Social Cognitive and Affective Neuroscience, 2021, 484–491

doi: 10.1093/scan/nsab016
Advance Access Publication Date: 1 February 2021
Original Manuscript

Anterior cingulate gyrus acts as a moderator of the relationship between problematic mobile phone use and depressive symptoms in college students

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Abstract

This study aimed to investigate the brain grey matter volume (GMV) related to problematic mobile phone use (PMPU), and whether these regions of GMV play a potential moderating role in the relationship between PMPU and depressive symptoms. We recruited 266 students who underwent magnetic resonance imaging (MRI) scanning. PMPU and depressive symptoms were assessed by a self-rating questionnaire for adolescent PMPU and patient health questionnaire-9, respectively. A multiple regression model was performed to detect GMV and white matter (WM) integrity associated with PMPU by voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) methods, and the moderating analysis was conducted by PROCESS using SPSS software. VBM analysis found an inverse correlation between the GMV of the anterior cingulate gyrus (ACC) and right fusiform gyrus (FFG) with PMPU ($P_{FDR} < 0.05$), and TBSS analysis revealed that fractional anisotropy (FA) in the body of the corpus callosum was negatively correlated with PMPU. The correlation between PMPU and depressive symptoms was moderated by the GMV of the ACC. These results suggest that the GMV of the ACC and right FFG, as well as FA in the body of the corpus callosum, was related to PMPU, and we further found that increased GMV of the ACC could reduce the relationship between PMPU and depressive symptoms in college students.

Key words: smartphone addiction; depression; moderating effect; adolescents; MRI

Received: 10 September 2020; **Revised:** 8 December 2020; **Accepted:** 29 January 2021

Introduction

With the rapid developments in electronic media experienced by younger generations, mobile phone use in children and adolescents has increased. Recent data from GlobalWebIndex (https://www.globalwebindex.com/) showed that the prevalence of mobile phone use is 90.8% globally, and there are 846.8 million mobile phone users—99.1% of the total population—in China (CNNIC, 2020). Despite many advantages of mobile phone use in daily life, there are potential negative consequences of mobile phone overuse. Problematic mobile phone use (PMPU) is a construct defined as excessive use, with features of craving, salience, tolerance, dependence and loss of control, leading to adverse health and functional consequences (Billieux *et al.*, 2015; De-Sola Gutierrez *et al.*, 2016; Lissak, 2018; Elhai *et al.*, 2019). PMPU has also been called mobile phone dependence, mobile phone addiction and smartphone addiction (Derevensky *et al.*, 2019).

Studies of the relationship between PMPU and mental health, especially those on depression, have received more attention in recent years (Demirci *et al.*, 2015; Zou *et al.*, 2019; Zhang *et al.*, 2020). For example, a study by Ng *et al.* (2020) reported that PMPU was associated with depression. Similarly, studies of South Korean and American adolescents found that problematic use of smartphones was significantly associated with depression (Park *et al.*, 2019; Grant *et al.*, 2019). Moreover, a 3-year longitudinal study found that mobile phone dependence at year 1 significantly predicted depression at year 3 (Zhang *et al.*, 2020). A systematic review of 10 studies by Elhai *et al.* (2017) revealed a significant association between problematic or general smartphone use and the severity of depression in different samples of adolescents and adults. However, little is known about the neurobiological mechanism underlying the relationship between PMPU and mental health symptoms.

Some studies have focused on the role of psychological factors, including life satisfaction, empathy, emotion and fear of missing out (Lachmann *et al.*, 2018; Elhai *et al.*, 2018, 2020). There is emerging evidence suggesting the involvement of brain structure and function in behavioural addictions. A recent meta-analytic study aimed to identify the functional and structural neural alterations in Internet gaming disorder (IGD), finding hyperactivation in the anterior cingulate gyrus (ACC) and posterior cingulate gyrus (PCC) caudate and posterior inferior frontal gyrus (IFG); hypoactivation in the anterior IFG and posterior insula; and reduced grey matter volume (GMV) in the ACC, orbitofrontal cortices, dorsolateral prefrontal cortices (PFCs) and premotor cortices in IGD compared to healthy controls (Yao *et al.*, 2017). There have been a few studies of moderating effects, introducing brain structures to the relationship between PMPU and depressive symptoms. We hypothesized that GMV and white matter (WM) integrity were correlated with PMPU, which could moderate the association between PMPU and depressive symptoms.

