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Orbitofrontal gray matter deficits as marker of Internet gaming disorder: converging evidence from a cross-sectional and prospective longitudinal design

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ABSTRACT

Internet gaming disorder represents a growing health issue. Core symptoms include unsuccessful attempts to control the addictive patterns of behavior and continued use despite negative consequences indicating a loss of regulatory control. Previous studies revealed brain structural deficits in prefrontal regions subserving regulatory control in individuals with excessive Internet use. However, because of the cross-sectional nature of these studies, it remains unknown whether the observed brain structural deficits preceded the onset of excessive Internet use. Against this background, the present study combined a cross-sectional and longitudinal design to determine the consequences of excessive online video gaming. Forty-one subjects with a history of excessive Internet gaming and 78 gaming-naive subjects were enrolled in the present study. To determine effects of Internet gaming on brain structure, gaming-naive subjects were randomly assigned to 6 weeks of daily Internet gaming (training group) or a non-gaming condition (training control group). At study inclusion, excessive Internet gamers demonstrated lower right orbitofrontal gray matter volume compared with Internet gaming-naive subjects. Within the Internet gamers, a lower gray matter volume in this region was associated with higher online video gaming addiction severity. Longitudinal analysis revealed initial evidence that left orbitofrontal gray matter volume decreased during the training period in the training group as well as in the group of excessive gamers. Together, the present findings suggest an important role of the orbitofrontal cortex in the development of Internet addiction with a direct association between excessive engagement in online gaming and structural deficits in this brain region.

Keywords brain structure, Internet addiction/Internet gaming disorder, orbitofrontal cortex, prospective design.

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INTRODUCTION

During the last decade, the availability of high-speed Internet has grown on a global scale. While the technological infrastructure has afforded tremendous opportunities, these have come together with the cost of potential negative consequences in terms of excessive or even addictive patterns of Internet use, which can interfere with aspects of daily life, such as academic performance, health, and social activities (Kuss 2013). Although there is still no consensus about the gold standard for the assessment of addictive behavior in this context, the available epidemiological data suggest a rapidly emerging public health issue with growing prevalence rates, particularly for problematic online video gaming (between 0.8 percent in Italy and 26.7 percent in Hong Kong; Kuss *et al.* 2014). Recent and upcoming developments in the international classification systems for mental disorders take account of this emerging health issue and have either included Internet gaming disorder (IGD) (DSM-5 appendix; section III, emerging disorders) or aim to include online computer and Internet addiction (ICD-11, expected 2017) to emphasize the need for further research in this area that might inform diagnostic decision making and promote the development of specialized treatment strategies.

The diagnostic criteria for IGD strongly overlap with symptoms of other addictive disorders, assuming that behavioral addictions such as IGD and pathological gambling share common characteristics with substance use disorders. Core symptoms include unsuccessful attempts to control the addictive patterns of behavior and continued use despite negative consequences indicating that a loss of regulatory control might represent a common key feature of IGD, as well as of behavioral and substance-related addictions (Koob & Volkow 2010; Goldstein & Volkow 2011; Brand, Young, & Laier 2014; Park, Han, & Roh 2016). Emotional and behavioral control strongly relies on the integrity of the prefrontal cortex (Bari & Robbins 2013; Etkin, Buchel, & Gross 2015), and in line with the proposed importance of this domain for the development and maintenance of addiction, studies in substance-dependent populations have consistently revealed impaired behavioral control (Jentsch *et al.* 2014) as well as disruptions in the underlying prefrontal neural circuits across substance-dependent populations (Daumann *et al.* 2011; Ersche *et al.* 2013). Although, these cross-sectional studies cannot differentiate whether prefrontal deficits represent a consequence or predisposing factor rendering individuals vulnerable for drug addition, initial findings indicate that brain structural deficits in prefrontal regions might represent a risk factor for the initiation of substance-dependence (Cheetham *et al.* 2012; Ersche *et al.* 2013; Becker *et al.* 2015) and that structural deficits particularly in the orbitofrontal and dorsolateral prefrontal cortex further deteriorate with the progress of addiction (Daumann *et al.* 2011; Goldstein & Volkow 2011; Ersche *et al.* 2013).

Accumulating evidence from initial studies using neuroimaging approaches and recent reviews suggests that brain functional and structural alterations in IGD partly resemble alterations observed in other addictive disorders, including substance use disorders and pathological gambling (Zhou *et al.* 2011; Brand *et al.* 2014; Park *et al.* 2016). In terms of brain functional indices, most consistently alterations in prefrontal, particularly orbitofrontal and dorsolateral, regions critically engaged in inhibitory control and decision making were observed in Internet addiction (Brand *et al.* 2014; Park *et al.* 2016). Although previous studies on gray matter (GM) alterations in Internet addiction provide some evidence for altered GM integrity in these regions (Yuan *et al.* 2011; Zhou *et al.* 2011; Weng *et al.* 2013), findings remained inconsistent, possibly because of the small sample sizes or heterogeneity of the subjects due to a focus on Internet addiction *per se* rather than on specific sub-facets such as IGD. Furthermore, the retrospective nature of these studies does not allow separation of predisposing alterations from those that accompany the development of Internet addiction/IGD.

