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The Psychological and Genetic Factors of the Addictive Behaviors (PGA) Study

Abbreviated title: Psychological and genetic factors of addictions

Eszter Kotyuk[1,2], Judit Farkas[1] , Anna Magi[1,3], Andrea Eisinger[1,3], Orsolya Király[1], Andrea Vereczkei[4], Csaba Barta[4], Mark D. Griffiths[5], Gyöngyi Kökönyei[1], Anna Székely[1], Mária Sasvári-Székely[4], Zsolt Demetrovics[1]

Affiliations

[1] Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

[2] Postdoctoral Research Program, Hungarian Academy of Sciences, Budapest, Hungary

[3] Doctoral School of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

[4] Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary

[5] International Gaming Research Unit, Psychology Department, Nottingham Trent University, Nottingham, UK

Corresponding author:

Zsolt Demetrovics

Department of Clinical Psychology and Addiction

Institute of Psychology, Eötvös Loránd University

Tel.: +36 1 461 4526

Email: demetrovics.zsolt@ppk.elte.hu

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ABSTRACT

Objectives: Most of the addiction studies focus on very specific aspects of addictions, often with contradictory results, and integrated studies are quite rare. Experimental studies comparing underlying mechanisms of addictions, and analyzing data from an integrative psychological and genetic perspective are almost non-existent. The aim of the present paper is to describe the research protocol of the Psychological and Genetic Factors of Addictive Behaviors (PGA) Study which applies an integrative approach to understanding the acquisition, development, and maintenance of addictive behaviors.

Methods: A wide-spectrum national study was carried out. Data were collected from 3003 adolescents. Addictions to both psychoactive substances and behaviors were thoroughly assessed via psychometrically robust scales which also included assessment related to a wide range of related psychological dimensions. Additionally, a DNA sample was also collected from participants.

Results: The paper presents the detailed methodology of the PGA Study. Data collection procedures, instrumentation, and the analytical approach used to attain the research objectives are described.

Conclusions: Future plans, along with potential contributions of the PGA study are also discussed. It is envisaged the study will provide a unique opportunity to test possible mechanisms and causal pathways mediating the associations of genetic factors, psychological characteristics, and addictions.

Keywords: substance use disorders; behavioral addictions; psychological addiction factors; addiction genetics; integrative approach

Psychological and neurological factors of addictions

Addiction phenotypes

Numerous family adaptation and twin studies have shown a significant role of heritable influences among individual differences concerning addictions (e.g., Agrawal & Lynskey, 2008). In the post-genomic area, many psychogenetic candidate gene studies and GWAS studies were carried out with the aim of identifying both genetic risk factors and protective factors of addictions. However, in most types of addiction, the results concerning genetic association are still inconsistent.

To date, addiction-related research has mainly focused on substance-related addictions. Despite the growing scientific attention concerning various behavioral addictions and the inclusion of Gambling Disorder (GD) as a behavioral addiction in the 'Substance-Related and Addictive Disorders' category in the latest (fifth) edition if the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2015), research examining behavioral addiction is still in its infancy. For example, in terms of genetic causes, there is a constant and growing body of research available on substance-related addictions, whereas with GD, which is the most widely studied behavioral addiction, a recent systematic literature review reported only 13 gene association studies (Gyollai et al., 2014). Thus, further genetic association studies including behavioral addiction phenotypes are needed.

It appears that even in case of the most extensively studied addictive phenomena, there is scarce knowledge concerning their underlying psychological and genetic mechanisms.

Psychological dimensions as possible phenotypes

Specific psychological characteristics may play an important role in the development of addictions. For example, studies have indicated that personality traits (e.g., sensation seeking, impulsivity) are associated with substance use addictions (Barnes et al., 2000; Sarramon et al., 1999) and behavioral addictions (Mehroof & Griffiths, 2010). However, the precise mechanisms of how these traits are risk factors of addictions are unknown.

Blum and colleagues (Blum et al., 2000; Blum et al., 2007; Comings & Blum, 2000) confirmed in several studies the idea of a hypodopaminergic trait leading to Reward Deficiency Syndrome that underlies impulsive and addictive behaviors. According to this biogenic model, specific genetic variants can cause dysfunctions in the brain reward cascade, evoking a

hypodopaminergic activity. The hypodopaminergic brain requires a dopamine fix to feel good, leading to multiple drug-seeking behaviors. They also propose a set of polymorphisms (e.g., dopamine, serotonin, norepinephrine, GABA, opioid, and cannabinoid genes) that could have a large impact in developing the reward deficiency syndrome. Consequently, it appears that widening the horizon of the studied addiction phenotypes and genotypes, might lead to new perspectives and help identify as yet unknown aspects of these behaviors.

