Problematic Internet use is associated with structural alterations in the brain reward system in females

Internet addiction and the brain reward system

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ABSTRACT

Neuroimaging findings suggest that excessive Internet use shows functional and structural brain changes similar to substance addiction. Even though it is still under debate whether there are gender differences in case of problematic use, previous studies by-passed this question by focusing on males only or by using gender matched approach without controlling for potential gender effects. We designed our study to find out whether there are structural correlates in the brain reward system of problematic Internet use in habitual Internet user females. T1-weighted Magnetic Resonance (MR) images were collected in 82 healthy habitual Internet user females. Structural brain measures were investigated using both automated MRi volumetry and voxel based morphometry (VBM). Self-reported measures of problematic Internet use and hours spent online were also assessed. Using MRi volumetry, problematic Internet use was associated with increased grey matter volume of bilateral putamen and right nucleus accumbens while decreased grey matter volume of orbitofrontal cortex (OFC). Similarly, VBM analysis revealed a significant negative association between the absolute amount of grey matter OFC and problematic Internet use. Our findings suggest structural brain alterations in the reward system usually related to additions are present in problematic Internet use.

Keywords: automated MRI volumetry; brain reward system; Internet addiction; MRI; voxel-based morphometry

INTRODUCTION

Our everyday habits can result in structural and functional brain alterations (Joseph 1999; Maguire *et al.* 2006; Löwdén *et al.* 2013). The Internet has not only become our external memory and an essential media source for social life and entertainment, but it also has full potential to become addictive (Sparrow *et al.* 2011; Brenner 1997). It is still a matter of discussion whether addition to the Internet is an independent psychiatric disorder (Griffiths 2000; Mitchell 2000; Morahan-Martin 2005). However, it seems reasonable to interpret problematic Internet use as a behavioural addiction or an impulse control disorder that is a result of excessive use of certain activities available on the Internet (Young 1999; Spada, 2014; Laconi *et al.* 2015).

Neuroimaging findings support the addiction theory frame as problematic Internet use has been related to changes in brain reward pathways usually associated with substance addiction (Dong *et al.* 2011; Kuss & Griffith 2012). While the majority of the Magnetic Resonance imaging (MRI) studies used functional paradigms, only few investigated possible structural correlates of excessive Internet use. However, structural and microstructural brain alterations have been already demonstrated in Internet addicted adolescents (relative to controls) in areas related to craving, motivation and cognitive control (Yuan *et al.* 2011; Zhou *et al.* 2011). Furthermore, one study demonstrated negative associations between excessive Internet use with grey matter and altered functional connectivity in the fronto-striatal circuitry in a large sample of healthy habitual user males (Kühn & Gallinat 2015).

A significant shortcoming of the previous brain imaging findings is related to the ongoing discussion whether gender differences are present in excessive Internet use. While clinical reports showed male predominance, others reported no significant gender difference or even female predominance (Shaw & Black 2008; Odaci & Çıkrıkçı 2014).

Additionally, gender difference is present in the preferred activities online (Morahan-Martin & Schumacher 2000; Durkee *et al.* 2012). However, previous neuroimaging studies by-passed this question by focusing on males only or by using a gender matched approach (Yuan *et al.* 2011; Liu *et al.* 2010; Lin *et al.* 2012).

Taking the above mentioned limitations into consideration, our aim was to investigate the structural correlates of problematic Internet use in the brain reward system in a large non-clinical sample of habitual Internet user females using both automated MRI volumetry and voxel-based morphometry (VBM). Based on previous neuroimaging findings and the known role of brain reward system in substance addictions, we hypothesized that regions of the fronto-striatal circuit (orbitofrontal cortex, caudate, putamen, nuclei accumbens) and amygdala -that provides important inputs to the striatum -would be associated with problematic Internet use (Volkow & Baler 2014). In the lack of well-established diagnostic criteria, we decided to use a multidimensional continuous measure of Problematic Internet use.

MATERIALS AND METHODS

Participants

Caucasian right-handed healthy female university students, aged between 18 and 30 were recruited based on advertisements placed at the local university. Eighty-two females met the inclusion criteria and took part in our study. Mean age was 22.83 (SD = 2.3) and all participants use the Internet on a daily basis. The study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to participating in the study.

