

RESEARCH ARTICLE

Age-related and individual variations in altered prefrontal and cerebellar connectivity associated with the tendency of developing internet addiction

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Abstract

Internet addiction refers to problematic patterns of internet use that continually alter the neural organization and brain networks that control impulsive behaviors and inhibitory functions. Individuals with elevated tendencies to develop internet addiction represent the transition between healthy and clinical conditions and may progress to behavioral addictive disorders. In this network neuroscience study, we used resting-state functional magnetic resonance imaging (rs-fMRI) to examine how and whether individual variations in the tendency of developing internet addiction rewire functional connectivity and diminish the amplitude of spontaneous low-frequency fluctuations in healthy brains. The influence of neurocognitive aging (aged over 60 years) on executive-cerebellar networks responsible for internet addictive behavior was also investigated. Our results revealed that individuals with an elevated tendency of developing internet addiction had disrupted executive-cerebellar networks but increased occipital-putamen connectivity, probably resulting from addiction-sensitive cognitive control processes and bottom-up sensory plasticity. Neurocognitive aging alleviated the effects of reduced mechanisms of prefrontal and cerebellar connectivity, suggesting age-related modulation of addiction-associated brain networks in response to compulsive internet use. Our findings highlight age-related and individual differences in altered functional connectivity and the brain networks of individuals at a high risk of developing internet addictive disorders. These results offer novel network-based preclinical markers of internet addictive behaviors for individuals of different ages.

KEYWORDS

aging, ALFF, functional connectivity, internet addiction tendency

1 | INTRODUCTION

Internet addiction (O'Reilly, 1996) is a behavioral and impulse control spectrum disorder caused by compulsive internet use (Cerniglia

et al., 2017; Holden, 2001; Li et al., 2015; Montag et al., 2015). Internet gaming disorder, a type of internet addiction, has been classified as a psychiatric disorder under section III of the Diagnostic and Statistical Manual v5 (DSM-5, American Psychiatric Association [APA], 2013) and

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investigated at behavioral and neuronal levels (First et al., 2021). Affected individuals suffer from psychological, physical, and affective negative consequences, including anxiety (Boettcher, Rozental, Andersson, & Carlbring, 2014; Kim, Jang, Lee, Lee, & Kim, 2018; Reger & Gahm, 2009), depression (Bessi re, Pressman, Kiesler, & Kraut, 2010; Morrison & Gore, 2010), sleep deprivation (Cheung & Wong, 2011; Tan, Chen, Lu, & Li, 2016), mood changes (Laier & Brand, 2017), and social isolation (Fallahi, 2011). Internet addiction, therefore, pose a growing threat to global public health (Mihajlov & Vejmelka, 2017) irrespective of age (M'hiri, Costanza, Khazaal, Zullino, & Achab, 2015).

Excessive internet use can increase the tendency of developing internet addiction and potentially progress to internet addictive disorder (Kuss & Lopez-Fernandez, 2016). Individuals with an elevated tendency of developing internet addiction likely represent the transition between healthy adults and those with fully developed addiction. Few studies have explored whether individual variations in the tendency of developing internet addiction modulate neural organization and brain networks. Li et al. used magnetic resonance imaging (MRI) and reported positive correlations between the dorsolateral prefrontal volume and a tendency of developing internet addiction in young adults, which possibly accounted for reduced inhibitory control (Li et al., 2015). Another MRI study examined how internet addiction influenced regional gray-matter volume and found negative correlations between the right frontal gray-matter volume and the tendency of developing internet addiction in young adults (K hn & Gallinat, 2015). A recent functional MRI (fMRI) study found that two different brain networks, mostly connected to the frontal regions, were positively and negatively correlated with internet addiction, respectively, suggesting their implications for cognitive control (Wen & Hsieh, 2016). Despite their contrasting findings, these studies indicate that frontal regions associated with cognitive control and inhibition are potential preclinical markers of brain dysfunction resulting from internet addiction (Feil et al., 2010; Hayashi, Ko, Strafella, & Dagher, 2013; Kuss & Griffiths, 2012).

Recent resting-state fMRI (rs-fMRI) studies have elucidated brain functions and neurocognitive mechanisms underlying psychological processes and psychiatric disorders across ages. Altered large-scale functional brain networks are considered to be common traits of behavioral and substance-related addictions. Participants with internet gaming disorder (Yuan et al., 2016; Zhang et al., 2017) and substance addictions (Arcurio, Finn, & James, 2015; Lin, Wu, Zhu, & Lei, 2015; Ma et al., 2011) showed disrupted default-mode network (DMN) connectivity, indicating comorbid symptoms. Moreover, the DMN and inhibitory control network (ICN), which controls impulsive behaviors (Dong, Devito, Du, & Cui, 2012; Dong, Zhou, & Zhao, 2011), were found to interact in young adults with internet addiction (Li et al., 2015).

Given the increased prevalence of internet addiction and its effects on people of all ages (M'hiri et al., 2015; Mihajlov & Vejmelka, 2017), we examined whether and how individual variations in the tendency of developing internet addiction modulate functional brain connectivity and spontaneous neural activities in both young

and aging brains using rs-fMRI. Previous studies demonstrated age-related alterations in the functional coupling of the default-executive and cerebro-cerebellar networks (Adnan, Beaty, Lam, Spreng, & Turner, 2019; Patil, Madathil, & Huang, 2021), which manifested as decreased modulation of the prefrontal cortex and suppression of the DMN. This indicated reduced neurocognitive flexibility of the default-executive control and cerebro-cerebellar coupling in older adults (Turner & Spreng, 2015; Varangis, Razlighi, Habeck, Fisher, & Stern, 2019). Furthermore, it implied that alterations in these networks that control impulsive behaviors and inhibitory functions were potential preclinical markers for internet addiction in the aging brain. This study has two aims: first, to examine how individual variations in the tendency of developing internet addiction re-wire functional brain connectivity and spontaneous brain activities of healthy brains; second, to investigate whether and how neurocognitive aging modulates the default-executive-cerebellar networks associated with preclinical markers of internet addiction.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-eight younger adults aged 20–28 years (mean age = 23.1 ± 1.92 years; 18 women) and 34 healthy community-dwelling older adults aged 50–76 years (mean age = 63.0 ± 7.65 years; 24 women) participated in the study. All of the participants were healthy, right-handed, and had a normal or corrected-to-normal vision and hearing ability. All of the participants were screened using a detailed self-report health questionnaire and none had a prior history of chronic illness, neurological disorders (e.g., epilepsy, traumatic head injury, or other neurological diseases), psychiatric disorders (e.g., anxiety and depression), or smoking/alcohol addiction. The study was approved by the Human Subject Research Ethics Committee, Academia Sinica, and National Chiao Tung University, Taiwan. All of the experimental procedures of the study followed the ethical standards of the institutional and national ethics committees. Informed consent was obtained from all participants before the study.