Integrative approach

There is a great overlap in genetic influences among different drug addictions, as well as across addiction and other externalizing disorders. Twin studies have shown only a modest support for specific gene variants, supporting the possible role of common pathways that connect distinct addictions (Agrawal et al., 2012). However, most of the studies only focus on one type of addiction, and quantifies it with the typical clinical characterization of individuals as affected versus unaffected for that specific addiction. This approach neglects the interrelatedness of addictions, and reinforces the possibility of general addiction vulnerability measurement instead of the lifetime occurrence of specific addictions.

Furthermore, and to date, knowledge is still limited concerning the possible association between genetic factors, neurobiology, personality traits, and addictive behaviors. In an early review (Gilbert & Gilbert, 1995), possible mechanisms and causal pathways mediating the associations of personality dimensions and psychological disorders with nicotine smoking have been summarized as: genetic linkage of predisposing genes, common predisposition, self-medication, selective quitting, and linkage of smoking changes in personality. The authors also proposed a model (the situation x trait adaptive response) model to integrate genetic, biological, psychological, and environmental factors of smoking. Another study (Kreek et al., 2005) also reviewed genetic variants indicated as risk factors of specific personality traits and addictions. They found many common genetic factors.

A promising study (Davis & Loxton, 2013) used the multilocus genetic profile method (MLGP, including six candidate dopamine related polymorphisms) to examine the genetic association with addictive behaviors in general. Instead of analyzing several addictive behaviors separately, the study examined a composite measure of different addictions (i.e., an aggregated measure of engagement in a variety of addictive behaviors). They found that higher MLPG

profile scores were related to more frequent engagement in addictive behaviors, and that this relationship was mediated by personality characteristics consistently associated with addiction disorders. Even though a few models have been proposed, psychological studies struggle in providing evidence on how personality traits mediate genetic effects. However, there are a few new methodologies that are promising. In short, although the multi-causality nature of addictions is undeniable, little is known about the specific molecular and psychological interactions.

Psychological and Genetic Factors of Addictive Behaviors (PGA) Study

The aims of the Psychological and Genetic Factors of Addictive Behaviors (PGA) Study are to: (i) explore the psychological characteristics of different types of addictions; (ii) analyze the relationship between different types of traditional addictions and new potentially addictive behaviors; (iii) explore the possible genetic markers not only for substance-related addictions, but for new potentially addictive behaviors; (iv) test the possible effect of new genetic variants; (v) explore the possible distinct and overlapping psychological and genetic characteristics of different types of substance use and behavioral addictions; and (vi) take a multidisciplinary approach, and test possible psychological and genetic interaction effects.

The PGA study utilizes an integrative research approach towards the examination of addictions. In conclusion, one of the main goals of the present study is to investigate the characteristics of these phenomena and to understand the degree to which they are related to each other by examining the addiction-specific psychological and genetic factors, and the possible overlaps of these factors in different addictions. This would also help to test if the addiction-concept of these behaviors is an appropriate approach and/or whether other approaches are needed. In other words, the goal was to reach a better understanding of these phenomena, especially their classification. The present paper provides a methodological overview and describes the research design of the PGA study. Data collection procedures, instrumentation, and the analytical approach used to attain the research objectives are described. Future plans, along with potential contributions of the PGA study are also discussed.

PGA study description

Sample

Non-familial young adults from several Hungarian education facilities participated in the study on a voluntary basis. Data collection was carried out in four waves, between 2011 and 2015 (Figure 1). Participants were recruited at high schools (only enrolling students older than 18 years) and at colleges and universities.

The total sample of the PGA study comprises data from 3003 participants collected via convenience sampling. The mean age of the total sample was 21 years (SD=2.8). The male/female ratio was almost equal at the first data collection wave (high school students), while at the college and university data collection points, more females participated then males (Table 1).

Procedure

The study protocol was designed in accordance with guidelines of the Declaration of Helsinki, and was approved by the Scientific and Research Ethics Committee of the Medical Research Council (ETT TUKEB). All participants provided written informed consent, provided buccal samples, and were administered questionnaires. Recruitment started with contacting the heads of several high schools and universities to acquire institutional consents. Afterwards, in case of the high schools, classes were visited asking the students to participate. Data collection was carried out in the classroom, collecting data from one class at the time. Buccal sample collection was guided by two research assistants for the whole class. In all cases, they followed the DNA sample collection procedure step-by-step. Questionnaire data were based on self-report. In case of the college and university students, data collection was carried out in dormitories in a systematic manner. More specifically, research assistants contacted all the students in the dormitories face-to-face to participate in the study. Following their consent, buccal swabs (assisted face-to-face by a research assistant) were taken and then the self-report questionnaire was administered. In all institutions, refusal to participate in the whole study was approximately 5%. The rate of students participating, but not providing buccal samples was less than 5%.

