# Association between In-scanner Head Motion with Cerebral White Matter Microstructure: A Multiband Diffusion-weighted MRI study

Diffusion-weighted MRI (DW-MRI) has emerged as a promising neuroimaging technique used to depict the biological microstructural properties of the human brain white matter. However, like any other MRI technique, DW-MRI remains subject to head motion during scanning. The association between motion and diffusion metrics is rarely understood. Previous studies have indicated that there are some regions showing significant relationship with diffusion metrics from traditional DW-MRI data with relative few gradient directions (e.g., 30 directions). As imaging techniques improves, additional gradient directions can be acquired in the same scan duration without a significant loss in spatial resolution. The current study examined the association between motion and diffusion metrics with the standard pipeline, tract-based spatial statistics (TBSS), with a multiband diffusion data (i.e., 137) directions). The diffusion metrics used in this study not only the included the commonly used metrics (i.e., FA and MD) in DW-MRI studies, but also a newly proposed inter-voxel metric, local diffusion homogeneity (LDH). The positive association was observed with MD, while the negative association with LDH. No significant association between motion and FA was observed. These results indicate that there is a similar link between motion and diffusion metrics in the multiband diffusion data. Finally, the motion-diffusion association is discussed.

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#### 11 Abstract

12 Diffusion-weighted MRI (DW-MRI) has emerged as a promising neuroimaging technique used to depict the 13 biological microstructural properties of the human brain white matter. However, like any other MRI technique, 14 DW-MRI remains subject to head motion during scanning. The association between motion and diffusion 15 metrics is rarely understood. Previous studies have indicated that there are some regions showing significant 16 relationship with diffusion metrics from traditional DW-MRI data with relative few gradient directions (e.g., 30 17 directions). As imaging techniques improves, additional gradient directions can be acquired in the same scan 18 duration without a significant loss in spatial resolution. The current study examined the association between 19 motion and diffusion metrics with the standard pipeline, tract-based spatial statistics (TBSS), with a multiband 20 diffusion data (i.e., 137 directions). The diffusion metrics used in this study not only the included the commonly used metrics (i.e., FA and MD) in DW-MRI studies, but also a newly proposed inter-voxel metric, 21 22 local diffusion homogeneity (LDH). The positive association was observed with MD, while the negative 23 association with LDH. No significant association between motion and FA was observed. These results indicate 24 that there is a similar link between motion and diffusion metrics in the multiband diffusion data. Finally, the 25 motion-diffusion association is discussed.

26 Keywords: Head Motion; White Matter; Microstructure

#### 27 Introduction

Diffusion-weighted MRI (DW-MRI) has become one of the most popular MRI techniques in brain research, as well as in clinical practice. One key application of DW-MRI is diffusion tractography which can be used for the visualization of white matter (WM) tracts (Golby et al. 2011) and construction of brain neuroanatomical connectome (Gong et al. 2009). Also, it has become a convenient tool for deriving regional measures of diffusivity and anisotropy. These metrics are believed to reflect biological microstructural properties of the white matter, and have been extensively applied as biological markers for studying WM under normal and clinical conditions (Johansen-Berg 2010; Le Bihan 2003; Le Bihan et al. 2001; Travers et al. 2012).

35 However, like any other MRI technique, DW-MRI remains subject to specific biological factors (e.g., 36 temperature), scanner noises (e.g., machine SNR, field shim) and, in particular, motion artifacts. Thus, 37 movement of the head during scanning is undesirable, which not only displaces the brain matter in space but also interferes with the readout of MR signals. Indeed, recent studies have discovered that head motion may 38 39 introduce unwanted biases. Ling and his colleagues have shown that head motion is associated with both 40 fractional anisotropy (FA) and mean diffusivity (MD), while the effect is greater for MD (Ling et al. 2012). A 41 recent study have also found group differences in head motion can induce group differences in white matter 42 tract-specific diffusion metrics, and such effects can be more prominent in some specific tracts than others 43 (Yendiki et al. 2013). However, these studies on head-motion artifacts have employed traditional DW-MRI data with relatively small number of gradient directions (e.g., n = 30 directions). In fact, previous works have 44 45 indicated the influence of the number of gradient directions on data acquisitions (Landman et al. 2007; Tijssen 46 et al. 2009). Recently, several promising imaging techniques have been proposed, including MR-47 encephalography (Zahneisen et al. 2011) and multiband echo planar imaging (Moeller et al. 2010). Using the multiband scanning protocol, additional gradient directions can be acquired in the same scan duration without a 48 49 significant loss in spatial resolution. It remains largely unknown whether the association would still exist in 50 DW-MRI data with large number of gradient directions.

