

Neurobiological basis of head motion in brain imaging

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Individual differences in brain metrics, especially connectivity measured with functional MRI, can correlate with differences in motion during data collection. The assumption has been that motion causes artifactual differences in brain connectivity that must and can be corrected. Here we propose that differences in brain connectivity can also represent a neurobiological trait that predisposes to differences in motion. We support this possibility with an analysis of intra- versus intersubject differences in connectivity comparing high- to low-motion subgroups. Intersubject analysis identified a correlate of head motion consisting of reduced distant functional connectivity primarily in the default network in individuals with high head motion. Similar connectivity differences were not found in analysis of intrasubject data. Instead, this correlate of head motion was a stable property in individuals across time. These findings suggest that motion-associated differences in brain connectivity cannot fully be attributed to motion artifacts but rather also reflect individual variability in functional organization.

resting-state fMRI | motion correction | connectome

Head motion has long been known as a confounding factor in brain imaging including MRI (1, 2), PET (3, 4), single-photon emission computerized tomography (5, 6), and near infrared spectroscopy (7), but has raised particular concerns recently following the growing prominence of resting-state functional connectivity MRI. Studies found that head motion can vary considerably across individuals and often demonstrates systematic group effects when contrasting different populations, especially in neurodevelopmental (8–10), aging (11, 12), and neuropsychiatric studies (13). Some recent work reported that head motion augmented local coupling of the blood oxygenation level-dependent (BOLD) signal but reduced distant coupling (14–16). These correlations between connectivity measures and head motion have raised appropriate concern that previously observed differences in connectivity are due to artifact induced by differences in head motion. For example, developmental changes in functional connectivity might also be predicted by head motion (15). The assumption has been that head motion causes distorted connectivity measurements that must be addressed through improved motion-correction techniques (15). However, this correlation could be driven by causal factors in the other direction. Specifically, individual differences in brain connectivity could determine how well a subject can lie still in the scanner. This is not unreasonable as individual differences in structural connectivity can predict trait anxiety and can be related to attention deficits (17, 18) and individual differences in resting-state functional MRI (fMRI) measures may relate to various behavioral differences, including impulsivity (19–22). In such a scenario, certain intersubject differences in connectivity measures could persist even after the most rigorous motion correction, as has been suggested in several earlier studies (23, 24).

To explore the relation between head motion and brain connectivity, we examined functional connectivity in different subject groups selected on the basis of head motion parameters from

a large database of 3,000+ participants, many of whom were scanned multiple times. These cohorts allowed us to compare intersubject and intrasubject differences in connectivity in high-versus low-motion scans. If motion causes connectivity differences, these should be similar both inter- and intrasubject. However, if connectivity differences include a stable trait that predisposes to head motion, then these differences should be present between subjects but not within subjects.

Results

We first investigated whether head motion is a reliable behavioral measure across MRI sessions. In 118 subjects scanned on 2 separate days (mean interval 128.59 ± 151.34 d), head motion across sessions was significantly correlated ($r = 0.54$, $P < 0.001$, Fig. S1). This reproducibility suggests that the tendency to move is generally a stable trait across subjects (16).

Next we investigated the intersubject difference in connectivity. First, we carefully selected 26 pairs of healthy young adults who were matched in all scanning parameters and demographics but differed in the averaged head motion (0.049 vs. 0.035 mm, $P < 0.001$, Table S1). To ensure that functional connectivity can be accurately estimated without being confounded by motion-related artifacts, image frames with a motion level (root mean square) exceeding 0.06 mm were scrubbed from the high-motion subjects (15), and then the same time points were also removed from the matched low-motion subjects. Therefore, the frames removed in the low-motion subjects were not necessarily the motion-contaminated frames (*Materials and Methods*). After this

Significance

This study expands our understanding of head motion in brain imaging. Complementing the common knowledge that motion artifacts can distort brain connectivity measures by causing artifacts, this study identifies a neurobiological trait that is linked to differences in motion. This correlate of head motion consists of reduced distant functional connectivity primarily in the default network areas in individuals with high head motion. Importantly, this correlate is stable within individuals across time. These findings may revise the interpretations of imaging findings in many neurodevelopmental, aging, and neuropsychiatric studies. In addition, differentiating the true disease effects from the correlates of motion tendency as reported here is critical for using connectivity markers in the clinical arena because correlates of motion may reduce specificity of biomarkers.

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scrubbing operation, no difference in head motion was found between these two groups (0.034 vs. 0.034 mm, $P > 0.80$, Table S1). The scrubbing had resulted in a loss of 23.5% of the data in both the high-motion and low-motion subjects, but all subjects included in the further analyses had at least 120 time points retained. The degree of distant connectivity was then calculated for each voxel by counting the number of voxels outside the immediate neighborhood (a sphere with the radius of 12 mm) (25) that were significantly correlated with the seed voxel [exceeding the threshold of $P < 0.01$ after the false discovery rate (FDR) correction]. Distant functional connectivity in a distributed set of regions, primarily in the default network, was found to be significantly greater in the 26 subjects with low head motion than in the 26 matched subjects with high head motion ($P < 0.05$, FDR-corrected, two-tailed, two-sample t test, Fig. 1A). These regions can be considered a potential marker of head motion.

Next we compared these intersubject differences in motion-related connectivity to intrasubject differences. We selected an independent dataset of 26 subjects who were scanned twice on separate days (mean interval 114.50 ± 126.52 d) but exhibited more sporadic head motion in one scanning session than in the other (Table S1). The motion level of this intrasubject dataset was matched to that of the intersubject dataset: there was no significant difference between the two high-motion groups (motion before scrubbing: 0.049 vs. 0.051 mm, $P = 0.24$; motion after scrubbing: 0.034 vs. 0.034 mm, $P = 0.79$) or between the two

low-motion groups (motion before scrubbing: 0.035 vs. 0.033 mm, $P = 0.06$; motion after scrubbing: 0.034 vs. 0.034 mm, $P = 0.44$). Any residual motion artifacts not removed by motion-correction techniques including scrubbing should be similar in the intersubject and intrasubject comparisons. However, potential neurobiological traits should show up only in the intersubject comparison.

Unlike the analysis of the intersubject dataset, no difference in distant connectivity was found between the low-motion sessions and the high-motion sessions of the same group of subjects (no voxel reached the significance level of $P < 0.05$, FDR-corrected, two-tailed paired t test, Fig. 1B). This result suggests that the intersubject difference shown in Fig. 1A likely includes a neurobiological trait effect beyond a residual motion artifact (see *SI Text* for discussions on the potential influence of anatomical variability).

To confirm that this neurobiological marker of head motion is not specific to one subject cohort, we replicated our findings in an independent dataset consisting of 30 pairs of demographically matched subjects ($r = -0.39$, $P < 0.005$, Fig. S2). We also used this replication dataset to confirm that regions showing the trait effect localized primarily to the default network (see *SI Text* and Fig. S3).

