Charles University

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Doctoral Thesis

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Third Faculty of Medicine

Doctoral Thesis

The role of the endocannabinoid system in the regulation of sexual response to visual stimuli

Role endokanabinoidového systému v regulaci sexuální odpovědi na vizuální stimul

Supervisor: Prof. MUDr. Jiří Horáček, PhD.

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Dedicated to my parents.

Věnováno rodičům.

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Abstract

My thesis explores the role of the brain endocannabinoid system (ECS) in human sexuality and its potential in the management of hypoactive sexual desire disorder (HSDD). In the *Foreword*, I discuss history of cannabis use and outline the structural and functional basics of the ECS in the human brain and body and its possible involvement in mental and bodily diseases. Furthermore, I introduce the main argument of this thesis, which is the utilization of the ECS in the management of the HSDD. This section will also elucidate the main sources of inspiration which eventually led to an experimental research study carried out during the years of my doctoral candidacy. In the theoretical part of my thesis, in the *Introduction* section I discuss the concept of HSDD. In the next two chapters the available evidence from animal and human studies on the relationship between ECS and sexuality is covered. In the following chapter, I discuss potential mechanisms of sexual desire enhancing properties of the ECS. In the closing chapter of the theoretical part, I summarize the previous chapters including the knowledge gaps and outline the experimental part of my thesis. This part, in the form of commentaries, covers the specific research steps taken to support my main argument (sexual desire enhancing effect of the ECS agonization). Firstly, I comment on our study of pharmacokinetics of phytocannabinoids in the blood, regarding the dosage, specimen and frequency of use, as these might prove crucial in the clinical case management. In the second commentary, I introduce our experimental finding that ECS agonization might indeed lead to the heightened responsivity of hypothalamus and nucleus accumbens to visual erotica and that this could possibly be a consequence of modified dopaminergic transmission. Thirdly, I comment on our study, which examined brain functional connectivity and its time course during intoxication. This commentary sheds light on the heightened sensuousness as often observed during intoxication – another effect advantageous to sexual desire. In the last chapter of my thesis, I re-introduce my main argument, summarize our main findings and discuss the caveats and possible implementation strategies.

Abstrakt v češtině

Má dizertační práce se zabývá rolí endokanabinoidového systému (EKS) mozku v regulaci sexuality a jeho potenciál pro terapii poruchy sexuální touhy. V *Předmluvě* je shrnuta historie užívání kanabis a představeny základní strukturní a funkční charakteristiky EKS v lidském mozku a těle, včetně role EKS v psychických a tělesných onemocněních. V *Předmluvě* je dále uvedena hlavní teze práce, a sice možné využití EKS pro léčbu poruchy sexuální touhy. Zároveň jsou zde osvětleny zdroje inspirace, které podnítily mou zvídavost, vedly k formulaci otázek a posléze k realizaci výzkumu. V teoretické části práce, v *Úvodu,* je představen koncept poruchy sexuální touhy a v navazujících sekcích uvádím dostupnou evidenci ze zvířecích a lidských studií mapující vztah mezi EKS a sexualitou. V následující kapitole jsou nastíněny možné mechanismy, kterými EKS může posílit sexuální touhu i vzrušení. V závěru teoretické části práce jsou shrnuty dosavadní poznatky a nastíněna osnova experimentální části práce. Ta je sestavena z komentářů k jednotlivým výzkumným studiím tvořícím podklad moji doktorské práce. V prvním komentáři představím studii o farmakokinetice fytokanabinoidů v krvi v závislosti na užitém množství, odrůdě a frekvenci užívání, jelikož jde o důležité parametry pro management klinických případů. V druhém komentáři uvedu náš nález, dle kterého aktivace EKS fytokanabinoidy může skutečně vést ke zvýšené odpovědi hypothalamu a nucleus accumbens na vizuální erotický stimul, a to pravděpodobně prostřednictvím modifikace dopaminergní transmise. Ve třetím komentáři shrnuji naše nálezy změn konektivity mozku během intoxikace a její časový průběh. To osvětlí jev zvýšené smyslové sensitivity, která je pro intoxikaci typická, jelikož jde o další efekt agonizace EKS s možným pozitivním dopadem na sexuální touhu. V poslední kapitole dizertační práce je znovuuveden hlavní argument, na který navazuje shrnutí a diskuze hlavních nálezů. V závěru uvádím možné směry implementace nálezů.

Abbreviations and acronyms

2-AG	2-arachidonylglycerol
AEA	anandamide (N-arachidonoyl-ethanolamine)
Aphro-	group which reported desire enhancing properties of cannabis
Aphro+	group which reported desire enhancing properties of cannabis
Ca^{2+}	calcium ion
cAMP	cyclic adenosine monophosphate
CB1	cannabinoid receptors type 1
CB2	cannabinoid receptor type 2
CBrec	cannabinoid receptors
DMN	default mode network
DSE	depolarization induced suppression of excitation
DSI	depolarization induced suppression of inhibition
E	estrogen-primed
ECS	endocannabinoid system
FAAH	fatty acid amide hydrolase
FDA	Food and Drug Administration U.S.
fMRI	functional magnetic resonance
Gi/o	inhibitory subunit of G protein
HSDD	hypoactive sexual desire disorder
Hyp	hypothalamus
K^+	potassium ion
MAGL	monoacylglycerol lipase
MMPI-2	Minnesota Multiphasic Personality Inventory-2
MR	magnetic resonance
NAcc_R	right nucleus accumbens
OH-THC	Δ^9-THC metabolite
OVX	ovariectomized

P	progesterone-primed
PET	positron emission tomography
SPECT	single-photon emission computed tomography
THC-COOH	Δ^9-THC metabolite
TRPV1	vanilloid receptor 1
Δ^9-THC	Δ^9-tetrahydrocannabinol

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I. Foreword

Cannabis smoking is an old "vice" of humankind. For centuries, a tall plant with slender leaves has been used to intoxicate oneself and bring various bodily and mental effects. Our knowledge of the mechanism behind its properties is rather recent compared to the long history of its therapeutic use, known by medicine-men from China, India, Tibet and later by physicians in the Middle East, Africa and Arabia (Zuardi, 2006). Flowers and leaves of the hemp plant have been used for variety of purposes - as antiemetic and antitussive, meditative and soporific, or appetite and desire stimulating agents (Mathre, 1997). By means of observation and experience, old experts also knew how to adjust its effects according to the timing, dosage and user-specific factors (Touw, 1981).

Despite impressive therapeutic and recreational exploitation, it wasn't until the end of the 19th century that efforts started to be made to isolate constituents of the cannabis plant (Pertwee, 2006). It took several more decades before the structure of cannabinol and cannabidiol (CBD) and a main psychoactive constituent Δ^9-tetrahydrocannabinol was described (Δ^9-THC) (Cahn, 1933; Adams, Pease & Clark, 1940; Wollner et al., 1942). This finally enabled a search for the neural substrate which could recognize these molecules. Interestingly, during the seventies, there was still a doubt about the existence of such a neural substrate (Gill & Lawrence, 1976). The principal events took place in 1988 when cannabinoid receptors (CB_{rec}) were discovered (Devane et al., 1988) and successfully cloned (Matsuda et al., 1990). A few years later, the natural binding molecules of these receptors, endogenous cannabinoids, N-arachidonoyl-ethanolamine/anandamide (AEA) and 2-arachidonylglycerol (2-AG) were identified (Devane et al., 1992; Mechoulam et al., 1995). Since then, a boom of interest in the endocannabinoid system (ECS) has commenced, reflected in the steep rise in the academic production on the topic – ranging from 1 article a year in the eighties to hundreds of papers each year nowadays (Fig. 1).

