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. S3*A*). The voxels exhibiting significantly stronger distant connectivity in low-motion subjects than in high-motion subjects (Fig. S3*A*, *Top*, as in Fig. 1*A*, *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. S3*A*.

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. S3*B*, $r = -0.44$, $P = 0.001$), but not in the 26 test–retest subjects with an inconsistent level of head motion in two sessions (Fig. S3*C*, $r = -0.11$, $P > 0.40$). 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. S4*A*). This inflation of distant coupling was replicated in the 26 low-motion sessions of the test–retest dataset (Fig. S4*B*).

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. S4*C*).

However, we found this random frame removal had a stronger inflation effect than the motion-based scrubbing operation shown in Fig. S4 *A* and *B*, especially in the posterior parietal cortex. The difference between these two methods is shown in Fig. S4*D*. 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. S4*D*.

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. 1*A*) 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. 1*A* (the 26 high-motion subjects and 26 low-motion subjects of the discovery sample). If our results in Fig. 1*A* 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. 1*A*.

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. 1*A*.

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

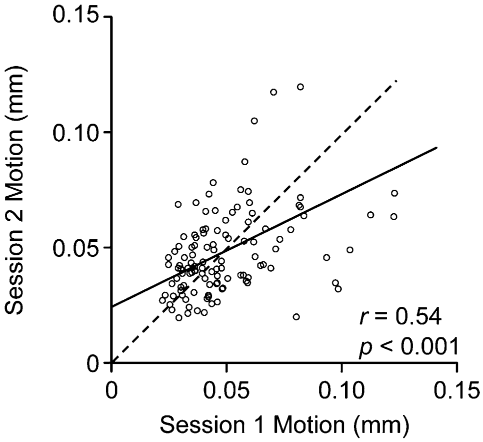

Fig. S1. Head motion is a relatively stable behavioral measure. Mean motion estimates are plotted for two scanning sessions conducted on separate days. Each data point represents a unique subject ($n = 118$). The solid line represents the best linear fit of the data, and the dashed line represents perfect 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.

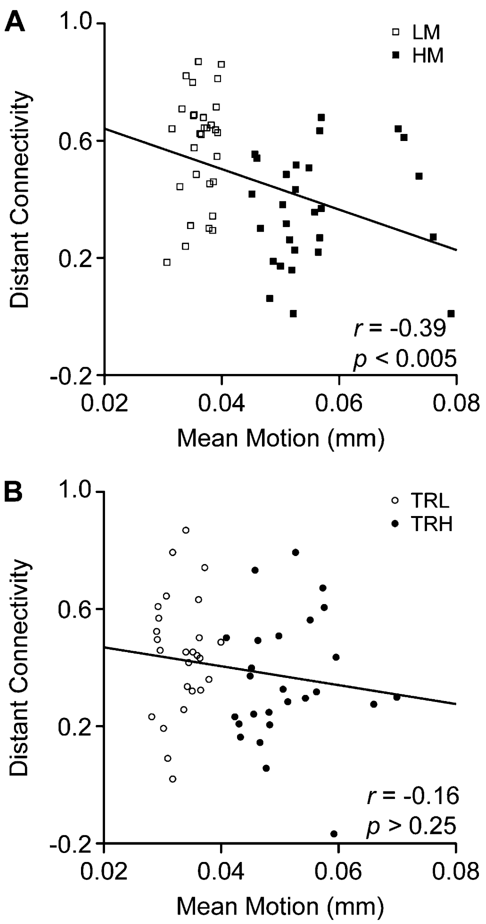

Fig. S2. The relation between distant connectivity and intersubject difference in head motion can be replicated in an independent dataset consisting of 30 pairs of demographically matched subjects. Distant connectivity averaged within the marker regions shown in Fig. 1*A* was strongly correlated with 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.