2.2 | Neurocognitive assessment

Before undergoing MRI scans, each participant completed a minimal state examination (MMSE; Folstein, Folstein, & McHugh, 1975) that assessed basic cognitive abilities, including orientation in time and space, attention and calculation, and memory and language functions. Furthermore, a battery of neuropsychological tests, such as the third version of the Wechsler adult intelligence scale (Wechsler, 1997a) and the third version of the Wechsler memory scale (Wechsler, 1997b), was used to measure age-related and individual differences in a variety of neurocognitive functions, including digit-symbol coding, symbol searching, block design, picture completion, matrix reasoning, arithmetic, letter-number sequencing, forward and backward digit span, vocabulary, and similarity.

2.3 | Assessment of a tendency of developing internet addiction

Both younger and older participants received a 26-item Chen internet addiction scale-revised questionnaire (CIAS-R; Chen, Weng, Su, Wu, & Yang, 2003; Wen & Hsieh, 2016) that assessed individual differences in the tendency of developing internet addiction. Based on the DSM-IV-TR addictive behaviors criteria, the CIAS-R was divided into two sections: core symptoms and related interpersonal and health problems. The questionnaire was based on five elements: compulsive internet use, withdrawal symptoms when the internet is taken away, tolerance, jeopardy of interpersonal health, and time management problems.

The 26 items were rated on a 4-point Likert scale that indicated low and high a tendency of developing internet addiction, with summed scores ranging from 26 to 104. The CIAS-R classifies the addiction level based on the scores that is, higher scores indicating the severity of internet addiction. In general participants with a score above 64 are classified as internet addicted participants. CIAS-R has shown high diagnostic accuracy (area under curve [AUC] = 89.6%; Ko et al., 2005) and internal consistency (Cronbach's $\alpha = .79-.93$; Chen et al., 2003). In this study, the participant's total CIAS-R scores were used as an indicator of the current status of internet addiction tendency.

2.4 | Imaging data acquisition

All of the measurements were performed using a 3 T Siemens MRI scanner (magnetron Trio, Siemens, Germany). Functional images were obtained using single-shot T2* weighted gradient echo-planar image (EPI) sequence (repetition time/echo time [TR/TE] = 2000/30 ms; flip angle = 90°; 33 axial slices with thickness 4 mm; field of view (FoV) = 256 × 256 mm²; matrix size = 64 × 64; in-plane resolution = 3.1 × 3.1 mm). Anatomical images were obtained using an isotropic T1-weighted three dimensional (3D)-ultrafast magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (TR/T1/TE: 3500/1100/3.5 ms; flip angle = 7°; slice thickness = 1 mm; FoV = 256 × 256 mm²). All anatomical images were visually verified by MRI experts and no brain abnormalities were found. The participants were asked to rest in the eyes-closed state for 5 min to acquire the imaging data. High-resolution T1 scans were obtained for anatomical normalization after functional imaging.

2.5 | Processing and analysis of functional MRI data

Pre-processing and denoising were carried out with Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>) run on MATLAB v. 2018b (<https://in.mathworks.com>). Pre-processing

consisted of slice-timing correction, motion correction, realignment, and normalization using the EPI template provided by the Montreal Neurological Institute (MNI) with a resampling voxel size of 3 mm³ and spatial smoothing with a Gaussian kernel at 8 mm full-width at half-maximum (FWHM).

2.6 | Head motion considerations

In the pre-processing steps, the resting-state functional data were realigned using the SPM12 realign and warp procedure (Anderson et al., 2011) which is used to address distortion-by-motion interactions by estimating derivatives of the deformation field concerning head motion. The scans were co-registered and resampled to the reference image using b-spline interpolation. This was followed by the slice-time correction.

After realigned and slice-corrected scans were scanned for outliers. The potential outlier scans were identified using the global blood-oxygen-level-dependent (BOLD) signal and the amount of motion by the participants in the scanner. Frame-wise displacement was calculated at each time point using the 140 × 180 × 115 mm bounding box. Frame-wise displacement >0.9 mm or global BOLD signal changes >5 SD were considered as potential outlier scans. The data were further normalized and smoothed using spatial convolution with an 8-mm full-width half-maximum Gaussian kernel.

Apart from the above noise correction, six head motion parameters were obtained from the motion correction step. The anatomical component noise correction (CompCor) (Behzadi, Restom, Liao, & Liu, 2007) was used for noise correction which included: (a) Noise correction in white matter (WM), cerebrospinal fluid (CSF)—confounding effects from the BOLD signal. Five potential noise components were obtained from WM and CSF. (b) Subject motion parameters—12 potential noise components including 3 translation, 3 rotation, and first-order derivatives, (c) identification of outlier scans- Remove the influence of outlier scans on the BOLD signal and (d) the canonical hemodynamic response function convolved with the linear BOLD signal and defined as additional noise components to reduce slow trends and initial magnetization transients.

