Original Article

Effect of green tea consumption on human brain function in resting-state functional MRI

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Background and Objectives: Green tea is reported to have wide benefits on psychological states and cognitive functions. Studies that focus on the underlying neural mechanisms of green tea are limited to its single composition while people usually benefit from green tea water that contains various composition. In this study, we examined the human brain activity changes after drinking natural green tea by using regional homogeneity and functional connectivity based on the resting-state functional MRI technique. **Methods and Study Design:** Fifteen healthy volunteers participated in two imaging sessions: a control (water) session and a green tea session, each session comprised a predrinking, drinking, and postdrinking section, during the drinking section, the subject consumed 200 mL of green tea infusion or water in 3 to 5 minutes. Then the post-tea and post-water imaging data were selected for regional homogeneity and functional connectivity analysis. **Results:** Our results revealed that, compared with the control group, the green tea group exhibited an increased regional homogeneity in the frontal, parietal, and occipital areas of the brain, decreased regional homogeneity values in the left cuneus and left lingual gyrus, mainly a decreased functional connectivity in the default mode network, somatosensory, visual cortex, and parieto-frontal areas and enhanced functional connectivity in brain regions associated with memory. **Conclusions:** This result indicates that green tea consumption impacts the brain activity during resting state.

Key Words: green tea, resting-state functional MRI, functional connectivity, brain function, default mode network

INTRODUCTION

Green tea is being recognized as one of the most popular beverages in the world with great potential benefits on human health.[1] The dietary components of tea demonstrate positive impacts on several chronic diseases by reducing blood cholesterol levels and preventing cardiovascular diseases and cancer.[2,3] Furthermore, a number of studies have reported that the intake of green tea or its main ingredients such as theanine, epigallocatechin gallate (EGCG) and caffeine also have various psychological and cognitive benefits to human beings.[4,5] A systematic review of observational studies that examined the association between green tea intake and dementia, Alzheimer's disease, mild cognitive impairment, or cognitive impairment, included three cohort studies and five cross-sectional studies,[6] and showed that two cohort study and four cross-sectional studies supported the positive effects of green tea intake,[7-12] one cohort study and one cross-sectional study showed no significant association of green tea intake.[13,14]

Studies using L-theanine at typical serving doses of tea (20 mg) or higher doses have reported that tea consumption promotes relaxation by stimulating the alpha brainwave activity that is normally associated with a wakeful relaxation state.[15,16] However, two other studies measuring electroencephalogram (EEG) after L-theanine consumption demonstrated that L-theanine may increase attention and plays a positive role in learning and concentration, but not relaxation.[17,18] It has been demonstrated that green tea has a beneficial role in cognitive functions, specifically in alertness, attention, and memory retention.[19,20] A higher consumption of green tea was not only significantly related to reduced cognitive impairments both in Alzheimer transgenic mice and older adults but also led to higher cognitive performances in healthy subjects.[12,21-23]

Recent research indicated that the beneficial impact of green tea on cognition is related to altered brain activity or connections.[5,24] Neuroimaging techniques have been

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used to examine the neural mechanisms of green tea extract on brain activation in 12 healthy males.[5] Increased brain activation has been demonstrated in the dorsolateral prefrontal cortex (DLPFC) after the administration of green tea extracts during a working memory processing task.[5] It has been proven that green tea intake is helpful in terms of cognitive functioning through modification of brain connections.[24] In this study, 12 healthy males drank either 250 or 500 mL milk whey-based soft drink containing 13.75 and 27.5 g of green tea extract, and the result showed that green tea extract increased the working memory and induced the modulation of the parieto-frontal connectivity.[24]

It has been suggested that spontaneous brain activity can yield essential information regarding the cognitive ability and function.[25] Resting-state functional MRI (fMRI) is a noninvasive imaging method that reflects the spontaneous brain activity and can be used to investigate functional changes in the brain. In the present study, we hypothesized that green tea consumption would change the spontaneous brain activity and examined thechanges by using the resting-state fMRI method and applying the regional homogeneity (ReHo) and functional connectivity (FC) analysis methods.

