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Transcranial Direct Current Stimulation for Online Gamers

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TITLE:

Transcranial Direct Current Stimulation for Online Gamers

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KEYWORDS:

Online game, transcranial direct current stimulation, positron emission tomography, dorsolateral prefrontal cortex, brain glucose metabolism, self-control

SUMMARY:

We present a protocol and a feasibility study for applying transcranial direct current stimulation (tDCS) and neuroimaging assessment in online gamers.

ABSTRACT:

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that applies a weak electric current to the scalp to modulate neuronal membrane potentials. Compared to other brain stimulation methods, tDCS is relatively safe, simple, and inexpensive to

administer.

Since excessive online gaming can negatively affect mental health and daily functioning, developing treatment options for gamers is necessary. Although tDCS over the dorsolateral prefrontal cortex (DLPFC) has demonstrated promising results for various addictions, it has not been tested in gamers. This paper describes a protocol and a feasibility study for applying repeated tDCS over the DLPFC and neuroimaging to examine the underlying neural correlates in gamers.

At baseline, individuals who play online games report average weekly hours spent on games, complete questionnaires on addiction symptoms and self-control, and undergo brain ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET). The tDCS protocol consists of 12 sessions over the DLPFC for 4 weeks (anode F3/cathode F4, 2 mA for 30 min per session). Then, a follow-up is conducted using the same protocol as the baseline. Individuals who do not play online games receive only baseline FDG-PET scans without tDCS. Changes of clinical characteristics and asymmetry of regional cerebral metabolic rate of glucose (rCMRglu) in the DLPFC are examined in gamers. In addition, asymmetry of rCMRglu is compared between gamers and non-gamers at baseline.

In our experiment, 15 gamers received tDCS sessions and completed baseline and follow-up scans. Ten non-gamers underwent FDG-PET scans at the baseline. The tDCS reduced addiction symptoms, time spent on games, and increased self-control. Moreover, abnormal asymmetry of rCMRglu in the DLPFC at baseline was alleviated after tDCS.

The current protocol may be useful for assessing treatment efficacy of tDCS and its underlying brain changes in gamers. Further randomized sham-controlled studies are warranted. Moreover, the protocol can be applied to other neurological and psychiatric disorders.

INTRODUCTION:

In recent years, increasing attention has been paid to excessive online game use since its association with negative impact on mental health and daily functioning as well as with internet gaming disorder (IGD) have been reported[1-3]. Although several treatment strategies including pharmacotherapy and cognitive-behavioral therapy have been evaluated, evidence for their effectiveness is limited[4].

Previous studies have suggested that IGD may share clinical and neurobiological similarities with other behavioral addictions and substance use disorders[5,6]. It has been reported that the dorsolateral prefrontal cortex (DLPFC) is closely involved in the pathophysiology of substance and behavioral addiction such as craving[7], impulse control[8], decision making[9], and cognitive flexibility[10]. Several neuroimaging studies on IGD have reported structural and functional impairments in the DLPFC[6]. In particular, structural neuroimaging studies revealed a reduction in gray matter density in the DLPFC[11,12] and a functional magnetic resonance imaging (fMRI) study found an altered cued-induced activity in the DLPFC of patients with IGD[13]. In addition, functional asymmetry of the brain may contribute to impulsivity and craving in addictions including IGD. For

instance, cue-induced craving for online gaming could be related to right prefrontal activations[14]. However, alterations of regional cerebral metabolic rate of glucose (rCMRglu) associated with excessive online game use or IGD remain to be further investigated compared to other brain deficits[15].

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that applies a weak electric current (1-2 mA) through electrodes attached to the scalp to modulate neuronal membrane potentials. Generally, the cortical excitability is increased under the anode electrode and decreased under the cathode electrode[16]. tDCS has become a popular method because it is simple, cheap, and safe to administer compared to other brain stimulation techniques such as transcranial magnetic stimulation (TMS) that uses a magnetic pulse to generate an electrical current in the brain tissue under the coil. According to a recent review, the use of conventional tDCS protocols has not produced any serious adverse effects or irreversible injury and is associated with only mild and transient itching or tingling sensation under the stimulation area[17].

Several studies have demonstrated favorable results of tDCS[18-20] and repetitive TMS[21,22] over the DLPFC for treating behavioral and substance addiction. However, further studies are needed to investigate the effects of brain stimulation techniques on online game use and the underlying brain changes.

The aim of this study is to present a protocol for applying repeated sessions of tDCS over the DLPFC and neuroimaging to examine the underlying neural correlates in gamers, as well as to assess its feasibility. Specifically, we focused on changes in addiction symptoms, average time spent on games, self-control, and asymmetry of rCMRglu in the DLPFC using ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET).

PROTOCOL:

All experimental procedures presented in this protocol have been approved by the Institutional Review Board and are in accordance with the Declaration of Helsinki.

1. Research participants

1.1. Recruit individuals who report that they play online games (the gamer group) and those who report that they do not play online games (the non-gamer group).

NOTE: Here, we included individuals with two or more IGD symptoms according to the Diagnostic and Statistical Manual of Mental Disorders-5[23] or those who play games at least one hour per day on average in the gamer group. The non-gamer group undergoes only baseline brain FDG-PET scans to compare rCMRglu with the gamer group and does not receive tDCS sessions.

1.2. For both groups, exclude individuals with (a) major medical, psychiatric, or neurological disorders, (b) history of traumatic brain injury, (c) history of alcohol or other substance abuse or

dependence, (d) use of psychotropic medications, or (e) any contraindications for tDCS such as severe headache, metal in the head, history of seizure, epilepsy, or brain surgery, or any lesions or other medical problems on the skin where tDCS electrodes will be attached.

1.3. Explain to each participant the aim of the study, the main experimental procedures, and any potential risks associated with participating in the study. After answering any questions, obtain written consent.

2. Baseline assessment

2.1. Evaluate clinical characteristics using the following questionnaires: Internet Addiction Test (IAT)[24] and Brief Self Control Scale (BSCS)[25]. In addition, ask participants to report average weekly hours spent playing games.

NOTE: The word "Internet" in the IAT is replaced with "online games" to assess severity of online game addiction.

