Charles University
Faculty of Science

Study program: Biology
Branch of study: Genetics, molecular biology, virology

Bc. Martina Polgar

The impact of “dopamine genes” polymorphisms on novelty seeking behavior.

Vplyv polymorfizmov “dopamínových génov” na správanie typu novelty seeking.

Diploma thesis

Division of microbiology and genetics
Supervisor: doc. Ing. Alexandr Popkov, Ph.D.

Prague, 2017

Honesty Statement

My signature below constitutes my pledge that this diploma thesis is my own work written based on references

Date: Prague 14.8.2017 **Signature:** _____

Acknowledgements

The topic of this diploma thesis was inspired by Professor Albert Gjedde, Danish neuroscientist, whose research focuses on the relation between neuroplasticity and neurotransmission.

First of all, I would like to thank to my supervisor doc. Ing. Alexandr Popkov, Ph.D. for his patience and valuable advice. I really appreciate his willingness to help me with my diploma thesis under very difficult conditions.

Further, I want to thank doc. Mgr. Anton Heretik, Ph.D., from Faculty of Arts, in Comenius University in Bratislava, that despite his very busy schedule, he found time for my questions. He also helped me find certain academic study materials which were difficult to locate and helped me procedure the evaluation tests.

I would like to thank to Mgr. Dagmar Bystřická, Ph.D., from laboratory Genlabs s.r.o. in České Budějovice for her help with the practical part of this thesis. I very much appreciate her time, advice and that she gave me the opportunity to work in her laboratory.

My special thanks belongs to my husband, Robert C. Polgar, who was standing next to me to during this entire project. I thank him for his absolute support, endless patience with my mood-swings and also for his intransigence, when I thought I couldn't continue. This paper was finished also because of him.

And last but not least, I would like to thank the volunteers, who donated their time to participate in this project, my dear friend Robert and my brother, Peter who helped me contact participants and collect material for DNA analyses.

Abstract

This diploma thesis examines the linkage between -141C Ins/Del polymorphism in dopamine receptor D2 gene and *novelty seeking behavior* (NSB). Novelty seeking is a personality trait characterized as a tendency to seek out various, complex and intense sensations and experiences at the cost of physical, social, legal, and financial risk. It also appears to be related to the onset of young drug use and aggressive behavior. It has been suggested that there is a relatively high occupancy of dopamine receptors in the brain of individuals with this characteristic feature. Generally, dopamine receptors are extensively studied in relation to many psychiatric diseases or personality disorders. Although there are studies focusing on personality traits such as novelty seeking, subjects of their research are mainly dopamine receptors D_1, D_3 or D_4. Very little is known about dopamine receptor D_2 and its relation to NSB despite the fact, that DRD_2 is the key negative regulator of dopamine action. Currently, determination of occupancy of dopamine D_2 receptors in the brain is possible with positron emission tomography (PET). However, using PET in neuropsychological research is not always financially viable. To date, only few studies associated with PET and NSB vs. D_2 receptors occupancy have appeared in published trades. Therefore, the aim of this thesis is to verify the relation between the DRD_2 polymorphism and NSB by genetic analyses. Results would serve as the basis for a more precise selection of PET screening candidates, thereby limiting the cost of this investigation.

Key words: novelty seeking behavior, dopamine, DRD_2, polymorphism, personality, TCI-R

Abstrakt

Diplomová práca skúma vzťah medzi -141C Ins/Del polymorfizmom v dopamínovom receptore D_2 a prejavmi tzv. *novelty seeking behavior* (NSB). Novelty seeking (vyhľadávanie nového) je povahová vlastnosť, charakterizovaná ako tendencia vyhľadávať rôzne, komplexné a intenzívne senzácie a zážitky za cenu fyzického, sociálneho, právneho a finančného risku. Pravdepodobne súvisí taktiež s nástupom užívania drog v mladom veku a agresívnym správaním. Uvažuje sa, že jedinci s touto charakteristickou črtou majú v mozgu relatívne vysokú obsadenosť dopamínových receptorov. Dopamínové receptory sú predovšetkým intenzívne skúmané v súvislosti s mnohými psychiatrickými ochoreniami alebo poruchami osobnosti. Hoci existujú práce, ktoré sa zameriavajú aj na povahové vlastnosti ako je novelty seeking, predmetom ich štúdia sú hlavne dopamínové receptory D_1, D_3 alebo D_4. Len veľmi málo sa vie o dopamínovom receptore D_2 a jeho vzťahu k NSB a to napriek faktu, že DRD_2 má kľúčovú úlohu v negatívnej regulácii pôsobenia dopamínu. Obsadenosť DRD_2 v mozgu je v súčasnej dobe možné určiť pomocou pozitrónovej emisnej tomografie (PET). Avšak využitie tejto metódy v neuropsychologickom výskume je finančne veľmi náročné. K dnešnému dňu sa v literatúre objavilo len pár publikácií zaoberajúcich sa NSB, ktoré na porovnávanie obsadenosti D_2 receptorov použili PET. Preto, cieľom tejto práce je overenie vzťahu medzi DRD_2 polymorfizmom a NSB pomocou genetickej analýzy. Výsledky by slúžili ako podklad pre presnejší výber kandidátov na PET screening, čím by sa ušetrili náklady na toto drahé vyšetrenie.

Kľúčové slová: novelty seeking behavior, dopamin, DRD_2, polymorfizmus, osobnosť, TCI-R

Content

Theoretical part

Theoretical part

1 Introduction

Novelty seeking behavior(NSB) is a personality trait characterized as a *"heritable tendency towards frequent exploratory activity and intense excitement in response strongly to novel stimuli"* (Cloninger, 1986, pp. 167).

Individuals exhibiting this behavior are permanentlyseeking out new and intense experiences that take the form of risky sports activities(Zuckerman, 2002), irresponsible financial activities, such as gambling (Lawrence et al., 2014), or experimenting with potentially addictive substances (Derringer et al., 2008). These behaviors are often accompanied by irresponsible and impulsive decisions (Cloninger, 1986; 1987a). In general, the enthusiasm and pleasure that individuals experience during these kinds of activities is caused by increased dopamine action, known as a "feel-good" substance (compiled in DeYoung, 2013).

The mechanism behind the dopamine action during exhilarating activities is similar to the mechanism involved in how addictive substances affect brain function. Many psychotropic substances directly (e.g. dopamine agonist, bromocriptine, by stimulating dopamine receptors) or indirectly (e.g. amphetamine by increasing its release into the synaptic cleft) alter the action of dopamine in the brain.(compiled in Crocker, 1994). The chronic use of addictive drugs causes a reduction in the number of dopamine receptors (Rouge-Pont et al., 2002; Nader et al., 2005; Lee et al., 2009; Ballard et al., 2015a, 2015b; Richter et al., 2017) and therefore, a decrease in dopamine activity occurs after a certain time.So, in order to produce the same effect, a higher dose of substance is needed and repeated self-administration is reinforced (Nader and Czoty, 2005).

Since exhilaratingactivities increase dopamine levels in the brain as well, the relation of novelty seeking to changes in the dopaminergic system have begun to be considered (Cloninger, 1986). Dopamine receptorsare studied in relation to NSB, but only little in known about dopamine receptor type D_2 (DRD_2). Some data showed that decreased availability of DRD_2 is in positive correlation with NSB (Gjedde et al., 2010). Several polymorphisms in DRD_2 gene have been discovered that are considered to affect density of the receptor in the brain and thus dopamine function (annex I; tab. 4).

2 Dopamine (DA)

Dopamine in the central nervous system (CNS)

Dopamine acts in the brain as a neurotransmitter and together with serotonin and noradrenaline regulates physiological, endocrine and behavioral functions. It is responsible for information processing, judgment and decision-making (Oswald et al., 2015). It contributes to retaining information, maintaining attention and creating long-term memory footprints.Additionally, dopamine plays a central role in the motivation system, where it is perceived to be responsible for the *desirefor a reward*, whereas endogenous opiates (endorphins), appear to be responsible for the feelings (pleasure, euphoria) *after reward* is obtained (compiled in DeYoung, 2013) and probably may have a role in damping the seeking behavior (Zuckerman, 1979).

Dopamine has an important modulation function in the neural pathways in basal ganglia. Disturbance of DA signaling in these areas results in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease or Schizophrenia. However, deregulation of dopaminergic pathways may also contribute to the development of depression, attention deficit disorder (ADHD), or food intake (anorexia nervosa, bulimia nervosa) (Schartzberg and Nemeroff, 2004; Trudell and Izenwasser, 2008).

Dopamine in the peripheral nervous system (PNS)

In addition to CNS, dopamine is also produced in the kidneys, where it acts as a paracrine hormone, regulating sodium excretion. Dopamine inhibits Na^+/K^+ ATPase activity, which results in increased sodium excretion by the urine (natriuresis), thereby regulating blood pressure (compiled in Crocker, 1994).

The dopamine precursor, L-DOPA is transportedinto the cells in proximal tubules by the sodium transporter in the apical membrane (Soares-da-Silva, 1998). While inside the cells, conversion of L-DOPA to dopamine is regulated by salt content and is independent of neural activity (Lee, 1993).

The dopamine is then secreted from the cells into the tubular lumen and into the peritubular space. Secretion may occur on the apical or basolateral surface. Basolateral transporter activity is dependent on sodium concentration and pH, but little is known about apical dopamine secretion (Soares-da-Silva, 1998).

2.1 Structure

Dopamine or *3,4-dihydroxyphenethylamine* belongs to the group of natural amines, in particular, *Catecholamines*. Catecholamines are monoamines which are characterized by a benzene ring with two hydroxyl groups, called catechol (fig. 1). Norepinephrine (noradrenaline) and epinephrine (adrenaline) also belong to this group (Wikipedia, c2017).

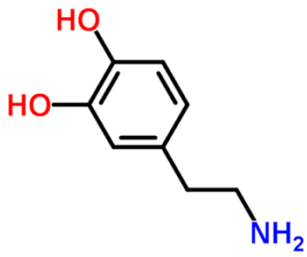

Figure 1: Structural formula of dopamine (http://chemspider.com)

2.2 Synthesis and degradation

Dopamine synthesis begins with the active transfer of non-essential L-tyrosine amino acid through the hematoencephalic barrier to the neurons (Schartzberg and Nemeroff, 2004). The first step is adding the hydroxyl group to the aromatic ring of L-tyrosine by the enzyme *tyrosine hydroxylase* (TH) to form *L-dihydroxyphenylalanine* (L-DOPA), which is a precursor of dopamine. L-DOPA is subsequently converted to dopamine by the enzyme *aromatic L-aminoacid decarboxylase* (AADC) (Guyton and Hall, 2006).

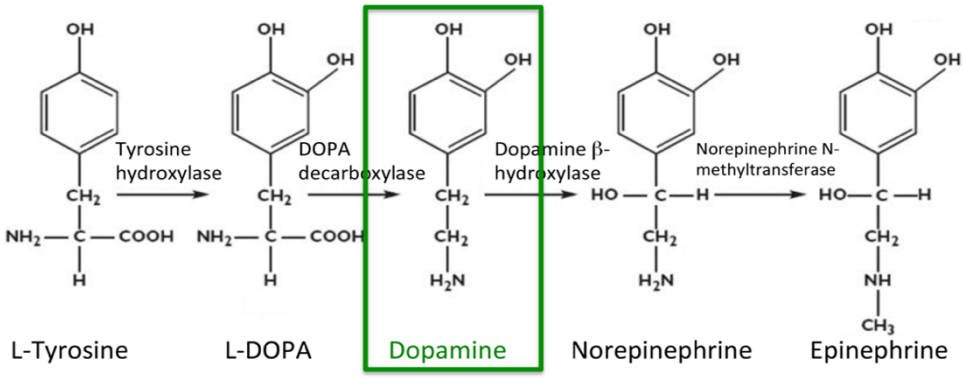

Figure 2: Scheme of synthesis pathway of Catecholamines
(https://journeywithparkinsons.com/2015/04/01/dopamine-a-symbol-of-hope/)

In adrenergic neurons, dopamine serves as a precursor for the synthesis of norepinephrine and epinephrine. The formation of norepinephrine is provided by the enzyme*dopamineβ-hydroxylase* by attachinga hydroxyl group to theβ-carbon. Epinephrine is formed by methylation of the amino group of norepinephrine via*phenylethanolamine N-methyltransferase*activity (compiled in Meiser et al., 2013).The cofactor *S-adenosylmethionine* is the donorfor methyl group (Alexander et al., 2015). Synthesis pathway of all three monoamines is shown in figure 2.

Dopamine is transported into the vesicles by VMAT2 transporters, which are ready to fuse with a presynaptic membrane of axon terminals. Consequently, secretion of dopamine has a quantal nature. Quantal releaseof dopamine has been found in dendrites and somas of neurons as well, i.e. somatodendritic release (Sulzer et al., 2016). Both processes, axonal release in the forebrain and somatodendritic release in the midbrain, are strongly dependent on Ca^{2+} (Ford et al., 2010) and similar with the respect to the amount of dopamine molecules (Kita et al., 2009). Spontaneous events can also occur,when leaked dopamine molecules are captured by presynaptic membrane transporters (Sulzer et al., 2016).

For termination of the effect of DA, molecules are actively transported back into the neuron viapresynaptic transporters. Dopamine is then transferred into the vesicles and ready for reuse. Dopamine molecules that escape to the cytoplasm are metabolized by a series of reactions catalyzed by*monoamine oxidase* (MAO), *aldehyde dehydrogenase* (ALDH) and*Catechol-O-methyl transferase* (COMT) (fig. 3):
Dopamine degradation in the neuron cytoplasm is initiated exclusively by the MAO enzyme. First reaction is therefore oxidative deamination producing H_2O_2 and highly-reactive *3,4-dihydroxyphenylacetaldehyde* (DOPAL). DOPAL is further oxidized by ALHD to *3,4 dihydroxyphenylacetic acid* (DOPAC). DOPAC diffuses into the extracellular space and into the surrounding cells, where it is subsequently methylated by COMT. In some cases,DOPALis reduced by*alcohol dehydrogenase* (ADH) to *3,4-dihydroxyphenylethanol* (DOPET). Reduction to alcohol is predominant in norepinephrine and epinephrine degradation (compiled in Meiser et al., 2013).

Dopamine is also transferred from the synaptic cleft into the surrounding glial cells, where the initial step of degradation can be provided by both MAO and COMT. Reactions catalyzed by MAO are the same as the reactions in neurons mentioned above. Degradation initiated by COMT represent dopamine methylation, with *3-methoxytyramine* (3-MT)as a product.

Subsequently, oxidative deamination catalyzed by MAO converts 3-MT to*3-methoxy-4-hydroxyphenylacetaldehyde*, which undergoes oxidation by ALDH enzyme as a last step. The final product of both pathways is *homovanilic acid* (HVA), which is excreted in urine (Schartzberg and Nemeroff, 2004) (Fig. 3).

Dopamine degradation in the kidneys is initiated by the same enzymes, COMT and MAO-A (Eklof 1997; Guimares and Soares-da-Silva, 1998).

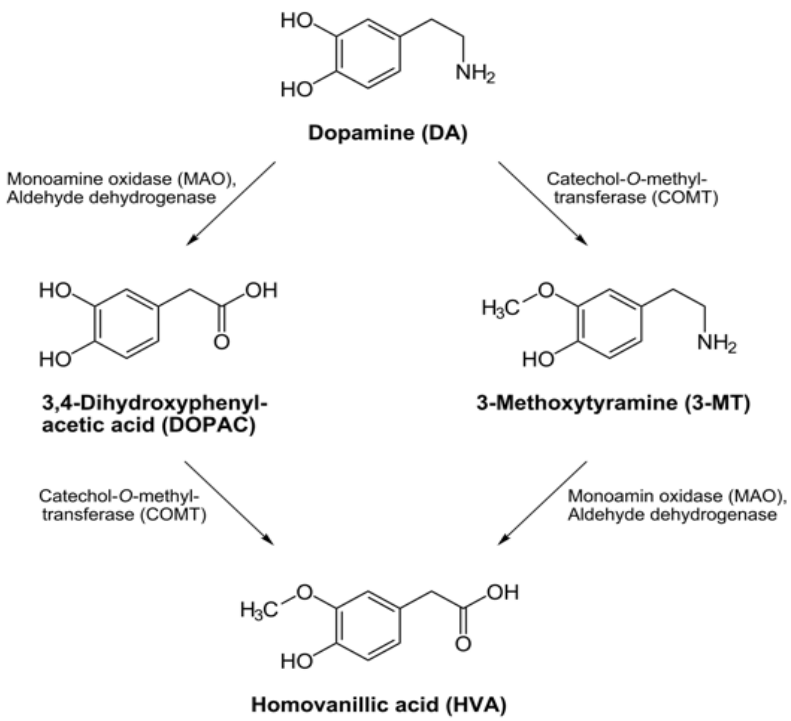

Figure 3: Scheme of two common ways of dopamine degradation. Dopamine degradation can be initiated by either monoamine oxidase (MAO) or catechol-O-methyl-transferase (COMT). Both pathways produce homovanilic acid (HVA) as a final product, which is excreted in urine(https://commons.wikimedia.org).

3 Dopamine receptors

Dopamine receptors are characterized by seven transmembrane domains in which they exhibit up to a 60-80% degree of similarity (Hubert, 1993). They belong to the superfamily of G-protein coupled receptors (Shenoy and Lefkowitz, 2005; Bourne et al., 2007), i.e. they are capable of regulating intracellular signaling cascades by activating heterotrimeric G-proteins (Kobilka et al., 1987; Gingrich and Caron 1993; Neve et al., 1991).

To date, five subtypes of dopamine receptors, D_{1-5}, are known. Depending on the structure and function, they have been divided into two classes: D_1-like and D_2-like dopamine receptors. The D_1-like class consists of receptor subtypes D_1 and D_5 and the D_2-like class include D_2, D_3 and D_4subtypes (Schatzberg and Nemeroff, 2004; Neve, 2010). These two groups differ from each other in their gene structure. The D_2-like dopamine receptor genes consist of coding exons and non-coding introns, whereas the D_1-like dopamine receptor genes are intron-less. Sequence analyses showed the presence of non-coding exon(s) upstream from the first coding exon. Although they have been found in both classes, in D_2-like class non-coding exons are separated from the coding region by several kilobases and just few base pairs in D_1-like class(Neve, 2010) (tab. 1).

Despite these structural differences, the general characteristic is similar. Regulating regions are rich in GC sequences, they lack TATA or CCAAT box and containseveral consensus binding sites for transcription factors such as Sp1/Sp3, AP1 or AP2.Presence of additional promoters has been discovered, which indicate different tissue- specific expression (Neve, 2010).

With respect to the different gene structure, D_1-like and D_2-like receptor groups show different localization and function in the brain. The D_1-like receptors are coupled with the G-proteins activating adenylate cyclase (AC), and therefore they increase cAMP synthesis(Kebabian et al., 1972; Schatzberg and Nemeroff, 2004). Whereas D_2-like receptors decrease cAMP production by interaction with inhibitory G-proteins (Albert et al., 1990). However, studies suggest that these receptors are likely to regulate signaling pathways also independently of the G-proteins via β-arrestins (Luttrell and Lefkowitz, 2002).

3.1 D_1-like dopamine receptors

The D_1-like receptors include subtypes D_1 and D_5 and activates AC by interaction with G_s/G_{olf}- proteins (Monsma et al., 1990) and is included in growth regulation of CNS (Lankford et al., 1987). The D_1 receptors predominates in the frontal cortex, but mRNA was found also in the striatum, nucleus accumbens, septum, hippocampus, thalamus and cerebellum. Probablythey have a role in higher cognitive functions. Receptors of type D_5 are predominantly found in limbic areas and thalamus (Fremeau et al., 1991; Schatzberg and Nemeroff, 2004).

3.1.1 Dopamine receptor D_1 (DRD_1, DRD_{1A})

The D_1 receptor is most abundant dopamine receptor in the central nervous system (CNS). Its gene is localized on the long arm of chromosome 5 atthe positon q35.2. (Grandy et al., 1990). Although, it was originally believed that the D_1 receptor gene was intron-less, the short intron (116 bp) in 5'UTR was found (Minowa et al., 1992).Thus, D_1 receptor consists of two exons, which one of them, exon 1, is non-coding. Since D_1 receptor gene has two promoter regions, alternative transcription initiation resultsin two transcriptional variants. Due to presence of the second promoter in exon 1, short version lacks this sequence. Studies suggest that expression of different versions of D_1 receptors is tissue-specific. Data shows that both promoters are activein neural cells, whereas in renal cells, only the intron promoter is active (Neve, 2010).

The D_1 receptors viaAC stimulate the growth and development of neurons, mediate behavioral responses, and modulate dopamine receptor D_2 mediated effects (Schatzberg and Nemeroff, 2004).

3.1.2 Dopamine receptor D_5 (DRD_5, DRD_{1B})

The DRD_5 gene is located on the chromosome 4 at the position p16.1 and consists of one coding and one non-coding exon. As other dopamine receptor genes, 5'UTR lack TATA and CCAAT box, but it is not GC rich. (Neve, 2010). Hybridization in situ revealed two additional loci on chromosomes 1 and 2 that carry non-functional pseudogenes. The pharmacological profile of D_5 is similar to D_1 but D_5 has a higher affinity for dopamine (Grandy et al., 1991). Studies suggest that DRD_5 is also involved in the activation of phospholipase C (PLC) by which it mobilizes intracellular Ca^{2+} (Mahan et al., 1989; Monsma et al., 1990).

3.2 D_2-like receptors

This group includes subtypes D_2, D_3 and D_4. The D_2-like receptors regulate cellular functions via activating G_i/G_o proteins (Albert et al., 1990) and, in addition to AC inhibition, they are involved in PLC signaling, K^+ channel and Ca^{2+} channel interaction (Schatzberg and Nemeroff, 2004). D_2-like receptors have specific role in regulationof development and morphogenesis of dopaminergic pathways. Stimulation of D_2 receptors increase the number and branching of neurons whereas stimulation of D_3 and D_4 receptors increase branching and extension of neurons (Swarzenski et al., 1997). The D_2 and D_3receptors have a similar distribution in the brain (Gurevich et al., 1999)

In the contrast to other members of the G-protein coupled receptor family, the D_2-like receptors differ in their exon-intron organization. For example, muscarinic or adrenergic receptor genes are encoded by a single exon (Kobilka et al., 1987; Frielle et al., 1987; Peralta et al., 1987) whereas D_2-like receptor gene sequences are interrupted by introns (Grandy et al., 1989a; Dal Toso et al., 1989).

3.2.1 Dopamine receptor D_2 (DRD_2)

The DRD_2gene is located on the long arm of chromosome 11 in the q22-23 region (Grandy et al, 1989a). It consists ofone non-coding exon and seven coding exons (Neve, 2010). In the isolated cDNA from human pituitary gland, two D_2 receptor variants were found that varied in number of bases (Grandy et al., 1989b). This 87 bp long section was found to be located in the third intracellular loop (ICL), which is considered a critical site of interaction with G-proteins (Kobilka et al., 1987; Cotecchia et al., 1990). Sequencing revealed the presence of two introns that delineate this segment. This led to the conclusion that the peptide X, as it was called, is a separated exon and so different receptor variants are the products of alternative splicing. The long form of D_{2A}/D_{2L} therefore has 29 amino acids more (444aa) than the short form, D_{2B}/D_{2S} (415aa) (Dal Toso et al., 1989; Neve et al., 1991).

Revealing alternative isoforms has shown that this extra segment is indeed responsible for selective interaction with G-proteins (Elazar et al., 1989; Montmayeur and Borrelli, 1990; Senogles, 1994). Probably due to the difference in amino acid charge, D_{2L} binds to another subtype of G-proteins and, in this way activates other signal pathways (Guiramand et al., 1995).

Isoforms of this dopamine receptor have a different distribution in the brain. The short form, D_{2S} is predominantly found in the midbrain and hypothalamus on dopaminergic neuron'sbodies and dendrites, whereas the D_{2L} form dominates in the pituitary gland, striatum and cortex on the axons ofdopaminceptive neurons (Neve et al., 1991, Khan et al., 1998). The large number of D_{2L}receptors in these regions are targets of the dopaminergic pathways (Schartzberg and Nemeroff, 2004) indicating their function as postsynaptic receptors. D_{2S}receptors have also been found in striatum and cortex, but exclusively on the axons of dopaminergic neurons (Khan et al., 1998).
Since the midbrain and hypothalamus are the regions of dopamine production (Schartzberg and Nemeroff, 2004), D_{2S}form functions here as auto-receptor (Aghajanian et al., 1977; Lindgren et al., 2003).

Axonal auto-receptors play a key role in the negative regulation of dopamine action (Lacey et al., 1987; Cragg and Greefield, 1997). By interacting with inhibitory G-proteins, they decrease cAMP production and thus PKA activity as well. Reduced phosphorylation activity of PKA has a negative influence on the activity of tyrosine hydroxylase and thus on the production of dopamine. At the same time, via decreased PLC activity, intracellular Ca^{2+} concentration is decreased and thus fusion of vesicles containing DA molecules with presynaptic membrane is reduced (Sulzer et al., 2016). It has been found that dopamine release is also inhibited by an H_2O_2, which actsas a neuromodulator (Patel and Rice, 2012). Glutamate acts excitably on AMPA receptors of striatal medial spine neurons (MSNs) and increases the production of H_2O_2 in mitochondria. H_2O_2 then diffuses into the extracellular matrix, where by opening the K^+ channels, helps to hyperpolarize the presynaptic membrane of dopaminergic neurons. Inhibitory neurotransmitter *γ-aminobutyric acid*(GABA) regulates the effect of H_2O_2 via $GABA_A$ receptors, which are also found on MSNs (Avshalumov et al., 2003). Reduction of dopaminerelease by activation of somatodendritic D_{2S} auto-receptors is also probably regulated via opening of K^+ channels (Tang et al., 1994). Activation of auto-receptors has also a positive feedback on dopamine transporter activity. MAP kinasesignaling pathway is likely to be involved (Sulzer et al., 2016).

In addition to these two major isoforms, a third variationas a result of alternative splicingwas found. This variant contained two amino acidsin the 3rd ICL, valine and glutamine, originally found in intron 5. Due to the new splicing site resulting from the point mutation, these amino acids became part of exon 6. This new, third isoform is longer than D_{2L} and therefore is called $D_{2Longer}$ (Seeman et al., 2000).The result of the mutation is the splicing site with TG

sequence, instead of usual AG, which is presence in remaining introns of the DRD_2 gene (Grandy et al., 1989b).

Aberrations in DRD_2 signaling are associated with the development of various psychiatric disorders such as Parkinson's disease (Muñoz and Aguilar, 2017) and schizophrenia (Grandy et al., 1989a, Grandy et al., 1898b, Arinami et al., 1997). Also, it has been shown that dopamine receptors play a role in substance addiction with amphetamines (Martinez et al., 2003), metamphetamine (Ballard et al., 2015a; 2015b), cocaine (Wiers et al. 2016) and caffeine (Volkow et al., 2015).

3.2.2 Dopamine receptor D_3 (DRD_3)

The dopamine D_3 receptor is encoded by a gene located on the long arm of chromosome 3 at site q13.31 and is composed of 10 exons. This receptor is located mainly in the limbic regions of the brain, which are associated with cognitive, emotional and endocrine functions, but mRNA has been discovered in SN, VTA, septum, thalamus, cortex and cerebellum (Schatzberg and Nemeroff, 2004). DRD_3 is examined in relation to the sensation seeking behavior and impulsivity (Johnson et al., 2003; Thomson et al., 2013) but also OCPD (Light et al., 2006). It is assumed that the C/T point substitution at codon 9 (rs6280), which results in replacing the amino acid serine to glycine (Ser9Gly), changes the affinity of the receptor for dopamine (cit).