Materials

In each wave of data collection, three basic topics were covered: demographic information, addictive behaviors, and psychological characteristics of the participants. Demographic questions covered basic participant information, such as date of birth, gender, and weight. In the case of

the addiction-related questions, the aim was to assess the extent and the problematic nature of several addictive behaviors. An important goal was to cover a wide range of addictions, including substance use disorders and behavioral addictions relevant to the specific age-range of the samples. In relation to the psychological dimensions, questions regarding self-regulation, obsessive-compulsive tendencies, dimensions of impulsivity, sensation seeking, and dissociation were asked chosen based on earlier models. Data concerning some behaviors were only assessed at specific points during data collection waves. Table 2 provides a complete list of all the assessed behaviors during the specific data collection waves.

Addiction-related measures

The issue of how best to conceptualize addictions and what to include under the umbrella of addiction has been the focus of considerable research attention. The latest (fifth) edition of the Diagnostic and Statistical Manual (DSM-5) and the latest (eleventh) International Classification of Disease (ICD-11) have attempted to address the nosological issue of whether 'addiction' should include not just substances, but also types of behavior, and if so, what types of behavior should be included. Consequently, gambling is included in the subsection of 'Nonsubstance-related disorders' of the DSM-5 (American Psychiatric Association, 2015), and further potentially addictive behaviors were considered (e.g., internet use disorder) although internet gaming disorder [IGD] was included in the Appendix of disorders requiring more research (Griffiths et al., 2014; Király et al., 2015). In the ICD-11 (WHO, 2018), gambling and gaming disorder were both included in the classification of psychiatric disorders (King et al., 2018; Kiraly & Demetrovics, 2017; Rumpf et al., 2018).

In light of the DSM-5 and ICD-11, in the present study, substance use disorders (nicotine, alcohol, cannabis, amphetamine, cocaine, heroin, magic mushrooms, LSD, GHB, mephedrone, steroids, alcohol with drugs, and non-prescribed sedatives) and gambling disorder are grouped together in the 'Substance use assessment' section. The assessment tools of internet-related behaviors (which were considered for inclusion in the DSM-5) are grouped together as 'potentially addictive behaviors'. Tools assessing exercise, hairpulling, and eating habits are addressed as 'Other compulsive behavior assessment scales'.

Substance use assessment

First time usage and most recent usage was asked from all participants for the following substances: nicotine (cigarettes), alcohol, cannabis, amphetamine, cocaine, heroin, magic mushrooms, LSD, GHB, mephedrone, steroids, alcohol with drugs, and non-prescribed sedatives. The most commonly used substances were further evaluated. Drinking frequency and amount of alcohol drunk at the most recent consumption, in the last 30 days, and in the last year was also assessed, as well as the frequency of getting drunk. Drinking motivation was assessed using the Drinking Motive Questionnaire Revised Short Form (DMQ-R-SF; Kuntsche & Kuntsche, 2009). The DMQ-R-SF has proven to be a reliable tool assessing drinking motives based on large samples of adolescents and young adults. Frequency and daily amount of cigarette smoking was also asked. Regarding cannabis use, the following measures were used: consumption frequency in the last 30 days, and in the last year. Severity of cannabis use was assessed using the Cannabis Abuse Screening Test (CAST; Legleye et al., 2013). This tool was originally designed as a short screening test for cannabis abuse among adolescents and young adults in general population surveys. Based on a study of 3266 French cannabis users aged 17 to 19 years from the general population, the CAST has demonstrated good screening properties for the moderate/severe class (Legleye et al., 2013). Also, the performance of the CAST in screening for the latent class structure was good and superior to those obtained with the DSM-IV diagnoses.

Gambling: Diagnostic Statistical Manual-IV-Adapted for Juveniles (DSM-IV-MR-J)

The Diagnostic Statistical Manual-IV-Adapted for Juveniles (DSM-IV-MR-J; Fisher, 2000) is a valid and reliable psychometric tool for assessing adolescent gambling and problem gambling. It contains nine items, and assesses important variables related to youth problem gambling (i.e., progression and preoccupation, tolerance, withdrawal and loss of control, escape, chasing, lies and deception, illegal activities, and family and school disruption). Participants rate the frequency of the behaviors in the statements on a scale from 1 (never) to 4 (frequently). Based on the work of Fisher (2000), a respondent who has four or more positive answers (positive responses differ among the specific items) is classified as a problematic gambler. Internal consistency of the scale was adequate in the PGA sample ($\alpha = 0.79$).

Assessment tools measuring potentially addictive behaviors In the PGA study, a number of different potentially addictive behaviors were assessed (i.e., problematic internet use, gaming disorder, problematic social networking use, gambling disorder, trichotillomania, and exercise addiction). The frequency of the given behavior was assessed with a screening question, while the severity of the behavior was assessed using specific psychometric instruments.