2.7 | Resting-state functional MRI data analysis

Functional connectivity measures were performed on MATLAB using the CONN toolbox (<https://web.conn-toolbox.org>). CONN uses the CompCor method to identify the principal components of white matter (WM) and cerebrospinal fluid (CSF) (Behzadi et al., 2007). A band-pass filter between 0.01 and 0.08 Hz was applied to the rs-fMRI data. The first-level confounders used were CSF, WM, and the realignment parameters as defined by Behzadi et al (Behzadi et al., 2007). We performed a region of interest (ROI-to-ROI) analysis, which is a connectivity metric used to examine functional connectivity across brain ROIs defined by CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012). The realignment parameters and the CIAS-R scores, gender, and

educational level were defined as first-level covariates. We further performed group-independent component analysis (ICA) to estimate independent spatial components on rs-fMRI data for both younger and older participants to identify major brain networks across age groups that reflected age-invariant resting-state networks (Patil et al., 2021). The group-ICA was performed to extract the resting-state brain networks from 30 independent components, with a reduction factor of 64. Furthermore, a spatial-to-template match was used to obtain the various resting-state brain networks. Our selection of the number of components was consistent with our previous work reported on the network neuroscience of aging (Patil et al., 2021).

2.8 | Connectivity analysis: Correlation between a tendency of developing internet addiction tendency and functional brain connectivity

We used the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) for the functional connectivity analysis. The ROI-to-ROI analysis performs the correlation between the individual differences and the functional connectivity was calculated using the bivariate correlation analysis in CONN. This analysis estimates the pairwise connectivity between every voxel of the brain and the selected seed ROI. In this analysis, no weighting was applied on 132 ROIs defined by the default CONN atlas, which combines the automated anatomical labeling (AAL) atlas and the fMRIB software library (FSL) Harvard-Oxford cortical and subcortical areas. The ROI-to-ROI connectivity analysis was performed to assess the resting-state connections of each participant.

The objectives of this study were twofold: the first was to understand the effect of individual differences on the tendency of developing internet addiction, as measured by CAIS-R, for all participants using resting-state connectivity; the second was to assess age-related differences in the tendency of developing internet addiction in younger and older adults and compare their effects on resting-state brain connectivity. The ROI-to-ROI results were normalized using Fisher z-transformation for normal distribution and averaged across all of the participants to produce average correlations (Jenkins & Donald, 1968). The brain regions associated with the tendency of developing internet addiction were then identified. We set $p < .05$ as the significance threshold, with a false discovery rate (FDR) correction applied for multiple testing, as done in previous rs-fMRI studies (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Geissmann et al., 2018; Manning et al., 2015).

2.9 | Amplitude of low-frequency fluctuation analysis

We analyzed the amplitude of low-frequency fluctuations (ALFFs) using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The blood oxygen level-dependent (BOLD) signal time series for each voxel was first transformed into the frequency domain using fast Fourier transform (FFT). The square root of the power spectrum was calculated by averaging the band pass-filtered frequency, that is, 0.01 to

0.08 Hz. Thus, the ALFFs at each voxel was computed (Yang et al., 2007). ALFFs are usually used to measure the absolute strength of the oscillations in the low-frequency domain. They are computed for every subject and divided by the global mean to reduce variability across participants (Yang et al., 2007).

We examined the effect of the tendency of developing internet addiction on the brain by examining the ALFFs of all participants. This analysis was performed to understand the effects of individual differences on the tendency of developing internet addiction, as indicated by the CIAS-R score. We also used ALFFs to understand the effects of age on the tendency of developing internet addiction in younger and older adults.

3 | RESULTS

All participants scored at least 25 on the MMSE (Folstein et al., 1975), with a mean score of 28.4 for younger and 28.7 for older adults. Younger and older adults had equivalent levels of verbal ability as measured on vocabulary and similarity tests (Wechsler, 1997a). In addition, older adults exhibited lower scores on digit span forward, digit span backward, and letter-number sequencing which measured working memory. This pattern, in which crystallized intelligence (i.e., vocabulary) is spared while fluid intelligence (i.e., speed, and working memory) decreases with age, is typical of most samples in the literature on normal cognitive aging (Fan et al., 2019; Huang, Polk, Goh, & Park, 2012; Park et al., 2002). The educational level in older adults was less compared to younger adults. The two age groups observed inter-individual differences in CIAS-R scores ($p < .001$), particularly in the subscale of internet addiction which measures related interpersonal and health problems. The demographics of both age groups are reported in Table 1.

3.1 | Head motion results

To control the influence of head motion on resting-state functional connectivity measures, we first calculated the mean frame-wise displacement (FD) and tested the correlations between the mean FD and behavioral measures—age, MMSE scores, and IAD scores. We found negative correlations between mean FD and MMSE ($r = -.04$) and IAD ($r = -.07$), and found positive correlation between mean FD and age ($r = .11$). We also assessed the between-subject differences in the mean FD and all behavioral measures and found no significant individual differences in the study ($p = .99$). The younger and older adults did not differ significantly in terms of maximum head motion (Younger: 0.78 ± 0.55 mm; Older: 0.92 ± 0.62 mm; $t[60] = -0.10$; $p = .5461$).

3.2 | Resting-state functional MRI results

The group-ICA was first performed on rs-fMRI data to reveal major brain networks across age groups (Patil et al., 2021). Eleven resting-

TABLE 1 Demographics of the participants

Demographics	Assessment	Younger adults (M ± SD)	Older adults (M ± SD)
Total	-	28	34
Women	-	18	24
Age range	-	20–28 years old	48–76 years old
Age	-	23.1 ± 1.92	63.0 ± 7.65
Years of education	-	16.0 ± 1.57	12.7 ± 3.30
Cognitive ability scores	MMSE	28.4 ± 5.60	28.7 ± 1.08
A tendency of developing internet addiction	IA-Sym	31.7 ± 6.85	23.0 ± 8.30
	IA-RP	25.0 ± 4.76	11.2 ± 3.95
	IAD	56.7 ± 11.01	41.4 ± 14.22

Abbreviations: IAD, internet addiction disorder; IA-RP, internet addiction-related interpersonal and health problems; IA-Sym, internet addiction core symptoms; M, mean; MMSE, mini-mental state examination; SD, standard deviation.

state brain networks from 30 ICA components were then obtained, which is consistent with our previous work that identified age-invariant resting-state networks (Patil et al., 2021).