D_3 receptors, as well as D_2, were found to have two splice variants (Lavant, 1997). The shorter version was detected on axons and dendrites of dopaminergic neurons (Tepper et al., 1997), however little is known about its function as auto-receptors (Sulzer et al., 2016). But it seems that D_2, not D_3 receptors are the major negative regulators of dopamine action (Millan et al. (2000). However, stimulation of D_2/D_3 heterodimers inhibits DA efflux by membrane hyperpolarization via opening K^+ channels (Tang et al., 1994).

3.2.3 Dopamine receptor D_4 (DRD_4)

The human D_4 receptor encoding gene is located on the short arm of chromosome 11 at p15.5 and is made up of four exons. D4 is expressed in the retina, frontal cortex, hippocampus, amygdala and hypothalamus (Schatzberg and Nemeroff, 2004). This gene is the subject of intensive research related to various behavioral disorders, such as ADHD (Faraone et al., 2001; Mill et al., 2001; Mill et al., 2002), personality behavior patterns such as novelty

seeking behavior (Sander et al., Strobel et al., 1999; Lakatos et al., 2003), but also serious psychiatric disorders such as schizophrenia (Kaiser et al., 2000).

	Gene organization [coding and 5′-regulatory region]	Features in promoter region	Upstream regulation	Regulation by transcription factors
D2-like dopamine receptors				
D_2 dopamine receptor	One non-coding exon separated from seven coding exons by large intron	Two promoter regions, initiator-like element, no CCAAT or TATA boxes, 80% GC	Two silencer regions in mammalian cell lines	AP1, retinoids Sp1/Sp3, Zif68, DRRF, nuclear factor-κB
D_3 dopamine receptor	Two non-coding exons separated from six coding exons by large intron	One promoter region, initiator-like element, no CCAAT or TATA boxes, 52% GC	Two silencer regions in neuroblastoma and hepatoblastoma cell lines	DRRF
D_4 dopamine receptor	Four or five coding exons (depends on species) separated by introns	One promoter region, no CCAAT or TATA boxes, CpG island, over 50% GC	Two silencer regions in neuroblastoma and retinoblastoma cell lines	Sp1
D1-like dopamine receptors				
D_1 dopamine receptor	One non-coding exon separated from the coding exon by small intron	Two promoter regions, no CCAAT or TATA boxes, 80% GC	Two activator regions and one silencer region in neuroblastoma cell lines	Sp1, POU, Brn4, Meis2, TGIF, ZIC, Sp3, DRRF
D_5 dopamine receptor	One non-coding exon separated from the coding exon by small intron	One promoter region, no CCAAT or TATA boxes, not GC rich	One activator and one silencer region in neuroblastoma cell lines	Not known to date

Table 1: Dopamine receptor gene subtypes: gene organization and regulation according to Neve (2010).

4 Dopamine projections

4.1 Simple overview of structures of the human brain(Dokládal and Páč, 2000):

1) Prosecephalon (forebrain)
    - Telencephalon (endbrain)
        - cortex cerebri (neocortex, allocortex)
        - basal ganglia
    - Diencephalon (interbrain)
        - epithalamus
        - thalamus
        - hypothalamus
        - subthalamus
        - metathalamus
2) Mesencephalon (midbrain)
    - tectum (dorsal part)
    - pedunculi/crura cerebri (ventral part)
        - tegmentum (ventral tegmental area)
        - substantia nigra (pars compacta, pars reticularis)
        - crura cerebri
3) Rhombencephalon (hindbrain)
    - cerebellum
    - pons Varoli
    - medulla oblongata
4) Medulla spinalis (spinal cord)

The **forebrain (prosencephalon)** represents the largest part of the brain (Dokládal and Páč, 2000). In ontogenesis, it develops from the anterior cerebral cam, which is consequently divided into the endbrain and the interbrain (Dorko et al., 2014).

In the ontogenetic development, the **endbrain (telencepalon)** differentiates into a middle unpaired part and two pair of cams. These cams are base for both hemispheres in which the thinner surface, cortex cerebri, differentiate and for the basal ganglia. The cerebral cortex is divided into paleocortex (the oldest structure), archicortex (hippocampal formation) and

neocortex. Neocortex occurs first in reptiles and develops fully in mammals. It plays a significant intellectual role in a human being. Paleocortex and archicortex are together referred to as allocortex (Dorko et al., 2014). Developed cerebral hemispheres are separated by a deep fissure (fissura longitudinalis cerebri) but remain connected by a coarse/massive bundle of white matter (corpus callosum). The surface of the endbrain is wrinkled with furrows (sulci) and ridges (gyri). Thanks to deep furrows; sulcus lateralis, sulcus centralis and sulcus parietoccipitalis, brain can be divided into four lobes: frontal, parietal, occipital and temporal (Dokorkal and Páč, 2000; Dorko et al., 2014).

The interbrain (diencephalon) originates from the anterior cerebral cam. It has a dorsal, sensitive part (thalamus, epithalamus, metathalamus) and the ventral, motoric part (hypothalamus, subthalamus). It contains the third brain chamber (Doktoral and Páč, 2000; Dorko et al., 2014). The largest part is the thalamus, which receives signals from all brain structures. After signal processing, signals from the thalamus are transmitted to the cortex or basal ganglia. Epithalamus contains an unpaired body (corpus pineale) in which melatonin is formed (Naňka and Elišková, 2015). The subthalmamic nuclei are functionally involved in the basal ganglia circuit. Hypothalamus is the control center of autonomic functions and is functionally connected to the limbic system. It is made up of nuclei and infundibulum, which continues into the hypophysis (pituitary gland). Hypothalamus regulates the action of adenohypophytis and itself forms the hormones vasopressin (ADH) and oxytocin, which are transported to neurohypophysis and then to blood stream (Dorko et al., 2014).

The midbrain (mesencephalon) is associated with vision, hearing, motor control, circadian rhythm, arousal and temperature regulation. There is an aqueductus cerebri, a channel that connects the 3rd and 4th chamber (Dokládal and Páč, 2000). This channel separates the smaller dorsal part (tectum) and the larger ventral part (pedunculus cerebri). The ventral part is further divided into tegmentum and crura cerebri which are separated by a strip of black-gray mass of substantia nigra (Dorko et al., 2014).

The hindbrain(rhombencephalon) consists of the cerebellum, the bridge (pons Varoli) and the prolonged spinal cord (medulla oblongata). The elongated spinal cord and the bridge together with the middle brain form the brain stem. These are phylogenetically the oldest parts of the CNS providing basic vital functions. Cerebellum is not part of the cerebral strain but is linked to it (Dorko et al., 2014). Cerebellum is the largest part of the back brain. It has evolved through stagnant information from various parts of the CNS. It has a rather complicated division. It forms hemispheres whose surface is wrinkled and can be

distinguished by lobes (Dokládal and Páč, 2000). The structures of the stem strain are planted routinely on the spinal cord.

Medulla spinalis (spinal cord) is a dorso-ventrally flattened bundle of nerve fibers (Dorko et al., 2014). It occupies the upper two-thirds of the vertebral canal and in contrast to the cerebral hemispheres, gray matter is surrounded by white matter (Swenson, 2006).

4.2 Dopamine projections

Dopamine is synthesized in dopaminergic neurons in the midbrain.In particular, in substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). SNc is the site of the largest dopamine production. Its neurons project axons into the basal ganglia region, in particular to the nucleus caudatus and putamen (dorsal striatum), regions involved in the control of motor function (Crocker, 1993). This pathway is called nigrostriatal pathway (Schartzberg and Nemeroff, 2004). Along with cortico-striatal glutamatergic projections from sensory motor cortex (Haber and Fudge, 1997), it plays an important role in the control of voluntary movement, in so called direct and indirect pathways(Barbeau, 1974; Smith, 2008).A disturbance of the nigrostriatal pathway is associated with motor deficits (Haber and Knutson, 2010)

Neurons from the VTA create both mesolimbic and mesocortical pathways. The mesocortical pathway leads the axons to the prefrontal, cingular and perirhinal cortex. It has a central role in cognitive, motivation and emotional response. The mesolimbic pathway innerves the limbic system. It modulates emotional-related behavior and regulates will and reward processes (Yim et al., 1980; Haber and Fudge, 1997). This pathway plays a key role in the addiction. Damaged mesocortico-limbic pathway is responsible for changes in cognitive and behavioral manifestations (Haber and Knutson, 2010).

Dopamine is also produced in a smaller amount in the hypothalamus from which the tuberoinfundibular pathway leads to the pituitary gland (Schartzberg and Nemeroff, 2004). Here, dopamine plays a role asan inhibitor of prolactin production (Senogles et al.,1987). It has been suggested that deregulation of this pathway, e.g. mutations in DRD_2, leads to hyperprolactinemia (Hansen et al., 2005; Calarge et al., 2010).

Dopaminergic pathways are shown in figure 4.

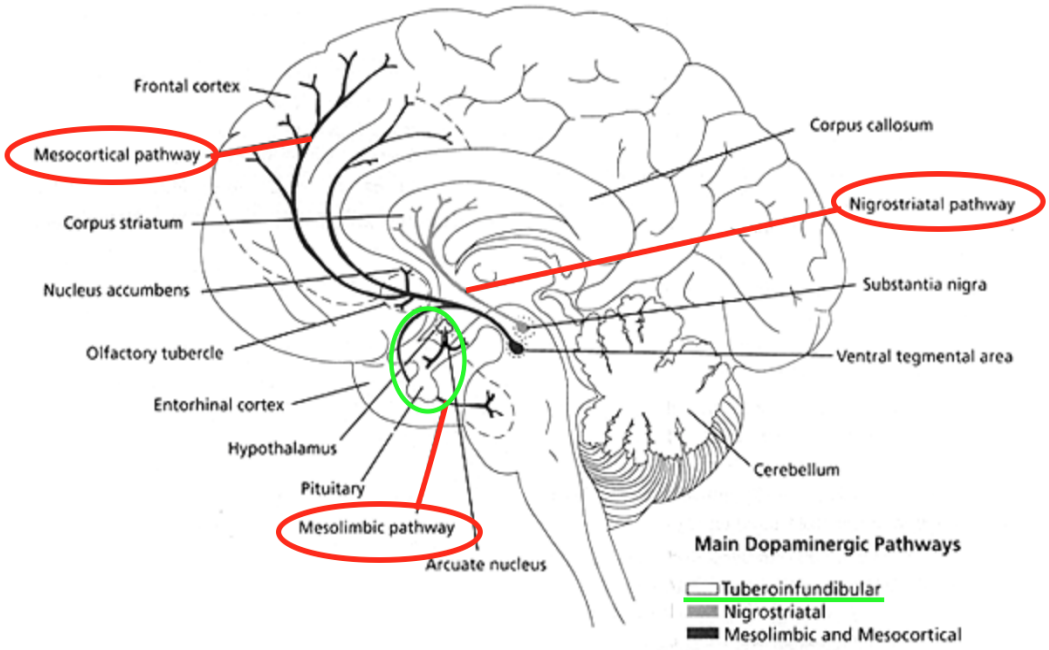

Figure 4: Sagittal section of the human brain. Dopaminergic projections: nigrostriatal pathway leads axons from substantia nigra pars compacta to the dorsal striatum, mesolimbic pathway projects axons from VTA to the ventral striatum, mesocortical pathway connects dopaminergic neurons from VTA with limbic cortex and tuberoinfundibular pathway leads from hypothalamus to pituitary gland. According to Crocker (1993).

4.3 Basal ganglia

The basal ganglia (nuclei basales) of the forebrain representclusters of gray matter involved in creation and regulation of direct and indirect pathways and various cognitive functions. Some of its parts are functionally part of the limbic system.

Anatomically related structures are big nuclei: nucleus caudatus, putamen and globus pallidus and small nuclei: corpus amygdaloideum (amygdala) and clastrum. Functionally linked to basal ganglia are the substancia nigra pars compacta (SNc), pars reticularis (SNr) and subthalamic nuclei, which are anatomically part of the midbrain (fig. 5).Disturbance of substantia nigra causes Parkinsonism (Dorko et al., 2014).

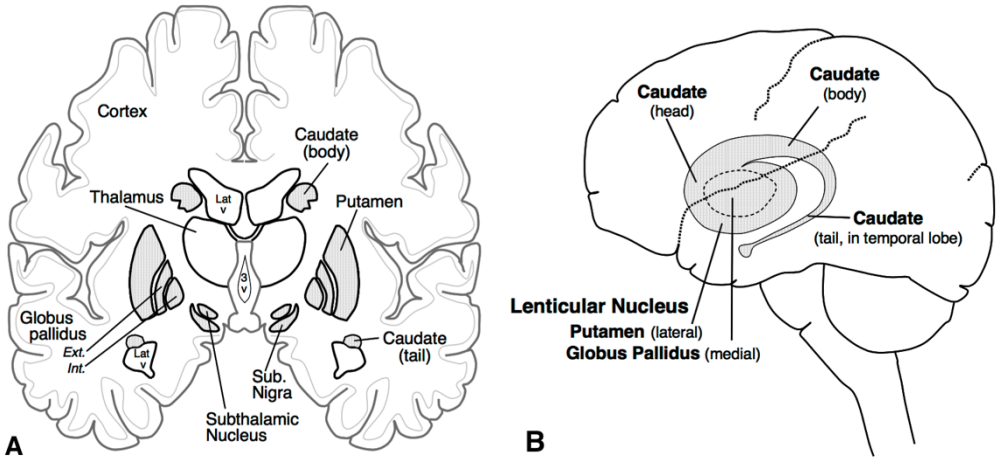

Figure 5: Nuclei of basal ganglia A) coronal section, top view, B) lateral view

(http://www.neuroanatomy.wisc.edu/coursebook/motor2.pdf)

Nucleus caudatusconsists of three parts: head (caput), body (corpus) and tail (cauda).Region situated ventrally from the head of nc. caudatus, referred to as *nucleus accumbens* (NAc), has a different microscopic structure than nucleus caudatus and it is predominantly composed of medium spiny neurons (MSNs). NAc along with the olfactory tubercle forms a ventral striatumwhich is a functional part of the limbic system (Dorko et al., 2014; Druga et al., 2014).

Putamen is an oval structure located laterally from the nucleus caudatus. These two structures are functionally and histologically related and together they form a neostriatum (striatum), which is refered also as dorsal striatum(Koukolík 2012). Huntington's chorea is caused by damage of the striatal cells (Dorko et al., 2014).

Globus pallidus (dorsal pallidum or paleostriatum) is phylogenetically the oldest part and is located medially from the putamen. In primates and humans, it consists of two parts, globus pallidus lateralis (external part; GPe) and globus pallidus medialis(internal part; GPi). Putamen together with globus pallidus form a lentil-shaped structure,nucleus. Damage ofthe globus pallidus aggravates motor activity and speech. (Dorko et al., 2014).

Amygdalais an almond-shaped body adjacent to the hippocampus. Morphologically and developmentally it belongs to the basal ganglia, but it is functionally part of the limbic system. Irritation of the amygdala causes a fury (Dorko et al., 2014).

Clastrum has the shape of a plate and lies between the capsulla externa and the capsulla interna of white matter. It has a rich axonal connection with the cerebral cortex (Dorko et al., 2014).

4.3.1 Direct and indirect pathways

The dopamine system plays an important role in coordinating movements. An important region for differential dopaminergic control of motor response is the dorsal striatum. Through dopamine D_1-like and D_2-like receptors, dopamine fine-tunes the balance between excitatory and inhibitory events, thereby controlling the intensity of motor activity (Robertson et al., 2015).

4.3.1.1 Direct pathway

The direct pathway is responsible for active movements. It is called direct because the striatal neurons transmit their axons directly into the globus pallidus internus (GPi). This path increases the excitatory effect of thalamus on the motor cortex (Swenson, 2006).

Thalamus is a structure that communicates with the motor cortex and through which it controls muscular movements. It is under the inhibitory effect of globus pallidus internus (GPi) and in cases of movement, this inhibition needs be alleviated. Cortico-striatal projections use glutamatergic pathways. Higher activity of the striatal neurons results in a greater outflow of the inhibitory neurotransmitter GABA and thus decreases GPi activity. This reduction in inhibition, *dis-inhibition*, results in greater thalamic, cortical motor and corticospinal tract activity, and ultimately movement(Swenson, 2006).The modulator of these events is dopamine, which has an excitatory effect via D_1 receptors (Robertson et al., 2015).

Production of dopamine in substantia nigra (SNc) is stimulated by subthalamic nuclei. Dopamine binds to dorsal striatal GABAergic neurons, resulting in increased GABA production and thus greater inhibition of GPi. SNc is able to reverse the subthalamic nuclei and thereby dampen its own activity(Swenson, 2006).

4.3.1.2 Indirect pathway

The Indirect pathway prevents unwanted movement. It is called Indirect because striatal projections lead first to the globus pallidus externa (GPe), then to the subthalamic nucleus and to the globus pallidus intern (GPi). The main task of this path is to reduce thalamus and motor cortex activity. Glutamatergic (excitation) moto-cortical projections innervate the

striatum and increase its activity. Higher inhibitory activity of GABAergic neurons in the striatum causes greater inhibition of GPe. Since GPe inhibits subthalamic nuclei by GABA release, reducing activity in GPe also reduces inhibition in subthalamic nuclei. Dis-inhibition of the nuclei results in increased activity of the subthalamic nuclei, i.e. greater production and secretion of glutamate, which acts excitably on GPi. Higher GPi activity means greater inhibition of thalamus and prevention of motion (Swenson, 2006).

Increased activity of the subthalamic nuclei also increases the production of dopamine in SNc. In this case, dopamine acts as an inhibitor modulator that binds to the D_2 receptor (Robertson et al., 2015) of glutamatergic neurons. These excitatory neurons enhance the activity of GPe inhibiting pathways. Binding of dopamine causes them to reduce their inhibition in GPe. This also causes higher activation of GPi and less thalamical activity. SNc is able to reverse the subthalamic nuclei and thereby dampen its own activity (Swenson, 2006).

Dopamine, hence binds both D_1 and D_2-type receptors, but the relative activation of either subtype depends on the intrasynaptic dopamine concentration and the respective affinities of the receptors for the neurotransmitter. D_2-type receptors, which have higher affinity than D_1-type receptors for dopamine, mediate tonic dopaminergic signaling (Robertson et al., 2015).

The functional counterpart of dopamine is a cholinergic system whose neurons (interneurons) inhibit striatal cells in the direct pathway, and vice versa, have striatum excitatory effects in the indirect pathway (Swenson, 2006).

4.4 Limbic system

In addition to motor activity, basal ganglia and their functionally linked nuclei have an important role in regulating emotional and motivational behavior (Swenson, 2006). Regions mediating these functions arereferred as a limbic system.

The Limbic system is the center of emotions, long-term memory, motivational behavior (Naňka and Elišková, 2015). It is not a structurally defined area, but instead, it represents functionally related nuclei from different regions.Part of the cerebral cortex (cingulate gyrus, parahippocampal gyrus and septal cortex) which belongs to this system is called the limbic cortex (Swenson, 2006) or limbic lobe. Other regions included within the limbic system are,

for example, the hippocampal formation, amygdala, ventral striatum, hypothalamus, septum pellucidum or mammillary body (Dorko et al., 2014)

Dopamine is likely to be a key neurotransmitter regulating function of the limbic system. As mentioned earlier, dopaminergic neurons projecttheir axons from VTA to ventral striatum creating a mesolimbic pathway. Neurons in mesolimbic pathway are connected with the thalamus which is linked to the cortex. The mechanism of dopamine action is similar to that which controls motor activity in direct and indirect pathways.Dopamine increases the activity of neurons in the ventral striatum which results in increased activity of the thalamus and cerebral cortex (Swenson, 2006).

An important role of the mesolimbic pathway is assumed to occur in substance dependence. Some substances, such as cocaine, cause addiction by affecting the action of dopamine transporters by blocking dopamine uptake. On the other hand, amphetamine (Jaworska et al., 2017), or methamphetamine act by stimulating release of dopamine from the nerve terminals (Riddle et al., 2006). Nicotine binds directly to the nicotine receptors of dopaminergic neurons and consequently increases the activity of mesolimbic neurons. Stimulation of opioid receptors inhibits the release of GABA, resulting in reduced inhibition of dopaminergic neurons of the VTA. It is likely that alcohol also acts in-part by modulating the VTA neuron activity (Davis et al., 2002). In addition to dopamine, alcohol addiction appears to be dependent on noradrenergic, serotonergic and opioid systems (Addolorat et al., 2005).

In addition to short-term effects (e.g., changes in neuronal activity, neurotransmitter release), the administration of addictive substances leads to long-term changes in gene expression and the synthesis of new proteins (Koob et al., 1998). It is perceived that such changes may be the basis for the development of a long-term pathological association memory, which seems to imply the compulsive use of substances. It is believed that these changes are also the basis for a delayed relapse characteristic of substance dependence (Davis et al., 2002).

5 Neuropathological diseases related to the dopaminergic system

Degeneration of the dopaminergic system is thought to play a major role in the development of e.g. Parkinson's disease Huntington's disease, Alzheimer's disease, Schizophrenia, Depression, Tourette's syndrome, but also substance dependence, ADHD or in eating disorders (compiled in Nieoullon, 2002; Bozzi and Borrelli, 2006).A common feature of these neuropathological diseases is insufficient production of dopamine, which is due to pathological loss of dopaminergic neurons in the midbrain. It is estimated that newborn human has approximately 400,000 dopamine-producing neurons in substantia nigra, while at the age of 60, it is only 250,000 on average, individuals with Parkinson's disease, have only about 60-120.000 at the same time period (Raz, 2001).

5.1 Alzheimer‘s disease

Alzheimer's disease (AD) is a neurological disorder characterized by cognitive and non-cognitive symptoms associated with atrophy of the brain (Nelson et al., 2012). Massive loss of neurons primarily affects hippocampus and cortex. Degrading memory of the patientsis a typical symptom is (D'Amelio and Rossini, 2012; Roy et al., 2016). In particular, there is a significant damage of cholinergic neurons, but research also shows the loss of dopaminergic neurons in substantia nigra (Palmer, 1993) and neurons producing noradrenaline in the locus coeruleus. With increased age higher activity of monoamine oxidase (MAO)has been observed. Therefore, in addition to decreasing the number of neuronal cells, it is assumed that the accelerated degradation of NE and 5-HT is also involved in AD (Roth and Růžička, 1998).

5.2 Parkinson‘s disease

Parkinson's disease (PD) belongs to severe neurodegenerative diseases. In patients, there is accelerated loss of dopaminergic cells is observed in substantia nigra (Steece-Collier et al., 2002). As a consequence of this loss, there is a deregulation of dopamine signaling in basal ganglia. Since basal ganglia are responsible for regulating motor function of the brain, deregulation causes typical symptoms:a resting tremor, bradykinesia and muscle stiffness (Hrabovská, 2014). Moreover, there are also degenerative changes in amygdala and the regions producing NE (locus coeruleus), 5-HT (raphe nuclei) (Lang and Lozano, 1998). Clinical symptoms are manifested gradually and usually only one part of the bodyis affected

on the beginning. Symptoms also include mental and emotional changes (fatigue, cognitive changes, depression, sleep disturbances), as well as problems with urination, bowel emptying or disturbances in the olfactory organs. (Hrabovská 2014). It has been shown that there is also a degeneration of the sympathetic terminals innervating heart, which may be the cause of autonomic dysregulation of the cardiovascular system (Goldstein et al., 2000, 2005).

The aim of the treatment is increasing the dopamine concentration in the presynaptic vesicles. A dopamine precursor (L-DOPA) is used which, unlike dopamine, passes through the blood-brain barrier. Dopamine agonists, i.e., release-enhancing agents and inhibitors of enzymes involved in dopamine degradation, are also administered. (Colcher, 2002).

5.3 Schizophrenia

Schizophrenia (SCZ) is a psychopathological disorder that affects the entire personality of the person (Kafka, 2003). Clinically, it is characterized by two main classes of symptoms, positive and negative. Positive symptoms are hallucinations, delusions and disorganized thinking and action. The negative symptoms include lack of volition, social isolation, or neglect of self-care and depression. In addition, cognitive functions are impaired (cognitive syndrome), e.g. work memory malfunction or disturbed speech fluency. (Pečeňák et al., 2005).

The primary cause was originally thought to be excessive dopaminergic activity (Abi-Dargham et al., 2000). However, it is probably a combination of hyperfunction in subcortical regions (mesolimbic pathway) leading to positive symptoms and hypofunction in the prefrontal cortex (mesocortical pathway) causing negative symptoms (Meyer-Lindenberg et al., 2002). There is evidence that deregulation of these dopaminergic pathways is caused by mutations in the dopamine D_2 receptor. In particular, the polymorphism rs1799732 (-141C Ins/Del) found in the promoter region is extensively investigated. An increased frequency of -141C Ins was observed in patients with Schizophrenia (Cordiero et al., 2009; Arinami et al., 1997).

In addition to decreasingthe number of dopaminergic neurons, there is probably an increased rate of dopamine metabolism. In the center of interest stands enzyme COMT. After dopamine in the prefrontal cortex (PFC) diffuses from the synaptic cleft to the extracellular space, it is metabolized by COMPT. It has been suggested that mutations in its gene is responsible for highest speed of dopamine degradation (Akil et al., 2003; Perlman et al., 2004). To date,

however, a multifactorial model of etiopathogenesisof Schizophrenia has been getting the most attention. Complex interactions between different neurotransmitter systems (Goff and Coyle, 2001; Laruelle et al., 2003; Tsai and Coyle, 2002; Wong and Van Tol, 2003) and the possible disruption of formation of neuron connections during ontogenesis are evaluated. The observed abnormalities could thus only be the secondary consequence of CNS developmental disorders (Carlsson et al., 2001; Sawa and Snyder, 2002; Freedman, 2003).

6 Models of personality

6.1 Eysenck‘s model of personality (*Big Three* model)

One of the founders of biologically-based psychology is a German psychologist, Hans-Jürgen Eysenck. He was convinced that differences in human behavior are conditioned by individual differences in certain brain areas, which he characterized as excitatory and inhibitory systems (compiled in Montag et al., 2012). Eysenck created a tridimensional model of human personality: *extraversion-introversion*, *neuroticism-stability* and *psychoticism-sociability* (compiled in Zuckerman, 1979).He characterized extraversion as a trait typical for a communicative nature, while introversion as a label for individuals who prefer quiet and are not particularly social. Neuroticism described as a trait of individuals who are emotionally unstable, shy or anxious and its counterpart *stability*, for individuals socially detached, independent, not empatheticwith minimal mood swings who, in general prefer a fixed routine. Psychotism-sociability, he saw as a trait associated with aggression (compiled in Montag et al., 2012).For clinical evaluation of these dimensions, he created a self-report Eysenck's personality questionnaire (EPQ) (compiled in Cloninger, 1986)

6.2 Gray‘s model of personality

Jeffrey Gray, inspired by Eysenck's ideas (Zuckerman, 1979), formulated the well-known *Reinforcement Sensitivity Theory*, where he tries to elucidate different human behaviorsthrough differences in brain pathways. Graycharacterized two major systems that he considered to be responsible for two types of behavior: *approach* and *avoidance behavior*(compiled in Montag et al., 2012). The first system, the *Behavioral Activation System* (BAS) is activated by new stimuli (compiled in Zuckerman, 1979) and initiates approach behavior, such as discovery of environment. The second system, the *Behavioral Inhibition System* (BIS) is responsible for avoidance behavior (anxious), which is triggered in new, potentially dangerous situations. It reduces the exploratory activity in order to "control of the situation". If the danger is confirmed, the third system, which Gray later identified as a *Fight FlightFreezingSystem* (FFFS) is activated. The BIS, BASsystems are interconnected through their ability to contain one another, so one inhibits the other and vice versa. He hypothesized BIS and FFFS to be associated with hippocampus and amygdala, and BAS with the brain stem with projections into the limbic system. To measure individual differences in these systems, the BIS/BAS scale is used (compiled in Montag et al., 2012).