Questionnaires

Without clear diagnostic criteria, it is highly recommended to measure excessive Internet use with a multidimensional and continuous questionnaire without using unclear cut-off scores (Ko *et al.* 2005). Therefore, we used Problematic Internet Use Questionnaire (PIUQ), a validated self-report scale with good reliability and validity characteristics (Demetrovics *et al.* 2008). PIUQ was created based on the factor analysis and psychometric analysis of the original and modified items of Young's Internet Addiction Test (Young 1998). A confirmatory factor analysis verified the three factor model of questionnaire (Koronczai *et al.* 2011). Each subscale contains six items and respondents answer each item using a 5-point scale, ranging from 1 to 5.

Obsession subscale refers to obsessive thinking about the Internet (daydreaming, rumination and fantasizing) and withdrawal symptoms caused by the lack of Internet use (anxiety, depression). *("How often do you feel tense, irritated, or stressed if you cannot use the Internet for as long as you want to?")*

Neglect subscale contains items about neglecting everyday activities, social life and essential needs. ("*How often do you spend time online when you'd rather sleep"*?

Control disorder subscale reflects difficulties in controlling time spent on the Internet. ("*How often do you realize saying when you are online, 'just a couple of more minutes and I will stop'*?")

Additional questions were administered to assess hours weekly spent on the Internet. To exclude possible neurological and psychiatric disorders, substance abuse and chronic illnesses, subjects also completed an exploratory questionnaire about lifestyle factors, mental and physical health. Handedness was measured using Edinburgh Handedness Inventory (EDI) (Oldfield 1971).

MRI examinations

MRI measurements were performed on a 3 Tesla MR scanner (Siemens Magnetom Trio Tim System, Siemens AG, Erlangen, Germany) with a 12-channel head coil. For the volumetric analysis a T1 weighted axial reformation of the isotropic sagittal magnetization-prepared rapid acquisition with gradient echo (MPRAGE) images were used: FoV=256x256^2 mm, TR=2530 ms, TE=3.37 ms, TI=1100 ms, slice thickness=1 mm, slice number=176, FA=7^o, bandwidth=200 Hz/pixel, 256x256 matrix.

MRI data post processing evaluation

Volumetric analysis

Freesurfer 4.5.0 was used for cortical reconstruction and volumetric segmentation of the images (http://surfer.nmr.mgh.harvard.edu/) to assess volumes of right and left amygdala, nucleus accumbens, putamen, caudate and orbitofrontal cortex. Freesurfer software provides one the most reliable automated brain segmentation methods for cortical and subcortical structures. It also allows us to assess the volume of the pre-defined brain structures in a large number of subjects (Fischl *et al.* 2002; Fischl *et al.* 2004, Morey *et al.* 2009; Pardoe *et al.* 2009).

Freesurfer's semi-automatic anatomical processing scripts (autorecon1, 2 and 3) were executed on all subjects' data. Manual verifications were performed in case of every subject after each script, and error corrections were applied wherever it was indicated (http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction/).
The volume-based stream is designed to preprocess MRI volumes and label subcortical tissue classes. All stages of the stream are fully described by Fischl *et al.* (2002). The final segmentation is based on a probabilistic atlas and the subject-specific measured values. Visual analysis of the images identified no brain abnormalities.

Statistical analyses for volumetry were performed using IBM SPSS 20.0 software package (IBM Corp., Armonk, NY). The following structures were investigated separately: bilateral amygdala, nuclei accumbens, putamen, caudate and orbitofrontal cortex. Multiple linear regression models were created for each structure as a dependent variable with all three subscales of PIUQ separately as an independent variable. Head correction was done using the statistical method: intracranial volume (ICV) was entered as additional independent variable (Perlaki *et al.* 2014). To test whether problematic Internet use is associated with volumetric alterations in the reward system, multiple linear regression models were created for all three PIUQ subscales with each investigated region with the control of age and intracranial volume.

All assumptions of multiple linear regression were satisfied, as judged by testing for linearity, normality assumptions of the residues, outliers, independence of errors, homoscedasticity and multicollinearity (Chan 2004).