Bergen Social Media Addiction Scale (BSMAS)

The Bergen Social Media Addiction Scale (Andreassen et al., 2012) is a screening instrument reflecting six core elements of addiction (salience, mood modification, tolerance, withdrawal, conflict, and relapse). The first validity and reliability tests involving a sample of 5961 adolescent participants showed that the Hungarian version of the BSMAS had promising psychometric properties (Banyai et al., 2017). The scale assesses the problematic use of social media use in general over the past 12 months. Items are answered on a 5-point scale ('never' to 'always') assessed on a scale between 6 and 30. A cut-off score of 19 points was suggested as the ideal threshold at and above which individuals are classified as at-risk of problematic social media use. Internal consistency was adequate in the PGA sample ($\alpha = 82$).

Problematic Internet Use Questionnaire (PIUQ)

The Problematic Internet Use Questionnaire (Demetrovics et al., 2008) is a reliable instrument for assessing problems related to the general use of the internet. Based on the scale's development study, the Cronbach Alpha values and the test-retest correlations were adequate when analyzed using a large online sample. The PIUQ assesses the problematic nature of internet use with three subscales: obsession, neglect, and control disorder. Items are assessed using a 5-point Likert scale from 1 (never) to 5 (always/almost always). In addition to the original 18-item scale, a short version has also been developed (Koronczai et al., 2011) which assesses the same characteristics with nine items. There is also a 6-item version of the PIUQ with a recommendation for a cut-off score for problematic use (Demetrovics et al., 2016). Based on this recent sensitivity and specificity analyses, it was recommended that a summarized score of 15 (out of 30) would be a good cut-off threshold dividing users at-risk of problematic internet use and those with no-risk. Internal consistency of the PIUQ-6 was adequate in the PGA sample ($\alpha = 0.75$).

Problematic Online Gaming Questionnaire Short-Form (POGQ-SF)

The original Problematic Online Gaming Questionnaire (POGQ, Demetrovics et al., 2012) assesses the problematic nature of online gaming on six factors: preoccupation, overuse, immersion, social isolation, interpersonal conflicts, and withdrawal. Items are assessed using a 5-point Likert scale from 1 (never) to 5 (almost always/always) with higher scores indicating more problematic use. Based on the developmental study on a large Hungarian online gamer sample and a subsequent study of the shorter, 12-item version of the questionnaire (i.e., POGQ-SF) (Papay et al., 2013) involving a nationwide Hungarian adolescent sample, both versions of the instrument are reliable tools for the assessment of gaming-related behavior. The latent profile analysis carried out in this latter study revealed that 4.6% of the adolescents belonged to the high-risk group and an additional 13.3% to the low-risk group of problematic use. Based on this study, a cut-off score of 32 was recommended to classify online gamers as problematic gamers. Cronbach Alpha value was excellent in the PGA sample ($\alpha = 0.92$).

Other compulsive behavior assessment scales

Exercise Addiction Inventory (EAI)

The Exercise Addiction Inventory (EAI; Griffiths et al., 2005; Terry et al., 2004) was developed to identify individuals at risk for exercise addiction. The EAI has a good internal reliability, content validity, concurrent validity, and construct validity and it is also quick and simple to administer with only six items. The Hungarian translation of the EAI (Demetrovics & Kurimay, 2008) showed the same one-factor structure as the original questionnaire in several studies (Griffiths et al., 2015; Mónok et al., 2012). Participants rate their agreement with the items of exercise-related statements from 1 (do not agree at all) to 5 (extremely agree) on a five-point summative response scale. Based on earlier studies (Griffiths et al., 2015; Mónok et al., 2012) the EAI cut-off score for individuals considered at-risk of exercise addiction was defined as 24, and 13 for those considered being symptomatic nondependent exercisers. Internal consistency was adequate in the PGA sample ($\alpha = 0.78$).

The Massachusetts General Hospital Hairpulling Scale (MGH-HPS)

The Hungarian version of the Massachusetts General Hospital Hairpulling Scale (Keuthen et al., 1995) assesses hair pulling habits. The scale demonstrated good test-retest reliability, convergent and divergent validity, and sensitivity to change in hairpulling symptoms (Keuthen et al., 2007; O'Sullivan et al., 1995). Seven items, rated for severity from 0 to 4, assess urges to pull, actual pulling, perceived control, and associated distress. The scale assesses severity, resistance, and control of the behavior over the past seven days on a scale ranging between 0 and 28. It has been suggested that the cutoff for clinical significance on this measure is 17 or higher (Keuthen et al., 2007; Woerner et al.). The items were translated and back-translated from English to Hungarian by three independent experts of both languages. Internal consistency was excellent in both a recently published Hungarian study (Maraz et al., 2017) and the PGA sample ($\alpha = 0.92$, $\alpha = 0.94$, respectively).