6.3 Zuckerman's model of personality

Zuckerman (1986), assumed that character features have a biological-evolutionary basis. He was convinced that there are certain fundamental factors that couldbe able to characterize the human personality. He was inspired by older model, the Five Factor Model (FFM or Big Five), which describes the personality of a person through five factors: *openness, conscientiousness, extraversion, agreeableness* and *neuroticism* (John and Srivastava, 1999). Zuckerman, however, disagreed with the conception of its categories, which, in his opinion, did not represent the basic factors. He formulated criteriabased on which he identified five temperaments: *impulsive sensation seeking (impSS), neuroticism-anxiety (N-Anx), aggression-hostility (Agg-Host), sociability (Sy)* and *activity (Act)* and created *Alternative Five Model*(Zuckerman, 2002).

The Zuckerman-Kuhlman Personality Questionnaire (ZKA-PQ), consisting of 100 items was created, trying to encompass all five characters(Zuckerman, 2002).

Sensation seeking

Generally, organisms have a natural tendency to be curious and Zuckerman observed that some seek out new stimulants more than the others. Moreover, in humans, it may manifest into a pathological behavior. Since he believes that human personality traits have a biological basis, he proposed catecholamine activity as a common biological background (Zuckerman, 1979). Based on data, Zuckerman characterized sensation seeking as trait which is*"in some part a function of the levels of the catecholamine norepinephrine and dopamine in the reward areas of the limbic system, as well as the neuroregulators that control their availability at the synapse within these neural systems"* (Zuckerman, 1979, p. 372).

In other words, high levels of dopamine would be responsible for high tendency towards exploration of new situations or environments and a high level of norepinephrine would reinforce the paths formed by positive stimuli. He also suggested that serotonin may function as a counterpart and also as a suppressor (Zuckerman, 1979). He notes that serotonin might be high in low sensation seekers and vice versa, low levels of serotonin are likely to be associated with impulsive behavior and aggression (Zuckerman, 1995).

6.4 Cloninger's model of personality

Cloninger (1986), proposed the *Unified Biosocial Theory of Personality*, which deals with the biological aspects of psychology and their heritability. He hypothesized that the personality is created by *"temperaments"* (Cloninger, 1986) and *"characters"* (compiled in Cloninger, 2003). He suggested that temperamentsthat developed in early age, are associated with evolutionary older parts of the brain and have a higher degree of heredity. On the other hand, character traitsare seen as largely influenced by the environment and develop in later adolescence (compiled in Montag et al., 2012). Based on genetic, neurological, pharmacological and psychological data, he created a personality model that originally included three dimensions of personality (temperaments): novelty seeking, harm avoidance (HA), and reward dependence (RD) (tab. 2) and characterized them as follows(Cloninger 1987a, pp 574-575):

Novelty seeking (NS) as *"a heritable tendency toward intense exhilaration or excitement in response to novel stimuli or cues for potential rewards or potential relief of punishment, which leads to frequent exploratory activity in pursuit of potential rewards as well as active avoidance of monotony and potential punishment".*

Harm avoidance (HA) as *"a heritable tendency to respond intensely to signals of aversive stimuli, thereby learning to inhibit behavior to avoid punishment, novelty and frustrative non-reward".*

Reward dependence (RD) as *"a heritable tendency to respond intensely to signals of reward and maintain or resist extinction of behavior that has previously been associated with rewards or relief from punishment".*

Brain System (Related Personality Dimension)	Principal Monoamine Neuromodulator	Relevant Stimuli	Behavioral Response
Behavioral activation (novelty seeking)	Dopamine	Novelty	Exploratory pursuit
		Potential reward	Appetitive approach
		Potential relief of monotony or punishment	Active avoidance, escape
Behavioral inhibition (harm avoidance)	Serotonin	Conditioned signals for punishment, novelty or frustrate non reward	Passive avoidance, extinction
Behavioral maintenance (reward dependence)	Norepinephrine	Conditioned signals foreword or relief of punishment	Resistance to extinction

Table 2: Original Tridimensional model: three major brain systems influencing stimulus-response characteristic according to Cloninger (1987a, p. 575).

In his theory, Cloninger suggests that individual dimensions are controlled by monoamine systems, which are genetically independent but interact with each other.He sees a novelty seeking temperament as a natural motivation, because individuals with high score in NS are often very active, exploratory, and intensely interested in everything new. Inspired by Gray's BAS/BIS concept, Cloninger considers novelty seeking (NS) as a part of the behavioral activation system BAS) and hypothesized dopamine as the leading neurotransmitter controlling this dimension (Cloninger, 1986).

Furthuremore, Cloninger hypothesize that behavioral inhibition system (BIS), which is likely to include limbic system and prefrontal cortex (PFC) is under the control of serotonin (5-HT).Serotonergic neurons project axons from the raphe nucleus in the brain stem to the substantia nigra in the midbrain (cit). In the case of punishment or non-reward, the activity of the serotonergic system inhibits nigrostriatal neurons. This inhibition reduces dopamine production and release in the striatum. The result is, for example a reduction in exploratory activity. The activity of this system can be observed by measuring levels of serotonin metabolite, *5-hydroxyindoleacetic acid* (5-HIAA) in cerebrospinal fluid (compiled in Cloninger, 1986; 1987b). In addition, punishment increases the level of stress hormones by activating the hypothalamic-pituitary-adrenal (HPA) axis (Takada and Curzon, 1995).

Individuals with a high score in the harm avoidance (HA)dimension, can easily create evasive responses to aversive stimuli, they are fearful, worried, and apprehensive. In extreme cases, these individuals can develop chronic anxiety. Individuals with low predisposition to HA have a weak ability of avoidance learning. Therefore, they are often carefree, socially attached and open to risky activities (Cloninger, 1986).

The third dimension, reward dependence(RD), reflects the relationship to conditional learning. It was found that individuals with high score in RD, has better developed the ability of conditional learning, if it is conditioned by reward or non-punishment. It seems that this system, also called *Behavioral Maintenance System* (BMS) is independent of the previous two dimensions (Cloninger, 1986).The main modulator of BMS is probably norepinephrine (NE), which has a role in learning and remembering new paired associations (42). Neurons producing this neurotransmitterproject their axons from the locus coeruleus (dorsal noradrenergic bundle) in pons Varoli to the hypothalamus, limbic system (amygdala, septum, hippocampus) and to the entire neocortex (Schatzberg and Nemeroff, 2004). However, more than 90% of cortical axons do not form synapses, but instead, they secrete NE into the

surrounding neuropilus, where is involved in maintaining a certain tonus of neuronal activity. After a stimulus, NE does both, inhibits spontaneous firing in the target neurons and at the same time it increases the response in other neurons. This is likely to increase the signal: noise ratio and thus to "pick up" an important stimulus from the background. The low basal activity of the noradrenergic system means a higher sensitivity to NE and is likely to be responsible for persisting in reward seeking behavior, even if the reward is not obtained(frustrative non-reward). This hypothesis is supported by the finding that lesions in locus coeruleus cause a defect in learning new associations and terminating old ones. Conversely, a lower sensitivity to NE due to high basal activity results in a faster quit activity when is no longer satisfying (compiled in Cloninger, 1986; Cloninger 1987b).

Individuals with high scores in RD are mostly sentimental, wishful thinkers with a need for social ties. It shows from Cloniger's practice that these types of individuals are very responsive to rewards, in the form of food, attention, well-being, power or fame. In extreme cases, addiction can be developed. Remission of rewards may even cause disruption or anxiety. Conversely, people who are not dependenton reward are practical, analytical andare socially detached (Cloninger, 1986).

Althoughbehavioral systems are genetically independent (Cloninger, 1987b), they interact with each another (Stallings et al., 1996). The activation system controlled by dopamine supports initiation of conditioned response to reward (positive reinforcement) and response to non-punishment (negative reinforcement). Noradrenergic pathways in the maintenance system are likely to support these initiative responses and allow the termination of the previous association (Cloninger, 1986; Zuckerman, 1995). Both systems are under the inhibitory influence of serotonergic pathways, e.g. the risk of punishment or omission of expected reward reduce both, DA and NE system activity (Cloninger, 1986; Stallings et al., 1996).

For the clinical measurement of these dimensions,Cloninger developed a *Tridimensional Personality Questionnaire* (TPQ), consisting of 100 self-report questions (Cloninger, 1987c). Based on observations, he later separated the fourth dimension*Persistence* (PS), which was originally included in the category Reward dependence. He concluded that PS is genetically independent and therefore has to be defined as an individual category. Later,Cloningerincluded three characters:*self-directedness* (SD), *cooperativeness* (CO) and

self-transcendence (ST) (compiled in Gillespie et al., 2003). The tool developed to measure all seven personality dimensions is known as a*Temperament and Character Inventory* (TCI) and its newer version as *Temperament and Character Inventory-Revised* (TCI-R) (compiled in Zuckerman and Cloninger, 1996) (tab. 3). Both versions of TCI and TPQ are important and widely used self-reporting psychological tests (Montag et al., 2012).

Scales and sub scales of TCI	
Novelty seeking (NS)	Exploratory and excitability (NS1), Impulsiveness (NS2), Extravagance (NS3), Disorderliness (NS4)
Harm avoidance (HA)	Anticipatory worry (HA1), Fear of uncertainty (HA2), Shyness (HA3), Fatigability (HA4)
Reward dependence (RD)	Sentimentality (RD1), Openness to warm communication (RD2), Attachment (RD3), Dependence (RD4)
Persistence (PS)	Eagerness of effort (PS1), Work hardened (PS2), Ambitious (PS3), Perfectionist (PS4)
Self-directedness (SD) (reliable, purposeful)	Responsibility (SD1), Purposeful (SD2), Resourcefulness (SD3), Self-acceptance (SD4), Enlightened second nature (SD5)
Cooperativeness (C) (tolerant, helpful)	Social acceptance (C1), Empathy (C2), Helpfulness (C3), Compassion (C4), Pure hearted conscience (C5)
Self-transcendence (ST) (self-forgetful, spiritual)	Self-forgetful (ST1), Transpersonal identification (ST2), Spiritual acceptance (ST3)

Table 3: Three characters andfour temperaments with subscales, edited according to Svrakic and Cloninger (2010).

6.5 Sensation seeking vs novelty seeking

To date, the tests mostly used for psychological analyses are Cloninger's TCI-R or Zuckerman's ZKA-PQ respectively, which have been reported to give similar results (García et al., 2012).Both authors, Zuckerman and Cloninger, defined a basic temperament, sensation seeking (SS) and novelty seeking (NS), which is typical for very active individuals, who are seeking out new, or potentially dangerous activities. Although the definition of SS and NS is not identical, correlation between them is very high(Zuckerman and Cloninger, 1996).

Zuckerman (1979, p. 27) characterizes a sensation seeking as a *"trait defined by need for varied, novel, and complex sensations and experiences and willingness to take physical and social risks for the sake of such experience"*.

Novelty seeking is characterized as a *"heritable tendency towards frequent exploratory activity and intense excitement in response strongly to novel stimuli"* (Cloninger, 1986, p. 167).

These activities can be related to gambling or extreme sports such as parachuting or scuba diving. Individuals trying new drugs, including marihuana and nicotine tend to be high in sensation seeking. Sensation/novelty seekers also have more liberal attitudes toward sexuality and they seem to have a high tolerance to the pain. Extreme forms of this trait are sociopathy, or manic-depressive psychosis in its manic phase. On the opposite side of sensation/novelty seeking scale stands social anxiety, neuroticism or chronic phobia and even obsessive-compulsivenessas an extreme case. Also individuals with Schizophrenia show low scores in sensation seeking (Zuckerman, 1979).

.

7 Factors affecting novelty/sensation seeking

There are many studies trying to find the source of differences between human personalities such as novelty/sensation seeking, but results are very inconsistent. There are several reasons for these discrepancies:

1) *Polymorphisms in different dopamine receptorsgenes*

Dopamine receptor genes, mostly studied in relation to novelty seeking are dopamine receptor D_3 and D_4.

Dopamine D_3 receptor contains polymorphisms that are thought to be related to changes in personality traits. In this context, rs6280 is the most frequently studied polymorphism. This is a point missense mutation resulting in a change of serine to glycine (Ser9Gly) (CIT). However, a survey in the Swedish population does not indicate the relationship between rs6280 and novelty seeking, but does not exclude its effect on psychiatric diagnoses (Jönsson et al., 2003). The Gly/Gly genotype is likely to have an impact on the development of obsessive-compulsive personality disorder (OCPD), since this genotype occured 2.4x higher in individuals with this diagnosis (Light et al., 2006). No association between ImpSS (ZKPQ) and rs6280 was found in a group of athletes, but a significant association occurred with another polymorphism, rs167771 (A/G). Individuals with genotype A/A reached the highest score in ImpSS, while those with genotype G/G reached the lowest (Thomson et al., 2013).

The D_4 dopamine receptor is extensively investigated in relation to various personality changes or behavioral disorders (Schoots and Van Tol, 2003). In the center of interest stands VNTR polymorphism in exon 3, which encodes the third ICL. This 48 bp long section repeats 2-10x (Hubert, 1993); later sources report up to 11x (cit.). It was found that the length of the repeats probably has an effect on the expression of the gene (Schools and Van Tol, 2003). There are several approaches to investigating the impact of this polymorphism. Some studies compare the effect of short (2-5R) and long (6-11R) variants. Sander et al. (1997) noted the increasing trend of long alleles in the anabolic subset of alcoholics. After evaluating the TPQ test (NS, HA and RD) he found that long-time alcoholics had higher scores in reward dependence. Ono et al. (1997) used the Japanese version of TCI and found a significant association between long alleles and the Novelty Seeking subscale of exploratory, excitability (NS1). Family studies have shown that NS (TPQ) was manifested in siblings with a long allele, indicating the heredity of this temperament (Benjamin et al., 2000). Other work

narrowed the allele selection and focusedonly on the relation betweenalleles 4R and 7R, respectivelyand NS. In the 7R allele, higher scores were observed not only for the whole category of novelty seeking but also for exploratory, excitability (NS1) and extravagance (NS2) subgroups. This trend was also found in other German versions of the TPQ test (Strobel et al., 1999). Some studies focused on impact of the presence or absence of the 7R allele itself, respectively (Gelernter et al., 1997). Bordy et al. (2006) suggests that 7R has a lower ability to inhibit cAMP production. Presenceof 7R was also significantly associated with novelty seeking (Ebstein et al., 1996; Hesterberg and Brayn, 2011).

In the context of NS, another SNP was examined in the promoter region, in particular -521C/T. Very significant association was found between this polymorphism and the novelty seeking. Individuals with C/C genotype achieved a higher score than the those with T/T genotype. By the transient expression method, the T allele has been shown to reduce the frequency of expression of the receptor (Okuyama et al., 2000). The study among Hungarian students showed a significant association between a high NS score and a C/C genotype. This correlation was more evident in women. Allele T had up to 49% lower expression than the C allele (Ronai et al., 2001). On the other hand, there are studies, which didn't find any correlations between DRD_4 polymorphism and personality differences. No significant effect of T allele on transcriptional activity was observed by Kereszturi et al. (2006). Any significant distribution differences were observed between C/T and T/T alleles and any of personality traits (Bookman et al., 2002). Although meta-analysis doneby Munafo et al. (2008) found a significant relationship between -521C/T polymorphismNS and ImpSS, association between personality traits and 48 bp VNTRpolymorphism was not observed.

Thomson et al., (2014) was studyingdifferent polymorphisms in the DRD_4 promoter (-1106T/C, -906T/C, -809G/A, -291C/T, 120bp duplication) and monitoring their association with impulsive sensation seeking (ImpSS). As an experimental group, 599 skiers and snowboarders, were selected to complete the ZKPQ questionnaire and then to undergo sampling for DNA analysis. The association between individual alleles and the ImpSS was not found.The study of polymorphisms in DRD_3 and DRD_4 found no association with novelty seeking or other temperament traits on the Temperament and Character Inventory (Joyce et al., 2003).

2) *Decreased dopamine degradation*

Dopamine degradation provides two enzymes: catechol-O-methyltransferase and monoamine oxidase.

Catechol-O-methyltransferase (COMT) is Mg^{2+}-dependent enzyme, which catalyzes the degradation of all catecholamines (dopamine, norepinephrine and epinephrine)(compiled in Meiser et al., 2013). It is the main dopamine regulator in the frontal cortex, because DAT is very restricted in these areas (Trudell and Izenwasser, 2008). There are two isoformsin mammals: soluble form (S-COMT) and membrane form (M-COMT)(compiled in Meiser et al., 2013). S-COMT is present mainly in periphery organs, such as liver, adrenal gland and kidney and M-COMT is more abundant in neurons. The gene is located on a long arm of chromosome 22 and consists of 6 exons, the first two non-coding (Tenhunen et al., 1994). Point mutation (G472A), discovered in exon 3, is considered to have an important role in human personality (Kotyuk et al., 2015).This substitution results in an amino acid exchange in the 158thcodon in M-COMT and in 108th codon in S-COMT, in particular valine for methionine (Val158/108Met). Minor Met allele (45%) causes up to 40% lower enzyme activity at body temperature. Mutated protein is less stable due to less hydrophilic character of methionine compared to valine (Chen et al., 2004).An association of Met allele with substance dependence, in particular heroin addiction in Hispanic women, has been discovered (Oosterhuis, et al., 2008). Demetrovics et al. (2010) compared distribution of Val and Met alleles in heroine abusers and control group in Hungarian population. He didn't find significant difference, but within these groups, Met/Met homozygotes reached higher NS score than Val/Met heterozygotes and Val/Val homozygotes. Val158Met polymorphism might have an influence on prefrontal cortex activity. Interestingly, individuals with Met/Met genotype showed better performance in Wisconsin Card Sorting Test (Malhotra et al., 2002; Nkam et al., 2017).

Patients with Schizophrenia who carried Met/Met genotype tended to be more aggressive and dangerous than Val/Val homozygotes (Strous et al., 1997a). However, the polymorphism itself does not seem to increased risk of developing the disease (Strous et al., 1997b).

Monoamine oxidase (MAO) is an enzyme containing flavin adenine dinucleotide (FAD) as cofactor. It catalyzes the oxidative deamination of monoamines (dopamine, norepinephrine, epinephrine, serotonin) to aldehydes. It is located on the outer mitochondrial membrane in almost all the cells of the body. It exists in two forms, MAO-A and MAO-B, which differ in their substrate specificity. The genes encoding MAO-A and MAO-B are located on a short

arm of chromosome X. Each of these consists of 15 exons and according to an identical intron-exon organization is thought to have been generated by duplication from the common gene (Grimsby et al., 1991).

MAO-A is predominantly found in the liver, gastrointestinal tract, pulmonary vascular endothelium and placenta, while MAO-B dominates in platelets (Tong et al., 2013). Both forms are found in the brain where MAO-A predominates in neurons, and MAO-B, was detected in astroglia and serotonergic neurons and also extracellularly (Tripton et al., 1984). Cell and tissue specific expression is due to their different organization in the promoter (Zhu et al., 1992; 1994).

Studies in mice showed that those who carried the pre-term termination codon in the MAOA gene (null allele) had higher levels of NE, 5-HT, and DA, and showed greater aggression than the control group (Shih and Thomson, 1999). In the promoter region of the human MAOA gene, polymorphism of the VNTR type, a 30 bp segment, which is likely to have an effect on the frequency of expression, has been discovered. It has been suggested that low frequency of expression is associated with aggressive behavior in humans as well.The study among more than 2.5 thousand participants compared the effect of the number of repeats (2-4x) of 30 bp on the frequency of expression and possible association with behavior. It was found that both men and women who reported more frequent criminal activity at the early adolescent age had 2R allele. Analyzes have shown that 2R allele has a lower expression rate than 3R and 4R (Guo et al., 2008). Alia-Klien et al. (2008) supported the claim that reduced MAOA expression was associated with higher aggression, but found that violent behavior was more common in those subjects who were exposed to external stressful conditions in early childhood. On the other hand, a twin study, which looked at the link between sexual harassment, drug use and antisocial behavior, did not find a correlation with MAOA polymorphism (Derringer et al., 2010b). The association was not found either with mood disorders or with a tendency to suicide, but there was a connection with high impulsivity in men (Huang et al., 2004). On the other hand, long alleles (3aR, 4R and 5R) were found to occur more frequently in women with panic disorder (Deckert et al., 1999).

3) *Reduced DA transport back to the presynaptic neuron*

Dopamine transport back into the presynaptic neuron is provided by the dopamine transporter (DAT). DAT is a highly conserved transmembrane protein. It is found on the cell bodies and dendrites of presynaptic dopaminergic neurons in the midbrain (SNc, VTA) and axons and

terminals in basal ganglia in the forebrain (caudatus, putamen and nc. accumbens) (Trudell and Izenwasser, 2008). DAT is a symporter, so dopaminetransmission from the synaptic cleft back into the neuron, it coupled with the energetically favorable Na^+/Cl^- symport (Schatzberg and Nemeroff, 2004). It is encoded by the DAT1 gene located on the short arm of chromosome 5 and consists of 15 exons. Repeat polymorphisms, that are probably related to changes in dopamine signalinghave been identified (Trudell and Izenwasser, 2008). The 40 bp variable number tandem repeat (VNTR) was found in 3'UTR. This section can be repeated from 3 to 13 times. The most frequent are alleles with 9 and 10 repeats (Vandenbergh et al., 1993). Some studies indicate that the number of repeats does not affect the frequency of DAT expression (Lafuente et al., 2007). However, recent analysisshowed that the 9R allele (R= repeat) has up to 50% lower expression rate than the 10R allele, and is responsible for a lower DAT density (VanNess et al., 2005). In addition, individuals with 9R allele, both homozygous and heterozygous, appear to be more sensitive in the subjective assessment of the effects of psychotropic substances (Dreher et al., 2009), in particular cocaine (Brewer et al., 2015). However, no association between these alleles and novelty seeking behavior was found (Sullivan et al., 1997).

Other, 30bp VNTR was discovered in intron 8. Two common alleles are considered to play an important role in cocaine dependence. In vitro, allele 2, which contains 5 repeats, showed higher expression frequency than allele 3 with 6 repeats. Positive association with allele 3 and cocaine abuse was observed (Guindalini et al., 2006).

DAT is the target of psychotic drugs that interact and block its function. Chronic cocaine use increases the density of DAT, which may bethe response in order to equalizethe increased number of DA molecules in the synaptic cleft (Song et al., 2012). Up-regulated DA re-uptake is the reason why greater doses of cocaine are needed to produce the same effect. If an individual does not receive the necessary dose, dopamine levels in the synapse drop rapidly (Trudell and Izenwasser, 2008). Low dopamine levels cause anhedonia, the inability to feel joy, but instead, individuals loses motivation, feels depressed and hopeless (Ayd, 1995, p. 42). To avoid these consequences, drug abusers repeat the self-administration (Nader et al., 2005). On the other hand, studies on monkeys showed that methamphetamine (MA) reduces the density of DAT and thus increases DA levels, but doesn't affect the DRD_2 availability (Groman et al., 2012). Chronic MA administration has also significant negative association with gray-matter volume, which might be the result of increased intrasynaptic dopamine level and its neurotoxic effect (Morales et al., 2015).

4) Single gene polymorphism has no significant impact

Since investigation of individual genes gives inconsistent results, researchers starteded to focusing on dopamine-related genes as one unit. These, so called "dopamine genes", represent the group of genes involved in the dopamine signaling pathway.

It was found that smokers who had a certain combination of DAT and COMT alleles had low resting dopamine levels in the tonic levels. Nicotine induced a higher DA (phasic levels) excursion than in individuals with another combination (Brody et al., 2006).

The meta-analysis of studies that followed the link between the different SNPs in dopamine-related genes and SS scales suggests that rather than individual SNPs, it is the effect of multiple markers that are together capable of affecting SS. Derringer et al. (2010a) therefore proposes a model of aggregating multiple SNPs across the genes within a single system.

Based on data from the study of five dopamine-related genes: DAT1 (9/10R), DRD_4 (7R), DRD_2 (-141C ins/del), DRD_2 Taq1A (C/T) and COMT (Val158Met) it has been suggested that single alleles are not able to induce a significant deviation in DA signaling and thus affect reward-related responses in the ventral striatum. The only exception was the DRD_2 allele (-141C ins/del), but the effect was marginally significant without threshold correction p '= 0.05. Alleles are therefore likely to have a cumulative effect. Individual genetic profile score might be a solution(Nikolova et al., 2011). Mapping individual differences in brain functions might be the way how to get better picture of personality traits and their biological background.

5) Different personality questionnaires

Both individual studies and complex meta-analysis, do not show unambiguous conclusions. Conflicting findings may arise from the problem of phenotype definition (Joyce et al., 2003; Savitz and Ramesar, 2004). Some personality models define different personality dimensions with same names or they have different characteristics for the same dimensions. Moreover, scales consist of different number of basic categories. For instance, Eysenck created three dimensional, later four dimensional models (Zuckerman et al., 1996), Zuckerman's model consists of five dimensions as well as Big Five and Cloninger's originally three dimensional model was later revised into seven dimensional model. But there are also some other scales used for research, e.g. Karolinska Scales of Personality (KSP), with six basic and nine additional factors (Ortet et al., 2002), which was originally created for measuring psychiatric disorders or Swedish universities Scales of Personality (SSP) which represents its revised

version (Gustavsson et al., 2000).

Another issue is the fact that personality inventories consist of self-reported items and therefore there is high probability of inconsistent results. For instance, alcoholism can affect how the individual person evaluates him/herself (Sullivan et al., 1998).

6) *Different age, sex and ethnicity group composition of tested groups:*

Age

Zuckerman (1979) observed different tendencies towards sensation seeking based on age and sex. Lusher et al. (2001) also suggested that the inconsistency of the age of volunteers may be another reason for different data.PET analysis shown that the availability of D_2 receptors, but not D3 in the striatum decreases with age (Nakajima et al., 2015). Similarly, the tendency towards sensation seeking (Steinberg et al., 2008), novelty seeking and reward dependence (Cloninger, 1986) declines with age. Cloninger (1987a) suggestedthat the experience gained during life might be an important environmental factor.

Higher MAO-B activity, but not MAO-A with increasing age was observed. This phenomenon is known in the case of Alzheimer's disease (Tripton et al., 1984). The density of the DAT decreases with age as well, which was also observed in patients with Parkinson's disease (Trudell and Izenwasser, 2008).

Gender

Twin comparison methods revealed an associationof sensation seeking with a gender. Experiments on animals revealed that both sex hormones, androgens and estrogens suppress activity of MAO enzyme. Estrogens are considered to have stronger reducing effect. Moreover, this interaction is likely to be dependent on the menstrual cycle. Although human studies didn't find this relation yet, receptors for sexual hormones were found also brain regions involved in reward (compiled in Zuckerman, 1979). However, anenvironmental impact was also observed. While in women the correlations between temperaments seemed to be more hereditary, in men the environmentseems to play animportant role. But the influence of the environment was significant in both sexes (Stallings et al., 1996).Significantscore differences in genders were observed by Gillespie et al. (2003). Women achieved lower scores in harm avoidance, reward dependence, novelty seeking and cooperativeness than men. However, their scores were higher in self-directedness.

Ethnicity

Lusher et al. (2001) suggested that different ethnicity may be involved in different outcomes. Based ondata from 27 studies, Lee et al. (2014) concluded that some polymorphisms related to the personality traits are associated with sex and ethnicity, namely COMT (Val158Met) polymorphism in a relation to anxiety. Although, some authors didn't confirm the impact of ethnic origin on personality trait differences (Malhotra et al., 2002), the culture of the society and education seems to play an important role (Derringer et al., 2008). Similarly, in traditional cultures, sex and age roles might be the cause of inconsistent results (McCrae and Terracciano, 2005).

7) Environmental impact

Twin studies revealed high inheritance of personality features (Cloninger, 2003). Identical twins showed significantly higher correlation in NS score, than siblings with different genotypes in DR_4, COMT and 5-HTT (Benjamin et al., 2000).