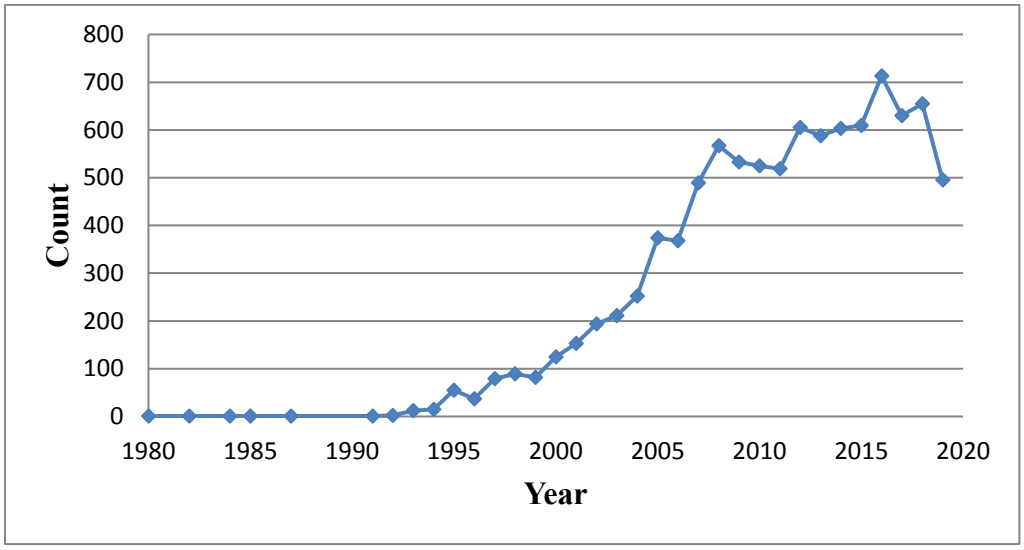

***Figure 1*. Number of entries indexed by a search term *endocannabinoid* by year.**

Note. Graph was produced by PubMed bibliometry feature accessed on 4th August 2019. Horizontal axis shows year, vertical axis shows number of results.

The ECS is a neuromodulatory system present in the brain and body, mediating the effects of Δ9-THC and other phytocannabinoids. It is comprised of the (1) cannabinoid receptors type 1 (CB1) and 2 (CB2), (2) their endogenous ligands AEA and 2-AG, which are produced *on demand* in the postsynaptic cell after the depolarization of a postsynaptic membrane, (3) a specific and not yet identified cellular uptake mechanism, and (4) the enzymes for endocannabinoid biosynthesis, N-acyl-phosphatidylethanolamine-selective phosphodiesterase or glycerophosphodiesterase E1 and diacylglycerol lipase α or β and (5) the enzymes for the inactivation of AEA and 2-AG, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Pazos et al., 2005). Further potential members of the ECS family include the vanilloid receptor 1 (TRPV1) channels, the putative CB1 antagonist peptides like hemopressins, peroxisome proliferator-activated receptor-α (PPAR-α) and γ (PPAR-γ) ligands, such as oleoylethanolamide (OEA) or palmitoylethanolamide (PEA), and N-arachidonoyl-dopamine (NADA), which activates both TRPV1 and CB1. Although the existence of a third cannabinoid receptor subtype has also been suggested (Begg et al., 2005), to date only CB1 and CB2 have been recognized as 7 transmembrane Gi/o coupled receptors for endocannabinoids (Pertwee et al., 2010). The CB1 and CB2 are

established as mediators of the biological effects induced by cannabinoids, either plant derived, synthetic, or endogenous. They are encoded by two different genes on human chromosomes: 6q14-q15 (CNR1) and 1p36.11 (CNR2), sharing 44 % protein identity. They also display different pharmacological profiles and patterns of expression, a dichotomy that provides a unique opportunity to develop pharmaceutical approaches (Di Marzo, 2011).

Today, many molecules binding to the CB_{rec} are known. According to their origin, we distinguish 1) endocannabinoids (endogenous ligands), 2) phytocannabinoids (active molecules from the *Cannabis* plant) and 3) synthetic cannabinoids (laboratory produced ligands of CB_{rec}). Endocannabinoids are natural lipid ligands of CB_{rec} produced in the brain and body and are all derivatives of previously mentioned arachidonic acid. AEA and 2-AG are the best known and were the first ones to be identified (Devane et al., 1992; Mechoulam et al., 1995). Since their discovery, new putative endogenous ligands have been identified: 2-Arachidonyl glyceryl ether (noladin ether) (Hanuš et al., 2001), N-arachidonoyl dopamine (NADA) (Bisogno et al., 2000) and Virodhamine (OAE) (Porter et al., 2002). Lysophosphatidylinositol (LPI) was identified in 2012 as a new endocannabinoid candidate acting on the recently discovered putative CB_{rec} GPR55 (Piñeiro & Falasca, 2012). Phytocannabinoids are lipid compounds found in the cannabis plant, which interact with the ECS in the brain and body. Approximately seventy such compounds are contained in the cannabis plant (ElSohly & Slade, 2005). The best known phytocannabinoid Δ9-THC is a partial agonist of both, CB1/CB2 and competes with endocannabinoids for the same binding site (Fišar, 2009). Also, mildly psychotropic CBD is a partial agonist for CB1/CB2 (A. Thomas et al., 2007). Other non-psychotropic phytocannabinoids, CBD and non-psychotropic metabolites of THC such as 11-hydroxy-Δ9-THC (OH-THC) and 11-nor-Δ9-THC-9-carboxylic acid (THC-COOH) are studied for immunosuppressive and anti-nociceptive effects (Mbvundula, Rainsford & Bunning, 2004). Synthetic cannabinoids are laboratory-produced molecules, designed for either experimental or pharmaceutical purposes and to also avoid legal restrictions connected to the cannabis plant itself. For example, laboratory isomer of Δ^9-THC known as Dronabinol (Marinol) and its analog Nabilone (Cesamet, Canemes) are used as anti-emetics and appetite-stimulants and improve painful, spastic and degenerative conditions (MacCallum & Russo, 2018). We further recognize several synthetic cannabinoid families like WIN-, CP-, UR-, JWH-, PB-, etc. (Hanuš &

Mechoulam, 2005). They are similar in structure of either phytocannabinoids or natural cannabinoids and are effective in low concentrations, i.e. they are much more potent than natural ligands. Some of these synthetic molecules found their way to the recreational drugs market on which they were sold legally as smoking blends under various names, e.g. “Spice”, “K2”, “Kronic” or “XLR-11”. In recent years, there have been multiple instances of serious health complications like severe bleeding or kidney failure (Banister et al., 2015), some of them with lethal consequences (Labay et al., 2016). Since then, synthetic cannabinoids became illegal in the majority of countries worldwide. Another potentially very dangerous molecule is CB1 antagonist Rimonabant (SR141716). It was developed as a powerful appetite-suppressing anti-obesity drug (Curioni & André, 2006), but was soon withdrawn from the market due to its harsh side-effects including depression, anxiety and suicidality (Sam, Salem & Ghatei, 2011).

