same session as the volumetric T1-weighted acquisitions that were used to obtain morphometric estimates. The rsfMRI-derived motion estimate was used as an explanatory variable in subsequent analyses of morphometric data. An assumption of our study is that individuals that move during the resting state fMRI also move during the T1-weighted MRI. In order to determine if this assumption is valid, we investigated if there is a relationship between the rsfMRI-based motion estimate and qualitative estimates of scan quality obtained by visual inspection of the T1-weighted MRI.

Specific hypotheses investigated in this study were:

1. Participant motion, estimated from resting state fMRI, will be related to qualitative estimates of scan quality of volumetric T1-weighted MRI.
2. Participant motion is related to diagnosis, age, gender and scanning site in ASD, ADHD, and schizophrenia.
3. Participant motion is related to cortical thickness, contrast between cortical gray matter and underlying white matter, and subcortical volumetric estimates.

2. Methods

2.1 Participant and MRI acquisition details

Autism Spectrum Disorder (ASD): T1 weighted whole brain and resting state fMRI data from the Autism Brain Imaging Data Exchange (ABIDE) database were used for our analyses [2]. Typical voxel resolutions for T1 weighted MRI were 1mm isotropic or similar. Image acquisition parameters for both the whole brain T1 weighted acquisition and the resting state acquisition varied by site (see Table 1 in [3] for a summary of T1w image acquisition parameters for the ABIDE study). Scan time for rsfMRI varied from 3:32 seconds to 10 minutes. A summary of ABIDE rsfMRI acquisition parameters is provided as supplementary material. Importantly, quality assurance protocols (QA) for image acquisition also varied by site. Nine sites stated that they did not remove scans that had motion or poor image quality, five sites stated that QA procedures were applied with a relative lack of information regarding the QA protocol, and three sites applied specific criteria for QA processing. Further information about the study can be found at the ABIDE website (http://fcon_1000.projects.nitrc.org/indi/abide/).

Attention Deficit Hyperactivity Disorder (ADHD): T1-weighted MRI and resting state fMRI data from the ADHD-200 sample were used for this analysis [4]. Image acquisition paramters are provided as supplementary material. T1 weighted whole brain MRI had voxel resolution of 1mm isotropic for 5 sites, 1.3 × 1 × 1.3 mm for two sites and 1 × 1 × 1.1 mm for one site. Further information about the study, including diagnostic criteria, can be found at the ADHD-200 website (http://fcon_1000.projects.nitrc.org/indi/adhd200/). QA procedures for the ADHD-200 study were not explicitly provided to the best of our knowledge.

Schizophrenia: The COBRE dataset was used for our analysis (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html). COBRE Whole brain T1-weighted MRI was acquired on a 3T Siemens Trio scanner using a multi-echo MPRAGE acquisition. Voxel resolution was 1 mm isotropic. Other acquisition parameters were: TE = 1.64, 3.5, 5.36, 7.22, 9.08 seconds, TR = 2530 ms, TI = 900 ms, flip angle = 7 degrees.

Recruitment information and image acquisition parameters are found at the COBRE website.

No identifying information was provided with the MRI scans in accordance with HIPAA guidelines. Each institution's human subjects research board established the criteria of informed consent. All available data from each study was used for our analyses.

2.2 Image processing

Subject motion was estimated using two methods; (i) coregistration of sequential image volumes obtained during resting state fMRI acquisition, and (ii) qualitative assessment of structural MRI quality by a reviewer blind to participant demographic and phenotypic information (RKH).

Participant motion was quantitatively assessed using the software tools *MCFLIRT* and *rmsdiff* provided as part of the FSL neuroimaging analysis software package [5]. *MCFLIRT* was used to estimate linear registrations between successive rsfMRI volumes. The transformation matrix describing the transformation between subsequent volumes was used as input to the *rmsdiff* program. The program *rmsdiff* calculates the root mean square deviation of rigid body alignment of successive image volumes obtained during a rsfMRI acquisition. It therefore provides a composite estimate (in mm) of both translation and rotation needed to align the two volumes. Rotations, which would typically be measured in radians or degrees, are converted to distance measures using an analytic formula that is applied over a sphere with a radius of 80 mm. After calculating the root mean square deviation for each sequential pair of images within the rsfMRI acquisition, these values were averaged to obtain an estimate of subject motion during the scan.