However, the effect of epigenetic mechanisms must be taken into account. Analysis of 40 genes in dopamine pathway showed different methylation pattern in 19 genes after chronic administration of olanzapine (Melka et al., 2013).Low expression of DRD_2 mRNA is likely to be associated with methylation of lysine 9 on the histone 3 in the promoter region. Interestingly, the significant positive correlation between the binding ratio of H3K9me3 at DRD_2promoter and the propensity to cocaine relapsein ratswas observed (Flagel et al., 2016).

Derringer et al. (2008), assumes that the genetic component has a larger impact in higher aged individuals and is more pronounced in men. Research on twins at the age of 14-17, studied the relationship between the use of different addictive substances and age, showed that the spectrum of used drugs was wider in older adolescents. She considers that preventive measures, such as education or parents influence are more effective in early puberty. The early onset of substance use may be the sign of the genetic predisposition (Harden et al., 2012), which will stabilize in the future. Reward-dependent processes are likely to be involved in creating this stability (Li et al., 2011).However, some authors reported, according to the EPQ-R scale, that the greater tendency to substance dependence was observed in the temperaments Negativity and Anxiousness than in Impulsiveness. External factors such as substance availability, sanctions, attitudes or expectations also influence the development of these tendencies (Davis and Loxton, 2013).

8 Novelty seeking behavior and DRD_2

Novelty seeking (NS) is a temperament that initiates activity towards new, unknown stimuli and potentially leads to reward. Individuals with a higher NS score than average are impulsive, exploratory, fickle, disorderly, and extravagant. They are very easy to engage in new, exciting activities, without first getting any complete details. Additionally, they quickly get bored and lose interest in activities and can be easily provoked. By contrast, individuals with a lower NS score than average need more time to decide whether to engage in new activities. They are focused on details and require a system. They are perceived as loyal, orderly and persistent. Novelty seeking is probably the result of a behavioral activation system that includes dopaminergic pathways. Its disturbance or other changes may lead to suppression of this behavior, but also to its hyperactivity (Cloninger, 1987a).

8.1 DRD_2 availability in the brain

The dopaminergic system is likely to be responsible for risky-decision making or seeking out new, risky experiences(Weiland et al.,2014) The basic premise is the higher activity of this system. It has been suggested that low basal activity of dopaminergic neurons causes a more responsive postsynaptic dopamine response, whereas high activity, in turn, is associated with "dulling" and therefore the individual is permanently searching for new activities (compiled in Cloninger 1987b).

Higher basal as well as stimulated extracellular dopamine levels in nc. accumbens (NAc) in subjects with a high NS score in compareto the low novelty responders were observed by Bradberry et al. (1991). A certain correlation between the "extravagance" (NS3) and synthesis capacity of DA in ventral striatum was found by PET. Men with a tendency towards financial irresponsibility or gambling had relatively higher capacities. Changes in the synthesis were not observedin dorsal striatum (Lawrence et al., 2014).

The relationship of risky financial activities and NS was also examined in studies of pathological gambling. During a test associated with this (IGT, Iowa Gambling Task), there was a high level of excitement that significantly correlated to dopamine release. Dopamine release was higher in pathological players than in the control group (Peterson et al., 2010; Linnet et al., 2010; Linnet et al., 2011). Increased activity of mesolimbic pathways seems to be related with the vision of immediate reward despite the risk of long-term loss (Linnet et al., 2010). The association of gambling and sensation seeking also appeared in the

majorpopulation, but did not represent a pathology. Differences occurred amongst the sexes, men reached higher scores than women. However, that tendency toward SS declines in the rising age of both genders. There was no association with SS in common sports which did not represent a high level of risk. The men had a surprisingly lower score in impulsive sensation seeking (ImpSS) than the control group. This has led to the conclusion that this factor is not significant in ordinary sports. But if they were potentially risky activities like climbing, sky diving, scuba diving, these individuals had a high SS score. Overall, athletes showed high results in "activity" and low in "neuroticism" in comparison to the control group. These results showed lower level of fear, because physical injury is a risk in sports generally (Zuckerman, 2002). However, Wilkinson et al. (2013) found a positive significant relationship also between less risky physical activities, dopamine system, and higher SS rating.

One of the factors of more intensive dopamine action can be reduced availability of dopamine D_2 receptors. This hypothesisis indirectly supported by the finding that the high binding potential of auto-receptors (D_{2S}) in the midbrain (SNc and VTA) significantly correlates with a low NS score (Zald et al., 2008). Analysis of the binding potential of D_{2L} and D_3 receptors by PET in the striatum also confirmed the association between NS score and occupancy of the receptors (Huang et al., 2010; Linnet et al., 2011). Negative relationship between lower striatal D_2/D_3 receptor availability and impulsiveness in methamphetamine users was observed (Lee et al., 2009).

8.2 Polymorphisms of DRD_2

Several polymorphisms that appear to have a significant effect on the expression of D_2 receptor mRNA have been discovered (annex I; tab. 4). The promoter region contains a silencer domain where a substitution transition was identified 844 bp upstream from the start codon (T-844C). There is an evidence that the minor allele (C) significantly increases the activity of the promoter even in a heterozygous state (Zhang et al., 2007).

Another polymorphismfound in the promoter region,insertion/deletion of cytosine at position -141(-141C ins/del; rs1799732) is considered to be associated with risk of Schizophrenia. Allele with deletion(-141C Del), whichis rare in the general population and reduces the expression of the receptor mRNAin vitro,was significantly less presented in patients with Schizophrenia in the Asian population (Arinami et al., 1997). However, study in in Turkish schizophrenic patients found no association between -141 Ins/Del allele distribution and risk

of Schizophrenia or disease severity (Kurt et al., 2011). Rs1799732 is studied also in the relation to alcohol dependence. However, study of European American population, didn't show significantdifferences in allele frequencies between alcohol dependent group and control group (Gelernter and Kranzler, 1999).

The missense mutation, rs18001028 (C960G) in exon 7 is also investigatedin relation to Schizophrenia.This transition results in amino acids exchange, in particular serine for cysteine in the 311th codon (Ser311Cys). The minor allele (G)is likely to reduce inhibition effect of DRD_2 on cAMP synthesis (Yao et al., 2014; He et al., 2016). Meta-analysis of 85 case-control studies concluded that rs18001028 (allele G) presents an increased risk of Schizophrenia in the Han Chinese population, but not in the Caucasian population (Zhao et al., 2016), while rs1799732 (-141C Del) is likely to function as a protective factor (He et al., 2016).

Another polymorphism discovered in exon 7 is substitution transition rs6277 (C957T). Allele T reduces gene expression by up to 50% in vitro, which is probably caused by lower mRNA stability (Duan et al., 2003). Another study, using PET to monitor the availability of the D_2/D_3 receptors in the striatum, showed a bilaterally increased binding potential of receptors with allele T in the ventral striatum and putamen, but not in nc. caudatus (Smith et al., 2017). Based on fMRI data, Richter et al. (2017) suggested that the lower expression of the receptors with T allele may cause a better memory for rewarded stimuli in German men and therefore be responsible for reward-related impulsivity. The allele C was also observed to be highly frequented in patients with Schizophrenia (Lawford et al., 2005).

Important single nucleotide polymorphisms, both substitution transversion (C>A) were found in intron 5 (rs1076560) and intron 6 (rs2283265). Minor allele A is responsible for the inclusion of exon 6 into the mRNAand so the preferential formation of the long form of the dopamine receptor (D_{2L}). Although these intron polymorphisms are closely related (LD = 1), they are likely to be able to influence the splicing result individually (Zhang et al., 2007). There is an evidence that auto-receptors D_{2S} play a key role in regulating dopamine synthesis and release. Therefore, the lower auto-receptor density is probably one of the factors of more intense dopamine activity. (Rouge-Pont et al., 2002). Binding of released dopamine molecules to the auto-receptors allows activation of the Gi-proteins, thereby decreasing activity in AC-cAMP-PKAsignaling pathway. Moreover, D_{2S}auto-receptors reduce tyrosine hydroxylase phosphorylation and thus L-DOPA production in nigrostriatal presynaptic

terminals (Lindgren et al., 2003). The association was found betweenthis polymorphismand opioid addiction, but not cocaine addiction (Clarke et al., 2014).

By using restriction fragment length polymorphism technique (RFLP), thesubstitution transition, rs1800497 (C>T; Glu713Lys), was discovered. It was named Taq1A,after the the restriction enzyme Taq1. Minor allele A1 (T) allele is cleaved by Taq1 to one fragment 6.6 kb long. Allele A2 (C) is a cleaved by Taq1 into two fragments, 2.9 and 3.7 kb respectively (Grandy et al., 1989a).

Originally, Taq1A was considered to be a part of the DRD_2 gene. But later experiments revealedthat Taq1A belongs to the separate gene, called ANKK1, located 10kb downstream of DRD_2. Ankyrin repeat and kinase domain containing 1 (ANKK1) is also known as the protein kinase PKK2 or sugen kinase 288 (SgK288) and belongs to the Ser/Thr protein kinase family. ANKK1 contains 12 Ankyrin repeats and polymorphism rs1800497 was found in eleventh repeat, which is located in exon 8. ANKK1 is involved in signal transduction and cellular responses to external stimuli and is likely to have animportant role in regulating DRD_2 expression (Neville et al., 2004).

It has been suggested that allele A1 alters the dopamine signaling in the limbic system changes, which may be the cause of increased food intake in obese people (Ariza et al., 2012). Since A1 (T) is likely to cause up to 40% lower D_2 mRNA expression (Grandy et al., 1989a) it is extensively studied for possible association with higher risk of cocaine dependence (Spellicy et al., 2014), opioid dependence (Cai et al., 2015) or alcohol dependence. In the Indian population the genotype A1/-141C ins had 2.5 times higher risk of addiction development than genotype A2/-141C del (Prasad et al., 2010). A study of the Finnish population (1019 men) did not find significant differences in genotype distribution among abstainers and non-abstainers. But within the non-abstention group, alcohol consumption was lowest in the A1/A1 homozygous genotype and highest in the A2/A2 homozygous genotype (Hallikainen et al., 2003). Taq1A is also studied in relation with novelty seeking behavior (Montag et al., 2010). Meta-analysis showed that Taq1A has a significant effect on the availability of D_2 receptors. Receptor binding potential is significantly lower in the presence of the minor A1 allele (Gluskin and Mickey, 2016). It is generally believed that there is an association of ANKK1 with various psychiatric disorders such as Schizophrenia (Arinami et al., 1997; Yao et al., 2014; He et al., 2016), Borderline Personality Disorder (BPD) (Nemoda et al., 2010) or Tourette Syndrome (Yuan et al., 2015).

Practical part

9 Aim of the diploma thesis

Dopamine receptor D_2 gene has an important role in dopamine signaling in the brain and it is also the key negative regulator of dopamine action (Rouge-Pont et al., 2002; Lindgren, 2003). There are several DRD_2 polymorphisms studied mostly in relation to Schizophrenia (Kurt et al., 2011; Zhao et al., 2016; He et al., 2016) or substance dependence (Gelernter and Kranzler, 1999; Clarke et al., 2014), but very little is known about their role in novelty seeking behavior (NSB).

SNP polymorphism, -141C Ins/Del is located in DRD2 promoter region (fig. 6). Minor allele (-141C Del) is considered to reduce DRD_2 gene expression (Arinami et al., 1997). The aim of this study is to verify its relation to NSBin athletes engaged in extreme or potentially dangerous activities.

DRD_2 gene structure

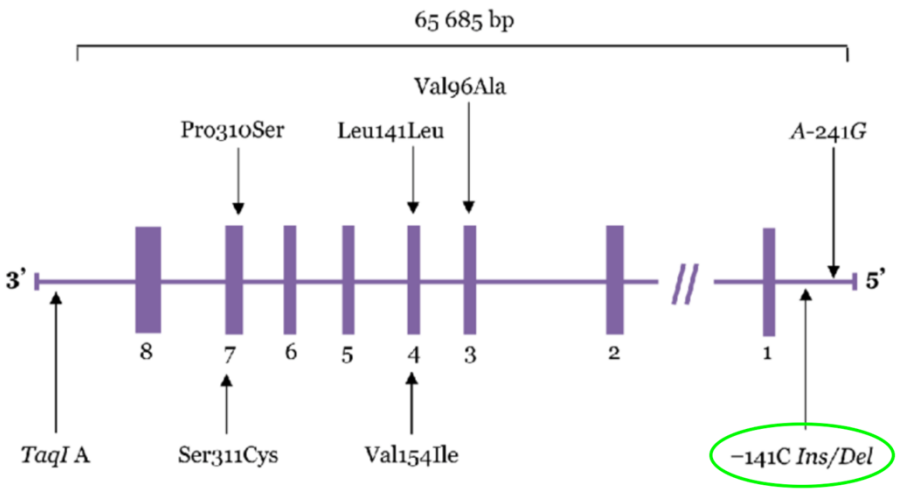

Figure 6: Dopamine receptor D_2 diagram with several polymorphisms (Zahari et al., 2011). Human dopamine receptor D_2 gene is located on the long arm of chromosome 11 at the position q22-23 (Grandy et al, 1989a). It is at least 52 kb long and contains 8 exons. Coding exons (2-8) are concentrated in a cluster about 13kb long. Non-coding exon 1 is, therefore very long (20 bp) and it is separated from the coding region by region at least 38 kb long (Neve, 2010).

10 Material and methods

10.1 Subjects

Since the alterations in dopaminergic system arethought to be associated with the frequent search for potentially dangerous activities, I decided tomonitorpeople who engage in "extreme sports" and compare their personality test scores with DNA analyses. The search for volunteers took place through social networks and addressing sports clubs and groups. The project involved 34 volunteers (16 men,18 women) who were divided into two groups. One group consisted of people who participate in sports (athletes) and the second group consisted of people randomly selected, with no interest in sport or relaxing activities only (control).

For the candidates to be included into the research, I set the criteria:

- age 18-45
- both men and women
- mentally healthy; without manifestations of severe depression, eating disorders or clinical signs of psychiatric pathologies such as schizophrenia
- ethnicity;not a condition, but with regard to the locality (Prague and the surrounding area), a significant representation of the Caucasian race was expected
- sports activities, e.g. mountaineering, sky diving, martial arts, military training, and so on.

10.2 Hypothesis

Hypothesis 1: There is a higher probability of a tendency towards novelty seeking behavior in individuals who engage in extreme sports than in the general population. Higher scores in the psychological test were expected to be achieved compared to the control group.

*Hypothesis 2:*The presence of minor allele (-141C Del) in dopamine receptor D_2influences the tendency to seek out extreme activities.

10.3 Methods

10.3.1 Psychological test

Temperament and Character Inventory-Revised (TCI-R), created by Professor of psychology C. Robert Cloninger is the personality test, which characterize four temperaments: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), persistence (PS) and three characters: self-directedness (SD), cooperativeness (CO) and self-transcendence (ST), each with several subscales (Tab. 2).TCI-R is a globally recognized and used tool in both psychological and neurobiological research. Special permission for usage was given to this study.

The Inventory consists of 240 items. Only 235 are self-reported questions with answers each on a five-points rating scale: 1=definitively false; 2=mostly or probably false; 3=neither true nor false, or about equally true or false; 4=mostly or probably true; 5=definitively true; and five validity items asking participants to choose particular number ("please, circle the number 1, 2, … ", etc.)

Questions are formulated as follows: "I often do things according to my current feeling without detailed thinking", "I usually stay calm and self-confident in situations that most people would find physically dangerous" or "I rather save money than to spend them on entertainment and excitement".

Slovak version of TCI-R was conducted online, through Google survey. To keep the anonymity, each participant was asked to fill out a unique identification number (at least 2 letters and 4 numbers) in the questionnaire. This identification number was only known to me as the author of the project. Participants noted their age and gender and type of the sport activity. In addition, they listed the size of the population in geographic region where they live (<5000; >5000; >100.000; etc.), the marital status and type of employment (student, working student, employed, unemployed, freelance).

10.3.2 Samplingof biological material

Based on the results obtained from the psychological analysis, the volunteers who scored the highest and lowest in the NSB were contacted. Buccal swab kits (Isohelix SK1 Buccal Swab) were sent by mail or delivered personally to the address indicated by the participants. Buccal cells were collected by cotton swabs from inside the surface of the mouth. Then, samples were sent to the laboratory, Genlabs- s.r.o. in České Budějovice for genetic analysis. together with signed informed consent.

Informed consent:

All volunteers were previously informed about the project goal, which was confirmed by their signature on informed consent to participate in the project (annex V). This included also consent to self-examination and expression with further treatment of samples and derived biological material at the end of the project (annex V, Part B3).

Protection of private data:

Information about the tested persons was kept in accordance with the applicable laws of the Czech Republic, especially with the Personal Data Protection Act no. 101/2000 Coll. as subsequently amended. Participating volunteers, by signing informed consent, agreed to collect and process their personal data in the laboratory database for the duration of the project. Personal details of subscribers are secured against abuse, and the laboratory does not provide them with any other person who does not engage in confidentiality. Informed consents, after signing, were archived in the laboratory in paper form and is only available to laboratory staff.

I, as an author and project developer, also committed to not provide data of project participants to third parties, with the contact information for DNA swabs kits delivery as the onlyexception.

10.3.3 DNA isolation

DNA from buccal cells was isolated by IsohelixDNA Isolation Kit (DDK-50) (tab. 5):

reagents	used volume (µl)
Lysis buffer (LS)	500
Proteinkinase K (PK)	20
Capture buffer (CT)	500
Re-hydration buffer (TE)	30

Table 5: IsohelixDDK Isolation Kit reagents (DDK-3/DDK-50). *Instead of TE, dH_2O was used in the same volume.

For each sample (21 in total), I prepared two 1,5 ml test tubes. Into the each test tube with cotton swabs with buccal cells, I added 500 µl of LS and 20 µl of defrosted PK. After short vortex (Microspin FV-2400; BioSan) and centrifugation (Centrifuge 5415 R; Eppendorf), samples were incubated in thermostat (Dry Block Thermostat TDB-120; BioSan) in 60°C for

1 hour. After incubation, samples were vortexed and centrifuged for a short time again. From each sample, I re-pipetted the supernatant into the new 1,5 ml test tubes and added 500 µl of CT. After a quick vortex, I left the samples centrifuged for 7 min. (13.000 RPM).
After centrifugation, without touching DNA pellet, I gently removed the supernatant and left the samples centrifuged again just for few minutes to be able to remove the rest of the supernatant. According to the official procedure, the next step would be adding 150 µl of TE or water, but this point was changed and I added 30 µl of sdH_2O instead to obtain high concentration of DNA in the sample and I left the mixture incubate in the room temperature (RT) for 5 min. After incubation, samples were vortexed and centrifuged for another 15 min (13.000 RPM) and I transferred the resulting supernatant with DNAagain into the new 1,5 ml test tubes.

10.3.4 Spectrophotometry

For evaluating the DNA concentration, Qubit™ Assays kit (tab.6) and Qubit® 2.0 Fluorometer (Invitrogen by Life Technologies) was used.

reagents	used volume (µl)
Quibit™ ds DNA BR reagent (200x in DMSO)	1
Quibit™ ds DNA BR buffer	199
Quibit™ ds DNA BR Standard #1	10
Quibit™ ds DNA BR Standard #2	10

Table 6: Qubit™ Assays kit reagents. Volumes used in the measurement.

Before measuring, I left both Standards to reach the RT and prepared 0.5 ml Qubit™ Assays tubes for each sample (21 samples and 2 Standards). Meanwhile, I prepared the Qubit™ Working Solution: 199 µlQubit™ ds DNA BR buffer mixed with 1 µlQubit™ ds DNA BR reagent. The mixture was vortexed for 15 s and centrifuged in the table centrifuge (Microspin FV-2400; Biosan). For standard measuring, I pipetted 190 µl of Working Solution into 0.5 ml Qubit™ Assays tubes and added 10 µlof each Qubit™ ds DNA BR Standard. For sample measuring, I mixed 198 µl of Working Solution and 2 µlof each DNA sample. After vortex, short centrifugation and incubation in the RT (2 min.), standards and samples concentrations were measured. DNA concentrations are shown in the table 7 (annex II; table 7).

10.3.5 Genotyping

DRD_2 gene polymorphism in the promoter region (-141 Ins/Del; I/D) was detected by PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method.

Hot Start Taq polymerase, EmeraldAmp® Max HS PCR Master Mix was obtained from Takara Bio Company.

Oligonucleotide primers for 5'-region flanking the -141 Ins/Del were ordered from ELISABETH PHARMACON®. Primers positions corresponded with nucleotide sequences -284 to -259 for forward primer (5'-ACT GGC GAG CAG ACG GTG AGG ACC C-3') and with -6 to +20 for reverse primer (5'-TGC GCG CGT GAG GTC GCC GGT TCG G-3').

Polymerase chain reaction (PCR)

Primers, delivered in powder form I dissolved in purified water,dH_2O (Aqua purificata; FAGRON, s.r.o.), to get 100 µM concentration. Further, I diluted primer solutions 5 times in dH_2O to get 20 µM concentration. The next step was to prepare PCR mixture. For each sample and positive control (PC) I prepared 25 µl reaction volume, containing 7.5 µl dH_2O, 12.5 µlEmeraldAmp® Max HS PCR Master Mix, 1 µl of each primer, 5% 1.25 µl DMSO and 2 µl DNA (Tab. 6), plus 23 µl reaction volume for negative control (NC). Final PCR product was fragment 303 or 304 bp long.

Reagents used in PCR technique are shown in table 8.

reagents	used volume (µl)
EmeraldAmp® Max HS PCR Master Mix	12.5
sterilized distilled water (Aqua purificata)	7.5
forward primer	1
reverse primer	1
DMSO	1.25
DNA	2

Table 8:PCR reagents; volumes (µl)used in the reaction.

DNA amplification was carried out in PCR cycler (MultiGene; Labnet). After initial denaturation (95℃, 5 min), process continued with 35 cycles, consisted of 30 s at 95℃ for denaturation,30 s at 63℃ for annealing and 30 s at 72℃ for extension were followed by 5 min at 72 ℃ for final extension (tab. 9).

PCR		
1 cycle	**temperature (℃)**	**time (min)**
Denaturation	95	2
35 cycles	**temperature (℃)**	**time (s)**
Denaturation	95	30
Annealing	63	30
Extension	72	30
1 cycle	**temperature (℃)**	**time (min)**
Extension	72	5

Table 9: PCR program profile.

RFLP

Since alleles in -141C Ins/Del polymorphism differ from each other in restriction site presentation, RFLP method was used to detect this polymorphism.

After DNA amplification, PCR products were digested with Mval (BstNI) restriction enzyme, which recognize CC^WGG sites. I pipetted 1 µl BstNI restriction enzyme (Thermo Scientific) and 2 µl Buffer R (10x)(Thermo Scientific) into the each test tube with DNA sample and incubated in thermostat (Dry Block Thermostat TDB-120; BioSan) in 37℃for at least 1 hour.

10.3.6 Agarose gel preparation and electrophoresis

Reagents used for agarose gel preparation and electrophoresis are shown in table 10 (tab. 10).

Agarose gel

To prepare the agarose gel, TBE working solutionwas the first step. I added 50 ml 10x TBE buffer (Invitrogen™), into the glass bottle (0.5 l) and I filled the volume with 450 ml purified water to get 1x TBE working solution.

For 4% gel, I diluted four agarose tablets (Nippon Genetics) in 50 ml 1x TBE working solution prepared in the first step. Then, I put this mixture into the microwave (max. power) to heat it for 3 min. until I got pure gel without bubbles. Consequently, I left the gel cool down little bit and poured it into electrophoretic form with combs to make wells. After cooling down (15 min.), I removed combs and transferred gel into the electrophoretic tub (Mupid® One Elecrophoresis System) with 1x TBE buffer.

Electrophoresis

After enzymatic digestion, I pipetted 5 µl FastGene®100 bp DNA LADDER H3RTU (Nippon Genetics) and 1 µlMidori Green Advanced DNA Stain into the first well, as a marker. Into the rest of the wells, I added 15 µldigested DNA from each sample stained with 0,5 µlMidori Green Advanced DNA Stain (Nippon Genetics) and I set the time of electrophoresis for 22 min. When electrophoresis finished, I put the gel on the detection system (FastGene® GelPic LED Box), which allowed me to take and save pictures of the gel (Fig. 7).

reagents	used volume/amount
1x TBE (working solution)	50 ml
agarose tablets	4x 0.5 g
Midori Green Advanced DNA Stain	15 µl
100 bp DNA LADDER H3RTU	5 µl

Table 10: Reagents for agarose gel preparation and electrophoresis. Volumes and amounts used in the measurement.

10.4 Statistical analysis

Statistical analysis of personality dimensions was carried out with version 24.0 of the SPSS statistical software. Calculation method indicated by R. Cloninger was used: scores of each dimension and subcategories was obtained by the sum of all correspondent items directly or after inversion for reverse items.

The mean score and standard deviation was calculated for each of the seven dimensions. The reliability of the psychometric test was estimated by Cronbach's α-reliability coefficient. Differences between groups were calculated with Student's t-test and data were considered significant with at $P < 0.05$.

10.5 Results

10.5.1 Psychometric analysis

Out of the total 36 volunteers recruited in this project, 34 (16 athletes: 12 men; 4 women and 18 controls: 4 men; 14 woman)filled the TCI-R. The mean age in the athlete group was 33 ± 8.4 and 30 ± 7.3 for control group. Although this paper is focusing on the novelty seeking trait to compare the relations between dimensions, I included all four temperaments into the analysis: novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (PS). Characters self-directedness (SD), cooperativeness (CO) and self-transcendence (ST) were not included.The mean scores and standard deviations for all four temperaments and their subscales are shown in table 11 (annex III; tab. 11).

Novelty seeking

In agreement with the first hypothesis, the mean score value in NS dimension was higher in athletes than in controls. However, no significant differences were obtained among these groups (105.88 ± 17.02 vs 97.78 ± 13.3; P=0.189) (fig. 8). The same result was observed in each of NS subscales: athletes scored higher in NS1 exploratory, excitability (34 ± 5.92 vs 31.72 ± 5.1; P= 0.242), NS2 impulsiveness (24 ± 6.19 vs 22.67 ± 6,19; P= 0.871), NS3 extravagance (27.25 ± 8.29 vs 26.06 ± 7.36; P= 0.7) and NS4 disorderliness, which was the only subscale where athlete's score was significantly higher than controls (20.63 ± 3.52 vs 17.33 ± 4.41; P= 0.021) (fig. 9).

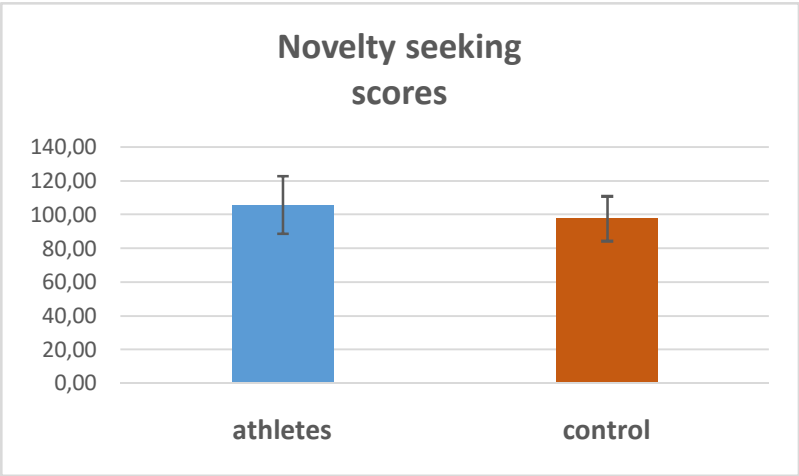

Figure 8: The scores of novelty seeking are higher in athletes than in control group, however scores didn't reach the significant between-group difference (105.88 ± 17.02 vs 97.78 ± 13.3; P=0.189); Student's t-test; α=0.05.

