The genetic correlates of impulsivity

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PhD thesis

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1. Introduction

The term impulsivity refers to actions that are risky and lack careful planning. Impulsivity is one of the basic factors of human behavior, a psychological phenomenon which is incorporated in numerous theories of personality, and can play a determining role in many areas of life. Impulsivity is a multidimensional construct, different aspects of which can be assessed by different measures. Questionnaire measures are suitable for assessing trait impulsivity. One of the most widely used questionnaires of impulsivity is the Barratt Impulsiveness Scale.

According to the findings of twin studies impulsivity shows approximately 50 % heritability. According to previous research the role of neurotransmitter systems seem to be dominant in the biological background of impulsivity. Literature shows the dopamine and serotonin functions are the most relevant factors, high impulsivity is associated with high dopamine and low serotonin levels. Considering the heritable nature of the construct and the identified biological background candidate, gene approach could confirm the genetic association between the genetic components of the dopamine and serotonin systems and impulsivity.

I tested the psychogenetic associations of impulsivity by analyzing the polymorphisms of the dopaminergic and serotonergic systems. Based on the consensual literature of the relationship between impulsivity and substance abuse, I also present an association study of a gene variant which influences the connection of opiate dependence and temperament. In this study I measured the novelty seeking dimension with the Character and Temperament Inventory.

To sum up I studied the genetic components of impulsivity and substance abuse with the application of a few genetic

polymorphisms. At the same time it is important to note that vast majority of psychological characteristics usually show polygenic inheritance, that is they are formulated under the influence of a much wider range of polymorphisms compared to what is presented in my dissertation, and the effect of environmental factors are also significant.

2. Objectives

The purpose of my doctoral thesis was to study the genetic background of impulsivity. The primary objective of my research was to develop a Hungarian impulsivity questionnaire which can be successfully applied in behavioral genetic analyses. I intended to analyze the hereditary factors of impulsivity with the application of the self-report data of a relatively large sample of young adults and a few candidate genes of the dopamine and serotonin neurotransmitter systems. Lastly I planned to explore the genetic correlates of temperament, which shows an intimate connection with impulsivity, using the self-report data of a sample of opiate dependent and control subjects.

1. The Hungarian adaptation of the Barratt Impulsiveness Scale

I planned to measure the impulsivity endophenotype with the 11th version of the Barratt Impulsiveness Scale in my association studies. My first objective was the Hungarian adaption of the Barratt Impulsiveness Scale along with testing how the well the original BIS-11 model fits the data of a nationwide representative sample and the college sample applied in the genetic association studies.

2. The association of impulsivity and polymorphisms of the dopaminergic and serotonergic systems on a sample of healthy young adults:

Previous research shows impulsivity is related to the function of dopamine and serotonin neurotransmitter systems, according to which it may be hypothesized, that the candidate genes of these systems are responsible for the heritability of impulsivity. The aim of the association studies of the present dissertation is the exploration of connections between impulsivity and dopaminergic polymorphisms (DRD4 48 bp VNTR, DRD2 ANKK Taq1A and COMT Val158Met). I also intended to explore the association of impulsivity and three serotonergic polymorphisms (HTTLPR, HTR1A -1019 C/G and HTR1B 1997 A/G). Based on the research highlighting the role of serotonin and dopamine in impulsivity I expected that the serotonergic and dopaminergic genes shape impulsivity in a closely interrelated manner.

3. The genetic variant shaping the temperament of opiate dependents

The connection of substance abuse and impulsivity is widely studied and accepted in the literature, however the genetic background of this connection is relatively understudied. I hypothesize that one of the genetic variants which influences the cerebral biochemical mechanism of substance abuse, can be connected to the temperament of substance abusers. First I tried to demonstrate with a case-control analysis, that the Met allele of the COMT Val158Met polymorphism which contributes to mesolimbic dopamine hypofunction is overrepresented in the opiate dependent group compared to the control group. Following this, I intended to investigate whether there are differences between the novelty seeking scores of opiate dependents and controls in relation to which gene variant the subject carries. I used dimensional analyses to assess these differences.

3. Methods

Data applied in the present thesis are based on a number of studies (FIRCAR03 TW007656-01A1, KAB-KT-09-0007, OTKA T048576 OTKA F046788). The study protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council (ETT TUKEB).

The genetic database was created by the Molecular Genetic Laboratory and contained the DNA numbers and genotypes of the analyzed polymorphisms. In the present work I used the data of the DRD4, DRD2, COMT, SERT, HTR1A, and HTR1B polymorphisms.