Although scrubbing is a useful method to minimize the impact of motion-related artifacts and improve distant coupling (15), this operation will cause loss of data and could lead to a biased estimate of distant connectivity. We found that the loss of data could inflate distant coupling, but primarily in the visual cortices and some posterior parietal regions (*SI Text* and Fig. S4). In the present results, we always scrubbed the data of matched groups in the same way; therefore, the inflation of distant coupling would have minimal impact on our results. However, to further examine whether the results in Fig. 1 were affected by data scrubbing, we repeated all analyses with unscrubbed data. The findings that distant connectivity in the potential biomarker regions correlates with intersubject difference ($r = -0.80$, $P < 0.001$), but not intrasubject variation in head motion ($r = -0.14$, $P > 0.30$), were largely replicated (see Fig. S5 for the inter- and intrasubject differences). In addition, the findings were replicated in a subset of the subjects matched based on a different scrubbing threshold (*SI Text* and Fig. S6), suggesting that this connectivity correlate of the trait for head motion is not contingent upon data scrubbing.

Although the image frames immediately contaminated by motion artifacts were removed, potential confounds might still arise from the movement-induced BOLD response, which could have a delay of ~ 10 s after the movement. To investigate how the delayed BOLD response may affect the connectivity marker, we performed a stringent scrubbing procedure on the data of 56 pairs of matched subjects (including the discovery sample and the 30 pairs of subjects in the replication samples). Whenever the head motion exceeded a threshold of 0.06 mm, two preceding frames (6 s) and five succeeding frames (15 s) were removed in addition to the noisy frames, ensuring that the delayed BOLD responses and other forms of extended motion effect were largely eliminated from the data. Taking the marker regions (shown in Fig. 1A) as a mask (binarized as shown in Fig. S7A), distant connectivity was computed based on the stringently scrubbed data and then averaged within the mask. Distant connectivity derived from the stringently scrubbed data still strongly predicted head motion ($r = -0.67$, $P < 0.001$, Fig. S7B), indicating that the delayed BOLD responses and temporally-extended artifacts had a minimal effect on the connectivity–motion correlation. In a further control analysis, we treated the time course of mean motion of each subject as the representation of a continuous movement task and then convolved this time course with the canonical hemodynamic response function. General Linear Model (GLM) analysis was performed to identify regions activated by this “continuous movement task,” and then the

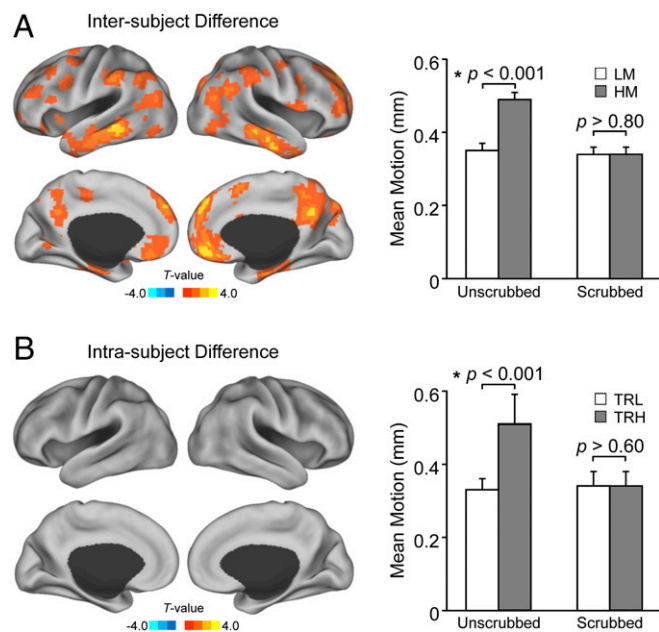


Fig. 1. Functional connectivity in a set of marker regions is a trait that predisposes to head motion but remains stable within subjects. (A) Distant connectivity in some cognitive regions (shown in red and yellow), mainly in the default network, was significantly greater in 26 subjects with low head motion than in 26 matched subjects with high motion ($P < 0.05$, FDR-corrected, two-tailed, two-sample t test). The motion level of the two groups was significantly different before data scrubbing ($P < 0.001$) but was the same after scrubbing ($P > 0.80$) (Right). (B) In an independent dataset of 26 subjects who exhibited a different level of sporadic head motion in two scanning sessions, no significant difference in distant connectivity was observed between the low-motion session and the high-motion session (no voxels reached the significance level of $P < 0.05$, FDR-corrected, two-tailed paired t test). The motion level of the two sessions was also significantly different before data scrubbing ($P < 0.001$) but was the same after scrubbing ($P > 0.80$) (Right). The motion level of this test–retest dataset was also matched to that of intersubject dataset (discovery sample); L/M/H/M, low-/high-motion individuals in the discovery sample; TRL/TRH, low-/high-motion sessions in the test–retest data.

maps were compared between the low-motion subjects and the high-motion subjects. No significant difference was observed between the two matched groups (no voxel reached the significance threshold of $P < 0.05$, FDR-corrected), indicating that the BOLD response induced by continuous movement may not account for the group difference identified in Fig. 1A.

We found that the marker for the tendency of head motion remained stable within individuals, although the intrasubject variability of motion over time could be large in some cases. If these subjects showed little head motion in one session but were not able to refrain from moving in another session, a further question is whether they possess a connectivity signature similar to those who move excessively or similar to those who consistently move less. To address this question, we compared the 26 test–retest subjects with high intrasubject variability of motion to the discovery sample. Distant connectivity was averaged in a mask derived from the independent replication sample by comparing the 30 low-motion with the 30 high-motion subjects ($P < 0.05$, FDR-corrected, two-sample t test). In the test–retest subjects, distant connectivity derived from the low-motion session was significantly weaker than the low-motion subjects of the discovery sample ($P = 0.03$, two-sample t test, Fig. 2), but similar to the high-motion subjects ($P = 0.23$, two-sample t test, Fig. 2). These findings suggested that the subjects who could not persistently remain still had a neural connectivity signature resembling those who tend to have excessive motion, even during the scan when they were still. The findings that the two groups with matched head motion showed a significant difference in distant connectivity, whereas the two groups with significantly different motion showed no difference in connectivity, further supported that the trait effect is dominant over residual motion artifacts after appropriate corrections. Although intrasubject variability of head motion was seen in these few subjects, the majority of the sample showed a consistent level of head motion (as shown in Fig. S1). We examined the distant connectivity in 18 test–retest subjects with consistent levels of head motion (motion difference < 0.01 mm between two sessions). In these subjects, distant connectivity averaged in the marker region was significantly correlated with the head motion both in session 1 ($r = -0.50$, $P = 0.03$) and in session 2 ($r = -0.51$, $P = 0.04$) (Fig. S8),