Scales assessing other psychological dimensions

Brief Sensation Seeking Scale (BSSS)

The Brief Sensation Seeking Scale (BSSS; Hoyle et al., 2002) demonstrated good psychometric properties in a sample of 7000 adolescents. It assesses sensation seeking via four factors: thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. It was found to be a particularly strong predictor of the intention to try cannabis in the future, and it also worked moderately well at identifying adolescents at risk for drinking and smoking cigarettes (Sargent et al., 2010; Stephenson et al., 2007). Participants rank how much they agree with the scale statements on a summative scale ranging between 1 (do not agree) and 5 (agree). The scale showed adequate internal consistency in the PGA sample ($\alpha = 0.71$).

Brief Symptom Inventory - BSI

The Brief Symptom Inventory (BSI; Derogatis, 1975, 1993; Derogatis & Melisaratos, 1983) is a brief psychological self-report symptom scale. Test-retest and internal consistency reliabilities, convergent validity, construct validity were shown to be very good. The 53-item scale briefly assesses the incidence of nine psychiatric symptoms during the past week: somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Participants rank their answers on a summative scale

ranging between 1 (not at all) and 5 (very much). The questionnaire showed excellent internal consistency in the PGA sample ($\alpha = 0.95$).

Center for Epidemiologic Studies Short Depression Scale - CESD Short

The CES-D scale (Radloff, 1977) is a short (10-item) self-report scale designed to assess depressive symptomatology in the general population. The CES-D appeared to be a reliable tool in both high school and college students (Radloff, 1991). Participants indicate how often they felt a specific way during the past week on a list of possible behaviors on a scale from 1 (rarely or none of the time) to 4 (all of the time). Internal consistency was adequate in the PGA sample ($\alpha = 0.77$).

Parental Bonding Instrument – Short (PBI)

The Parental Bonding Instrument is an assessment of perceived parenting (Parker et al., 1979). The PBI appears to be a reliable and valid instrument. Moreover, a 20-year period review of the instrument indicated long-term stability over time (Wilhelm et al., 2005). It assesses the perceived maternal care, and overprotection, as well as paternal care and overprotection. The scale showed adequate to excellent internal consistency when asking both the participants' mother ($\alpha = 0.82$) and father ($\alpha = 0.93$) in the PGA study.

Somatic Complaint List (SCL)

The SCL is a scale suitable for assessing somatic complaints including exhaustion, headache, and nausea in school-aged children. Its psychometric properties and stability have been shown to be good (Jellesma et al., 2007). The 11-item questionnaire assesses the somatic complaint frequency over the past two weeks. Participants rank their answers on a summative scale ranging between 1 (almost never) to 5 (frequently). Its internal consistency was adequate in the PGA sample ($\alpha = 0.60$)

Strengths and Difficulties Questionnaire (SDQ)

The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) is a self-report inventory behavioral screening questionnaire for children and adolescents. The SDQ asks questions concerning 25 attributes, some positive and others negative. The 25 items are divided between

five scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. Participants ranked their answer on a scale ranging between 1 (not true) to 3 (definitely true). The questionnaire showed adequate internal consistency in the PGA sample ($\alpha = 0.69$).

Ten-Item Personality Inventory (TIPI)

The ten-item TIPI covers the same Big Five personality dimensions as other leading personality questionnaires, but with only 10 items (Gosling et al., 2003). The biggest advantage of the TIPI is its brevity, while assessing the 'Big Five' factors of personality (Extraversion, Agreeableness, Conscientiousness, Emotional Stability, Openness to Experiences). However, due to its low number of items its reliability and validity are somewhat inferior to standard multi-item instruments. The TIPI can be a useful tool in cases when personality is not the primary topic of interest, or researchers can tolerate the somewhat diminished psychometric properties associated with this very brief measure. Participants rate the extent to which they agree or disagree with the statements on a scale from 1 to 7. Internal consistency of the scale was low in the PGA sample ($\alpha = 0.42$).

Resilience and Youth Development Module (RYDM)

The Resilience and Youth Development Module (RYDM) assesses environmental and internal assets associated with positive youth development and school success (Hanson & Kim, 2007). Participants rank their answers on statements regarding their relationships with others at home on a scale ranging between 1 (not true) to 4 (true). Internal consistency was very good in the PGA sample ($\alpha = 0.87$).