VBM

VBM was performed with FSL-VBM (http://www.fmrib.ox.ac.uk/fsl) to assess OFC grey matter volume. An 'optimised' VBM protocol (Good et al. 2001) was carried out with FSL tools (Smith *et al.* 2004). First, structural images were brain-extracted using BET (Smith 2002). Next, tissue-type segmentation was carried out using FAST (Zhang *et al.* 2001). The resulting grey-matter partial volume images were then aligned to MNI152 standard space using non-linear registration (Andersson *et al. 2007*). The resulting images were averaged together with their respective mirror images to create a left–right symmetric study-specific gray matter template. The registered partial volume images were then modulated (to correct for local expansion or contraction owing to both affine and nonlinear components of the registration) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

Finally, to test association between OFC and each subscales of PIUQ, voxelwise general linear models (GLM) were applied using permutation-based non-parametric testing (5000 permutations), correcting for multiple comparisons across space. Results were considered significant for $p<.05$, corrected for multiple comparisons using "threshold-free cluster enhancement" (TFCE), which avoids making an arbitrary choice of the cluster-forming threshold, while preserving the sensitivity benefits of clusterwise correction (Smith & Nichols 2009). Similar to volumetry, head correction was done by entering ICV to GLM as as an independent variable. Age was also included as a control variable for all comparisons.

RESULTS

Descriptives

Mean score for the PIUQ was 28.71 (SD = 7.76; range 18-53). Mean score on the PIUQ subscales were 8.39 (SD = 2.28; range 6-16) for Obsession, 1.13 (SD = 2.28; range 6-21) for Neglect and 1.18 (SD = 2.28; range 6-20) for Control Disorder. Participants spent 12.85 hours (SD = 9.33) on the Internet per week on average. They used 31% of their time on the Internet on working/or studying, 22% on surfing, 19% on social networking, 15% on corresponding to emails, 10% on chatting and only 3% on online games. The time spent on the Internet was significantly correlated with Obsession (r_s = .291; $p < .01$), Neglect (r_s = .322; $p < .01$) and Control Disorder (r_s = .325; $p < .01$).

Volumetry

Significant positive associations were found between Control disorder and both left and right putamen and between Obsession and right nucleus accumbens. Obsession also showed a significant negative association with both left and right OFC while Neglect was negatively related to left OFC (see results for all investigated regions in Table 1).

The average hours spent online was also added to all significant models to test its possible cofounding effect. However, it did not contribute significantly to the prediction of the volume of the investigated regions.

VBM

Subscales of PIUQ were used separately to predict absolute amount of OFC grey matter in GLM while controlling for intracranial volume and age. A significant negative correlation was found between the absolute amount of grey matter in left OFC with Neglect (Figure 1.), and between the absolute amount of grey matter in right OFC and Control disorder (Figure 2.), while OFC showed no significant association with Obsession. Other regions of interest were not predicted significantly by any of PIUQ subscales.

DISCUSSION

In this study, structural correlates of subclinical Internet addiction tendencies were demonstrated in the brain reward system in a large group of habitual Internet user females. We assessed a multidimensional continuous measure of problematic Internet use, PIUQ (Demetrovics *et al.* 2008). The three subscales of PIUQ capture different signs of addictive tendencies that are often present in behavioural and chemical addictions: Since PIUQ subscales represent different aspects of addictive symptoms that may have distinguishable role in the brain reward system, we decided to investigate their potential affect separately.

To identify structural brain changes MRI volumetry and VBM were used. These volumetric methods follow different approach and therefore enables different conclusions: while volumetry is based on automatic segmentation of brain regions, VBM provides "voxelwise overview of regional morphological effects" (Morey *et al.* 2009; Good *et al.* 2001; Keller & Roberts 2009; Perlaki *et al.* 2014). Previous structural neuroimaging studies about Internet addiction used the VBM approach. For example, a VBM study (Zhou *et al.* 2011) in Internet addicted adolescents compared to normal controls found lower grey matter density in areas related to craving, motivation, emotional behaviour regulation (left anterior cingulate cortex, left posterior cingulate cortex, left insula, and left lingual gyrus). Here, we demonstrated structural brain changes in the reward system in females with both techniques. As a result of MRI based volumetry, increased grey matter volume of bilateral putamen, and right nucleus accumbens and decreased grey matter volume of OFC were associated with PIUQ subscales. The significant negative associations between the absolute amount of grey matter bilateral OFC and PIUQ subscales were also present in the VBM analysis. These relationships remained significant even after controlling for average hours spent online, suggesting that the effect of addictive tendencies are not simply the result of the amount of time on the world wide web (Chou *et al.* 2005).

