Magn Reson Med Sci 2021; 20; 338–346
doi:10.2463/mrms.mp.2020-0081

Published Online: October 27, 2020

MAJOR PAPER

Effects of Head Motion on the Evaluation of Age-related Brain Network Changes Using Resting State Functional MRI

Sanae Kato[1], Epifanio Bagarinao[2,3*], Haruo Isoda[1,2,3], Shuji Koyama[1,2,3], Hirohisa Watanabe[2,4,5], Satoshi Maesawa[2,6], Daisuke Mori[2,7], Kazuhiro Hara[5], Masahisa Katsuno[2,5], Minoru Hoshiyama[2,3], Shinji Naganawa[2,8], Norio Ozaki[2,7], and Gen Sobue[2]

Purpose: The estimation of functional connectivity (FC) measures using resting state functional MRI (fMRI) is often affected by head motion during functional imaging scans. Head motion is more common in the elderly than in young participants and could therefore affect the evaluation of age-related changes in brain networks. Thus, this study aimed to investigate the influence of head motion in FC estimation when evaluating age-related changes in brain networks.

Methods: This study involved 132 healthy volunteers divided into 3 groups: elderly participants with high motion (OldHM, mean age (±SD) = 69.6 (±5.31), N = 44), elderly participants with low motion (OldLM, mean age (±SD) = 68.7 (±4.59), N = 43), and young adult participants with low motion (YugLM, mean age (±SD) = 27.6 (±5.26), N = 45). Head motion was quantified using the mean of the framewise displacement of resting state fMRI data. After preprocessing all resting state fMRI datasets, several resting state networks (RSNs) were extracted using independent component analysis (ICA). In addition, several network metrics were also calculated using network analysis. These FC measures were then compared among the 3 groups.

Results: In ICA, the number of voxels with significant differences in RSNs was higher in YugLM vs. OldLM comparison than in YugLM vs. OldHM. In network analysis, all network metrics showed significant (P < 0.05) differences in comparisons involving low vs. high motion groups (OldHM vs. OldLM and OldHM vs. YugLM). However, there was no significant (P > 0.05) difference in the comparison involving the low motion groups (OldLM vs. YugLM).

Conclusion: Our findings showed that head motion during functional imaging could significantly affect the evaluation of age-related brain network changes using resting state fMRI data.

Keywords: *head motion, resting state networks, functional connectivity, network analysis, graph theory*

Introduction

Recent applications of MRI are not only limited to the acquisition of morphological images, but are also being used to indirectly image the function of the brain. Resting state functional MRI (fMRI) is a method that can be used to evaluate the functional connectivity (FC) of the brain at rest by observing synchronous fluctuations in the blood-oxygen-level-dependent (BOLD) signal between 2 brain regions over time. Metrics that characterize FC obtained from the analysis of resting state fMRI have been proposed as new biological indicators.[1,2]

An important application of network analysis using resting state fMRI is in the study of normal aging. Age-related changes in brain function, such as cognitive decline, could reflect various changes in large-scale brain networks.[3–6] To better understand the aging process, it is therefore critical to characterize alterations in brain networks with age.

[1]Department of Radiological and Medical Laboratory Sciences, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[2]Brain & Mind Research Center, Nagoya University, Nagoya, Aichi, Japan
[3]Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[4]Department of Neurology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan
[5]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[6]Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[7]Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[8]Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
*Corresponding author: Brain & Mind Research Center, Nagoya University, 1-1-20, Daiko Minami, Higashi-ku, Nagoya, Aichi 461-8673, Japan. Phone: +81-52-719-1864, Fax: +81-52-719-1864, E-mail: ebagarinao@met.nagoya-u.ac.jp

Received: May 25, 2020 | Accepted: August 25, 2020

However, the estimation of FC measures is often influenced by head movement during the examination, which could manifest as spurious increases in connectivity.[7–9] The purpose of this study was to examine the effects of head motion during imaging of healthy volunteers on the estimation of FCs in order to accurately evaluate age-related changes in FC during normal aging using resting state fMRI.

Materials and Methods

Study subjects

This study involved 132 healthy volunteers carefully selected from those enrolled in our ongoing Brain & Mind Research Center Aging Cohort Study.[10] The volunteers were divided into 3 groups: the elderly group with high head motion (OldHM, N = 44), the elderly group with low head motion (OldLM, N = 43), and the young group with low head motion (YugLM, N = 45). The elderly participants were over 60 years old (average age in years: 69.1 ± 1.23) and the young participants were under 40 years old (average age in years: 27.6 ± 5.26). There was no significant difference (2 sample t-test, P = 0.41) in age between OldHM and OldLM. All participants provided written informed consent before joining the study, which was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