Response to Positive Affects (RPAQ)

The RPA Questionnaire (Feldman et al., 2008) is a self-report measure of ruminative and dampening responses to positive affect with three subscales: dampening, self-focused positive rumination, and emotion-focused positive rumination. Based on the psychometric results, it has an acceptable structural validity, internal consistency, and demonstrated an evidence of convergent and incremental validity with concurrent measures. On the 17 item questionnaire

participants rank their answer on a scale 1 (almost never) to 4 (almost always). The questionnaire showed an adequate internal consistency on the PGA sample (α =0.81)

WHO Wellbeing Index

The five-item World Health Organization Well-Being Index (WHO-5; World Health Organization, 1998) is among the most widely used scales assessing subjective psychological wellbeing. Based on a recent review of 213 studies it has adequate validity both as a screening tool for depression and as an outcome measure in clinical trials (Topp et al., 2015). The total score is calculated by summing the answers ranging from 1 (at no time) to 4 (all of the time). Therefore, the total score ranges from 5 to 20, 5 representing worst possible and 20 representing the best possible quality of life. Internal consistency was adequate in the PGA sample (α = 0.75). In addition, a few newly developed scales (e.g. regarding Reward Deficiency Syndrome) were utilized at selective points in the data collection waves (see Table 2).

Genetic analysis

Non-invasive DNA sampling was performed by collecting buccal swabs from participants. Genomic DNA (for detailed isolation protocol see (Boor et al., 2002)) are extracted using the DNA-purification kit obtained from Gentra (Minneapolis, US) in the Laboratory of Molecular Genetics at the Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest. The samples are stored at the in-house Biobank until subsequent analysis is required.

Genotyping was performed as described earlier (DRD4 gene*:* -521 C/T SNP (Ronai et al., 2001), 120 bp duplication (Seaman et al., 1999), DRD4 VNTR (Ronai et al., 2000)). The -521 CT polymorphism was determined by two independent methods (Lakatos et al., 2002), and only genotypes with identical results were accepted. Published protocols (Castiglione et al., 1995; Grandy et al., 1993; Kidd et al., 1996; Ronai et al., 2000; Szantai et al., 2005; Tarnok et al., 2007; Vandenbergh et al., 1992) were used for the genotyping procedures, including restriction fragment length polymorphism, allele-specific amplification, and real-time PCR.

Gene and polymorphism selection were based on earlier results in the literature, but novel genetic targets were also considered. For example, Blum et al. (2014) recently proposed a model called the Genetic Addiction Risk Score (GARS). They proposed to select a number of genes,

their polymorphisms, and associated risks for reward deficiency syndrome based on a thorough review of the available literature. The proposed list of 11 gene variants predisposing reward deficiency syndrome mainly focuses on dopaminergic genes, and gene variants related to the methylation and deacetylation on chromatin structure, and may be an interesting target for genetic association analysis of addictions. The GARS score identifies alleles known to impart vulnerability to addiction and makes an assessment of the degree of vulnerability of an individual to develop addictive behavior. It also predicts the severity of addiction in an individual. This information could help in individualized selection of the type and duration of a non-pharmacological therapy at the present time, and in future it could be used to formulate gene therapy. The aim of the PGA study is to test the GARS panel on the patient and control population to test the association between GARS and vulnerability to addiction.

Genotyping is underway for the following polymorphisms: Polymorphisms proposed in the Genetic Addiction Risk Score (GARS) by Blum et al. (2014): the DRD2/ANKK1 *Taq*IA (rs1800497), the DRD2 *Taq*IB (rs1079597) and *Taq*ID (rs1800498), the SLC6A3 40 bp VNTR in the 3' untranslated region, the DRD4 48 bp VNTR in exon 3 and 120 bp duplication in the promoter region, the DRD4 -616 C/G (rs747302), -615 A/G (rs936462), -521 C/T (rs1800955) and the COMT Val158Met (rs4680), and 32 further SNPs (see SNP list in Table 3).

Planned analysis and statistical approach

The PGA study includes data concerning substance use and behavioral addictions, related psychological aspects, and genetic data. First, the plan is to carry out an epidemiological analysis focusing on the prevalence of these substance use and behavioral addictions and the co-occurrences of these behaviors. This will be followed by the analysis of the genetic data, investigating the possible genetic risk factors of these behaviors. The aim is to investigate addiction-specific genetic effects, and the possible overlaps between the genetic markers of different addictions by carrying out genetic association analysis of the assessed 32 SNPs and the addictions. These analyses are planned to be carried out one-by-one, examining each SNPs' possible association with the measured phenotypes separately. Finally, the study will perform an integrated analysis of psychological and genetic data with particular emphasis on modeling pathways mediating the associations of genetic factors, psychological characteristics, and addictions. Since the underlying theoretical constructs of these conditions is very inconsistent

covering several different factors and models, these analyses will be carried out separately (i.e., addiction-by-addiction), but also focusing on the potential overlaps.