METHODS

Subjects

All subjects signed informed consent forms before participating in the study. The study protocol was in accordance with the guidelines issued in the Declaration of Helsinki. Fifteen healthy volunteers (aged 18–25 years, including nine men and six women) participated in this study. All subjects were instructed to refrain from ingesting tea for at least 12 hours prior to being scanned. Six subjects with head movements exceeding 2 mm (rotation or translation) were excluded, and nine subjects were retained for further analysis.

Tea preparation

Tea (Lipton), purchased from a local store, was prepared by pouring 200 mL of freshly boiled water onto a tea bag in a cup. Each tea bag was soaked for 2 minutes before its removal. The cup of tea was then placed in the scanning room and connected to the subject through a straw.

Experimental protocol

All subjects participated in two imaging sessions as follows: a control (water) session and a green tea session that lasted for 480 scans; the interval between each session was 1 week. Each session comprised a predrinking, drinking, and postdrinking imaging section; finally, two groups of data were selected for subsequent analysis, namely post-tea and post-water. During the drinking section, the subject consumed 200 mL of green tea infusion or water in 3 to 5 minutes. The predrinking and postdrinking sections were investigated as resting states, and subjects were instructed to lie still in the scanner but to not fall asleep.

Image acquisition

All imaging procedures were conducted at the Shanghai Key Laboratory of Magnetic Resonance (East China Normal University, Shanghai, China) on a Siemens 3.0 T Trio Tim MR system (Siemens, Erlangen, Germany). The functional images that contained 480 time points were obtained using an echo-planar image (EPI) pulse sequence sensitive to blood oxygen level-dependent (BOLD) contrast, 40 axial slices with a thickness of 3.5 mm, a repetition time (TR) of 5000 ms, an echo time (TE) of 35 ms, a flip angle of 90°, a matrix size of 128 × 128, a field of view of 220 × 220 mm2, and a voxel size of 3.4 × 3.4 × 3 mm^3.

Data preprocessing

The functional images were preprocessed using the toolboxes of the Data Processing Assistant for resting-state fMRI (DPARSF version 4.1, http://www.restfmri.net/forum/DPARSF), Statistical Parametric Mapping (SPM version 12, http://www.fil.ion.ucl.ac.uk/spm/), and Resting-state fMRI Data Analysis Toolkit (REST version 1.8, http://www.restfmri.net/forum/REST_V1.8) by Matlab version 7.10.0.499 (R2010a).

The first 10 volumes of the functional images were abandoned. Two sections (Pre: 70 time points before drinking, Post: 120 time points after drinking) were selected from the remaining 470 time points for slice timing correction, head-motion correction, realignment, spatial normalization (using the EPI templates resampled to 3 × 3 × 3 mm3 voxels in Montreal Neurological Institute [MNI] stereotaxic space), spatial smoothing (using a Gaussian filter of 4 mm full width at half maximum, FWHM), time course detrending, nuisance covariates regression, and band-pass filtering (0.01-0.08 Hz). All subjects with head movements exceeding 2 mm, regardless of the movement being rotation or translation, were excluded from our further analysis. A whole-brain mask provided by DPARSF was selected as the target region of the brain during data preprocessing.

Regional homogeneity

ReHo analysis, calculating Kendall's coefficient of concordance, was performed for each subject by using the DPARSF software package to measure the similarity of the time series of one voxel to its neighbor voxel within the whole-brain mask. Subsequently, smoothing with 4 × 4 × 4 mm3 voxels was performed for all images.

Functional connectivity

FC analysis, which depends on the BOLD contrast mechanism, was performed using the software DPARSF package. Regions of interest (ROIs) used as the seeds for FC analysis were constructed by creating a sphere (6 mm in radius) around the peak load-related activation coordinates obtained from areas with significant ReHo differences between the post-tea group and the post-water group with a family-wise error (FWE) corrected of $p<0.05$. Seeds with spheres around the coordinates were created using the REST toolbox.