According to the chemical structure of the binding molecules, we can distinguish several types of cannabinoids. There are the classical CB1/CB2 agonists which are dibenzopyran derivatives like (1) phytocannabinoid Δ9-THC and synthetic cannabinoid HU210, (2) non-classical CB1/CB2 agonists which lack the pyran ring, like full agonist CP 55,940, (3) aminoalkylindoles like full agonist WIN 55,212-2 and (4) eicosanoids, i.e. endogenous partial agonists AEA and 2-AG, both derivatives of arachidonic acid. Synthetic agonists like HU210, CP 55,940 and WIN 55,212-2 possess very high receptor affinities and efficacies in low nanomolar concentrations. Endocannabinoids AEA and 2-AG are less efficient and need a higher concentration to fully occupy the binding site on CB1 and to attain the full effect. They are also rapidly inactivated (Mechoulam, Fride & Di Marzo, 1998). Phytocannabinoids like Δ9-THC are partial agonists and need medium nanomolar concentrations to effectively bind CB_{rec} (Pertwee, 2000). On the behavioral level, effective dosage in rat models is in tens of μg/kg for synthetic agonists, and units of mg/kg for Δ9-THC, AEA and 2-AG. Synthetic antagonists like SR141716 (rimonabant) and AM251 belong to diaryl pyrazoles and produce inverse canabimimetic effects (Jagerovic, Fernandez-Fernandez, & Goya, 2008). CB_{rec} indirect agonists like URB597 (inhibitor of FAAH) and AM404 (AEA reuptake inhibitor/FAAH inhibitor) block inactivation of cannabinoids and are used to increase extracellular concentrations of cannabinoids and thus indirectly enhance CB_{rec} functionality (Di Marzo, 2008).

As mentioned above, endocannabinoids are produced “upon demand after cellular

depolarization or receptor stimulation in a calcium-dependent manner“ (de Fonseca et al., 2004, p. 8). Their primary targets are located retrograde – presynaptic GABA-ergic neurons and to a lesser extent presynaptic glutamatergic neurons (Marsicano & Lutz, 1999). After binding endocannabinoids, receptors “couple to Gi/o to inhibit cAMP production, decrease Ca2+ conductance, increase K+ conductance, and increase mitogen-activated protein kinase activity“ (Howlett et al., 2004, p. 345). This is the way, by which a depolarized postsynaptic neuron regulates the amount of a transmitter expelled into the synaptic cleft and thus enables short- or long-term retrograde plasticity. Two major forms of retrograde synaptic plasticity, which depend on whether GABA-ergic or the glutamatergic presynaptic neuron is bound, are called the depolarization induced suppression of inhibition (DSI) and the depolarization induced suppression of excitation (DSE) (Diana & Marty, 2004). Short and long term plastic changes related to DSI/DSE were observed in cerebellum, hippocampus, amygdala, striatum, nucleus accumbens and cortex (Diana & Marty, 2004). Whether it will be a short or a long form of plasticity, might depend on the duration of CB_{rec} occupation (Chevaleyre & Castillo, 2003).

CB1 are ubiquitous in the brain (Fig. 2), with highest densities in the prefrontal cortex, parietal lobe, basal ganglia, temporal lobe and cerebellum (Terry et al., 2010). CB1 can be found in virtually all areas with the exception of brain stem, where they are sparse, which renders them clinically safe from the viewpoint of basic vital functions (Herkenham et al., 1990). The reason for its wide distribution throughout the brain could be connected to the fact, that the ECS seems to be a primary deliverer of the DSI and DSE (Kreitzer & Regehr, 2001a,b; Ohno-Shosaku, Maejima & Kano, 2001; Wilson & Nicoll, 2001). The highest densities of CB_{rec} are found in the hippocampus and lateral and basal amygdala and in the I and V/VI lamina of neocortex, especially in associative prefrontal and limbic parts, less in the primary and secondary sensory and motor cortices, in thalamic nuclei, in pallidal complex, in substantia nigra pars reticulata, molecular layer of cerebellum and dorsal motor nucleus of nervus vagus; they are present at moderate/low densities in the periaqueductal gray, central and medial amygdala, nucleus accumbens, thalamus and medulla (Fišar, 2009). CB1 are co-distributed along estrogen and androgen, opiate, dopamine and also serotonin receptors (Biegon & Kerman, 2001; Pertwee & Ross, 2002; Burns et al., 2007; Wagner, 2016), therefore binding them by external agents affects normal functioning of receptors’ respective

systems. CB1 are also located in neurons of the dorsal raphe nucleus and in the locus coeruleus which are the major sources of serotonin (5-HT) and noradrenalin (NE) in the brain (Häring et al., 2007; Oropeza, Mackie, & Van Bockstaele, 2007). Pattern of distribution suggest a role in the cognitive, motor, motivational and vegetative sensory function (Glass, Faul & Dragunow, 1997). CB1 are also found in non-neuronal cells of the brain, such as oligodendrocytes, microglia, and astrocytes (Mackie, 2005). The cannabinoid CB2 are mainly distributed in immune tissues and inflammatory cells throughout the body, although they are also detected in glial cells, and to much lesser extent, in neurons of several brain regions such as amygdala, hippocampus, cerebral cortex, hypothalamus and cerebellum (Van Sickle et al., 2005; Gong et al., 2006; Sviženská, Dubový & Šulcová, 2008). Both, CB1 and CB2 are activated by endocannabinoids AEA and 2-AG (Di Marzo, Bisogno & De Petrocellis, 2005).

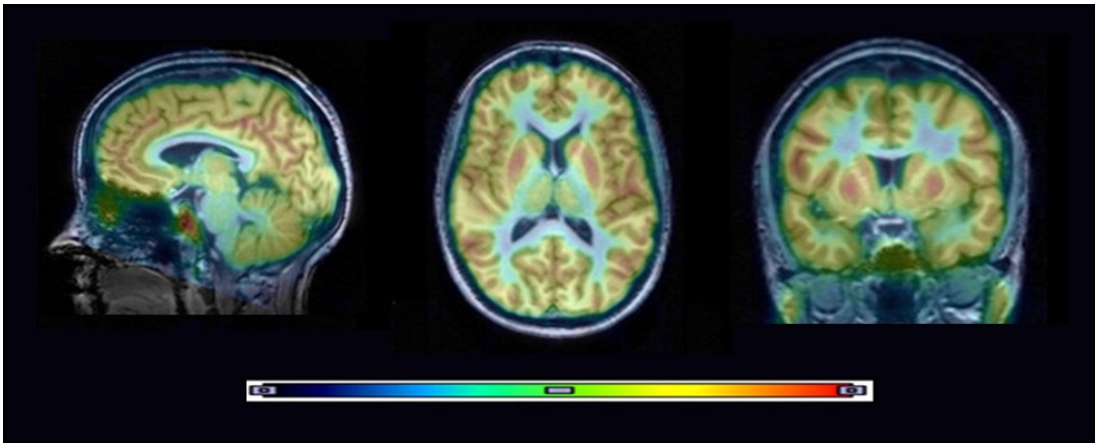

Figure 2. **Quantification of CB1 receptors in the human brain using 18F-Labeled Inverse Agonist Radioligands.**
Note. Red, green and blue color code highest, average and lowest CB1 densities, respectively. Adapted from „Imaging and quantitation of cannabinoid CB1 receptors in human and monkey brains using 18F-labeled inverse agonist radioligands," by G. E. Terry et al., 2010, Journal of Nuclear Medicine, 51(1), p.115. Copyright [2010] by the Name of Copyright Holder.

