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Original Article

Altered default-mode network functional connectivity in college students with mobile phone addiction

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Abstract: Objective: The present study aimed to determine whether Default-Mode Network (DMN) connectivity at resting-state is altered in college students with mobile phone addiction (MPA) by functional magnetic resonance imaging (fMRI). Methods: The fMRI data were acquired during resting state from 24 college students with MPA and 16 age- and gender-matched normal control college students. Synchronized low-frequency fMRI signal fluctuations were monitored to determine posterior cingulate cortex (PCC) connectivity in all subjects. In order to assess the relationship between MPA behavioral features and alteration in functional connectivity, the z value of areas that exhibited abnormal PCC connectivity in 24 subjects with MPA were correlated with the scores of the Self-Rating Anxiety Scale (SAS), Self-rating Depression Scale (SDS), Barratt Impulsiveness Scale-11 (BIS-11), Rosenberg Self-esteem Scale, Pittsburgh sleep quality index (PSQI), Sensation Seeking (SS), Smartphone Addiction Inventory (SPAI) and Mobile Phone Addiction Index (MPAI). Results: Compared with the control group, functional connectivity in the anterior cingulate, bilateral middle frontal gyrus, bilateral inferior frontal gyrus, right middle temporal gyrus, and right inferior temporal gyrus increased in subjects with MPA. Subjects with MPA revealed higher SAS ($P = 0.0293$), SDS ($P = 0.0056$), BIS-11 ($P<0.0001$), PSQI ($P = 0.001$), SPAI ($P<0.0001$) and MPAI ($P<0.0001$) scores and lower RSS ($P = 0.0002$) scores, compared to controls. No significant correlations were found between altered functional connectivity and MPA behavioral features. Conclusion: College students with MPA present different behavioral features and DMN functional connectivity, especially in cerebral regions related to cognitive control.

Keywords: Mobile phone addiction, behavioral addiction, fmri, functional connectivity, default-mode network

Introduction

In the past decade, mobile phone use has dramatically progressed [1-3]. A growing number of studies have accumulated suggesting that excessive mobile phone use can induce a number of negative physiological and psychosocial consequences, such as low self-esteem [4], anxiety [5], loneliness, depression [2], impulsivity [6], poor sleep quality and quantity [7]. A survey of smartphone addiction completed by the National Information Society Agency in 2012 revealed that, the percentage of smartphone addiction was 8.4%, while the internet addiction of 7.7% [8]. Chóliz, et al thought MPA should be included in the DSM-V [9].

Mobile phone addiction (MPA) can be considered a behavioral addiction needing further investigating [10-12]. Some potential factors that may be related to MPA have been identified in previous studies, however, the underlying neural mechanisms are unclear and no research has been performed that related to possible brain functional connectivity alterations in MPA.

In the present study, the resting-state functional magnetic resonance imaging (fMRI) was used to investigate DMN connectivity in college students with MPA to 1) determine whether there are any different behavioral and personality features between college students with MPA and controls, 2) investigate altered resting-state FC of the DMN, and 3) examine whether there are any associations of altered FC with behavioral and personality measures in subjects with MPA.

The default mode network (DMN) is a group of brain regions that exhibit robust low frequency oscillations coherence during resting-state and are typically deactivated during the process of cognitive tasks [13]. The cingulate cortex, hippocampus, medial prefrontal and inferior parietal cortices and other brain regions have been identified as parts of the DMN [14]. Some studies have revealed that functional connectivity (FC) of DMN was altered in heroin users [15], cocaine addiction [16], cigarette smokers [17] and internet game addiction [18]. We hypothesiz that the brain fMRI at resting state in subjects with mobile phone addiction would show connective abnormalities of DMN, especially in those involved functional cerebral regions in previous studies on addiction disorders [15-18].

Materials and methods

Subjects

The enrollment of the present study was comprised of 24 subjects with MPA and 16 age- and gender-matched healthy individuals at the interns of our hospital. They are college students from Hennan Medical College. Their age ranged between 20-26 years old. MPA that mainly characterized by excessive use of mobile phones and unable to control themselves, resulting in impaired mental, physical and social functions, affecting normal work, study and life, was diagnosed according to the criteria modified from the Diagnostic Questionnaire for Internet Addiction [19]. All subjects were right-handed, and none of them were smoked.