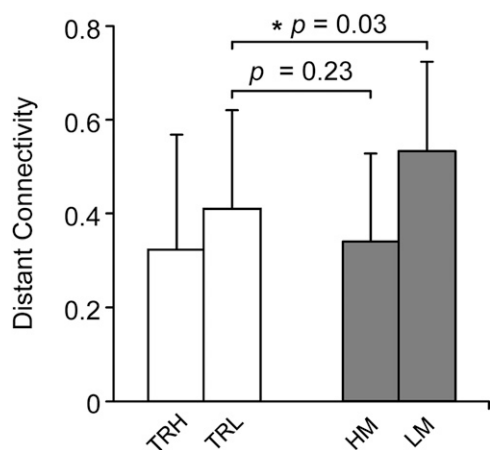


Fig. 2. Distant connectivity in the test–retest subjects demonstrating higher variability in head motion resembled those subjects with excessive motion. Distant connectivity was averaged in a mask derived from the independent replication sample by comparing the low-motion with the high-motion subjects ($P < 0.05$, FDR-corrected, two-sample t test). Distant connectivity in the 26 test–retest subjects was significantly different from the 26 subjects in the discovery sample with low head motion ($P = 0.03$), but similar to the 26 subjects with high head motion ($P = 0.23$).

and the correlation was not different between the two sessions (ANCOVA, $P > 0.95$). These results indicate that the connectivity marker could reliably predict head motion in subjects with a consistent level of head motion, who constitute the majority of the population.

Discussion

The present study suggests a correlate of head motion during brain imaging that reflects a neurobiological trait rather than simply a technical artifact. The bidirectional relationship between head motion and brain connectivity could have substantial implications for functional connectivity studies.

Distant connectivity in a distributed set of cortical regions, primarily in the default network, was significantly stronger in subjects with low head motion than in subjects with high head motion. Because similar differences were not seen with intrasubject differences in head motion, this connectivity property appears to be a neurobiological trait of head motion tendency. Special attention is needed when interpreting findings of individual differences that overlap with these marker regions. For example, alterations of connectivity in the default network have been suggested in many neuropsychiatric and neurological diseases (26). Determining whether these changes are specific to a disorder or a secondary effect of factors that relates to the tendency of head motion is critical for identifying the treatment target and the development of treatment strategy. If head motion is generally elevated in a patient population, a disease biomarker independent from the marker of motion as identified in the current study might be expected to provide better specificity.

It is intriguing that the marker for the tendency of motion involves the association cortices but not the primary sensorimotor cortex. The default network has been suggested to subserve internal mentation (e.g., ref. 27). Strong distant connectivity within this network may reflect the effective monitoring of internal states. Our data indicated that subjects with greater distant connectivity in the marker region could consistently refrain from moving, whereas subjects with weak distant connectivity in the marker region could not persistently remain still. Head motion therefore may be an indicator of specific cognitive control capacity in the individual brain. Future investigations may explore whether this control of motor behavior or some other indirect correlate of head motion (e.g., respiration) is predictive of other higher cognitive capabilities that are subserved by the same brain regions.

Remarkably, the connectivity marker for the tendency of head motion was stable within individuals. The fact that distant connectivity in the default network explains intersubject difference but not the intrasubject variability in head motion strongly suggests that the marker identified in this study was not due to motion artifacts. This finding has direct implications for the development of motion-correction techniques.

Although the connectivity marker reported in the present study correlates with interindividual difference in head motion and may reflect a trait of motor restlessness, the results should be interpreted with some caveats. First, these results should not be taken as an argument against motion correction. The cause-and-effect relationship between functional connectivity and head motion is two-way. The difference in motion artifacts can lead to the difference in connectivity estimates whereas the neural connectivity difference could also cause difference in motion. One should not simply focus on one side of this relationship and ignore the other. Although interindividual differences in connectivity as shown in Fig. 1A are dominated by the trait effect, it is likely that this map includes a residual motion artifact that persists despite rigorous scrubbing. Our analyses suggest that any remaining artifact effect is small relative to the trait effect (Fig. 1B and Fig. S5B); however, full dissociation of artifact and trait effects may be possible with future advances in motion-correction technology. Some recent development in this direction, such as a more specific model of the

motion artifact (28) or separating the artifact component from the neural component based on fMRI data acquired using multiple echo times (TEs) (29), could eventually improve the specificity of biomarkers. Second, our analyses were based on a specific type of connectivity measure, distant connectivity, and therefore the results should not be extrapolated to all types of connectivity measures without careful examination. Finally, the influence of physiological functions such as respiratory and cardiac rates was not monitored in the current study (30). The aliased respiration- and cardiac-related low-frequency variations, as well as the arterial carbon dioxide concentration and blood pressure variations, cannot be removed by the low-pass filtering strategy (31). These physiological processes may also have neurobiological correlates (31). Although the marker regions for the tendency of head motion identified here are largely distinct from the regions demonstrating significant respiratory-induced BOLD signal change (32, 33), the potential physiological confounds on the connectivity marker as reported in this study warrant further investigation.

Materials and Methods

Participants. Data were acquired as part of the Brain Genomics Superstruct Project. Participants were enrolled by multiple local laboratories, all acquiring similar data on matched 3 Tesla MRI scanners located at Harvard and at the Massachusetts General Hospital. All participants were native English speakers and had normal or corrected-to-normal vision. Participants were excluded with a history of neurological or psychiatric illness. Data were selected using the following criteria: 12-channel head coil, age between 18 and 35 y, and fMRI slice-based temporal signal-to-noise ratio >100. All participants provided written informed consent in accordance with guidelines set by Institutional Review Boards of Harvard University or Partners Healthcare. Portions of these data have been previously reported (16, 34, 35).

Datasets. The analyses described in this article used three separate resting-state fMRI datasets. Unless specifically noted, these datasets were treated identically in processing and analysis.

Dataset 1 consisted of a total of 56 pairs of subjects from a pool of 3,000+ participants (34); each pair of subjects was matched in scanner, coil, scanning date (difference <105 d), ethnicity, sex (37F/19M), handedness (5L/51R), age (≤ 3 y, $P > 0.80$), and education (≤ 3 y, $P > 0.95$), but not in head motion (mean motion: 0.036 ± 0.002 vs. 0.053 ± 0.009 mm, $P < 0.001$). All subjects had two BOLD runs (each run had 124 time points). Twenty-six pairs were regarded as the discovery sample (Table S1), and the remaining 30 pairs were used as the replication sample.

Dataset 2 consisted of a total of 26 test-retest subjects with inconsistent levels of head motion during two scanning sessions (sex: 17 females/9 males; handedness: 2L/24R; age: 20.3 ± 2.38 y; education: 14.04 ± 1.89 y; mean motion difference >0.01 mm between the low-motion sessions and high-motion sessions, $P < 0.001$), and each session had one or two BOLD runs. The interval between two sessions was 114.50 ± 126.52 (between 2 and 446) days, and only three subjects had a delay exceeding 1 y. The dataset was matched with the discovery sample in demographics as well as the head motion before and after motion scrubbing (Table S1).