According to our results, structural brain changes in three regions of the cortico-striatal network are present in healthy females. It is difficult to relate our findings to previous neuroimaging reports about Internet addition, since no study has been conducted in females in this specific field. However, craving and reinforcement of addictive behaviour has already been related to functional changes in the nucleus accumbens in long term drug users and online gaming addict males (Kalivas & Volkow, 2005; Ko *et al.* 2009). In our study, grey matter volume of right nucleus accumbens was positively related to Obsession, a preoccupation with Internet related thoughts. It may be hypothesized that our result is a structural correlate of Internet craving. Functional changes in the striatum have already been related to misuse of the Internet, as putamen is revealed to be the mostly involved subcortical region of the brain reward system with decreased functional connectivity (Hong *et al.* 2013). At the cellular level, Internet addicts have reduced dopamine D2 receptor availability in the right putamen (Kim *et al.* 2011). In line with previous findings, structural changes in putamen related to Control disorder may reflect a deficit of the reward processing mediated by the cortico-striatal network related to compulsive Internet use (Jung *et al.* 2013).

The OFC plays an essential role in executive functions, emotional regulation and motivation and it has been linked to the compulsive aspect of addiction (Goldstein & Volkow 2002; Volkow *et al.* 2003). Bilateral atrophy in OFC was already found in problematic Internet user teenager boys compared to controls (Yuan *et al.* 2011). In our study the negative association between grey matter of OFC and subscales of PIUQ was proved by both volumetry and VBM. Out of the PIUQ subscales, Neglect was related to both decreased volume and absolute amount of grey matter of the left OFC. This may be a result of decreased sensitivity for biological rewards and decreased control over Internet use.

Taken together, our results suggest that problematic Internet use has structural brain correlates in the reward system in healthy habitual Internet user females. Since similar associations have been identified in the fronto-striatal circuit in habitual Internet user males (Kühn & Gallinat 2015), our findings can be interpreted as a proof for morphological brain alterations related to excessive Internet use in both gender. However, Possible gender related associations between brain morphology and Internet habits should be further investigated as sexual dimorphism in the brain structure can contribute to behavioural differences (Mutlu *et al.* 2013; Sun *et al.* 2015). Longitudinal studies are highly needed to test whether these structural correlates are the result of overall additive tendencies or specific to maladaptive Internet use.

Limitations

Since we investigated habitual Internet user females, our findings are limited to female population. Due to the cross-sectional nature of the study, the directionality of the relationship cannot be ascertained.

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Authors contribution

JJ, AA, RH and ZC were responsible for study concept and design. AA, EP, GD, GP, RH, GO, SAN performed the experiments with PB, AS, NK, SK and JJ as supervisors. GP, RH, GO and SAN prepared the dataset and assisted with analyses. AA, EP and GD carried out the analyses. AA drafted the manuscript, ZC and JJ provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version of the manuscript.

		Predictor								
		Obsession			Neglect			Control Disorder		
Investigated brain regions		β	R^2	F	β	R^2	F	β	R^2	F
Left-sided structures	Amygdala	.188	.162	6.234	.050	.129	4.995	.082	.133	5.150
	Accumbens	.210	.085	3.516	.102	.051	2.453	.047	.043	2.199
	Caudatum	.118	.132	5.100	.067	.122	4.760	.178	.150	5.772
	Putamen	.160	.140	5.413	.093	.123	6.821	**.229***	.169	6.486
	OFC	**-.226***	.120	4.688	**-.232***	.124	4.816	-.125	.084	3.491
Right-sided structures	Amygdala	.197	.144	5.544	.027	.105	4.171	.000	.104	4.146
	Accumbens	**.238***	.105	4.165	.113	.061	2.739	.156	.072	3.101
	Caudatum	.065	.126	4.906	.023	.123	4.774	.108	.134	5.182
	Putamen	.194	.182	7.012	.124	.160	6.133	**.237***	.202	7.835
	OFC	**-.297****	.238	9.433	-.056	.151	5.809	-.072	.153	5.891

Table 1. Association of the investigated brain structures with Problematic Internet Use subscales controlled for ICV and age. df= 81 in all models; **p* <.05; **p<0.1