This study was approved by the Ethics Committee of our hospital. These participants were informed of the purposes of this study before magnetic resonance imaging (MRI) were performed. All subjects provided a full and written informed consent.

Inclusion and exclusion criteria

After undergoing a simple physical examination including blood pressure and heart rate measurements, and all participants were interviewed by a psychiatrist regarding their medical history of nervous, motor, digestive, respiratory, circulation, endocrine, urinary, and reproductive problems. Then, a screening of psychiatric disorders was performed on these subjects with the Mini International Neuropsychiatric Interview (MINI) version 5.0.0 [20]. Exclusion criteria included history of substance abuse or dependence, previous hospitalization for psychiatric disorders, or a history of major psychiatric disorders such as schizophrenia, depression, anxiety disorder and psychotic episodes. Subjects with MPA were not treated with psychotherapy or any medication.

The diagnostic questionnaire for MPA was adapted from Young's criteria for internet addiction [19]. The diagnostic questionnaire used for this study comprised of eight "yes" or "no" questions that were translated into the Chinese language. The questionnaire included the following questions: (1) Do you feel preoccupied with your mobile phone (think about the subject's previous mobile phone activity or anticipate next the mobile phone session)? (2) Do you feel the need to use your mobile phone with increasing amounts of time to achieve satisfaction? (3) Have you repeatedly made unsuccessful efforts to control, cut back, or stop mobile phone use? (4) Do you feel restless, moody, depressed, or irritable when attempting to cut down or stop mobile phone use? (5) Do you use your mobile phone longer than the time you originally planned? (6) Have you jeopardized or risked the loss of a significant relationship, job, educational, or career opportunity due to mobile phone use? (7) Have you lied to family members, therapists, or others people to conceal the extent of involvement with your mobile phone? (8) Do you use the mobile phone as a way of escaping from problems, or relieving a dysphoric mood (e.g. feelings of helplessness, guilt, anxiety, or depression)? In Young's criterion, subjects that asserted five or more "yes" responses to the eight questions were considered a dependent user. In the present study, this criterion was used to classify the state of the respondents: subjects who answered five or more "yes" and had related symptoms in eight questions that continued for over a year were classified as suffering from MPA, and respondents who had no "yes" answers were classified as controls.

Behavioral and personality assessments

The demographic information such as gender, age, and hours of mobile phone use per day, were acquired using a basic information ques-

tionnaire. Eight questionnaires were used to assess the participants' behavioral and personality features, namely, the Self-Rating Anxiety Scale (SAS) [21], Self-rating Depression Scale (SDS) [22], Barratt Impulsiveness Scale-11 (BIS-11) [23], Rosenberg Self-esteem Scale (RSS) [24], Pittsburgh sleep quality index, PSQI [25], Sensation Seeking (SS), Smartphone Addiction Inventory (SPAI) [26], and Mobile Phone Addiction Index (MPAI). All questionnaires were initially developed in the English language and subsequently translated into the Chinese language.

MRI acquisition

A 3.0T MRI scanner (Discovery 750, GE Healthcare, Milwaukee, USA) was used for MRI scanning. A standard 8-channel birdcage head coil was used with restraining foam pads, in order to minimize head motion and diminish scanner noise. During the resting-state fMRI, subjects were instructed to keep their eyes closed, remain motionless, stay awake, and not to think of anything in particular. Functional imaging was performed using a gradient-echo echo planar sequence. Thirty-eight transverse slices [repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, field of view (FOV) = 220×220 mm] aligned along the anterior commissure-posterior commissure line were acquired. The duration of each fMRI scan was for 480 seconds. Scanning using several other sequences, including (1) a sagittal T1-weighted 3D magnetization-prepared rapid acquisition gradient-echo sequence [TR = 9.4 ms, TE = 4.6 ms, flip angle = 15 u, FOV = 256×256 mm, 155 slices, 1×1×1 mm voxel size], (2) axial T1-weighted fast field echo sequences [TR = 331 ms, TE = 4.6 ms, FOV = 256×256 mm, 34 slices, 0.560.564 mm voxel size], and (3) axial T2W turbo spin-echo sequences [TR = 3,013 ms, TE = 80 ms, FOV = 256×256 mm, 34 slices, 0.5×0.5×4 mm voxel size], were also performed.