Multiple lines of evidence have shown that ECS dysregulation (both in terms of cannabinoid receptors and ligands) is associated with several pathological conditions such as pain and inflammation (Luongo, Maione & Di Marzo, 2014), obesity and metabolic disorders (Silvestri

and Di Marzo, 2013) or gastrointestinal (Gerich et al., 2015), hepatic (Mallat, Teixeira-Clerc & Lotersztajn 2013), neurodegenerative (Micale, Mazzola, & Drago, 2007) and psychiatric disorders (Micale et al., 2013; Kucerova et al., 2014). However, the exact patophysiological mechanisms are not fully elucidated yet. Therefore, the therapeutic potential of might be enormous - also thanks to its ability to bypass medullar and pontine centers for respiration and regulation of the cardio-vascular effects, as in these brain areas CB1 are sparse (B. F. Thomas, Wei & Martin, 1992). This renders cannabinoids relatively safe to use. The medical effects of cannabis and synthetic cannabinoids range from relieving chronic pain, through the treatment of inflammation, spasticity, seizures, nausea and vomiting, to the management of sleep obstructions, anorexia, hyperactivity with attention disorder, depression, social anxiety and addiction (MacCallum & Russo, 2018). One prominent feature of cannabinoids, however, still remains to be fully exploited. The so called "psychoactive" properties have, by and large, been omitted from the medical scope of interest, even if these are often stated as an important reason for illicit cannabis use (Bonn-Miller et al., 2014). These effects include relaxation and anxiolysis, heightened sensuousness, and various social effects (Green, Kavanagh & Young, 2003). In my thesis, I will explore probably the most taboo of these social effects of cannabis, i.e. its effect upon human sexuality.

First, in the theoretical introduction, I will review the available human and animal evidence as to the involvement of the ECS in the regulation of sexuality. Possible knowledge gaps which hinder a comprehensive grasp upon the role of the ECS in sexuality will be outlined and trajectories of further research will be delineated. In the experimental section, I will specifically comment on several experiments we carried out in order to address intricacies and fill in the knowledge gaps.

II. Theoretical part: Endocannabinoid system and human sexuality

II.1 Introduction

Sexuality is an evolutionary determined set of precopulatory and copulatory behaviors which brings together male and female gametes and secures the survival of species and genetic variance. It is critically regulated by the regimen of signaling molecules – first of all, by steroids like testosterone and estrogen, then by neuropeptides (e.g. prolactin, oxytocin) and neurotransmitters, such as dopamine (DA) or serotonin (5-HT) (Hull et al., 1999; Hull, Muschamp & Sato, 2004; De Jong et al., 2006). Even if secretly, a large part of adult human life is occupied by sexuality and if it is satisfactory, it can undoubtedly increase general well-being and life satisfaction (McCabe, 1997; Rosen & Bachmann, 2008; Stephenson & Meston, 2015). On the other hand, the inability to initiate, receive and enjoy sexual feelings might also generate low self-esteem, depression and anxiety (Graziottin & Leiblum, 2005; Atlantis & Sullivan, 2012).

One instance of mental health complication related to unsatisfactory sexual life is without a doubt a condition called the *hypoactive sexual desire disorder* (HSDD)[1]. It is a clinical condition which associates the concept of "low sexual desire" with personal distress (West et al. 2008). Despite the conceptual uneasiness to define "low" or "high" sexual desire, there were previous attempts to quantify distribution of sexual desire within the population, either using frequency and/or intensity measures. For example, Beutel et al. (2008) determined, in the representative German sample, that rare/occasional feelings of sexual desire (as opposed to frequent/very frequent) are quite prevalent, with almost 30 % and more than 40 %, in men and women (age = 18-30), respectively. In the same sample, moderate/low intensities were reported by 60 % of women and 39 % of men in the same age category. Other studies brought slightly lower, but still surprisingly high numbers: approximately 30 % and 20 % of women and men respectively (Meana, 2010). Low desire is not in itself a mental health problem but it might become one, as soon as it starts provoking mental health issues, like depression and anxiety (Leiblum et al. 2006), a

[1] Female hypoactive sexual desire disorder diagnosis in DSM-5 (American Psychiatric Association, 2013) merged with the female arousal disorder into one category: Female sexual interest/arousal disorder (302.72). Hypoactive sexual desire disorder has changed its name into Male hypoactive sexual desire disorder (302.71). In ICD-10 (World Health Organization, 2004) and ICD-11 (World Health Organization, 2018), which will come into effect in 2022, this diagnosis is found under the name Hypoactive sexual desire disorder (F52.0).

condition referred to as HSDD[2]. ICD-10 defines HSDD as "absent/reduced desire or motivation to engage in sexual activity" which should be manifested by any of the following: 1) reduced/absent spontaneous desire (sexual thoughts or fantasies), 2) reduced or absent responsive desire to erotic cues and stimulation, and/or 3) inability to sustain desire or interest in sexual activity once initiated (World Health Organization, 2004). Prevalence of this disorder is about 6–9% in human females (West et al., 2008) and up to 3% in human males (Simons & Carey, 2001). Mechanisms by which this condition arises in men and women may also differ (Donahey & Carroll, 1993). Etiology of HSDD could follow multiple trajectories, given that sexual desire is a complex state involving motivational, cognitive, emotional and behavioral aspects. Various medical conditions, like post-stroke period, eating disorders, renal failure or HIV may result in lowered desire (Meuleman & Van Lankveld, 2005). Hormonal deficiency (like hypogonadism) or natural decline in hormones with age (like in menopause) account for high prevalence of HSDD (West et al., 2008; Gacci et al., 2010). Apart from the apparent biological causes, psychogenic trajectories of HSDD are often the cause. Sexual intercourse involves a less vigilant, vulnerable state of mind (Porges, 1997), which might be hard to establish if there is distress of any kind. HSDD might be associated with various cognitive intrusions during sexual situations, taking on a form of spectating/inability to maintain self-focus on one's body (Masters & Johnson, 1981), sudden intrusive thoughts (Géonet, De Sutter & Zech, 2013) and mind wandering (Brotto & Woo, 2010). Desire/arousal concerns are often accompanied also by the feelings of disgust (De Jong, van Overveld & Borg, 2013) or anxiety (Van Minnen & Kampman, 2000). Following disappointment and dissatisfaction might prevent further intimate contacts with a partner and might further exacerbate HSDD (Charest & Kleinplatz, 2018).

Currently, HSDD therapy utilizes hormonal replacement or non-hormonal medications (like serotonergic drug flibanserin) and plant-derived substances (like adrenergic alkaloid yohimbin) with variable efficacy and safety (Bolour & Braunstein, 2005). Flibanserin, sold in the U.S. under the name Addyi, is indicated to improve hypoactive sexual desire in pre-menopausal women. It is a 5-HT_{1A} agonist and 5-HT_{2A} antagonist drug, with its mechanism of action being the

[2] Interpersonal issues in partnership or incompatibility of the respective sex drives might often be connected to the lack of sexual desire. However, they cannot become the basis for the HSDD diagnosis (see DSM 5 and ICD 10 for a differential diagnosis).

local suppression of serotonin release and disinhibition of dopamine and norepinephrine release, mainly in prefrontal and limbic areas (Stahl, Sommer & Allers, 2011). While this pharmacological profile might seem ideal, flibanserin therapy is of low efficacy (Jaspers, 2016). Yohimbin, on the other hand, acts as antagonist on α1- and α2-adrenergic receptors, 5-HT_{2A} receptors and dopamine D_2 receptors (Millan et al., 2000). However, it is not recommended for long-term use, as it induces side effects (nausea, anxiety) in a substantial portion of users which do not fatigue over time and it is contraindicated in multiple medical conditions (Jacobsen, 1992). Alternatively, psychotherapies which use techniques like “sensate focus" (Weiner & Avery-Clark, 2014) or cognitive-behavioral protocols (Trudel et al., 2001), also show some efficacy (Frühauf et al., 2013). Nevertheless, a clinical need for safe and effective medication still remains.