Qualitative assessment of T1-weighted volumetric image quality was determined by a single reviewer for the ABIDE, ADHD-200 and COBRE datasets (RKH). T1 weighted images were rated on a scale between 1 and 5, with 1 indicating the lowest quality images with severe motion artifact, and 5 indicating images with no detectable motion artifact. The quantitative rsfMRI motion estimates (mm), and qualitative structural MRI assessments (rating 1 – 5) were compared using a linear model with the qualitative assessment as the predictor ordinal variable and the quantitative assessment as the response variable.

The relationship between quantitative rsfMRI-derived motion estimates and diagnosis, age, gender and site was investigated using a general linear model, with participant motion as the response variable and diagnosis, age, gender and site as predictor variables. Statistical analyses were carried out for each study (ABIDE, ADHD-200, COBRE) independently. For the purposes of visualization of the relative magnitude of the effects of diagnosis, age and gender across clinical populations, figures will be presented with combined data from the three subject groups. For visualization of the relationship between participant motion and age, the function *stat_smooth* provided with the R package ggplot2 was used [6].

Structural MRI scans were processed using Freesurfer v5.3. Average whole brain cortical thickness was obtained by averaging cortical thickness over all cortical vertices. Vertex-wise cortical contrast (WM-GM contrast) was obtained using the script *ptsurfcon* supplied with Freesurfer v5.3. Vertex-wise cortical contrast is calculated as a percentage:

$$Contrast_{GM/WM} = \frac{100 \times (WM_{signal} - GM_{signal})}{\frac{WM_{signal} + GM_{signal}}{2}}$$

Default *ptsurfcon* settings were used for our study. WM signal was measured 1 mm into the white matter from the WM surface, and GM signal was measured at 30% of the thickness of the cortex. Vertex-wise cortical contrast was averaged over the cortical sheet to obtain average whole brain measurements. Volumetric estimates were obtained using the standard Freesurfer subcortical segmentation pipeline.

The relationship between participant motion and cortical thickness, WM-GM contrast and volumetric estimates were investigated using separate general linear models for ABIDE, COBRE and ADHD-200 data respectively, with thickness, contrast and volume as response variables, and motion, diagnosis, age, gender and site included as predictor variables. These analyses were carried out with subjects that had structural MRI with only the highest qualitative rating (rating of "5" only). Statistical inference was carried out using the R software package [7].

The spatial distribution of the relationship between participant motion and thickness and cortical contrast was investigated by carrying out similar inference procedures as those described above but using vertex-wise cortical thickness/contrast estimates rather than whole brain average measures. Individual surfaces were coregistered to the Freesurfer fsaverage template using the standard Freesurfer spherical coregistration method. Thickness and contrast surface maps were smoothing using a 10mm FWHM surface-based smoothing filter. Following vertex-wise inference, maps of the estimated effect size (mm per mm motion for cortical thickness, % contrast per mm motion for cortical contrast) and associated p-values were saved. False discovery rate thresholding was applied using the Benjamini-Hochberg procedure to correct for multiple comparisons ($q < 0.05$). FDR-corrected p-value maps were converted to binary masks, which were then applied to the effect size maps to create maps of regions in which there was a significant relationship between motion and thickness or contrast. Scripts for carrying out the described analyses, as well as data used in the study, are provided at http://sites.google.com/hpardoe/motion.

3. Results

2131 subjects (1591 male, 540 female, mean age = 16.35 ± 9.26 years) from the three imaging databases were included in our study. Participants were excluded if image processing failed or datasets were incomplete.

3.1 rsfMRI-derived motion as a proxy measure of motion during the T1w MRI acquisition

Quantitative rsfMRI derived motion estimates were highly correlated with qualitative visual assessment of motion artifact on T1w MRI, with an average decreased motion of 0.26 mm for each unit change in qualitative category ($p < 2 \times 10^{-16}$). This demonstrated that our rsfMRI-derived quantitative estimate was a good proxy measure of motion during the structural MRI acquisition over the entire subject group of 2131 subjects.