Statistical analysis

All statistical analyses were performed using a paired t test (SPM version 12). To detect the ReHo and FC differences among the four groups, each ReHo result and FC result was used for the second-level group statistics ob-

tained through the paired t test. These results were reported as significant when they survived at an uncorrected height threshold of p=0.001 together with a FWE-corrected extent threshold of p=0.01 (ReHo) and p=0.05 (FC) at the cluster level.

RESULTS

Regional homogeneity

Compared with the post-water group, the post-tea group revealed significantly increased ReHo values in the right inferior frontal gyrus (IFG.R), right and left middle frontal gyrus, right medial frontal gyrus (MFG.R), left inferior parietal lobule (IPL.L), right supramarginal gyrus, right angular gyrus, right and left precentral gyrus, right and left postcentral gyrus (PCG.L), left middle occipital gyrus (MOG.L), left fusiform gyrus, left cuneus, right and left superior temporal gyrus, and thalamus (Figure 1). The surviving clusters were assigned thresholds at a level of p<0.001 and FWE-corrected to p<0.01 at the cluster level. By contrast, only the left cuneus and left lingual gyrus exhibited decreased ReHo values (p<0.001 uncorrected).

Functional connectivity

Five ROIs (Figure 2) were obtained from the ReHo results to investigate the connectivity (seed-to-voxel) between each ROI and the remaining voxels in the brain within each subject by using a voxel-wise method.

The group differences in FC between the post-tea and post-water group are depicted in Table 1. For the IFG.R seed, only decreased FC in the post-tea group was found compared with the post-water group, include significantly decreased FC in the right middle frontal gyrus, right inferior parietal lobule, and right middle temporal gyrus compared with the post-water group.

Both enhanced and decreased FC values were found in the post-tea group compared with the post-water group for the MFG.R, IPL.L, PCG.L, and MOG.L seeds. Compared with the post-water group, the MFG.R in the post-tea group revealed significantly enhanced FC in the right superior frontal gyrus, bilateral precentral gyrus, bilateral cuneus, right middle occipital gyrus, right parahippocampa gyrus, and right cerebellum posterior lobe and decreased FC in the left middle frontal gyrus, bilateral inferior parietal lobule, and right precuneus.

In the post-tea group, the IPL.L displayed enhanced FC in the right supramarginal gyrus and right inferior parietal lobule and decreased FC in the left inferior frontal gyrus, left middle temporal gyrus, and right precuneus compared with the post-water group.

The PCG.L in the post-tea group revealed significantly enhanced FC over the post-water group in the right middle frontal gyrus and right inferior parietal lobule but significantly decreased FC in the left precentral gyrus, bilateral postcentral gyrus, left inferior temporal gyrus, left