MRI

We used a 3T MR scanner (MAGNETOM Verio 3T; Siemens, Erlangen, Germany) with a 32-channel head matrix coil. A T_1-weighted (T_1W) MR image was acquired using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE[11]) with the following parameters: TR/MPRAGE TR = 7.4/2500 ms, TE = 2.48 ms, TI = 900 ms, FA = 8°, 192 sagittal slices with a distance factor of 50% and 1-mm thickness, FOV = 256 mm, acquisition matrix dimension = 256 × 256, and in-plane voxel resolution of 1.0 × 1.0 mm^2, with a total scan time of 5 min 49 s. Resting state fMRI scans were also acquired using a GE echo planar imaging sequence with the following parameters: TR = 2.5 s, TE = 30 ms, 39 transverse slices with a 0.5-mm inter-slice interval and 3-mm thickness, FOV = 192 mm, 64 × 64 matrix dimension, FA = 80°, 3 × 3 × 3 mm^3 voxel resolution and a total of 198 volumes. Participants were instructed to close their eyes during the scan but not to fall asleep.

Preprocessing for resting state fMRI data

All images were preprocessed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) running on Matlab R2018a (MathWorks, Natick, MA, USA). The T_1W images were segmented using SPM12's segmentation approach[12] into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and other non-brain tissue components. Bias-corrected T_1W image and the transformation information from subject space to the Montreal Neurological Institute (MNI) space were also obtained. For resting state fMRI data, the first 5 volumes of the BOLD image were excluded to account for the initial scanner inhomogeneity. The remaining volumes were realigned to the mean functional image to correct for the effect of head movement during the scan using a two-pass approach as implemented in SPM12 after initially correcting for the difference in imaging timing of each slice within 1 volume (slice timing correction). The realigned images were then normalized to the MNI space using the transformation information obtained in the segmentation step. After normalization, the images were resampled into a 2 × 2 × 2 mm^3 isotropic voxel resolution, and finally smoothed with an 8-mm full-width-at-half-maximum 3D Gaussian filter. In addition, we also regressed out 24 motion-related regressors[13] to correct for head motion as well as signals from WM and CSF, the global signal (GS), and the signals' corresponding derivatives to correct for other physiological noise. Finally, the data were bandpass filtered within 0.01–0.1 Hz.

Evaluation of head motion

We used the mean of the framewise displacement (FD)[8] of the resting state fMRI data as an evaluation index of head movement. Using the estimated realignment parameters for each resting state fMRI data, the FD of the ith volume was computed using the following formula:[8] $FDi = |\Delta x_i| + |\Delta y_i| + |\Delta z_i| + |\Delta\alpha_i| + |\Delta\beta_i| + |\Delta\gamma_i|$, where $\Delta x_i = x_{(i-1)} - x_i$ represents the difference of the estimated realignment parameters along the x-axis for volumes $i - 1$ and i, and similarly for the other parameters (x, y, and z for translation and α, β, and γ for rotation). Rotational parameters were also converted from degrees to millimeters by computing the equivalent displacement on a surface of a sphere with radius equal to 50 mm.[8] The mean FD value for each FD series was then computed.

Subjects with mean FD values < 0.2 mm were considered to have low head motion while those with 0.2 mm or more were considered to have large head motion.[8] The average values of the mean FD across participants in each group are 0.114, 0.121, and 0.254 mm for YugLM, OldLM, and OldHM, respectively. There was significant difference in mean FDs between OldHM and OldLM (P < 0.000) as well as between OldHM and YugLM (P < 0.000), and no significant difference in mean FDs between OldLM and YugLM (P = 0.178). Raincloud plots showing the distribution, average values, and scatter plots of mean FDs for the 3 groups are shown in Fig. 1. FD plots of representative participants from the OldHM and OldLM groups are also shown in the inset.

Independent component analysis

In the first set of analysis, we extracted several large-scale resting state networks (RSNs) using independent component analysis (ICA). Specifically, we performed group ICA on the preprocessed data using multivariate exploratory linear optimized decomposition into independent components