The current study aimed to detect brain structural regions correlated with PMPU by voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) methods and to explore whether these regions moderate the association between PMPU and depressive symptom in college students.

Materials and methods

Participants

This study was performed between April 2019 and May 2019, and no examinations were conducted during this period. The study enrolled 268 college students from two schools and five different majors at Anhui Medical University. All of the participants provided written informed consent before the survey, and the study was approved by the Ethics Committee of Anhui Medical University. The survey collected basic information including age, gender, residential area (rural/urban), any siblings, perceived family income and academic performance.

Measures

Problematic mobile phone use. The Self-rating Questionnaire for Adolescent Problematic Mobile Phone Use (SQAPMPU) (Tao *et al.*, 2013) consists of 13 items (e.g. 'I do not have enough time for sleeping due to the time I spend on my mobile phone', 'I think I need to spend more time on my mobile phone to be satisfied' and 'I feel lost without my mobile phone') rated using a 5-point Likert scale (Not true at all = 1, Slightly true = 2, Moderately true = 3, Strongly true = 4 and Extremely true = 5), used to assess PMPU in the participants. It covers three dimensions: withdrawal symptoms, craving, and physical and mental health status. The total score ranges from 13 to 65; the Cronbach's alpha coefficient was 0.90.

Patient health questionnaire-9. The patient health questionnaire (PHQ)-9 is a 9-item self-reported questionnaire that assesses depressive symptoms over the previous 14 days (January and Chimbari, 2018). Items include 'Little interest or pleasure in doing things', 'Feeling down, depressed, or hopeless', and 'Trouble falling or staying asleep, or sleeping too much'. Each item on the measure contains four options to describe how often each feeling occurred in the previous 14 days, including 0 (not at all), 1 (several days), 2 (more than half the days) and 3 (nearly every day). The total score ranges from 0 to 27 by totalling the scores of nine items, with higher scores indicating more severe depressive symptoms. In the present study, the Cronbach's alpha coefficient was 0.87.

Image acquisition. All of the MRI examinations were performed with 3.0 T Philips Ingenia CX scanner (Philips, Best, Netherlands) in the Ping An Healthcare Diagnostics Center (Hefei, Anhui, China). Polyurethane foam pads were used to minimize head motion and reduce scanner noise. The 3D high-resolution T1-weighted structural images were acquired by fast field echo technique with echo time (TE) = 3.2 ms, repetition time (TR) = 7.1 ms, field of view (FOV) = 256 × 256 mm^2, slice thickness = 1 mm, voxel size 1 × 1 × 1 mm^3 and number of slices = 180. The acquisition time was 5 min and 5 s. DTI images were acquired by echo planar imaging sequence with TE = 84 ms, TR = 8400 ms, FOV = 256 × 256 mm^2, slice thickness = 3 mm, slice gap = 0, $b = 0.1000$ s/mm^2 and direction = 32.

VBM analysis

Image processing was performed using statistical parametric mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/). First, the structural images were segmented for GM, WM and cerebrospinal fluid by a unified segmentation model (Harrison *et al.*, 2007). Subsequently, we performed the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) method for registration of the GM template (Ashburner, 2007). Then, the images were normalized to the standard anatomic space of the Montreal Neurological Institute (MNI). Finally, the resulting images were modulated by the Jacobian

determinants derived from the spatial normalization procedure and then smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum.

Voxel-based multiple regression analyses (based on general linear model) were performed by SPM12, with the voxel-wise GMV value as the dependent variable and SQAPMPU scores of PMPU as a covariate of interest. In addition, age and gender were used as external regressions to control their effects on both brain structure and PMPU. Intracranial volume (ICV) was not added as a covariate because there was no correlation between ICV and PMPU in this study ($r = -0.06$, $P = 0.324$). We excluded two participants due to missing SQAPMPU and PHQ-9 scores during this process. We used a cluster-extent-based threshold which was suggested by Woo *et al.* (2014), applying a primary significant threshold of uncorrected value of $P < 0.001$. Based on this height threshold, SPM12 provided the critical cluster size for non-stationary cluster extent correction with a false discovery rate (FDR) maintained at $P < 0.05$. We also extracted GMV from these brain regions to perform further moderating analyses.