Dataset 3 consisted of a total of 18 test-retest subjects with consistent level of head motion (sex: 9F/9M; handedness: 5L/13R; age: 19.33 ± 1.71 y; education: 13.44 ± 1.62 y; mean motion: 0.039 ± 0.013 mm; mean motion difference <0.01 mm between two sessions, $P > 0.95$), and each session has one or two runs.

Data Acquisition and Preprocessing. All data were collected on matched 3T Tim Trio scanners (Siemens) using a 12-channel phased-array head coil. Images were acquired using a gradient-echo echo-planar pulse sequence sensitive to BOLD contrast [repetition time (TR) = 3,000 ms, TE = 30 ms, flip angle = 85° , 3-mm isotropic voxels, field of view (FOV) = 216; 47 slices collected with interleaved acquisition with no gap between slices]. Slices were aligned to the anterior commissure–posterior commissure plane using an automated alignment procedure to ensure consistency across subjects (36). Each resting-state (eyes open) fMRI run lasted 6 min and 12 s. Structural data used a high-resolution multiecho T1-weighted magnetization-prepared gradient-echo image (TR = 2,200 ms; inversion time = 1,100 ms; TE = 1.54 ms for image 1 to 7.01 ms for image 4; flip angle = 7° ; 1.2-mm isotropic voxels; and FOV = 230). Subjects were instructed to stay awake, keep their eyes open, and minimize head movement; no other task instruction was provided.

Resting-state fMRI data were processed using previously described procedures (16). The first four volumes of each run were discarded to allow for T1-equilibration effects. The following steps were performed: (i) slice timing correction (SPM2, Wellcome Department of Cognitive Neurology, London); (ii) rigid body correction for head motion with the FSL package (Functional MRI of the Brain, Oxford); (iii) atlas registration with an EPI template in the Montreal Neurological Institute atlas space, resampling to 2-mm isotropic voxels and spatially smoothing using a 6-mm full-width half-maximum Gaussian kernel; (iv) normalization for global mean signal intensity across runs; (v) linear detrend and low-pass temporal filtering (<0.8 Hz); and (vi) regression of nuisance variables including the six parameters obtained by rigid-body head-motion correction, global signal, ventricular and white matter signals, and the first temporal derivatives of all of the above.

Motion Scrubbing. In the current study, we used mean motion as the central metric of head motion (15), which represents the mean absolute displacement of each brain volume compared with the previous volume and was estimated from the translation parameters in the x (left/right), y (anterior/posterior), and z (superior/inferior) directions.

To ensure that the data were minimally affected by motion-related artifacts, motion scrubbing was used to remove frames with high motion (15). Importantly, head motion was matched after scrubbing across all groups including the low-motion and high-motion groups in the discovery sample, replication sample, and test-retest samples (Table S1). In addition, head motion was further matched across the high-motion datasets before scrubbing. The details are described below.

For dataset 1 (discovery sample and replication sample), frames with a motion level exceeding 0.06 mm were scrubbed from the high-motion data, and then the same time points were scrubbed from the matched low-motion data. Therefore, the frames removed in the low-motion subjects were not necessarily the frames of higher motion. Removing the same frames in the high-motion and the low-motion data ensured that the effects caused by data loss were comparable in these two groups. After scrubbing, the low-motion data and high-motion data were matched in head motion ($P > 0.80$). This operation had resulted in an exclusion of 23.5% of the data, but all subjects included in the analyses had at least 120 time points left.

Similarly, the frames to be removed were based on the high-motion sessions exceeding thresholds for dataset 2 (26 test-retest sample), and the corresponding time points were also scrubbed from the low-motion sessions. After scrubbing, the low-motion sessions and the high-motion sessions were matched in head motion ($P > 0.60$). This operation resulted in an exclusion of 26.0% of the data, but all sessions included in the analyses had at least 80 time points left.

Frames with a motion level exceeding 0.06 mm were removed for both sessions of dataset 3 (18 test-retest sample). After scrubbing, each subject still showed a consistent level of head motion between two sessions (mean motion difference <0.01 mm, $P > 0.90$). This operation resulted in an exclusion of 12.4% of the data, but all sessions included in the analyses had at least 100 time points left.

Characterizing Distant Functional Connectivity with Distant Degree Connectivity Map.

Degree of distant functional connectivity was calculated for each subject or session as described in detail elsewhere (25). Degree centrality is a network measure that quantifies the number of edges that are connected to a node in a graph (37). Here brain voxels are the nodes, and positive correlations between voxels with $P < 0.01$ (FDR-corrected) are the edges. To speed up the computation, data were down-sampled to 4-mm isotropic voxels. Distant connectivity was calculated for each voxel by counting the number of edges to other voxels outside the immediate neighborhood (12-mm radius). The output was a whole-brain distant degree connectivity map for each subject. The maps were then standardized by Z-score transformation so that maps across participant maps could be compared (25, 38). In the present study, all of the difference maps (as shown in Fig. 1 and Figs. S4 and S5) were whole-brain-corrected for multiple comparisons at a significance level of $P < 0.05$ via FDR.

Estimating Intersubject Difference in Distant Connectivity Related to Head Motion.

Distant connectivity map was computed for each subject of the discovery sample. To estimate intersubject difference in distant connectivity related to head motion, the distant connectivity maps of the 26 low-motion subjects were compared with those of the 26 high-motion subjects of the discovery sample by two-tailed, two-sample *t* tests (Fig. 1A).

Replication analysis was conducted on the replication sample consisting of 30 pairs of subjects from dataset 1. The distant connectivity map was computed for each subject. Taking the brain regions showing significant intersubject connectivity difference in the discover study as a mask, distant connectivity was averaged within the mask for each subject, and then correlation analysis was performed between the distant connectivity and head motion (Fig. S2A).

Estimating Intrasubject Variation in Distant Connectivity Related to Head Motion. Dataset 2, consisting of 26 test–retest subjects with an inconsistent level of head motion in two scanning sessions, was used to estimate intrasubject variation in distant connectivity related to head motion. The distant connectivity map was computed for each session, and the maps of the low-motion sessions were compared with those of the high-motion sessions by two-tailed paired *t* tests (Fig. 1B). Furthermore, taking the brain regions showing significant intersubject connectivity difference in the discover study as a mask, correlation analysis was performed between the distant connectivity averaged within the mask and head motion for these test–retest subjects (Fig. S2B).

Scrubbing Effect Estimation and Replication of the Main Finding in the Unscrubbed Data. Motion scrubbing will cause the loss of data and may introduce spurious distant connectivity. To understand the impact of scrubbing on distant connectivity, we compared the distant connectivity maps of the scrubbed data to those of the unscrubbed data based on the low-motion subjects in the discovery sample using two-tailed paired *t* tests (Fig. S4A). Similar analysis was conducted on the data of the low-motion sessions of the test–retest subjects (Fig. S4B). To further test the reliability of the main finding, we used the unscrubbed data to estimate intersubject and intrasubject difference in distant connectivity related to head motion (Fig. S5).