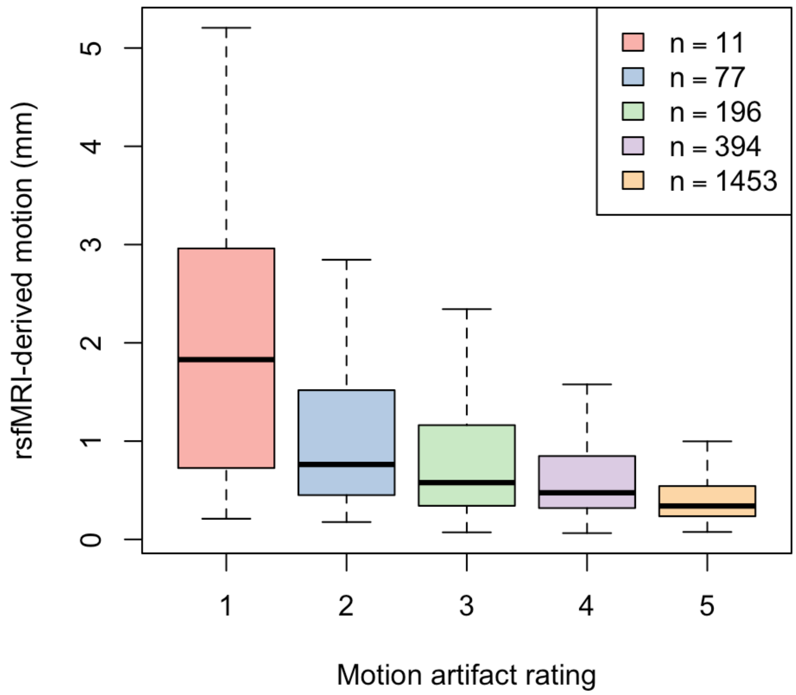

Figure 1. Resting state fMRI-derived motion estimates are a reasonable proxy measure of motion during structural MRI acquired in the same imaging session. The boxplot demonstrates that individuals with poor quality structural MRI scans (low rating) also have high motion during rsfMRI. Note outliers were omitted from the plot.

3.2 Motion during MR acquisition in autism, ADHD and schizophrenia

In the ABIDE MRI dataset, motion is increased in individuals with ASD (0.16 mm, $p = 0.0012$), males (0.15 mm, $p = 0.04$) and younger participants (-0.014 mm per year, $p = 0.00135$). A number of imaging centers had significant variability in participant motion, (range -0.21 mm to 0.67 mm, p value range = 0.98 to 3×10^{-9}, 5/23 sites with $p < 0.05$ when using NYU as the reference site). For the ADHD-200 dataset, motion was increased in ADHD participants (0.15 mm, $p = 9.5 \times 10^{-5}$), and younger participants (-0.017 mm per year, $p = 0.013$). No significant sex effect was observed in the ADHD-200 dataset (0.024 mm increase in males, $p = 0.49$). Differences in motion between sites were also observed in the ADHD-200 study (range 0.04 mm to -0.23 mm, p value range = 0.86 to 6.15×10^{-4}, 2/6 sites with $p < 0.05$).

Individuals with schizophrenia had higher motion than controls in the COBRE study (0.16 mm motion, $p = 0.049$). No relationship was observed between motion and age (0.002 mm per year, $p = 0.52$) or sex (0.048 mm increase in motion in males, $p = 0.59$) for the COBRE dataset.

Visualization of the relationship between motion estimates and demographic and phenotypic variables across the three studies is informative (Figure 2). As one might expect, younger children moved more than adults during the acquisition of the MRI scan. As participant age increased beyond 40, motion during MR acquisition also increased. Comparing the magnitude of motion estimates across diagnosis, age, sex and site variables, it can be seen that the imaging site is the single factor associated with the most variability in motion during acquisition.