3.3 | Connectivity analysis: Correlation between a tendency of developing internet addiction tendency and functional brain connectivity

We first performed the ROI-to-ROI analysis to examine the correlation between the tendencies of developing internet addiction on the functional brain connectivity of all participants, regardless of age. We further examined whether and how an elevated tendency of developing internet addiction affected age-related alterations in the functional connectivity of younger and older brains.

With respect to the effect of individual variations on the tendency of developing internet addiction, we observed stronger connectivity with the right angular gyrus ($t = 3.83$, p -FDR = .0421) and left cerebellum (crus 10) ($t = 3.56$, p -FDR = .0487) when the left superior temporal gyrus ($x = -62$, $y = -29$, $z = 4$) was selected as a seed ROI. When the left planum polare ($x = -47$, $y = -6$, $z = -7$) was selected as a seed ROI, we observed stronger connectivity with both left ($t = 4.15$, p -FDR = .0092) and right occipital pole ($t = 4.07$, p -FDR = .0092). When the left lateral occipital cortex ($x = -32$, $y = -73$, $z = 38$) was selected as a seed ROI, we observed weaker connectivity with the vermis (lobule 3) ($t = -3.79$, p -FDR = .0475). When the right putamen ($x = -24$, $y = 0$, $z = 0$) was selected as a seed ROI, we observed stronger connectivity with both left ($t = 3.59$, p -FDR = .0447) and right supracalcarine cortex ($t = 3.76$, p -FDR = .0447). Vermis (lobule 1 2) ($x = 1$, $y = -39$, $z = -20$) found weaker connections with right cerebellum (crus 1) ($t = -4.12$, p -FDR = .0161) and right cerebellum (crus 2) ($t = -4.05$, p -FDR = .0203) when selected as seed ROI. When the right occipital pole ($x = 18$, $y = -95$, $z = 8$) was selected as a seed ROI, weaker connectivity was observed with the right frontal operculum cortex ($t = 3.59$, p -FDR = .0449) (Figure 1 and Table 2).

With respect to the effect of the tendency of developing internet addiction in younger adults, we observed stronger connectivity in the

right precentral gyrus ($t = 3.67$, p -FDR = .0350) as well as in the right superior parietal lobule ($t = 3.44$, p -FDR = .0474) when the right cerebellum (crus 10) ($x = 26$, $y = -34$, $z = -41$), was selected as a seed ROI. When the left inferior frontal gyrus (opercularis) ($x = -51$, $y = 15$, $z = 15$) was selected as a seed ROI, we observed decreased connectivity was observed in the right cerebellum (crus 7b) ($t = -3.81$, p -FDR = .0446). When the right post central gyrus ($x = 38$, $y = -26$, $z = 53$) was selected as a seed ROI, we observed stronger connectivity in the right cerebellum (crus 10) ($t = 4.44$, p -FDR = .0054) and in the left accumbens ($t = 3.77$, p -FDR = .0254). When the right cerebellum (crus 3) ($x = 12$, $y = -35$, $z = -19$) was selected as a seed ROI, we observed stronger connectivity in the vermis (lobule 10) ($t = 4.07$, p -FDR = .0191).

With respect to the effect of the tendency of developing internet addiction in older adults, we observed stronger connectivity in the vermis (lobule 9) ($t = 4.21$, p -FDR = .0121), when the right parietal operculum ($x = 49$, $y = -28$, $z = 22$) is selected as a seed ROI. When the right supracalcarine cortex ($x = 8$, $y = -74$, $z = 14$), was selected as a seed ROI, we observed stronger connectivity in the right putamen ($t = 3.87$, p -FDR = .0372). When the left supracalcarine cortex ($x = -8$, $y = -73$, $z = 15$) was selected as a seed ROI, we observed stronger connectivity in both right ($t = 4.43$, p -FDR = .0056) (Figure 2 and Table 3).

3.4 | ALFFs: Effect of the a tendency of developing internet addiction

We used a voxel-based analysis that relied on ALFFs to analyze the rs-fMRI data. We found a cluster with significantly higher ALFFs in older adults than in younger adults. We first used ALFFs to compute the effects of individual variation on the tendency of developing internet addiction across both younger and older adults. All of the results were voxel threshold-corrected at $p < .05$, and cluster threshold-corrected at $p < .05$ with FDR correction applied for multiple testing.

Our analysis of the effects of individual variations on the tendency of developing internet addiction showed a significant decrease in the ALFFs of the right precentral gyrus, bilateral supplementary