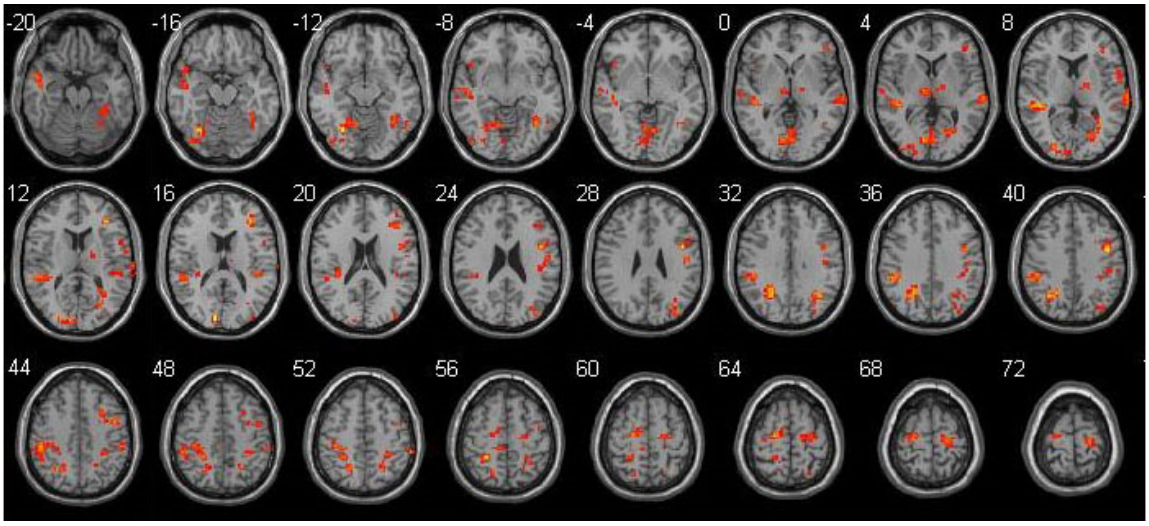

Figure 1. Significantly increased ReHo in the post-tea group compared with the post-water group. The surviving clusters were assigned with thresholds at a level of p < 0.001 and family-wise error (FWE) corrected to p<0.01 at the cluster level.

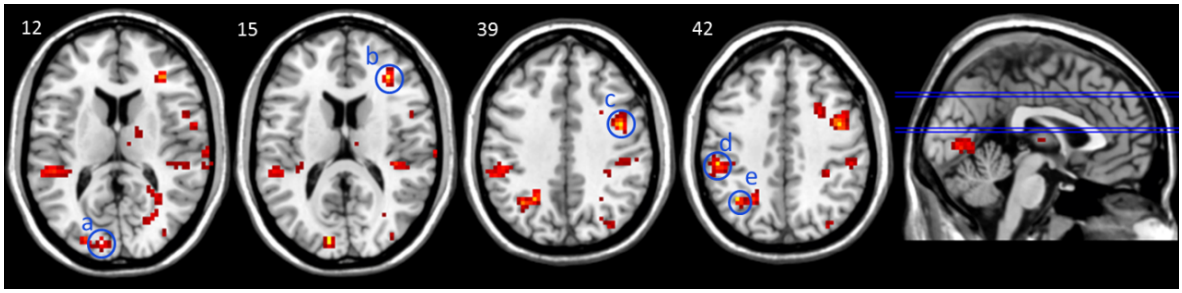

Figure 2. Five peak value coordinates that survived from the ReHo analysis with a family-wise error (FWE) corrected to p<0.05 were used as the center to create the seeds of the functional connectivity. a: left middle occipital gyrus (MOG.L; X, Y, and Z=-12, -90, and 12 mm), b: right inferior frontal gyrus (IFG.R; X, Y, and Z=33, 36, and 15 mm), c: right middle frontal gyrus (MFG.R; X, Y, and Z=42, 0, and 39 mm), d: left postcentral gyrus (PCG.L; X, Y, and Z=-51, -30, and 42 mm), e: left inferior parietal lobule (IPL.L; X ,Y, and Z=-36, -57, and 42 mm).

Table 1. Significant intergroup differences in functional connectivity between the post-tea and post-water groups