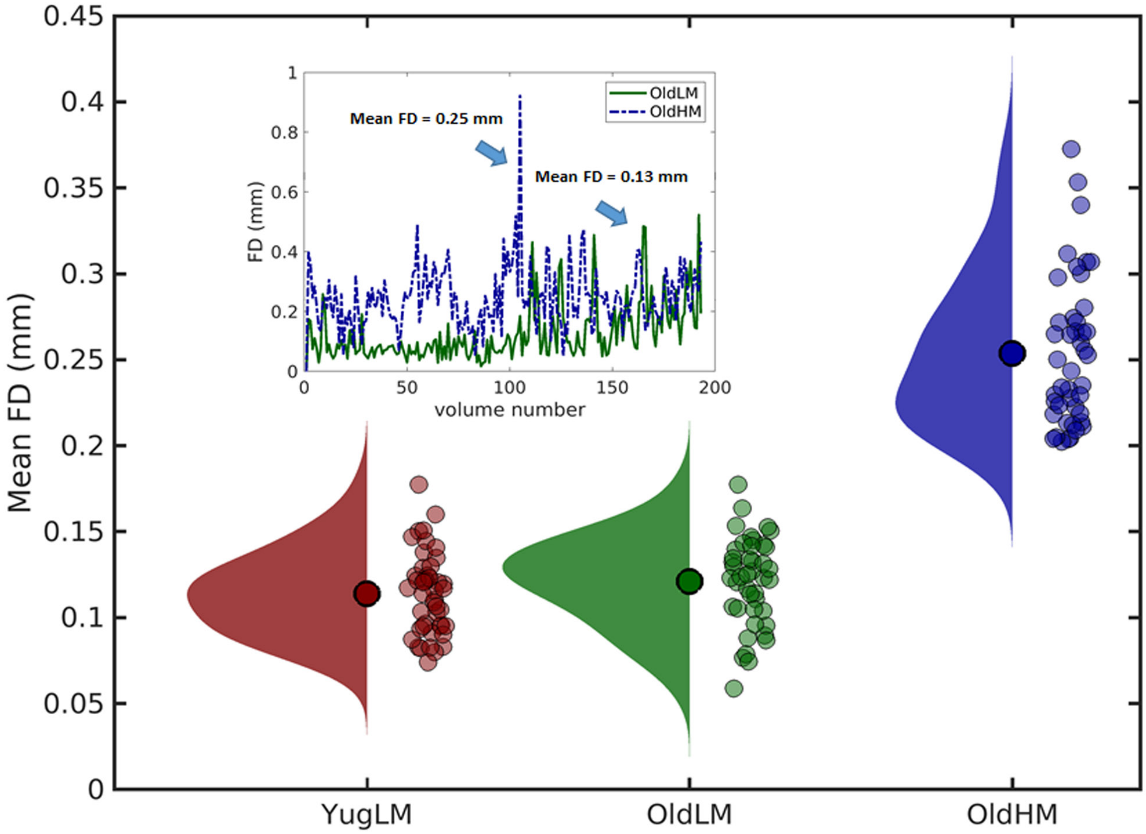

Fig. 1 Mean FD values. Distribution, average values, and scatter plots of the mean FD values of all participants in all groups are shown. FD plots of 2 representative participants, one from the OldLM group (solid line) and the other from the OldHM group (broken line) are also shown in the inset. FD, framewise displacement.

(MELODIC),[14] a component of the FMRIB Software Library (FSL) software package, to extract group-level RSNs. We used a temporal concatenation approach where all preprocessed resting state fMRI data from all participants were temporally concatenated. Following Shirer et al.,[15] 30 group-level independent components (ICs) were then extracted. The extracted components were compared to the reported functional atlas of large-scale networks (http://findlab.stanford.edu/functional_ROIs.html) to identify only the relevant RSNs, which were used in the succeeding dual regression analysis.[16]

In dual regression, the temporal variation of each subject's resting state fMRI data with respect to each group-level IC was obtained by performing a regression analysis with the 30 group-level ICs used as spatial regressors. Using the estimated time series associated to each ICs as temporal regressors, a second regression analysis was performed to extract participant-specific RSNs. These RSNs were then used in unpaired sample *t*-tests using a nonparametric permutation approach with 5000 permutations[17] to identify regions that showed significant differences in FC. For all comparisons, a threshold-free cluster enhancement technique[18] was used and the resulting statistical maps were corrected for multiple comparisons by controlling family-wise error (FWE) rate with $P < 0.05$.

Using the computed participant-specific RSNs, we also performed regression analysis for each group, with the mean FD as regressor, to further examine the effect of head motion in the FC of the different RSNs. Regions with significant linear association with the mean FD were identified using a nonparametric permutation approach with 5000 permutations. Statistical maps were corrected for multiple comparisons using FWE-correction with $P < 0.05$.

Network analysis

In the second set of analysis, we performed whole-brain network analysis using graph theory. We used the Power template,[19] consisting of 264 functional regions, as network nodes. FC matrices were constructed from the preprocessed resting state fMRI data using Graph Theoretical Network Analysis Toolbox (GRETNA; Beijing Normal University, Beijing, China)[20] with the static correlation option. To construct the binary networks, the FC matrices were thresholded using values ranging from 0.1 to 0.4, with a 0.01 interval (31 values in total), and thresholding was applied on the value of the matrix element. The choice of the range of threshold values was motivated by our earlier study[21] where we found threshold-dependent association of network metrics with age using threshold values ranging from 0.2 to 0.4. We extended this range from 0.1 to 0.4 as head-motion-affected FC values could be in the lower range. We also used GRETNA to compute several global network metrics from the generated binary networks including clustering coefficient, characteristic path length, global efficiency and local efficiency. For all network metrics, we used the area under the curve (AUC) value as the summary index (for all threshold values) to characterize the whole-brain network. To compare the network metrics, we performed unpaired sample *t*-tests.