The study of the genetic background of impulsivity is based on the genetic and questionnaire data of 687 subjects, which is a part of a larger sample that was collected between 2008 and 2013. I collected data from approximately 5-600 subjects from the total sample of 687 which I used in my dissertation. I measured impulsivity with the Hungarian translation of the 11th version of the Barratt Impulsiveness Scale. The Scale consist of 30 items, for of which are reversed. Items can be rated on a 4 point scale (1-rarely/never, 2-occasionally, 3-often, 4-almost always/always). BIS-11 has three subscales, these are Attentional impulsiveness (lack of attention and cognitive instability), Motor impulsiveness (motor activity and lack of perseverance), and Non-planning impulsiveness (lack of self-control and cognitive complexity).

The sample applied for the Hungarian adaptation of BIS-11 was provided by the *National Survey on Addiction Problems in Hungary* (NSAPH), which was a nationwide representative survey. The target population of the survey was the total population of Hungary between the ages of 18 and 64 (6,703,854 persons). The sampling frame consisted of the whole resident population with a valid address, according to the register of the Central Office for Administrative and Electronic Public Services on January 1, 2006

(6,662,587 persons). Data collection was executed on a gross sample of 3,183 people, stratified according to geographical location, degree of urbanization and age (overall 186 strata) representative of the sampling frame. The net sample size was 2,710 (response rate: 85.1%).
The nationwide representative sample applied for the Hungarian adaptation of BIS-11 also contained the Brief Symptom Inventory (BSI) besides the BIS-11, along with impulsivity related behavioral variables.

The sample applied in the association study is somewhat smaller, due to its psychopathological nature (N=241). The heroin user sample met the criteria of opiate dependence (F11.22 and F11.24 according to the International Statistical Classification of Diseases, 10th Revision and were recruited from the methadone substitution program of Nyírő Gyula Hospital Drug Outpatient Center, Budapest, Hungary. Of the 200 patients maintained on methadone at the outpatient center 117 agreed to participate in the study. Participants were maintained on a daily dose of 50 to 150 mg of methadone and none of them showed any withdrawal symptoms at the time of assessment. Control subjects were healthy Hungarian university students recruited at the Institute of Psychology, Eötvös Loránd University on a voluntary basis. They had no lifetime history of diagnosis or treatment for psychiatric disease, but those individuals with a history of experimental or recreational drug use were not excluded from the study. Temperament profile of the subject was assessed with the Hungarian version of the Temperament and Character Inventory (TCI). TCI is a self-report questionnaire which consists of 240 items in four for temperament and three character scales. Temperament scales are Novelty seeking, Harm avoidance, Reward dependence and Persistence. In the present study I applied the 56 item brief version of TCI, I assessed the temperament scales and conducted the association analyses on them.

4. Results

1. The Hungarian adaptation of the Barratt Impulsiveness Scale required the development of a new model and a new impulsivity measure

I measured the impulsivity phenotype with the BIS-11, confirmatory factor analysis of which however did not unequivocally confirm the original factor structure suggested by Barratt and colleagues. Therefore as a part of my dissertation I developed another three factor model (BIS-11-R) and I applied it in the association analyses along with the original BIS-11.

The psychometric testing of the representative and college samples applied in the research shows the following results:

(1) The average scores of the two samples did not show significant difference.

(2) Confirmatory factor analysis of both samples showed weak fit with the original model.

(3) Based on the exploratory factor analysis I established a new impulsivity factor structure, factors of which resemble those of the original model, but they indicate different constructs (the new subscales are: Self-control, Impulsive Behavior and Impatience).

2. The role of dopaminergic and serotonergic polymorphisms in impulsivity

According to the literature impulsivity is unequivocally related to dopamine and serotonin neurotransmitter functions, thus variant of the genes coding the proteins of these systems may have an important role in the inheritance of this feature. In my association analyses, I tested the relationship of three dopaminergic and three serotonergic polymorphisms with the main scale and subscales of both BIS-11 and BIS-11-R. I also tested the possible interactions of the genes of these two biologically closely connected systems.

Results of the analyses conducted with BIS-11 data:

(1) The impulsivity main scale showed significant association with two dopaminergic (DRD4 48 bp VNTR, p=0,006; COMT Val158Met, p=0,047) and one serotonergic (HTR1B 1997 A/G, p=0,004) polymorphism. Error resulting from multiple testing was corrected with Bonferroni correction, after which however only the effect of two polymorphisms remained significant: impulsivity scores were lower in the presence of the 7 repeat allele of DRD4 48 bp VNTR and G allele HTR1B 1997 A/G.