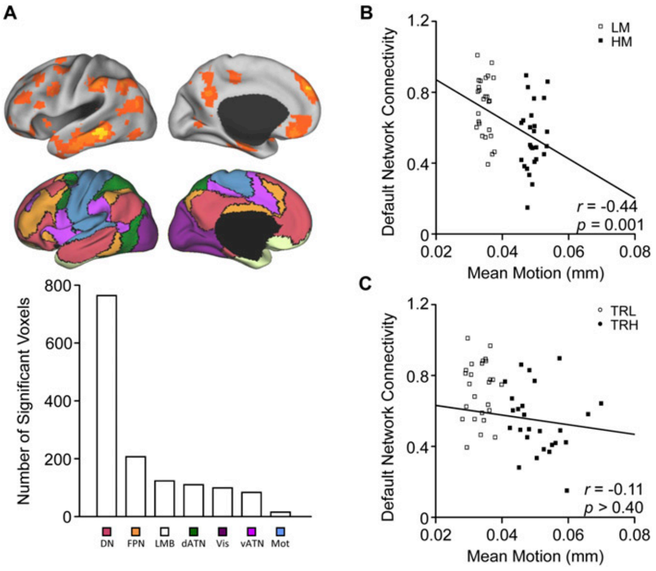

Fig. S3. The default network may play an important role in the trait related to head-motion control. (*A*) Voxels showing significantly stronger distant connectivity in low motion subjects than in high motion subjects (*Top*, as in Fig. 1*A*) were counted in seven functional networks. The seven networks 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.

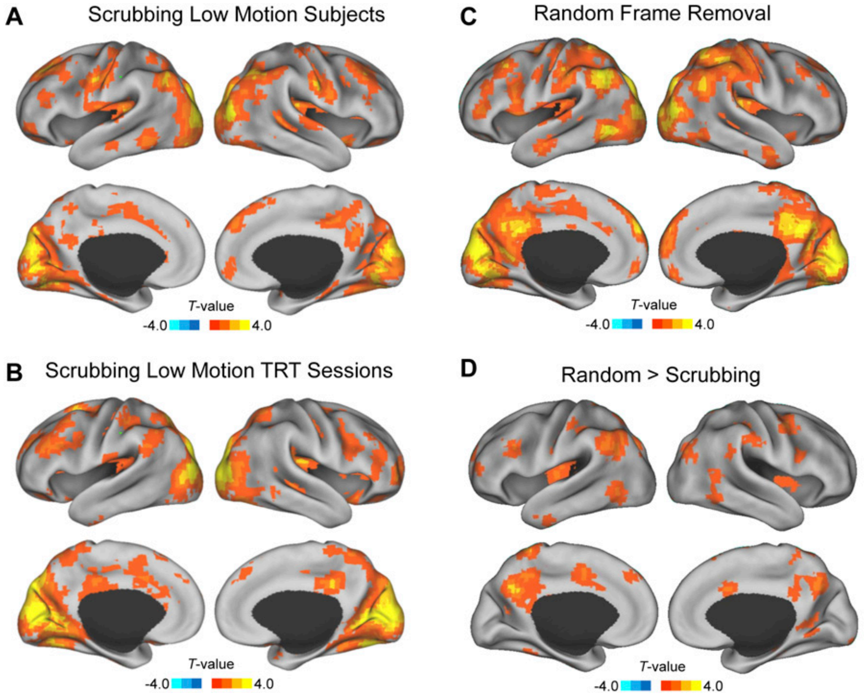

Fig. S4. Scrubbing could cause the loss of data and introduce spurious distant connectivity in specific brain regions. To reveal the potential negative effect of scrubbing, distant connectivity was computed based on the low-motion data both before and after scrubbing. Data segments in the low-motion 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).

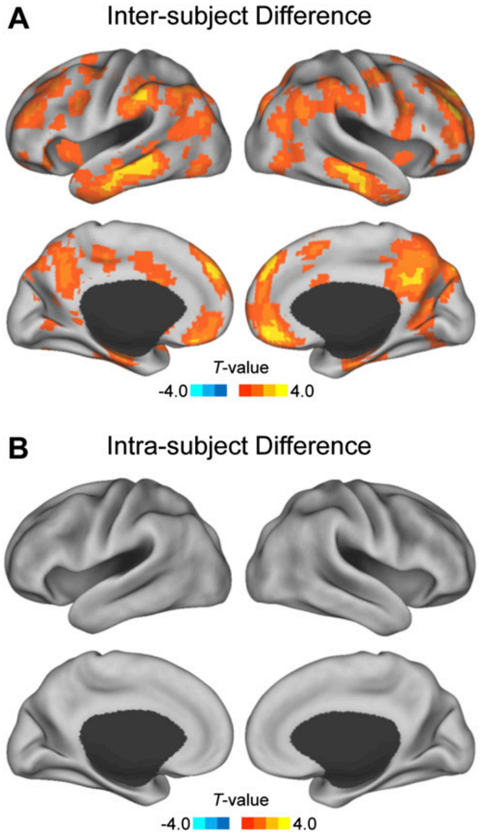

Fig. S5. The finding that distant functional connectivity is related to intersubject difference but not intrasubject variation in head motion can be replicated in the unscrubbed data. (*A*) In the discovery sample, distant connectivity computed based on the unscrubbed data were significantly stronger ($P < 0.05$, 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*.