Results

Age-related changes in functional connectivity

We observed a large number of voxels showing significant differences in FC between young and elderly participants with low head motion (OldLM vs. YugLM) in multiple RSNs (Table 1). This is particularly the case in visual (primary, high, and medial), executive control (left and right), and auditory networks. In contrast, these numbers were significantly lower in the comparison between young and elderly participants with high head motion (OldHM vs. YugLM). Direct comparison between elderly participants with low and high head motion (OldHM vs. OldLM) also showed several voxels with significant differences in FC in several RSNs such as the cerebellum, medial sensorimotor and auditory networks. Contrast maps for representative networks showing regions where significant differences in FC were observed for the different group comparisons are shown in Fig. 2.

Association between FC and mean FD

Results of the regression analyses between FC and mean FD for the different RSNs are summarized in Table 2. In the YugLM group, only a small number of voxels have connectivity with the precuneus network that showed positive linear relationship with mean FD. In the OldLM group, some clusters have FC values with the precuneus network as well as with other networks that also showed either positive or negative association with mean FD. However, the extent of these clusters are very limited. In contrast, in the OldHM group, large clusters have FC values with the anterior salience, auditory, cerebellum, and right executive control networks that showed either positive or negative linear relationship with mean FD. Most of the positive relationship with mean FD where observed in regions within networks, while the negative relationship where observed in regions outside the network.

Age-related changes in network properties

Unpaired sample *t*-test results for each metric are shown in Table 3. There were significant differences ($P < 0.05$) in all network metrics between high head motion and low head motion groups (OldHM vs. OldLM, OldHM vs. YugLM). In contrast, there were no significant differences ($P > 0.05$) in

Table 1 Number of voxels exhibiting significant difference in FC for different RSNs

Resting state networks	OldHM vs. OldLM		OldHM vs. YugLM		OldLM vs. YugLM	
	OldHM > OldLM	OldHM < OldLM	OldHM > YugLM	OldHM < YugLM	OldLM > YugLM	OldLM < YugLM
Primary visual	135	145	1206	290	16126	8031
Dorsal default mode	0	1	106	231	597	198
Right executive control	0	0	887	366	4451	2009
Cerebellum	7173	86	802	806	260	3366
Anterior salience	164	370	512	149	979	1100
Higher visual	91	90	127	783	9110	13467
Left executive control	0	0	2594	981	7237	2632
Visuospatial	556	443	162	581	5408	6842
Language	0	0	138	563	1140	1808
Precuneus	290	66	855	1407	1529	3087
Ventral default mode	0	258	1684	332	462	2756
Medial visual	634	107	0	0	3471	7121
Posterior salience	0	0	447	1917	847	1507
Basal ganglia	0	0	1977	563	255	1285
Medial sensorimotor	2042	174	140	28	1828	3989
Auditory	1222	4874	5049	592	5560	7105
Sensorimotor	34	0	1887	4656	1692	6439

FC, functional connectivity; fMRI, functional magnetic resonance imaging; OldHM, old participants with high motion group; OldLM, old participants with low motion group; RSNs, resting state networks; YugLM, young participants with low motion group.