The ECS might soon become the emergent therapeutic horizon for the treatment of HSDD. Its role in the regulation of vertebrate sexuality is unquestionable, yet still little understood. Multiple parameters like specimen, timing, dosage, user-specific traits (Touw, 1981) enter the equation and complicate attempts to drive any clear-cut conclusions. There are also perspectives, which claim that functionalities of the ECS are comparable to those of the opioid system, and thus connected to the sexual quiescence (Pfaus, 2009). Yet, this seems oversimplifying, given that sexual-enhancement is a frequently reported effect in the community of cannabis users (Green, Kavanagh & Young, 2003). In the following, I will outline the current state of scientific knowledge on the relationship between the ECS and sexuality and address discrepancies currently present.

II.2 Animal studies

Animal models of human sexuality are diverse, and it is sometimes difficult to tell whether they offer a reliable analogue human condition or measure states remote from it. There are protocols which use behaviors like "proximity keeping", conditioned place preference or maze running-time, as models of “mate preference” or “sexual motivation”. There are other measures, which are more closely related to the copulatory act and they might examine time to first mount, to first

intromission and to ejaculation, or simply a number of these components in males. In females, researchers might examine the quality of lordosis[3], "ear wiggling", "hopping and darting", etc. Even if the animal-to-human translation of knowledge is problematic, animal studies have brought major findings about the relationship of the ECS and sexuality.

For example, Δ9- THC, a nonselective phytocannabinoid CB1 and CB2 agonist (Merari, Barak & Plaves, 1973; Cutler, Mackintosh & Chance, 1975; Murphy et al., 1994; Dhawan & Sharma, 2003) and the synthetic nonselective cannabinoid CB1/CB2 agonist HU-210 (Ferrari, Ottani & Giuliani, 2000; Riebe et al., 2010) were shown to increase, either acutely or chronically, latency to first mount, first intromission and ejaculation. In these studies, Δ9- THC did not seem to affect the number of mounts and intromissions, while HU-210 effectively reduced the number of these components. In castrated mice, a low dose of Δ9- THC (0.5 mg/kg) effectively reduced latency to the first mount[4], but did not improve the threshold for intromission and ejaculation, which were significantly delayed (if occurring at all) in comparison with the intact animals (Shrenker & Bartke, 1985). The endogenous CB1 agonist AEA at low doses reduced latency to intromission and ejaculation, reduced the number of intromissions required to achieve ejaculation and increased the number of ejaculations in sexually active rats (Canseco-Alba & Rodríguez-Manzo, 2014). In non-copulating male rats, AEA facilitated sexual contacts in 50% of cases (Canseco-Alba & Rodríguez-Manzo, 2013). In sexually sluggish rats, AEA decreased ejaculatory threshold (Rodríguez-Manzo & Canseco-Alba, 2015a). Even if there are no visible hormonal differences among „normal", sexually sluggish and non-copulating animals, they might differ in the utilization of circulating androgen (Whalen, Beach & Kuehn, 1961) and perhaps, the effect observed was due to the interaction of the ECS with gonadal androgen via effects on the hypothalamus and the anterior pituitary (Gorzalka & Dang, 2012). Higher AEA doses increased intromission latencies and decreased the number of ejaculations (Martinez-Gonzalez et al., 2004; Canseco-Alba & Rodríguez-Manzo, 2014), possibly through the recruitment of vanilloid TRPV1 channels (Rodríguez-Manzo & Canseco-Alba, 2015a). This effect, known as biphasicity, describes

[3] Lordosis is a specific posturing typical for sexually receptive female mammals of many species, characterized by the inward arching of the back and presenting genitalia.

[4] A tentative animal analogue of human desire/motivation (Ventura-Aquino, Portillo & Paredes, 2018).

a scenario, when different concentrations of a transmitter (e.g. AEA) result in the recruitment of different receptors, in this case TRPV1 instead of CB1 (Moreira et al., 2012). CB1 antagonism by AM251 results in the reduction of ejaculation threshold and the number of intromissions necessary to induce ejaculation in sexually active animals (Gorzalka, Morrish & Hill, 2008; Canseco-Alba & Rodríguez-Manzo, 2014), but not in sexually sluggish ones in which the ejaculation threshold was lowered by AEA, as mentioned previously (Rodríguez-Manzo & Canseco-Alba, 2015a). Indirect facilitation of the AEA signaling by FAAH inhibitors like URB597, oleamide or by the reuptake inhibitor AM251 did not bring any compelling results (Martinez-Gonzalez et al., 2004; Gorzalka, Morrish & Hill, 2008).

The dependency of ECS agonization effects on the central hormonal status is best visible in female rats. Not only does the density of cannabinoid CB1 and endocannabinoid levels fluctuate along the oestral cycle, but the effects of experimental treatments vary greatly depending on whether the female rat is intact, ovariectomized (OVX) unprimed or OVX primed by estrogen only (OVX + E) or estrogen and progesterone (OVX + E + P; full estrus). The cannabinoid CB1 undergo significant down-regulation from diestrus (the period of sexual inactivity) to estrus (the period of heat) in the hypothalamus (De Fonseca et al., 1994), while AEA levels in the anterior pituitary and hypothalamus, increase and decrease, respectively (Gonzales et al., 2000). Interestingly, dopamine receptor densities also co-fluctuate across the oestral cycle, in response to the changing hormonal milieu (Levesque and Di Paolo, 1990; Morissette & Di Paolo, 1993). In hypothalamus, D1 (Pasqualini et al., 1984) and CB1 (De Fonseca et al., 1994) densities were high during diestrus and proestrus, but decreased significantly in the afternoon of proestrus shortly before the estrus. These changes coincide with prolactin surge, which happens at around the same time shortly before estrus (Pasqualini et al., 1984). In OVX + E rats, the production of AEA in the medial basal hypothalamus is higher and CB1 expression in the pituitary gland is lower than in OVX rats (Gonzales et al., 2000; Scorticati et al., 2004). In OVX + E females, Δ^9-THC administration induced lordosis, which is normally attained only in fully hormonally primed females, i.e. OVX + E + P females (Gordon et al., 1978; Mani, Mitchell & O'Malley, 2001; Turley Jr & Floody, 1981). Potent CB1/CB2 receptor agonist HU-210 caused decreased frequency and quality of lordosis in fully hormonally primed rats (Ferrari, Ottani & Giuliani, 2000). Treatment by the synthetic CB1/CB2 agonist

CP55,940 negatively affected socio-sexual behaviors like proximity keeping, speed of running for sexual mate in a maze or a conditioned place preference induced by the presence of a sexual mate, possibly through the increase of social anxiety or inhibition of estrus (López et al., 2010). Furthermore, daily CP55,940 treatment during adolescence inhibited sexual motivation in adult female rats (Chadwick, Saylor & Lopez, 2011). Synthetic CB1 antagonist SR141716 (rimonabant) significantly decreased sexual motivation in OVX + E rats (Memos et al., 2014). CB1 agonization by Δ^9-THC had a deleterious effect upon a fully hormonally primed (oestral) female but had an aphrodisiacal effect in estrogen-only primed females (i.e. in females with a hormonal status that corresponds to the early proestrus). These effects are likely mediated via the interaction among CB1, dopamine D1 and progesterone receptors because blockade of either of these receptors prevented these effects (Mani, Mitchell & O'Malley, 2001).