Testing the Impact of Movement-Induced BOLD Responses on Intersubject Difference in Distant Connectivity Related to Head Motion. To minimize the impact of movement-induced BOLD responses on connectivity measurements, a stringent motion scrubbing was performed. When head motion exceeded the threshold of 0.06 mm, two preceding frames (6 s) and five succeeding frames (15 s) were removed in addition to the immediate frames to ensure the delayed BOLD responses were eliminated from the data. Due to limited sample size, the entire dataset 1, including 56 pairs of matched subjects, was included. After the stringent scrubbing, only 26 pairs of subjects had no less than 80 time points and were used in the following analysis. Among them, 14 pairs of subjects were overlapping with the subjects in the discovery sample. Distant connectivity was computed based on the stringently scrubbed data and averaged within the

mask described above. Correlation analysis was then performed between the distant connectivity and head motion. In the next control analysis, the mean motion curve of each subject was treated as the stimulus function and then was convolved with the canonical hemodynamic response function. The GLM analyses were performed on the unscrubbed data of the discovery sample without temporal filtering and regression processing. Brain regions where the BOLD signals corresponded to the response induced by the head movement were identified, and then the maps were compared between the low-motion subjects and high-motion subjects.

Characterizing the Distant Connectivity in the Test–Retest Subjects. To characterize the distant connectivity in the 26 test–retest subjects with inconsistent level of head motion, we compared the distant connectivity of the test–retest subjects with that of the discover sample. Distant connectivity was averaged in the mask described above and then was compared with that of the 26 subjects with low head motion and that of the 26 subjects with high head motion (Fig. 2).

Distant connectivity was then examined in 18 test–retest subjects with consistent level of head motion in two sessions (dataset 3). Correlation analysis was performed between the distant connectivity averaged in the mask described above and head motion for two scanning sessions, respectively. The connectivity–motion correlation in two sessions was compared using ANCOVA (Fig. S8).

Visualization. All imaging results were projected onto the inflated PALS cortical surface using CARET for the purpose of visualization (39).

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Supporting Information

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SI Text

Potential Role of the Default Network in the Trait of Motor Restlessness. We performed several analyses to investigate the potential contribution of the default network to the trait of motor restlessness.

In the first analyses, we quantified the contribution of different functional networks to the trait effect. The analysis used our prior parcellation of the cerebral cortex based on 1,000 healthy subjects (1). The voxels had been clustered into seven networks, namely the default network (DN), frontoparietal control network (FPN), limbic network (LMB), dorsal attention network (dATN), visual (Vis) network, ventral attention (vATN), and sensory-motor (Mot) networks (Fig. S3A). The voxels exhibiting significantly stronger distant connectivity in low-motion subjects than in high-motion subjects (Fig. S3A, *Top*, as in Fig. 1A, *Upper*) were counted within the mask of each network. We found that the voxels showing significant trait effect fell mainly within the default network. The count of voxels exceeding the significance threshold of $P < 0.05$ [false discovery rate (FDR) corrected] in each network is shown in the bar plots of Fig. S3A.

We then performed more detailed analyses to investigate the contribution of the default network to the trait of motor restlessness. We averaged the distant connectivity values within the default network. Similar to the analysis above, we used the networks defined by a parcellation approach based on 1,000 subjects (1). We found that distant connectivity in the default network mask was strongly correlated with head motion in the 26 pairs of subjects of the discovery sample (Fig. S3B, $r = -0.44$, $P = 0.001$), but not in the 26 test–retest subjects with an inconsistent level of head motion in two sessions (Fig. S3C, $r = -0.11$, $P > 0.40$). When the same analysis was repeated for the rest of the networks, none of them showed a similar pattern as the default network. Distant connectivity in the frontoparietal control network and ventral attention network exhibited a moderate trend (both $r = -0.29$, $P = 0.04$ before correction) of decrease with increasing head motion; however, neither of them would survive the multiple comparison correction.

In the final analyses, we investigated the connectivity among several core regions of the default network, including the posterior cingulate cortex (Montreal Neurological Institute coordinates: 0, -53, 26), medial prefrontal cortex (0, 54, -4), and left and right inferior parietal lobule (-46, -48, 36, and 50, -62, 32, respectively). These four regions of interest (ROIs) were defined as spheres with a radius of 4 mm. Functional correlations among these ROIs were computed and converted to z -values using Fisher's r -to- z transformation. The z -values among these ROIs were then averaged in each subject. In the 26 pairs of subjects in the discovery sample, we found that the mean connectivity among these default network ROIs showed a trend of decrease with increasing head motion ($r = -0.25$, $P = 0.08$). However, in the 26 test–retest subjects, the default network connectivity showed no intrasubject difference between the low-motion session and the high-motion session ($r = 0.05$, $P > 0.70$).

These above analyses all suggest that the default network is likely to play an important role in the neurobiological trait of motor restlessness.

Effect of Frame Removal on Distant Connectivity. Although scrubbing is a useful method to minimize the impact of motion-related artifacts, this operation will cause loss of data and may lead to a biased estimate of distant connectivity.

To reveal the potential negative effect of scrubbing, distant connectivity was computed based on the low-motion data both

before and after scrubbing. Data segments in the low-motion subjects of the discovery sample were scrubbed solely according to frames exceeding the motion threshold (0.06 mm) in the matched high-motion subjects. In these low-motion subjects, data length was significantly shortened by scrubbing, but the mean head motion remained unchanged (mean motion: 0.035 vs. 0.034 mm, $P > 0.30$). Scrubbing the data of 26 low-motion subjects of the discovery sample enhanced the distant connectivity measure in the primary visual and sensorimotor cortices, as well as in some posterior parietal areas (Fig. S4A). This inflation of distant coupling was replicated in the 26 low-motion sessions of the test–retest dataset (Fig. S4B).

To further understand the effect of data loss, we randomly removed frames from the 26 low-motion subjects of the discovery sample. The number of frames to be removed in each low-motion subject was again determined solely based on how many frames were removed in the matched high-motion subject (i.e., exceeded the threshold of 0.06 mm). Distant connectivity was computed before and after the random frame removal. Similarly, we found inflated distant connectivity in a set of brain regions, especially in the visual cortex and posterior parietal cortex (Fig. S4C).

However, we found this random frame removal had a stronger inflation effect than the motion-based scrubbing operation shown in Fig. S4A and B, especially in the posterior parietal cortex. The difference between these two methods is shown in Fig. S4D. Because the scrubbing operation in the low-motion subjects was based on what time points were removed in the high-motion subjects, the frames to be removed are usually continuous and not entirely independent. We speculated that the information loss might be more severe if the frames are randomly removed, leading to a stronger inflation effect as shown in Fig. S4D.

