Study Title

Investigation of the Relationship Between Serum BDNF and GDNF Levels and Impulsivity, Reward/Punishment Sensitivity in Children Diagnosed With Internet Gaming Disorder

Case/Control Study

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Study Protocol

Location of the Study:

University of Health Sciences, Istanbul Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Department of Child and Adolescent Psychiatry, Istanbul, Türkiye

Purpose of the Study:

Research and knowledge regarding the neurobiology of behavioral addictions and Internet Gaming Disorder (IGD) remain limited compared to substance and alcohol use disorders. However, IGD is increasingly causing significant functional impairment, particularly in the child and adolescent population. The primary objective of this study is to measure the serum levels of Brain-Derived Neurotrophic Factor (BDNF) and Glial-Derived Neurotrophic Factor (GDNF)—both known for their roles in neurogenesis and neuroprotective effects—in a patient group aged 10-14 and a healthy control group. Additionally, the study aims to investigate the relationship between these neurotrophic factor levels and disease severity, as well as various behavioral and emotional parameters evaluated through psychometric assessments, to identify differences between the patient and healthy populations.

Material and Methods of the Study:

Between May 2026 and December 2026, informed consent and assent will be obtained from participants and their parents/legal guardians after a comprehensive explanation of the study objectives, psychometric scales, and psychiatric evaluation protocols. This research is designed as a cross-sectional case-control study. The patient group will include children and adolescents diagnosed with Internet Gaming Disorder (IGD) according to DSM-5 criteria. The control group will consist of age- and gender-matched individuals attending psychiatry or pediatric outpatient clinics or volunteers who meet the control inclusion criteria and have provided written informed consent. The primary investigator will conduct clinical psychiatric interviews with all participants in both the case and control groups to verify eligibility and diagnostic status. The following psychometric instruments will be administered:

For children (Case and Control groups): Internet Gaming Disorder Scale-Short Form (IGDS9-SF), Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ), UPPS-P Impulsive Behavior Scale for Children (C-UPPS-P), Screen for Child Anxiety Related Emotional Disorders (SCARED) - Child Form, and Children's Depression Inventory (CDI).

For parents (Case and Control groups): SCARED - Parent Form, and the Turgay DSM-IV-based Screening and Assessment Scale for Disruptive Behavior Disorders (Turgay ADHD Scale).

Joint Assessments: The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) and a sociodemographic data form will be administered to both the children and their parents by the researcher.

For biochemical analysis, peripheral venous blood samples will be collected from all participants following a 10-12 hour fasting period between 09:00 and 12:00. Samples will be drawn into gold-top (serum separator) tubes and transported within 2-3 hours to the Brain and Neurodegenerative Diseases Research Laboratory at Istanbul University-Cerrahpaşa, Institute of Neurological Sciences, Department of Neuroscience. Blood tubes will be centrifuged at 5000 rpm for 10 minutes. The separated serum will be aliquoted into 1.5 ml microcentrifuge tubes and stored at -80°C until the final analysis. Once the sample collection phase is complete, serum BDNF and GDNF levels will be determined using Human BDNF (ELH-BDNF-1, RayBiotech) and Human GDNF (ELH-GDNF-1, RayBiotech) ELISA kits. ELISA assays will be conducted strictly following the manufacturers' protocols at the aforementioned laboratory.

Inclusion Criteria:

- For IGD Patient Group:
    - Being between 10 and 14 years of age.
    - Ability to read and write fluently.
    - Voluntary participation with written informed consent obtained from both the participants and their parents/legal guardians after a comprehensive briefing on the study procedures and scales.
    - Meeting the DSM-5 diagnostic criteria for Internet Gaming Disorder (IGD) and scoring above the clinical cutoff on the Internet Gaming Disorder Scale-Short Form (IGDS9-SF).
- For Healthy Control Group:
    - Children between 10 and 14 years of age.
    - Ability to read and write fluently.
    - No history or current diagnosis of any neuropsychiatric disorder, confirmed through clinical psychiatric assessment.
    - Voluntary participation with written informed consent obtained from both the participants and their parents/legal guardians after a comprehensive briefing on the study procedures and scales.