2.2. Perform brain FDG-PET scans.

2.2.1. Inject participants with 185 - 222 MBq of FDG and have participants rest for 45 min of an uptake period during which they are awake and resting in supine position in a dark and quiet room with their eyes closed.

2.2.2. Conduct brain FDG-PET scans using a PET-CT scanner. Acquire 47 transaxial emission images (pixel size = 1.95 × 1.95 mm, slice thickness = 3.27 mm) and 16 slices of CT images in about 15 minutes. Apply attenuation correction, standard filtering, and standard reconstruction techniques.

3. Application of tDCS

3.1. Within a week after the baseline assessment, apply tDCS to participants. Prepare tDCS sessions with following materials: a tDCS device, wet wipes, saline solution, two sponge electrodes (6 cm in diameter), a cable, and a headband.

3.2. Have the participant sit on a chair.

3.3. Set the stimulation parameters for the tDCS device: 2 mA for 30 min (current density = 0.07 mA/cm^2). Set the current so it ramps up to 2.0 mA over 30 s, remains at 2.0 mA for 29 min, and ramps down to 0 mA over the last 30 s.

3.4. Place two sponge electrodes in the rubber holders of the headband and soak them with saline solution.

3.5. Use wet wipes to remove any makeup, dirt, or sweat on the skin where the electrodes will be applied.

3.6. Put the headband on the participant's head to place the anodal electrode over the left DLPFC (F3; 10 - 20 EEG system) and the cathodal electrode over the right DLPFC (F4).

3.7. Connect the electrodes to the tDCS device using the cable and turn on the device.

3.8. Ask the participant to report any adverse effects during or after the tDCS session.

3.9. At the end of the 30 minutes of stimulation, turn off the device and remove the electrodes from the participant.

3.10. Administer a total of 12 tDCS sessions (3 times per week for 4 weeks).

4. Follow-up assessment

4.1. Perform the follow-up assessment within a week after the last tDCS session using the same protocol as the baseline assessment.

5. Data analysis

5.1. Use an appropriate software package to preprocess the PET images (e.g., Statistical Parametric Mapping 12).

5.1.1. Convert DICOM files to NIFTI files.

5.1.2. Spatially normalize all PET images to the standard PET template.

5.2. Create binary masks for the left and right DLPFC (e.g., WFU PickAtlas toolbox). The DLPFC is defined by the middle frontal gyrus in the Automated Anatomical Labeling atlas.

5.3. Extract rCMRglu of the left and right DLPFC using the masks (e.g., MarsBaR toolbox). The rCMRglu is normalized to global mean uptake using proportional scaling.

5.4. Calculate asymmetry index (AI) of rCMRglu in the DLPFC as (rCMRglu right - rCMRglu left) / [(rCMRglu right + rCMRglu left) / 2] × 100. Positive AI indicates right-greater-than-left asymmetry of glucose metabolism.

REPRESENTATIVE RESULTS:

A total of 15 gamers (**Table 1**) and 10 non-gamers were recruited. The mean age of the gamer group (21.3 ± 1.4) was significantly lower than that of the non-gamer group (28.8 ± 7.5) ($t = -3.81$, $p < 0.001$). There were 8 men in the gamer group and 6 men in the non-gamer group ($\chi^2 = 0.11$, $p = 0.74$). In the gamer group, 7 out of 15 were diagnosed with IGD.

Behavioral results using linear mixed models indicate that the tDCS sessions successfully lowered the IAT score ($z = -4.29$, $p < 0.001$), weekly hours spent playing games ($z = -2.41$, $p = 0.02$), and improved the BSCS score ($z = 2.80$, $p = 0.01$) in the gamer group (**Table 1** and **Figure 1**). No adverse events were reported during the tDCS sessions.

A significant negative correlation was found between changes in the IAT score and those in the BSCS score in gamers ($r = -0.77$, $p < 0.001$) (**Figure 2**). In addition, a decrease of the time spent on games was associated with an increase of the BSCS score in the gamer group at a marginal level ($r = -0.50$, $p = 0.06$).

PET analysis revealed that the AI of the DLPFC was significantly different between the gamer group and the non-gamer group ($t = 3.53$, $p = 0.002$) at baseline (**Figure 3**). Despite the significant difference in age between the two groups, rCMRglu may not be affected by aging in young adults[26]. Following the tDCS sessions, the AI of the DLPFC in the gamer group was significantly decreased ($z = -2.11$, $p = 0.04$) (**Figure 3**).

FIGURE AND TABLE LEGENDS:

Figure 1: Changes in clinical characteristics of the gamer group. Scores of (**A**) Internet Addiction Test, (**B**) weekly hours spent playing games, and (**C**) Brief Self Control Scale before and after transcranial direct current stimulation (tDCS). Error bars indicate standard errors.

Figure 2: A correlation between changes in the Brief Self Control Scale and those in the Internet Addiction Test in the gamer group.

Figure 3: Asymmetry index of regional cerebral metabolic rate of glucose (rCMRglu) in the dorsolateral prefrontal cortex. Asymmetry index was defined as (rCMRglu right - rCMRglu left) / [(rCMRglu right + rCMRglu left) / 2] × 100. Error bars indicate standard errors. This figure has been modified from Lee et al[27]. tDCS, transcranial direct current stimulation.

Table 1: Demographic and clinical characteristics of gamers. The gamers received a total of 12 tDCS sessions over the dorsolateral prefrontal cortex (2 mA for 30 min per session, 3 times per week for 4 weeks).

DISCUSSION:

We have presented a tDCS and neuroimaging protocol for online gamers and assessed its feasibility. The results demonstrated that repeated sessions of tDCS over the DLPFC reduced online game addiction symptoms and average time spent on games and increased self-control. An increase in self-control was correlated with a decrease in addiction symptoms. Moreover, the abnormal asymmetry of rCMRglu in the DLPFC where the right side was greater than the left side was improved after the tDCS sessions in the gamer group. These results may suggest the feasibility of tDCS for reducing online game use. However, since our experiment did not have a sham control group and the participants were aware of the aim of the study at the time of recruitment, further randomized sham-controlled studies are warranted to evaluate the efficacy of tDCS in online gamers. In addition, the long-term effects of tDCS should also be investigated.