Against this background, the present study aimed to comprehensively examine brain structural alterations associated with excessive Internet gaming in a sample of individuals exhibiting excessive Internet gaming behavior. Within the field of Internet gaming, massively multiplayer online role-playing games (MMORPGs) are among the most popular games (Nagygyörgy *et al.* 2013) and bear a particular high risk for escalating use (Smyth 2007). To facilitate a homogenous sample, we focused on participants with excessive use of World of Warcraft (WoW), a popular MMORPG with a recognized addictive potential (Sun *et al.* 2012). To this end, a sample of n = 44 excessive WoW players and 87 matched WoW-naive non-gamers were recruited. All subjects underwent a comprehensive assessment of general online gaming and WoW-specific gaming activities as well as an acquisition of brain structure at study inclusion [timepoint 1 (T1)]. To specifically disentangle predisposing alterations from consequences of excessive Internet gaming, WoW-naive subjects were randomly assigned to 6 weeks of WoW-gaming (at least 1 hour a day) or a control (no gaming) condition followed by a re-assessment of Internet gaming addiction scores and brain structure [timepoint 2 (T2)]. To comprehensively characterize brain structural alterations associated with WoW gaming, we implemented different analysis strategies. In a cross-sectional analysis, structural differences in excessive Internet gamers were characterized by directly comparing the T1 structural data of the WoW gamers with age/gender-matched and education-matched WoW-naive controls. A pattern classification approach was additionally implemented to further explore the diagnostic value of the observed cross-sectional between-group brain volumetric differences, within and across both timepoints. Finally, to disentangle predisposing alterations from direct consequences of excessive Internet gaming, a longitudinal analysis approach was implemented that evaluated self-reported online gaming addiction tendencies and brain volumetric changes over the course of the training period.

Based on previous neuroimaging studies in populations with excessive Internet use and current conceptualizations of Internet addiction (Brand *et al.* 2014; Dong & Potenza

2014; Park *et al.* 2016), we expected (1) cross-sectional associations between excessive WoW gaming and lower GM volume (GMV) in the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (dlPFC) and (2) that WoW gaming during the interim training period would be associated with a decrease of GMV in these regions in the training group (TRG), reflecting brain structural changes as a direct consequence of increasing engagement in online video gaming.

MATERIALS AND METHODS

Participants

A total of n = 131 healthy young participants (male: 71/female: 60; mean age = 23.80, SD = 3.97) were enrolled in the present study. Exclusion criteria for all participants were a history of or current psychiatric/neurological disorders, regular drug use or apparent brain structural alterations. Inclusion criteria for the WoW gaming group (WoW) were (1) >7 hours/week WoW gaming [mean years of experience was 6.28 (SD = 2.10)], and—to facilitate a homogenous sample—(2) <7 hours a week other multiplayer games and (3) no ego-shooter games. Based on the exclusion criteria or quality assessments of the magnetic resonance imaging data, n = 12 participants were excluded from all further analysis. The final sample consisted of n = 119 participants (male: 63/female: 56; mean age = 23.61, SD = 3.89; n = 78 gaming-naive controls; n = 41 WoW gamers).

Controls (n = 78; male: 38/female: 40; mean age = 22.96, SD = 3.48) had no history of WoW gaming and displayed very low online video game addiction scores (Tables 1 and 2) to facilitate the determination of WoW-gaming associated brain structural alterations in the cross-sectional and longitudinal analyses. For the longitudinal assessment of WoW gaming-associated brain structural changes, WoW-naive subjects were randomly assigned to a 6-week period of daily WoW gaming (TRG; minimum play of 1 hour per day, validated by tracking on the computer), or no gaming during this period (TCG, training control group) (Tables 1 and 2 for sociodemographics). After this period, brain structure and Internet gaming behavior were reassessed. Of note, the three groups did not differ in gender distribution (gender: χ^2 = 2.08, d.f. = 2, P = 0.35), but did however, in age ($F_{(2,116)}$ = 4.03, P = 0.02). A least significant difference (LSD) *post hoc* test revealed a significant difference between the WoW and TCG (P = 0.006) with WoW players being significantly older. To control for potential confounding effects of personality traits, the Big Five personality traits were assessed using the NEO Five Factor Inventory (NEO-FFI). Groups differed in extraversion, with the WoW group having significant lower extraversion compared with controls ($F_{(2,116)}$ = 4.970, P = 0.008) (Table 1). Finally, education levels differed between groups (χ^2 = 22.90, d.f. = 8, P = 0.003) with more individuals in the WoW group having lower educational attainment. To account for these between-group differences in the analysis of cross-sectional brain structural differences, WoW gamers were individually matched regarding age and education with subjects from the WoW-naive samples at T1. To further control for between-group differences in age and extraversion on WoW addiction and brain structural indices, analyses

Table 2 Descriptive statistics of administered questionnaires assessing online gaming addiction and other WoW-related variables.