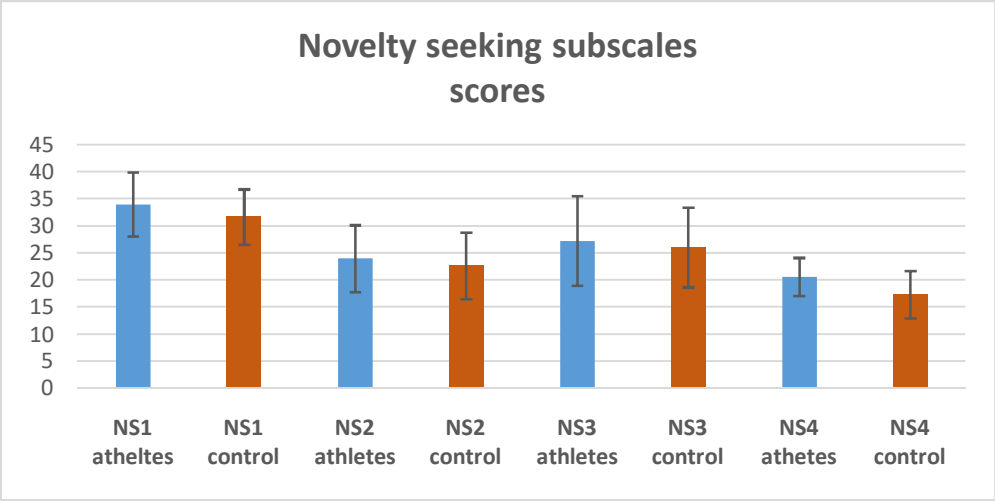

Figure 9:The scores of novelty seeking subscales: although athletes reached higher scores in every subscale than controls, their scores didn't reach the significant difference in any of them, except NS4 (20.63 ± 3.52 vs 17.33 ± 4.41; P= 0.021); Student's t-test; α= 0.05.

Individual NS scores vs sport activity

In athletes group, the highest score (137) reached the man active in alpine tourism, crossfit, biking and jogging. The second highest score (124) was observed in man active in marathon, mountain biking. On the other hand, surprisingly, the lowest score reached men engaged in indoor and outdoor skydiving (79) and climbing (78).

Individuals with scores around the mean value were engaged in variety of sports such as football, biking, mountain climbing, snowboarding, crossfit, martial arts, box, ice hockey or swardplay (tab. 12A)

Gender	Age	Sport activity	NS
M	39	running, crossfit, biking, alpine tourism	137.00
M	32	marathon, mountain biking	124.00
W	22	floorball	119.00
W	20	competitive swardplay	118.00
M	33	football, moutain climbing	118.00
M	31	shooting, moutain climbing, martial arts	115.00
W	31	triathlon, basketball, floorball	115.00
M	27	running, fitness, biking, mountain climbing snowboarding	115.00
		mena score	**105.88**
M	33	crossfit	104.00
W	57	nordic walking	100.00
M	26	football, fitness, biking	99.00
M	34	ice hockey	98.00
M	40	biking	90.00
M	30	Krav Maga, box, jiu jitsu, kettlbell	85.00
M	34	indoor skydiving, skydiving	79.00
M	31	climbing, running	78.00

Table 12A: Novelty seeking score and sport activities comparison in athletes group.

In the control group, the highest score (134) reached woman interested in volleyball and yoga and second highest score (116), woman engaged in swimming. The lowest score (76) reached the women active in trampoline jumping and woman doing fitness (78). Individuals with scores around the mean value were generally not interested in any sport or just relaxing activities such as yoga, swimming, fitness or horse riding (tab. 12B)

Gender	Age	Sport activity	NS
W	31	volleyball, hot yoga	134.00
W	29	swimming	116.00
M	45	football, tennis, biking, fitness, swimming	108.00
W	31	horse riding	104.00
M	42	none	102.00
M	35	biking, nordic walking	101.00
W	20	none	100.00
W	20	yoga	100.00
		mean score	**97.78**
M	24	streetworkout/calisthenics	97.00
W	33	none	98.00
W	20	none	94.00
W	37	yoga	93.00
W	31	fitness, HIIT	93.00
W	26	none	91.00
W	28	running, yoga	88.00
W	28	none	87.00
W	31	fitness	78.00
W	20	trampoline jumping	76.00

Table 12B: Novelty seeking score and sport activities comparison in control group.

Harm avoidance

Marginally significant difference was observed in HA dimension. As expected, athletes reached lower scores than controls (79.31± 21.21 vs 94.28 ± 21.87; P= 0.052) (fig. 10). Among HA subscales; athletes reached significantly lower score in HA2 fear of uncertainty (18.38 ± 5.9 vs 23.67 ± 4.98; P= 0.009) and moderately lower score in HA4 fatigability (16.63 ± 5.94 vs 21.33 ± 7.58; P= 0.051). There was no significant difference in HA1 anticipatory worry (25.5 ± 7.47 vs 29.94 ± 8; P= 0.104) and HA3 shyness (18.81 ± 5.23 vs 19.33 ± 7.05; P= 0.807) (fig. 11).

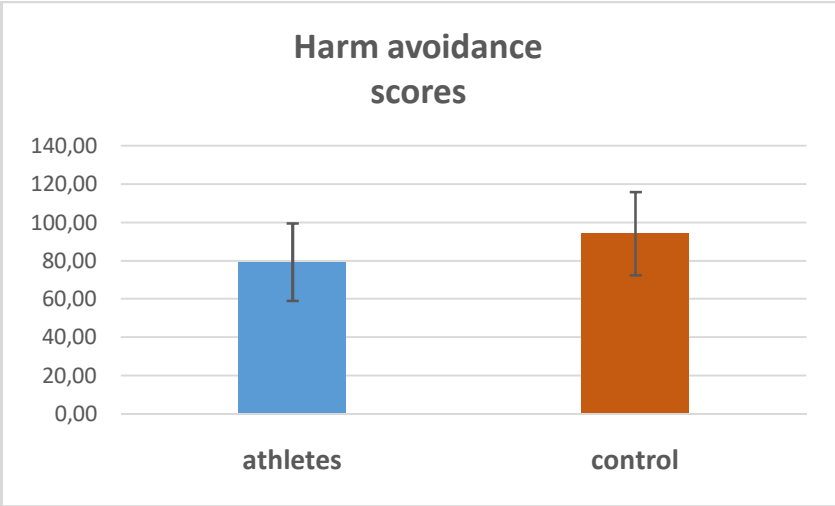

Figure 10:Harm avoidance were lower in athletes than in control group. The score difference showed to be only marginally significant (79.31± 21.21 vs 94.28 ± 21.87; P= 0.052); Student t-test; α=0.05.

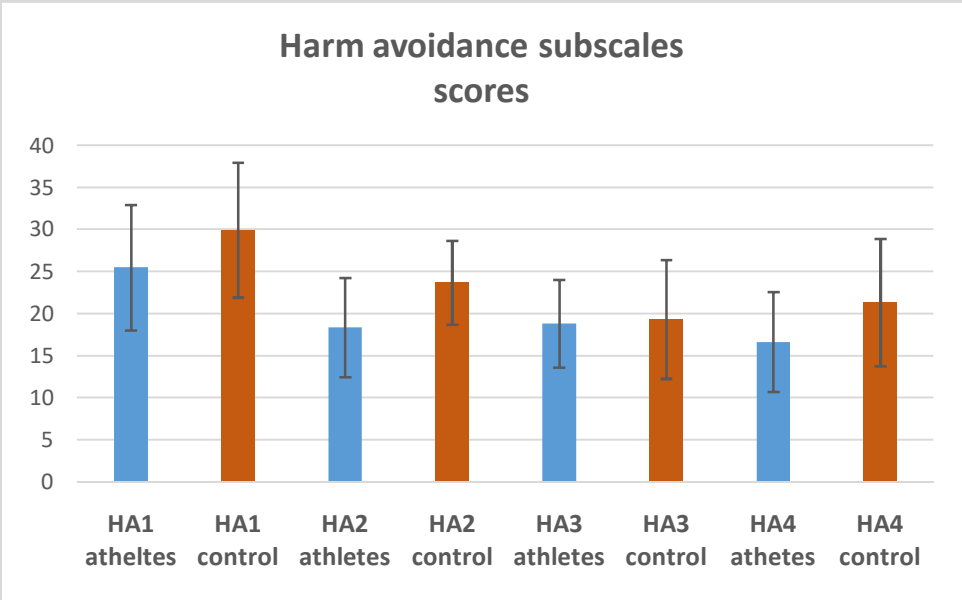

Figure 11: Harm avoidance subscales: although athletes reached lower scores in every subscale than controls, their scores reach the significant difference only in HA2 (18.38 ± 5.9 vs 23.67 ± 4.98; P= 0.009) and moderately difference in HA4 (16.63 ± 5.94 vs 21.33 ± 7.58; P= 0.051); Student t-test; α=0.05.

Reward dependence

Although the tendency towards lower score in athletes in RD scale was observed, no significant differences were obtained (104.81 ± 11 vs 109.39 ± 13.74; P= 0.289) (fig.12). In subscales RD1 sentimentality (29.06 ± 4.02 vs 29.94 ± 4.22; P= 0.538) and RD2 openness to warm communication (37.06 ± 6.23 vs 37.78 ± 5.85; P= 0.733) both groups reached almost the same score. In RD3 attachment athletes scored lower, but not significantly than controls (20.19 ± 5.29 vs 21.11 ± 18.5; P= 0.618). Only exception was RD4 dependence, where athletes reached moderately lower score than controls (18.5 ± 3.22 vs 20.56 ± 3.67; P= 0.092) (fig. 13).

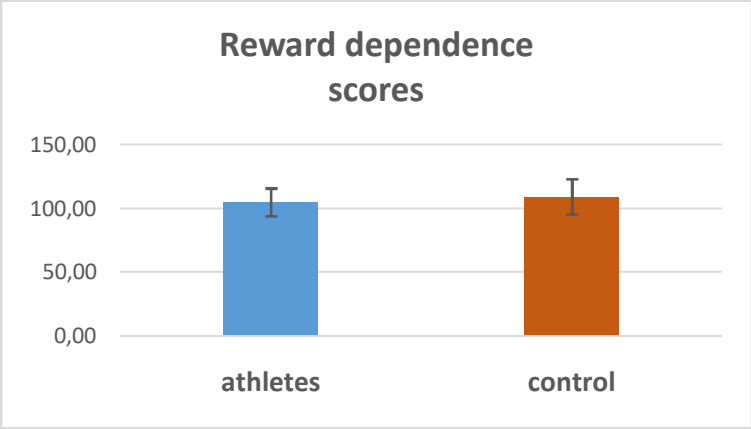

Figure 12: Rreward dependence scores are lower in athletes than in control group, however scores didn't reach the significant between-group difference (104.81 ± 11 vs 109.39 ± 13.74; P= 0.289); Student t-test; α=0.05.

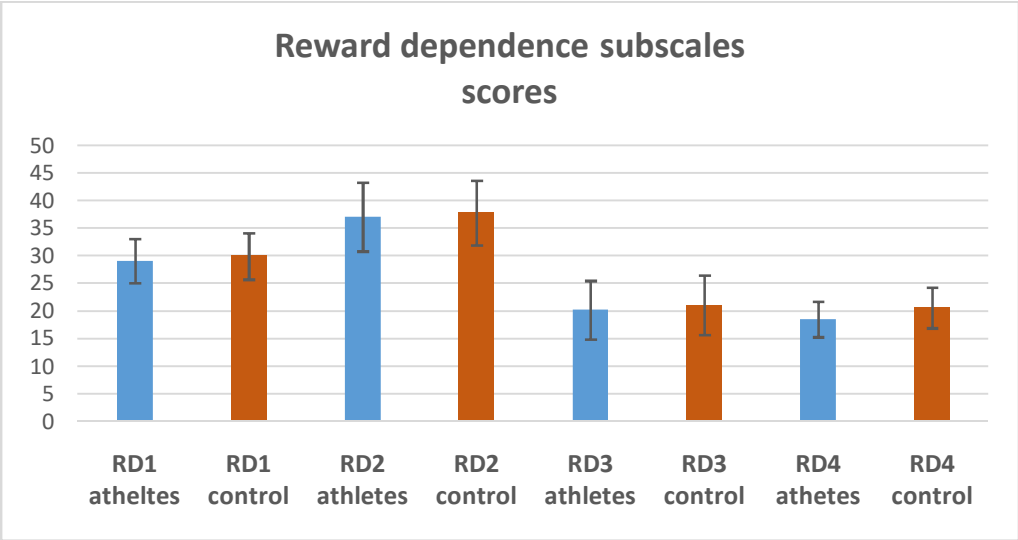

Figure 13: Reward dependence subscales: although athletes reached lower scores in every subscale than controls, differeneedidn't reach the level of significance, except, RD4, where they reached moderately lower score than controls (18.5 ± 3.22 vs 20.56 ± 3.67; P= 0.092)Student t-test; α=0.05.

Persistence

Although athletes scored higher than controlsin PS scale, neither for this personality dimension, score differences didn't reach the level of significance (130.13± 16.8 vs 120 ± 19.22; P= 0.145) (fig. 14). Higher scores in athlete group were also observed in subscale PS1 eagerness of effort (30.94 ± 4.95 vs 29.94 ± 4.99; P= 0.565), PS2 work hardened (30.69 ± 4.44 vs 28.78 ± 3.93; P= 0.197) and PS4 perfectionist (29.19 ± 5.18 vs 27.89 ± 5.6; P= 0.488). Non of these data represent significant difference. Only in PS3 ambitious, athletes showed significantly higher results than control group (39.31 ± 6 vs 34.28 ± 7.32; P= 0.035) (fig. 15).

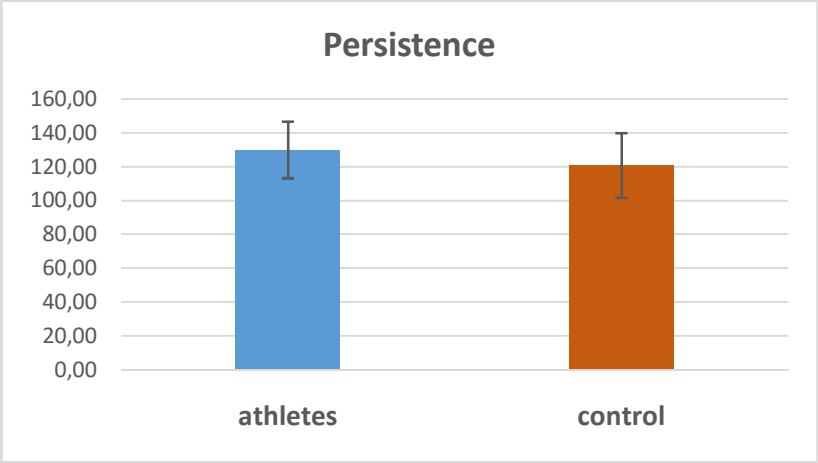

Figure 14: Persistence: athletes reached higher score than controls, however scores didn't reach the significant between-group difference (130.13± 16.8 vs 120 ± 19.22; P= 0.145); Student t-test; α=0.05.

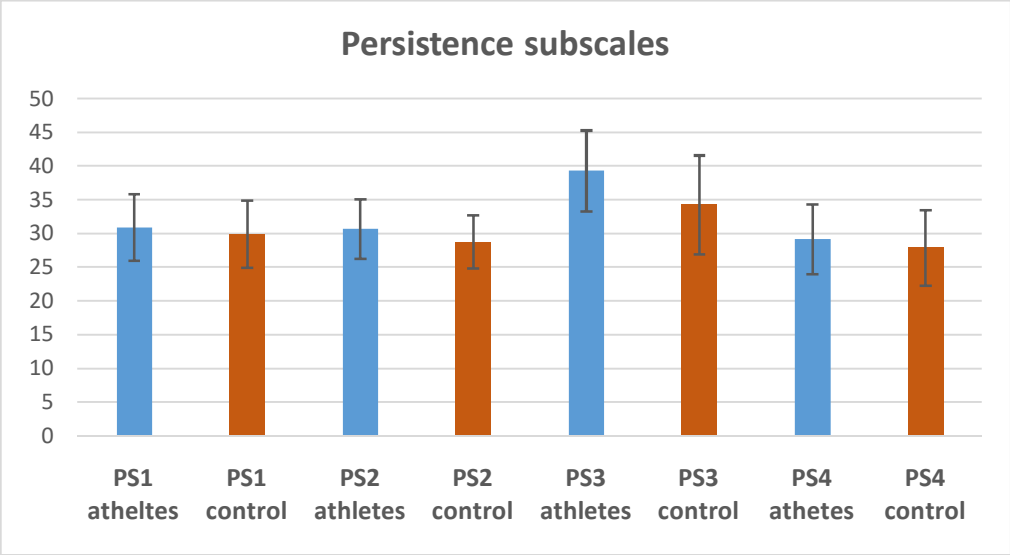

Figure 15: Persistance subscales: no significant score differences were observed, except PS3 (ambitious), where athletes scored significantly higher than controls (39.31 ± 6 vs 34.28 ± 7.32; P= 0.035). Student t-test; α=0.05.

Men vs women

In any of four temperaments, no significant score differences were observed between men and women among groups (tab. 13). For athletes: surprisingly, men scored lower than women in NS dimension (103.5 ± 18.69 vs 113 ± 8.83; P= 0.198), and higher than women in HA (81.75 ± 20.93 vs 72 ± 18.46; P= 0.411) and PS dimension (131.46 ± 22.75 vs 135.75 ± 23.88; P= 0.955). Only in RD dimension, men reached marginally significantly higher score than women (107.5 ± 10.83 vs 96.75 ± 7.72; P= 0.067). For control group: in NS, men reached higher score than women (102 ± 4.55 vs 96.57 ± 14.82; P= 0.252) and lower score in HA (77 ± 27.19 vs 99.21 ± 18.34; P= 0.199). In RD dimension, both men and women reached the same score (109.25 ± 9.81 vs 109.43 ± 14.99; P= 0.978) and in PS, men were lower than women (112.75 ± 20.66 vs 123.21 ± 18.93; P= 0.405). Non of these score differences reached the level of significance.

Athletes	***NS men***	***NS women***	***HA men***	***HA women***	***RD men***	***RD women***	***PS men***	***PS women***
Mean	103.5	113	81.75	72	107.5	96.75	134.85	135.75
t Stat	-1.36		0.88		2.16		-0.06	
P(T<=t) two-tail	0.198		0.411		0.067		0.955	
t Critical two-tail	2.18		2.45		2.36		2.36	
Control	***NS men***	***NS women***	***HA men***	***HA women***	***RD men***	***RD women***	***PS men***	***PS women***
Mean	102	96.57	77	99.21	109.25	109.43	112.75	123.21
t Stat	1.19		-1.54		-0.03		-0.91	
P(T<=t) two-tail	0.252		0.199		0.978		0.405	
t Critical two-tail	2.12		2.78		2.31		2.57	

Table 13: Statistical score differences between men and women.

10.5.2 Genetic analysis

From a total amount of 36 volunteers participating in this study, 22 underwent DNA analysis and only 19 samples were successfully isolated and amplified. The rest of the participants (14) either disagreed with biological material sampling or were excluded for medical reasons.

Although the final studied sample was not statistically significant (19), genotype analyses shows that homozygotes for -141C Ins/Ins (II) represented majority in both athletes (83.3%) and controls (71.43%), compared to heterozygotes Ins/Del (ID). Homozygotes for Del/Del (DD) were not detected (tab. 14).

Group (n)	**DRD2 genotypes**			**DRD2 alleles**	
	II n (%)	ID n (%)	DD n (%)	I n (%)	D n (%)
Athletes (12)	10 (83.3)	2 (16.6)	0	20 (91.6)	2 (8.33)
Control (7)	5 (71.43)	2 (28.57)	0	12 (85.7)	2 (14.28)

Table 14: The DRD2 -141C Ins/Del genotypes and alleles percentage representation in athletes and controls.

Based on presence or absence of -141C nucleotide, either DNA fragment of 303 bp (-141C Del) or 304 bp (-141C Del) was obtained from PCR reaction. Since -141C insertion creates the restriction site, two fragments of 160 bp and 144 bp (-141C Ins) are generated by BstNI digestion. Therefore, three possible results could be observed: homozygotes for Ins/Ins (II) have fragments of 160+144 bp, homozygotes for Del/Del (DD) have fragment of 303 bp only and heterozygotes Ins/Del (ID) have three different fragments of 303 bp, 160 bp and 144 bp (fig. 8).

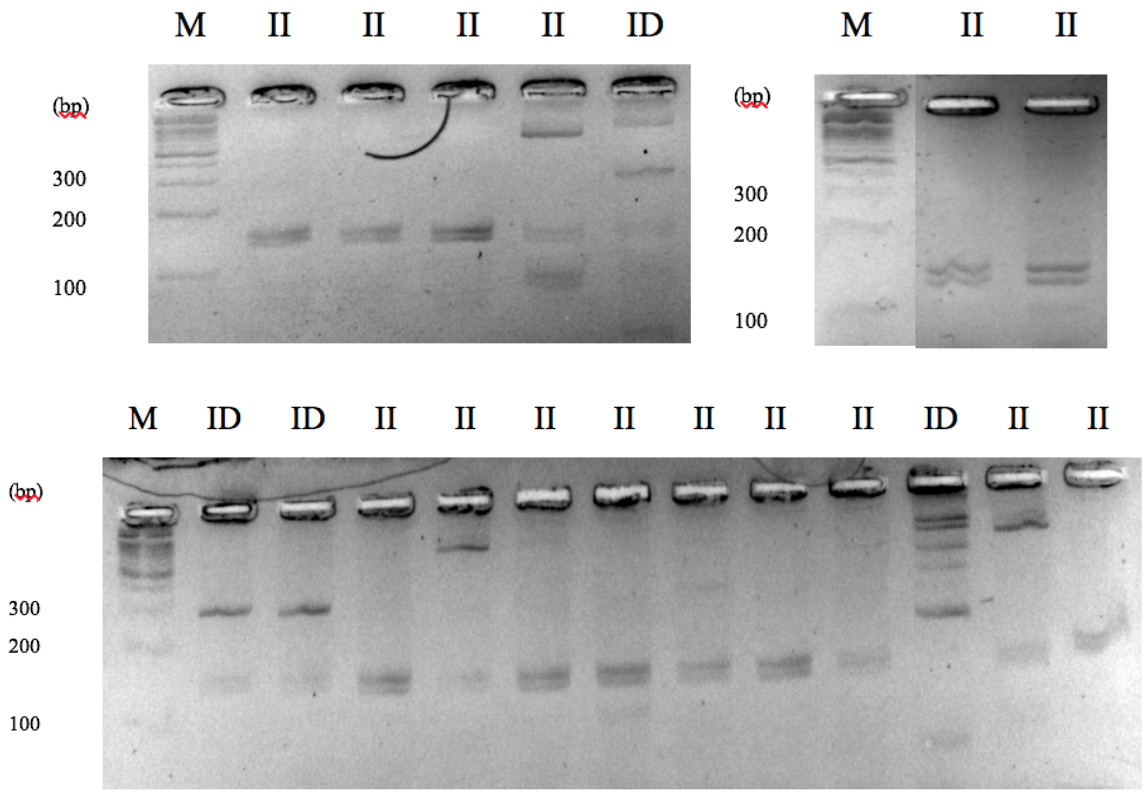

Figure 7: DRD_2-141C Ins/Del polymorphism genotyping. M= marker(100 bp DNA LADDER H3RTU), II= homozygotes for Ins/Ins, heterozygotes for ID= Ins/Del. DD=homozygotes for Del/Del (not detected).Amplified DNA was digested by BstNI restriction enzyme (Thermo Scientific) and fragments were separated by horizontal electrophoresis on 4% agarose gel. To visualize DNA fragments, Midori Green Advanced DNA Stain (Nippon Genetics) was used. Three possible results could be obtained after enzymatic digestion: homozygotes IIwith fragments of 160+144 bp, homozygotes for DD with fragments of 303 bp only and heterozygotes IDwith three different fragments of 303 bp, 160 bp and 144 bp.

10.5.3 Novelty seeking vs -141C Ins/Del polymorphism

From total 19 volunteers, whose DNA samples were successfully isolated and amplified, one was excluded because of unfinished personality questionnaire. Therefore, 18 samples left to compare DNA analyses with novelty seeking score (tab. 15).

Group 1	No.	Sample	Gender	Age	Sport activity	NS score	Ins/Del
Athletes (11)	1	PET8	M	26	football, fitness, bike	99.00	II
	2	PET5	M	31	sport climbing, running	78.00	II
	3	PET22	M	30	Krav Maga, box, jiu jitsu	85.00	ID
	4	PET10	M	34	ice hockey	98.00	II
	5	PET6	M	34	indoor/outdoor skydiving	79.00	II
	6	PET9	M	31	mountain climbing, martial arts	115.00	II
	7	PET18	M	33	football, mountain climbing	118.00	II
	8	PET3	M	33	crossfit	104.00	ID
	9	PET4	W	31	triathlon, basketball, floorball	115.00	II
	10	PET7	M	27	mountain climbing, snowboard	115.00	II
	11	PE16	M	39	crossfit, bike, alpine tourism	137.00	II
Group 2	**No.**	**Sample**	**Gender**	**Age**	**Sport activity**	**NS score**	**Ins/Del**
Control (7)	12	PET13	W	20	yoga	100.00	ID
	13	PET14	W	31	volleyball, hot yoga	134.00	II
	14	PET19	M	45	football,tennis,fitness,swimming	108.00	II
	15	PET18	W	29	swimming	116.00	II
	16	PET17	W	31	fitness	78.00	II
	17	PET2	W	37	yoga	93.00	ID
	18	PET11	M	24	streetworkout/calisthenics	97.00	II

Table 15: Individual NS scores and DRD_2-141C Ins/Del polymorphism compared with sport activities. Heterozygotes (ID) are highlighted with red font. Individuals with the highest and the lowest scores are shown in the yellow boxes and represent homozygotes (II) in both groups.

No association was found between -141C Ins/Del polymorphism and novelty seeking score in athletes or in control group. Volunteers with the highest and the lowest score represented homozygotes for Ins/Ins (II) in both groups. However, individuals with minor allele (-141C Del), two men in athletes and two women in controls reached the score about the mean value or lower (tab, 15).

11 Discussion

It has been suggested, that tendency towards novelty seeking is associated with altered function of dopaminergic system (Cloninger, 1986). In particular, high basal activity is likely to be acause of desensitization of dopamine receptors and therefore there is a need for higher dose of dopamine, which represents the same mechanism caused by drugs. Individuals are therefore "pushed" to seek out new activities in order to increase dopamine level (Zuckerman, 1995). DRD_2 genotype-dependent behavioral responses led to the suggestion, that polymorphisms in this particular gene may have a dominant effect on personality differences (Richter et al., 2017).

The aim of this thesis was to examine the association between novelty seeking behavior (NSB) and -141C Ins/Del polymorphism in dopamine receptor D_2. Since this SNP is positioned in DRD_2 promoter region, I was interested if minor allele -141C Del affects tendency towards novelty seeking. Volunteers were asked to fill the personality questionnaire (TCI-R) and subsequently underwent the sampling of biological material (buccal cells) for DNA analysis.

TCI-R

No significant score differences were observed among groups neither in novelty seeking (NS) nor other main personality dimensions. However, in agreement with Cloninger's Unified Biosocial Theoryof Personality(Cloninger, 1986),athletes scored generally higher in novelty seeking dimension (fig. 8) and lower in harm avoidance (HA) dimension compared to controls (fig. 10). In NS subscales, only significant difference was observed in NS4 disorderliness(fig. 9), where athletes scored higher then controls. In HA subscales, there was only marginally significant difference in HA2 fear of uncertainty and HA4 fatigability, where athletes scored lower compared to controls (fig.11). In other words, these data suggest that individuals engaged in intense sports (e.g. triathlon, martial arts) or potentially dangerous activities (e.g. box, mountain climbing, snowboarding, skydiving) have higher tendency to often seek out new activities, explore unknown environment, they are less worried about themselves and willing to stand uncomfortable conditions then those who were not interested in any sports or only in relaxing activities (e.g. yoga, swimming).