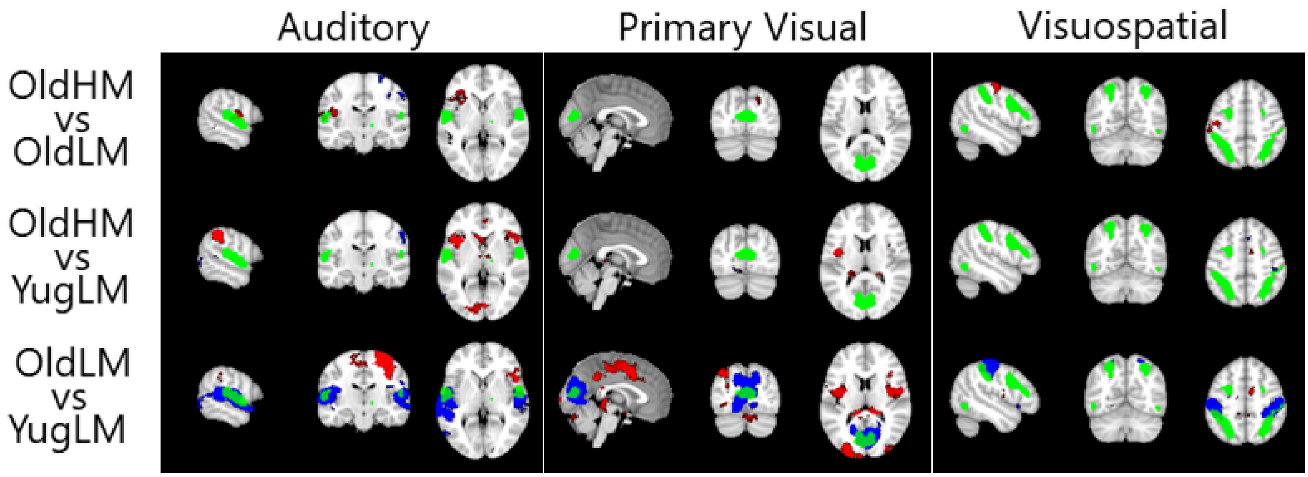

Fig. 2 Voxels showing significant connectivity changes for some representative large-scale resting state networks. Voxels in which significant differences in functional connectivity were observed for the different comparisons in the auditory, primary visual and visuospatial networks are shown. Green regions indicate resting state networks, red regions for left group > right group contrast, while blue regions for left group < right group contrast. OldHM, old participants with high motion group; OldLM, old participants with low motion group; YugLM, young participants with low motion group.

Table 2 Number of voxels with FC showing significant linear relationship with mean FD for different RSNs

Resting state networks	YugLM		OldLM		OldHM	
	Positive	Negative	Positive	Negative	Positive	Negative
Primary visual	0	0	0	0	0	16
Dorsal default mode	0	0	0	0	271	0
Right executive control	0	0	0	0	28	600
Cerebellum	0	0	42	0	787	202
Anterior salience	0	0	0	0	3657	582
High visual	0	0	51	4	0	0
Left executive control	0	0	1	0	17	86
Language	0	0	0	0	0	26
Precuneus	109	0	175	196	0	0
Visuospatial	0	0	0	0	29	74
Basal ganglia	0	0	0	0	121	0
Medial sensorimotor	0	0	17	0	0	0
Auditory	0	0	13	0	1	3009
Sensorimotor	0	0	0	0	7	67

FC, functional connectivity; FD, framewise displacement; OldHM, old participants with high motion group; OldLM, old participants with low motion group; RSNs, resting state networks; YugLM, young participants with low motion group.

all network metrics between young and elderly participants with low motion. To investigate further the reason of the absence of any significant differences between the OldLM and the YugLM groups, the values of each metric were plotted as a function of the FC threshold used to construct the binary networks, and the shapes of the graphs were examined (Fig. 3). For clustering coefficient (Fig. 3a), global efficiency (Fig. 3c), and local efficiency (Fig. 3d), the OldHM group has significantly higher values compared to the other two groups for all threshold values. On the other hand, for the characteristic path length (Fig. 3b), the OldHM group has significantly lower values compared to the low motion groups for all threshold values. For comparisons involving low motion groups (OldLM vs. YugLM), no significant differences were observed in the AUCs of all network metrics, but the within-group mean values of these metrics changed as a function of the threshold used to generate the binary networks. The rate of change differed between YugLM and OldLM groups resulting in the plots of the mean values to intersect at some threshold value.

Table 3 Unpaired-sample *t*-test results for network metrics

		t	*P*
AUC of clustering coefficient	OldHM vs. OldLM	3.17	0.00215
	OldHM vs. YugLM	3.41	0.000981
	OldLM vs. YugLM	0.478	0.634
AUC of characteristic path length	OldHM vs. OldLM	−4.28	0.0000493
	OldHM vs. YugLM	−4.46	0.0000243
	OldLM vs. YugLM	0.0816	0.935
AUC of global efficiency	OldHM vs. OldLM	4.44	0.0000265
	OldHM vs. YugLM	4.28	0.0000480
	OldLM vs. YugLM	−0.273	0.786
AUC of local efficiency	OldHM vs. OldLM	3.40	0.00104
	OldHM vs. YugLM	3.85	0.000228
	OldLM vs. YugLM	0.684	0.496

AUC, area under the curve; OldHM, old participants with high motion group; OldLM, old participants with low motion group; YugLM, young participants with low motion group.

Discussion

In this study, we examined the effect of head motion in estimating age-related changes in FC measures. As a baseline, we evaluated changes in large-scale RSNs as well as several network metrics using resting state fMRI data from young and elderly participants with low head motion. We then performed similar comparisons using data from elderly participants with high head motion. Our findings showed that head motion can (1) significantly reduced the number of voxels exhibiting significant differences in FC in multiple RSNs and (2) significantly biased the estimation of network metrics that could lead to a likely spurious significant difference in these metrics when comparing young and elderly participants. These findings clearly demonstrated the significant effect of head motion in the evaluation of age-related changes in FC measures and should therefore be carefully taken into consideration when evaluating such changes.