Questionnaires	*TCG*	*TRG*	*WoW*
OVGA T1	7.78 ± 1.77	7.80 ± 1.74	14.80 ± 5.05
OVGA T2	7.97 ± 2.94	9.20 ± 2.93	14.70 ± 4.58
WoW T1	N/A	N/A	86.24 ± 23.26
WoW T2	N/A	54.95 ± 19.92	81.93 ± 22.00
Hours T1	N/A	N/A	16.37 ± 7.07
Hours T2	N/A	9.74 ± 3.57	16.80 ± 10.19

Hours = hours per week; N/A = not applicable; OVGA = online video gaming addiction; TCG = training group; TRG = training group; WoW = World of Warcraft group; T1 = timepoint 1; T2 = timepoint 2.

Table 1 Gender distribution, mean Big Five personality traits and mean age including standard deviation for the three groups in the experiment.

		TCG (n = 38)	*TRG* (n = 40)	*WoW* (n = 41)
Age (years)		22.45 ± 3.11	23.45 ± 3.78	24.85 ± 4.34
Gender (male)		20	18	25
Big Five	Neuroticism	2.56 ± 0.71	2.70 ± 0.64	2.58 ± 0.59
	Extraversion	3.70 ± 0.47	3.48 ± 0.57	3.32 ± 0.53
	Openness	3.74 ± 0.61	3.57 ± 0.66	3.48 ± 0.59
	Agreeableness	3.73 ± 0.51	3.66 ± 0.62	3.49 ± 0.47
	Conscientiousness	3.63 ± 0.80	3.52 ± 0.57	3.52 ± 0.56

TCG = training group; TRG = training group; WoW = World of Warcraft group.

that included the WoW group and controls were rerun including age and extraversion as covariates. All participants provided written informed consent and received monetary compensation. The study was in accordance with the latest Declaration of Helsinki and had full ethical approval of the local ethic committee at the University of Bonn, Bonn, Germany.

Behavioral data acquisition and assessments

Assessment of Internet gaming behavior and addiction severity

Addiction severity was assessed using validated self-report questionnaires for WoW gaming addiction (Peters & Malesky 2008; internal consistencies of the German version for the WoW sample at T1 were $\alpha = 0.89$; internal consistencies at T2 including both the WoW and TRG, $\alpha = 0.91$). The WoW scales were administered to the WoW group at both timepoints, whereas subjects in the TRG, who were WoW-naive at study inclusion, only filled in the WoW scales at T2. In addition, general online video gaming addiction (OVGA) was assessed using a modified version of the short version of the video game addiction questionnaire (Lemmens, Valkenburg, & Peter 2009; internal consistencies of the OVGA, T1: $\alpha = 0.88$; T2: $\alpha = 0.87$). To assess training-induced changes in the OVGA, the OVGA was administered to all three groups at T1 and T2. As additional validation of gaming behavior, we collected self-report information on the hours played each week before T1 (only answered by the WoW group) and the hours played each week between T1 and T2 (answered by both the WoW and TRG). To additionally facilitate a more objective assessment of gaming behavior, hours spent WoW gaming during the study period (6 weeks) were tracked with a specific program on the computers of the participants.

Addiction severity questionnaires

Differences in age between the three groups were calculated with an ANOVA and differences in gender/education distribution between groups (WoW, TRG and TCG) with a χ^2 test. Differences in the addiction scores of the questionnaires between groups (such as WoW, TRG, TCG or gender) were tested with ANCOVAs considering age as a covariate given the older age of WoW players compared with the TCG. Of note, age was also correlated with some of the addiction scores, but there were no associations with online video game addiction in the three participant groups but with age and WoW addiction in the training group ($\rho = .44$, $P = .005$). These analyses were carried out for T1 and T2 separately. Moreover, repeated measures ANCOVAs were employed to test for changes in the addiction scores between T1 to T2.

Magnetic resonance imaging (MRI) data acquisition and statistical analyses

Data acquisition

High-resolution T1-weighted brain structural data were acquired on a Siemens Avanto System (Erlangen, Germany) at 1.5 Tesla using a Magnetization Prepared Gradient Echo (MP-RAGE) sequence with 160 sagittal slices with 1-mm slice thickness (in-plane resolution 1 × 1 mm, field of view 256 × 256).