(2) Analysis of the possible interactions of the two genetic factors which showed significant association revealed the unambiguous additive effect of these two hereditary factors, in case of the impulsivity main scale and also the Attentional, Motor and Non-planning subscales.

Results of the analyses conducted on BIS-11-R data:

(1) Impulsivity endophenotype based on the new model also showed significant association with the DRD4 48 bp VNTR (p=0,011) and HTR1B 1997 A/G (p=0,012) polymorphisms.

(2) A direction of the additive effect s are the same as the ones experienced with the analysis of the original scale; which confirms the impulsivity lowering effect of the DRD4 48 bp VNTR 7 repeat allele and the HTR1B 1997 A/G G allele.

(3) The analysis exploring the interaction of these gene variants unequivocally confirmed the additive effect of the dopaminergic and serotonergic polymorphisms on the Self-control, Impulsive behavior and Impatience subscales of the new impulsivity construct as well.

3. Association analyses of substance abuse, temperament and the COMT Val158Met polymorphism

One of the candidate polymorphisms of substance abuse and impulsivity related temperament dimensions is COMT Val158Met, case-control and dimensional psychogenetic association analyses of which I conducted on a sample of opiate dependents and control subjects with the application of a self-report data of temperament.

(1) According to the results of the case-control design the distribution of the COMT Val158Met genotypes did not show significant difference (p=0,708).

(2) Based on the dimensional analysis of questionnaire data of heroin addicts and control subjects I identified the significant main effect of COMT Val158Met polymorphism in case of the temperament dimension Novelty seeking (p=0,01), along with significant group effect (0,001). The highest Novelty seeking score was shown by heroin addicts who were carriers of the Met/Met genotype.

5. Conclusions

Impulsivity is an important personality trait both for healthy people and psychiatric patients, heritability of which is confirmed by twin studies. Several studies aimed to explore the biological background mechanisms of this trait, however the possibility of investigating the relationship of impulsivity and the specific genetic components is feasible only in the past fifteen years. Based on the research of the biological background of impulsivity, there is an outstanding role of cerebral dopamine and serotonin neurotransmitter systems. Studies of the dopamine system suggest high dopamine level is correlated with high impulsivity, and studies of the serotonin system delineate the relationship of low serotonin level and high impulsivity. Candidate gene studies of impulsivity presented in my dissertation confirm the results of the studies of the biological background of

impulsivity on the level of genetic polymorphisms. Out of the six observed polymorphisms of the dopamine and serotonin neurotransmitter systems, I demonstrated the association of DRD4 48 bp VNTR and HTR1B 1997 A/G and impulsivity measured with BIS-11. Carriers of the 7 repeat allele of DRD4 48 bp VNTR and the G allele of HTR1B 1997 A/G are characterized with significantly lower impulsivity compared to non-carriers. The DRD4 and HTR1B polymorphisms show an additive effect in my study, namely impulsivity was lower among both the carriers of the 7 repeat allele and the G allele, and the lowest scores were observed among the carriers of both alleles. This relationship was also observed with the subscales. I repeated the association analyses with the BIS-11-R which was developed during the Hungarian adaptation of BIS-11, and results confirmed the findings of the association analyses conducted with BIS-11.

The other association study presented in my thesis I analyzed the genetic correlates of opiate dependence and its hypothesized relationship with temperament. The heritability of addiction was confirmed by several studies. The role of the dopamine system, more specifically the role of the mesolimbic dopamine system in addiction disorders is delineated in the literature. Based on these findings, I investigated the COMT Val158Met, one of the widely studied polymorphism of the dopamine system,. According to my results the case-control design did not reveal significant difference in the distribution of COMT Val158Met genotype between the heroin addict group and the control group. However the dimensional analyses showed significant association of the COMT Val158Met and TCI Novelty seeking score. The relationship of the COMT polymorphism and Novelty seeking was present in both the heroin addict and the control group, in addition the heroin addicts were characterized with higher Novelty seeking than the control subjects.

My results correspond to the model of Cloninger, who hypothesized that Novelty seeking is originates in dopamine functions.