The power of genetic association studies is an issue of small genetic effects and multiple testing (see GWAS study methodology described in the 'Genetic background of addictions' section). The most commonly used approach in genetic association studies to augment multiple testing issues is to apply false discovery rate (FDR) controlling procedures. The FDR is a method of conceptualizing the rate of type I errors in null hypothesis testing when conducting multiple comparisons, and which will be applied during the genetic association tests. The issue of small effects is harder to address in the field of genetic association studies, since the effects by nature are very small. G*Power software (Faul et al., 2007; Mayr et al., 2007) was used to determine the minimum necessary sample size to find significant genetic effects. With a 0.003 effect size partial eta square value (the average partial eta square value observed in genetic association studies) by two groups (representing the two alleles of a specific polymorphism) by a power set to be at least 0.80, it was determined that a minimum of 2612 participants were needed in the total sample to determine such an association. Therefore, the PGA study with its 3003 participants will demonstrate reliable genetic associations.

The importance of the PGA study and research contributions

The primary aim of the present paper was to introduce the Psychological and Genetic Factors of Addictive Behaviors (PGA) Study, describing its methodological aspects and data collection procedures. The longer term aim of the PGA study is to investigate the possible psychological and genetic factors of substance use disorders and behavioral addictions. During the four data collection waves, a total of 3003 young adults participated in the study. Participants were asked to complete a comprehensive battery of psychometric scales, as well as to provide buccal swab samples for DNA isolation, and identification of specific polymorphisms.

In addition to the thorough assessment of potential substance and behavioral addictions, the study also included validated scales regarding psychological aspects. As far as genotyping, polymorphisms proposed in the Genetic Addiction Risk Score (GARS) by Blum et al. (2014), and 32 further SNPs are under genotype assessment. The detailed psychological information and genetic association analysis of several substance and behavioral addictions means that the PGA study provides a unique opportunity to test possible mechanisms and causal pathways in the

background of addictions. . Given that only a minority of the population becomes addicted to these psychoactive substances or behaviors, it is reasonable to ask what factors differentiate those who do become addicted from those who do not. Based on the collected psychological and genetic data, the PGA study aims to identify the characteristics of risk-taking behaviors, and will contribute to the scientific literature of understanding the molecular and psychological mechanisms involved in many different addictions.

The present study has a few limitations. One is the convenience nature of the sample, which decreases the generalizability of the results. The PGA study targeted a very specific age group, thus interpretations should be handled with caution. In some cases, the assessed brief instruments did not show good internal consistency on the present sample (e.g. Ten-Item Personality Inventory). Furthermore, despite the wide range of addictions that were assessed, the study neglects some potentially interesting behaviors (e.g., compulsive sexual behavior, compulsive buying, nail biting, etc.).

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Figure 1. Overview of the PGA study

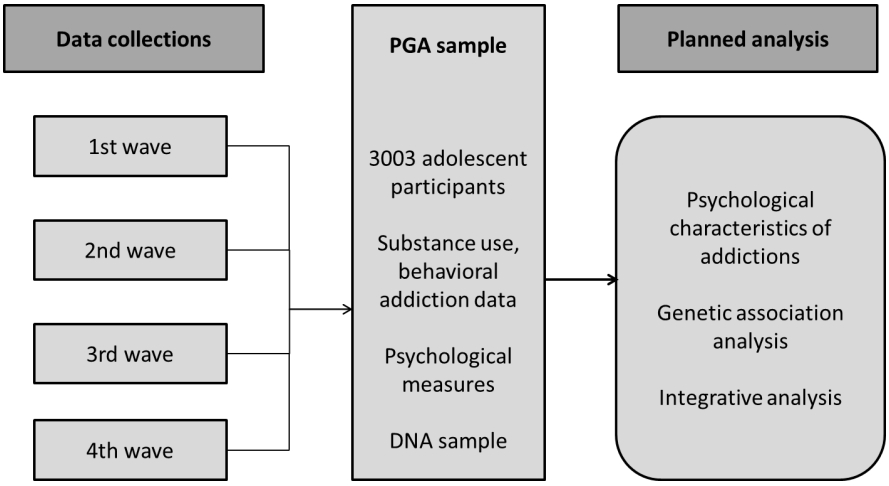

Table 1. Data collection waves

	N	Year of data collection	Mean age (±StD)	Male/Female percent
1st wave	662	2011-2012	18 ± 1.5 years	50.2% / 49.8%
2nd wave	606	2014	22 ± 5.6 years	36.6% / 63.4%
3rd wave	1139	2014	21 ± 2.0 years	43.3% / 56.7%
4th wave	596	2015	22 ± 1.9 years	39.1% / 60.9%
Total	**3003**		21 ± 2.8 years	42.6% / 57.4%