TBSS analysis

DTI images were processed by the FMRIB Software Library (FSL 5.0) software package (http://www.fmrib.ox.ac.uk/fsl). Data preprocessing was as follows: (i) the eddy current correction within FMRIB's Diffusion Toolbox (FDT) corrected was used for eddy currents and head motion; (ii) a brain mask was created by the Brain Extraction Tool (Smith, 2002) and (iii) FDT was used to fit the tensor model and to calculate the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) values.

Voxel-wise analysis of whole-brain WM multiple diffusion metrics (FA, MD, AD and RD) was performed by TBSS (Lee *et al.*, 2007). In brief, all individuals' FA maps were nonlinearly registered to a standard space at resolution of 1-mm isotropic voxels. Then, a mean FA image was created by averaging the aligned FA maps and thinned to create a mean FA skeleton using the default FA threshold of 0.2 to exclude non-WM voxels. Finally, each subject's aligned FA map was projected onto the skeleton for further analyses.

To uncover whether WM integrity was correlated with PMPU, voxel-based multiple regression analyses (based on general linear model) were performed on the skeletonized DTI maps by permutation tests using threshold-free cluster enhancement (TFCE) option with the Randomise tool in FSL. The number of permutations was set to 5000. Correction for multiple comparisons used the family-wise error method. We also extracted the surviving results of DTI values and used them as a moderator.

Statistical analysis

The statistical analysis was conducted using SPSS software, version 23.0 (SPSS, Chicago, IL, USA). The descriptive statistics used were the mean (s.d.) and median for continuous variables and frequencies and percentages for categorical variables. A linear regression analysis was performed to explore the association between PMPU and depressive symptoms, including PHQ-9 scores as outcomes and SQAPMPU scores as predictors. A moderation analysis was performed with SQPMPU scores for PMPU as the independent variable, extracted GMV or microstructural integrity values that were strongly ($P_{FDR} < 0.05$ for GMV and $P_{FWE} < 0.05$ for microstructural integrity values) correlated with PMPU as moderators, and depressive symptoms as a dependent variable by the SPSS PROCESS macro (Preacher *et al.*, 2007). Simple slopes showed the associations between PMPU and depressive symptoms at low (M − 1 s.d.) and high (M + 1 s.d.) levels of the moderator. The statistical significance was set at $P < 0.05$.

Table 1. Demographic characteristics of participants

	n	Mean ± s.d./%
Age	266	19.02 ± 0.83
Gender		
Male	60	22.6%
Female	206	77.4%
Residential area		
Rural	157	59%
Urban	109	41%
Any siblings		
Yes	59	22.2%
No	207	77.8%
Perceived family income		
Low	55	20.6%
Medium	196	73.7%
High	15	5.7%
Academic performance		
Poor	48	18.0%
Medium	167	62.8%
Good	51	19.2%
Father's educational level		
Primary school or lower	56	21.1%
Middle school	182	68.4
College or above	28	10.5%
Mother's educational level		
Primary school or lower	126	47.4%
Middle school	127	47.7%
College or above	13	4.9%
SQAPMPU scores	266	24.63 ± 8.33
PHQ-9 scores	266	4.45 ± 4.08

Results

Sample characteristics

The descriptive statistics of the sample characteristics are summarized in Table 1. We enrolled 268 participants at the beginning and excluded two students from the VBM and TBSS analyses. Finally, we included 266 students with a mean age (s.d.) of 19.02 (0.83) years old in this study. There were 60 men (22.6%), and 157 (59.0%) students came from rural areas. It was reported that 59 (22.2%) of the participants had siblings, and 196 (73.7%) students came from medium-income families. Moreover, 48 of them stated that they had poor academic performance in school. The SQAPMPU and PHQ-9 scores of the total participants were 24.63 ± 8.33 and 4.45 ± 4.08, respectively.

VBM results

SQAPMPU score was negatively correlated with GMV of the ACC (coordinates: $x = -8$, $y = 40$, $z = 10$) and right fusiform gyrus (FFG) (coordinates: $x = 24$, $y = 9$, $z = -45$) ($P < 0.05$, FDR corrected, Figure 1, Table 2).

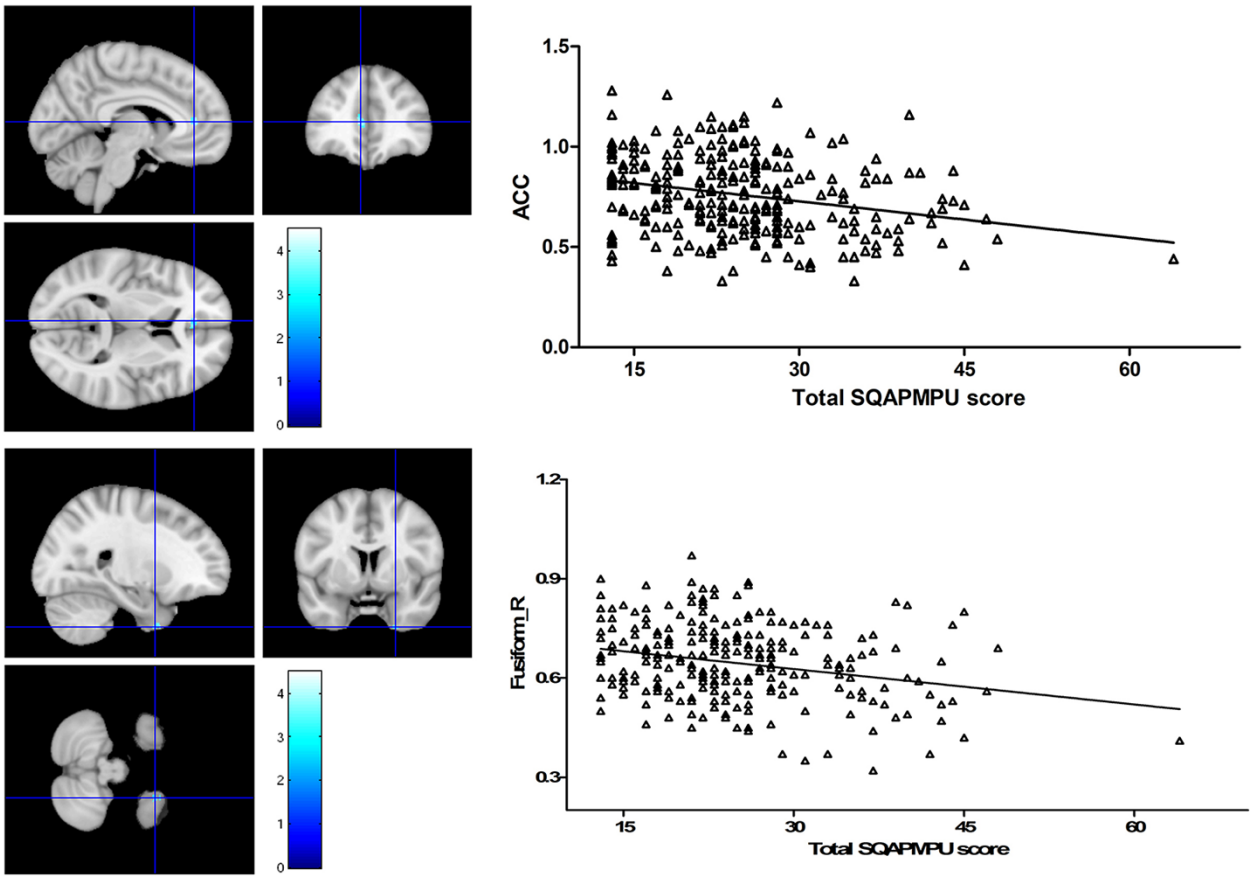

Fig. 1. The blue-light colour indicates negative correlation of SQAPMPU score and GMV in the anterior cingulate gyrus (ACC) and right fusiform. The colour scale represents *t* values. The threshold for displaying was set to $P < 0.05$, FDR corrected. The scatterplots show the association between SQAPMPU score and GMV values that are extracted from significant clusters of each subject.