No significant score differences were observed neither in reward dependence (RD). But tendency towards lower scores in RD in athletes compared to controlswas observed (fig.12). In particular, athletes scored lower in RD4 perfectionist than controls (fig.13).This might be associated with the fact, that individuals who tend to be higher in NS, seek out new experience, potentially leading to reward, whereas individuals high in RD dimension are rather interested in activities, about which they know are associated with reward.

Although athletes reached higher scores in persistence (PS), no significant difference in test scores were obtained among groups (fig.14). Only significant difference was in subscale PS3 ambitious where athletes reached higher scores than controls (fig.15). Higher scores in PS in athletes, in particular PS3 ambitious, might be due to the effort which they put into every activity.

There were also no significant score differences between sexes in either group. But in controls, as expected, women tended to be lower in novelty seeking and higher in harm avoidance than men. Women also reached higher score in persistence. However, both men and women reached the same score in reward dependence. Surprisingly, in athletes group, women tended to be higher in novelty seeking and lower in harm avoidance than men. Women engaged in sports reached also lower score in reward dependencecompared to men. However, for persistence, both sexes reached the same scores (tab. 13)

One of the reason, why scores among groups didn't reach the level of significance is, first of all, the size of the testing group. From total of 35 volunteers recruited in to this study, only 18 underwent both, psychological test TCI-R and DNA analyses. This reduction of tested group caused unequal representation of men and women within the groups. There were only four women in athletes and four men in controls presented, so it was not possible to obtain statistically significant results. However, unequal representation of sexes were evindet also on very beginning ot the project, which suggests that interest in sports is still predominant in men.

Second of all, there was high diversity in sports activities in athletes: skydiving, wall climbing, mountain climbing, alpine tourism, martial arts, ice hockey, gun shooting, triathlon, snowboarding, floorball or football. Some of them might be potentially dangerous, but I was not successful to recruit only (or majority) individuals engaged in so called extreme sports. However, it is possible to see, that volunteers in athlete group are involved not in one, but in many different activities (tab. 12A).

DNA analyses

Because of small group, I didn't provide statistical analyses of …, but instead, I compared NS scores in individual cases with results from DNA genotyping.

In both athlete and control group, individuals with the highest and lowest NS score didn't differ in genotype from each other. They carried insertion on both chromosomes (-141C Ins/Ins; II). There was also no relation in sport activity and NS score. In athletes, heterozygote (II) with the highest score (137) was interested in crossfit and alpine tourism, whereas heterozygotes (II) with the lowest score are engaged mountain climbing (78) and skydiving (79). All of them were men. In controls, heterozygote (II) with the highest score (134) is practicing yoga and with the second higest score (116) likes swimming. The lowest score (78) in this group reached heterozygote (II) practicing fitness (tab. 15)

Individuals with minor allele, heterozygotes (ID) reached the scores only about the mean value or less (tab. 15), which might suggest, that those who carry this allele are not novelty seekers. This can be caused by reduced promoter activity by one nucleotide deletion. Further study with larger group is needed.

As mentioned in chapter 7, there are many factors affecting novelty seeking behavior. Therefore, for next research, I would recommnend genotyping DRD_2 polymorphisms, which are considered to be important for receptor density or function (annex I, tab. 4). Moreover, I would definitely include epigenetic analyses, since studies suggest high environmental impact (Stoel et al., 2006; Melka et al., 2013; Flagel et al., 2016).

However, human personality is very complex and both individual studies and meta-analyses suggest, that there is no single gene strong enough to influence personality feature (Derringer et al., 2010a).

So, in ideal case, individual genetic profile scoresuggested by Nikolova et al.(2011), i.e. genes involved in dopamine metabolism and singaling patways ("dopamine genes") would be the best way of studying personality of humankind.

12 Conclusion

Novelty seeking is a personality trait characterized by prof. Cloninger (1986) as a basic temperament, responsible for natural curiosity and exploration of new and unknown environment or stimuli, potentially leading to reward. He proposed, considered when taking into consideration biochemical nature, that the major monoamine neurotransmitter modulating this kind of behavior is dopamine.

Dopaminergic neurons play central role in motor and reward brain system (Girault and Greengard, 2004). Dopamine, together with serotonin is involved in cognitive, behavioral and mood processes, learning and memory (Khanzada et al., 2017). Moreover, it has been suggested that dopamine has an important function in attention in both adult and early stages of life (Holmboe et al., 2010). Since dopamine plays a key role in reward responses, it's action is responsible for development of addiction in many ways. Novelty seeking, in extreme cases, e.g. extreme or "adrenaline" sports, may be seen as a form of addiction. Individuals engaged in this kind of activities seek out more intensive pleasure or excitement caused by greater release of dopamine molecules.
Although twin studies shown that personality traits are highly inheritable (Cloninger, 1987a; 2003), they are not inherited as such, but it is rather the unique genetic background (Zuckerman, 1995), giving the individual alterations in brain circuits (Holmes et al., 2016). On the other hand, the impact of the environment is not negligible (Stoel et al., 2006).

High novelty seeking could serve as an evolutionary advantage, which helped the humankind to survive. However, in modern times, humans in many parts of the world, have available everything what they need immediately and on daily basis. This easy accessibility might be the reason, why some individuals have a need of exiting activities despite the risk of injury or even death.

This case-control study didn't reveal a significant differences in novelty seeking scores among tested groups or between men and women. However, in agreement with the first hypothesis, there was a tendency towards higher scores in individuals engaged in intense or potentially dangerous activities compared to the control group.

Further, I didn't find an association between high novelty seeking score and -141C Ins/Del polymorphism. However, I observed that heterozygotes (ID) scored only about the mean

value or lower, which may suggest, according to the secont hypthesis, that minor allele D affects NSB towards lower score. Although the final number of participantswas too small for statistical analysis, this result might show the direction for PET screening, i.e. individuals with ID genotype would be excluded from PET analyses.However, further study with larger group and more specified sport activity is needed, to statistically compare novelty seeking scores and I/D alleles distribution.

These results also suggest that novelty seeking doesn't necessarily mean that individuals are interested in potentially dangerous activities. Novelty seeker may rather prefer frequent traveling, meeting new people, learning and developing new skills or he/she is generally open, flexible and available to adapt faster in the new situations. Characteristics of individual levels of novelty seeking are shown in tab. 16 (annex IV; tab. 16).

Explanation of terms

Ankyrin repeats

33- amino acids long protein motif: helix-loop-helix-β-hairpin/loop fold. Generally, number of repeates is 4-6 times, but can be repeated up to 24 times. Ankyrin repeats form a structures, called the Ankyrin repeat domains, which are involved in protein-protein interactions(Mosavi et al., 2004).

Anorexia nervosa

Multifactorial eating disorder that occurs mostly in adolescent women. Distortion of body image and persistent pursuit of thinness by food avoidance is considered to be the main diagnosis (Ayd, 1995,p. 43).

Anxiety

Anxiety is subjective emotion which can characterized by feelings of apprehension, dread or panic without presence of external stimulus (Ayd, 1995, p 51).

Attention Deficit Hyperactivity Disorder (ADHD)

Brain disorder with typical pattern of inattention and/or hyperactivity- impulsivity. It affects functioning or development of particular individual (National Institute of Mental Health, [online], available from:https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml, [cit. 2017-07-24]).

Borderline Personality Disorder (BPD)

Serious mental disorder with symptoms such as mood instability, depression and anxiety. Individuals may show suicidal and impulsive behavior (National Institute of Mental Health, [online], available from: https://www.nimh.nih.gov/health/topics/borderline-personality-disorder/index.shtml, [cit. 2017-07-18]).

Bulimia nervosa

Multisymptomatic disorder mostly occurred in young women. It is characterized by disrupted eating patterns, when bulimic patients binge eating multiple times during the week. This behavior is followed by depressed mood, self-criticism and often vomiting. Disturbances in neuroendocrine system were observed, which may be the cause of impulsive behavior (Ayd, 1995, p. 93).

Huntington disease

Involuntary movement disorder characterized by hypotonic-hyperkinetic syndrome resulting from damage of striatal neurons (Ayd, 1995, p.321; Dorko et al., 2014, p. 121).

Hyperprolactinemia

Increased levels of prolactin in the blood. It can lead to infertility in both women and men. The pituitary adenoma also may occur (Ayd, 1995, p. 324).

Iowa Gambling Task (IGT)

IGT is a psychological test (Wikipedia [online], available from:https://en.wikipedia.org/wiki/Iowa_gambling_task, [cit. 2017-08-10]).

Neuropil (lat. neuropilus)

The part of the gray matterconsisted ofunmyelinated axons and dendrites of neurons and glial branchingswith a small number of neuron bodies (Dictionary.com [online], available from:http://www.dictionary.com/browse/neuropil, [cit. 2017-07-18]).

Obsessive Compulsive Personality Disorder (OCPD)

Illness characterized by recurrent thoughts and compulsive, stereotyped, repetitive behavior, such as handwashing or counting. Although patients considered this behavior to be irrational, trying to stop makes them feel anxious (Ayd, 1995, p. 471).

Panic Disorder (PD)

Series of severe and unexplained panic attacks accompanied by multiple autonomic symptoms without phobic stimulus (Ayd, 1995, p. 483).

Parkinson's syndrome

Hypertonic-hypokinetic syndrome characterized by muscle rigidity, movement restriction and resting tremor, which disappears during learned movements and sleep (Dorko et al., 2014, p. 121).

Reward Deficiency Syndrome (RDS)

Syndrome related to many distinct mental illnesses such as addictions, compulsive or impulsive behaviors. It is likely to be associated with minor allele A1 in ANKK1 gene, located next to the dopamine receptor D2 (Encyclopedia.com [online], available from: http://www.encyclopedia.com/medicine/encyclopedias-almanacs-transcripts-and-maps/reward-deficiency-syndrome-rds#A, [cit. 2017-07-24]).

Substance dependence

Substance dependence is characterized as a chronic relapsing disorder manifested by compulsive use of the drugs, an inability to limit its intake and the appearance of withdrawal symptoms when discontinuing its intake sets (Wikipedia [online], available from:https://en.wikipedia.org/wiki/Substance_dependence, [cit. 2017-08-14]).

Tourette Syndrome (TS)

Severe to mild neuropsychiatric disorder characterized by sudden, fast and repeated tics (movement or sound), mostly of the face. Movements can differ in intensity and frequency and often stop during the sleep (MedlinePlus [online], available from:https://medlineplus.gov/ency/article/000733.htm, [cit. 2017-07-29]).

Wisconsin Card Sorting Test(WCST)

WCST is a neuropsychological test used for evaluating the prefrontal cognitive function. It measures ability of prefrontal cortex to generate hypotheses, establish response sets and fluently shift sets (Wikipedia [online], available from:https://en.wikipedia.org/wiki/Wisconsin_Card_Sorting_Test, [cit. 2017-08-10]).

List of abbreviations

5-HT 5-hydroxytriptamine or serotonin

5-HTT/SERT serotonin transporter

aa amino acid

AC adenylyl cyclase

ANKK1

BAS behavioral activation system

BIS behavioral inhibitory system

BMS behavioral maintenance system

bp base pair

cAMP cyclic adenosine monophosphate

COMT catechol-O-methyltransferase

DA dopamine

DAG diacylglycerol

DAT dopamine transporter

EPQ Eysenck's Personality Questionniare

Gly glycine

HA harm aviodance

IP3 inositol trisphosphate

kb kilobase

MAO monoamine oxidase

Met methionine

MSNs medium spiny neurons

NAc nucleus accumbens

NE norepinephrine

NS novelty seeking

PET positron emission tomography

dH_2O purified water (Aqua purificata)

PKA cAMP dependent protein kinase

PKC protein kinase

PLC phospholipase C

PS persistence

R repeat

RD reward dependence

RT room temperature

SNc substantia nigra pars compacta

SNP single nucleotide polymorphism

SNr substantia nigra pars reticularis

SS sensation seeking

TCI Temperament and Character Inventory

TCI-R Temperament and Character Inventory-revised

TH tyrosine hydroxylase

TPQ Temperament Personality Questionnaire

TBE Tris/Borate/EDTA

Val valine

VNTR variable number of tandem repeats

VTA ventral tegmental area

ZKA-PQ

References

Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Pro Natl AcadSci.*U S A 2000; 97: 8104-8109.

Aghajanian GK, Bunney BS. Dopamine "Autoreceptors": Pharmacological characterization by microiontophoretic single cell recording studies. *N S Arch Pharmacol*. 1977;297(1): 1-7. doi: 10.1007/BF00508803.

Akil M, Kolachana BS, Rothmond DA, Hyde TM, Weinberger DR, Kleinman JE. Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. *JNeurosci..* 2003; 23: 2008-2013.

Albert PR, NeveQ KA, Bunzow JR, Civellill O. Coupling of a Cloned Rat Dopamine-Da Receptor to Inhibition of Adenylyl Cyclase and Prolactin Secretion* We have previously described a cDNA which encodes a binding site with the pharmacology of the D2-dopamine receptor. *J Biol Chem*. 1990;265(4):2098-2104.

Alexander SP, Fabbro D, Kelly E, Marrion N, Peters, JA Benson HE, Faccenda E, Pawson AJ, Sharman JL, Southan C, Davies JA. THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: Enzymes. *Br J Pharmacol*. 2015;16(172):6024-6109. doi:10.1111/bph.13354/full.

Alia-Klein N, Goldstein RZ, Kriplani A, Logan J, Tomasi D, Williams B, Telang F, Shumay E, Biegon A, Craig IW, Henn F, Wang G-J, Volkow ND, Fowler JS. Brain monoamine oxidase A activity predicts trait aggression. *J Neurosci*. 2008;28(19):5099-5104. doi:10.1523/JNEUROSCI.0925-08.2008.

Archer NP, Wilkinson AV, Ranjit N,Wang J,Zhao H,Swann AC,Shete S. Genetic, psychosocial, and demographic factors associated with social disinhibition in Mexican-origin youth. *Brain Behav*. 2014;4(4):521-530. doi:10.1002/brb3.236.

Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Hum Mol Genet*. 1997;6(4):577-582. doi:10.1093/hmg/6.4.577.

Avshalumov MV, Chen BT, Marshall SP, Peña DM, Rice ME. Glutamate-dependent inhibition of dopamine release in striatum is mediated by a new diffusible messenger, H2O2. *J Neurosci*. 2003;23(7):2744-2750. doi:23/7/2744 [pii].

Ayd FJ, Jr.Lexicon of Psychiatry, Neurology and the Neurosciences. *Maryland: Williams & Wilkins*. 1995. ISBN 0-683-00298-9.

Ballard ME, Dean AC, Mandelkern MA, London ED. Striatal dopamine d2/d3 receptor availability is associated with executive function in healthy controls but not methamphetamine users. *PLoS One*. 2015;10(12). doi:10.1371/journal.pone.0143510.

Ballard ME, Mandelkern MA, Monterosso JR, Hsu E, Robertson CL, Ishibashi K, Dean AC, London ED. Low Dopamine D2/D3 Receptor Availability is Associated with Steep Discounting of Delayed Rewards in Methamphetamine Dependence. *IntlJ Neuropsychopharmacol*. 2015:1-10. doi:10.1093/ijnp/pyu119.

Barbeau A. High-level levodopa therapy in Parkinson's disease: five years later. *Trans Am Neurol Assoc.* 1974;99:160–163.

Beaulieu J-M, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011;63(1):182-217. doi:10.1124/pr.110.002642.182.

Benjamin J, OsherY, Kotler M, Gritsenko I, Nemanov L, Belmarker RH, Ebstein RP. Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT). *Mol Psychiatry*. 2000;5(1): 96-100. doi: 10.1038/sj.mp.4000640.

Bookman EB, Taylor RE, Adams-Campbell L, Kittles RA. DRD4 promoter SNPs and gender effects on Extraversion in African Americans. *Mol Psychiatry*. 2002;7(7):786-789. doi:10.1038/sj.mp.4001075.

Bourne H, Horuk R, Kuhnke J, Michel H (Eds).GPCRs: From Deorphanization to Lead Structure Identification.*Verlag Berlin Heidelberg: Springer*. 2007, pp. 5-15. ISBN 978-3-540-48981-8.

Bozzi Y, Borrelli E. Dopamine in neurotoxicity and neuroprotection: what do D2 receptors have to do with it? *Trends Neurosci.* 2006; 29:167–174. doi:10.1016/j.tins.2006.01.002

Bradberry CW, Gruen RJ, Berridge CW, Roth RH. Individual differences in behavioral measures: Correlations with nucleus accumbens dopamine measured by microdialysis. *Pharmacology Biochemistry and Behavior*. 1991;39(4): 877-882. doi: 10.1016/0091-3057(91)90047-6. ISSN 00913057.

Brewer AJ, Nielsen DA, Spellicy CJ, Hamon SC, Thompson-Lake DGY, Nielsen EM, Mahoney JJ, Kosten R, Newton TF, De La Garza R. Genetic Variation of the Dopamine Transporter (DAT1) Influences the Acute Subjective Responses to Cocaine in Volunteers with Cocaine Use Disorders. *Pharmacogenet Genomics*. 2015;6:296-304. doi:10.1097/FPC.0000000000000137.

Brody AL, Mandelkern MA, Olmstead RE, Scheibal , Hahn, E, Shiraga S, Zamora-Paja E, Farahi J, Saxena S, London ED, McCracken JT. Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Arch Gen Psychiatry*. 2006;63(7):808-816. doi:10.1001/archpsyc.63.7.808.

Cai M, Su Z, Zou H, et al. Association between the traditional Chinese medicine pathological factors of opioid addiction and DRD2/ANKK1 TaqIA polymorphisms. *BMC Complementary and Alternative Medicine*. 2015;15:209. doi:10.1186/s12906-015-0727-z.

Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu RevPharmacol Toxicol.* 2001; 41: 237-260.

Chen J, Lipska BK, Halim N, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet*. 2004;75(5):807-821. doi:10.1086/425589.

Cloninger CR. A systematic method for clinical description and classification of personality variants: A proposal. *ArchGene Psychiatry*. 1987a;44(6):573-588. doi:10.1001/archpsyc.1987.01800180093014.

Cloninger CR. Neurogenetic Adaptive Mechanisms in Alcoholsm. *Sciense*. 1987b;236:410-416.doi: 10.1126/science.2882604.

Cloninger CR. Unified biosocial theory of personality and its role in the development of anxiety states. *Psychiatric Developments*. 1986;3:167-226

Colcher A. Management of Parkinson's disease. *Expert RevNeurotherapeutics.* 2002; 2: 97-104. doi:10.1586/14737175.2.1.97

Cotecchia S, Exum S, Caron MG, Lefkowitz RJ. Regions of the alpha 1-adrenergic receptor involved in coupling to phosphatidylinositol hydrolysis and enhanced sensitivity of biological function. *Proc Natl Acad Sci U S A*. 1990;87(8):2896-2900. http://www.pnas.org/content/87/8/2896.short%5Cnpapers2://publication/doi/10.1211/jpp.58.9.0011.

Cragg SJ, Greenfield SA. Differential autoreceptor control of somatodendritic and axon terminal dopamine release in substantia nigra, ventral tegmental area, and striatum. *JNeurosci*. 1997;17(15):5738-5746.

Crocker AD. Dopamine- mechanisms of action. *Aust Prescr.* 1994;17(1):17-21. doi: 10.18773/austprescr.1994.023.

Cusin C, Serretti A, Lattuada E, Lilli R, Lorenzi C, Smeraldi E. Association study of MAO-A, COMT, 5-HT2A, DRD2, and DRD4 polymorphisms with illness time course in mood disorders. *Am J Med Genet - Neuropsychiatr Genet*. 2002;114(4):380-390. doi:10.1002/ajmg.10358.

D'Amelio M, Rossini PM. Brain excitability and connectivity of neuronal assemblies in Alzheimer's disease: from animal models to human findings.*Prog. Neurobiol*. 2012; 99: 42–60.

Dal Toso R, Sommer B, Ewert M, Herb A, Pritchett DB, Bach A, Shivers BD, Seeburg PH. The dopamine D2 receptor: two molecular forms generated by alternative splicing. *The EMBO Journal*. 1989;8(13):4025-4034.

Davis C, Loxton NJ. Addictive behaviors and addiction-prone personality traits: Associations with a dopamine multilocus genetic profile. *Addict Behav*. 2013;38(7):2306-2312. doi:10.1016/j.addbeh.2013.02.012.

Davis KL, Charney D, Coyle JT, Nemeroff C (Eds). Neuropsychopharmacology: The Fifth Generation of Progress. *Lippincott Williams & Wilkins, Philadelphia*, 2002:2080

Demchyshyn L, Sunahara RK, Miller K, Teitler M, Hoffman BJ,Kennedy JL, Seeman P,Van Tol PHH, Niznik HB. A human serotonin 1D receptor variant (5HT1D beta) encoded by an intronless gene on chromosome 6. *Proc Natl Acad Sci U S A*. 1992;89(12):5522-5526. doi:10.1073/pnas.89.12.5522.

Demetrovics Z, Varga G, Szekely A, Vereczkei A, Csorba J, Balazs H, Hoffman K, Sasvari-Szekely M, Barta C.Association between Novelty Seeking of opiate-dependent patients and the catechol-O-methyltransferase Val158Met polymorphism. *Compr Psychiatry*. 2010;51(5):510-515.doi:10.1016/j.comppsych.2009.11.008.

Derringer J, Krueger RF, Dick DM, Saccone S, Grucza RA, Agrawal A, Lin P, Almasy L, Edenberg HJ, Foroud T,Nurnberger JI, Jr., Hesselbrock VM, Kramer JR, Kuperman S, Porjesz B, Schuckit MA, Bierut LJ.The aggregate effect of dopamine genes on dependence symptoms among cocaine users: Cross-validation of a candidate system scoring approach. *Behav Genet*. 2012;42(4):626-635. doi:10.1007/s10519-012-9531-4.

Derringer J, Krueger RF, Dick DM. Predicting Sensation Seeking from Dopamine Genes. *Psychol Sci.*2010a;(April 2017). doi:10.1177/0956797610380699.

Derringer J, Krueger RF, Irons DE, Iacono WG. Harsh discipline, childhood sexual assault, and MAOA genotype: An investigation of main and interactive effects on diverse clinical externalizing outcomes. *Behav Genet*. 2010b;40(5):639-648. doi:10.1007/s10519-010-9358-9.

Derringer J, Krueger RF, McGue M, Iacono WG. Genetic and environmental contributions to the diversity of substances used in adolescent twins: A longitudinal study of age and sex effects. *Addiction*. 2008;103(10):1744-1751. doi:10.1111/j.1360-0443.2008.02305.

DeYoung CG. The neuromodulator of exploration: A unifying theory of the role of dopamine in personality. *Front Hum Neurosci*. 2013;7(November):762. doi:10.3389/fnhum.2013.00762.

Dorko F, Výborná E, Tokarčík J. Základy anatomie pro nelékařské obory. Ostravská univerzita v Ostravě. Ostrava; c2014: 120-132. ISBN: 987-80-7464-595-2

Dreher J-C, Kohn P, Kolachana B, Weinberger DR, Berman KF.Variation in dopamine genes influences responsivity of the human reward system. *Pro Natl Aca Sci.* 2009;106(2): 617-622. doi: 10.1073/pnas.0805517106.

Druga R, Grim M, Dubový P. Základy anatomie: 4a. Centrální nervový systém. 2nd ed. Praha: Galén;c2014. Chapter 10.6, Koncový mozek, telencephalon; p101-154. ISBN 978-80-7262-938-1.

Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics*. 1996;12:78-80. doi:10.1038/ng0196-78.

Ehrlich S, Morrow EM, Roffman JL, et al. The COMT Val108/158Met polymorphism and medial temporal lobe volumetry in patients with schizophrenia and healthy adults. *Neuroimage*. 2010;53(3):992-1000. doi:10.1016/j.neuroimage.2009.12.046.

Eklof A-C, Holtback U, Sundelof M, Chen S, Aperia A. Inhibition of COMT induces dopamine-dependent natriuresis and inhibition of proximal tubular Na^+,K^+-ATPase. *Kidney Int.* 1997; 52: 742–747.

Elazar Z, Siegel G, Fuchs S. Association of two pertussis toxin-sensitive G-proteins with the D2-dopamine receptor from bovine striatum. *TheEMBO Journal*. 1989;8(8):2353-2357.

Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001;158(7):1052-1057. doi:10.1176/appi.ajp.158.7.1052.

Flagel SB, Chaudhury S, Waselus M,Kelly R, Sewani S, Clinton SM, Thompson RC, Watson SJ, Akil H. Genetic background and epigenetic modifications in the core of the nucleus accumbens predict addiction-like behavior in a rat model. *Proc Natl Acad Sci*. 2016:201520491. doi:10.1073/pnas.1520491113.

Ford CP, Gantz SC, Phillips PEM, Williams JT. Control of extracellular dopamine at dendrite and axon terminals. *J Neurosci*. 2010;30(20):6975-6983. doi:10.1523/JNEUROSCI.1020-10.2010.

Freedman R. Schizophrenia. N Engl J Med 2003; 349: 1738-1749.doi: 10.1056/NEJMra035458

Fremeau RT, Duncan GE, Fornaretto MG,Dearry A, Gingrich JA, Breese GR, Caron MG. Localization of D1 dopamine receptor mRNA in brain supports a role in cognitive, affective, and neuroendocrine aspects of dopaminergic neurotransmission. *Proc Natl Acad Sci U S A*. 1991;88(9):3772-3776. doi:10.1073/pnas.88.9.3772.

Frielle T, Collins S, Daniel KW, Caron MG, Lefkowitz RJ, Kobilka BK. Cloning of the cDNA for the human β1-adrenergic receptor. *Proc Natl Acad Sci U S A*. 1987;84(22):7920-7924.

Gelernter J, Kranzler H. D2 Dopamine Receptor Gene (DRD2) Allele and Haplotype Frequencies in Alcohol Dependent and Control Subjects: No Association with Phenotype or Severity of Phenotype. *Neuropsychopharmacol*. 1999;20(6): 640-649.

Gelernter J, Kranzler H, Coccaro E, Siever L, New a, Mulgrew CL. D4 dopamine-receptor (DRD4) alleles and novelty seeking in substance-dependent, personality-disorder, and control subjects. *Am J Hum Genet*. 1997;61(5):1144-1152. doi:10.1086/301595.

Girault J-A, Greengard P. The Neurobiology of Dopamine Signaling. *Arch Neurol*. 2004;61(5):641. doi:10.1001/archneur.61.5.64.

Gjedde A, Kumakura Y, Cumming P, Linnet J, Møller A. Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. *Proc Natl Acad Sci*. 2010;107(8):3870-3875. doi:10.1073/pnas.0912319107.

Gluskin BS, Mickey BJ. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. *Transl Psychiatry*. 2016;6(3):e747. doi:10.1038/tp.2016.22.

Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry*. 2001; 158: 1367-1377.doi:10.1176/appi.ajp.158.9.1367.

Goldstein DS, Eldadah BA, Holmes C, Pechnik S, Moak J, Saleem A, Sharabi Y. Neurocirculatory abnormalities in Parkinson disease with orthostatic hypotension:

independence from levodopa treatment. *Hypertension*. 2005; 46: 1333-1339.doi:10.1161/01.HYP.0000188052.69549.e4.

Goldstein DS, Holmes C, Li ST, Bruce S, Metman LV, Cannon RO. Cardiac sympathetic denervation in Parkinson disease. *Ann Intern Med*. 2000; 133: 338-347.doi: 10.7326/0003-4819-133-5-200009050-00009.

Grandy DK, Litt M, Allen L, Bunzow JR, Marchionni M, Makam H, Reed L, Magenis RE, Civelli O. The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. *Am J Hum Genet*. 1989a;45(5):778-785.

Grandy DK, Marchionnit MA, Makam H, Stofko RE, Alfanot M, Frothinghamt L, Fischert JB, Burke-Howiet KJ, Bunzow,JR, Servert AC, Civelli O. Cloning of the cDNA and gene for a human D2 dopamine receptor (schizophrenia/alternative splicing/DRD2/introns/receptor evolution). *Biochemistry*. 1989b;86:9762-9766.