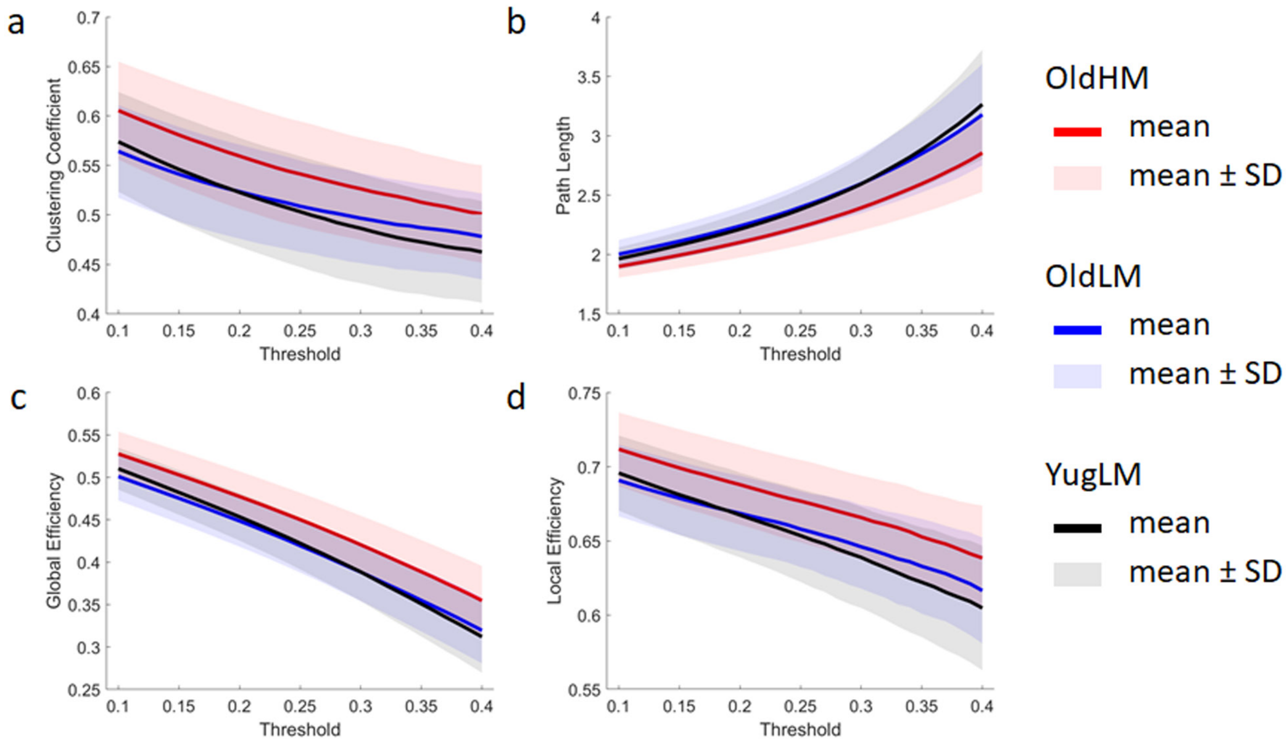

Fig. 3 Network metrics evaluated at different threshold values. Mean values (solid lines) and SD (shaded portion) of the different network metrics evaluated with increasing connectivity threshold value for the 3 groups: OldHM (red), OldLM (blue), and YugLM (black) are shown. For clustering coefficient (**a**), global efficiency (**c**), and local efficiency (**d**), the OldHM group has the highest mean values across all thresholds as compared to the other two groups. Moreover, the graphs of the mean of the network metrics of OldLM and the YugLM groups intersect as the threshold value increases. For the characteristic path length (**b**), only the OldHM group has significantly low mean values across thresholds, while the graphs of the OldLM and the YugLM also intersect with increasing threshold. OldHM, old participants with high motion group; OldLM, old participants with low motion group; SD, standard deviations; YugLM, young participants with low motion group.

Effects of head motion in the estimation of age-related changes in functional connectivity

Many studies have reported age-related changes in many large-scale RSNs that occur with normal aging. The major changes commonly reported involved significant reduction in connections within large functional networks. Specifically, significant decreases in FC were frequently observed within the default mode, salience, and executive control/attention networks with age.[22–29] On the other hand, the aging brain has also been shown to have increased connections with areas outside these RSNs.[26,30,31] Together, these findings suggest that the connectivity within brain networks tends to decrease, while the connectivity between networks tends to increase with aging.