Here, the primary aim was therefore to investigate the relationship between head motion and diffusion metrics estimated from multiband data with 137 directions. In this study, we examined two tensor-based metrics most typically reported (i.e., FA and MD). Given the fact that they only reflect diffusion properties solely within the voxel, we also examined a newly proposed model-free inter-voxel metric, referred to as local diffusion homogeneity (LDH) (Gong 2013). We hypothesized that movement would be more or less related to diffusion metrics, even in the multiband DW-MRI data used here. It has been suggested that head motion alters 57 the measure of diffusion metrics even after motion correction (Ling et al. 2012; Tijssen et al. 2009; Yendiki et al. 2013), and that it may also provide information regarding neuronal processing (Yan et al. 2013a; Yan et al. 58 59 2013b). Moreover, LDH is a recently proposed metrics and has not been fully validated yet (Gong 2013). In addition, unlike FA and MD, LDH directly depends on the raw diffusivity series without assuming a prior 60 61 diffusion model (Gong 2013). Therefore, we also hypothesized that the association between head motion and 62 LDH would be quite different to the tenser-based metrics, and may be more sensitive to motion artifacts. We 63 tested these hypotheses by (1) confirming the test-retest reliability of both diffusion metrics and head motion 64 across scan sessions, and (2) by examining the relationship between the averaged diffusion metrics and head 65 motion. We also examined the relationship in each scan session.

#### 66 Materials and Methods

#### 67 Dataset

The dataset used in this study was from the NKI-RS Multiband Imaging Test-Retest Pilot Dataset (Mennes et al. 2012). There were 20 participants ( $34.3 \pm 14.0$  years). And for each participant, the DW-MRI scans were performed twice (session 1 and session 2), around one week apart. Diffusion weighted images were collected a standard pulse sequence with 2-mm-thick axial slices and 137 directions: TE 85 ms; TR 2400 ms; b value, 1500 s/mm2; flip angle, 90°.

#### 73 Image Processing

DW-MRI images were processed with FMRIB's Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl). Nonbrain tissue was removed using the Brain Extraction Tool (BET) with a factional intensity threshold of 0.2, and then raw DW images were corrected for motion and eddy currents effects using affine registration to the non-DW image. Then, by fitting a tensor model at each voxel using DTIFit from the FSL (Smith et al. 2004), we obtained the fractional anisotropy (FA) and mean (MD) diffusivity, used in subsequent TBSS analysis (Smith et al. 2006; Smith et al. 2007).

To compare between subjects, TBSS framework was used. In detail, first, we non-linearly aligned individual FA map to FSL's standard 1 mm isotropic FA template (FMRIB58\_FA) and averaged them to generate a study specific mean FA map. Next, thinning was applied to the mean image and thresholded it at an FA value of 0.2 to create a white matter "skeleton". The resulting skeleton contained WM tracts common to all subjects. Individual FA maps were then projected onto the mean FA skeleton by filling the skeleton with FA values from the nearest tract center. The same non-linear transformations derived for the FA maps were applied to the MD maps.