Image analysis

Two-sample t-tests were used for group comparisons, in order to analyze the differences in the age, SAS, SDS, BIS-11, RSS, PSQI, SS, SPAI and MPAI score between these two groups, and comparison between genders was performed using X^2-tests. A two-tailed *P*-value of 0.05 was considered statistically significant for all analyses.

Functional imaging data analysis was performed using DPARSF (http://www.restfmri.net/), which is based on SPM8 and REST (http://www.restfmri.net/). Functional data were spatially realigned, co-registered to the anatomical data, normalized and smoothed (8 mm kernel). Then, group analysis was performed based on GLM using the block design. Family-wise error (FWE) corrected values of $P<0.05$ were considered significant.

The 10 initial scans of all experiment runs were discarded since the initial MRI signals were instable and subjects required to undergo initial adaptation to the situation. Data preprocessing included the following steps. First, the image data were slice-timing and motion corrected, and no participant was excluded due to movement. Second, all functional images were transformed into standard Montreal Neurological Institute (MNI) space by linearly registering to the anatomical data and the MNI152 standard brain. The normalized volumes were resampled to a voxel size of 3×3×3 mm. Third, all datasets were smoothed using a 6-mm FWHM Gaussian spatial kernel. Fourth, data were detrended to eliminate the linear trend of time courses, and filtered with low frequency fluctuations (0.008-0.01 Hz) [27, 28]. Finally, a set of regressors, including six head motion parameters, white matter mask, cerebrospinal fluid mask, and global mean signal, were regressed out of the EPI time series [29-32].

The PCC template, which consisted of Brodmann's areas 23, 29, 30, and 31, was selected as the region of interest (ROI) using SPM's Anatomy Toolbox [33]. The reference time-series was produced by averaging blood oxygenation level-dependent signal time-series in the voxels within the seed region. For each subject and seed region, a correlation map was generated by calculating the correlation coefficients between the reference time-series and the time-series from all other brain voxels. Then, the normality of the distribution was increased by using Fisher's z-transform to convert these correlation coefficients z values, in [33]. The individual z-scores were evaluated using one-sample t-test by the SPM8 software, in order to identify brain regions with significant connectivity to the PCC within each group. Individual scores were also evaluated using

Table 1. Demographic and behavioral characteristics of the included participants

	Phone Addiction group Mean ± SD	Control group Mean ± SD	Statistic	*P* values
Number of subjects	24	16		
Age (years)	23.25±1.33	23.88±0.86	t = 1.723	0.0763
Gender (M/F)	11/13	4/12	1.778	0.1824
Self-Rating Anxiety Scale (SAS)	42.50±7.67	35.47±12.22	t = 2.263	0.0293
Self-rating depression scale (SDS)	46.88±9.918	37.71±9.771	t = 2.934	0.0056
Barratt Impulsiveness Scale-11 (BIS-11)	66.13±6.230	54.18±6.840	t = 5.811	<0.0001
Rosenberg Self-esteem Scale (RSS)	33.88±1.101	41.00±1.255	t = 4.206	0.0002
Pittsburgh sleep quality index (PSQI)	7.750±2.817	4.625±2.579	t = 3.553	0.001
Sensation Seeking (SS)	40.25±9.506	40.65±7.874	t = 0.1412	0.8885
Smartphone Addiction Inventory (SPAI)	82.42±11.10	46.18±14.10	t = 9.203	<0.0001
Mobile Phone Addiction Index (MPAI)	57.46±7.331	33.29±8.622	t = 9.666	<0.0001

Abbreviation: SD: standard deviation. Two-sample t test was used for group comparisons and chi-square was used for gender comparison.

Table 2. Significant between-group differences in functional connectivity between specific brain and the posterior cingulate cortex

Structure	Peak MNI coordinate region	MNI coordinate			Cluster size (voxels)	Peak T score
		X	Y	Z		
Left Inferior Frontal Gyrus	Left Middle Frontal Gyrus	-39	36	15	446	3.7599
Left Middle Frontal Gyrus						
Right Inferior Frontal Gyrus	Anterior Cingulate	9	24	21	1185	4.5516
Right Middle Frontal Gyrus						
Anterior Cingulate						
Right Middle Temporal Gyrus	Right Middle Temporal Gyrus	48	-63	12	497	3.9944
Right Superior Temporal Gyrus						
Right Middle Frontal Gyrus	Right Middle Frontal Gyrus	36	3	63	228	3.4172