Table 2. Brain regions in which GMV was significantly correlated with SQAPMPU scores

Cluster	Region	Cluster size	Peak MNI(mm)			Peak t value
			x	y	z	
1	Anterior cingulate gyrus	77	−8	40	10	4.49
2	Right fusiform gyrus	25	24	9	−45	3.81

Note: Height threshold $P < 0.001$, corrected for FDR, cluster size = 25.

TBSS results

TBSS analysis revealed that the FA in the body of the corpus callosum was negatively correlated with SQAPMPU score, and we did not find that MD, AD or RD was correlated with SQAPMPU score (Figure 2).

Association of PMPU and depressive symptoms and the moderation analyses

Linear regression analyses showed significant relations between PMPU and depression [$F(1264) = 137.31$, $P < 0.05$, $R^2 = 0.34$]. For moderation analysis, we found a significantly moderating effect of the GMV of the ACC on the relationship between PMPU and depressive symptoms ($\beta = 0.274$, $\Delta R^2 = 0.018$, $P < 0.01$) and did not find a moderate effect of any other PMPU-related GMVs or microstructural integrity values. Moreover, the ACC moderating effect was still significant after controlling for some sociodemographic variables (Table 3, Figures 3 and 4).

Discussion

The present study sought to explore the moderate effects of brain structure on the relationship between PMPU and depressive symptoms in college students. In line with our hypothesis, PMPU was correlated with the GMV of the ACC, right FFG and FA in the body of the corpus callosum. Moreover, moderation analysis found that a greater GMV of the ACC could reduce the relationship between PMPU and depressive symptoms.

To detect PMPU-related brain structures, our VBM results were not consistent with three of the previous studies of PMPU, which found smaller GMVs in the right superior frontal gyrus, right IFG, bilateral thalamus, right lateral orbitofrontal cortex,

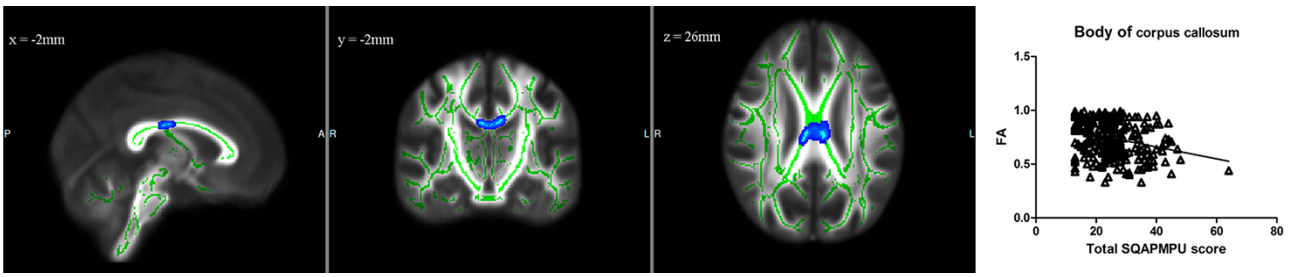

Fig. 2. The blue-light blue colour indicates negative correlation between SQAPMPU score and FA in the body of corpus callosum ($P < 0.05$, TFCE corrected). Green represents mean FA skeleton of all participants. x, y, z is MNI coordinate. The scatterplots show the association between SQAPMPU score and FA values that are extracted from significant clusters of each subject.

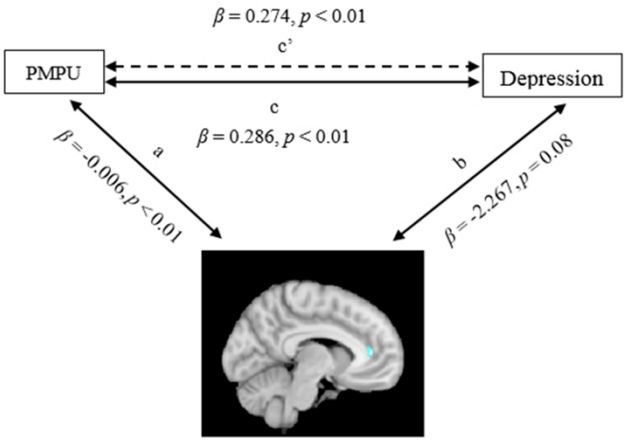

Fig. 3. Association between PMPU and depressive symptom was moderated by GMV of ACC. Path a illustrates the association between PMPU and GMV of ACC, Path b indicates the association between GMV of ACC and depressive symptom, Path c illustrates the association between PMPU and depressive symptom and Path c' illustrates the association between PMPU and depressive symptom after being moderated by GMV of ACC.

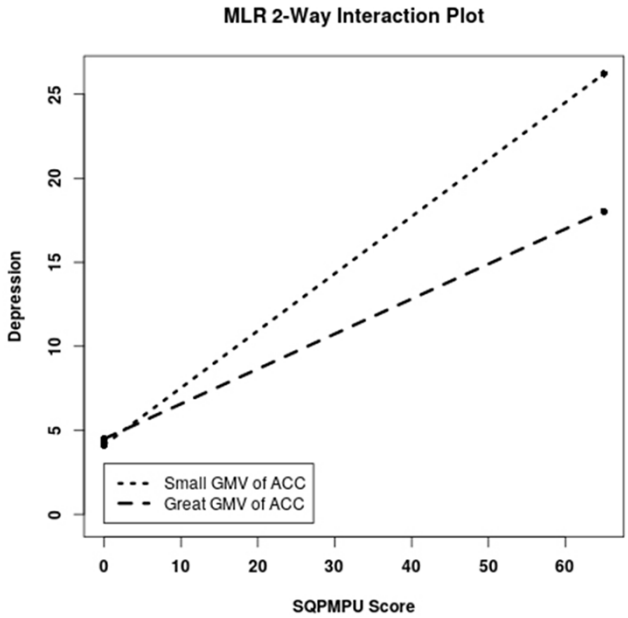

Fig. 4. GMV of ACC moderated the association between PMPU and depressive symptom. Simple slopes are plotted at low (M − 1 s.d.) and high (M + 1 s.d.) GMV of ACC.

left anterior insula, left inferior temporal cortex and left parahippocampal cortex of the PMPU group than healthy controls (Wang *et al.*, 2016; Lee *et al.*, 2019; Horvath *et al.*, 2020). However, our findings of ACC-related PMPU were consistent with previous studies of IGD and Internet addiction (Zhou *et al.*, 2011; Weinstein *et al.*, 2017; Lee *et al.*, 2018). Moreover, our results were also consistent with the findings of previous functional MRI study of IGD, which found alteration in brain activity of the ACC and right FFG (Ding *et al.*, 2014; Jin *et al.*, 2016; Qi *et al.*, 2016).

In addition, TBSS analysis found that FA of the body of the corpus callosum was negatively correlated with SQAPMPU score. Reduced WM integrity of the corpus callosum has been associated with many addictive behaviours (Pfefferbaum *et al.*, 2010; Jeong *et al.*, 2016). Our result was consistent with previous studies of Internet addiction, which found reduced FA in the corpus callosum in Internet-addicted adolescents compared to controls (Bi *et al.*, 2015). Moreover, He *et al.* (2018) found the excessive social media use was correlated with abnormal WM integrity of the corpus callosum. Thus, it is possible that PMPU is related to inter-hemispheric communication deficits.

Nevertheless, there have been limited studies detecting the moderating effect of brain structures on the relationship between PMPU and depressive symptoms. Our results found that greater GMV of the ACC could reduce the relationship between PMPU and depressive symptoms in college students. In the context of the research, the current study expanded new evidence of brain structures playing a role in moderating the effect of the relationship between behaviour problems and emotional symptoms.

The ACC has been identified as a part of the reward system that encodes reward prediction error and plays a key role in attention and the motor control processes involved in behavioural adjustment (Hayden *et al.*, 2011; Lee *et al.*, 2018). Dong *et al.* (2011, 2012) revealed that IGD decreased activation in the ACC during a loss condition–based functional MRI study using the Probabilistic Guessing Task and STROOP Task, suggesting poor error monitoring and cognitive control. Therefore, altered GMV in the ACC, which contributes to rewards and cognitive control, could be associated not only with the pathophysiology of IGD, but also with PMPU.