II.3 Human studies

The available data on the ECS and sexuality in humans is relatively scarce and derive largely from self-report studies of cannabis users or anecdotal evidence. Considerably large portions of cannabis users confirmed positive effects of intoxication upon various aspects of sexuality - desire, pleasure, sensuality, quality of orgasm and sexual satisfaction, in both sexes (Green, Kavanagh & Young, 2003). Among these effects, increased sexual satisfaction (cca 90%) and pleasure (cca 70%) was most common (Lyons et al., 1997). The proportion of users indicating heightened sexual pleasure might range from relatively small - 23.8 % (Soueif, 1971), to very large - 81% (Halikas, Weller & Morse, 1982). It should be noted, that women report pro-sexual effects more often than men. Heightened desire was observed less often in comparison to sexual pleasure, although still by a significant portion of users - cca 50% (Lyons et al., 1997; Green, Kavanagh & Young, 2003). Interestingly, Koff (1974) observed inverted proportions of motivational and hedonic effects - 71% and 43% of women, indicated increased desire and pleasure, respectively. Interestingly, some users even use cannabis as a systematic preparation for sexual intercourse or

petting (Weller & Halikas, 1984; Hendershot, Magnan & Bryan, 2010). Sexually enhancing effects also seem to be most likely observed in regular, but not heavy or rare users (Weller & Halikas, 1984) meaning that a certain level of experience with the drug is necessary but not up to the point of heavy chronic use. Enhanced sexual pleasure might be associated or perhaps even explained by the increased bodily focus and sensuality, especially sensitivity to touch (Goode, 1970; Tart, 1970; Weller & Halikas, 1984). Other effects included increased length of intercourse which was reported by 27% (Weller & Halikas, 1984) or 39% (Halikas, Weller & Morse, 1982) of male users. It should be of note, that while the increased length of copulation is often interpreted as detrimental to animal sexuality, it might be largely viewed as beneficial in humans. In terms of vaginal lubrication, number and/or intensity of orgasms, no change was reported (Kolodny, Masters & Johnson, 1979). In contrast, perceived quality of orgasm was better as indicated by 58–68% of male users and 32–42% of female users (Halikas, Weller & Morse, 1982; Weller & Halikas, 1984). Sexual effects of cannabis seem to be inversely dosage-dependent in both sexes. In general, lower dosages are more likely to bring sexual enhancement while higher doses have the opposite effect (Koff, 1974), possibly via general motor retardation or sedation (Chopra & Jandu, 1976).

A substantial part of the narrative which attributes harmful sexual effects to cannabis possibly derives from the studies on male fertility. Human sperm cells and seminal plasma contain bioactive lipids and cannabinoid receptors (Francavilla et al., 2009) and fertility seems to be related to high level of AEA, reduced expression of cannabinoid CB1 and increased expression of cannabinoid CB2 in sperm cells (Rapino et al., 2014). CB2 also seems to be involved in the optimization of endothelial function as was shown previously in an animal model (Fraga-Silva et al., 2013). Therefore, it seems that a balance of ECS elements in reproductive organs is critical for fertility. Decreased testosterone levels (Kolodny et al., 1974), endothelial and erectile dysfunction (Aversa et al., 2008), decreased sperm motility (Whan et al., 2006) and decreased sperm count (Kolodny et al., 1974) were documented in chronic heavy users[5].

Follicle stimulating hormone and testosterone fluctuate acutely during intoxication but tend to return back to baseline after the intoxication wanes (Cohen, 1976). Therefore, chronicity is likely

[5] For a comprehensive review of reproduction health effects of cannabinoids, see Sadeu et al. (2010).

to play a crucial role, since detrimental effects were not reproduced in short time heavy use (Mendelson et al., 1974). In women, there is also ample evidence of the ECS involvement in reproductive functions. E.g., peripheral circulation of AEA and 2-AG is significantly negatively correlated with subjective and physiological indices of sexual arousal in women (Klein et al., 2012). Menstruation cycle is marked by the gradual decrease of AEA levels and increase of FAAH from the follicular to the luteal phase (Bari et al., 2002; Rapino et al., 2014), which seem to be necessary for successful implantation (Maccarrone et al., 2002). AEA levels in the human ovary and follicular fluid affect follicular maturation and development in humans (El-Talatini et al., 2009).

In summary, ECS agonization shows various sexually enhancing effects – from a heightened desire, through increased sensuousness, pleasure and satisfaction, to prolonged intercourse and better quality of orgasm. On the other hand, it has a profound detrimental impact upon the maturation of gametes and fertility-related processes, especially in heavy chronic use. In this respect, careful clinical consideration should be in place prior to the utilization of cannabinoids for sexual purposes.

II.4 Additional considerations

Apart from the direct actions upon a sexual motivational state, there might be other promising effects of cannabinoids. With a degree of simplification, we might say that ECS agonization by cannabis intoxication favors the “rest and digest" or “anti-stress” behavioral repertoire (Pfaus, 2009). Activation of the hypothalamic homeostatic sites in combination with sympathoinhibitive properties and suppression of adrenaline release (Niederhoffer, Schmid & Szabo, 2003; Szabo, Nordheim & Niederhoffer, 2001; Niederhoffer et al., 2001) seem to be the key events in the establishment of the famous “high” often reported by cannabis users. It is firmly established now, that CB1 agonization stimulates feeding behaviors, sleep, pain reduction and anxiolysis. Feeding behaviors (also including suckling reflex in newborns) seem to be stimulated through the suppression of anorexogenic effects of leptin in the arcuate nucleus of hypothalamus

(Mechoulam & Fride, 2001; DiMarzo et al., 2001); sleep promotion is possibly connected to the ability of the ECS to increase adenosine and thus suppress wakefulness-promoting neurons in the basal forebrain, lateral hypothalamus, and tuberomammillary nucleus (Murillo-Rodriguez et al., 2003) or possibly through the excitation of melanin concentrating neurons in the lateral hypothalamus (Prospéro-García et al., 2016). Antinociceptive properties, like pain reduction in stressful situations, is probably mediated by the disruption of the activity of nociceptive neurons in the ventralposterior lateral nucleus of the thalamus which projects to the cortex (Martin, Hohmann & Walker, 1996) or perhaps by the dis-coupling of anterior cingulate and sensorimotor cortex connectivity (Weizman et al., 2018). Another part of the complex cannabis experience involves euphoria, which is likely delivered through the μ-opiate dependent mechanism, possibly through the direct disinhibition of μ-opioid receptors and/or through the disinhibition of dopaminergic neurons in the ventral tegmental area (French, Dillon, & Wu, 1997; Tanda, Pontieri, & Di Chiara, 1997).