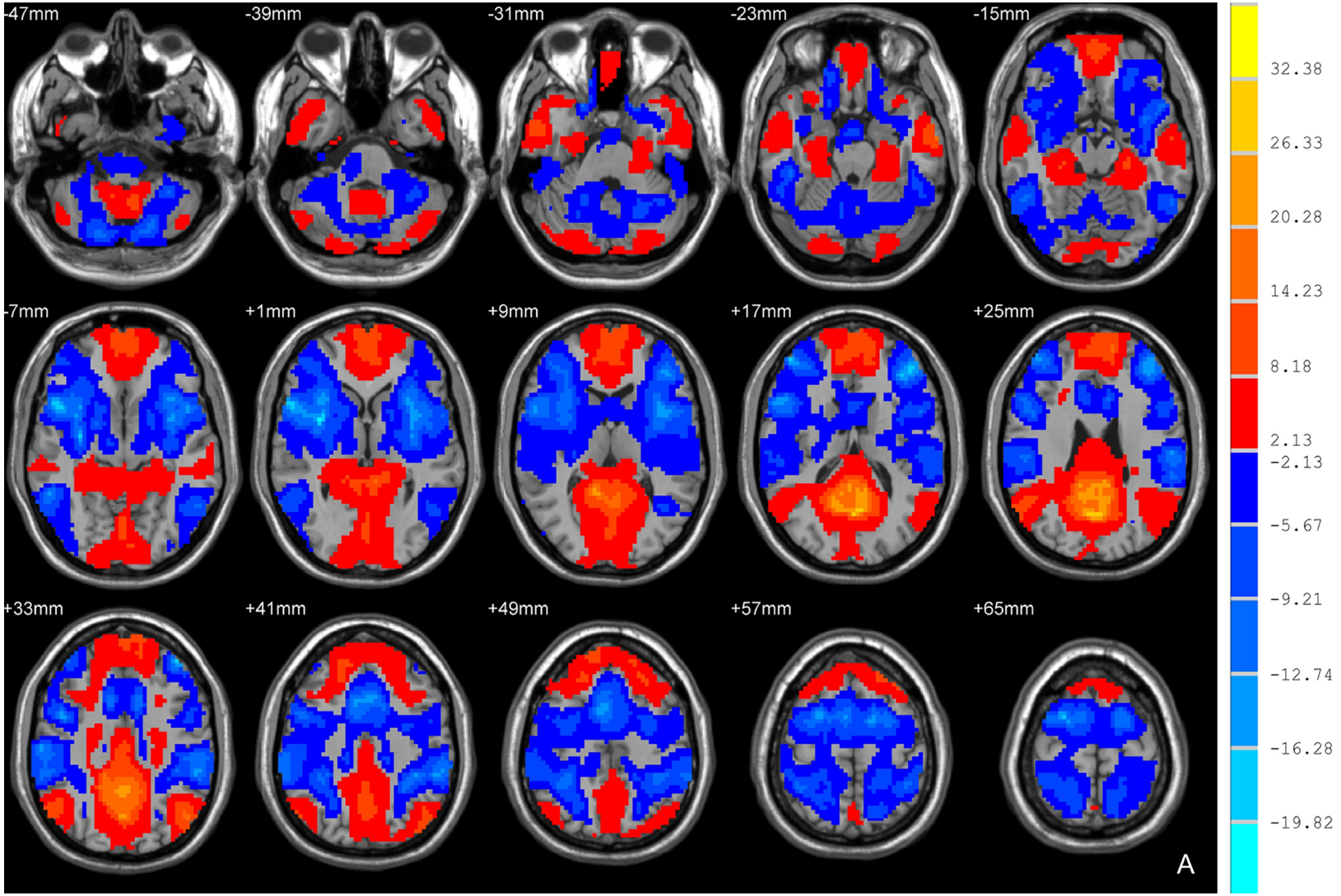
(P<0.05, AlphaSim-corrected, extent threshold = 228 voxels). Note: T>0 indicated MPA>controls in functional connectivity in PCC. The MNI brain was defined based on a series of magnetic resonance images of the normal human brain. The purpose is to analyse different subjects in the same space. The coordinate 0, 0, 0 is defined at the anterior commissure (AC), and the anterior/posterior commissural line (AC/PC line) is defined as the plane where z = 0. In present paper, the information of x y z was reported by software REST. The T score was calculated by two sample t-test and indicated the degree of difference between two groups. Specific T score were also reported by software REST.