Exclusion Criteria:

- Meeting the DSM-5 diagnostic criteria for Autism Spectrum Disorder, Schizophrenia, Bipolar I Disorder, or Bipolar II Disorder.
- Having a moderate to severe intellectual disability and/or a neurological disease in either the child or the caregiver that would impede the ability to understand instructions or provide reliable responses during the interview.
- Refusal to participate voluntarily or failure to sign the informed consent/assent form by the children or their parents/legal guardians after receiving a detailed explanation of the study’s purpose and the assessment scales to be administered.

Statistical Analysis Plan (SAP)

Power analysis was performed using G*Power 3.1, referencing studies comparing serum BDNF (Demirci et al., 2023) and GDNF (Jeong et al., 2019) levels in patients with Internet Gaming Disorder (IGD) and healthy controls. While the literature reported effect sizes (Cohen's d) of 0.82 for BDNF and 1.69 for GDNF, a more conservative effect size of $d=0.7$ was adopted to account for potential fluctuations in pediatric serum levels, with an α error probability of 0.05 and a power (1–β) of 0.80. Based on a two-tailed hypothesis test, a minimum of 34 participants per group was required; however, 80 patients and 40 controls will be recruited to enhance statistical power and accommodate the planned Multiple Linear Regression (MLR) analysis.

Statistical analyses will be conducted using IBM SPSS Statistics (Version 25.0) and jamovi (Version 2.6). Descriptive statistics will be presented as mean, SD, median, and IQR. Normality of variables will be assessed via the Shapiro–Wilk test, skewness and kurtosis values, and histograms. Provided that assumptions are met, group comparisons will be performed using ANCOVA, adjusted for age, sex, BMI, and comorbid scale scores (SCARED, CDI, and Turgay ADHD scale). Unadjusted group comparisons will be reported via independent samples t-test or Mann–Whitney U test where appropriate. The relationships between biomarker levels and clinical scale scores, as well as the prediction of disease severity, will be evaluated within the patient group using MLR models, with results reported as β coefficients, 95% CI, and p-values.

Informed Consent Form (ICF)

For Child Participants

RESEARCH TITLE: Investigation of the Relationship Between Serum BDNF and GDNF Levels and Impulsivity, Reward/Punishment Sensitivity in Children Diagnosed With Internet Gaming Disorder

You are being invited to participate in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being conducted, how your information will be used, what the study involves, and its possible benefits, risks, and any potential discomforts. Please take the time to read the following information carefully and discuss it with your doctor if you wish.

The decision to participate in this study is entirely yours. If you decide to take part, you will be given this form to sign. Even after deciding to participate, you are free to withdraw from the study at any time. Your withdrawal will not affect the standard of medical care or treatment you receive.

In this research, we will compare the blood levels of growth factors known as BDNF and GDNF, which play a role in brain development, between adolescents with Internet Gaming Disorder (IGD) and a healthy control group. We will also investigate the relationship between these levels and impulse control and behavioral regulation. Your current medical treatment will continue as required by your clinical status. This study will never take precedence over your proven medical treatments. There is no cost associated with participating in this study. Any new information that may emerge during the study and could affect your willingness to continue will be communicated to you immediately. Furthermore, by participating, you will be helping other children and young people in similar situations. We thank you in advance for your potential and significant contribution to the scientific community.

Participant's Declaration

I have been informed by Dr. Kerim Kızıltan regarding a medical research project to be conducted at the University of Health Sciences, Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Department of Child and Adolescent Psychiatry. Following this briefing, I have been invited to take part in this research as a "participant."

I believe that the confidentiality of my personal information, which must remain between my physician and me, will be handled with great care and respect during this research. I have been given sufficient assurance that my personal data will be strictly protected during the use of research results for educational and scientific purposes.

I am aware that I may withdraw from the research at any time during the project without providing any reason. However, I understand that it is appropriate to notify the researchers in advance of my withdrawal to avoid placing them in a difficult position. I also understand that the researcher may remove me from the study if it is deemed necessary for my medical well-being. I hold no financial responsibility for the expenses of the research, and I will not receive any payment for my participation. I have been assured that in the event of any health problem arising directly or indirectly from the research application, all necessary medical interventions will be provided. I understand that I will not incur any financial burden regarding such medical interventions.

In the event of a health problem during the research, I know that I can reach Dr. Kerim Kızıltan at the Department of Child and Adolescent Psychiatry. I understand that I am not obligated to participate in this research. I have not encountered any coercive behavior regarding my participation. I also know that if I refuse to participate, it will not harm my medical care or my relationship with my physician.