Influence of the Scrubbing Threshold. To test if our reported results are dependent on the scrubbing threshold, we performed the analyses without data scrubbing, and the main results could be well replicated (Fig. S5).

To further confirm that the results are not dependent on the scrubbing threshold, we reanalyzed the data with a motion cutoff of 0.07 mm on dataset 1 (56 pairs of subjects). With this slightly more lenient threshold, a subset of 20 pairs of subjects met the matching criteria and were selected for further analyses. These subjects were matched in head motion after scrubbing ($P = 0.17$) and had no less than 120 time points. Fig. S6 shows that distant connectivity (within the same mask as shown in Fig. 1A) predicts the intersubject difference in head motion ($r = -0.73$, $P < 0.001$), consistent with the results derived from the motion cutoff of 0.06 mm and the results without motion scrubbing.

Potential Influence of Anatomical Variability. Intersubject comparison is subject to the influence of anatomical variability whereas the intrasubject comparison is not. Here we performed several analyses to confirm that the effect of anatomic variability is limited and did not affect our results.

First, we compared the 26 high-motion subjects of the discovery sample with the 30 high-motion subjects of the replication sample. Because these subjects represent some random samples from a very large dataset, it is reasonable to assume that the level of anatomic variability between these two high-motion groups is comparable to that between the two groups involved in Fig. 1A (the 26 high-motion subjects and 26 low-motion subjects of the discovery sample). If our results in Fig. 1A were dominated by anatomical variability instead of the trait of motor restlessness,

then we would expect a similar distant connectivity difference between the 26 high-motion subjects and the 30 high-motion subjects. However, no significant difference was found between these two high-motion groups: no voxel reached the significance level of $P < 0.05$ (FDR-corrected, two-tailed, two-sample t test) either before or after the data scrubbing. In addition, we compared the 26 low-motion subjects of the discovery sample with the 30 low-motion subjects of the replication sample. Similarly, no significant difference in distant connectivity was found between these two low-motion groups. These results indicated that the anatomical variability alone could not explain the intersubject difference reported in Fig. 1A.

Second, we considered the possibility that the impact of anatomical variability on the intersubject comparison is not simply additive but is more severe when difference in motion is larger. We then performed two intersubject comparisons to explore this possibility. The first comparison was between the 26 high-motion (HM) subjects of the discovery sample and the low-motion sessions of the 26 test–retest subjects (test–retest low-motion session,

TRL); the second comparison was between the 26 low-motion (LM) subjects of the discovery sample and the low-motion sessions of the 26 test–retest sample (TRL). It is reasonable to assume that the anatomical variability between groups was at a similar level in these two comparisons. The main distinction between these two comparisons is that the two groups differ in motion in the first comparison, but not in the second comparison.

If the impact of anatomical variability on intersubject comparison is magnified by the group difference in head motion and such impact dominates our reported results, one would predict a strong intersubject difference in the first comparison (HM vs. TRL) where the two groups differed in motion, but not in the second comparison (LM vs. TRL) where the two groups had equal motion. However, our data suggest the opposite. No significant difference was found in the first comparison ($P = 0.23$) (Fig. 2). In the meantime, we found a significant difference in the second comparison ($P = 0.03$) (Fig. 2). These results suggest that the anatomical variability cannot account for the intersubject difference shown in Fig. 1A.

1. Yeo BTT, et al. (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 106(3):1125–1165.

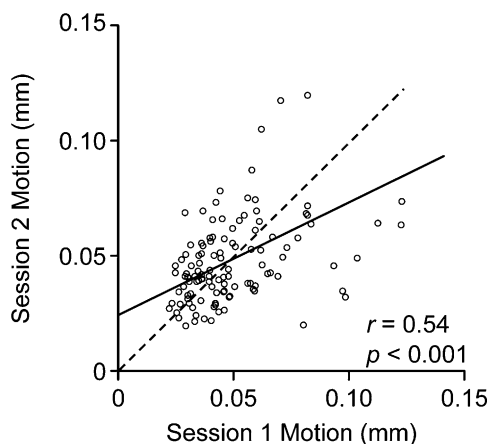


Fig. S1. Head motion is a relatively stable behavioral measure. Mean motion estimates are plotted for two scanning sessions conducted on separate days. Each data point represents a unique subject ($n = 118$). The solid line represents the best linear fit of the data, and the dashed line represents perfect equality of head motion in two sessions. The significant correlation between two sessions ($r = 0.54$, $P < 0.001$) indicates that head motion behaves like a subject-specific trait and may reflect specific neurobiological underpinning. Although most data points fall around the perfect equality line, a few subjects demonstrate inconsistent head motion between two sessions, providing an opportunity to differentiate the neurobiological signature related to head motion from the motion-related artifacts.

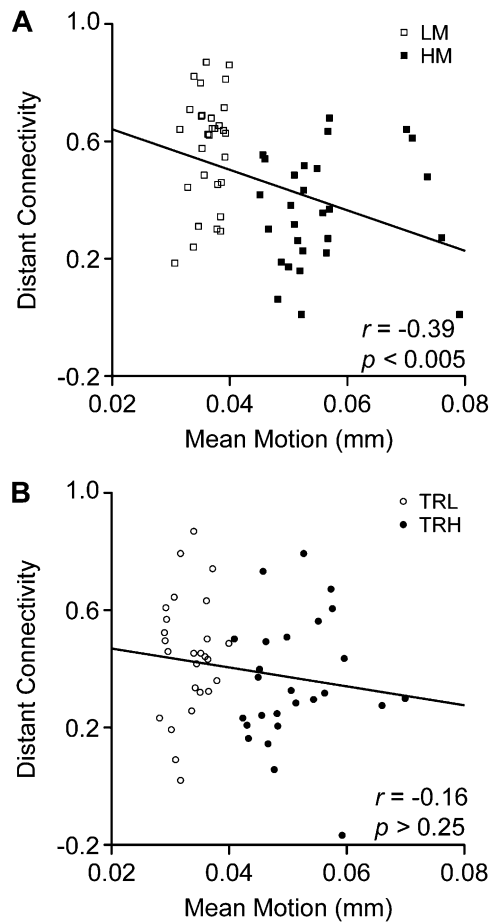


Fig. S2. The relation between distant connectivity and intersubject difference in head motion can be replicated in an independent dataset consisting of 30 pairs of demographically matched subjects. Distant connectivity averaged within the marker regions shown in Fig. 1A was strongly correlated with head motion in the replication dataset (A: $r = -0.39$, $P < 0.005$), but not in the 26 test-retest subjects with inconsistent level of head motion in two sessions (B: $r = -0.16$, $P > 0.25$). LM/HM, low-/high-motion individuals; TRL/TRH, low-/high-motion sessions in the test-retest sample.