ROI	Predominant regions in cluster	Cluster size	PeakT value	MNI coordinates		
				x	y	z
Post-tea >Post-water						
MFG.R						
	Right superior frontal gyrus	21	8.12	18	57	33
	Right precentral gyrus	18	8.55	36	-9	36
	Left precentral gyrus	33	9.89	-36	-12	33
	Right cuneus	129	8.78	21	-81	12
	Left cuneus	25	6.73	-9	-105	12
	Right middle occipital gyrus	15	8.56	21	-99	12
	Right parahippocampa gyrus	17	4.61	24	-54	0
	Right cerebellum posterior lobe	42	8.51	27	-72	-21
IPL.L						
	Right supramarginal gyrus	30	17.0	36	-48	30
	Right inferior parietal lobule	24	7.1	66	-42	36
PoCG.L						
	Right middle frontal gyrus	18	8.69	33	18	33
	Right middle frontal gyrus	21	6.54	36	6	63
	Right inferior parietal lobule	21	7.77	63	-51	42
MOG.L						
	Right precuneus	38	3.57	21	-69	36
Post-tea < Post-water						
IFG.R						
	Right middle frontal gyrus	22	12.5	54	30	33
	Right inferior parietal lobule	50	10.5	51	-45	54
MFG.R						
	Right middle temporal gyrus	15	8.56	51	-51	-12
	Left middle frontal gyrus	26	7.56	-27	3	51
	Right inferior parietal lobule	64	9.87	36	-51	42
	Left inferior parietal lobule	49	11.3	-33	-57	39
	Left inferior parietal lobule	17	9.56	-60	-39	45
	Right precuneus	59	7.48	36	-78	42
	Right precuneus	29	7.71	12	-69	51
IPL.L						
	Left inferior frontal gyrus	47	12.0	-36	27	12
	Left middle temporal gyrus	25	11.8	-54	-42	-15
	Right precuneus	33	8.32	36	-78	45
PoCG.L						
	Left precentral gyrus	48	8	-33	-21	66
	Right postcentral gyrus	32	10.8	33	-27	45
	Left postcentral gyrus	28	11.2	-42	-24	63
	Left postcentral gyrus	24	9.25	-51	-30	39
	Left postcentral gyrus	23	8.29	-39	-30	45
	Left inferior temporal gyrus	29	8.47	-48	-69	-6
	Left precuneus	25	7.67	-21	-51	51
	Right cuneus	33	8.06	15	-87	24
	Left insula	22	7.33	-39	-18	6
MOG.L						
	Left middle occipital gyrus	49	9.6	-45	-84	12
	Left middle occipital gyrus	41	8.55	-15	-93	12
	Right middle temporal gyrus	26	6.69	39	-69	12
	Right cuneus	16	8.12	21	-75	6
	Left cuneus	20	6.94	-6	-93	12
	Left fusiform gyrus	22	7.56	-21	-57	-12

IFG.R: right inferior frontal gyrus; MFG.R: right middle frontal gyrus; IPL.L: left inferior parietal lobule; PCG.L: left postcentral gyrus; MOG.L: left middle occipital gyrus.
The significance threshold was set at the whole-brain level as $p<0.001$ and FWE cluster-corrected as $p<0.05$.

precuneus, right cuneus, and left insula.

In addition, the MOG.L in the post-tea group exhibited significantly enhanced FC over the post-water group in the right precuneus but significantly decreased FC in the left middle occipital gyrus, right middle temporal gyrus, bilateral cuneus, and left fusiform gyrus.

Functional connectivity in default mode network

The FC between the three ROIs and the corresponding linked brain areas located in the default network was extracted from the FC analysis results. The materials of the FC in default mode network (DMN) are displayed in Table 2 and were mapped onto the cortical surfaces, as illustrated in Figure 3, by using the BrainNet Viewer software package.

Table 2. The intergroup differences in functional connectivity in the default mode network between the post-tea and post-water group were extracted from Table 1

ROI	Predominant regions in cluster	Cluster size	PeakT value	MNI coordinates		
				x	y	z
Post-tea > Post-water						
MFG.R						
	SFG.R	21	8.12	18	57	33
	PHG.R	17	4.61	24	-54	0
IPL.L						
	SMG.R	30	17.0	36	-48	30
	IPL.R	24	7.1	66	-42	36
Post-tea < Post-water						
IFG.R						
	MFG.R	22	12.5	54	30	33
	IPL.R	50	10.5	51	-45	54
	MTG.R	15	8.56	51	-51	-12
MFG.R						
	MFG.L	26	7.56	-27	3	51
	IPL.R	64	9.87	36	-51	42
	IPL.L	49	11.3	-33	-57	39
	IPL.L	17	9.56	-60	-39	45
	PCUN.R	59	7.48	36	-78	42
	PCUN.R	29	7.71	12	-69	51
IPL.L						
	IFG.L	47	12.0	-36	27	12
	MTG.L	25	11.8	-54	-42	-15
	PCUN.R	33	8.32	36	-78	45