Although we defined our inclusion criteria broadly to include both normal gamers and individuals with IGD, it may also be informative to only include IGD patients as study participants in future studies. Otherwise, the effects of tDCS can be compared between normal gamers and IGD patients in larger samples. In addition, any contraindications for tDCS such as severe headache, metal in the head, history of seizure or epilepsy, and lesions on the scalp should be carefully screened for safety.

Using appropriate tDCS parameters is also a critical step for the current protocol. In general, higher current intensity (or current density) and longer stimulation duration are associated with stronger and longer-lasting effects. In most studies, a current intensity and a stimulation duration range from 1 to 2 mA and from 10 to 30 min, respectively[28]. Although a single session of tDCS with current up to 4 mA was safe and tolerable in stroke patients[29], 2 mA is recommended as a safety threshold for human studies[30]. In addition, some studies reported that an increase in stimulation duration alters the effects of polarity, suggesting that the effects of current intensity and stimulation duration may not be necessarily linear[30].

Electrode size influences the current density and the spatial focality. Since smaller electrodes may be associated with not only larger current density but also shunting effect[31], electrode sizes between 25 and 35 cm^2 are commonly used[30]. With regard to the stimulation polarity, a previous tDCS study in alcohol dependence reported that both anodal F3/cathodal F4 and anodal F4/cathodal F3 montages significantly reduced alcohol craving[18]. Thus, the effects of these two montages may also be compared in future tDCS studies in gamers.

For cumulative and long-lasting effects, we applied a total of 12 tDCS sessions over 4 weeks. This schedule consists of a relatively large number of sessions over long period compared to previous tDCS studies[32]. Recently, remotely supervised portable tDCS has been developed for repeated self-administration at home and would be convenient and time-saving for participants[33,34]. Since

anatomical variability including the head size, skull thickness, and morphologies of cortical gyri and sulci may influence the current distribution, computational models of tDCS can be applied to predict the current flow and to optimize and individualize the electrode montages[35].

For the sham tDCS protocol, the current may be set to ramp up to 2 mA over 30 s and ramp down to 0 mA over next 30 s. With this sham protocol, participants have difficulties distinguishing between active and sham stimulation because they feel the same sensations under the electrodes as in active tDCS sessions in the beginning. This initial and short stimulation has been proven to be a reliable technique for sham tDCS[36] and to be one of the advantages of tDCS over other noninvasive neuromodulation techniques. Further research is warranted to optimize and standardize various tDCS parameters for gamers.

Regarding the protocol for assessing addiction severity for games, other scales have been developed and validated[37], and therefore can be used instead of IAT. In the imaging analysis, although we focused on asymmetry of rCMRglu in the target site, analyzing whole-brain voxel-wise changes in rCMRglu may also be informative. Furthermore, other imaging modalities such as fMRI can be used to investigate changes of the brain induced by tDCS. For instance, an fMRI study reported that bupropion treatment decreased cue-induced activity in the DLPFC in patients with Internet video game addiction[38].

Our protocol showed the feasibility and safety for reducing addiction severity and online game use using tDCS and for evaluating the underlying neural correlates. With appropriate modifications, it could be applicable for other neurological and psychiatric disorders.

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DISCLOSURES:

The City University of New York (CUNY) has IP on neurostimulation system and methods with Marom Bikson as inventor. Marom Bikson has equity in Soterix Medical Inc and serves as a consultant for Boston Scientific Inc. All other authors declare no financial conflicts of interest.