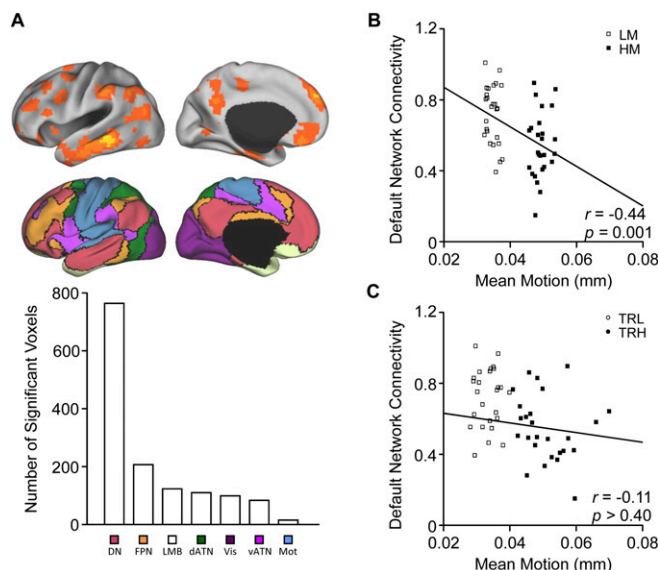


Fig. 53. The default network may play an important role in the trait related to head-motion control. (A) Voxels showing significantly stronger distant connectivity in low motion subjects than in high motion subjects (Top, as in Fig. 1A) were counted in seven functional networks. The seven networks were defined based on our prior parcellation of the cerebral cortex using a clustering approach (Middle) (1). The count of significant voxels within the mask of each network is shown in the bar plots. (B) Distant connectivity averaged within the mask of the default network (1) was strongly correlated with head motion in the discovery sample ($r = -0.44$, $P = 0.001$), but not in (C) the 26 test-retest subjects with inconsistent level of head motion in two sessions ($r = -0.11$, $P > 0.40$). LM/HM, low-/high-motion individuals; TRL/TRH, low-/high-motion sessions in the test-retest data.

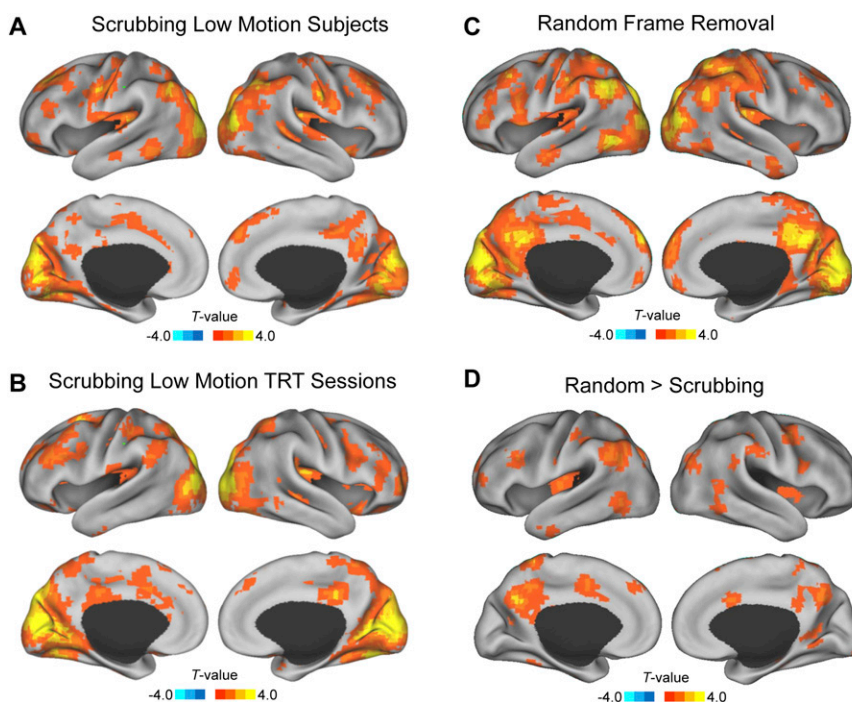


Fig. 54. Scrubbing could cause the loss of data and introduce spurious distant connectivity in specific brain regions. To reveal the potential negative effect of scrubbing, distant connectivity was computed based on the low-motion data both before and after scrubbing. Data segments in the low-motion subjects of the discovery sample were scrubbed solely according to frames exceeding the motion threshold (0.06 mm) in the matched high-motion subjects. In these low-motion subjects, data length was significantly shortened by scrubbing but the mean head motion remained unchanged (mean motion: 0.035 vs. 0.034 mm, $P > 0.30$). Scrubbing the data of 26 low-motion subjects of the discovery sample enhanced the distant connectivity measure in the primary visual and sensorimotor cortices, as well as in some association areas ($P < 0.05$, FDR-corrected, two-tailed paired t test) (A). This inflation of distant coupling was replicated in the 26 low-motion sessions of the test-retest dataset (B). Similar inflation effect can be found when frames were randomly removed (C). After random frame removal, the 26 low-motion subjects of the discovery sample showed enhanced distant connectivity in some occipital and parietal areas ($P < 0.05$, FDR-corrected, two-tailed paired t test). However, random frame removal showed a stronger inflation effect on distant connectivity than the scrubbing operation (D). Distant connectivity in some brain regions, especially in the posterior parietal region, was more inflated by random frame removal than by the scrubbing operation ($P < 0.05$, FDR-corrected, two-tailed paired t test).

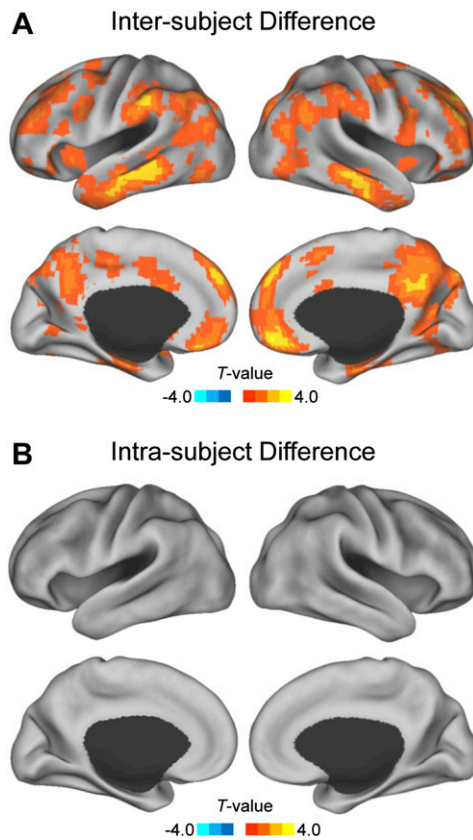


Fig. S5. The finding that distant functional connectivity is related to intersubject difference but not intrasubject variation in head motion can be replicated in the unscrubbed data. (A) In the discovery sample, distant connectivity computed based on the unscrubbed data were significantly stronger ($P < 0.05$, FDR-corrected, two-tailed two-sample t tests) in the 26 subjects with low motion than in the 26 matched subjects with high motion. (B) In the test-retest subjects, distance connectivity computed based on unscrubbed data did not show significant intrasubject difference between low, motion and high, motion sessions (no voxel reached the significance level of $P < 0.05$, FDR, corrected, two-tailed paired t tests), indicating that the motion-related artifacts may not account for the distant connectivity difference in A.