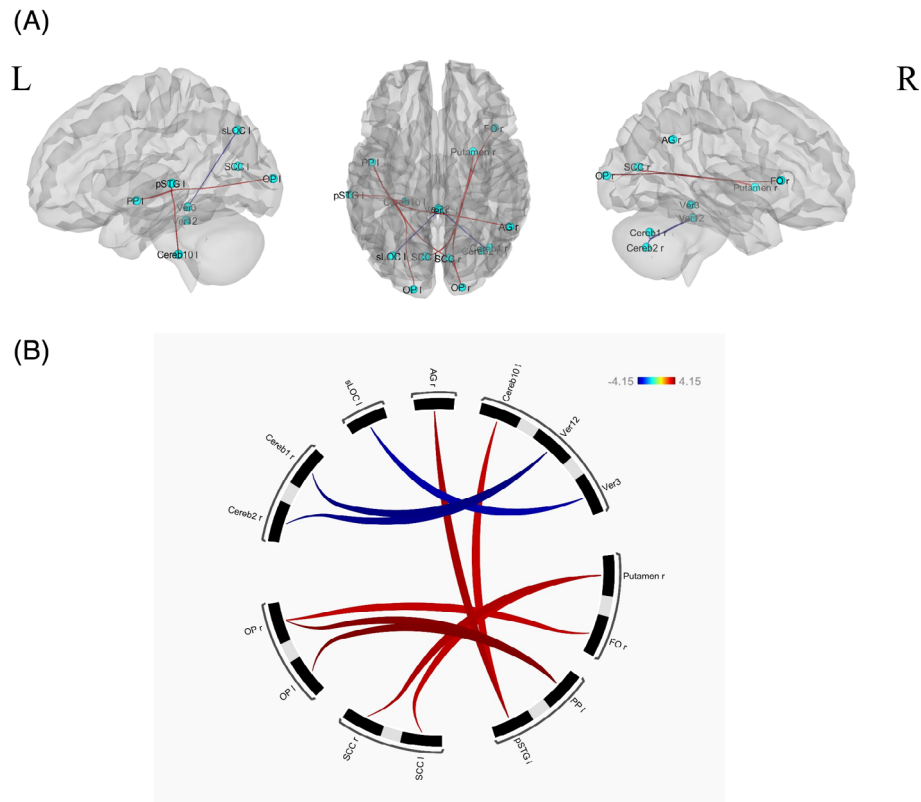


FIGURE 1 The connectome representing resting-state functional brain connectivity of the brain of participants with the tendency of developing internet addiction. (a) Significant effects of the tendency of developing internet addiction on the brain as represented using a three-dimensional glass brain. The cyan dots represent brain regions and the red and blue connections represent positive and negative connections, respectively between the brain regions. (b) Functional connectome representing the effect of a tendency of developing internet addiction on the human brain. The results for (a) and (b) were thresholded at $p < .05$ with a false discovery rate correction applied for multiple testing. *Cereb 1r*: right cerebellum (crus 1b); *Cereb 2r*: right cerebellum (crus 2b); *OP l*: left occipital pole; *OP r*: right occipital pole; *SCC l*: left supra-calcarine cortex; *SCC r*: right supracalcarine cortex; *pSTG l*: left superior temporal gyrus; *PP l*: left planum polare; *FO r*: right frontal opercular cortex; *Putamen r*: right putamen; *Ver 3*: vermis (lobule 3); *Cereb 10 L*: left cerebellum (crus 10); *AG r*: right angular gyrus; *sLOC l*: left lateral occipital cortex; L: left; R: right

TABLE 2 Effect of individual variations on the correlation between a tendency of developing internet addiction and functional brain connectivity

ROI 1	BA	ROI 2	BA	Beta	t	p-FDR
Left superior temporal gyrus	41	Right angular gyrus	39	.01	3.83	.0421
Left superior temporal gyrus	41	Left cerebellum (crus 10)	-	.00	3.56	.0487
Left lateral occipital cortex	19	Vermis (lobule 3)	-	-.01	-3.79	.0475
Left planum polare	41	Left occipital pole	17	.01	4.15	.0092
Left planum polare	41	Right occipital pole	17	.01	4.07	.0092
Right occipital pole	17	Right frontal opercular cortex	44	.00	-3.57	.0306
Right putamen	8	Right supracalcarine cortex	17	.01	3.59	.0449
Right putamen	8	Left supracalcarine cortex	17	.01	3.76	.0447
Right cerebellum crus 1	-	Vermis (lobule 1 2)	-	.01	3.59	.0447
Right cerebellum crus 2	-	Vermis (lobule 1 2)	-	-.00	-4.12	.0161

Note: The threshold for the results was set at $p < .05$, with an FDR correction applied for multiple testing. Abbreviations: BA, Brodmann area; FDR, false discovery rate; ROI, region of interest.

motor cortex, bilateral thalamus, right superior frontal gyrus, right caudate, anterior cingulate gyrus, vermis (lobule 45 and 6), right lingual gyrus and left cerebellum (crus 6) (Figure 3 and Table 4).

Our analysis of age-related effects on the tendency of developing internet addiction showed a significant increase in the ALFFs of the right temporal pole, right frontal orbital cortex, right parahippocampal

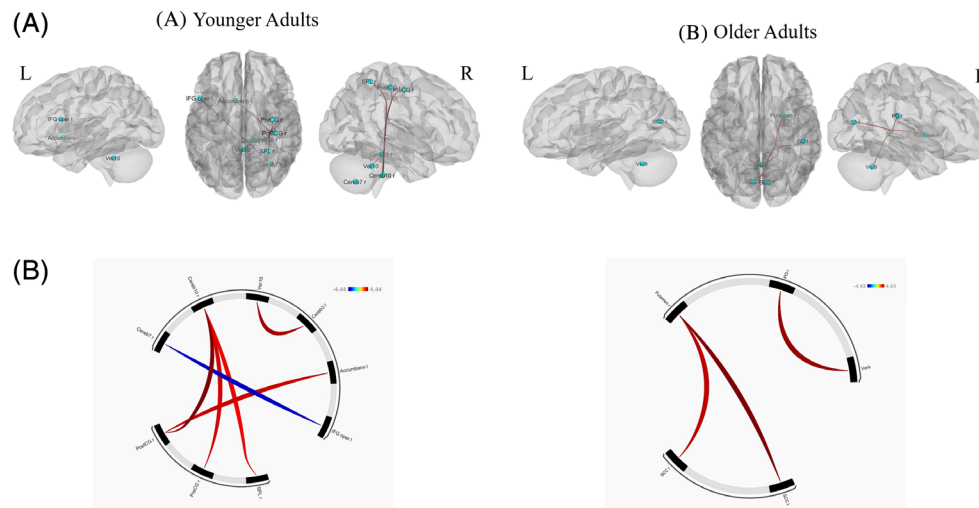


FIGURE 2 The connectome representing resting-state functional brain connectivity of a tendency of developing internet addiction for younger adults and older adults. (a) Significant effects of the tendency of developing internet addiction on the brain, as represented using a three-dimensional glass brain in (A) younger adults and (B) older adults. The cyan dots represent brain regions and the red and blue connections represent positive and negative connections, respectively, between the brain regions. (b) Functional connectome representing the effect of a tendency of developing internet addiction on the human brain in (A) younger adults and (B) older adults. The results for (a) and (b) were thresholded at $p < .05$ with a false discovery rate correction applied for multiple testing. For younger adults: *PostCG r*: right postcentral gyrus; *PreCG r*: right precentral gyrus; *SPL r*: right superior parietal lobule; *IFG oper l*: left inferior frontal gyrus (operculum); *Accumbens l*: left accumbens; *Cereb 3r*: right cerebellum (crus 3); *Cereb 10r*: right cerebellum (crus 10); *Cereb 7r*: right cerebellum (crus 7); *Ver 10*: vermis (lobule 10). For older adults: *Putamen r*: right putamen; *PO r*: right parietal operculum; *Ver 9*: vermis (lobule 9); *SCC l*: left supra calcarine cortex; *SCC r*: right supracalcarine cortex; L: left; R: right