Preprocessing

Structural magnetic resonance imaging data were analyzed with FSL-VBM (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM, Douaud *et al.* 2007), an optimized VBM protocol (Good *et al.* 2001) implemented in FSL (Smith *et al.* 2004). Non-brain tissue from structural images was extracted using BET, and tissue-type segmentation was carried out using FAST. We aligned the GM images to the MNI152 standard space using non-linear registration (Andersson, Jenkinson, & Smith 2007). The spatially normalized images were averaged to create a study-specific template. Next, the full set of all native GM images were non-linearly normalized onto the study-specific template and modulated to correct for local contraction/enlargement due to the non-linear component of the spatial transformation. Finally, all modulated registered GMV images were smoothed with an isotropic Gaussian kernel (sigma 4 mm).

Region of interest selection and thresholding

Based on our a priori regional hypothesis and previous studies on online gaming addiction/IGD/Internet addiction (Ko *et al.* 2009; Hong *et al.* 2013; Weng *et al.* 2013; Lin *et al.* 2015a), the analyses focused on the OFC and dlPFC as a priori defined regions of interest. To this end, a single mask including both regions (9348 voxels in total) was constructed (details in Supporting Information). To achieve accurate inference including full correction for multiple comparisons over space, we used nonparametric permutation methods (Nichols & Holmes 2002). The null distribution at each voxel was constructed using 10,000 random permutations of the data. All analyses were obtained on a voxel-level height of $P < 0.05$, family-wise error (FWE) corrected across the predefined anatomical mask; for completeness findings from exploratory whole-brain analyses, corrected at $P < 0.05$ FWE are reported.

Cross-sectional analysis

Given that at T1 the WoW group and the WoW-naive subjects differed in sample size (WoW, $n = 41$; WoW-naive, $n = 78$) and mean age (WoW, mean age = 24.85 ± 4.34;

WoW-naive, mean age = 22.96 ± 3.48, $P = .011$), WoW subjects were matched with a subgroup of gaming-naive subjects for the between-group comparison ($n = 41$, male: 25, mean age = 24.56 ± 3.79). Difference in cortical GMVs between WoW and matched controls were assessed using a general linear model implemented in the software package FSL with WoW group and 41 age-matched, gender-matched and education-matched healthy subjects' (20 of them from the TCG and the rest from the TRG) T1 structural data. To account for differences in extraversion between the WoW and the matched control group ($P = 0.044$), the analysis was rerun including extraversion and age as covariates.

Associations between World of Warcraft addiction severity and brain structure at T1

To determine associations between self-reported WoW addiction severity and brain structure, a voxel-wise multiple regression model was employed using WoW addiction scores as predictor for the volume of GMV within the a priori defined mask. For this analysis, the WoW group's T1 data were preprocessed separately. In order to cross-validate the robustness of the association, we additionally extracted T1 WoW group GMV from a 12-mm-diameter sphere centered at the peak voxel and subsequently performed bivariate correlations with online gaming addiction levels as assessed by the OVGA.

Multi-voxel pattern analysis

A multi-voxel pattern analysis approach was used for discriminating between WoW subjects and WoW-naive subjects. Specifically, a radial basis function kernel support vector machine (SVM) approach was employed with LIBSVM (www.csie.ntu.edu.tw/~cjlin/libsvm), and smoothing was omitted to facilitate higher spatial specificity. The SVM was trained using extracted T1 GMV of TRG and WoW from a 12-mm-diameter sphere centered at the peak coordinates of the between-group difference from the cross-sectional comparison using the two-sample *t*-test. Classification accuracy for WoW-addicted subjects versus the WoW-naive subjects was evaluated using extracted GMV of TCG and WoW from the same sphere at T2. To further evaluate the robustness of our discriminative results, we also used the extracted T2 GMV (TCG and WoW) to train a model and applied it to the T1 GMV (TRG and WoW) to estimate its discriminating accuracy. Training set was scaled to $[-1, 1]$, and the testing set was scaled using the same scaling factors before applying SVM (Hsu, Chang, & Lin 2003) (details in Supporting Information). To test whether classification accuracy and area under curve (AUC) exceeded chance level, we used permutation tests to simulate the probability distribution of the classification. For each analysis, the group labels were randomly shuffled, and then, the same classification was performed (repeated 10,000 times). To cross-validate the results, an additional permutation test randomly assigned labels at each timepoint separately to keep the independent information.

Longitudinal analysis

For a more causal approach to examine the effects of WoW gaming on brain structure, a longitudinal analysis approach as implemented in the optimized FSL-VBM module was employed to determine GMV changes over the course of the 6-week follow-up period. After obtaining modulated GMV images for each timepoint, individual difference images (T1 > T2) were computed and smoothed with an isotropic Gaussian kernel (sigma 4 mm). To examine the interaction between group and time, we preprocessed the data from the three group's two timepoints together, and then, the resultant preprocessed GM images were subjected to a one-way ANOVA model. To further examine effects of gaming on brain structure, we computed changes across both gaming groups (TRG and WoW) using a one-sample *t*-test model. For this analysis, training and the WoW groups' two timepoints were preprocessed together. Again, an additional analysis was performed with age and extraversion as covariates. To further explore whether extraversion might constitute a risk or protective factor for gaming-associated addiction development or associated brain changes, associations between extraversion, addictive behavior and GMV changes between T1 and T2 were examined.

RESULTS

Potential confounders

The WoW gamers were significantly older than the TCG and showed lower educational attainment and lower extraversion compared with both gaming-naive groups (see Participants section), and these variables were therefore controlled for in the following behavioral analyses.

Addiction severity—cross-sectional comparison

At study inclusion, subjects in the WoW groups showed considerable high WoW addiction scores (Table 2). At both timepoints, the variable group (WoW, TRG and TCG) significantly influenced the OVGA (T1, $F_{(2,115)} = 60.47$; T2, $F_{(2,114)} = 39.20$, both $P < 0.001$; inserting age and extraversion as covariates results in T1, $F_{(2,113)} = 51.97$; T2, $F_{(2,112)} = 31.86$, both $P < 0.001$) with WoW gamers showing significantly higher scores on the OVGA than both the TRG (T1, T2, LSD, both $P < 0.001$) and the TCG (T1, T2, LSD, both $P < 0.001$).

Brain structure—cross-sectional comparisons

There was no significant difference in gender (25 male participants in each group), age ($P = 0.746$) or education ($P = 0.136$, Mann–Whitney *U*-test) between WoW group and matched gaming-naive subjects; however, the WoW group had significantly lower extraversion ($P = 0.044$). The direct comparison of the groups at T1 revealed significantly lower GMV in cluster located in the posterior right lateral OFC, bordering the insular cortex [BA 47, peak voxel coordinates, (40, 14, −4), $t_{(80)} = 3.97$, voxel-wise FWE-corrected $P = 0.033$] in the WoW group relative to controls (Fig. 1a). Results remained stable after including extraversion and age as covariates [peak voxel coordinates, (40, 14, −4), $t_{(78)} = 3.91$, voxel-wise FWE-corrected $P = 0.036$]. Exploratory whole-brain analysis did not reveal significant findings.

Associations between World of Warcraft addiction severity and brain structure

Examining associations between WoW addiction scores and inter-individual GMV variations within the WoW group revealed a negative correlation with regions in right lateral OFC [BA 47, peak voxel coordinates, (32, 32, −8), $t_{(39)} = 4.35$, voxel-wise FWE-corrected $P = 0.022$] (Fig. 1b), indicating that higher WoW addiction severity was directly associated with lower OFC GMV (Fig. 1c). Examination of the robustness of this association with OVGA confirmed the negative correlation between higher OVGA and lower OFC GMV ($r_{(39)} = -0.49$, $P = 0.001$) (Fig. 1d). Including age as a covariate did not change the main findings [peak voxel coordinates, (32, 32, −8), $t_{(38)} = 4.36$, voxel-wise FWE-corrected $P = 0.023$]. Exploratory whole-brain analysis did not reveal significant findings.

Multi-voxel pattern classification

The multi-voxel pattern analysis model revealed a best cost parameter of 0.891 and a best gamma parameter of 0.126, and applying the discrimination model obtained from the T1 dataset to the T2 dataset yielded good classification accuracy (84.81 percent, both permutation tests $P < 0.001$). Receiver operating characteristic (ROC) analysis indicated a high AUC of 0.93, suggesting excellent classification power (both permutation tests $P < 0.001$). In addition, applying the discrimination model obtained from the T2 dataset (best $C = 0.891$, best $\gamma = 0.178$) to the T1 dataset also yielded a comparable high classification accuracy (82.72 percent, both permutation tests $P < 0.001$) and AUC (0.88, both permutation tests $P < 0.001$).