IFG.R\L: right\ left inferior frontal gyrus; IPL.R\L: right\left inferior parietal lobule; MFG.R\L: right\left middle frontal gyrus; MOG.L: left middle occipital gyrus; MTG.R\L: right\left middle temporal gyrus; PHG.R: right parahippocampa grus; SFG.R: right superior frontal gyrus; SMG.R: right supramarginal gyrus; PCUN.R: right precuneus;

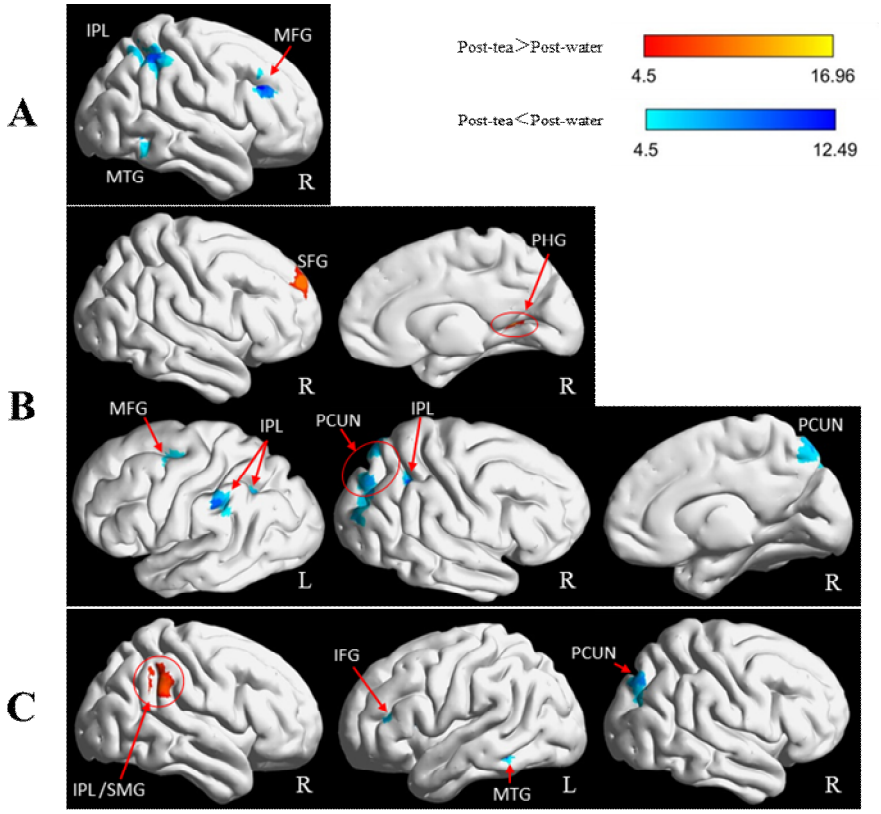

Figure 3. Map of the functional connectivity changes in the default mode network between the post-tea and post-water group using the BrainNet Viewer software package (http://www.nitrc.org/projects/bnv). A: right inferior frontal gyrus as the seed region. B: right middle frontal gyrus as the seed region. C: left inferior parietal lobule as the seed region. IPL: inferior parietal lobule; MFG: middle frontal gyrus; MTG: middle temporal gyrus; SFG: superior frontal gyrus; PHG: parahippocampa gyrus; PCUN: precuneus; SMG: supramarginal gyrus; IFG: inferior frontal gyrus.

DISCUSSION

The effects of green tea consumption on the neural activity was investigated in this study by using resting-state fMRI. The differences in ReHo and FC between the green tea consumption and control groups were explored.

ReHo detects the temporal similarity between one voxel and its nearest neighbors within a functional cluster, whereas a decrease or increase in ReHo indicates that the functional activity in certain regions is poorly or highly synchronized, respectively, compared with the controls. Our study revealed that ReHo was obviously enhanced by green tea consumption in brain areas, these enhanced areas are associated with improved working memory, learning, attention and alertness as previous research reported. It has been reported that green tea extract can modulate the brain activity in the DLPFC and heighten parieto-frontal connectivity, correlating with an improvement in task performance during working memory tasks.[5,24] Theanine, one of the main components of green tea, has been reported to increase the alpha brain-wave activity in the occipital, parietal, and frontal areas.[12] 300 mg Epigallocatechin gallate administration in 31 volunteers was associated with a significant overall increase in the alpha, beta, and theta activity in the frontal and medial frontal gyrus,[26] and 100 mg caffeine was reported to modulate the activation in the left thalamus during working memory maintenance, indicating an effect on arousal.[27] The alpha brain-wave activity in humans is indicative of wakeful relaxation and improved learning and concentration. In another study, the highly significant increase in theta waves after the consumption of green tea was regarded as evidence of its putative role in alertness and attention.[19] Similarly, in this study, the enhanced ReHo could be regarded as suggestive of the putative beneficial effects of green tea consumption on the brain function. Left cuneus and left lingual gyrus, the two brain areas with decreased ReHo, are part of the visual system. This may indicate that green tea consumption reduced subject's environment monitoring whilst increasing their concentration levels.[19]

FC reveals the temporal correlation of the neuronal activity between spatially independent brain areas.[28] In our study, the FC results in the post-tea group can be summarized by three points. First, our results mainly revealed decreased FC among regions located in the DMN, and a minority appeared to be enhanced as illustrated in Figure 1. The DMN performs two possible functions: monitoring the external environment when the focused attention is relaxed;[29,30] and supporting the internal mentation that is largely detached from the external world.[19] Therefore, the decreased FC in the DMN might indicate a decrease in the aforementioned two functions. On the contrary, the connectivity between the middle frontal gyrus and parahippocampal gyrus was enhanced. This may be correlated to the enhanced effect of green tea on the working memory. Second, the decrease in FC results in the postcentral gyrus and middle occipital gyrus was mainly located in the somatosensory cortex and visual cortex, such as the postcentral gyrus, cuneus, precuneus, middle occipital gyrus and temporal lobe, and insula, which implies self-awareness. In addition, a positive decrease in connectivity was observed between the temporal lobe and most of the ROIs except for the middle frontal gyrus. In conclusion, the two aforementioned points are an indication that green tea weakens the internal mentation and a broad low-level focus of attention on the external environment. This is in agreement with the previous research according to which green tea plays a positive role in learning and concentration.[19,31]

Finally, the connectivity between the prefrontal lobe and inferior parietal lobule decreased during the resting state. This finding is not in agreement with previous research that reported that green tea extract enhanced the parieto-frontal connectivity, which was positively correlated with the improvement in working memory task performance.[24] Currently, we have no explanation for this discrepancy; we can only speculate that this might due to a different task state.

There are limitations to this study, such as the fact that the effect of green tea consumption on vascular mechanisms that give rise to resting-state BOLD connectivity has not been detected, because numerous pharmacological agents are likely to affect the BOLD connectivity through neurovascular coupling. Although we aimed to examine the effect of natural green tea, brewing green tea in boiling water has an effect on EGCG content and antioxidant potential, this would influence the comparison between the results of this paper and other studies. There are only 9 individuals in the current study, this small number may have an effect on the results, more subjects will be necessary in future studies. Finally, the exact composition of green tea in the water was not tested.

Conclusion

This work demonstrated that green tea consumption changes the regional homogeneity and FC during resting state. In particular, FC in the DMN, somatosensory, and visual cortex was mainly reduced by green tea consumption. Combined with previous research, these results indicate that green tea consumption may influence the cognitive function by changing the neural activity.

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AUTHOR DISCLOSURES

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