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Figure1

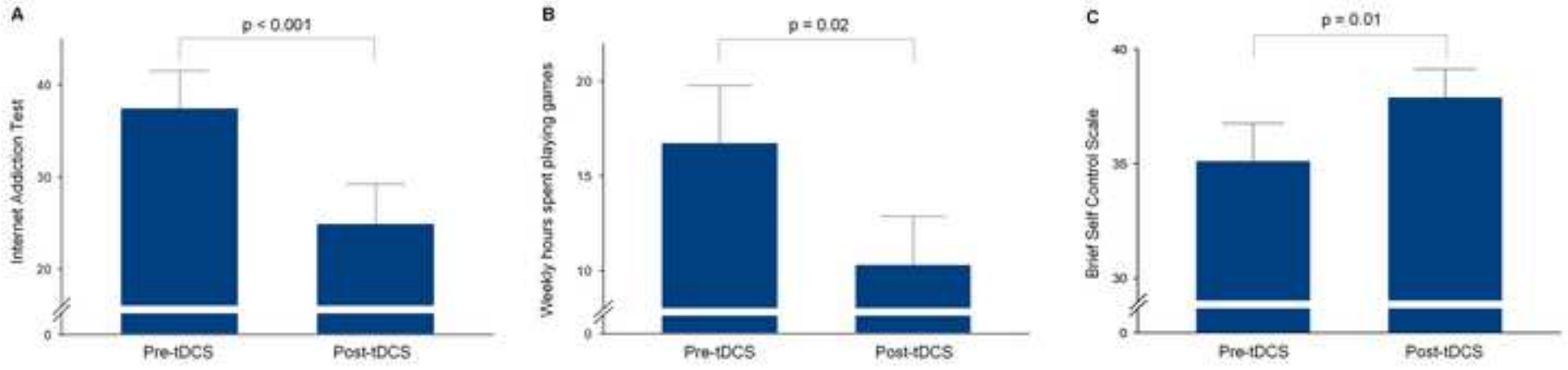

Figure2

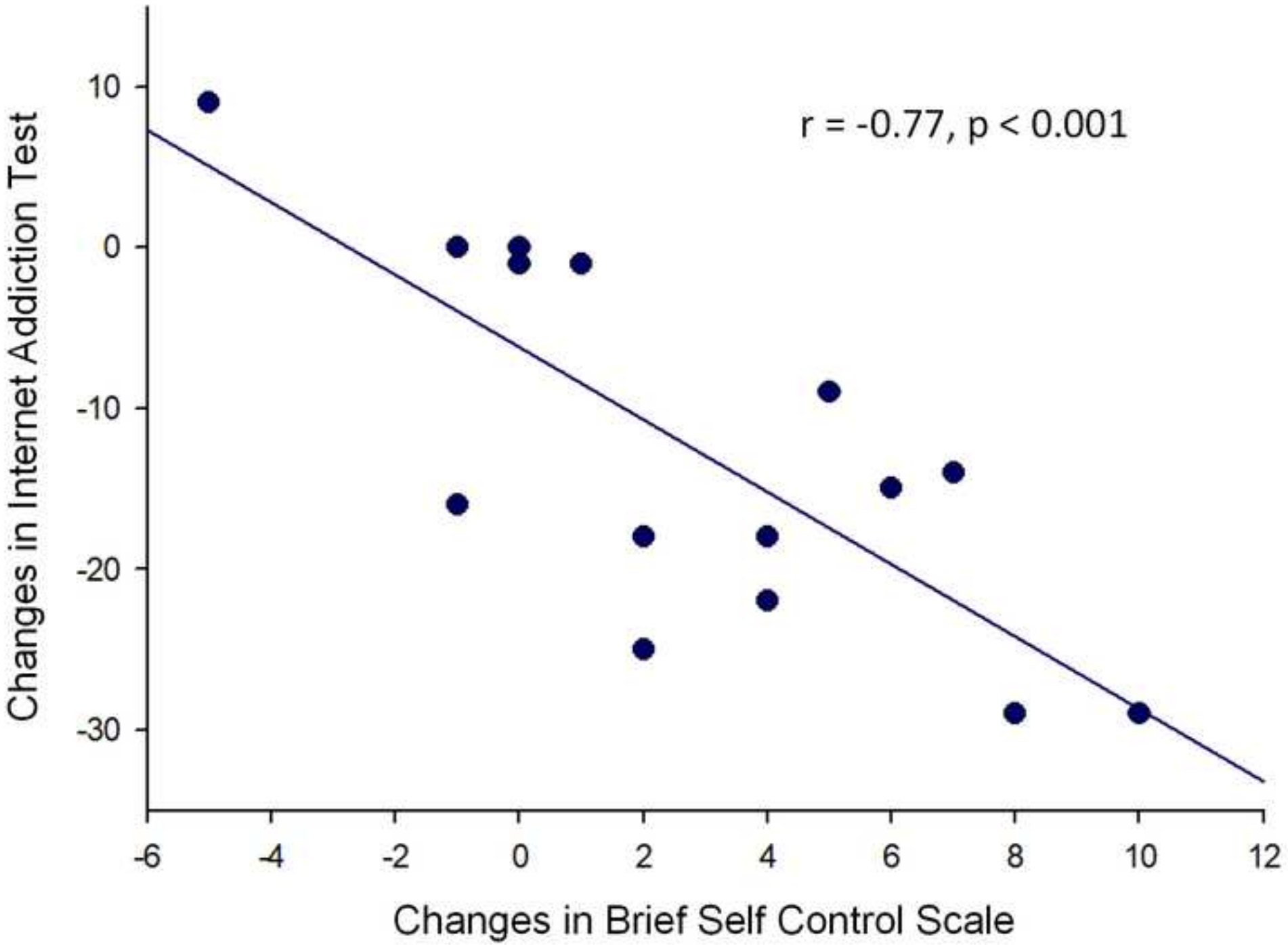

Figure3

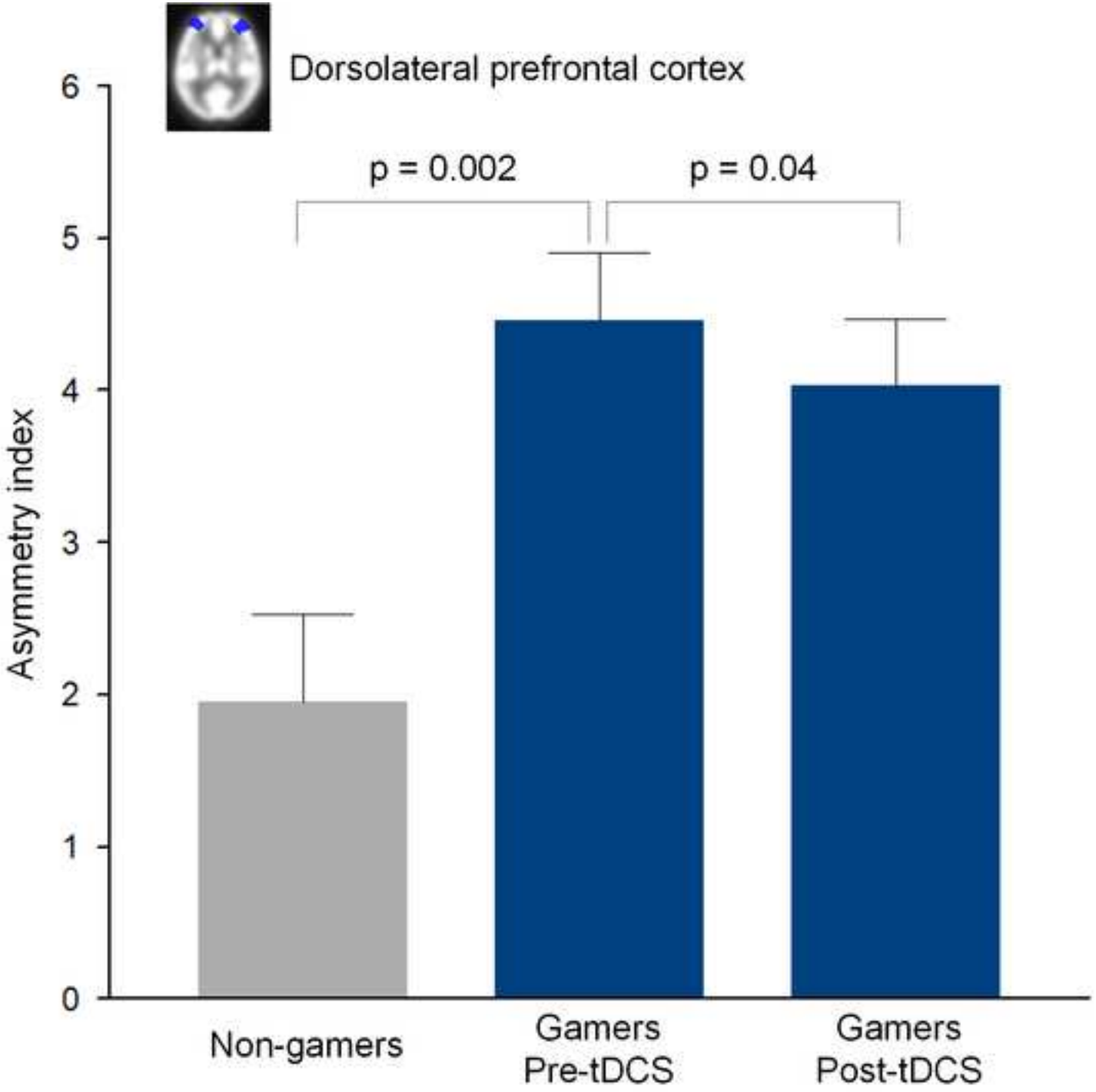

Table 1. Demographic and clinical characteristics of gamers

Characteristics	Pre-tDCS (mean ± SD or n)	Post-tDCS (mean ± SD)	Test statistics
Age	21.3 ± 1.4		
Sex (male/female)	8/7		
Internet gaming disorder	7		
Internet Addiction Test	37.5 ± 15.7	24.9 ± 16.7	z = -4.29, p < 0.001
Weekly hours spent playing games	16.8 ± 11.7	10.3 ± 9.9	z = -2.41, p = 0.02
Brief Self Control Scale	35.1 ± 6.4	37.9 ± 4.7	z = 2.80, p = 0.01

Note. SD, standard deviation; tDCS, transcranial direct current stimulation.

The gamers received a total of 12 tDCS sessions over the dorsolateral prefrontal cortex (2 mA for 30 minutes per session, 3 times per

week for 4 weeks).

Name of Material/Equipment	Company	Catalog Number
Discovery STE PET/CT Imaging System	GE Healthcare	
MarsBaR region of interest toolbox for SPM	Matthew Brett	
Statistical Parametric Mapping 12	Wellcome Centre for Human Neuroimaging	
Transcranial direct current stimulation device	Ybrain	YDS-301N
WFU_PickAtlas	ANSIR Laboratory, Wake Forest University School of Medicine	

Comments/Description
Neuroimaging analysis software; http://marsbar.sourceforge.net/
Neuroimaging analysis software; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/
Neuroimaging analysis software; https://www.nitrc.org/projects/wfu_pickatlas/

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RESPONSE LETTER

The authors would like to thank the editor and reviewers for their careful review of our manuscript and for their insightful comments and suggestions that have helped us improve the quality of manuscript. We have prepared a point-by-point response to all comments. The comments of the editor and the reviewers are presented in gray-shaded boxes, while revised or newly added text/figures/tables are shown in white text boxes below. All revisions are also shown in blue text in the revised manuscript.

Editorial comments

Changes to be made by the author(s):
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We have thoroughly proofread the manuscript to check that there are no spelling or grammar errors.

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We used a figure from our previous paper which has been published in the Journal of Behavioral Addictions.

According to the journal’s website (https://akademiai.com/loi/2006), it states “The Journal of Behavioral Addictions is a fully open access journal. Readers can read, download, copy, distribute, print, search or link to the full texts of articles, or use them for any other non-commercial lawful purpose. Articles are distributed under Creative Commons Attribution-NonCommercial 4.0 International Licenses.”

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3. Please revise lines 102-104, 194-196, 198-199, 228-229, 254-259, and 277-279 to avoid previously published text.

We thank the editor for kindly attention. We either modified or removed the mentioned lines in the revised manuscript.