There has been emerging evidence suggesting that rewards function is associated with affective disorders, such as depression, and is critical to the aetiology, development and pathophysiology of depression (Forbes, 2011; Forbes and Dahl, 2012). Previous studies identified decreased FA in the cingulum in adolescents with high familial risk for depression compared to

Table 3. Results from the moderated regression analysis predicting depressive symptoms

	Predictors	Model 1						Model 2					
		β	SE	t	R^2	ΔR^2	F	SE	t	R^2	ΔR^2	F	
1	PMPU	0.274	0.026	10.561**	0.363	0.018	7.444**	0.279	0.027	10.381**	0.370	0.016	6.462*
	ACC	0.929	1.078	0.862				1.028	1.119	0.919			
	PMPU × ACC	−0.340	0.125	−2.728**				−0.323	0.127	−2.542*			
2	PMPU	0.273	0.026	10.519**	0.351	0.009	3.437	0.278	0.027	10.338*	0.359	0.007	2.725
	FFG_R	−0.311	1.834	−0.170				−0.347	1.973	−0.176			
	PMPU × FFG_R	−0.357	0.192	−1.854				−0.325	0.197	−1.651			
3	PMPU	0.295	0.026	11.570**	0.346	0.001	0.345	0.299	0.026	11.373**	0.355	0.001	0.340
	body of corpus callosum	3.483	3.070	1.134				3.146	3.145	1.000			
	PMPU × body of corpus callosum	0.239	0.407	0.588				0.244	0.418	0.583			

Notes: *P < 0.05, **P < 0.01, model 1 was not adjusted by any variables, model 2 was adjusted by age, gender, residential area, any siblings, perceived family income, academic performance and parent's educational level. ACC, anterior cingulate gyrus; FFG, fusiform gyrus; PMPU, problematic mobile phone use; R, right.

adolescents with no family history of mood disorders (Huang *et al.*, 2011; Keedwell *et al.*, 2012). A recent meta-analysis found that ACC was consistently disrupted across a variety of task contexts for neural responses in adolescent depression (Miller *et al.*, 2015). Moreover, Strikwerda-Brown *et al.* (2015) reported that weaker subgenual ACC functional connectivity with PCC, angular gyrus and dorsal prefrontal cortex at baseline, and weaker subgenual ACC functional connectivity with the dorsomedial prefrontal cortex at follow-up, were associated with worse depressive symptoms. In addition, ACC was regarded as a promising predictor for antidepression response from several studies (Dunlop *et al.*, 2017; Godlewska *et al.*, 2018; Wolke *et al.*, 2019). Based on the above, it can be deduced that ACC might play a key role linking behavioural problems and mood disorders.

The current study had several limitations that should be acknowledged. First, there were some limitations in our measures of PMPU through well-validated self-reported questionnaires because there is no standardized measurement for the diagnosis of PMPU at present. Second, although this sample was relatively large, the cross-sectional design did not infer our findings' stability, and we assume that the direction in behaviour to emotional symptoms supports the "displacement hypothesis" theory. (Boers *et al.*, 2019). Longitudinal studies are needed in the future to detect the possible psychological and physiological mechanisms of the relationship between PMPU and depressive symptoms. Third, while only the brain structural results were reported in this study, we also got some brain functional results (not published) focusing on other aspects of PMPU. However, we believe that our findings could be helpful, at least in part from the neurobiological aspect, to have a moderating effect on the relationship between PMPU and depressive symptoms in college students.

This study demonstrated that PMPU was associated with depressive symptoms and this association was moderated by the GMV in the ACC, which was correlated with PMPU. In future, more longitudinal studies are needed to explore such moderating effects on the relationship between addictive behaviours and mental health.

Acknowledgements

We sincerely thank all the adolescents and their schools for kind participation, as well as staffs of the Ping An Healthcare Diagnostics Center.

Funding

This study was supported by the National Natural Science Foundation of China (81773455 and 81803257) and Scientific Research of BSKY from Anhui Medical University (XJ201824).

Conflict of interest

The authors declare that they have no conflict of interest.

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