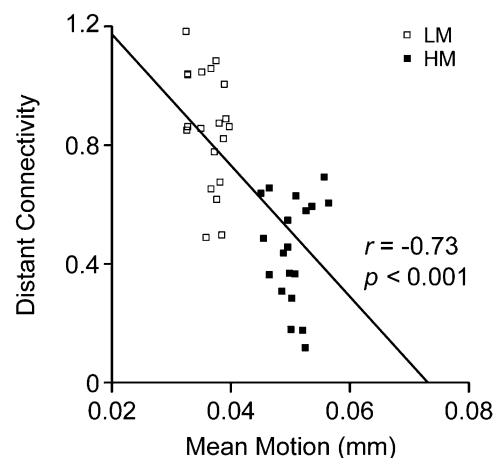


Fig. S6. The finding that distant functional connectivity is related to intersubject difference in head motion can be replicated in the scrubbed data of 20 pairs of well-matched subjects with motion cutoff of 0.07 mm. Distant connectivity averaged within the marker regions shown in Fig. 1A was strongly correlated with head motion in the data with a motion cutoff of 0.07 mm ($r = -0.73$, $P < 0.001$). LM/HM, low-/high-motion Individuals.

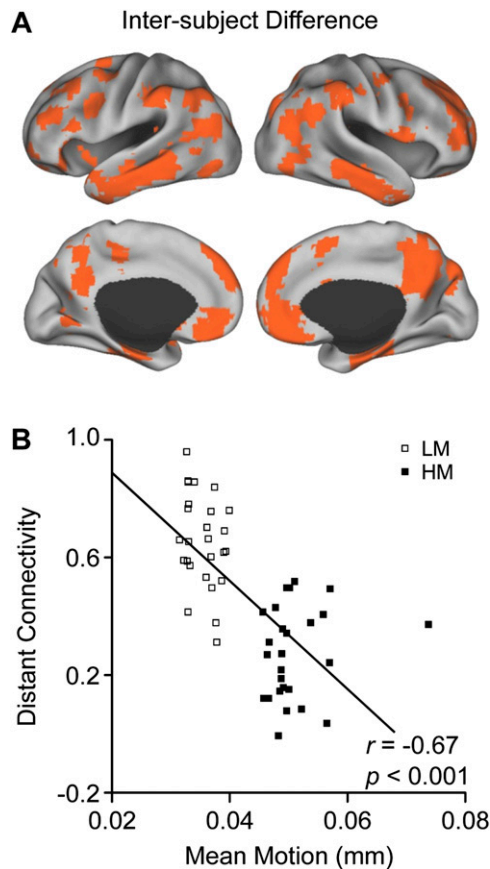


Fig. S7. Relation between distant connectivity and intersubject difference in head motion is unlikely due to the movement-induced blood oxygenation level-dependent (BOLD) responses. To minimize the impact of movement-induced BOLD responses, which could have a delay of ~ 10 s after the movement, a stringent motion scrubbing was performed. When head motion exceeded the threshold of 0.06 mm, two preceding frames (6 s) and five succeeding frames (15 s) were removed in addition to the noisy frames to ensure the delayed BOLD responses were eliminated from the data. (A) The brain regions showing stronger distant connectivity in low-motion subjects (same regions as in Fig. 1A) were taken as a mask. Distant connectivity was then computed based on the stringently scrubbed data and averaged within this mask. (B) Distant connectivity within the mask showed strong negative correlation with head motion even in the stringently scrubbed data ($r = -0.67$, $P < 0.001$), indicating that the movement-induced BOLD responses may not explain the intersubject difference in distant connectivity observed in Fig. 1A. Each square in the plot represents a unique individual in the 26 matched pairs of subjects who had no less than 80 time points after the stringent scrubbing. Among them, 14 pairs of subjects overlapped with the subjects shown in Fig. 1A. Motion values in x axis were the motion before scrubbing. LM/HM, low-/high-motion individuals.

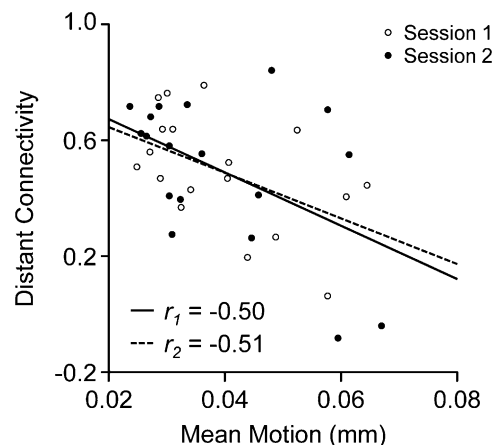


Fig. S8. In 18 test-retest subjects with a highly consistent level of head motion (< 0.01 mm between two sessions), distant connectivity was significantly correlated with the head motion in session 1 (solid line: $r_1 = -0.50$, $p_1 = 0.04$) and session 2 (dashed line: $r_2 = -0.51$, $p_2 = 0.03$). The correlation was not different between two sessions (ANCOVA, $P > 0.95$), indicating that distant connectivity can reliably predict head motion in these subjects.

Table S1. Subject demographics of the intersubject dataset (discovery sample) and the intrasubject dataset (test-retest sample)

Variable	Intersubject dataset		Intrasubject dataset	
	High-motion sample	Low-motion sample	High-motion session	Low-motion session
Sample size	26	26	26	26
Sex (female/male)	17/9	17/9	17/9	17/9
Handedness (left/right)	2/24	2/24	2/24	2/24
Age (y)	19.69 ± 1.81 (18~25)	19.92 ± 2.00 (18~25)	20.29 ± 2.31 (18~27)	20.29 ± 2.31 (18~27)
Education (y)	13.69 ± 1.44 (12~16)	13.77 ± 1.86 (12~18)	14.06 ± 1.88 (12~18)	14.06 ± 1.88 (12~18)
Prescrubbing motion (mm)	0.049 ± 0.002 (0.046 ~ 0.054)	0.035 ± 0.002 (0.032~0.038)	0.051 ± 0.008 (0.041~0.070)	0.033 ± 0.003 (0.028~0.040)
Postscrubbing motion (mm)	0.034 ± 0.002 (0.031~0.038)	0.034 ± 0.002 (0.029~0.038)	0.034 ± 0.004 (0.028~0.042)	0.034 ± 0.004 (0.028~0.040)