4. Abstract: Please revise to focus on the method being presented rather than the results of a specific experiment. Include a statement about the purpose of the method. A more detailed overview of the method and a summary of its advantages, limitations, and applications is appropriate. Please focus on the general types of results acquired.

We have revised the manuscript according to the editor's suggestions. Please see our revised manuscript.

5. Introduction: Please revise to include all of the following:
a) A clear statement of the overall goal of this method
b) The rationale behind the development and/or use of this technique
c) The advantages over alternative techniques with applicable references to previous studies
d) A description of the context of the technique in the wider body of literature
e) Information to help readers to determine whether the method is appropriate for their application

We have revised the manuscript to include a) to e) in the Introduction. Please see our revised manuscript.

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We have moved the information regarding specific commercial names from the manuscript to the Table of Materials.

7. Please revise the Protocol to contain only action items that direct the reader to do something (e.g., "Do this," "Ensure that," etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as "could be," "should be," and "would be" throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a "NOTE."

We have revised the Protocol to contain only action items in the imperative tense and used a "NOTE" for any text that cannot be written in the imperative tense.

8. Please add more details to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol. Please ensure you answer the "how" question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. See examples below.

According to the editor's suggestions, we have provided more details to the Protocol. Please see our revised manuscript.

9. 3.3: Please describe how processing steps are actually done.

We have rewritten this part under 5. Data Analysis in the revised manuscript.

PROTOCOL:

5. Data Analysis

5.1. Use an appropriate software package to preprocess the PET images. We used Statistical Parametric Mapping 12.

5.1.1. Convert DICOM files to NIFTI files.

5.1.2. Spatially normalize all PET images to the standard PET template.

5.2. Create binary masks for the left and right DLPFC. We used the WFU PickAtlas toolbox.
NOTE: The DLPFC is defined by the middle frontal gyrus in the Automated Anatomical Labeling atlas.

5.3. Extract rCMRglu of the left and right DLPFC using the masks. We used the MarsBaR toolbox.
NOTE: The rCMRglu is normalized to global mean uptake using proportional scaling.

5.4. Calculate asymmetry index (AI) of rCMRglu in the DLPFC as (rCMRglu right - rCMRglu left) / [(rCMRglu right + rCMRglu left) / 2] × 100.
NOTE: Positive AI indicates right-greater-than-left asymmetry of glucose metabolism.

10. 4.5: Please describe how to deliver tDCS.

We have added more details on how to deliver tDCS under 3. Application of tDCS in the revised manuscript.

PROTOCOL:

3. Application of tDCS

3.1. Within a week after the baseline assessment, apply tDCS to participants. Prepare tDCS sessions with following materials: a tDCS device, wet wipes, saline solution, two sponge electrodes (6 cm in diameter), a cable, and a headband.

3.2. Have the participant sit on a chair.

3.3. Set the stimulation parameters for the tDCS device: 2 mA for 30 minutes (current density = 0.07 mA/cm^2). The current is set so it ramps up to 2.0 mA over 30 seconds, remains at 2.0 mA for 29 minutes, and ramps down to 0 mA over the last 30 seconds.

3.4. Place two sponge electrodes in the rubber holders of the headband and soak them with saline solution.

3.5. Use wet wipes to remove any makeup, dirt, or sweat on the skin where the electrodes will be applied.

3.6. Put the headband on the participant's head to place the anodal electrode over the left DLPFC (F3; 10 - 20 EEG system) and the cathodal electrode over the right DLPFC (F4).

3.7. Connect the electrodes to the tDCS device using the cable and turn on the device.

3.8. Ask the participant to report any adverse effects during or after the tDCS session.

3.9. At the end of the 30 minutes of stimulation, turn off the device and remove the electrodes from the participant.

3.10. Administer a total of 12 tDCS sessions (3 times per week for 4 weeks).

11. 4.6: How long is each session?

Each session is 30 minutes long. This information is provided in 3.3. and 3.9. of the Protocol.

PROTOCOL:

3.3. Set the stimulation parameters for the tDCS device: 2 mA for 30 minutes (current density = 0.07 mA/cm^2). …

3.9. At the end of the 30 minutes of stimulation, turn off the device and remove the electrodes from the participant.

12. Line 204: Figure 3 does not exist. Please revise.

We apologize for the confusion. We have provided Figure 3 in the revised manuscript.

13. JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please revise the Discussion to explicitly cover the following in detail in 3-6 paragraphs with citations:
a) Critical steps within the protocol
b) Any modifications and troubleshooting of the technique
c) Any limitations of the technique
d) The significance with respect to existing methods
e) Any future applications of the technique

We have revised the Discussion according to the editor’s suggestions. Please see our revised manuscript.

14. Please upload Table 1 to your Editorial Manager account as an .xlsx file.

We have uploaded Table 1 to our Editorial Manager account as an .xlsx file.

15. Table of Materials: Please ensure that it has information on all relevant supplies, reagents, equipment and software used, especially those mentioned in the Protocol. Please sort the items in alphabetical order according to the name of material/equipment.

We have provided the information regarding all the equipment and software used in the Table of Materials.

16. References: Please do not abbreviate journal titles.

We corrected the references accordingly.

Reviewer 1

Manuscript Summary:
In this study 12 sessions of active tDCS are applied to gamers and non-gamers. The aim was to evaluate efficacy and tolerability of this treatment. Results suggest a positive effect of this treatment.

We thank the reviewer for the summary of our manuscript. We have incorporated the reviewer's specific comments in the preparation of the revised version of the manuscript.

Major Concerns:
The major concern of this paper is the lack of a sham group. Why is no sham group included in this study? This should really be explained since it is 2019 and sham groups are golden standard in this research field. If the active treatment is not compared to sham treatment, all words like "effect" and "efficacy" are not valid. The only thing investigated here is feasibility, so this is a feasibility study no efficacy study.

We agree with the reviewer that the lack of a sham group is a limitation of our study. We removed words like “effect” and “efficacy” and used “feasibility” instead in our revised manuscript.

DISCUSSION:

… However, since our experiment did not have a sham control group and the participants were aware of the aim of the study at the time of recruitment, further randomized sham-controlled studies are warranted to evaluate the efficacy of tDCS in online gamers. …

Introduction:
The introduction lacks explanation of relationship between online gaming and why PET-CT scan is performed. Currently it is only mentioned very briefly after the research questions was introduced. A more extensive explanation should be given earlier in the text, and examples of previous studies showing the relationship or relevance of asymmetry in gaming addiction (or addiction in general) should be given.

As the reviewer suggested, we provided the rationale for investigating online gaming using PET-CT in the Introduction of the revised manuscript. Moreover, a previous study which notes the relevance of asymmetry in craving for online gaming was added as a reference.

[14] Gordon, H. W. Laterality of Brain Activation for Risk Factors of Addiction. *Current Drug Abuse Reviews*. **9** (1), 1-18 (2016).

[15] Tian, M. *et al*. PET imaging reveals brain functional changes in internet gaming disorder. *European Journal of Nuclear Medicine and Molecular Imaging*. **41** (7), 1388-1397, doi:10.1007/s00259-014-2708-8, (2014).

INTRODUCTION:

… In addition, functional asymmetry of the brain may contribute to impulsivity and craving in addictions including IGD. For instance, cue-induced craving for online gaming could be related to right prefrontal activations[14]. However, alterations of regional cerebral metabolic rate of glucose (rCMRglu) associated with excessive online game use or IGD remain to be further investigated compared to other brain deficits[15].

Method:
- What is the purpose of the non-gamer group? Does this group get tDCS treatment or not? If this group is needed for the PET-CT comparison please explain. Also describe it is assessed that these individuals do not do online gaming.

We apologize for the confusion. The non-gamer group was included to compare rCMRglu with the gamer group at baseline. The non-gamer group did not receive tDCS treatment. Individuals in the non-game group reported that they do not play online game. We provided this information in the Abstract and the Protocol.

ABSTRACT:

Individuals who do not play online games receive only baseline FDG-PET scans without tDCS. Changes of clinical characteristics and asymmetry of regional cerebral metabolic rate of glucose (rCMRglu) in the DLPFC are examined in the gamers. In addition, asymmetry of rCMRglu is compared between gamers and non-gamers at baseline.

PROTOCOL:
1.1. Recruit individuals who report that they play online games (the gamer group) and those who report that they do not play online games (the non-gamer group).
NOTE: For our experiment, we included individuals with two or more IGD symptoms according to the Diagnostic and Statistical Manual of Mental Disorders-5[23] or those who play games at least one hour per day on average in the gamer group. The non-gamer group undergoes only baseline brain FDG-PET scans to compare rCMRglu with the gamer group and does not receive tDCS sessions.

- During recruiting, what was instructed to the participants? If individuals are told they will participate in a study focusing on reducing online gaming, it is very obvious you will find an effect on gaming. Please elaborate on this, especially since there is no sham group.

We thank the reviewer for bringing this important point to our attention. The participants were informed that they are participating in a study which investigates the effects of tDCS on addiction symptoms and time spent on games. This issue has been added as a limitation in the Discussion.

DISCUSSION:

... However, since our experiment did not have a sham control group and the participants were aware of the aim of the study at the time of recruitment, further randomized sham-controlled studies are warranted to evaluate the efficacy of tDCS in online gamers.

Results:
- Sometimes it is unclear on whether the results concern comparisons between the gamer and non-gamer group, or only within the gamer group.

We thank the reviewer for pointing this out. Demographic characteristics such as age and sex and AI at baseline were compared between the gamer group and non-gamer group. Changes in clinical characteristics and AI between baseline and follow-up assessments were compared within the gamer group. We made this more clear in the Results.

- Is the AI of the non-gamer group reported? And is this AI of the gamer group compared to the non-gamer group after stimulation?

Yes, the AI of the non-gamer group is reported. Only the baseline comparison is reported since the non-gamer group did not receive stimulation.

REPRESENTATIVE RESULTS:

PET analysis revealed that the AI of the DLPFC was significantly different between the gamer group and the non-gamer group ($t = 3.53$, $p = 0.002$) at baseline (Figure 3).

Discussion:
During the discussion the words "effects", "demonstrated", "improved", "evidence" are being used to explain results. These words should all be downsized into something like: the tDCS treatment seems to be feasible in reducing online gaming. The major drawback of the lack of a sham control group should be mentioned much earlier since the results should be read bearing this in mind.

As suggested, we toned down the discussion and mentioned the lack of a sham group as a limitation of the study. Please see our revised manuscript.

Reviewer 2

Manuscript Summary:
In this paper the authors explore the effects of 4-week tDCS applied over the Dorsolateral Prefrontal Cortex in a sample of 15 online gamers, treated in an open-label single-arm setting. Moreover, the authors explored the neurobiological correlates by using 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) scan. They suggest a potential utility of this treatment to rebalance the right/left asymmetry in terms of glucose prefrontal uptake. The study is interesting, but some minor issues should be addressed before publication.

The authors are grateful for the reviewer's summary as well as the thoughtful comments. We have incorporated the reviewer's specific comments in the preparation of the revised version of the manuscript.

Minor Concerns:

- Introduction section, line 70
In the definition of tDCS in contrast with TMS, probably would be more precise to state differences exposed are not complete. rTMS determines the depolarization of neurons throughout the application of a magnetic field, while currents used in tDCS determine the modulations of targeted brain areas. Also, could be interesting to state that rTMS has been also recently studied for the treatment of behavioral addictions (i.e., Gay et al, 2017; Pettorruso, Addict Behav 2019).

We thank the reviewer for bringing this important issue. As suggested, we elaborated on the differences between tDCS and TMS. Moreover, we included the suggested references in the revised manuscript.

[21] Gay, A. *et al*. A single session of repetitive transcranial magnetic stimulation of the prefrontal cortex reduces cue-induced craving in patients with gambling disorder. *European Psychiatry*. **41** 68-74, doi:10.1016/j.eurpsy.2016.11.001, (2017).

[22] Pettorruso, M. *et al*. Dopaminergic and clinical correlates of high-frequency repetitive transcranial magnetic stimulation in gambling addiction: a SPECT case study. *Addictive Behaviors*. **93** 246-249, doi:10.1016/j.addbeh.2019.02.013, (2019).

INTRODUCTION:

tDCS has become a popular method because it is simple, cheap, and safe to administer compared to other brain stimulation techniques such as transcranial magnetic stimulation (TMS) that uses magnetic pulse to generate an electrical current in the brain tissue under the coil.

…

Several studies have demonstrated favorable results of tDCS[18-20] and repetitive TMS[21,22] over the DLPFC for treating behavioral and substance addiction.

- Introduction section, line 75.
I guess the authors consider the application of tDCS to online gaming a consequence of similarities that Internet Online Gaming share with other behavioral addictions. I think this link should be better detailed.

According to the reviewer's suggestion, we provided further details and additional references.

[5] Weinstein, A. M. An Update Overview on Brain Imaging Studies of Internet Gaming Disorder. *Frontiers in Psychiatry*. **8** 185, doi:10.3389/fpsyt.2017.00185, (2017).

[6] Park, B., Han, D. H. & Roh, S. Neurobiological findings related to Internet use disorders. *Psychiatry and Clinical Neurosciences*. **71** (7), 467-478 (2017).

INTRODUCTION:

Previous studies have suggested that IGD may share clinical and neurobiological similarities with other behavioral addictions and substance use disorders[5,6].

- In the Abstract is not reported that the authors compared online versus non online gamers (both using clinical and PET scan scales).

According to the reviewer's comment, we revised the Abstract as follows.

ABSTRACT:

… Individuals who do not play online games receive only baseline FDG-PET scans without tDCS. Changes of clinical characteristics and asymmetry of regional cerebral metabolic rate of glucose (rCMRglu) in the DLPFC are examined in the gamers. In addition, asymmetry of rCMRglu is compared between gamers and non-gamers at baseline.

In our experiment, a total of 15 gamers received tDCS sessions and completed baseline and follow-up assessments. Ten non-gamers underwent FDG-PET scans at baseline.

- Discussion section, line 244
To improve the comprehensiveness of the discussion, consider also the report of the application of tDCS in gambling disorder (Martinotti et al., J Behav Addict. 2018) and to reduce substance-craving (i.e., Martinotti et al., J ECT 2019).

- Discussion section, line 253
In this paragraph involving DLPFC, could be also interesting to highlight the relevance of DLPFC in cognitive inflexibility (Fujimoto, Transl Psychiatry 2017),

- Discussion section, Limitation paragraph, line 273
Add a reference sustaining the statement that in young adults could be irrelevant the difference of ages in terms of glucose PET uptake.