From the perspective of HSDD treatment, sympatoinhibitive properties including relaxation and anxiolysis and endorsement of the parasympathetic tone, which is necessary for the establishment of genital arousal, might prove useful[6]. The exact mechanism by which the ECS agonization commands anxiolysis and relaxation is not known, but it was hypothesized, that these effects occur primarily through the "pacifying" effect of Δ^9-THC on the amygdala, as observed via sensitivity to social threat signals in humans (Phan et al., 2008). However, in this study, Δ^9-THC also "pacified" areas like cingulate and insula, which is suggestive of a higher-order cortical mechanism. Topological pattern of CB1 throughout the neocortex shows highest densities in the dorsolateral prefrontal cortex, cingulate gyrus, insula, auditory association cortex, and the entorhinal cortex predominantly on inhibitory terminals (Eggan et al., 2010), which renders a higher-order mechanism plausible. Recently, important insights from the brain connectivity studies

[6] In stimulants, anxiolysis is reached by the increase in a perceived own social aptness and self-assertion (Higgins et al., 1993; Hart et al., 2001), sometimes up to a point of aggression (Licata et al., 1993; Wright & Klee, 2001). In cannabis though, anxiolysis likely occurs in the opposite way, by means of reducing the need for social self-assertion or aggressiveness (Hoaken & Stewart, 2003) sometimes up to a point of social isolation (Ritter, Broers, & Elger, 2013). This is nicely illustrated by the way a person uses the drug. It is often at home or in familiar settings alone (Lau et al., 2015) or with a group of close friends (Bell et al., 1998).

started to appear. For example, Pujol et al. (2014) found that reductions in anxiety correlated significantly with the loss of insular coupling to the default mode network (DMN)[7] and a parallel increase in the local connectivity of the anterior insula. Anterior insula generates visceral and bodily awareness (Craig, 2009) and relay this information to the DMN, which seems to give a "social" meaning to the situation and thus exert self-control (Schilbach et al., 2008). Thus, disconnection of the default and insular networks might bring cessation to the self-monitoring tendency. This could be interesting for the treatment of HSDD, because in some patients, self-monitoring (i.e. taking a third person perspective during the intimate sexual situation) and self-conscious behaviors are often present (Cacioppo, 2017).

II.5 Summary

The main purpose of this review was to categorize the available animal and human evidence, in order to see which behavioral and subjective effects are brought by the modification of the normal ECS functioning. The available evidence clearly documents, that the ECS is enigmatically, yet undeniably related to the regulation of sexuality. Given the co-fluctuation of hormones and ECS elements, it is undoubtable, that the pre-existent hormonal status or the ability to utilize circulating hormones will play a major role in determining the effects of ECS agonization. We have also seen that animals with sub-optimal sexual reactivity (sluggish and non-copulating male rats and not fully oestral female rats) were able to benefit sexually from the ECS agonization whereas the animals with optimal sexuality were not. In humans, variable but generally large percentages of users report pro-sexual effects. The sympathoinhibitive properties of the ECS agonization, resulting in anxiolysis, decreased self-consciousness and self-control, and general relaxation, could also contribute to the enhancement of sexual desire.

Previously, adverse effects of cannabinoids upon sexuality were greatly stressed, based on

[7] "Default mode network" refers to the large scale brain network which is typically activated during a wakeful rest and is connected to the social cognition, autobiographical memory or self-referencing processes. It was also called a task-negative network because it was first identified during relaxed non-task states during neuroimaging (Raichle, 2015).

animal research or infertility studies. In this respect, it is necessary to acknowledge that sexuality is not a unitary function but a highly complex system. Claims about the adverse sexual effects should be put into perspective by stating which part of sexuality is affected and how. For example, in female rodents, three basic components of sexuality exist: attractivity (behavioral and chemical signals leading to mate attraction), proceptivity (behaviors leading to the approach to a potential mate, marked by the exchange of anti-aggressive cues) and receptivity (behaviors leading to effective genital union, male ejaculation and possibly conception) (Beach, 1976). ECS agonization could be detrimental to one component (for example, attractivity behaviors like partner location, running for a partner and a partner-induced place preference) but not to the other (copulatory behaviors). This view is also endorsed by functional anatomy - CB1 populate mainly basolateral amygdala (Katona et al., 2001) and lesions here, unlike lesions in the central amygdala, have little effect on copulatory behavior (Kondo, 1992). On the other hand, lesions of the basolateral amygdala might be deleterious to the attractive behaviors, given that responsivity towards sexual pheromones and odorants is regulated from here (Moncho-Bogani et al., 2005). Second, intoxication causes changes in time perception (Sewell et al., 2013), pace of movement (Flavel, White, & Todd, 2013) and sensory awareness (Crenshaw & Goldberg, 1996). Under such circumstances, it is problematic to interpret increased time delays as decreased motivation. Third, some animal models used drug-naïve animals, which receive cannabinoid for the first time at testing. It is known, that the first-time cannabis experience often evokes stressful reactions (D'Souza et al., 2008) and it takes a certain experience until the effect fully develops, stabilizes and becomes more enjoyable (Tart, 1990). Older studies also often employed high dosages of cannabinoids, which were beyond human-relevant range (Hollister, 1986). Fourth, there could be individual differences in the reaction to cannabis. ECS modulates dopaminergic system in the limbic brain and dopaminergic status could vary significantly across people (Smillie & Wacker, 2014). This topic will be discussed in further detail in the commentary section on the original research article by Androvicova et al. (2017a), which is a part of this thesis. Bearing all this in mind, even further intricacies exist – for example effect variability in different specimens of cannabis (especially in terms of CBD:THC ratio) and frequency of use. Last, results of various studies are certainly affected by diverse methodologies – e.g. using different species (rats vs. mice)

or strains (CWF vs B6D2F1 vs ICR mice), different experimental protocols (drug administration route; prenatal vs postnatal treatment, the selection of behavioral measures) or basal stress-related conditions.

In order to ascertain the potential of cannabinoids, either plant derived or synthetic, in the treatment of HSDD, several knowledge gaps need to be remediated. First of all, pharmacokinetics of cannabinoids need to be addressed, especially with regard to the liposolubility of cannabinoids enabling a deposition of cannabinoids in the fat tissue and slow re-release, a phenomenon known in regular use of cannabis. Second, not all users of cannabis report aphrodisiacal effects. In order to aim for a personalized treatment, biomarkers which could identify patients with a potential to benefit from the administration of cannabinoids, should be determined. Third, the mechanisms of the aphrodisiacal effect should be elucidated on the brain level, not only to offer a strong theoretical background for the therapeutic exploitation of cannabinoids, but also to be able to use neuroimaging results as another possible biomarker for a personalized treatment.

III. Experimental part

III.1 Brief overview of the experimental part

In the experimental part of my thesis, several knowledge gaps outlined in the previous chapter are addressed. These are re-introduced by three original research papers. First of all, a study by Balíková et al. (2014), who explored pharmacokinetics of phytocannabinoids in the blood of our volunteers, shows the time- and dosage- dependent properties of intoxication, as these variables may strongly determine perceived effects of cannabis. Then I comment on the original experiment (Androvicova et al., 2017a), which aimed to determine whether cannabis facilitates the response of the key motivational brain structures to erotic stimuli and whether this is a general or individually-specific property, possibly mediated by different neurobiological response to cannabis. Last, the study by Zaytseva et al. (2019) addresses the topic of subtlety of intoxication, which is rather difficult to capture by standard imaging protocols. This study shed some light upon brain connectivity changes, which might underlie the sympathoinhibitive properties of the ECS agonization. This could be a useful feature within the treatment of HSDD. Finally, I put our findings into wider perspective in the discussion section and I conclude with the summary and further recommendations for research and application.

III.2 Pharmacokinetics and pharmacodynamics of phytocannabinoids in human users

Commentary on the original research paper:

Balíková, M., Hložek, T., Páleníček, T., Tylš, F., Viktorinová, M., Melicher, T., Androvičová, R., Tomíček, P., Roman, M., & Horáček, J. (2014). Časový profil hladin THC v krevním séru u rekreačních a chronických kuřáků marihuany po akutním užití drogy – implikace pro řízení motorových vozidel [Time profile of serum THC levels in occasional and chronic marihuana smokers after acute drug use - implication for driving motor vehicles]. *Soudní Lékařství*, *59*(1), 2-6.