TABLE 3 The correlation between a tendency of developing internet addiction and functional brain connectivity in younger and older adults

ROI 1	BA	ROI 2	BA	Beta	t	p-FDR
Younger adults						
Left inferior frontal gyrus (opercularis)	45	Right cerebellum (crus 7b)	-	-.01	-3.81	.0446
Right post central gyrus	1/2/3	Right cerebellum (crus 10)	-	.01	4.44	.0054
Right post central gyrus	1/2/3	Left accumbens	25	.01	3.77	.0254
Right cerebellum (crus 3)	-	Vermis (lobule 10)	-	.01	4.07	.0191
Right cerebellum (crus 10)	-	Right precentral gyrus	-	.01	3.67	.0350
Right cerebellum (crus 10)	-	Right superior parietal lobule	5/7	.01	3.44	.0474
Older adults						
Right parietal operculum	40	Vermis (lobule 9)	-	.01	4.21	.0121
Right supracalcarine cortex	17	Right putamen	8	.01	3.87	.0372
Left supracalcarine cortex	17	Right putamen	8	.01	4.43	.0056

Note: The threshold for the results was set at $p < .05$, with an FDR correction applied for multiple testing.

Abbreviations: BA, Brodmann area; FDR, false discovery rate; ROI, region of interest.

gyrus, and right amygdala and a significant decrease in the ALFFs of the precuneus cortex and posterior cingulate gyrus in older adults over those of younger adults (Figure 4 and Table 5).

4 | DISCUSSION

Several studies have suggested that psychiatry- and behavior-related disorders may stem from the reorganization of functional brain

networks (Fox & Greicius, 2010). This network neuroscience-based rs-fMRI study investigated whether and how individual variations in the tendency of developing internet addiction alter functional brain connectivity and diminish ALFFs in healthy brains. We also examined the influences of neurocognitive aging on executive-cerebellar networks responsible for internet addictive behaviors. Our findings revealed disrupted executive-cerebellar networks but increased occipital-putamen connectivity, probably resulting from addiction-sensitive cognitive control processes and bottom-up sensory capabilities in