We thank the reviewer for the suggestions. When preparing for the revised version of the manuscript, we reorganized the texts so that we focused on the methods-related discussions in the Discussion according to the editor's suggestions. Consequently, the texts that are not methods-related have been moved to either the Introduction or the Representative Results. Accordingly, we added the suggested references in the Introduction and the Representative Results of the revised manuscript.

[10] Fujimoto, A. *et al*. Deficit of state-dependent risk attitude modulation in gambling disorder. *Translational Psychiatry*. **7** (4), e1085, doi:10.1038/tp.2017.55, (2017).

[19] Martinotti, G. *et al*. Gambling disorder and bilateral transcranial direct current stimulation: A case report. *Journal of Behavioral Addictions*. **7** (3), 834-837, doi:10.1556/2006.7.2018.85, (2018).

[20] Martinotti, G. *et al*. Transcranial Direct Current Stimulation Reduces Craving in Substance Use Disorders: A Double-blind, Placebo-Controlled Study. *Journal of ECT*. doi:10.1097/YCT.0000000000000580, (2019).

[26] Bentourkia, M. *et al*. Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. *Journal of the Neurological Sciences*. **181** (1-2), 19-28 (2000).

INTRODUCTION:

It has been reported that the dorsolateral prefrontal cortex (DLPFC) is closely involved in the pathophysiology of substance and behavioral addiction such as craving[7], impulse control[8], decision making[9], and cognitive flexibility[10].

Several studies have demonstrated favorable results of tDCS[18-20] and repetitive TMS[21,22] over the DLPFC for treating behavioral and substance addiction.

REPRESENTATIVE RESULTS:

… Despite the significant difference in age between the two groups, rCMRglu may not be affected by aging in young adults[26].

- Add the limitation of the lack of long-term effects of the intervention explored

As suggested by the reviewer, the lack of the long-term effects of the intervention has been added as a limitation.

DISCUSSION:

… In addition, the long-term effects of tDCS should also be investigated.

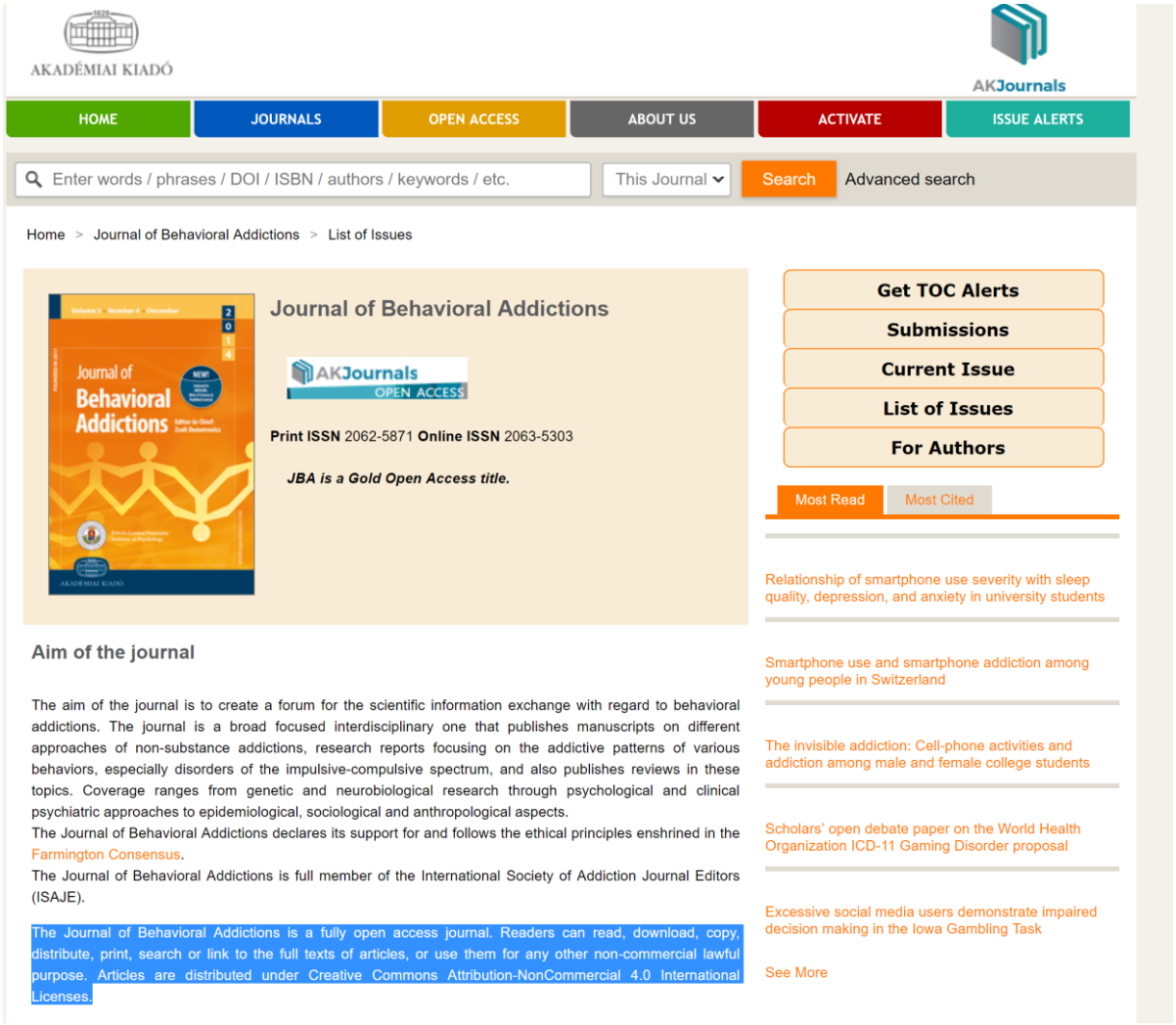
- Caption of Table 1
Specify the time of assessment (p-ost tDCS) and the details about the intervention applied to the sample.

We thank the reviewer for this suggestion. We have provided the details about the intervention in Table 1.

Table 1.

The gamers received a total of 12 tDCS sessions over the dorsolateral prefrontal cortex (2 mA for 30 minutes per session, 3 times per week for 4 weeks).

https://akademiai.com/loi/2006



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