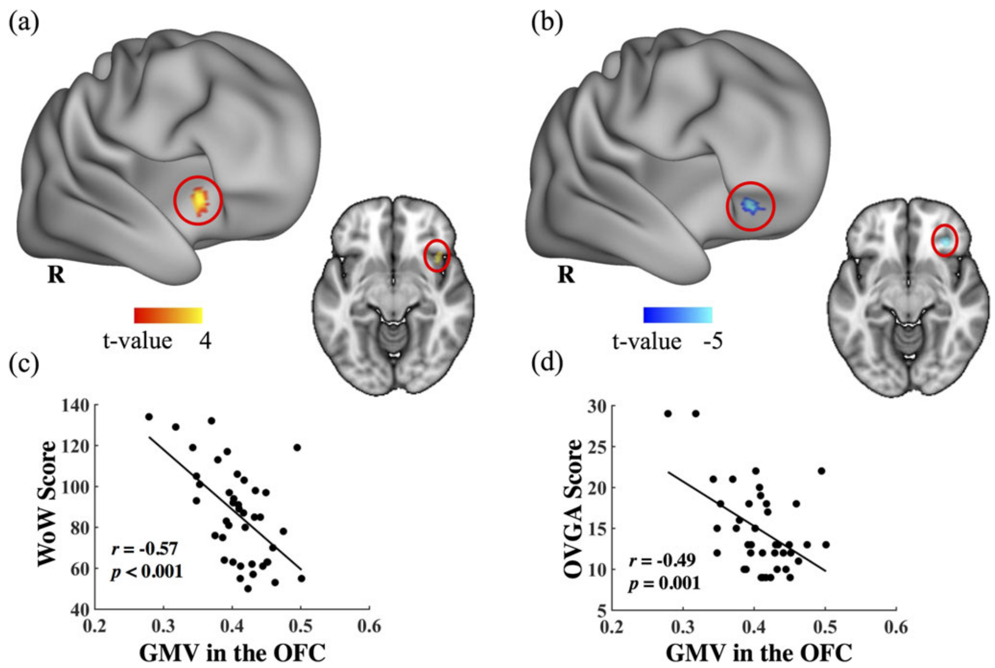

Figure 1 (a) Statistical (*T*) maps for comparison of gray matter volume (GMV) between World of Warcraft (WoW) subjects and matched WoW-naive subjects. Hot color indicates WoW-naive subjects > WoW subjects. (b) Statistical (*T*) maps of negative correlations between gray matter volume in the orbitofrontal cortex (OFC) and WoW addiction score. All images were thresholded at $P < 0.001$ uncorrected for display purposes, statistical analyses were performed using family-wise error voxel level correction with a $P < 0.05$ within the a priori defined OFC–dlPFC mask. (c) Plot of gray matter volume in the OFC against WoW addiction score. (d) Plot of gray matter volume in the OFC against online video game addiction score. dlPFC = dorsolateral prefrontal cortex; OVGA = online video gaming addiction

Longitudinal analysis

Gaming behavior during the course of the study

Self-reported WoW gaming behavior confirmed that the TRG group spent >1 hour per day playing WoW (11 self-reports are missing, n = 29; Table 2). Tracking data from the computer further revealed that during the 6 weeks, the WoW group spent a mean cumulative time of 88.15 hours (±45.07) and TRG a mean of 54.98 hours (±25.97) playing WoW (refers to n = 35 TRG and n = 40 WoW, data from n = 6 persons were lost because of technical issues). With regard to differences between the WoW and TRG groups in self-reported weekly gaming in hours between T1 and T2, the WoW group reported significant longer times spent on WoW ($t_{(67)} = -3.57$, $P = 0.001$; Table 2), as well as higher WoW addiction scores as assessed by the WoW scales at T2 ($t_{(78)} = -5.75$, $P < 0.001$; n = 40 participants in both the WoW and TRG).

Training-induced changes in online video game addiction

Repeated measure ANOVA revealed a time × group (WoW/TRG) interaction effect on OVGA scores ($F_{(1,78)} = 5.87$, $P = 0.02$) with the TRG group demonstrating an increase over the course of the training (Fig. 2a). Including age and extraversion as covariate and gender as second independent variable in the model did not change these results ($P < 0.05$). The number of played hours for WoW before and during the 6 weeks between T1 and T2 in the WoW group did not change significantly ($F_{(1,39)} = 0.084$, $P = 0.77$). Although self-reported WoW scores significantly decreased from T1 to T2 ($F_{(1,39)} = 6.65$, $P = 0.01$) in the WoW group, their general WoW addiction severity remained at a considerable high level during the course of the study (Table 2).