I have read all the explanations in this informed assent form. A written and oral explanation regarding the subject and purpose of the research has been provided to me by the physician named below. I have understood all the explanations in detail. Following a period of personal consideration, I have decided to participate in this research project as a "participant." I acknowledge that my participation is voluntary and that I may withdraw at any time with or without justification. I agree to participate in the study of my own free will, without any pressure or coercion, and I consent to the use of the samples collected for this and future studies.

Participant:

Name-Surname:

Phone:

Signature:

Witness:

Name-Surname:

Phone:

Signature:

Principal Investigator:

Name-Surname: **Dr. Kerim Kızıltan (MD)**

Date:

Signature:

Informed Consent Form (ICF)

For The Participant's Parents / Legal Guardians

RESEARCH TITLE: Investigation of the Relationship Between Serum BDNF and GDNF Levels and Impulsivity, Reward/Punishment Sensitivity in Children Diagnosed With Internet Gaming Disorder

You and your child are being invited to participate in this scientific research study. Before deciding whether or not to take part, it is important for you to understand why the research is being conducted, how your and your child's information will be used, what the study involves, and its possible benefits, risks, and any potential discomforts. Please take the time to read the following information carefully.

The decision to participate in this study is entirely yours. If you decide to take part, you will be provided with this informed consent form to sign. Even after deciding to participate, you are free to withdraw from the study at any time. This will not affect the standard of medical care or treatment your child receives. If you wish, your physician will be informed of your participation in this clinical study.

Your child's clinical diagnosis and treatment plan have already been determined by your physician. Therefore, your decision regarding participation in this study will not affect the treatment provided. The aim of our study is to compare the blood levels of growth factors known as BDNF (Brain-Derived Neurotrophic Factor) and GDNF (Glial-Derived Neurotrophic Factor), which are influential in brain development, between patients with Internet Gaming Disorder (IGD) and a healthy control group, and to examine their relationship with impulse control and behavioral regulation. Ethical committee approval has been obtained for this research. The principal investigator, Dr. Kerim Kızıltan, will be available to answer your questions and assist with the resolution of any potential issues.

For the research, a psychiatric interview will be conducted with you and your child, and various assessment scales will be administered. To measure the blood levels of the relevant growth factors, a venous blood sample will be collected from your child between 09:00 and 12:00 following a 10-12 hour fasting period. There is no foreseen immediate additional benefit of this research for your child's current treatment, and no change in the course of treatment should be expected. It is hoped that the results obtained from this research will contribute to the scientific community and benefit the treatment of others in the future. All procedures and related expenses will not be charged to you or any private or public institution

under whose coverage you are. No payment will be made to you within the scope of the research. Identity information and all medical data belonging to you and your child will be kept confidential. Even if the research is published, your identifying information will not be shared. However, study monitors, auditors, ethics committees, and official authorities may access your medical information when necessary. You may also access your own medical information upon request. The number of volunteers participating in this research is 120.

You may withdraw from the research at any time without any penalty or loss of rights. The principal investigators may remove you from the research without your consent due to reasons such as disrupting the research program or being exposed to an adverse effect that may develop depending on or independent of the research. The results of the research will be used for scientific purposes; in the event of your withdrawal or removal by the investigator, your medical data may still be used for scientific purposes if necessary.

Declaration of Consent

I have read the information provided above, which must be given to the participant/volunteer before the research, and I fully understand the scope and purpose of the study and my responsibilities as a volunteer. I have been given sufficient information and assurance that the research results will be used for educational and scientific purposes and that my personal information will be kept confidential during this process. A written and oral explanation about the study was provided by the investigator named below; I have asked my questions and received satisfactory answers. The potential risks and benefits of the study were also explained to me orally. I understand that I can leave this study at any time and without having to provide any reason, and that I will not face any negative consequences if I do so; however, I am aware that it is appropriate to notify the researchers in advance of my withdrawal to avoid placing them in a difficult position. Under these conditions, I agree to participate in the said study of my own free will, without any pressure or coercion, and I consent to the use of the samples collected for this and future studies.

Participant:

Name-Surname:

Parent or Legal Guardian:

Name-Surname:

Phone:

Signature:

Principal Investigator:

Name-Surname: **Dr. Kerim Kızıltan (MD)**

Date:

Signature: