The role of a „survivor" gene variant in affecting individual differences in body mass index, executive functions and competitiveness

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PhD Thesis

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Budapest, 2019

1. Introduction

The field of my PhD Dissertation belongs to psychogenetics which is an interdisciplinary field combining specialties of both psychology and molecular genetics. It focuses on exploring inherited factors of individual differences in psychological phenotypes. In my research I aimed to examine associations between a dopamine gene variant and certain psychological features.

According to the literature the 7-repeat variant of the dopamine D4 receptor gene is linked to risk-taking behavior and different addictions. This gene variant also seems to be important in the heritability of longevity, it is considered a „longevity enabling factor" according to recent results. Moreover, this variant is not as „ancient" as the 4-repeat form of the DRD4. It is hypothesized that the 7-repeat variation mutation occurred 30 000 years ago. Due to positive selection mechanisms nowadays, it is widespread around the world. Thus, it certainly deserves the „survivor" marker.

In my doctoral research I investigated variables that may be mediator variables in the association of DRD4 7R allele and longevity. Thus, I focused mainly on life-way factors (e.g. physical activity, body mass index) and psychological factors (e.g. personality traits, competitiveness, executive functions).

According to available data and my findings, in this dissertation I present psychogenetic analyses in two main topics. **First, in the field of obesity that may influence longevity, I analyzed body mass index and executive functions and their association with the DRD4 7R allele. Second, I present results of link between the DRD4 7R and competitiveness. Interestingly, a gene-environment interaction could well explain sex differences of my results.**

2. Objectives

Based on previous literature, some of the life-way and psychological factors may be possible mediators in the association of DRD4 7R and longevity. In my research I focused on variables that were not investigated before in literature relating to DRD4 7R, some were examined, but only in special populations. I analyzed psychogenetic relationships between these variables and DRD4 7R allele, but uncovering their possible role as mediators is my future objective.

1.) DRD4 7R and body mass index:

Body mass index is related to nutrition, food intake, and „food-addiction". Mechanisms of obesity and addictions are similar. Previous results of the association between DRD4 7R and body mass index are inconsistent, and these studies mainly focused on small, special samples (e.g. subjects with mood disorder). Thus, **one main objective of my work was to analyze association of DRD4 7R and body mass index in a large, healthy, Hungarian sample from wide age-range.**

2.) DRD4 7R, body mass index, and executive functions

Executive functions – particularly inhibitory control - are related to both nutrition and the dopamine system. Based on this connection, I investigated **psychogenetic association of the DRD4 7R, body mass index, and markers of inhibitory control, in a partial sample of the one described above.**

3.) Association analysis of DRD4 7R and competitiveness:

Competitiveness (a trait related to risk-taking behavior) was not investigated earlier in connection to DRD4 7R. Thus, **the third part of my research uncovers associations between the DRD4 7R, competitiveness, sex differences, anxiety and depression.**

3. Methods

This research was carried out within the Psychogenetic Research Group of the Psychology Institute, at ELTE. Study protocols have been approved by the Ethical Commission of the Hungarian Medical Research Council. Participants were collected by convenience sampling at courses of ELTE PPK, at different events (e.g. The Night of Research), and elderly homes. DNA samples were collected in a painless, non-invasive way. Participants completed the computerized version of Stroop task, answered questions related to their health status, sex, age, body weight and height, diabetes, depression and other psychiatric illnesses. They completed self-report questionnaires (e.g. Hypercompetitiveness Attitude Scale – HCA, Self-Development Competitive Attitude Scale – PDCA, Hospital Anxiety and Depression Scale – HADS).

In my doctoral work genetic, body weight and height data of 1307 subjects were analyzed. I collected about half of the data-set.

Allele variants of DRD4 gene were determined from the previously collected DNA samples by our collaborators working at the Molecular Genetic Laboratory, Semmelweis University. Body mass index (or BMI) was calculated from self-reported body weight and height.

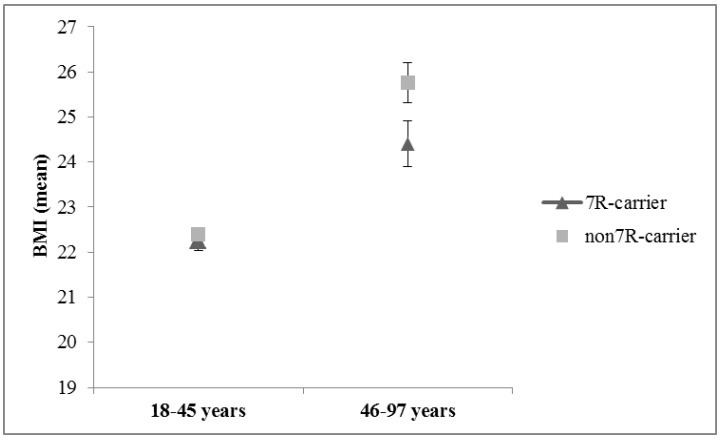
The computerized Stroop task was completed by a subset of the whole sample (152 young subjects had valid data suitable for analyses). Another subset (395 participants within the age-range of 18-35 years) had valid data of competitiveness, anxiety and depression.

4. Results

1. Association analysis of DRD4 7R and body mass index

Dopamine system is key element of reward system, as well as in food-intake regulation. I investigated association of the DRD4 7R and body mass index in **a sample of 1307 genetically independent subjects from wide age-range, who had no self-reported diabetes, depression or any psychiatric illnesses in the present or in the past:**

ANOVA analysis showed that main effect of the DRD4 7R ($p = 0.016$) and age groups ($p < 0.001$) was present, and the interaction effect of these factors were also significant ($p = 0.04$) on body mass index, besides a significant covariant effect of sex ($p < 0.001$). Older subjects showed higher BMI as compared to younger, and DRD4 7R carriers had lower BMI than non-carriers. Males showed higher BMI as compared to females. In the older age group, the difference in BMI between 7R carriers and non-carriers (with lower BMI of 7R carriers) was more pronounced than in the younger age group.



Thus, interaction effect of DRD4 7R and age on BMI is presumable.

2. Association analysis of the DRD4 gene variants, executive functions and body mass index:

Inhibitory control is related to food-intake regulation and is one of the executive functions. Thus, body mass index may be in association with performance in a Stroop task. Thus, **I examined links between the DRD4 polymorphism, error number and reaction time in a Stroop task and body mass index in a sample of 152 genetically independent subjects.**

ANOVA showed a significant main effect of the type of stimuli: congruent/incongruent ($p < 0.001$) and a significant main effect of body mass index ($p = 0.033$) on **error number**. A significant interaction effect of these two factors also emerged ($p = 0.022$). Subjects made more errors when addressing incongruent stimuli as compared to congruent stimuli. Overweight/obese and underweight/abnormally lean subjects made more errors than subjects in the normal interval. Overweight/obese and underweight/abnormally lean participants made more errors than normal weight subjects only when faced with incongruent stimuli. To summarize, **when inhibitory control was necessary, subjects with extreme body weight showed weaker performance in the Stroop task demanding executive functions as compared to subjects in the normal weight group.**

When analyzing **reaction time** data of the Stroop task, only the main effect of type of stimuli emerged ($p < 0.001$). Main effect of body mass index category was not significant. Nonetheless, type of stimuli and BMI category showed a significant interaction effect on reaction time. For incongruent stimuli, subjects needed more time to give answers than for congruent stimuli. In the underweight/abnormally lean category this difference was more pronounced, as compared to the two other groups. **Results suggest that in underweight/abnormally lean category the Stroop effect was stronger as compared to the other weight groups.**

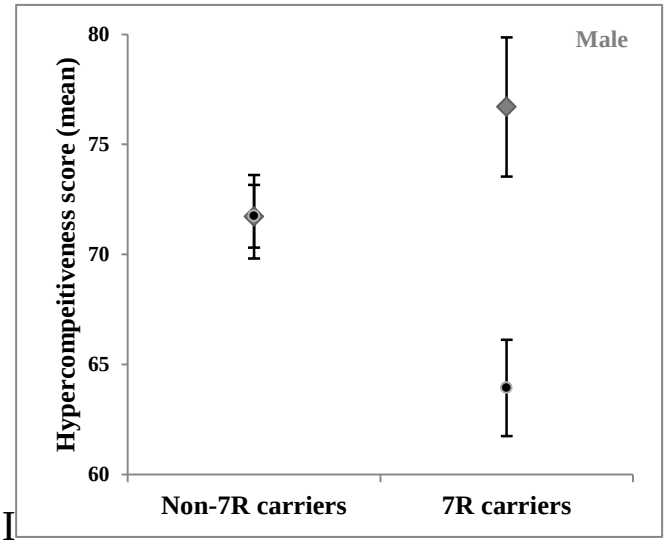
DRD4 7R tendentiously influenced congruent and incongruent error number: 7R carriers made slightly more errors. DRD4 7R and BMI category showed no interaction on error number, only main effect of BMI category emerged on incongruent error number ($p = 0.018$). Neither the main effect of DRD4 7R, BMI category, nor their interaction was significant on reaction time, but on Stroop effect, the main effect of BMI category prevailed. **According to these results, association of the DRD4 7R with executive functions (as measured by the Stroop task) and BMI has not been shown.**

3. Association analysis of DRD4 7R and competitiveness

Association of the DRD4 7R and competitiveness was not examined previously in the literature. However, variables related to competitiveness (e.g. risk-taking behavior and school performance) showed association with this gene variant.

I've carried out association analysis between the DRD4 7R polymorphism and self-reported hypercompetitiveness and also self-development competitiveness using data from 399 genetically independent, young subjects, who had no diabetes, depression or any psychiatric illnesses in the present or in the past.

ANOVA showed that males are more hypercompetitive ($p = 0.006$) than females. DRD4 7R showed no association with hypercompetitiveness. Interaction effect of sex and DRD4 7R ($p = 0.006$) emerged on hypercompetitiveness: 7R carriers males showed much higher hypercompetitiveness than females while by non-carriers, no such differences were detected.



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When assessing self-development competitiveness, only the main effect of sex emerged ($p = 0.001$), with higher score of males.

To summarize results **in the group of 7R carriers, sex difference in hypercompetitiveness was more pronounced than in non-carriers. This could reflect a gene-environment interaction.**

Based on these results I examined the relationship between hypercompetitiveness and anxiety, and depression, in both sexes.

In females significant positive association emerged between hypercompetitiveness and anxiety (r = 0.34), and between hypercompetitiveness and depression (r = 0.28). In males, no such relationship emerged. It seems that **hypercompetitive females show higher anxiety and depression than less hypercompetitive females.**

Based on the results above, I compared correlation of hypercompetitiveness and anxiety/depression in the DRD4 7R carrier and non-carrier females. In 7R carrier females correlation of hypercompetitiveness and anxiety was high (r = 0.45), and a similar pattern emerged for hypercompetitiveness and depression (r = 0.53). This relationship was lower and non-significant in 7R non-carrier females (r = 0.17). To summarize: **higher anxiety and depression scores of hypercompetitive females was explicit in 7R carrier females but was not detectible in non-carriers.**

5. Conclusion

According to previous literature DRD4 7R showed association with phenotypes like risk-taking behavior, different addictions, and longevity. Based on these findings I analyzed association between the DRD4 7R and BMI, executive functions, and competitiveness in a healthy Hungarian sample.