Grandy DK, Zhang YA, Bouvier C, Zhou QY, Johnson, RA, Allen L, Buck K, Bunzow JR, Salon J, Civelli O. Multiple human D5 dopamine receptor genes: a functional receptor and two pseudogenes. *Proc Natl Acad Sci U S A*. 1991;88(20):9175-9179. doi:10.1073/pnas.88.20.9175.

Grandy DK, Zhou Q, Allen L, Litt R, Magenis RE, Civelli O, Litt M. A human D1 dopamine receptor gene is located on chromosome 5 at q35.1 and identifies an EcoRI RFLP. *Am J Hum Genet*. 1990;47(5):828-834.

Groman SM, Lee B, Seu E, James AS, Feiler K, Mandelkern MA, London ED, Jentsch JD. Dysregulation of D2-mediated Dopamine Transmission in Monkeys after Chronic Escalating Methamphetamine Exposure. *J Neurosci.* 2012;32(17):5843-5852. doi: 10.1523/JNEUROSCI.12.2012.

Guimares JT, Soares-da-Silva P. The activity of MAO A and B in rat renal cells and tubules. *Life Sci.*1998;62: 727–737.

Guiramand J, Montmayeur JP, Ceraline J, Bhatia M, Borrelli E. Alternative Splicing of the Dopamine D2 Receptor Directs Specificity of Coupling to G-proteins. *Journal of Biological Chemistry*. 1995;270(13):7354-7358. doi: 10.1074/jbc.270.13.7354. ISSN 00219258.

Guo G, Ou X-M, Roettger M, Shih JC. The VNTR 2 repeat in MAOA and delinquent behavior in adolescence and young adulthood: associations and MAOA promoter activity. *Eur J Hum Genet*. 2008;16(5):626-634. doi:10.1038/sj.ejhg.5201999.

Gurevich EV, Joyce JN. Distribution of Dopamine D3 Receptor Expressing Neurons in the Human Forebrain: Comparison with D2 Receptor Expressing Neurons. *Neuropsychopharmarmacology*. 1999;20(1):60-80.

Gustavsson JP, Bergman H, Edman G, Ekselius L, von Knorring L, Linder J. Swedish universities Scales of Personality (SSP): construction, internal consistency and normative data. *Acta Psychiatr Scand*. 2000;102(3):217-225. doi:10.1034/j.1600-0447.2000.102003217.

Guyton AC, HallJE. Textbook of Medical Physiology. (11th ed.) *Elsevier*.2006;11. ISBN 978-0-7216-0240-0.

Hansen KA, Zhang Y, Colver R, Tho SPT, Plouffe L, McDonough PG. The dopamine receptor D2 genotype is associated with hyperprolactinemia. *Fertil Steril*. 2005;84(3):711-718. doi:10.1016/j.fertnstert.2005.03.040.

Harden KP, Quinn PD, Tucker-Drob EM. Genetically Influenced Change in Sensation Seeking Drives the Rise of Delinquent Behavior during Adolescence. *Developmental Science*. 2012;15(1):150-163. doi:10.1111/j.1467-7687.2011.01115.x.

He H, Wu H, Yang L, Gao F, Fan Y, Feng J, Ma X. Associations between dopamine D2 receptor gene polymorphisms and schizophrenia risk: a PRISMA compliant meta-analysis. *Neuropsychiatr Dis Treat*. 2016;12:3129-3144. doi:10.2147/NDT.S118614.

Heyer NJ, Echeverria D, Martin MD, Farin FM, Woods JS. Catechol O-Methyltransferase (COMT) VAL158MET Functional Polymorphism, Dental Mercury Exposure, and Self-Reported Symptoms and Mood. Journal of toxicology and environmental health Part A. 2009;72(9):599-609. doi:10.1080/15287390802706405.

Holmboe K, Fearon RMP, Sasvari-Szekely M, Nemoda Z, Csibra G, Johnson MH. Polymorphisms in Dopamine System Genes are Associated with Individual Differences in Attention in Infancy. *Dev Psychol*. 2010;46(2):404-416. doi:10.1037/a0018180.

Holmes AJ, Hollinshead MO, Roffman JL, Smoller JW, Buckner RL. Individual Differences in Cognitive Control Circuit Anatomy Link Sensation Seeking, Impulsivity, and Substance Use. *J Neurosci*. 2016;36(14):4038-4049. doi:10.1523/JNEUROSCI.3206-15.2016.

Huang HY, Lee IH, Chen KC, Yeh TL, Chen PS, Yang YK. Association of novelty seeking scores and striatal dopamine D_2/D_3 receptor availability of healthy volunteers: single photon emission computed tomography with ^{123}i-iodobenzamide. *J Formos Med Assoc*. 2010;109(10):736-739. doi:10.1016/S0929-6646(10)60119-2.

Huang Y, Cate SP, Battistuzzi C, Oquendo MA, Brent D, Mann JJ. An Association between a Functional Polymorphism in the Monoamine Oxidase A Gene Promoter, Impulsive Traits and Early Abuse Experiences. *Neuropsychopharmacology*. 2004;29(8):1498-1505. doi:10.1038/sj.npp.1300455.

Jaworska N, Cox SM, Casey KF, Boileau I, Cherkasova M, Larcher K, Dagher A, Benkelfat C, Leyton M. Is there a relation between novelty seeking, striatal dopamine release and frontal cortical thickness? 2017;12(3):1-19. doi:10.1371/journal.pone.0174219.

John OP, Srivastava S. The Big Five trait taxonomy: History, measurement, and theoretical perspectives. *Handb Personal Theory Res*. 1999;2(510):102-138. doi:citeulike-article-id:3488537.

Jönsson EG, Burgert E, Crocq M-A, Gustavsson JP, Forslund K, Mattila-Evenden M, Rylander Gunnar, Flyckt LK, Bjerkenstedt L, Wiesel F-A, Asberg M, Bergman H. Association study between dopamine D3 receptor gene variant and personality traits. *Am J Med Genet B Neuropsychiatr Genet*. 2003;117B(1):61-65. doi:10.1002/ajmg.b.10009.

Joyce PR, Rogers GR, Miller AL, Mulder RT, Luty SE, Kennedy MA. Polymorphisms of DRD4 and DRD3 and risk of avoidant and obsessive personality traits and disorders. *Psychiatry Res*. 2003;119(1-2):1-10. doi:10.1016/S0165-1781(03)00124-0.

Kaiser R, Könneker M, Henneken M, Dettling M, Müller-Oerlinghausen B, Roots I, Brockmöller, J. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. *Mol Psychiatry*. 2000;5(4):418-424. doi:10.1038/sj.mp.4000729.

Kebabian JW, Petzold GL, Greengard P. Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the “dopamine receptor”. *Proc Natl Acad Sci U S A*. 1972;69(8):2145-2149. doi:10.1073/PNAS.69.8.2145.

Kereszturi E, Kiraly O, Barta C, Molnar N, Sasvari-Szekely M, Csapo Z. No direct effect of the -521 C/T polymorphism in the human dopamine D4 receptor gene promoter on transcriptional activity. *BMC Mol Biol*. 2006;7(1):18. doi:10.1186/1471-2199-7-18.

Khan ZU, Mrzljak L, Gutierrez A, de la Calle A, Goldman-Rakic PS. Prominence of the dopamine D2 short isoform in dopaminergic pathways. *Proc Natl Acad Sci U S A:Neurobiology*. 1998;95(13):7731-7736.doi:10.1073/pnas.95.13.7731.

Khanzada N, Butler M, Manzardo A. GeneAnalytics Pathway Analysis and Genetic Overlap among Autism Spectrum Disorder, Bipolar Disorder and Schizophrenia. *Int J Mol Sci*. 2017;18(3):527. doi:10.3390/ijms18030527.

Kita JM, Kile BM, Parker LE, Wightman RM. In vivo measurement of somatodendritic release of dopamine in the ventral tegmental area. *Synapse*. 2009;63(11):951-960. doi:10.1002/syn.20676.

Kobilka BK, Dixon R, Frielle T, et al. cDNA for the human β2-adrenergic receptor: a protein with multiple membrane-spanning domains and encoded by a gene whose chromosomal location is shared with that of the receptor for platelet-derived growth factor. *Proc Natl Acad Sci U S A*. 1987;84(1):46-50. doi:10.1073/pnas.84.1.46.

Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. *Neuron*. 1998; 21: 467-476.

Kotyuk E, Duchek J, Head D, Szekely A, Goate AM, Balota DA. A genetic variant (COMT) coding dopaminergic activity predicts personality traits in healthy elderly. *Pers Individ Dif*. 2015;82:61-66. doi:10.1016/j.paid.2015.03.012.

Koukolík F. Lidský mozek: Funkční systémy. Norma a poruchy. 3rd ed. Praha: Galén; c2012. Chapter 7.2, Bazální ganglia; p. 220-224. ISBN 978-80-7262-771-4.

Kurt H, Dikmen M, Basaran A, et al. Dopamine D2 receptor gene -141C Insertion/Deletion polymorphism in Turkish schizophrenic patients. *Mol Biol Rep*. 2011;38(2):1407-1411. doi:10.1007/s11033-010-0244-6.

Lacey MG, Mercuri NB, North RA. Dopamine acts on D2 receptors to increase potassium conductance in neurones of the rat substantia nigra zona compacta. *J Physiol*. 1987;392:397-416. doi:10.1113/jphysiol.1987.sp016787.

Lafuente A, Bernardo M, Mas S, Crescenti A, Aparici M, Gassó P, Catalan R, Mateos JJ, Lomeña F, Parellada E. Dopamine transporter (DAT) genotype (VNTR) and phenotype in extrapyramidal symptoms induced by antipsychotics. *Schizophr Res*. 2017;90(1):115-122. doi:10.1016/j.schres.2006.09.031.ISSN 09209964.

Lakatos K, Nemoda Z, Birkas E, Ronai Z, Kovacs E, Ney K, Toth I, Sasvari-Szekely M, Gervai J. Association of D4 dopamine receptor gene and serotonin transporter promoter polymorphisms with infants' response to novelty. *Mol Psychiatry*. 2003;8(1):90-97. doi:10.1038/sj.mp.4001212.

Lang AE, Lozano AM. Parkinson's disease: First of two parts. *N Engl J Med* 1998; 339: 1044-1053.

Lankford KL, Demello FG, Klein WL. Inhibit Growth. *Neurobiology*. 1988;85(April):2839-2843.

Laruelle M, Kegeles LS, Abi-Dargham A. Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Ann NY Acad Sci* 2003; 1003: 138-158.

Lavant B. The D3 Dopamine Receptor: Neurobiology and Potential Clinical Relevance. *Pharmacol Rev*. 1997;49(3):231-252.

Lawford BR, McD. Young R, Swagell CD, et al. The C/C genotype of the C957T polymorphism of the dopamine D2 receptor is associated with schizophrenia B. *Schizophr Res*. 2005;73:31-37. doi:10.1016/j.schres.2004.08.020.

Lawrence AD, Brooks DJ. Ventral striatal dopamine synthesis capacity is associated with individual differences in behavioral disinhibition. *Front Behav Neurosci*. 2014;8(March):86. doi:10.3389/fnbeh.2014.00086.

Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA. Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci*. 2009;29(47):14734-14740. doi:10.1523/JNEUROSCI.3765-09.2009.

Lee LO, Prescott CA. Association of the catechol-O-methyltransferase val158met polymorphism and anxiety-related traits: a meta-analysis. *Psychiatr Genet*. 2014;24(2):52-69. doi:10.1097/YPG.0000000000000018.

Li T, Yu S, Du J, Chen H, Jiang H, Xu K, Fu Y, Wang D, Zhao M. Role of novelty seeking personality traits as mediator of the association between COMT and onset age of drug use in Chinese heroin dependent patients. *PLoS One*. 2011;6(8). doi:10.1371/journal.pone.0022923.

Light KJ, Joyce PR, Luty SE, Mulder RT, Frampton CM , Joyce LRM, Miller AL, Kennedy M. Preliminary evidence for an association between a dopamine D3 receptor gene variant and obsessive-compulsive personality disorder in patients with major depression. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141B(4):409-413. doi:10.1002/ajmg.b.30308.

Lindgren N, Usiello A, Goiny M, Haycock J, Erbs E, Greengard P, Hö Kfelt T, Borrelli E, Fisone G. Distinct roles of dopamine D2L and D2S receptor isoforms in the regulation of protein phosphorylation at presynaptic and postsynaptic sites.*Proc Natl Acad Sci*. 2003;100(7):4305-4309. doi: 10.1073/pnas.0730708100. ISSN 00278424.

Linnet J, Møller A, Peterson E, Gjedde A, Doudet D. Dopamine release in ventral striatum during Iowa Gambling Task performance is associated with increased excitement levels in pathological gambling. *Addiction*. 2011;106(2):383-390. doi:10.1111/j.1360-0443.2010.03126.

Linnet J, Peterson E, Doudet DJ, Gjedde A, Møller A. Dopamine release in ventral striatum of pathological gamblers losing money. *Acta Psychiatr Scand*. 2010;122(4):326-333. doi:10.1111/j.1600-0447.2010.01591.

Lusher JM, Chandler C, Ball D. Dopamine D4 receptor gene (DRD4) is associated with Novelty Seeking (NS) and substance abuse: the saga continues... *Mol Psychiatry*. 2001;6(5):497-499. doi:10.1038/sj.mp.4000918.

Luttrell LM, Lefkowitz RJ. The role of β-arrestins in the termination and transduction of G-protein-coupled receptors signals. *J Cell Sci.* 2002;115:455-465

Mahan LC, Burch RM, Monsma FJ, Sibley DR. Expression of striatal D1 dopamine receptors coupled to inositol phosphate production and Ca2+ mobilization in Xenopus oocytes. *Proc Natl Acad Sci U S A*. 1990;87(6):2196-2200.

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry*. 2002;159(4):652-654. doi:10.1176/appi.ajp.159.4.652.

McAllister TW. Polymorphisms in Genes Modulating the Dopamine System: Do They Influence Outcome and Response to Medication After Traumatic Brain Injury? *The Journal of head trauma rehabilitation.* 2009;24(1):65-68. doi:10.1097/HTR.0b013e3181996e6b.

Martinez D, Slifstein M, Broft A, et al. Imaging Human Mesolimbic Dopamine Transmission With Positron Emission Tomography. Part II: Amphetamine-Induced Dopamine Release in the Functional Subdivisions of the Striatum. *J Cereb blood flow Metab*. 2003;23:285-300. doi:10.1097/01.WCB.0000048520.34839.1A.

McCrae RR, Terracciano A. Universal Features of Personality Traits From the Observer's Perspective: Data From 50 Cultures. *J Pers Soc Psychol*. 2005;88(3):547-561. doi:10.1037/0022-3514.88.3.547.

Melka MG, Castellani CA, Laufer BI, Rajakumar RN, O'Reilly R, Singh SM. Olanzapine induced DNA methylation changes support the dopamine hypothesis of psychosis. *J Mol psychiatry*. 2013;1(1):19. doi:10.1186/2049-9256-1-19.

Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF. Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci 2002; 5: 267-271.

Mill J, Curran S, Kent L,Kent L, Richards S, Gould A, Virdee V, Huckett L, Sharp J, Batten C, Fernando S, Simanoff E, Thompson M, Zhao J, Sham P, Taylor E, Asherson P. Attention deficit hyperactivity disorder (ADHD) and the dopamine D4 receptor gene: evidence of association but no linkage in a UK sample. *Mol Psychiatry*. 2001;6(4):440-444. doi:10.1038/sj.mp.4000881.

Mill JS, Caspi A, McClay J, Sugden KPS, Asherson P, Craig I, McGuffin P, Braithwaite A, Poulton R, Moffitt TE. The dopamine D4 receptor and the hyperactivity phenotype: A developmental-epidemiological study. *Mol Psychiatry*. 2002;7:383-391. doi:10.1038/sj.mp.4000984.

Millan M, Dekeyne A, Rivet J, Dubuffet T, Lavielle G. S33084, a Novel, Potent, Selective, and Competitive Antagonist at Dopamine D3-Receptors: II. Functional and Behavioral Profile Compared with GR218, 231 and L741, 626. *J Pharmacol Exp Ther*. 2000;293(3):1063-1073.

Minowa MT, Minowa T, Monsma FJ, Sibley DR, Mouradian MM. Characterization of the 5' flanking region of the human D1A dopamine receptor gene. *Proc Natl Acad Sci U S A*. 1992;89:3045-3049. doi:10.1073/pnas.89.7.3045.

Monsma FJ, Mahan LC, McVittie LD, Gerfen CR, Sibley DR. Molecular cloning and expression of a D1 dopamine receptor linked to adenylyl cyclase activation. *Proc Natl Acad Sci U S A*. 1990;87(17):6723-6727.

Montag C, Jurkiewicz M, Reuter M. The role of the catechol-O-methyltransferase (COMT) gene in personality and related psychopathological disorders. *CNS Neurol Disord Drug Targets*. 2012;11(3):236-250. doi:10.2174/187152712800672382.

Montag C, Markett S, Basten U, Stelzel C, Fiebach C, Turhan Canli T, Reuter M. Epistasis of the DRD2/ANKK1 Taq Ia and the BDNF Val66Met Polymorphism Impacts Novelty Seeking and Harm Avoidance. *Neuropsychopharmacology*. 2010;35(9):1860-1867. doi:10.1038/npp.2010.55.

Montmayeur JP, Borrelli E. Transcription mediated by a cAMP-responsive promoter element is reduced upon activation of dopamine D2 receptors. *Proc Natl Acad Sci U S A*. 1991;88:3135-3139. doi:10.1073/pnas.88.8.3135.

Morales AM, Kohno M, Robertson CL, Dean AC, Mandelkern MA, London ED. Gray-matter volume, midbrain dopamine D2/D3 receptors and drug craving in methamphetamine users. *Mol Psychiatry*. 2015a;20(6):764-771. doi:10.1038/mp.2015.47.

Mosavi LK, Cammett TJ, Desrosiers DC, Peng Z. The ankyrin repeat as molecular architecture for protein recognition. *Protein Science : A Publication of the Protein Society*. 2004;13(6):1435-1448. doi:10.1110/ps.03554604.

Munafò MR, Yalcin B, Willis-Owen SA, Flint J. Association of the Dopamine D4 Receptor (DRD4) Gene and Approach-Related Personality Traits: Meta-Analysis and New Data. *Biol Psychiatry*. 2008;63(2):197-206. doi:10.1016/j.biopsych.2007.04.006.

Nader MA, Czoty PW. PET imaging of dopamine D2 receptors in monkey models of cocaine abuse: Genetic predisposition versus environmental modulation. *Am J Psychiatry*. 2005;162(8):1473-1482. doi:10.1176/appi.ajp.162.8.1473.

Nakajima S, Caravaggio F, Boileau I, et al. Lack of age-dependent decrease in dopamine D3 receptor availability: a [11C]-(+)-PHNO and [11C]-raclopride positron emission tomography study. *J Cereb Blood Flow Metab*. 2015;35(October 2014):1812-1818. doi:10.1038/jcbfm.2015.129.

Naňka O, Elišková M. Přehled Anatomie. 3rd ed. Praha: Galén, c2015. Chapter 16, Centrální nervový system;p. 269-299. ISBN 978-80-7492-206-0.

Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Del Tredici K, et al. Correlation of Alzheimer Disease Neuropathologic Changes With Cognitive Status: A Review of the Literature. *J. Neuropathol. Exp. Neurol.*2012;71(5):362-381. doi:10.1097/NEN.0b013e31825018f7.

Nemoda Z, Lyons-Ruth K, Szekely A, Bertha E, Faludi G, Sasvari-Szekely M. Association between dopaminergic polymorphisms and borderline personality traits among at-risk young adults and psychiatric inpatients. *Behav Brain Funct*. 2010;6(1):4. doi:10.1186/1744-9081-6-4.

Nemoda Z, Szekely A, Sasvari-Szekely M. Polymorphisms in adolescence and young adulthood. *Neurosci Biobehav Rev*. 2011;35(8):1665-1686. doi:10.1016/j.neubiorev.2011.04.002.PSYCHOPATHOLOGICAL.

Neve, KA (ed.). The Dopamine Receptors. 2nd ed. Portland, USA: Humana Press, 2010. ISBN 978-1-60327-332-9.

Neve KA, Neve RL, Fidel S, Janowsky A, Higgins G. Increased abundance of alternatively spliced forms of D2 dopamine receptor mRNA after denervation. *Proc Natl Acad Sci U S A*. 1991;88(7):2802-2806. doi:10.1073/pnas.88.7.2802.

Neville MJ, Johnstone EC, Walton RT (2004). Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat 23: 540–545. doi:10.1002/humu.20039.

Nieoullon A. Dopamine and the regulation of cognition and attention. *Prog Neurobiol.* 2002; 67: 53-83.

Nikolova YS, Ferrell RE, Manuck SB, Hariri AR. Multilocus Genetic Profile for Dopamine Signaling Predicts Ventral Striatum Reactivity. *Neuropsychopharmacology*. 2011;36(9):1940-1947. doi:10.1038/npp.2011.82.

Nkam I, Ramoz N, Breton F, Mallet J, Gorwood P, Dubertret C. Impact of DRD2/ANKK1 and COMT polymorphisms on attention and cognitive functions in schizophrenia. *PLoS One*. 2017;12(1):1-15. doi:10.1371/journal.pone.0170147.

Okuyama Y, Ishiguro H, Nankai M, Shibuya H, Watanabe a, Arinami T. Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. *Mol Psychiatry*. 2000;5(1):64-69. doi:10.1038/sj.mp.4000563.

Ono Y, Manki H, Yoshimura K, et al. Association between dopamine D4 receptor (D4DR) exon III polymorphism and novelty seeking in Japanese subjects. *Am J Med Genet - Neuropsychiatr Genet*. 1997;74(5):501-503. doi:10.1002/(SICI)1096-8628(19970919)74:5<501::AID-AJMG9>3.0.CO;2-Q.

Ortet G, Ibáñez MI, Llerena A, Torubia R. The Underlying traits of the Karolinska Scales of Personality (KSP). *Eur J Psychol Assess.* 2002;18(2):139-148

Oswald LM, Wand GS, Wong DF, Brown CH, Kuwabara H, Brašić JR. Risky decision-making and ventral striatal dopamine responses to amphetamine: A positron emission tomography [11C]raclopride study in healthy adults. *Neuroimage*. 2015;113:26-36. doi:10.1016/j.neuroimage.2015.03.022.

Palmer AM, DeKosky ST. Monoamine neurons in aging and Alzheimer's disease. J Neural Transm Gen Sect 1993; 91: 135-159.

Patel JC, Rice ME. Classification of H2O2 as a neuromodulator that regulates striatal dopamine release on a subsecond time scale. *ACS Chem Neurosci*. 2012;3(12):991-1001. doi:10.1021/cn300130b.

Pečeňák J. Symptomatika schizofrénie: Schizofrénia – koncepty, symptómy, diagnostické kritériá. Bratislava: *Univerzita Komenského v Bratislave*. 2014:pp. 20-23. ISBN 978-80-223-3540-9.

Peralta EG, Ashkenazi A, Winslow JW, Smith DH, Ramachandran J, Capon DJ. Distinct primary structures, ligand-binding properties and tissue- specific expression of four human muscarinic acetylcholine receptors Ernest. *EMBO J*. 1987;6(13):3923-3929.

Perlman WR, Weickert CS, Akil M, Kleinman JE. Postmortem investigations of the pathophysiology of schizophrenia: the role of susceptibility genes. *J Psychiatry Neurosci.* 2004; 29: 287-293.

Peterson E, Møller A, Doudet DJ, Bailey CJ, Hansen KV, Rodell A, Linnet J, Gjedde A. Pathological gambling: Relation of skin conductance response to dopaminergic neurotransmission and sensation-seeking. *Eur Neuropsychopharmacol*. 2010;20(11):766-775. doi:10.1016/j.euroneuro.2010.07.010.

Pritchett DB, Bach W, Wozny M, Taleb O, Dal Toso R, Shih JC, Seeburg PH. Structure and functional expression of cloned rat serotonin 5HT-2 receptor. *EMBO J*. 1988;7(13):4135-4140.

Ray LA, MacKillop J, Hesterberg K, Bryan A, McGeary J, Hutchison KE. The Dopamine D4 Receptor (DRD4) Gene Exon III Polymorphism, Problematic Alcohol Use, and Novelty Seeking: Direct and Mediated Genetic Effects. Addiction biology. 2009;14(2):238-244. doi:10.1111/j.1369-1600.2008.00120.x.

Robertson CL, Ishibashi K, Mandelkern MA, Brown AK, Ghahremani DG, Sabb F, Bilder R, Cannon T, Borg J, London ED. Striatal D1- and D2-type Dopamine Receptors Are Linked to Motor Response Inhibition in Human Subjects. *J Neurosci*. 2015;35(15):5990-5997. doi:10.1523/JNEUROSCI.4850-14.2015.

Ronai Z, Szekely A, Nemoda Z, Lakatos K, Gervai J, Staub M, Sasvari-Szekely M. Association between Novelty Seeking and the −521 C/T polymorphism in the promoter region of the DRD4 gene. *Mol Psychiatry*. 2001;6(1):35-38. doi:10.1038/sj.mp.4000832.

Roth J, Růžička E. Nemoci extrapyramidoveho systemu. Stručný klinickýpřehled. Sanofi, Praha 1998:1-57.

Rouge-Pont F, Usiello A, Benoit-Marand M, Gonon F, Piazza PV, Borrelli E. Changes in extracellular dopamine induced by morphine and cocaine: crucial control by D2 receptors. *J Neurosci*. 2002;22(8):3293-3301. doi:20026322.

Roy DS, Arons A, Mitchell TI, Pignatelli M, Ryan TJ, Tonegawa S. Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. *Nature*. 2016;531(7595):508-512. doi:10.1038/nature17172.

Haber SN, Knutson B. The Reward Circuit: Linking Primate Anatomy and Human Imaging.*Neuropsychopharmacology*. 2010;35(1):4-26. doi:10.1038/npp.2009.129.

Sander T, Harms H, Dufeu P, Kuhn S, Rommelspacher H, Schmidt LG. Dopamine D4 receptor exon III alleles and variation of novelty seeking in alcoholics. *Am J Med Genet - Neuropsychiatr Genet*. 1997;74(5):483-487. doi:10.1002/(SICI)1096-8628(19970919)74:5<483::AID-AJMG5>3.0.CO;2-P.

Savitz JB, Ramesar RS. Genetic variants implicated in personality: A review of the more promising candidates. *Am J Med Genet - Neuropsychiatr Genet*. 2004;131 B(1):20-32. doi:10.1002/ajmg.b.20155.

Sawa A, Snyder SH. Schizophrenia: diverse approaches to a complex disease. *Science.* 2002;296(April):692-695.

Schatzberg AF, Nemeroff CB (Eds).Textbook of Psychopharmacology. 3rd eddition. Washington, D.C.: *American Psychiatric Publishing,* 2004:6-87. ISBN 1-58562-060-2.

Schoots O, Van Tol HHM. The human dopamine D4 receptor repeat sequences modulate expression. *Pharmacogenomics J*. 2003;3(6):343-348. doi:10.1038/sj.tpj.6500208.

Seeman P, Nam D, Ulpian C, Liu ISC, Tallerico T. New dopamine receptor, D2(Longer), with unique TG splice site, in human brain. *Mol Brain Res*. 2000;76:132-142. doi:10.1016/S0169-328X(99)00343-5.ISSN 0169328x.

Seeman MV, Seeman P. Psychosis and Positron Tomography. *Can J Psychiatry*. 1988;33(May)

Senogles SE. The D2 Dopamine Receptor Isoforms Signal Through Distinct Giα Proteins to Inhibit Adenylyl Cyclase: A Study with Site-Directed Mutant Giα Proteins. *J Biol Chem*. 1994;269(37):23120-23127.