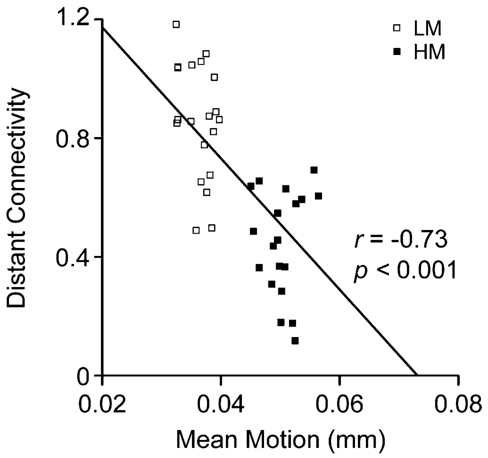

Fig. S6. The finding that distant functional connectivity is related to intersubject difference in head motion can be replicated in the scrubbed data of 20 pairs of well-matched subjects with motion cutoff of 0.07 mm. Distant connectivity averaged within the marker regions shown in Fig. 1*A* was strongly 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.

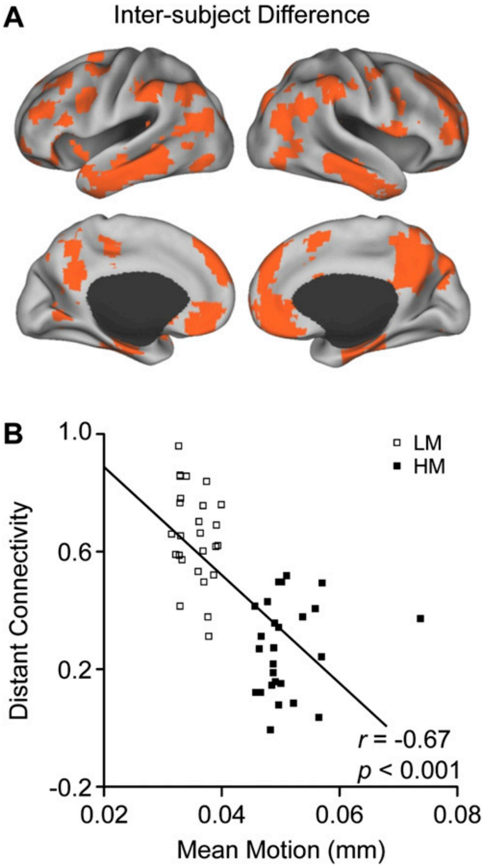

Fig. S7. Relation between distant connectivity and intersubject difference in head motion is unlikely due to the movement-induced blood oxygenation level-dependent (BOLD) responses. To minimize the impact of movement-induced BOLD responses, which could have a delay of ~10 s after the movement, a stringent 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. 1*A*) 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. 1*A*. 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. 1*A*. Motion values in *x* axis were the motion before scrubbing. LM/HM, low-/high-motion Individuals.

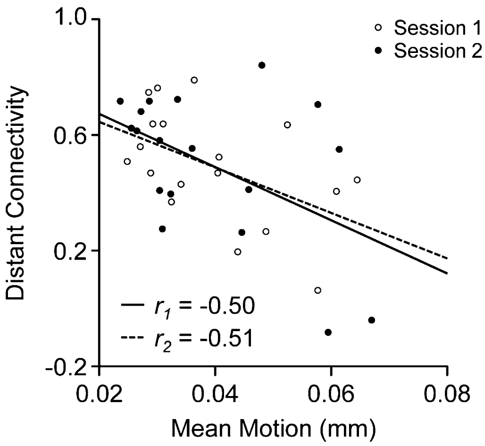

Fig. S8. In 18 test–retest subjects with a highly consistent level of head motion (<0.01 mm between two sessions), distant connectivity was significantly correlated with the head motion in session 1 (solid line: $r_1 = -0.50$, $p_1 = 0.04$) and session 2 (dashed line: $r_2 = -0.51$, $p_2 = 0.03$). The 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)

	Intersubject dataset		Intrasubject dataset	
Variable	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)