In terms of the LDH metric, it is a novel model-free metric that defines the regional inter-voxel coherence of diffusion series (Gong 2013). Technologically, LDH is quantified within the neighbors (n = 27) via the Kendell's coefficient concordance (KCC), after the estimation of the diffusivity strengths along each gradient direction. To compare between subjects, the LDH maps were also projected onto the WM skeleton mask using the TBSS framework described above. In addition, we used another approach for quantifying the regional coherence with information theory (Kong et al., 2014), and the results were all similar to those of the original LDH (data not shown).

The DW-MRI data preprocessing and TBSS analysis pipelines were both implemented using Nipype (Gorgolewski et al. 2011), a flexible, lightweight and extensible neuroimaging data processing framework in python. The pipeline for calculating both original and improved LDH was implemented in python.

## 97 Assessment of in-scanner head motion

To retrospectively estimate head motion during scanning, DW images were realigned to the non-DW image with FMRIB's Linear Image Registration Tool (FLIRT), and at the same time, a rigid transformation matrix was obtained for each image. Then for each image, the root-mean-square (RMS) deviation, which summarizes 6 translations and rotations across 3 axes, was calculated from 2 transformations of consecutive images (Jenkinson et al. 2002). That is, in-scanner head motion was measured as the displacement of each brain volume relative to the preceding one (Satterthwaite et al. 2012; Van Dijk et al. 2012). Finally, head motion was calculated by averaging the RMS deviations for all volumes.

### 105 Test-retest reliability of diffusion metrics and head motion estimate

106 The voxel-wise test-retest reliability for each diffusion metrics was calculated with the intra-class correlation

107 coefficient (ICC) (Shrout & Fleiss 1979).

$$ICC = \frac{BMS - EMS}{BMS + (k-1)EMS}$$

The formula estimates the correlation of the subject signal intensities between sessions, modeled by a twoway ANOVA, with random subject effects and fixed session effects. In this model, the total sum of squares is split into subject (BMS), session (JMS) and error (EMS) sums of squares; the k is the number of repeated sessions. The reliability measure for whole-brain analysis was implemented in python and can be accessed from Nipype (Gorgolewski et al. 2011). The test-retest reliability for head motion estimate was also calculated with ICC.

#### 114 Relationship between In-Scanner Head Motion and Diffusion Metrics

To maximize signal to noise ratio of head motion estimates, first we calculated the average head motion for 115 116 each participant across two sessions. Analogously, for accurate measures of microstructure estimates, the MD, FA and LDH metrics finally used were also taken from the average of the TBSS results across the two sessions. 117 118 To examine the possible relationship between head motion and diffusion regional metrics, we conducted a 119 statistical analysis using general linear model (GLM), for the three metrics respectively, with head motion as 120 the variable of interest. In these models, gender, age and handiness that were available in the dataset were 121 controlled as confounding covariates. Voxel-wise statistical analysis was performed with Threshold-Free 122 Cluster Enhancement (TFCE) correction (Smith & Nichols 2009) for multiple comparisons, considering fully 123 corrected p-value < 0.05 as significant. In addition, the same statistical procedure was conducted for both 124 session 1 and session 2 respectively.

#### 125 Results

### 126 Test-retest reliability of diffusion metrics and head motion estimate

127 All of the diffusion metrics in this study showed relative high test-retest reliability: FA: Mean = 0.71; MD:

128 Mean = 0.71; LDH: Mean = 0.75. In addition, the magnitude of head motion seemed acceptable (Table 1) and

129 showed medium reliability (ICC = 0.54), which is consistent with previous studies (Van Dijk et al. 2012).

130 Although all of the diffusion metrics, as well as head motion estimate is relative reliable across the two scans,

131 they were not exact the same due to some random artifacts, including motion artifacts and machine noises.

- 132 Thus, for accurate measures of this microstructure and head motion estimate, we first averaged the head motion
- 133 and diffusion metrics across the two sessions and mainly examined the results with the averaged data.
- ---insert Table 1. ---

#### 135 Relationship between head motion estimate and diffusion metrics

In Table 1, we also show a basic summary of the main head motion results of diffusion metrics across all threeanalyses.