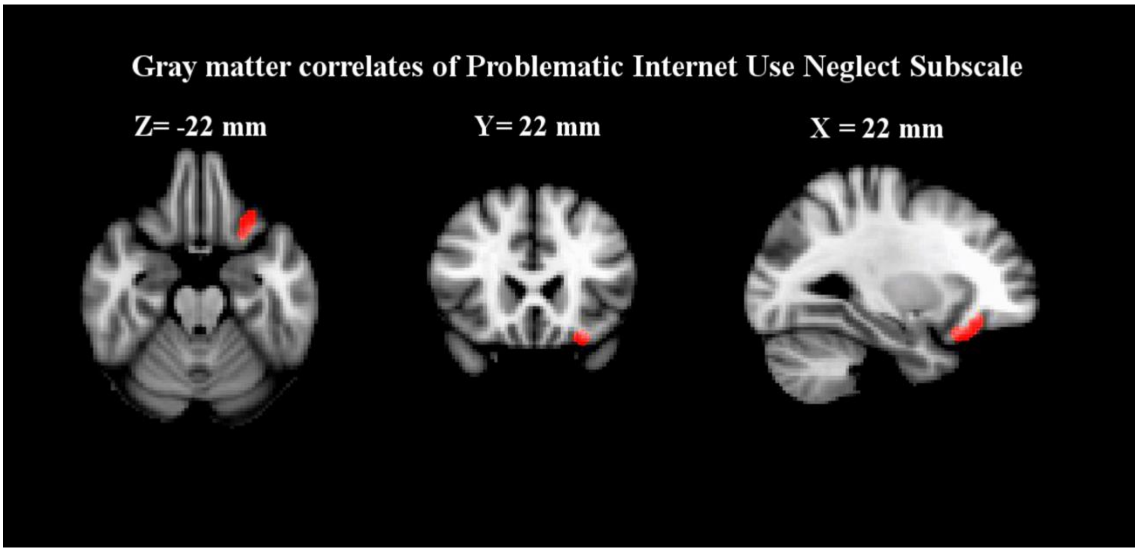

Figure 1. Voxelwise analysis of the grey matter of the OFC using the data of 82 female including Neglect, age and ICV as independent variables in the statistical model. Red voxels are demonstrating significant negative correlation between Neglect subscale and grey matter in left OFC (corrected p<.05). The background image is the MNI152 standard space T1 template. X-, Y- and Z-values indicate the MNI slice coordinates in millimetre. Images are shown in radiological convention

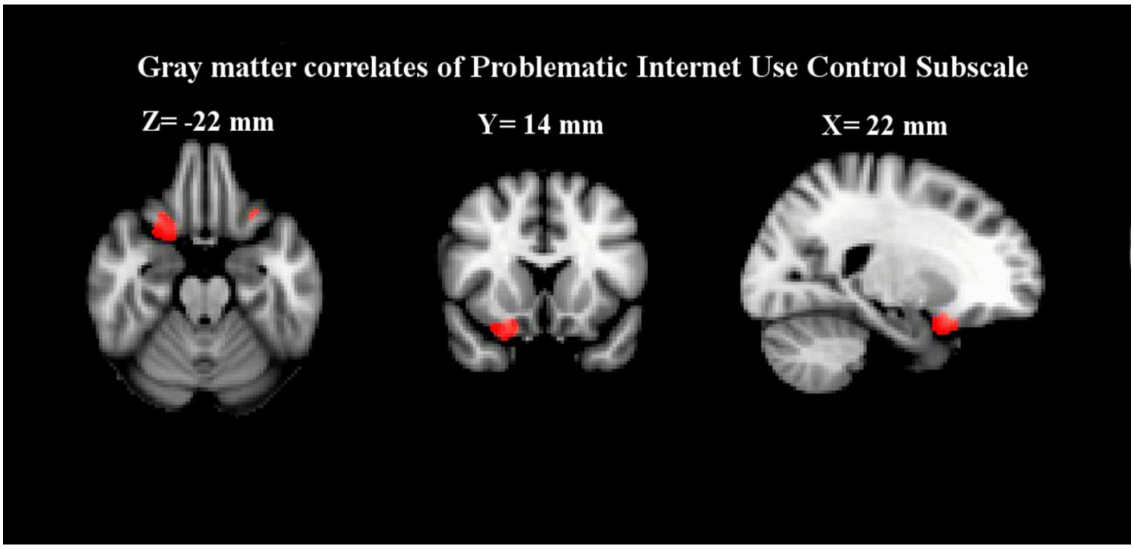

Figure 2. Voxelwise analysis of the grey matter of the OFC using the data of 82 female including Control subscale, age and ICV as independent variables in the statistical model. Red voxels are demonstrating significant negative correlation between Control subscale and grey matter in right OFC (corrected p<.05). The background image is the MNI152 standard space T1 template. *X*-, *Y*- and *Z*-values indicate the MNI slice coordinates in millimetre. Images are shown in radiological convention

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