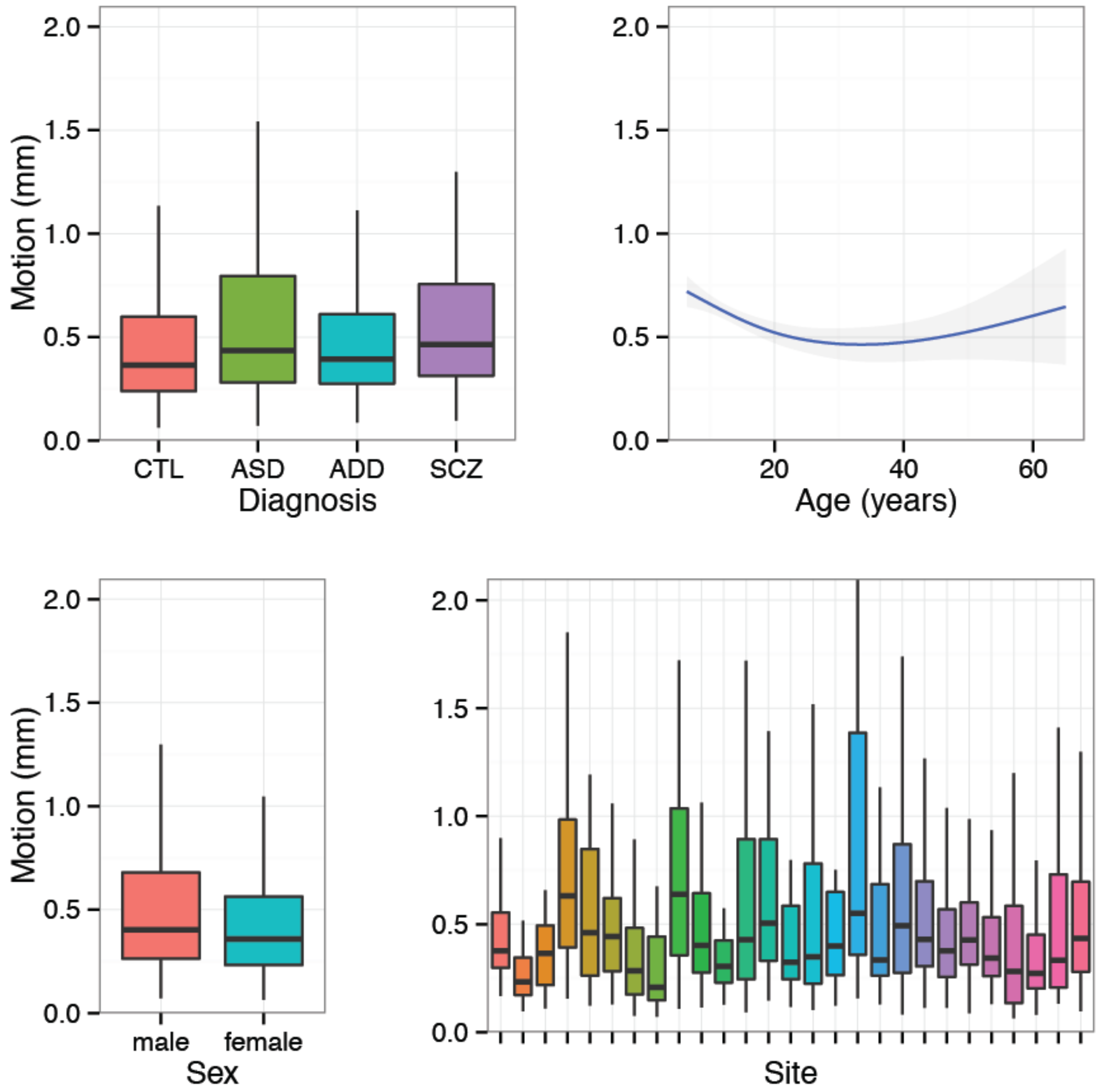

Figure 2. Motion variability between clinical groups and other demographic variables. Motion is increased in diagnostic categories relative to healthy controls (top left plot, CTL = healthy controls, ASD = autism spectrum disorder, ADD = Attention Deficit Hyperactivity Disorder, SCZ = Schizophrenia). Motion is higher in younger participants, decreases to age 20 years, and increases at a lower rate after age 40. There is evidence for a slight increase in motion in males. Motion during acquisition is highly variable between scanning sites, which presumably reflects variability in QA policy between sites. Note the data presented in these plots is raw data that has not been corrected for covariates.

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	Cortical thickness		Cortical GM-WM contrast	
	Effect size (mm per mm motion)	p value	Effect size (% contrast change per mm motion)	p value
ABIDE	-0.01	0.0013	-0.91	1.92×10^{-9}
ADHD-200	-0.055	2.02×10^{-5}	-1.41	8.77×10^{-4}
COBRE	-0.01	0.69	-0.53	0.103
Combined	-0.02	4.03×10^{-5}	-0.95	5.25×10^{-11}

Table 1. Participant motion is strongly correlated with average cortical thickness and contrast in individuals with MRI scans that have been qualitatively assessed as free from motion-related artifact.

3.3 Motion and morphometric estimates

3.3.1 Cortical thickness and motion

We found that participant motion was inversely related to average whole brain cortical thickness; as motion increased, average whole brain cortical thickness decreased. There was a reduction of -0.02 mm thickness per mm motion ($p = 4.03 \times 10^{-5}$) for scans qualitatively free of any motion artifact, when cortical thickness was averaged over the cortical sheet. Reduced whole brain average cortical thickness with increased motion was consistently observed across all three datasets (Table 1). The relationship between motion and cortical thickness is significant over most of the cortical sheet, with a particularly strong effect in the anterior temporal regions and along the precentral gyrus (Figure 3). The occipital lobe and postcentral gyrus show an opposite effect to that observed over the rest of the cortex. In these regions, increased motion is associated with increased estimated cortical thickness.