Effects of training on brain structure

No significant interaction effects between group (TRG, TCG and WoW) and time (T1 and T2) were found. However, findings from the longitudinal analyses examining effects of gaming in the pooled TRG and WoW sample revealed decreased GMV in the left lateral OFC [peak voxel coordinates, (−42, 36, −4), $t_{(80)} = 3.97$, voxel-wise FWE-corrected $P = 0.049$] and the left dlPFC [peak voxel coordinates, (−44, 30, 32), $t_{(80)} = 3.94$, voxel-wise FWE-corrected $P = 0.053$] from T1 to T2 (Fig. 2b). Findings in the OFC remained stable after including age as a covariate [peak voxel coordinates, (−42, 36, −4), $t_{(79)} = 3.96$, voxel-wise FWE-corrected $P = 0.050$], as well as including age and extraversion as covariate [peak voxel coordinates, (−42, 36, −4), $t_{(78)} = 3.93$, voxel-wise FWE-corrected $P = 0.054$, trend-to-significant]. Further exploratory analysis of group-specific changes of extracted parameter estimates from a 12-mm-diameter sphere centered at the peak coordinates from the longitudinal OFC effects revealed that control group's mean GMV was not significantly changed over time ($P = 0.553$), whereas GMV in this region significantly decreased, in both the TRG ($P = 0.025$) and the WoW group ($P = 0.002$) (Fig. 2c**)**. No associations were found between extraversion and changes in addiction severity or OFC GMV (all $P > 0.5$), suggesting that although groups differed at T1 in extraversion, extraversion does not represent a vulnerability or protective factor for gaming-associated changes. Exploratory whole-brain analysis did not reveal significant findings.

DISCUSSION

In line with our first hypothesis, the cross-sectional comparison revealed convergent evidence for lower GMV

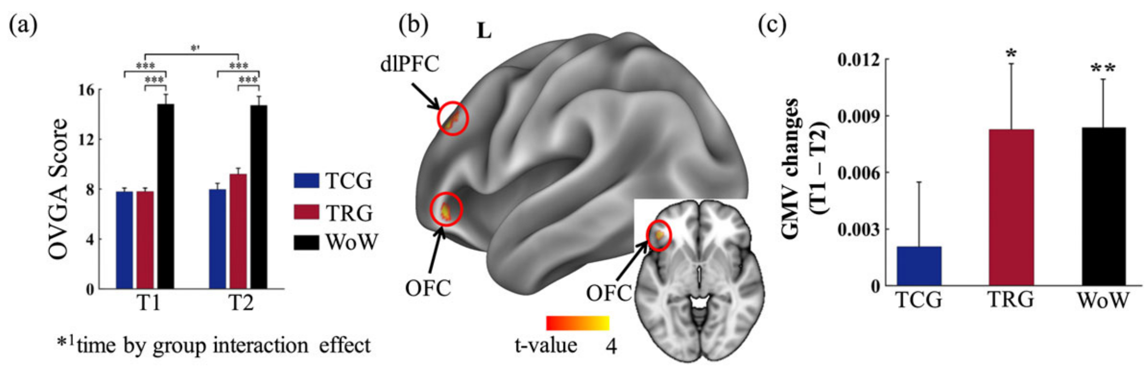

Figure 2 (a) Longitudinal changes in online video game scores. (b) Statistical (T) maps for longitudinal comparison between timepoint 1 and timepoint 2, thresholded at $P < 0.001$ uncorrected for display purposes, statistical analyses were performed using family-wise error voxel level correction with a $P < 0.05$ within the a priori defined OFC–dlPFC mask. Hot color indicates timepoint 1 > timepoint 2. (c) Gray matter volume (GMV) changes between timepoint 1 and timepoint 2. Error bars reflect the standard error of the mean. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. OFC = orbitofrontal cortex; OVGA = online video gaming addiction; TCG = training control group; TRG = training group; WoW = World of Warcraft group

in the lateral OFC in excessive WoW gamers. Regression analysis further revealed that within the group of WoW gamers, higher indices of addictive WoW engagement were negatively associated with GMV in this region, indicating a direct relationship between IGD severity and regional specific GMV in the lateral OFC. The specific importance of this region with respect to WoW gaming addiction was further emphasized by the high accuracy of individual OFC volumes in classifying WoW-addicted subjects and controls. In line with our second hypothesis, an exploratory analysis demonstrated that WoW training resulted in decreased OFC GMV in the context of increased online gaming addiction scores in a group of initially WoW-naive subjects, suggesting a causal relationship between excessive engagement in online gaming activities and GMV loss in this region. Interestingly, OFC GMV further decreased in the group of excessive WoW gamers during the 6-week follow-up interval, indicating progressive loss of OFC volume during the progression of Internet gaming addiction.

The cross-sectional findings from the present study are in line with a series of previous studies in Internet-addicted populations, reporting lower OFC GMV in individuals with excessive Internet use (Yuan *et al.* 2011; Hong *et al.* 2013; Park *et al.* 2016). In line with previous findings, lower GMV in this region was directly associated with the severity of addictive symptoms within the group of gamers (Zhou *et al.* 2011; Weng *et al.* 2013). Importantly, findings from the present longitudinal analysis add to the existing literature that GM loss in the OFC represents a direct consequence of excessive engagement in online video gaming rather than a predisposition to engage in excessive online video gaming, thus providing the first empirical evidence that increasing engagement in online gaming activities leads to both increased addiction symptoms as well as decreased OFC structural integrity. Despite some descriptive evidence for GMV decreases in the dlPFC during the training period the present study was not able to replicate previous cross-sectional findings on decreased dlPFC GMV in Internet addiction (Yuan *et al.* 2011). The lack of consistent findings with regard to the dlPFC might be explained in different sampling strategies: whereas Yuan *et al.* (2011) included subjects with high Internet addiction scores, the present study aimed at specifically examining GMV alterations in a specific subgroup of Internet addiction. To facilitate a homogenous sample of subjects with excessive Internet gaming, only extensive MMORPG gamers were included in the present study, suggesting that decreased OFC volume might specifically characterize individuals with excessive Internet gaming.