Our findings comparing young and elderly participants with low head motion are mostly consistent with existing results. As shown in Table 1 (OldLM vs. YugLM), widespread FC differences can be observed in all RSNs investigated. Significantly lower FC values in elderly participants were mostly observed within networks, while higher FC values were observed with connections outside the network (Fig. 2).

Comparisons in FC between young and elderly participants with high head motion still show regions with significant differences in FC, but the spatial extent of these regions was significantly reduced (OldHM vs. YugLM, Table 1). This can be clearly seen, for example, in the visual network (primary, higher, and medial), which showed a significant drop in the number of voxels exhibiting age-related FC changes in OldHM vs. YugLM comparison as compared to the OldLM vs. YugLM (Table 1 and Fig. 2). A direct comparison between elderly groups (OldHM vs. OldLM) showed that participants with high motion had FC values that significantly differed from those with low head motion in a number of RSNs, which would explain the observed difference in the spatial extent of the obtained age-related FC changes between OldLM vs. YugLM and OldHM vs. YugLM comparisons.

The observed differences in FC values between OldHM and OldLM groups are consistent with the effect of head motion. Head motion has been shown to be one of the critical factors that could significantly influence the results of resting state fMRI analysis.[7–9] The changes in BOLD signal due to head motion are complex, vary in form, but are often similar across voxels. Changes caused by head movements could result in increased spatial correlations because adjacent voxels move in the same way as well as increased in temporal correlations because the movement could take some time. As a result, motion-related changes in the BOLD signal could lead to an increase in the estimated FC in a distance-dependent manner, both during and after motion.[13] Power et al.[8] has also reported that movement increases correlation in neighboring regions while decreases correlation at distant regions, although overall, head motion mainly increases FC.[7–9] This is further supported by the results of the additional within-group regression analyses with mean FD. Our findings showed a considerably larger number of voxels with FC to several RSNs exhibiting significant association with the amount of head motion in the high motion group (OldHM) as compared to the low motion groups (YugLM, OldLM). Positive linear relationships were mostly observed with regions within network, while negative associations were observed with regions outside the network. We do note that regression only captures the linear association with mean FD but the overall effect of head motion could be more complex. These findings do suggest that the effects of head motion are becoming more prominent as the amount of head motion increases. Considering the distance-dependent effect of head motion, the results of the comparison between OldHM and YugLM suggest that head motion could lead to the underestimation of age-related changes in FC due to the motion-related increases in within-network connectivity (neighboring regions) as well as decreases in between-network connections (distant regions), which is opposite to that of aging.

Effects of head motion in the estimation of age-related changes in network metrics

In terms of network analysis, results from previous studies have shown that the whole-brain network tends to progress towards a more integrated network with age.[21] This parallels the results of voxel-level connectivity studies showing increase connectivity with regions outside the network in the aging brain. For example, the characteristic path length, which is an index of functional integration, has been shown to decrease with age[21,32,33] indicating a more connected brain network with shorter paths in-between nodes in the aging brain.

Using AUC as the index for comparison, we observed significant differences in all metrics investigated between OldHM and OldLM as well as between OldHM and YugLM (Table 3). In contrast, no significant difference was observed between OldLM and YugLM. This suggests that head motion has a significant effect on the evaluation of network changes with aging. Intriguingly, the direction of change points toward a more integrated network with lower path length, higher global and local efficiencies, and higher clustering coefficient in elderly participants with high head motion as compared to young and elderly participants with low head motion (Fig. 3). This is again consistent with the effect of head motion, which tends to increase connectivity across different brain regions. This finding therefore suggests that head motion could lead to an overestimation of network metrics associated with network integration.

Finally, we note that although no significant difference was observed in the AUC of the different network metrics between YugLM and OldLM, the within-group mean values of these metrics changed as a function of the connectivity threshold value used to construct the binary networks (Fig. 3). The rate of change differed that at some threshold value, the plots of the mean values intersected. For instance, the mean value of the clustering coefficient is higher in YugLM compared to that in OldLM for lower connectivity threshold values, while the opposite is true for higher values. This indicates that the characteristics of the generated binary network showed some dependences with the threshold used to generate the binary networks. Considering that the brain consists of several large-scale RSNs,[14] high threshold values could be influenced more by connections within these large networks while low threshold values by the connections with regions outside of these networks. Since aging affects differently for within- and between-network connections, age-related changes in network metrics could therefore be influenced by the used threshold value. This may explain conflicting results observed in previous studies for network metrics that changed with age. For example, modularity, a network metric indicating functional separation, has been shown to decrease with age,[30] but opposite findings have also been reported.[34] This suggests that careful consideration should be exercised when investigating age-related changes in network properties as the estimation of the network metrics could be affected by both head motion as well as the threshold value used to form the binary networks.