Senogles SE, Benovic JL, Amlaiky N,Unson C, Milligan G, Vinitsky R, Spiegel M, Caron M G. The D2-dopamine receptor of anterior pituitary is functionally associated with a pertussis toxin-sensitive guanine nucleotide binding protein. *J Biol Chem*. 1987;262(10):4860-4867.

Shih JC, Thompson RF. Monoamine oxidase in neuropsychiatry and behavior. *Am J Hum Genet*. 1999;65:593-598. doi:10.1086/302562.

Smith Y, Villalba R. Striatal and extrastriatal dopamine in the basal ganglia: an overview of its anatomical organization in normal and Parkinsonian brains. *Mov Disord.* 2008;23(S3):S534–S547. doi: 10.1002/mds.22027.

Smith CT, Dang LC, Buckholtz JW, Tetreault AM, Cowan RL, Kessler RM, Zald DH. The impact of common dopamine D2 receptor gene polymorphisms on D2/D3 receptor availability: C957T as a key determinant in putamen and ventral striatum. *Transl Psychiatry*. 2017;7(4):e1091. doi10.1030/tp.2017.45

Soares-da-Silva P, Serrao MP, Vieira-Coelho MA. Apical and basolateral uptake and intracellular fate of dopamine precursor L-DOPA in LLC-PK 1 cells. *Am Physiol Soc.* 1998; 274(2): F243–F251.

Spellicy CJ, Harding MJ, Hamon SC, Mahoney JJ, Reyes JA, Kosten TR, Newton TF, De La Garza R, Nielsen DA.A variant in *ANKK1* modulates acute subjective effects of cocaine: a preliminary study. *Genes Brain Behav*. 2014;13(6):559-564. doi:10.1111/gbb.12121.

Spencer HG. The correlation between relatives on the supposition of genomic imprinting. *Genetics*. 1918;52(1):399-433. doi:10.1017/S0080456800012163.

Stallings MC, Hewitt J, Cloninger CR, Heath AC, Lindon JE. Genetic and Environmental Structure of the Tridimensional Personality Questionnaire: Three or Four Temperament Dimensions? *Journal of Personality and Social Psychology*. 1996;70(1):127-140. doi:10.1037/0022-3514.70.1.127.

Steece-Collier K, Maries E, Kordower JH. Etiology of Parkinson's disease: Genetics and environment revisited. *Proc Natl Acad Sci U S A*. 2002; 99: 13972-13974.

Steinberg L, Albert D, Cauffman E, Banich M, Ucla SG, Woolard J. Age Differences in Sensation Seeking and Impulsivity as Indexed by Behavior and Self-Report: Evidence for a Dual Systems Model. *Dev Psychol*. 2008;44(6):1764-1778. doi:10.1037/a0012955.

Stoel RD, De Geus EJC, Boomsma DI. Genetic analysis of sensation seeking with an extended twin design. *Behav Genet*. 2006;36(2):229-237. doi:10.1007/s10519-005-9028-5.

Strobel A, Wehr A, Michel A, Brocke B. Association between the dopamine D4 receptor (DRD4) exon III polymorphism and measures of Novelty Seeking in a German population. *Mol Psychiatry*. 1999;4(4):378-384.

Strous RD, Bark N, Parsia SS, Volavka J, Lachman HM. Analysis of a functional catechol-O-methyltransferase gene polymorphism in schizophrenia: Evidence for association with aggressive and antisocial behavior. *Psychiatry Res*. 1997a;69(2-3):71-77. doi:10.1016/S0165-1781(96)03111-3.

Strous RD, Bark N, Woerner M, Lachman HM. Lack of association of a functional catechol-O-methyltransferase gene polymorphism in schizophrenia. *Biol Psychiatry*. 1997b;41(4):493-495. doi:10.1016/S0006-3223(96)00474-X.

Sullivan PF, Fifield WJ, Kennedy MA, Mulder RT, Sellman DJ, Joyce PR. No association between novelty seeking and the type 4 dopamine receptor gene (DRD4) in two New Zealand samples. *Am J Psychiatry*. 1998;155(1):98-101.

Sullivan PF, Fifield WJ, Kennedy MA, Mulder RT, Sellman JD, Joyce PR. Novelty Seeking and a Dopamine Transporter Gene Polymorphism. *Biol Psychiatry*. 1997;42(42):1070-1072. doi:10.1016/S0006-3223(97)00346-6.

Sulzer D, Cragg SJ, Rice ME. Striatal Dopamine Neurotransmission: Regulation of Release and Uptake.*Basal Ganglia.*2016;6(3):123-148. doi:10.1016/j.baga.2016.02.001.

Svrakic DM, Cloninger RC. Epigenetic Perspective on Behavior Development, Personality, and Personality Disorders. *Psychiatria Danubina*. 2010;22(2):153-166.

Swarzenski BC, Tang L, Oh YJ, O'Malley KL, Todd RD. Morphogenic potentials of D2, D3, and D4 dopamine receptors revealed in transfected neuronal cell lines. *Proc Natl Acad Sci U S A*. 1994;91(2):649-653.

Takada A, Curzon G.Serotonin in the Central Nervous System and Periphery. Amsterdam, Netherlands: *Elsevier Science B.V*. 1995:3-96. ISBN 0-444-81965-7.

Tang L, Todd RD, O'Malley KL. Dopamine D2 and D3 receptors inhibit dopamine release. *J Pharmacol Exp Ther*. 1994;270(2):475-479.

Tepper JM, Sun BC, Martin LP, Creese I. Functional roles of dopamine D2 and D3 autoreceptors on nigrostriatal neurons analyzed by antisense knockdown in vivo. *J Neurosci*. 1997;17(7):2519-2530. ISSN: 0270-6474

Thomson CJ, Carlson SR, Rupert JL. Association of a common D3 dopamine receptor gene variant is associated with sensation seeking in skiers and snowboarders. *J Res Pers*. 2013;47(2):153-158. doi:10.1016/j.jrp.2012.11.004.

Thomson CJ, Rajala AK, Carlson SR, Rupert JL. Variants in the dopamine-4-receptor gene promoter are not associated with sensation seeking in skiers. *PLoS One*. 2014;9(4). doi:10.1371/journal.pone.0093521.

Tong J, Meyer JH, Furukawa Y, et al. Distribution of Monoamine Oxidase Proteins in Human Brain: Implications for Brain Imaging Studies. *J Cereb Blood Flow Metab*. 2013;33(6):863-871. doi:10.1038/jcbfm.2013.19.

Trillo L, Das D, Hsieh W, Medina B, Moghadam S, Lin B, Dang V, Sanchez MM, De Miguel Z, Ashford JW, Salehi A. Ascending monoaminergic systems alterations in Alzheimer's disease. translating basic science into clinical care.*Neurosci Biobehav Rev*. 2013;37:1363–1379. doi: 10.1016/j.neubiorev.2013.05.008.

Tripton KF, Dostert P, BenedettiMS. *Monoamine Oxidase and Disease: Prospects for Therapy with Reversible Inhibitors*. Orlando, Florida 32887: *Academic Press.* 1984:291-330. ISBN 0-12-691660-8.

Trudell ML, Izenwasser S. *Dopamine Transporters: Chemistry, Biology, and Pharmacology*. New Jersey: *John Wiley& Sons*. 2008:4-62. ISBN 978-0-470-11790-3.

Tsai G, Coyle JT. Glutamatergic mechanisms in schizophrenia. Annu Rev Pharmacol Toxicol 2002; 42: 165-179.

Twarog BM, Page IH. Serotonin content of some mammalian tissues and urine and a method for its determination. Am J Physiol 1953; 175: 157-161.

Usiello A, Baik J-H, Rougé-Pont F, Picetti R, Dierich A, LeMeur M, Piazza PV, Borrelli, E. Distinct functions of the two isoforms of dopamine D2 receptors. *Nature*. 2000;408(6809):199-203. doi: 10.1038/35041572. ISSN 00280836.

Van Tol HHM. The Dopamine Receptor D4. In: The National Institute on Drug Abuse: Archives [online]. Maryland: The National Institute on Drug Abuse. 1993:20-38. [cit. 2017-07-27]. Available form: https://archives.drugabuse.gov/pdf/monographs/monograph161/020-038_VanTol.pdf

Volkow ND, Wang G-J, Logan J, Logan J, Alexoff D, Fowler JS, Thanos PK, Wong C, Casado V, Ferre S, Tomasi D.nCaffeine increases striatal dopamine D2/D3 receptor availability in the human brain. *Transl Psychiatry*. 2015;5(4):e549. doi:10.1038/tp.2015.46.

Weiland BJ, Heitzeg MM, Zald D, Cummiford C, Love T, Zucker RA, Zubieta JK. Relationship between impulsivity, prefrontal anticipatory activation, and striatal dopamine release during rewarded task performance. *Psychiatry Res - Neuroimaging*. 2014;223(3):244-252. doi:10.1016/j.pscychresns.2014.05.015.

Wiers CE, Shumay E, Cabrera E, Shokri-Kojori E, Gladwin TE, Skarda E, Cunningham SI, Kim SW, Wong TC, Tomasi D, Wang G-J, Volkow ND. Reduced sleep duration mediates decreases in striatal D2/D3 receptor availability in cocaine abusers. *Transl Psychiatry*. 2016;6:e752. doi:10.1038/tp.2016.14.

Wilkinson AV, Gabriel KP, Wang J, Bondy M, Dong Q, Wu X, Shete S, Spitz MR. Sensation-seeking genes and physical activity in youth. *Genes, Brain Behav*. 2013;12(2):181-188. doi:10.1111/gbb.12006.

Wong AH, Van Tol HHM. Schizophrenia: from phenomenology to neurobiology. *Neurosci Biobehav Rev*. 2003; 27: 269-306.

Yao J, Pan Y-q, Ding M, Pang H, Wang B-j. Association between DRD2 (rs1799732 and rs1801028) and ANKK1 (rs1800497) polymorphisms and schizophrenia: A meta-analysis. *Am J Med Genet Part B*. 2014;168B:1-13. doi:10.1002/ajmg.b.32281.

Yim CY, Mogenson GJ. Electrophysiological studies of neurons in the ventral tegmental area of Tsai. *Brain Res.* 1980;181(2):301–313. doi: 10.1016/0006-8993(80)90614-9.

Yuan A, Su L, Yu S, Li C, Yu T, Sun J. Association between *DRD2/ANKK1* TaqIA Polymorphism and Susceptibility with Tourette Syndrome: A Meta-Analysis. Lustig AJ, ed. *PLoS ONE*. 2015;10(6):e0131060. doi:10.1371/journal.pone.0131060.

Zald DH, Cowan RL, Riccardi P, et al. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. *J Neurosci*. 2008;28(53):14372-14378. doi:10.1523/JNEUROSCI.2423-08.2008.

Zahari Z, Salleh MR, Zahri @ Johari MK, Musa N, Ismail R. A Nested Allele-Specific Multiplex Polymerase Chain Reaction Method for the Detection of DRD2 Polymorphisms. *The Malaysian Journal of Medical Sciences : MJMS*. 2011;18(4):44-57.

Zhang S, Jiang W, Tang X, et al. Association study of dopamine transporter gene (DAT1) variable tandem repeat sequence (VNTR) with obsessive-compulsive disorder in Chinese Han population. *Int J Clin Exp Med*. 2015;8(3):4606-4610.

Zhang Y, Bertolino A, Fazio L, et al. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *ProcNatlAcadSci U S A*. 2007;104(51):20552-20557. pm:18077373.doi: 10.1073/pnas.0707106104.

Zuckerman, M. Sensation Seeking: Beyond the optimal level of arousal. Hillsdale, New Jersey: *Lawrence Erlbaum Associates*. 1979. ISBN 978-1-84872-469-3.

Zuckerman M. Good and bad humours: Biochemical bases of personality and its disorders. *Psychol Sci*. 1995;6(6):325-332.

Zuckerman M. Sensation Seeking: Beyond the optimal level of arousal. Hillsdale, New Jersey: *Lawrence Erlbaum Associates.* 1979. ISBN 978-1-84872-469-3.

Zuckerman M. Zuckerman-Kuhlman Personality Questionnaire (ZKPQ): An alternative five-factorial model. *Big Five Assess*. 2002;103(3):377-396. doi:10.1037/0022-3514.65.4.757.

Zuckerman M, Cloninger CR.NOTES AND SHORTER COMMUNICATIONS. Relationships between Cloninger's, Zuckerman's, and Eysenck's dimensions of personality. *Person individ diff.* 1996;21(2):283-285.

Internet sources:

Attention Deficit Hyperactivity Disorder. NIMH. [online].[cit. 2017-07-24]).available from:https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml

Borderline personality disorder. NIMH [online]. [cit. 2017-07-18]. Available from: https://www.nimh.nih.gov/health/topics/borderline-personality-disorder/index.shtml

Catecholamine. Wikipedia [online]. [cit. 2017-08-13]. Available from: https://en.wikipedia.org/wiki/Catecholamine

Hrabovská A. Parkinsonova choroba. In: *Slovenská Lekárenská Komora* [online]. Bratislava: Slovenská Lekárenská Komora, c2017 [cit. 2017-07-07]. Available from: https://slek.sk/c79de6c87cb5fedec1257daf0052025a/$FILE/Parkinsonova%20choroba_Hrabovska.pdf

Iowa gambling task - Wikipedia. [online]. [cit. 2017-08-10].Available from: https://en.wikipedia.org/wiki/Iowa_gambling_task

Kafka J. K otázke vedomia: III. Poruchy vedomia. In: Psychiatria-časopis [online]. Pezinok: *PSYCHIATRIA - PSYCHOTERAPIA – PSYCHOSOMATIKA*. 2003;10(1): 19-25. [cit. 2017-

07-16]. Available form: http://www.psychiatria-casopis.sk/files/psychiatria/1-2003/psy1-2003-cla5.pdf.

Neuropil. Define Neuropil at Dictionary.com. Dictionary.com | Meanings and Definitions of Words at Dictionary.com [online]. Copyright © [cit. 2017-07-18]. Available from: http://www.dictionary.com/browse/neuropil

Reward Deficiency Syndrome- Encyclopedia.com | Free Online Encyclopedia [online]. [cit. 2017-07-24]).Available from: http://www.encyclopedia.com/medicine/encyclopedias-almanacs-transcripts-and-maps/reward-deficiency-syndrome-rds#A

Substance dependence - Wikipedia. [online]. [cit. 2017-08-14].Available from:https://en.wikipedia.org/wiki/Substance_dependence

Swenson R. Chapter 8C - The Basal Ganglia. In: Dartmouth Medical School [online]. Hanover: Dartmouth Medical School. c2006 [cit. 2017-07-07]. Available from: https://www.dartmouth.edu/~rswenson/NeuroSci/chapter_8C.html

Tourette syndrome: MedlinePlus Medical Encyclopedia. MedlinePlus - Health Information from the National Library of Medicine [online]. [cit. 2017-07-29]. Available from: https://medlineplus.gov/ency/article/000733.htm

Wisconsin Card Sorting Test - Wikipedia. [online].[cit. 2017-08-10]).Available from: https://en.wikipedia.org/wiki/Wisconsin_Card_Sorting_Test

Annexes

Annex I

Gene	Region	Code	Mutation		Effect
DRD2	promoter	rs1799732	SNP	-141C ins/del	increased expression
DRD2	promoter	rs12364283	SNP	T-844C	increased expression
DRD2	intron 5	rs2283265	SNP	C/A	adding exon 6
DRD2	intron 6	rs1076560	SNP	C/A	adding exon 6
DRD2	exon 7	rs6277	SNP	C957T	altered folding
DRD2	exon 7	rs1801028	SNP	C960G	altered function
ANKK1	exon 8	rs1800479	SNP	C32806T	altered substrate sp.

Table 4: Table of the most common single nucleotide polymorphism (SNP) in DRD2 dene.The rs1799732 located in the promoter region (Arinami et al., 1997) and rs12364283 in the conserved suppressor domain have an effect on the gene expression (Zhang et al., 2007). Polymorphisms rs2283265 in intron 5 and rs1076560 in intron 6 alter the expression ratio of splice isoforms in favor of a long variant D_{2L} (Zhang et al., 2007). The rs6277 in exon 7 affects stability of mRNA (Duan et al., 2003) and thus receptor availability (Smith et al., 2017). The rs1801028 in exon 7 is likely to reduce inhibitory effect of DRD_2 on cAMP synthesis (Yao et al., 2014) and rs1800479 in the vicinity of the ANKK1 gene affects the expression of DRD_2 (Grandy etal., 1989a) and substrate specificity (Neville et al., 2004).

Annex II

No.	sample	DNA concentration (ng/µl)
1	PET1	56.3
2	PET2	18.7
3	PET3	13.8
4	PET4	167
5	PET5	37.7
6	PET6	2.36
7	PET7	32.9
8	PET8	38.3
9	PET9	5.67
10	PET10	5,32
11	PET11	3,75
12	PET13	26.12
13	PET15	31
14	PET16	43.8
15	PET17	128
16	PET18	39,3
17	PET19	213
18	PET20	53.1
19	PET21	7.4
20	PET22	19.6
21	PET23	288

Table 7: DNA concentration measured by Qubit® 2.0 Fluorometer (Invintrogen by Life Technologies).

Annex III

Group 1 (athletes)	Total (16)		men (12)		women (4)	
	mean	SD	mean	SD	mean	SD
Novelty seeking (NS)	**105.88**	**17.02**	**103.50**	**18.69**	**113.00**	**8.83**
Exploratory excitability (NS1)	34.00	5.92	33.08	6.44	36.75	3.10
Impulssiveness (NS2)	24.00	6.19	23.08	6.68	26.75	3.77
Extravagance (NS3)	27.25	8.29	26.42	8.11	29.75	9.57
Disorderliness (NS4)	20.63	3.52	20.92	4.03	19.75	0.96
Harm avoidance (HA)	**79.31**	**20.21**	**81.75**	**20.93**	**72.00**	**18.46**
Anticipatory worry (HA1)	25.50	7.47	27.17	7.80	20.50	3.32
Fear of uncertainty (HA2)	18.38	5.90	18.42	6.63	18.25	3.59
Shyness (HA3)	18.81	5.23	18.58	3.94	19.50	8.89
Fatigability (HA4)	16.63	5.94	17.58	5.88	13.75	5.91
Reward depencence(RD)	**104.81**	**11.00**	**107.50**	**10.83**	**96.75**	**7.72**
Sentimentality (RD1)	29.06	4.02	30.00	3.33	26.25	5.12
Openness to warm communication (RD2)	37.06	6.23	38.08	5.45	34.00	8.29
Attachement (RD3)	20.19	5.29	20.67	5.16	18.75	5.32
Dependence (RD4)	18.50	3.22	18.75	3.28	17.75	3.40
Persistence (PS)	**130.13**	**16.80**	**131.46**	**22.75**	**135.75**	**23.88**
Eagerness of effort (PS1)	30.94	4.95	30.25	5.07	33.00	4.55
Work hardened (PS2)	30.69	4.44	30.17	3.88	32.25	6.24
Ambitious (PS3)	39.31	6.00	38.67	4.91	41.25	9.22
Perfectionist (PS4)	29.19	16.80	29.17	5.34	29.25	5.44
Group 2 (control)	**Total (18)**		**men (4)**		**women (14)**	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**
Novelty seeking (NS)	**97.78**	**13.30**	**102.00**	**4.55**	**96.57**	**14.82**
Exploratory excitability (NS1)	31.72	5.10	32.75	8.06	31.43	4.31
Impulssiveness (NS2)	22.67	6.19	21.00	6.78	23.14	6.20
Extravagance (NS3)	26.06	7.36	29.50	6.81	25.07	7.45
Disorderliness (NS4)	17.33	4.41	18.75	2.99	16.93	4.75
Harm avoidance (HA)	**94.28**	**21.87**	**77.00**	**27.19**	**99.21**	**18.34**
Anticipatory worry (HA1)	29.94	8.00	22.75	9.03	32.00	6.67
Fear of uncertainty (HA2)	23.67	4.98	21.50	8.85	24.29	3.54
Shyness (HA3)	19.33	7.05	15.25	9.98	20.50	7.35
Fatigability (HA4)	21.33	7.58	17.50	9.81	22.43	6.80
Reward depencence(RD)	**109.39**	**13.74**	**109.25**	**9.81**	**109.43**	**14.99**
Sentimentality (RD1)	29.94	4.22	25.50	3.32	31.21	3.60
Openness to warm communication (RD2)	37.78	5.85	41.00	2.45	36.86	6.26
Attachement (RD3)	21.11	5.39	21.75	5.32	20.93	5.59
Dependence (RD4)	20.56	3.67	21.00	2.16	20.43	4.05
Persistence (PS)	**120.89**	**19.22**	**112.75**	**20.66**	**123.21**	**18.93**
Eagerness of effort (PS1)	29.94	4.99	26.25	5.85	31.00	4.39
Work hardened (PS2)	28.78	3.93	28.25	2.50	28.93	4.32
Ambitious (PS3)	34.28	7.32	33.25	7.85	34.57	7.45
Perfectionist (PS4)	27.89	5.60	25.00	5.23	28.71	5.61

Table 11: Mean scores and standard deviations of four temperaments and their subscales: novelty seeking, harm avoidance, reward dependence and persistence., Cronbach's α, the coefficient for internal consistency, was higher than 0.7 for each personality dimension (data not shown).

Annex IV

Summary of Novelty seeking scale	
+3	Severely high: consistently seeking for adventure and exploration, disorderly and unpredictable, intolerant of structure and monotony regardless of consequences, decisions based on impressions and intuitions, interests of friendships shifts rapidly without any sustained commitments
+2	Moderately high: usually seeks exhilaration from thrilling ventures and exploration of unknown places and situations, intolerant of structure and routine, trying to break rules, easily excitable, quick tempered and engaged in new ideas or people, convincing at role playing and dramatic exaggeration, prefers impulse spending but able to save for special occasions
+1	Mildly high: prefers pursuit of exciting thrills and exploration to familiar routines unless benefits from stable routines are highly likely, tolerates structure and discipline without much difficulty, more excitable and easily engage than average and more easily becomes disinterested and bored by monotony, prefers quick decisions based on impressions rather than detailed analysis, mildly histrionic, spends on impulse but responsibility avoids major debt
0	Average: equally tolerant of novelty and routine with choices depending on on what appears most beneficial, balanced in logical analysis and intuition, average amount of role playing and attention to saving, average excitability and rate of engagement/disengagement with people, activities or ideas
-1	Mildly low: prefers to stay with familiar routines unless benefits from new venture are highly likely. well organized but usually try to impose stable structures. slower to become excited than average, enjoy thrills and novelty when encountered but does not seek them out, usually prefers logical analysis over intuitive hunches but also often acts on first impression. limited role in playing and dramatic exaggeration, strong preference for saving and spending according to budgets
-2	Moderately low: prefers to stay in familiar routines unless benefits are from new ventures are nearly certain, orderly and disciplined, usually trying to impose stable structure and organization, reserved and controlled, slowly becomes excited, angry or enthusiastic or interested or attached, prefers detailed analysis but sometimes uses impressions tentatively, limited role playing and dramatic exaggeration, strong preference for saving
-3	Severely low: resists nearly all attempts to modify familiar routines, disinterested in novelty and exploratory pursuits regardless potential benefits, highly organized, trying to impose stable structure and consistent routine, highly controlled, rarely becoming angry or excited quickly, always required detailed analysis of complete information, direct and honest without playing or exaggeration, highly frugal with consistent effort to save budget, loyal and stoical, highly slow to form and change interests and social attachments

Table 16: Summary of novelty seeking scale: characterization of the individual NS dimension degrees in the original threedimensional model (TPQ). TPQ usesquestions with true/false answers with seven/point scale as a result, insetad of five-point scale as in TCI-R. However, characteristics remain the same. According to Cloninger (1987a, pp 576).

Annex V: Informed consent (page 1)

Genlabs s.r.o.
Poliklinika Medipont
Matice školské 1786/17
370 01 České Budějovice

Souhlas s účastí na vědeckém projektu: The Impact of "Dopamine Genes" on Novelty seeking Behavior.

Projekt je zaměřen na vyšetření polymorfizmů genu pro dopaminový receptor D_2 (DRD_2) a jejich vztahu k Novelty seeking behavior (NSB). NSB je povahová vlastnost, charakterizovaná jako tendence vyhledávat různé, komplexní a intenzivní senzace a zážitky za cenu fyzického, sociálního, právního a finančního risku. Předpokládá se, že jedinci s touto charakteristickou črtou mají v mozku relativně vysokou obsazenost dopamínových receptorů D2. Projekt bude mít vědecký přínos, kterého snahou je objasnit vlyv genů na lidskou povahu. Získaná data budou v anonymní podobě statisticky zpracována a poslouží jako podklad pro publikaci ve vědeckém časopise a podání grantové přihlášky na rozsáhlejší výzkum.

Jméno a příjmení vyšetřované/ho:……

Rodné číslo:……

Kontaktní adresa/email/telefon:……

A. Účel genetického laboratorního vyšetření

- Zjištění variantních polymorfismů v genu pro DRD_2.

B. PROHLÁŠENÍ VYŠETŘOVANÉ OSOBY

B. 1. Za výše uvedeným účelem souhlasím s poskytnutím bukálního stěru, který si provedu sám pomocí poskytnuté odběrové soupravy dle přiloženého návodu a s provedením níže uvedeného molekulárně genetického vyšetření:

Vyšetření polymorfismů v genu pro DRD_2 souvisejících s možným výskytem novelty seking behavior.

B. 2. Souhlas vyšetřované osoby s účastí na projektu:
Potvrzuji, že mi bylo poskytnuto řádné vysvětlení k tomuto genetickému laboratornímu vyšetření a že jsem poskytnuté informaci porozuměl/a.

AnnexV: Informed consent (page 2)

B. 3. Rozhodl/a jsem, že se vzorkem bude po ukončení testování naloženo takto:

Souhlas se skladováním

- Pokud to bude možné a/nebo účelné, bude můj vzorek skladován pro další vyšetření provedená k mému prospěchu a prospěchu mých příbuzných. Před genetickým vyšetřením, které by se provádělo za jinými účely než uvedeno v části A., budu řádně poučen/a a toto vyšetření bude vždy provedeno až s novým informovaným souhlasem. Vzorek bude skladován u poskytovatele zdravotních služeb uvedeného v záhlaví nebo v laboratoři spolupracujícího poskytovatele a to nejvýše po dobu 5 let.
- Jestliže bude vzorek mého biologického materiálu dále skladován, **souhlasím/nesouhlasím** s jeho využitím ke kontrole kvality DNA diagnostiky (vzorek je zcela anonymně použit jako kontrola pro vyšetření jiného pacienta).
- **Souhlasím/nesouhlasím*** s tím, že mohu být znovu kontaktován/a, na uvedené adrese, za účelem souhlasu s využitím mého skladovaného biologického materiálu v konkrétním výzkumném projektu.

Nesouhlas se skladováním

- Můj vzorek bude po provedení genetického laboratorního vyšetření zlikvidován s tím rizikem, že nebude již možné v budoucnosti výsledek vyšetření v případě potřeby znovu ověřit a že zlikvidování vzorku může vést ke zhoršení dostupnosti diagnostiky u rodinných příslušníků. Dále jsem si vědom/vědoma, že pro další genetické testování bude nutný nový odběr materiálu.

B. 4. Dále si přeji následující:

- Abych s výsledky genetického laboratorního vyšetření : **byl(a) / nebyl(a) seznámen(a)***

Souhlasím s účastí na projektu týkajícího se výzkumu genetických variant souvisejících s novelty seeking behavior.

Na základě tohoto poučení prohlašuji, že souhlasím s odběrem příslušného vzorku z mého těla a s provedením výše popsaného genetického laboratorního vyšetření s podmínkami uvedenými výše. Jsem si vědom/a, že svůj souhlas mohu kdykoliv písemně odvolat.

Podpis vyšetřované osoby

V …… Dne……..……

Podpis: …….

* vybranou variantu označte