Ma results showed that lower BMI of DRD4 7R carriers was present in the whole sample, but it was more pronounced in the older age group than by the younger. **It is possible, that protective role of DRD4 7R against obesity prevails only in older age.**

Extreme low or high food intake showed relationship with weaker inhibitory control based on previous results. My results support these previous findings; overweight/obese and underweight/abnormally lean subjects performed weaker in a Stroop task. Role of the DRD4 R7 was only partially detectable – to further examine this possible association, a larger sample would be necessary.

My results showed that in 7R carriers, males reported higher, while females reported lower hypercompetitiveness as compared to non-carriers (where scores of males and females were almost the same). **It is presumable that DRD4 7R modulates hypercompetitiveness according to expectations of the society.** In females, competitive attitudes (particularly hypercompetitiveness) are less acceptable. These assumptions are underlined by my further results related to correlation analyses of hypercompetitiveness, anxiety and depression in 7-repeat carriers and non-carriers: Hypercompetitive females report higher anxiety and depression than less hypercompetitive females. This relationship was explicit in 7R carriers.

Results related both to BMI and competitiveness reflect the potential adaptive role of DRD4 7R: it may modulate reactions to environmental cues in an optimal way. This notion is in line with the previous assumption that **the wide-spread frequency of 7R is the result of positive selection.** Moreover, **it may also influence longevity.** To examine this, I propose pathway analysis in the future. It may reveal such endophenotypes, through which a genotype may influence a phenotype or illness. These results could help to clear out some of the inconsistent results in the psychogenetic association literature.

Findings also reflect that in psychogenetic research there are many important factors such as age, sex, culture and society, and that these may also have an influence on the outcome. We must emphasize the

role of environment, since genes are not the only factors responsible for a phenotype, **gene-environment interactions are out most important, and this is often ignored in psychogenetic literature.** In the present dissertation I found a clear interaction effect related to sex-related differences in the association of hypercompetitiveness and the DRD4 gene variants. Since inheritance of these traits are complex, involving many genes and their complex interactions with the environment. Uncovering these complicated relations is a well suited task for the future.

Journal publications of the PhD candidate

Publications on them the dissertation was based on:

Bircher, J., Kotyuk, E., Fülöp, M., Vereczkei, A., Ronai, Z., Varga, K., & Szekely, A. (2019): Gene-sex interaction in Hypercompetitive Attitude suggests beneficial effect of the DRD4 7-repeat allele in adaptation. *Neuropsychopharmacologia Hungarica, 21*(2), 47-58.

Bircher, J., Kotyuk, E. Cserjesi, R., Vereczkei, A., Szekely, A., & Nagy, G.: A végrehajtó funkciók kapcsolata a testtömeg-indexszel és a DRD4 VNTR 7-es alléllal *(Orvosi Hetilap, publikálásra elfogadva)*

Bircher, J., Szekely, A., Kotyuk, E., Ronai, Zs., & Cserjesi, R. (manuscript under submission): The aging effect on R7 genotype in the frame of BMI and cognitive control (Tervezett folyóirat: *European Health Psychology Society*)

Systematic review published due to doctoral works and cited in the dissertation:

Bircher, J., Griffiths, M. D., Kasos, K., Demetrovics, Z., & Szabo, A. (2017). Exercise addiction and personality: a two-decade systematic review of the empirical literature (1995-2015). *Baltic Journal of Sports and Health Sciences, 3*(106), 19-33. ISSN 2351-6496

Further cited publications:

Szekely, A., Kotyuk, E., **Bircher, J.,** Vereczkei, A., Balota, D. A., Sasvari-Szekely, M. és Ronai, Z. (2016). Association between Age and the 7 Repeat Allele of the Dopamine D4 Receptor Gene. *PLoS ONE, 11,* e0167753.

Kotyuk, E., Biro, V., **Bircher, J.,** Elek, Z., Sasvari, M., és Szekely, A. (2017). ABCA1 polymorphism, a genetic risk factor of harm avoidance. *Journal of Individual Differences, 38,* 189-195.