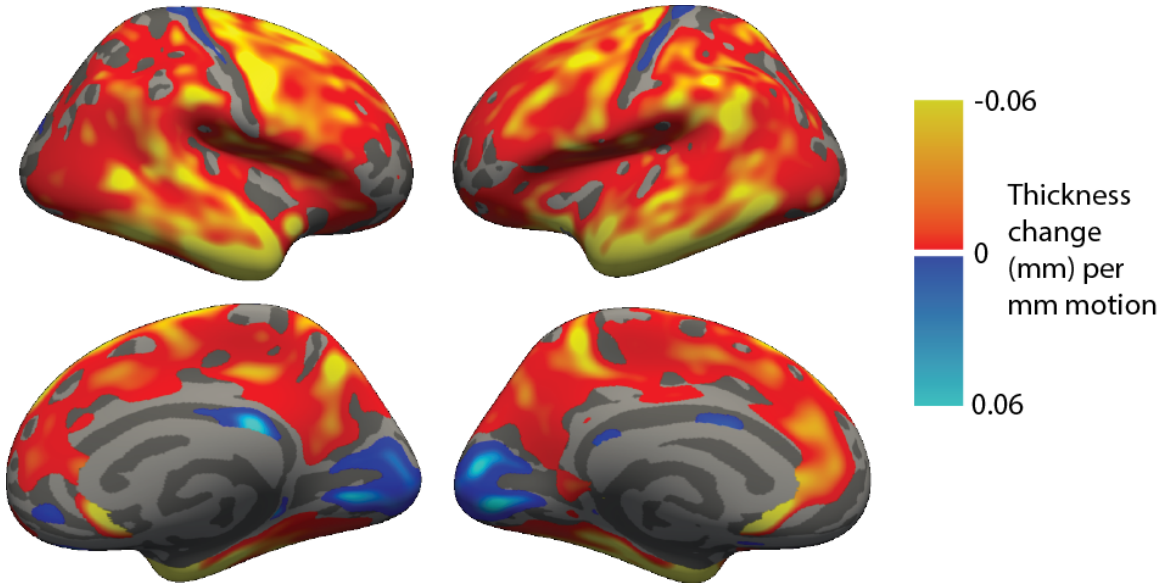

Figure 3. Motion is correlated with cortical thickness over most of the cortex. “Hot” colors indicate regions in which increased motion is associated with reduced cortical thickness. “Cold” colors indicate regions in which increased motion is associated with increased cortical thickness, such as the occipital lobe and postcentral gyrus. Maps show regions that are significant following FDR control for multiple comparisons ($q < 0.05$).

3.3.2 Cortical GM and white matter contrast and motion

Participant motion was inversely proportional to contrast between cortical GM and the underlying white matter averaged over the whole cortical surface; as motion increased, contrast was reduced. We estimate that there is a reduction of 0.95 % contrast per mm motion ($p = 5.25 \times 10^{-11}$), using MRI scans that are qualitatively free of motion artifact. Reduced average contrast over the whole cortical sheet with increased motion was observed across all three datasets (Table 1). Vertex-wise maps of brain regions where contrast is significantly correlated with participant motion are shown in Figure 4.