Decreased OFC volumes have been previously reported across substance-dependent populations, including alcohol use disorder (Asensio *et al.* 2016) and stimulant use disorder (Daumann *et al.* 2011; Ersche *et al.* 2013), suggesting that excessive online gaming partly resembles brain structural maladaptations observed in substance-related addictions. Moreover, decreased OFC volumes have been found to be associated with lower conscientiousness (Kunz et al. 2017), a personality trait, which is linked to Internet addiction (Montag *et al.* 2012). Importantly, examining behavioral addictions, such as IGD, allows for the control of brain morphological adaptations associated with chronic substance use, such as potential neurotoxic effects of the substances, with the present findings suggesting that GM loss in the OFC might represent a direct consequence of the development of addictive patterns rather than substance-induced changes *per se*.

The prefrontal cortex is critically engaged in flexible behavioral adaptations in the face of changing environmental reward values because of its critical role in decision making and behavioral control. The OFC in particular has been implicated in the representation of reward contingencies and of stimuli that have been previously associated with reward (Cox, Andrade, & Johnsrude 2005). The lateral OFC has been specifically engaged in the emotional evaluation of the experienced reward value (Li *et al.* 2016) and of previous choices (Levens *et al.* 2014) as well as inhibitory control of reward-related impulses (O'Doherty *et al.* 2003), thereby critically contributing to both signaling the need for behavioral changes and implementing behavioral control. Previous preclinical and clinical research examining behavioral deficits following chronic substance use has demonstrated that the development of substance-related addictions is associated with deficits in these functional domains, which critically rely on intact OFC functioning (Everitt *et al.* 2007). A growing number of recent studies in Internet gaming-addicted populations suggest a similar pattern of behavioral deficits in subjects with IGD, with pronounced deficits in the domains of decision making and impulse control (Lin *et al.* 2015b; Wang *et al.* 2016) and a failure to adapt behavior flexibly in the context of changing reward values (Yao *et al.* 2014). Together with evidence from animal lesion models (Solbakk & Løvstad 2014) and patients with focal OFC lesions (Gläscher *et al.* 2012), which indicate a critical contribution of the OFC to value-based decision making and flexible inhibitory control, the present findings suggest that excessive engagement in online gaming might compromise the functional integrity of these domains. As such, disrupted integrity of the OFC might contribute to the clinical core symptomatology of IGD promoting continued use despite negative consequences due to a loss of regulatory control and disadvantageous decision making. Deficits in these executive functions and associated frontal brain regions have been central to current conceptualizations of substance as well as behavioral addictions (Bechara 2005; Goldstein & Volkow 2011; Brand *et al.* 2016). With respect to IGD, the findings from the present prospective data suggest that gaming-associated decreased OFC integrity can already be observed during very early stages (following 6 weeks of regular gaming) and progresses in excessive gamers during a rather brief follow-up interval. As such, the observed changes and deficient executive functions might critically contribute to the development as well as maintenance of addictive disorders.

The present design allowed a detailed examination of gaming-associated brain morphological changes in healthy subjects; however, based on recent reports on potential mediating influences of subclinical pathology levels on brain structural alterations in IGD (Choi *et al.* 2017), the additional assessment of subclinical pathology might have revealed important information. Moreover, OFC findings from the cross-sectional and the longitudinal analysis were located in different hemispheres. Although some functions in the OFC are strongly lateralized, meta-analytic data indicate an involvement of the bilateral lateral OFC in emotional control and decision making (e.g. Kohn *et al.* 2014).

Together, the present results highlight the contribution of the OFC in the development of IGD and further emphasize that similar pathological mechanisms might underlie the development and maintenance of behavioral as well as substance-related addictions. Importantly, findings from the longitudinal analysis provide the first direct evidence that decreased integrity of a region critically engaged in regulatory control and decision making might represent a direct consequence of regular engagement in behavior with addictive potential.

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Conflict of Interest

The authors declare no conflict of interest.

Authors Contribution

CM designed the study. RS and BL contributed to the acquisition of the data. FZ, BB and CM analyzed the data, interpreted the results and drafted the manuscript. MR, PT, KMK, BW and SM provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

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