The results of the association studies of impulsivity and opiate dependence are indirectly connected to each other. On the level of phenotypes, two factors indicate the connection of the results. One lies in the connection of impulsivity and novelty seeking, the other is the relationship of impulsivity and substance abuse. Impulsivity and Novelty seeking are related constructs, on the one hand they are both approach related traits, on the other hand the Novelty seeking of Cloninger includes impulsivity. It is important to note that the connection of impulsivity and novelty seeking is strongly indirect, since I did not have BIS-11 and TCI data from the same subjects. The connection of impulsivity and substance abuse is less speculative, numerous studies confirmed that substance abusers of different substances manifests high impulsivity, which also points out the connection of the genetic results. If impulsivity and substance abuse are both heritable, and the two characteristics are highly correlated, it is logical to assume that they are influenced by similar or partly overlapping genetic factors.

6. Publications of the PhD candidate

Publications in the topic of the dissertation

Varga G., Szekely A., Antal P, Sarkozy P., Nemoda Z., Demetrovics Z., Sasvari-Szekely M. (2012) Additive effects of serotonergic and dopaminergic polymorphisms on trait impulsivity. American Journal of Medical Genetics Part B-Neuropsychiatric Genetics 159 B:(3) pp. 281-288.

Demetrovics Z., **Varga G.**, Szekely A., Vereczkei A., Csorba J., Balazs H., Hoffman K., Sasvari- Szekely M., Barta C. (2010) Association between Novelty Seeking of opiate-dependent patients and the catechol-O-methyltransferase Val(158)Met polymorphism. Comprehensive Psychiatry 51:(5) pp. 510-515.

Varga G., Szekely A., Sasvari-Szekely M. (2011) Candidate gene studies of dopaminergic and serotonergic polymorphisms: Dopaminerg és szerotonerg polimorfizmusok kandidáns génvizsgálatai. Neuropsychopharmacologia Hungarica 13:(2) pp. 93-101.

Varga G., Székely A. (2012). The Genetic background pf personality. [A személyiség genetikai háttere]. In Bereczkei T & Hoffman G. (szerk.) *Genes, thinking, personality: Introduction to human behavioral genetics. [Gének, gondolkodás, személyiség*: *Bevezetés a humán viselkedésgenetikába.]* Akadémia Kiadó, Budapest. 273-302.

Demetrovics Z., **Varga G.**, Szekely A., Vereczkei A., Csorba J., Balazs H., Hoffman K., Sasvari-Szekely M., Barta C. (2012) Association between novelty seeking of opiate-dependent patients and the catechol-O-methyltransferase Val 158Met polymorphism: Asociación entre la búsqueda de novedades y el polimorfismo Val. Psiquiatria Biologica 19:(2) pp. 39-45.

Oral presentations on Hungarian academic conferences:

Varga G., Székely A., Sasvári-Székely M. The relationship of monoamine polymorphisms and impulsivity In: XIV. Hungarian Neuropsychopharmachological Congress. Tihany, Hungary, 2011.10.06-08. Budapest: La Découverte, pp. 46-47.

Varga G., Halmai Z., Sasvári-Székely M., Veres-Székely A. Genetic risk factors in the background of impulsivity and aggression In: András Vargha (Ed.) Hungarian Psychological Association XIX. Annual National Academic Conference: the individual and culture: Psychology's response to present challenges. 227 p. Pécs, Hungary, 2010.05.27-2010.05.29. (Hungarian Psychological Association) Budapest: Hungarian Psychological Association, 2010. pp. 17-18

Poster presentations on Hungarian academic conferences:

Varga G., Székely A., Nemoda Z., Sasvari-Szekely M. Dopaminergic és serotonergic genetic effects in the background of impulsivity VIIIth Congress of the Hungarian Society of Human Genetics, Debrecen, 2010 09. 2-4.

Varga G., Demetrovics Z., Barta C., Halmai Z., Veres-Székely A. Heroin against boredom - genetic background of the novelty seeking of substance abusers. The Conference of the Budapest Prison, Budapest, 2009. 05. 14.

Varga G., Székely A. The psychogenetic associations of the biogenic amines and impulsivity. Hungarian Psychological Association XIX. Annual National Academic Conference, Nyíregyháza, 2008. 05. 22-24.

Co-author oral presentations on Hungarian academic conferences:

Szekely A., **Varga G**., Katonai E., Sasvári-Székely M. Candidate gene study of reaction time in cognitive tasks. VIIIth Congress of the Hungarian Society of Human Genetics, Debrecen, 2010 09. 2-4.

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