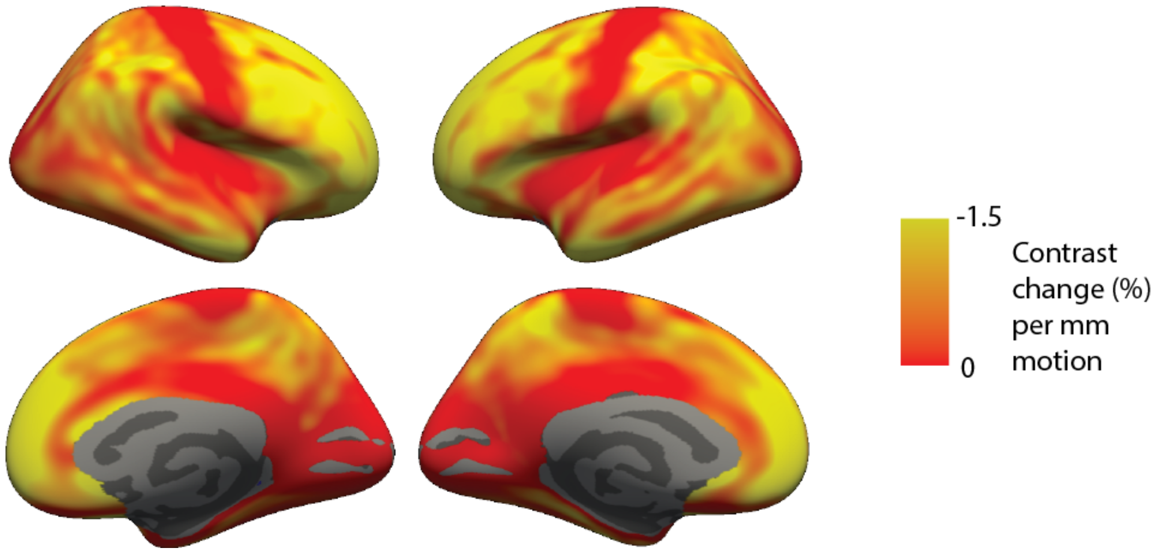

Figure 4. Increased motion is associated with reduced cortical contrast over most of the cortex. Maps show regions that are significant following FDR control for multiple comparisons ($q < 0.05$).

3.3.3 Volumetric estimates and motion

Most subcortical structures segmented using the Freesurfer subcortical processing pipeline did not show a significant relationship between volume and participant motion (see supplementary material). However we did observe a relationship between volume and motion in some important structures. Total brain volume is reduced as participant motion increases in individuals qualitatively assessed as being free from artifact (supratentorial volume estimate, -11189 mm^3 per mm motion, $p = 1.3 \times 10^{-4}$). It appears this effect is primarily driven by cortical volume (-8935 mm^3 per mm motion, $p = 2.94 \times 10^{-6}$), since no significant relationship was observed between total subcortical volume and motion ($p = 0.22$) or white matter volume and motion ($p = 0.22$). The relationship between brain volume and participant motion is important because total brain volume is often used as an explanatory variable in statistical volumetric analyses of sub-structures of the brain.

Other subcortical structures whose volume is related to participant motion include the left and right amygdala (-27 left and -29 mm right mm^3 per mm motion, p = 0.0058 left, 0.025 right), and the white matter hypointensity label (171 mm^3 per mm motion, $p = 1.92 \times 10^{-5}$). Note that unlike other subcortical volume estimates, white matter hypointensity volume increased as participant motion increased.

It is important to also note that there were a number of structures who showed a significant inverse relationship between volume and participant motion in the total dataset (including all scans that had a QA rating lower than 5), but had p-values greater than 0.05 in the reduced dataset (QA rating = 5 only). These structures included caudate nucleus, putamen and accumbens (bilateral), white matter volume and subcortical gray matter volume. These findings suggest that removing poor quality scans reduces the likelihood of introducing systematic bias in volume estimates of these brain structures.

4. Conclusions

We have found that participant motion is more likely to occur in younger children, clinical groups (autism, ADHD and schizophrenia) and males. Increased motion is associated with reduced average cortical thickness and WM-GM contrast, and changes in volumetric estimates. Our findings indicate that participant motion is a potential source of error in studies of brain morphometry in clinical populations. We have also demonstrated that a visual QA assessment is not adequate to completely control for motion-related effects.

Although we demonstrated that motion estimated during the resting state acquisition may be used as a reasonable proxy measure of motion during the structural acquisition, anyone who is familiar with running an MRI scan knows that this assumed relationship

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will not always be true at the individual level. Sometimes an individual will move during the structural MRI and not during the rsfMRI acquisition, and vice versa. Furthermore rsfMRI may not always be available. Therefore based on the results of our study, we recommend that improved methods are required to control for motion during structural MRI. Various approaches may be appropriate for reducing the effects of motion, including acquisitions that track and correct for motion [8-10], or techniques that measure motion during acquisition [11, 12], which may then be controlled statistically at the analysis stage. These approaches have been discussed at length in recent papers [1, 13, 14].

An important finding from our study was that participant motion varied considerably between different scanning sites. The magnitude of between-site differences in motion was larger than differences between clinical groups or demographic variables. These differences may be responsible for obscuring disease or demographic related morphometric differences of interest, and may explain variability in findings that have been reported in many studies. These results underscore the need to statistically model site as an explanatory variable when analysing multisite morphometric data.

In summary, we used a large collection of MRI data across a number of clinical disorders to demonstrate that participant motion may be a source of error in analyses of neuroanatomical differences.

5. Acknowledgements

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