
1 **Head motion in children with ADHD during resting-state brain imaging**

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7
8 **Abstract**

9 Resting-state functional MRI (rs-fMRI) has become an important method for analyzing the neural
10 mechanisms underlying mental disorders. But studies targeting head motion during an rs-fMRI
11 examination are rare. Since head motion may pollute the data in the neural imaging studies and
12 further mislead the understanding of the causes of some disorders, systematic investigations on
13 this topic were badly needed. To this end, in this study, children with
14 attention-deficit/hyperactivity disorder (ADHD) and demographically-matched typically
15 developing control (TDC) participants underwent an rs-fMRI examination. We obtained a
16 summary motion index and six mean single head motion parameters (three translational and three
17 rotational) for each participant. With the summary index, we found that motion was significantly
18 increased in the ADHD group and the results showed that the increase was mainly contributed by
19 the motion around and along the superior-to-inferior direction. Moreover, the classification
20 analysis showed that these head motion parameters during scanning could accurately distinguish
21 children with ADHD from the healthy control group. These results suggest that accounting for
22 head motion during scanning may be helpful for ADHD diagnosis and treatment with
23 neuroimaging.

24
25 Keywords: Head Motion, ADHD, rest-state fMRI

1 1. Introduction

2 For many years, in-scanner head motion has been widely considered as an artifact in task
3 functional MRI (fMRI) (Friston et al., 1996; Jenkinson et al., 2002; Yoo et al., 2005; Epstein et al.,
4 2007; Mayer et al., 2007) and diffusion tensor imaging (DTI) (Jezzard et al., 1998; Reese et al.,
5 2003; Rohde et al., 2004; Chen et al., 2006; Aksoy et al., 2008; Tijssen et al., 2009). Recently,
6 several studies have come to the conclusion that in-scanner head motion leads to systematic biases
7 in the analyses of functional connectivity based on resting-state fMRI (rs-fMRI) data (Power et al.,
8 2012; Van Dijk et al., 2012; Satterthwaite et al., 2012). Moreover, these biases in rs-fMRI may
9 overthrow some leading theories on certain disorders (e.g., autism spectrum disorders) (Deen and
10 Pelphrey 2012). These all suggest that we should do more careful research about the head motion
11 during rs-fMRI scanning.

12 In fact, many patients, particularly those with motor control difficulties, will move much
13 more than the healthy controls during scanning, even without any task. Although this seems an
14 obvious problem, it has been rarely investigated. In addition, only a handful of research focuses on
15 task-related head motion on schizophrenics (Bullmore et al., 1999; Yoo et al., 2005; Mayer et al.,
16 2007) and stroke patients (Seto et al., 2001). It still requires additional investigations about head
17 motion during rs-fMRI scanning. Additionally, studies in other patient population are also needed.

18 Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric
19 disorders among childhood. It is conservatively estimated that 3% to 9% of school-aged children
20 are suffering from this disease (Anderson et al., 1987; Bird et al., 1988; Szatmari et al.,
21 1989). Brain imaging studies on ADHD typically compare a group of ADHD children with the
22 disorder to a group of typically developing control (TDC) (for a recent review, see Liston et al.,
23 2011). In addition, it is commonly known that children with ADHD typically move more than
24 TDC children do. However, there is still no systematic research about in-scanner head motion
25 comparisons between ADHD and TDC groups. In fact, the head motion characteristics of ADHD
26 patients warrant detailed investigation.

27 This report is aimed to show detailed comparisons of head motion parameters between
28 children with and without ADHD under rs-fMRI examinations. So we first evaluated the head
29 motion parameters of all children with rs-fMRI data and then quantitatively compared the results
30 between the two groups. Also, we examined the predictability of ADHD on the basis of head
31 motion during scanning. These results may help researchers to deal with head motion bias in their
32 specific brain imaging studies. Furthermore, taking in-scanner head motion into account is

expected to improve clinical diagnosis and evaluation of treatment for patient with ADHD and even other disorders.

2. Methods

2.1 Participants and data acquisition

The dataset used in this study was from the ADHD-200 Consortium (see ADHD-Consortium, 2012 and Brown et al., 2012). We used the data collected from Beijing to minimize the variability across institutions. There were 245 children, 143 of whom were TDC (59 females; mean age = 11.43 ± 1.86 years), and the rest 102 were patients with ADHD (12 females; mean age = 12.08 ± 2.04 years). All participants (ADHD and TDC) were evaluated by the Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version (KSADS-PL) with one parent for the establishment of the diagnosis.

The resting-state fMRI images were collected using a T2*-weighted gradient-echo EPI (GRE-EPI) sequence: TR = 2 s, TE = 30 ms, flip angle = 90°, FOV = 220 mm, matrix size = 64 × 64, 30 axial slices, slice thickness = 4.5 mm. Participants were instructed to keep their eyes closed and to relax during scanning. The total scan time lasted 8 min. Foam padding was used to restrict head motion within the scanner. In-scanner head motion was calculated from the resting-state fMRI images using the procedures described below.

Other details about measurements and inclusion criteria are available on the website ADHD-200.

2.2 In-scanner head motion calculation.

In neuroimaging studies, it is a standard practice to estimate the position of the head at each volume and to realign all volumes using affine transformations. Head motion estimation involved these series of affine transformations, T_i , where i indexes volume and T_i spatially registers volume i to a select reference volume (e.g., the first volume). Each transformation can be expressed as a combination of rotation and displacement components. Thus,

$$T_i = \begin{bmatrix} A_i & t_i \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

where A_i is a 3x3 rotation matrix and it is a 3x1 column vector of translations. A_i can be factored into three elementary rotations (pitch, yaw, and roll) about each of the three axes.

Differentiating the transformations across contiguous volumes, yields A , a 3x3 rotation matrix, and t , a 3x1 column vector of displacements.

$$T_i - T_{i-1} = T_i T_{i-1}^{-1} = \begin{bmatrix} A & t \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Three rotation parameters and three displacement parameters can be evaluated with the method above. In practice, root mean squared (RMS) deviation, a summary statistic of in-scanner head motion, is widely used, since it summarizes six translations and rotations across all three axes (Jenkinson, 2002). The summary head motion RMS has been widely used in fMRI and DTI images processing to check the extent of head motion and make decisions about cohort formation or matching. It can be calculated directly from the affine matrices (Jenkinson, 1999). That is,

$$\text{RMS} = \sqrt{\frac{1}{5}R^2\text{Trace}(A^T A) + t^T t}$$

where RMS is the RMS deviation in mm, R is a radius specifying the volume of interest (R = 80 mm, approximately the mean distance from the cerebral cortex to the center of the head).

In this study, we obtained one affine transformation for each brain volume registering to the first volume using FLIRT from FSL (<http://www.fmrib.ox.ac.uk/fsl/>). First, we got the six translational and rotational parameters for each volume from each transformation using *avscale* from FSL. In addition, the summary head motion RMS was calculated from two transformations for two continuous volumes using *rmsdiff* from FSL. That is, the in-scanner head motion was measured as the displacement of each brain volume as compared to the previous volume, which is often used to test the head motion effects (e.g., Van Dijk et al., 2012; Satterthwaite et al., 2012). All the seven head motion parameters were averaged across all volumes for each participant.

Ten participants (6 ADHD and 4 TDC) showed large head movements (with the 1.5*IQR rule of the summary head motion RMS, 0.2 mm) and thus were excluded from our analyses. In addition, 28 patients who had taken psycho-stimulant medications within 48 hours prior to scanning were also excluded to avoid the medicine effects. Our analyses were based on the data of the remaining 207 participants: 67 ADHD (9 female; mean age = 12.26 ± 2.04 years) and 140 TDC (59 female; mean age = 11.43 ± 1.85 years).

2.3 Prediction of ADHD with in-scanner head motion

The predictability of ADHD on the basis of in-scanner head motion was examined. The summary head motion index and six single head motion parameters, along with gender and age, were used as the classification features, whereas children's statuses (i.e., ADHD or TDC) were used as the classification labels. Support Vector Machine (SVM) algorithm (insert reference) was used and validated with the leave-one-out cross-validation method. The statistical significance was computed by a permutation test: the probability distribution of correct classification was estimated by running the same SVM analysis on 1000 surrogate samples created by randomizing their labels.

1 The significance of the prediction accuracy with the original data was then estimated as the
2 probability that the original accuracy was exceeded by chance.

3

4 **3. Results**

5 ***3.1 Overview of motion parameters within each group***

6 First, we examined the six head motion parameters within each group. The mean single head
7 motion parameters were plotted in Fig. 1A, 1B. In terms of these parameters, the mean head
8 motion parameters were much less than 1 mm for translations or 1° for rotations during rs-fMRI
9 data acquisition for both control and patient groups. This indicates that most of the participants
10 were able to undergo the rest-state fMRI scanning without significant head motion.

11 We performed paired t-tests to compare the pairs of head motion parameters within each
12 group. For translation parameters, motion along the x-axis (left-to-right) was significantly less
13 than motion along the y- and z-axis for both groups (ADHD: $t(66) > 8.40$, $p < 0.001$, corrected
14 with Bonferroni correction; TDC: $t(139) > 10.00$, $p < 0.001$, corrected). In terms of rotational
15 parameters, the pitch rotation (around the x-axis) was significantly greater than rotations about the
16 two other axes for both groups (ADHD: $t(66) > 3.50$, $p < 0.001$, corrected; TDC: $t(139) > 5.10$, $p <$
17 0.001 , corrected). There was no significant difference in other pairs of head motion parameters
18 ($p_s > 0.15$), except that for patients group, motion along z-axis (superior-to-inferior) was
19 significantly greater than motion along the y-axis ($t(66) = 3.32$, $p = 0.001$, corrected). In addition,
20 the translations along the z-axis (superior-to-inferior) and pitch rotation were the most significant
21 motion patterns for both control and patients groups.

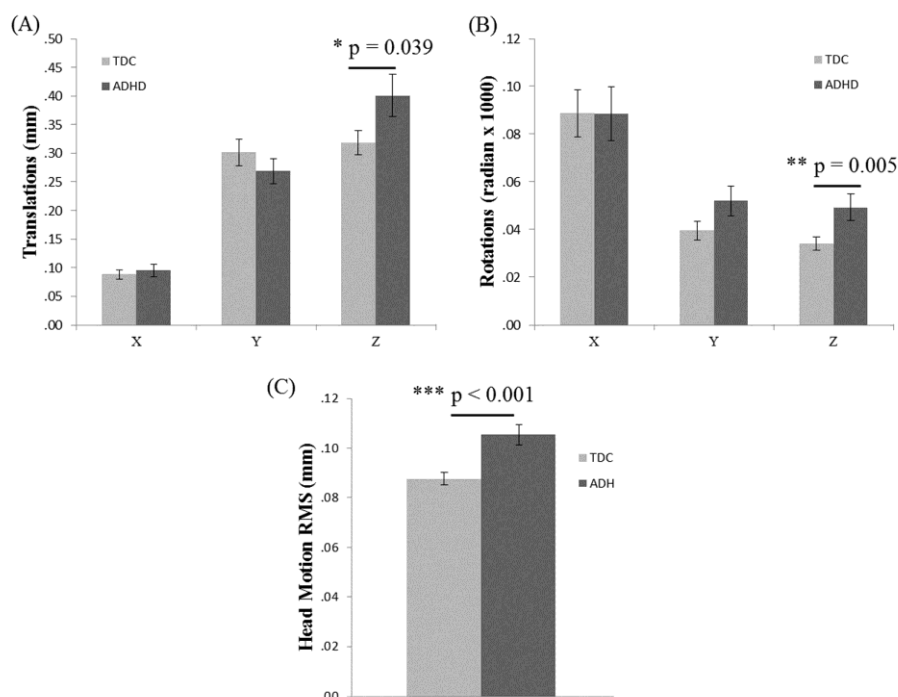


Fig. 1. Group difference in magnitude of head motion parameters. In (A), three translation parameters for each group were shown. In (B), three rotation parameters for each group were shown. In (C), the summary index of head motion was increased in the ADHD group compared to the TDC group. Error bars indicate ± 1 SE. Asterisks indicate a significant difference between groups (* $p < .05$, ** $p < .01$, *** $p < .001$).

3.2 Group comparison of motion parameters

Independent-samples t-tests were applied to the six head motion parameters and the summary head motion RMS, comparing children with and without ADHD. In terms of the six parameters, we found that the yaw rotation (around the z-axis) was increased in ADHD group compared to that in the TDC group ($t(205) = 2.82$, $p = 0.005$, corrected; Fig. 1B). Similarly, we found that the motion along the z-axis also tended to increase in ADHD group compared to the TDC group ($t(205) = 2.07$, $p = 0.039$, uncorrected; Fig. 1A). We did not find any group difference in the remaining four motion parameters (all $p > 0.15$), only a marginal significant group difference in the roll rotation (around the y-axis; $p = 0.069$, uncorrected). In terms of the summary RMS, we found that the motion was increased in ADHD group compared to the TDC group ($t(205) = 4.00$, $p < 0.001$, corrected; Fig. 1C). This suggests that, though there was no ‘sudden’ bad head motion for both groups, children with ADHD actually showed greater head motion than the control group, particularly in terms of the rotation around z-axis and motion along z-axis.

3.3 Prediction of ADHD with in-scanner head motion

The leave-one-out across-validation showed that the average accuracy of the prediction of children's status was 71.5% ($p < 0.001$, permutation test). These results suggest that the head motion parameters during scanning could accurately distinguish children with ADHD from the healthy control.

4. Discussion

Although there have been numerous rs-fMRI studies conducted on patients with mental disorders, studies targeting head motion during an rs-fMRI exam have been rare. Since head motion biases may undermine a leading theory on the cause of some disorders in brain imaging studies (Deen and Pelphrey 2012), systematic research about it are sorely needed. In addition, not only may detailed studies about head motion help to deal with the head motion biases, but they also help researchers in understanding the mental disorders.

In this study, we first investigated the head motion characteristics within ADHD and TDC groups. From the analysis of single motion parameters, we found that in both groups, motion along the x-axis (left-to-right) was the smallest in those along the three axes and the pitch rotation (around the x-axis) was the greatest in those three rotations. Specially, for ADHD group, motion along z-axis (superior-to-inferior) was significantly greater than those along other two axes. Furthermore, to test the hypothesis that children with ADHD move more than TDC population, we conducted independent-samples t-tests on single motion parameters. As expected, we found a significant increase on the motion in patient group compared to the control group. And the increase was mainly due to the yaw rotation (around the z-axis) and motion along z-axis (superior-to-inferior). In addition, the final classification analysis showed that the head motion parameters during scanning could accurately distinguish children with ADHD from the healthy control group.

To date, few studies have quantitatively examined the amount of the head motion that occurs during rs-fMRI examinations between ADHD and TDC. One early study with task fMRI reported increased head motion in ADHD compared with TDC (Epstein et al., 2007). However, they did not find any significant difference, which might be due to the small sample size ($n = 12$). Moreover, they did not examine the group difference in head motion along/around single directions, which may be more important for prevention of head motion during imaging children with ADHD. An interesting aspect from the data is that the increase of head motion in the ADHD group was mainly contributed by the motion along and around z-axis, rather than other four motion parameters. In the view of reducing head motion biases, a mock scanner compliance training protocol (e.g., Seto

et al., 2001; Epstein et al., 2007) or passive head restraints (e.g., Green et al., 1994; Menon et al., 1997) specific to these two kinds of motion may largely reduce the group difference. Additionally, move much more around/along z-axis may be a behavioral marker for ADHD diagnosing and treatment. Further studies are needed to examine the different head motion patterns for each subtype of ADHD, such as ADHD-Combined, ADHD-Hyperactive/Impulsive, and ADHD-Inattentive (Barkley, 1997).

There are some limitations in our study. First, the head motion was measured indirectly using registration of volumes. In the future studies, using actometers or infrared CCD-based methods may give more direct measurement. Second, in consideration of the coupling effect of head motion in the fMRI signals, we didn't include fMRI metrics in this study. Using independent scanning runs to get the fMRI metrics and head motion may be a possible approach to explore the neural basis of head motion. Nevertheless, our study, for the first time, quantitatively showed the in-scanner head motion characteristics and the group differences between children with and without ADHD using rs-fMRI. We demonstrated that children with ADHD had different head motion patterns compared with TDC children. In this way, when using local and global brain neuroimaging parameters, taking head motion into account is expected to improve clinical diagnosis and evaluation of treatment for children with ADHD, and to have wider applications in diagnosis of other mental disorders. In addition, head motion behaves like a psychological trait and this possibility may be carefully considered in genetic and heritability analyses.

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