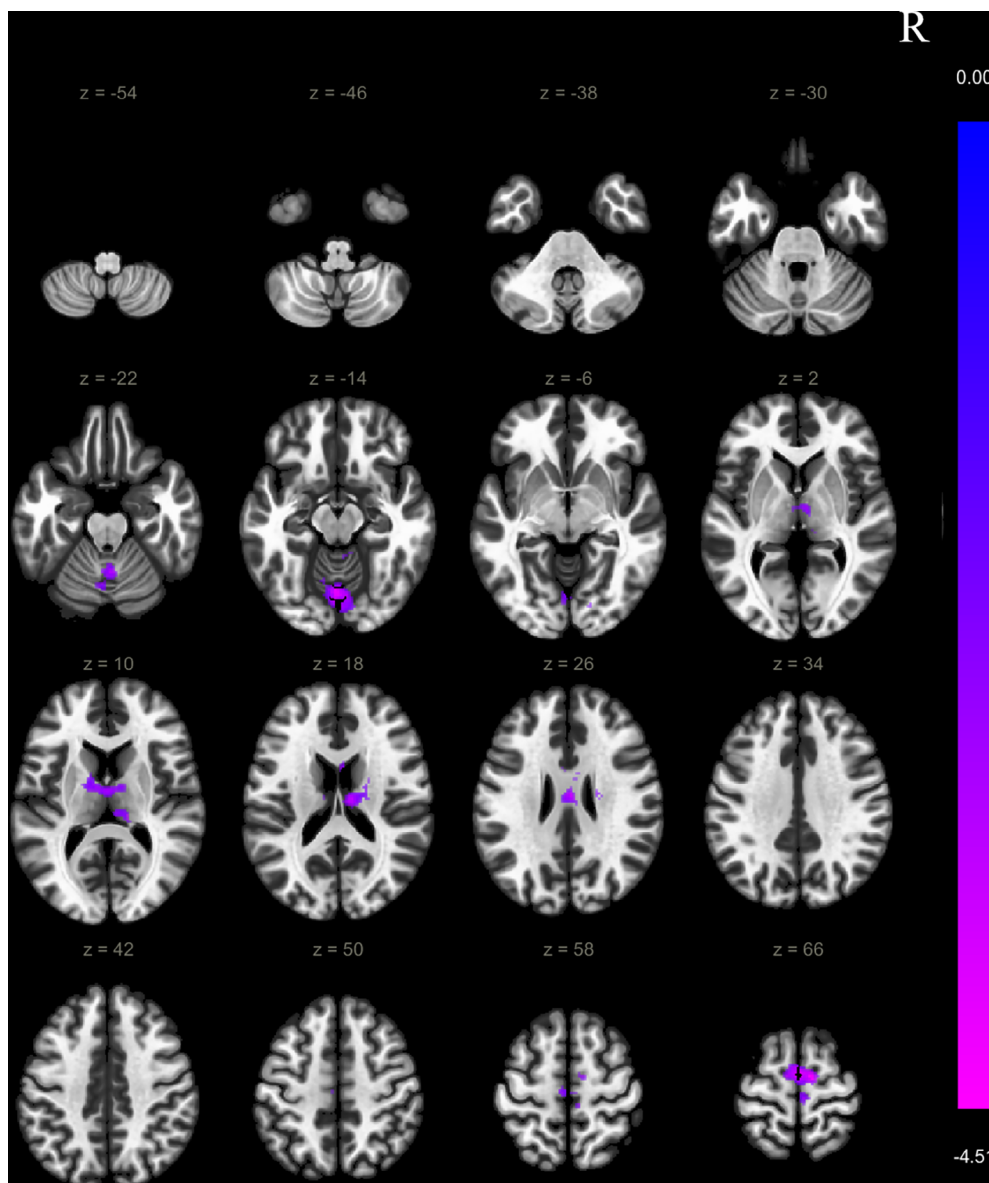


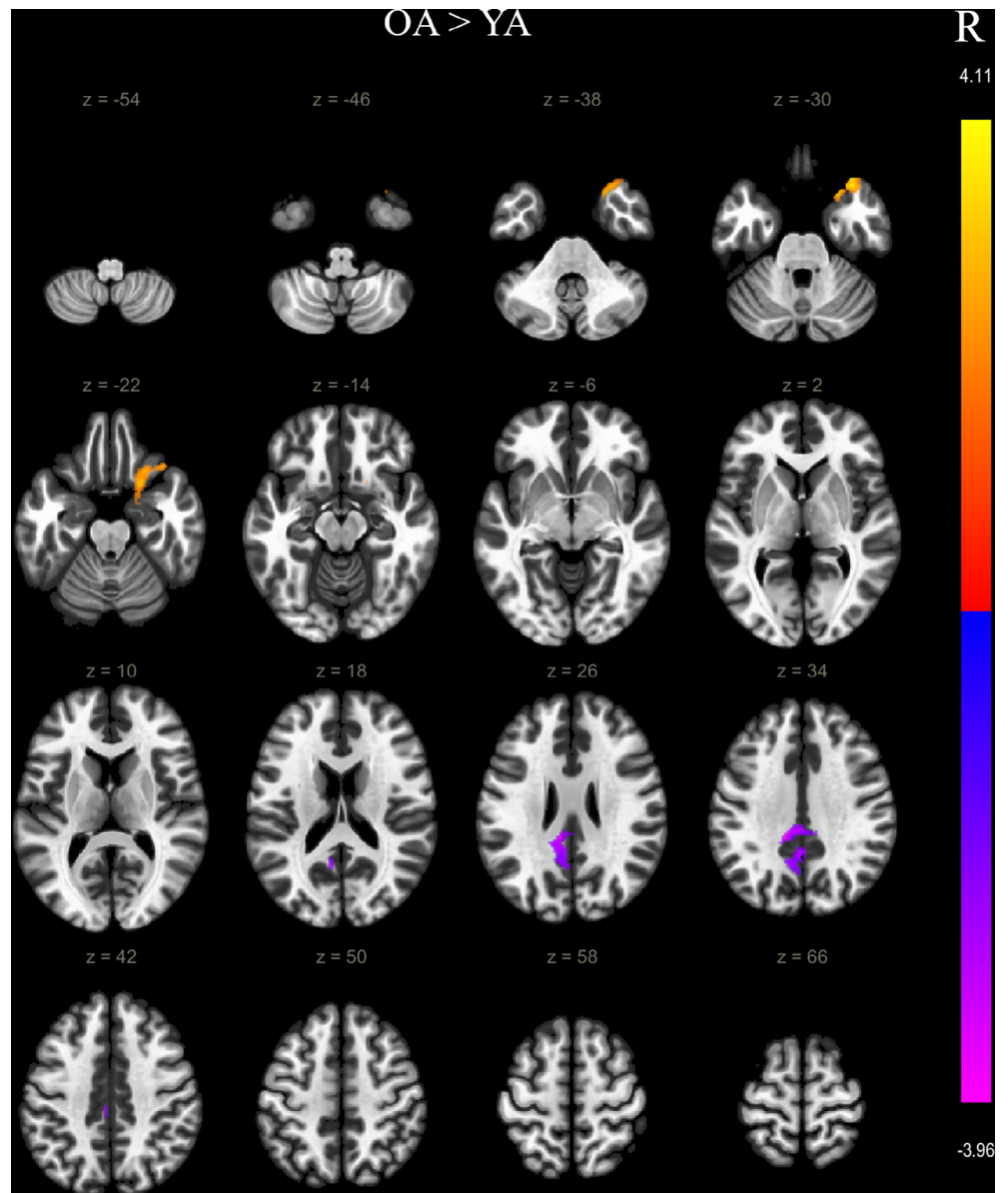
FIGURE 3 The Analysis of the effect of individual differences on brain regions associated with the tendency of developing internet addiction, showing a significant decrease in the amplitude of low-frequency fluctuations (ALFFs) across all participants. Analysis of the effect of individual differences on the tendency of developing internet addiction and associated brain regions showed a significant decrease in the ALFFs in all participants. The brain regions that showed reduced ALFFs were the right precentral gyrus, bilateral supplementary motor area, right superior frontal gyrus, bilateral thalamus, right caudate; anterior cingulate gyrus, right lingual gyrus, and regions of the cerebellum. The clusters were voxel threshold-corrected at $p < .05$ and cluster threshold-corrected at $p < .05$, with a false discovery rate correction applied for multiple testing. The color bar indicates the range of the t value; R: right

TABLE 4 The individual variations in the amplitude of low-frequency fluctuations associated with a tendency of developing internet addiction

Cluster	Region	Voxels	Cluster size	x	y	z	p	t
1	Right precentral gyrus	223	830	8	-8	66	.0209	-4.79
	Right supplementary motor cortex	141						
	Left supplementary motor cortex	117						
	Right superior frontal gyrus	71						
2	Right thalamus	260	731	4	6	22	.0229	-4.71
	Left thalamus	126						
	Right caudate	18						
	Anterior cingulate gyrus	13						
3	Vermis (lobule 6)	201	672	2	-54	-18	.0249	-4.96
	Left cerebellum crus 6	132						
	Right lingual gyrus	87						
	Vermis (lobule 4 5)	83						

Note: The results were voxel threshold-corrected at $p < 0.05$ and cluster threshold-corrected at $p < .05$ with a false discovery rate correction applied for multiple testing.