Among the two mostly commonly used regional diffusion metrics (i.e., FA and MD), these results indicated that head motion was mainly associated with the MD values. The degree of head motion was positively associated with increased MD mainly within white matter tracts in left hemisphere, including anterior limb of internal capsule, posterior limb of internal capsule, genu of corpus callosum and body of corpus callosum (Fig. 1). In the current report, we focus on voxels survived the TFCE correction (p < 0.05) (Smith & Nichols 2009) across the whole white matter skeleton. For the analyses examining FA, no voxel survived correction for multiple comparisons.

For the analyses examining the inter-voxel diffusion metric (i.e., LDH), we found wide-spread white matter showed significant negative association with head motion (p < 0.05, TFCE corrected; Fig. 1). This association mainly involved bilateral superior longitudinal fasciculus, body and genu of corpus callosum, cingulum, superior, anterior and posterior corona radiate, retrolenticular part of internal capsule, fornix, cerebral peduncle, middle cerebellar peduncle, right anterior and posterior limb of internal capsule, right external capsule and sagittal stratum.

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#### ---insert Fig. 1. ---

Overall, with the same criterion of significance (p < 0.05, TFCE corrected), we found the most number of motion-related voxels with MD (2686 voxels, 2.51%) and then LDH (34551 voxels, 32.25%). No voxel survived with FA.

In addition, we also examined the association between head motion and diffusion metrics with data from the two sessions respectively. Although no voxel survived statistical correction for multiple comparisons (p < 0.05) in most of the analyses (except LDH in Session 2), there were some voxels showed a significant trend (p < 0.10, TFCE corrected; Fig. 2).

## 160 **Discussion**

161 Like any other MRI technique, DW-MRI signal is subject to motion artifacts, however, the relationship 162 between diffusion metrics and head motion remains incompletely understood. Previous studies have shown 163 significant relationship between diffusion metrics and head motion along different axes (Ling et al. 2012). The 164 current study expands on previous work (Ling et al. 2012) by exploring the relationship between motion and 165 diffusion metrics (including the newly proposed inter-voxel metric, LDH) with a multiband dataset with 137 166 directions. Our primary conclusions suggest that there are significant association between head motion and 167 diffusion metrics (except FA), but that the effect is much more pronounced in LDH. Importantly, these results 168 are present following standard methods for diffusion data correction.

169 Previous studies suggested a positive association between motion and MD, with increased magnitude of 170 MD as a result of increased motion along one axes (i.e., right-left, anterior-posterior and inferior-superior) 171 (Ling et al. 2012). Current results replicate this finding, as a positive relationship between head motion and 172 magnitude of MD was present in the left hemisphere tracts. The significant association mainly located in the 173 deeper white matter (e.g., corpus callosum and the internal capsule). Interestingly, these tracts have often been 174 reported in the literature to differ between a variety of clinical populations and healthy subjects (Carrasco et al. 175 2012; Travers et al. 2012). For examining FA, we found no significant relationship between head motion and 176 FA after multiple comparison correction. This may be due to the relative high SNR since the diffusion data used 177 in this study was acquired with much more gradient directions than the previous study (Ling et al. 2012). But 178 this appears consistent with the previous finding that the head motion's bias is more pronounced in MD.

179 More importantly, we also explored the relationship between head motion and LDH values and found that 180 there were widespread voxels significantly associated to head motion. This appears to be quite likely caused by 181 motion artifacts. Indeed, the significant voxels rarely located in the occipital white matter tracts, where motion 182 artifacts may be much weaker than that in prefrontal lobe when subjects laying supine. These results suggest 183 that LDH values might be more subject to head motion artifacts. And the increased susceptibility may be due to 184 the fact that it is directly calculated with raw diffusivity series. Though previous studies have shown LDH 185 values change during aging, the newly proposed metric has not yet well validated (Gong 2013) and simulation 186 and experimental work is required to confirm the motion-LDH association.