Table 2 A list of assessed questionnaires by data collection waves

	1st wave	2nd wave	3rd wave	4th wave
Demographic information (e.g., date of birth, gender, weight)	✔	✔	✔	✔
Socio-economic status (e.g., parents' highest level of education)	✔	✔	✔	✔
Substance use assessment				
Prevalence and frequency data on several types of substance use	✔	✔	✔	✔
Cannabis Abuse Screening Test (CAST)	✔	✔	✔	✔
Diagnostic Statistical Manual-IV-Adapted for Juveniles (DSM-IV-MR-J)	✔	✔	✔	✔
Drinking Motive Questionnaire Revised Short Form (DMQ-R-SF)	✔	✔	✔	✔
Assessment tools assessing potentially addictive behaviors				
Prevalence and frequency data on several types of behavioral addiction	✔	✔	✔	✔
Bergen Social Media Addiction Scale (BSMAS)			✔	✔
Problematic Internet Use Questionnaire (PIUQ)	✔	✔	✔	✔
Problematic Online Gaming Questionnaire Short-Form (POGQ-SF)	✔	✔	✔	✔
Problematic playing on tablet/cell phone		✔		
Other compulsive behavior assessment scales				
Exercise Addiction Inventory (EAI)	✔	✔	✔	✔
The Massachusetts General Hospital Hairpulling Scale (MGH-HPS)			✔	✔
SCOFF Questionnaire	✔	✔	✔	✔
Scales concerning possible related psychological dimensions				
Brief Sensation Seeking Scale (BSSS)	✔	✔	✔	✔
Brief Symptom Inventory (BSI)	✔	✔	✔	✔
Center for Epidemiologic Studies Short Depression Scale (CESD Short)	✔	✔	✔	✔
Parental Bonding Instrument – Short (PBI)	✔	✔	✔	✔
Somatic Complaint List (SCL)	✔	✔		
Strengths and Difficulties Questionnaire (SDQ)	✔	✔		
Ten-Item Personality Inventory (TIPI)	✔	✔		
Resilience and Youth Development Modul (RYDM)	✔	✔		
Response to Positive Affects (RPAQ)	✔	✔		
List of Chronic diseases	✔	✔		
Questions regarding Bullying	✔	✔		
Questions regarding chronotypes			✔	✔
Questions regarding friendships	✔	✔		
Questions regarding the Reward Deficiency Syndrome			✔	✔
WHO Well being	✔	✔	✔	✔

Table 3 List of the 32 single nucleotide polymorphisms (SNPs)

dbSNP No.	Allele 1	Allele 2	Gene
rs886205	A	G	aldehyde dehydrogenase 2 family (mitochondrial); acyl-Coenzyme A dehydrogenase family; member 10
rs1693482	C	T	alcohol dehydrogenase 1C (class I); gamma polypeptide
rs698	C	T	alcohol dehydrogenase 1C (class I); gamma polypeptide
rs2073478	G	T	aldehyde dehydrogenase 1 family; member B1
rs1800497	A	G	ankyrin repeat and kinase domain containing 1;dopamine receptor D2
rs3800737	C	T	caldesmon 1
rs1051730	A	G	cholinergic receptor; nicotinic; alpha 5;cholinergic receptor; nicotinic; alpha 3
rs16969968	A	G	cholinergic receptor; nicotinic; alpha 5;cholinergic receptor; nicotinic; alpha 3
rs6474412	C	T	cholinergic receptor; nicotinic; beta 3
rs806380	A	G	cannabinoid receptor 1 (brain)
rs2023239	C	T	cannabinoid receptor 1 (brain)
rs6277	A	G	dopamine receptor D2
rs324420	A	C	fatty acid amide hydrolase
rs4713916	A	G	FK506 binding protein 5
rs1360780	C	T	FK506 binding protein 5
rs759364	A	G	forkhead box N3
rs279858	C	T	gamma-aminobutyric acid (GABA) A receptor; alpha 2
rs9457	C	G	hypothetical LOC100129623;Wolfram syndrome 1 (wolframin)
rs1046322	A	G	hypothetical LOC100129623;Wolfram syndrome 1 (wolframin)
rs1799971	A	G	opioid receptor; mu 1
rs978739	C	T	taste receptor; type 2; member 16
rs4532	**C**	T	DRD1
rs6280	**C**	T	DRD3
rs1800955	**C**	T	DRD4
rs4680	A	G	COMT
rs3812047	C	T	GDNF
rs11111	C	T	GDNF
rs2910702	C	T	GDNF
rs1549250	A	C	GDNF
rs2973033	C	T	GDNF
rs1981844	C	G	GDNF
rs3096140	A	G	GDNF