random effect analysis and two-sample t-tests by SPM8, in order to identify regions that exhibit significant differences in connectivity to PCC between these two groups. Multiple comparison correction was performed using the AlphaSim program in the Functional Neuroimages software package, as determined by Monte Carlo simulations. Statistical maps of the two-sample t-tests were created using a combined threshold of $P<0.05$ and a minimum cluster size of 228 voxels, resulting in a corrected threshold of $P<0.05$. Regions that exhibit statistically significant differences were masked on the MNI brain templates. Then, contrast images representing areas of the correlation between z-scores in the seed region and SAS, SDS, BIS-11, RSS, PSQI, SS, SPAI and MPAI scores were produced for the 24 participants with MPA, in order to assess the relationship between behavioral features and PCC connectivity, using a threshold of $P<0.05$.

Results

Demographic and behavioral measures

Table 1 shows the demographic and behavioral measures for subjects with MPA and controls. The differences in the distribution of age and gender between these two groups were not sta-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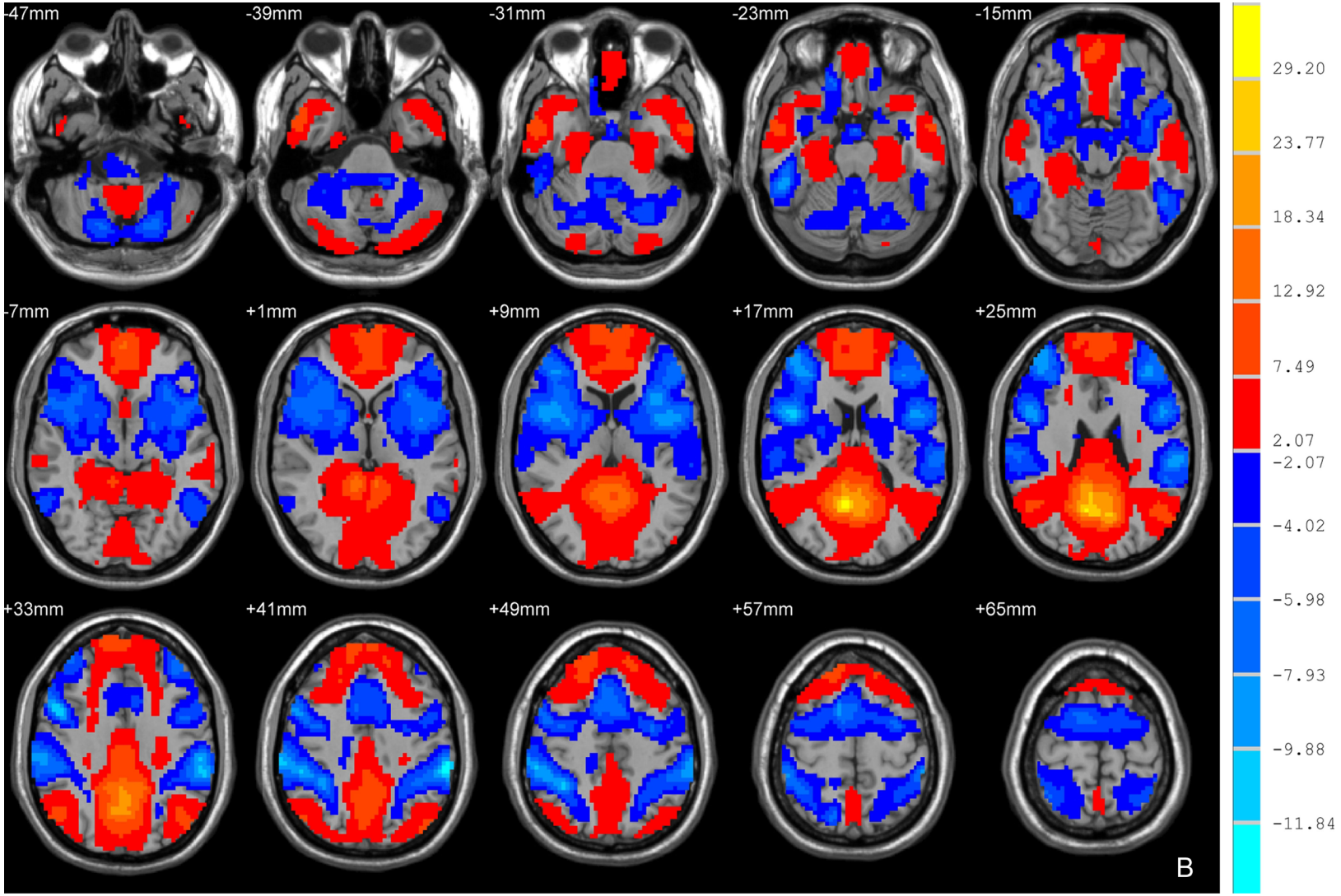
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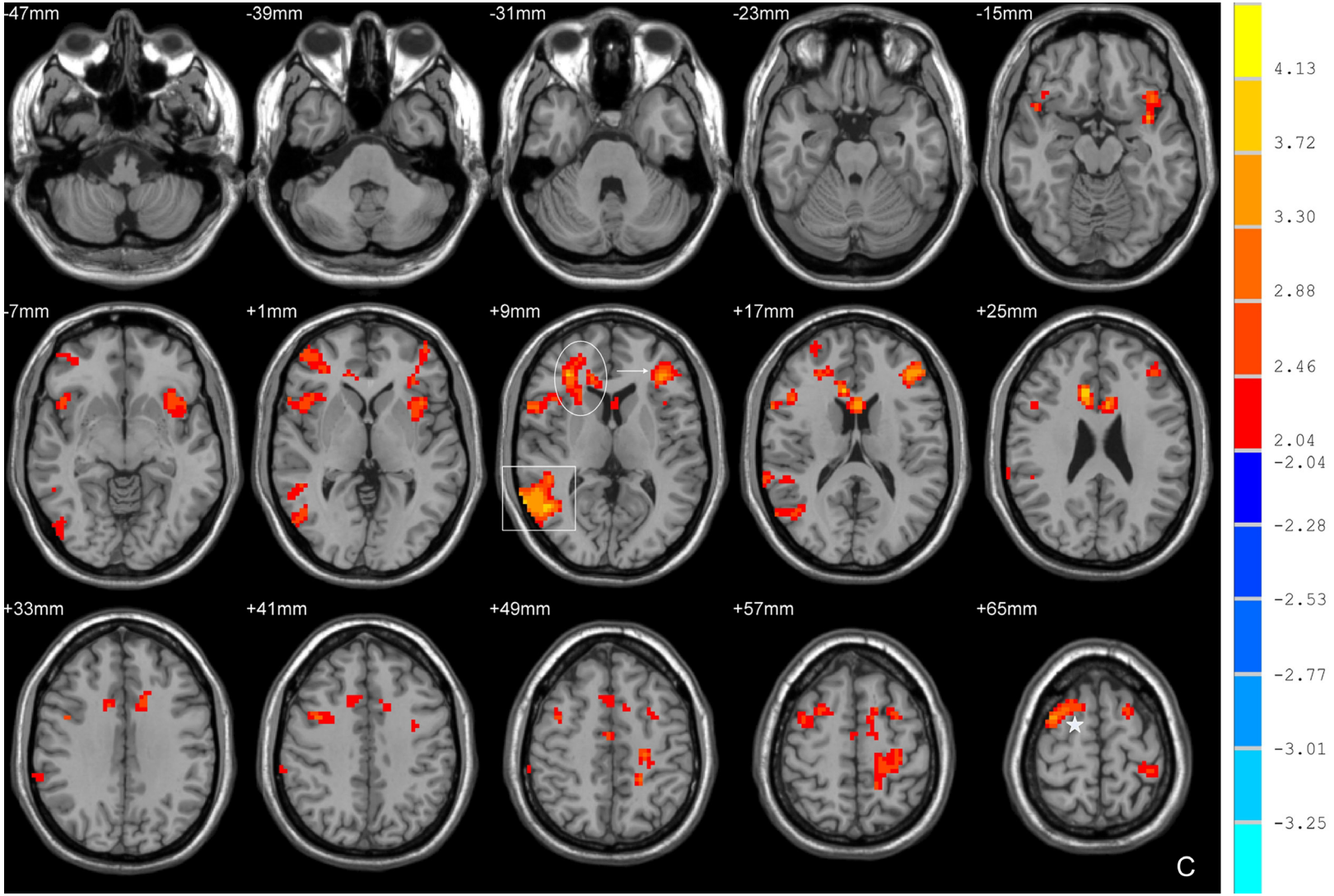

Figure 1. A. Functional connectivity between specific brain and the posterior cingulate cortex in healthy control subjects. B. Functional connectivity between specific brain and the posterior cingulate cortex in MPA. C. Significant between-group differences in functional connectivity between healthy control subjects and MPA. Compared with the control group, subjects with MPA exhibited increased FC in the Left Inferior Frontal Gyrus (→), Left Middle Frontal Gyrus (→), Right Inferior Frontal Gyrus (○), Right Middle Frontal Gyrus (○), Anterior Cingulate (○), Right Middle Temporal Gyrus (□), Right Superior Temporal Gyrus (□), Right Middle Frontal Gyrus (☆). ($P<0.05$, AlphaSim-corrected). The t-score bars are shown on the right. Red indicates MPA>controls and blue indicates MPA<controls. Note: The left part of the figure represents the patient's right side. MPA = Mobile phone addiction; FC = functional connectivity.

Table 3. Significant correlation between MPA behavioral features and altered FC with the PCC

Statistic and *P* values	Left Middle Frontal Gyrus	Anterior Cingulate	Right Middle Temporal Gyrus	Right Middle Frontal Gyrus
Self-Rating Anxiety Scale (SAS)	r = 0.1194	r = 0.1497	r = -0.0426	r = -0.0870
	P = 0.5785	P = 0.4851	P = 0.8433	r = 0.6861
Self-rating depression scale (SDS)	r = -0.0657	r = -0.0941	r = -0.2861	r = -0.3159
	P = 0.7604	P = 0.6617	P = 0.1754	P = 0.1327
Barratt Impulsiveness Scale-11 (BIS-11)	r = -0.2268	r = -0.3496	r = -0.2087	r = -0.2329
	P = 0.2865	P = 0.094	P = 0.3276	P = 0.2735
Rosenberg Self-esteem Scale (RSS)	r = 0.2765	r = -0.0648	r = -0.2071	r = 0.0700
	P = 0.1910	P = 0.7636	P = 0.3316	P = 0.7451
Pittsburgh sleep quality index (PSQI)	r = -0.0530	r = -0.0251	r = -0.1562	r = -0.1558
	P = 0.8057	P = 0.9074	P = 0.4661	P = 0.4672
Sensation Seeking (SS)	r = -0.1014	r = 0.2799	r = 0.0433	r = -0.2431
	P = 0.6374	P = 0.1853	P = 0.8408	P = 0.2524
Smartphone Addiction Inventory (SPAI)	r = -0.2086	r = -0.1828	r = -0.0123	r = -0.1104
	P = 0.3279	P = 0.3925	P = 0.9544	P = 0.6074
Mobile Phone Addiction Index (MPAI)	r = 0.1015	r = 0.0717	r = 0.0636	r = -0.0146
	P = 0.637	P = 0.7391	P = 0.7677	P = 0.9459

tistically significant. Subjects with MPA had higher SAS ($P = 0.0293$), SDS ($P = 0.0056$), BIS-11 ($P<0.0001$), PSQI ($P = 0.001$), SPAI ($P< 0.0001$) and MPAI ($P<0.0001$) scores, and lower RSS ($P<0.0001$) scores, compared with controls. No differences in SS ($P = 0.8885$) were found between these two groups.

Inter-group analysis of PCC connectivity

A inter-group analysis was performed using two-sample t-test in SPM5. Compared with the control group, subjects with MPA presented increased FC in the anterior cingulate, bilateral middle frontal gyrus, bilateral inferior frontal gyrus, right middle temporal gyrus and right inferior temporal gyrus. No decreased connectivity was found (**Table 2** and **Figure 1**).

Correlation between PCC connectivity and SAS, SDS, BIS-11, RSS, PSQI, SS, SPAI and MPAI scores in subjects with MPA

There was no significant correlation between MPA behavioral features and altered FC with the PCC (**Table 3**).

Discussion

Presently, the incidence of MPA has increased worldwide, and accumulating research suggests that the excessive use of mobile phones can be or should be called an "addiction" [34]. However, the neurobiological mechanism of MPA remains unclear.

People experiencing MPA show clinical features that include their inability to control cravings, anxious and lost feelings, withdrawal and escape, productivity loss [35], more depressive symptoms, and low self-esteem [35]. We found that subjects with MPA had higher SAS ($P = 0.0293$), SDS ($P = 0.0056$), BIS-11 ($P<0.0001$), and RSS ($P<0.0001$) scores than in the controls. This indicates that subjects with MPA exhibited more anxious, depressive and impulsive feelings, and lower self esteem, compared to controls. These clinical features are similar or identical with those in patients with substance addiction. However, the neurobiological mechanism of these features has not been fully elaborate.

Several scholars [16, 17, 36] have performed resting-state fMRI on patients with substance and behavioral addiction, in order to further explore its mechanism and help explain its behavioral and neuropsychological disorders. A variety of studies have identified key brain regions that involve in addiction disorders, such as the nucleus accumbens [37], orbital frontal cortex (OFC) [38], dorsal anterior cingulate cortex (dACC)39, prefrontal cortex (PFC) [39] and hippocampus [40]. These regions are involved in brain networks, including reward, motivation,

cognitive control, and learning and memory circuits.

We found that subjects with MPA presented increased FC in the anterior cingulate, bilateral middle frontal gyrus, bilateral inferior frontal gyrus, right middle temporal gyrus and right inferior temporal gyrus.

The anterior cingulate cortex (ACC) revealed increased FC in subjects with MPA. ACC is suggested to play a key role in cognitive control [41]. The brain circuits of cognitive control are believed to be impaired in addiction [42]. In addicts, dysfunction in ACC was found to be correlated with their compromised ability in inhibitory control [15, 40] and error processing [43]. Inhibitory control and error processing are two core components of cognitive control, which are associated with specific neural networks: inhibitory control to implement the inhibition of inappropriate behavior, and error processing to monitor performance errors to prevent future mistakes [44].

The bilateral middle frontal gyrus and bilateral inferior frontal gyrus revealed increased FC in subjects with MPA. This region mainly includes the bilateral prefrontal cortex (PFC). The prefrontal cortex (PFC) has long been verified to play an important role in addiction, which is not only due to its function of regulating limbic reward regions [45], but also based on its role in cognitive control [46]. Previous addiction studies have shown that smokers have greater response to smoking cues in the right dorsolateral prefrontal cortex (DLPFC) [47].

In the present study, in MPA, dACC and bilateral PFC revealed increased contributions of FC in DMN. ACC and PFC are important structures in cognitive control. This indicates that individuals with MPA may have impairment of cognitive control. However, this needs to be confirmed through follow-up studies.

The right middle temporal gyrus and right inferior temporal gyrus revealed increased FC in subjects with MPA. The temporal gyrus exhibits one of the higher levels of the ventral stream of audio and visual processing, and involves in the representation of complex object features [48]. A previous study revealed that the bilateral middle temporal gyruse exhibited increased FC in subjects with internet gaming addiction, but the right inferior temporal gyrus revealed decreased FC. They thought that this may be the consequence of the long engagement of game playing [18]. Our results partially support this hypothesis, and we consider that increased FC with the temporal gyrus may be the consequence of the long duration of using mobile phones, which should be investigated in future studies.

A limitation of the present study is that only a small sample size of normal participants was recruited. Thus, the generalizability of these results may be limited. These reported results should be confirmed in future studies with larger sample sizes. Furthermore, the diagnosis of MPA was mainly based on results of self-reported questionnaires, which could cause some error classification. As a cross-sectional study, our results do not definitely reveal whether the psychological characteristics prior to the development of MPA or were an impact of the overuse of mobile phones. Therefore, future prospective studies should be carried out to confirm the causal relations between MPA and psychological measures.

In the present study, we investigated MPA-related abnormal brain regions of resting-state DMN FC using the seed region of PCC. We found that the anterior cingulate, bilateral middle frontal gyrus, bilateral inferior frontal gyrus, right middle temporal gyrus and right inferior temporal gyrus exhibited increased FC in DMN. Some of these alterations are similar or identical with those in patients with other addictions, particularly in areas related to cognitive control.

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Disclosure of conflict of interest

None.

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