Conclusion

In this study, we examined the effect of head motion in evaluating age-related changes in FC measures using resting state fMRI. Our findings showed that head motion could lead to the underestimation of FC changes in large-scale RSNs as well as overestimation of network metrics in the elderly as compared to the young participants. These findings clearly demonstrate the significant effect of head motion during imaging in the evaluation of age-related brain network changes using resting state fMRI data and should therefore be carefully taken into consideration when evaluating such changes.

Acknowledgments

This work was supported by Grants-in-Aid from the Research Committee of Central Nervous System Degenerative Diseases by the Ministry of Health, Labor and Welfare and from the Integrated Research on Neuropsychiatric Disorders project carried out under the Strategic Research for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan. This work was also supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (grant number 80569781), and a Grant-in-Aid for Scientific Research on Innovative Areas (Brain Protein Aging and Dementia Control; 26117002) from MEXT. This work was also supported by the Management Expenses Grants from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34:537–541.
2. Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994; 2:56–78.
3. Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 2004; 5:87–96.
4. Grady C. The cognitive neuroscience of ageing. Nat Rev Neurosci 2012; 13:491–505.
5. Sala-Llonch R, Bartrés-Faz D, Junqué C. Reorganization of brain networks in aging: a review of functional connectivity studies. Front Psychol 2015; 6:663.
6. Ferreira LK, Busatto GF. Resting-state functional connectivity in normal brain aging. Neurosci Biobehav Rev 2013; 37:384–400.
7. Van Dijk KRA, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 2012; 59:431–438.
8. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 2012; 59:2142–2154.
9. Satterthwaite TD, Wolf DH, Loughead J, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage 2012; 60:623–632.
10. Bagarinao E, Watanabe H, Maesawa S, et al. An unbiased data-driven age-related structural brain parcellation for the identification of intrinsic brain volume changes over the adult lifespan. Neuroimage 2018; 169:134–144.
11. Mugler JP, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). Magn Reson Med 1990; 15:152–157.
12. Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005; 26:839–851.
13. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 2014; 84:320–341.
14. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond, B, Biol Sci 2005; 360:1001–1013.
15. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex 2012; 22:158–165.
16. Filippini N, MacIntosh BJ, Hough MG, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci USA 2009; 106:7209–7214.
17. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002; 15:1–25.

18. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009; 44:83–98.
19. Power JD, Cohen AL, Nelson SM, et al. Functional network organization of the human brain. Neuron 2011; 72:665–678.
20. Wang J, Wang X, Xia M, Liao X, Evans A, He Y. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. Front Hum Neurosci 2015; 9:386.
21. Bagarinao E, Watanabe H, Maesawa S, et al. Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. Sci Rep 2019; 9:11352.
22. Andrews-Hanna JR, Snyder AZ, Vincent JL, et al. Disruption of large-scale brain systems in advanced aging. Neuron 2007; 56:924–935.
23. Jones DT, Machulda MM, Vemuri P, et al. Age-related changes in the default mode network are more advanced in Alzheimer disease. Neurology 2011; 77:1524–1531.
24. Onoda K, Ishihara M, Yamaguchi S. Decreased functional connectivity by aging is associated with cognitive decline. J Cogn Neurosci 2012; 24:2186–2198.
25. Tomasi D, Volkow ND. Aging and functional brain networks. Mol Psychiatry 2012; 17:471, 549–558.
26. Betzel RF, Byrge L, He Y, Goñi J, Zuo XN, Sporns O. Changes in structural and functional connectivity among resting-state networks across the human lifespan. Neuroimage 2014; 102 Pt 2:345–357.
27. Damoiseaux JS, Beckmann CF, Arigita EJ, et al. Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex 2008; 18:1856–1864.
28. Geerligs L, Renken RJ, Saliasi E, Maurits NM, Lorist MM. A brain-wide study of age-related changes in functional connectivity. Cereb Cortex 2015; 25:1987–1999.
29. Song J, Birn RM, Boly M, et al. Age-related reorganizational changes in modularity and functional connectivity of human brain networks. Brain Connect 2014; 4:662–676.
30. Chan MY, Park DC, Savalia NK, Petersen SE, Wig GS. Decreased segregation of brain systems across the healthy adult lifespan. Proc Natl Acad Sci USA 2014; 111:E4997–E5006.
31. Meier TB, Desphande AS, Vergun S, et al. Support vector machine classification and characterization of age-related reorganization of functional brain networks. Neuroimage 2012; 60:601–613.
32. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLoS Comput Biol 2007; 3:e17.
33. Sala-Llonch R, Junqué C, Arenaza-Urquijo EM, et al. Changes in whole-brain functional networks and memory performance in aging. Neurobiol Aging 2014; 35:2193–2202.
34. Meunier D, Achard S, Morcom A, Bullmore E. Age-related changes in modular organization of human brain functional networks. Neuroimage 2009; 44:715–723.