FIGURE 4 Analysis of the effect of age on brain regions associated with the tendency of developing internet addiction, showing a significant increase in the amplitude of low-frequency fluctuations (ALFFs) in older healthy adults compared with younger healthy adults. The analysis of the effect of age on brain regions associated with the tendency of developing internet addiction showed a significant increase in the amplitude of ALFFs in older adults compared to younger adults. The regions with reduced ALFFs were the posterior cingulate gyrus and precuneus cortex whereas increased ALFFs were found in the right temporal pole, right frontal orbital cortex, right parahippocampal gyrus, and right amygdala. The clusters were voxel threshold-corrected at $p < .05$ and cluster threshold-corrected at $p < .05$, with a false discovery rate correction applied for multiple testing. The color bar indicates the range of the t value; R: right



healthy adults with elevated tendencies to develop internet addiction. The rs-fMRI scans showed altered functional and brain network connectivity as a consequence of age-related and individual variations, which play a critical role in defining the risk of developing internet addictive disorders. This network neuroscience and supportive evidence-based rs-fMRI study can be used to validate preclinical markers of internet addictive behavior in older adults.

Previous neuroimaging and neurological studies have shown the importance of the cerebellar network in neurocognitive functions and neuropsychiatric disorders such as addictive behaviors (Anderson et al., 2006; Grant et al., 1996; Schneider et al., 2001). A few studies based on fMRI and positron emission tomography (PET) have outlined the roles of increased activity and metabolism in the cerebellum in response to drug-conditioned cues (Grant et al., 1996; Wang et al., 1999). Other studies have explored the modulation of the cerebellum during decision-making behaviors and inhibitory control

associated with addiction (Bolla, Eldreth, Matochik, & Cadet, 2005; Hester & Garavan, 2004). Wang et al. used rs-fMRI to compare the effects of heroin addiction; they assessed ALFFs in heroin addicts and normal controls (Wang et al., 2013) and found higher ALFFs in the cerebellum and the superior temporal and occipital gyrus in heroin addicts than in healthy controls. Our rs-fMRI study focused on internet addiction and demonstrated diminished ALFFs in the cerebellum and reduced connections of the cerebellum with other regions such as the supplementary motor cortex, temporal pole, and subcallosal cortex. Our results indicated low-frequency fluctuations in the cerebellum could serve as preclinical markers of internet addiction. More importantly, our findings support previous reports stating that altered cerebellar networks and reduced cerebellar functions reflect domain-general neurobiological signatures of a variety of addictive disorders, including substance-related and behavioral addiction.

TABLE 5 Age-related alterations in the amplitude of low-frequency fluctuations associated with the tendency of developing internet addiction

Cluster	Region	Voxels	Cluster size	x	y	z	p	t
Older > young								
1	Posterior cingulate gyrus	322	649	-8	-34	28	.0491	-4.33
	Precuneous	149						
2	Right temporal pole	308	611	34	22	-26	.0491	3.92
	Right frontal orbital cortex	178						
	Right parahippocampal gyrus	20						
	Right amygdala	4						

Note: The results were voxel threshold-corrected at $p < .05$ and cluster threshold-corrected at $p < .05$ with a false discovery rate correction applied for multiple testing.

The prefrontal cortex is known to play a key role in addictive behaviors as it controls several neurocognitive functions (Goldstein & Volkow, 2011) and regulates the limbic reward system (Brenner, 1997; Goldstein & Volkow, 2011). Of the numerous regions that connect the prefrontal cortex and limbic reward system, the nucleus accumbens is a central hub that mediates reward circuitry and reinforces food-related and sexual behaviors (Koob & Volkow, 2010). The bi-directional connections to the distributed frontal areas have been reported to be strongly associated with impulsivity (Behan, Stone, & Garavan, 2015). Addiction has also been linked to changes in connectivity between the nucleus accumbens and the prefrontal cortex. Several studies have investigated the effects of addictions such as internet gaming disorder, alcohol abuse, and internet addiction on the human brain. Altered connections in the cognitive control network (Weinstein, 2017) have been characterized in the context of substance addiction. Moreover, strong connections between the dorsolateral prefrontal cortex and temporoparietal junction have been observed in individuals with internet addiction (Han, Kim, Bae, Renshaw, & Anderson, 2017) and other cognitive disorders (Anderson et al., 2011; Anderson et al., 2013). ICN activation has been observed in correlational studies on problematic internet use, suggesting insufficient control of internet overuse and consequent behavioral addictions (Darnai et al., 2019; Grant, Potenza, Weinstein, & Gorelick, 2010; Ko et al., 2008). Our study found stronger associations between the accumbens and the postcentral gyrus in younger adults than in older adults. We also observed activations of the orbitofrontal cortex, which is involved in inhibitory control. Our study revealed a greater degree of ALFF activation in the orbitofrontal cortex and parahippocampal and temporal pole regions, indicating a stronger role for ALFF regulation in the tendency of developing internet addiction in older adults than in younger adults.

Our study was the first to examine the influences of neurocognitive aging on executive-cerebellar networks responsible for internet addictive behaviors. Previous studies that examined age-related addiction showed orbitofrontal tissue loss due to aging in older adults (Resnick, Lamar, & Driscoll, 2007). We found increased occipital-putamen connectivity in older participants

indicating diminished cognitive control and decision-making processes in older adults. Our findings elucidate the effects of age and individual differences on altered brain network connectivity, indicating that the tendency of developing internet addiction is subject to age-related modulation of brain networks. Our findings can help develop useful preclinical markers in the form of altered brain connectivity. These markers can help to identify individuals of different ages who are at a high risk of developing internet addictive behaviors.

In conclusion, this network neuroscience-based rs-fMRI study revealed that participants with an elevated tendency of developing internet addiction showed diminished cognitive control and decision-making processes. Our analysis of the effects of neurocognitive aging suggested age-related modulation of addictive brain networks in response to compulsive internet use. The study further showed that age-related alterations to connectivity between functional brain networks are associated with a higher risk of developing internet addictive disorders in healthy individuals. The findings can contribute to the development of preclinical markers of the tendency of developing internet addiction in older adults.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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