187 So, why does the association between motion and diffusion metrics exist? The dominant view at present is 188 that head motion introduces artifacts into diffusion signals, similar to be noted in the fMRI literature (Bullmore 189 et al. 1999; Friston et al. 1996; Hajnal et al. 1994), which influence the calculation of diffusion metrics and 190 further results of cross-subject analysis. A common strategy for controlling motion effects in neuroimaging 191 cross-subject analysis is to regress or match motion estimates (Zuo et al. 2010a; Zuo et al. 2012; Zuo et al. 192 2010b). Another strategy for mitigating head-motion artifacts is to remove time series of high motion, which is 193 called 'scrubbing' (Power et al. 2012). However, these strategies have their limitations. On the one hand, 194 scrubbing volumes with high motion could not fundamentally change the relationship between motion and 195 values of diffusion metrics (Ling et al. 2012). On the other hand, they may also reduce the ability to detect a 196 significant effect of interest, and/or introduce sampling bias (Satterthwaite et al. 2012; Wylie et al. 2014).

While researchers attempt to propose more sophisticated algorithms, there is growing perception in the field that head motion reflects individual differences in psychological traits and clinical conditions. For instance, previous studies showed that head motion was correlated with impulsivity (Kong et al., under review) and autism symptom severity scores (Yendiki et al. 2013). In addition, previous studies suggest that the association may reflect the neural processing related to head motion (Yan et al. 2013a; Yan et al. 2013b). Thus, they suggest that head motion not be considered as a random variable (Yan et al. 2013a; Yan et al. 2013b; Kong et al., under review).

204 Taken together, as articulated previously (Van Dijk et al. 2012; Wylie et al. 2014; Yendiki et al. 2013), 205 these findings demonstrate the significance of developing motion-compensated acquisition methods for DW-206 MRI and incorporating them into neuroimaging studies in the future. Nevertheless, with current technologies, it 207 appears impossible to not perfectly eliminate the motion effects. As a temporary solution, examining both 208 models with and without motion being regressed out will be expected. But researcher shall keep in mind that 209 motion does not only influence MRI signals, but also correlated with some meaningful individual differences. 210 Alternatively, replication in an independent sample would be helpful, since the effects of head motion on 211 diffusion metrics are usually random and not specific to some brain regions. Nevertheless, for now, researchers 212 shall be cautious when doing MRI data analysis and interpretation.

In sum, current results indicate that, in the multiband diffusion data, there are also significant associations between head motion and diffusion metrics. Head motion was associated with both MD and LDH, while the effect was greater for LDH. However, no significant effect was found for FA. Future studies should be to investigate the association between head motion and diffusion metrics with larger multiband datasets.

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# Table 1(on next page)

A basic summary of head motion and the results about relationship between head motion and DTI metrics.

Samp le	Mean MRD	Motion	Motion-Brain Association	
		FA	MD	
		FA	MD	LDH
Averaged	1.18(0.29)	n.r.	+**	_**
Session 1	1.1(0.32)	n.r.	+*	_*
Session 2	1.26(0.38)	n.r.	+*	_**

n.r.: null results, +: positive relationship, -: negative relationship; \*: p < 0.10 TFCE corrected, \*\*: p < 0.05 TFCE corrected; MRD = mean relative displacement.

# Figure 1

The association between head motion and diffusion metrics with data from the two sessions respectively.

Since no voxel survived statistical correction for multiple comparisons (p < 0.05) in most of the analyses (except LDH in Session 2), they are displayed at a more tolerant threshold (p < 0.10, TFCE corrected).



# Figure 2

Results from the tract-based spatial statistics (TBSS) analyses depicting the voxels that showed a significant association between head motion diffusion metrics.

Data are presented for the analyses involving both Mean Diffusivity (MD; A) and local diffusion Local Diffusion Homogeneity (LDH; **B**) as the dependent measure. Participants with higher motion exhibited higher values of MD, but lower values of LDH. Voxels survived the TFCE correction (p < 0.05) across the whole white matter skeleton are displayed.