The predictability of the pharmacokinetic and pharmacodynamic properties of a drug is a *sine qua non* of its potential therapeutic exploitation. In this respect, phytocannabinoids are complicated. Due to their small molecular size and lipid-solubility, they cross barriers between various tissues very easily. In the case of inhalation, they readily enter the bloodstream via pulmonary capillaries and rapidly cross the blood brain barrier. This being said, we might expect an abrupt onset and rapid decline of effects. However, this is not the case. Phytocannabinoids are attracted to lipid particles and after binding to them, they are deposited in the adipose tissue, becoming inactive for a time. They are then subject to a gradual and slow redistribution into the blood stream which depends upon the breakup of fat tissue, i.e. upon individual metabolic parameters. For example, the redistribution is accelerated in food-deprived individuals (Gunasekeran et al., 2009). The deposition of cannabinoids in fat tissue might also long survive discontinuation of use, as can be seen in some chronic users with persistently heightened blood levels (Karschner et al., 2009a,b). Individual metabolic characteristics also affect how quickly Δ9-THC is metabolized into OH-THC, a molecule, considered by many, to be an even stronger psychoactive agent. Due to these complexities, cannabis pharmacology is not easy to "pin down".

Generally speaking, maximum plasma concentration precedes the onset of psychoactive effects by several minutes. Bioavailability varies greatly from 2 to 56% depending on the route of administration (inhalation, oral, intravenous, rectal, etc.), frequency of use (Grotenhermen, 2003) and skill (Lindgren et al., 1981; Azorlosa et al., 1992). Two most utilized routes are by inhaling and orally. For example, the inhalation technique might vary in terms of "[the] depth of inhalation, puff duration and breathhold" (Grotenhermen, 2003, p. 332). In case of inhaling, effects are believed to appear within 15–30 minutes and diminish within 2–3 hours (idem, p.328), i.e. long after the occurrence of peak blood levels. There might also be a marked variability of Δ^9-THC and CBD interaction, because mutual facilitation and inhibition were both reported previously (Kalant, 2001). The tendency to overcome this complexity, by using pure cannabinoids as opposed to the cannabis plant, might be at odds with the individual preference for cannabis-derived, natural products.

Our contribution to this debate was by addressing the lack of data on pharmacokinetics in occasional and heavy cannabis users. As a matter of fact, most data on the pharmacological

properties of cannabinoids are based on acute single-dose studies, in non-users, while therapeutic regimens might require regular or chronic administration (Kalant, 2001). In our study (Balíková et al., 2014), we gathered and examined data from twenty-five regular users of cannabis. Fourteen subjects were classified as occasional users (≤ 4 joints/month – light users; ≤ 12 joints/month – medium users), eleven as chronic users (> 12 joints/month). Blood was collected from each participant at several time points – 30 minutes prior to inhalation (control sample) and then 30 min, 1.5 hour, 4.5 hour and 24.5 hours after inhalation. All collected blood samples were centrifuged at room temperature and then stored at -20 °C until analyses. These samples were analyzed at the Institute of Forensic Medicine and Toxicology in Prague, 1st Faculty of Medicine, Charles University in Prague, Czech Republic. Δ^9-THC and metabolites were evaluated in 1 ml of blood serum by an in-house developed and subsequently certified GC-MS method (certified by Police Presidium of the CR, ref. no.: PPR-31123-7/CJ-2015-990530 / evidence no.: 16/2015).[8] The data was analyzed using two-way repeated measures ANCOVA, which allowed us to determine the effects of time and frequency of use as factors, controlling for the basal Δ^9-THC blood levels (residual levels).

A significant main effect of time but not of the group was observed. Chronic and recreational users further differed in several aspects – first of all, basal levels of Δ^9-THC were significantly higher in chronic users, although this effect was driven by only half of chronic users (5 out of 11). Detectable residual content was not observed in any occasional user. Higher basal levels in chronic users were likely due to the ability of fat tissue to bind cannabinoids and release them into the blood for a longer period of time, depending on individual metabolic factors. Second, the content of Δ^9-THC in the samples of cannabis (all samples à 0.5 g) provided by chronic users was significantly higher than in samples provided by occasional users. It was reflected in the specimen chosen – chronic users preferred "skunk" (high Δ^9-THC content varieties, often grown indoors under artificial light), while occasional users tended to bring "ganja" samples (outdoors low Δ^9-THC content varieties). Post hoc tests revealed that chronic users had significantly higher Δ^9-THC blood content at 30 min. and 4.5 hours after smoking, but not at the 1.5 hour time point.

[8] For further details on quantification see Attachment I.

In the majority of occasional users, the Δ^9-THC content was not detectable in the blood after 4.5 hours after smoking. Average peak levels (30 min. after smoking) of Δ^9-THC content were 10.2 ng/ml in occasional users and 21.3 ng/ml in chronic users, respectively. Peak blood levels of Δ^9-THC were attained at 30 minutes after inhalation in both groups. In recreational users, levels were still significantly increased above the baseline after 1.5 hour since inhalation ($p < 0.01$). Importantly, although a correlation between the dosage of Δ^9-THC and its subsequent blood content was detected on the whole group level ($r = 0.52$; $p < 0.05$), there were cases in both groups, when high Δ^9-THC content in the joint was not reflected in the blood content, not even 30 minutes after smoking. Apparently, individual metabolic parameters or technique of smoking may have played a role. Some authors claim that meaningful correlations are hard to attain within the first hour after administration, because cannabinoids are still being redistributed at this time (Chiang & Barnett, 1984). Lastly, the absence of Δ^9-THC in the blood does not imply that Δ^9-THC was also cleared from the brain, as a postmortem study revealed (Mura et al., 2005). In this article, we recommended no tolerance policies in respect to driving motor vehicles precisely because the link between the dosage, blood levels and subjective/behavioral effects is very individual and difficult to establish.

My responsibility in this project was to recruit participants and research assistants, administer research protocol, manage blood data collection and cannabis sample collection, collect information on specimen and smoking habits, distribute samples and data to further collaborators, and contribute to the results interpretation and manuscript writing.

III.3 Sexual effects of cannabis intoxication in human users

Commentary on the original research paper:

Androvičová, R., Horáček, J., Tintěra, J., Hlinka, J., Rydlo, J., Ježová, D., Balíková, M., Hložek, T., Mikšátková, P., Kuchař, M., Roman, M., Tomíček, P., Tylš, F., Viktorinová, M. & Páleníček, T. (2017). Individual prolactin reactivity modulates response of nucleus accumbens to erotic stimuli during acute cannabis intoxication: an fMRI pilot study. *Psychopharmacology*, *234*(13), 1933-

1943. https://doi.org/10.1007/s00213-017-4601-1

The treatment of HSDD still remains a state-of-the-art intervention, mainly due to a limited understanding of HSDD etiology and conceptual discrepancies. A rather constrained pool of hormonal, non-hormonal medical or herbal treatments is available, with a variable efficacy, limited indication, concerns about safety and often a lack of evidence from randomized controlled studies (Bolour & Braunstein, 2005). A popular "dual control model" (Janssen & Bancroft, 2007), which seeks to explain the inter-individual variability in proneness towards sexual dysfunction, finds a relative balance between the excitation and inhibition of the sexual system, to be a key principle. On the molecular basis, this balance is likely achieved by the interplay between norepinephrine, dopamine and testosterone on one hand and neuropeptides/neuroendocrine hormones (prolactin) and serotonin on the other hand, as excitatory and inhibitory agents, respectively (Bancroft & Janssen, 2000). One may thus alleviate sexual inhibition either by the enhancement of excitation or by the suppression of inhibition, or in a synergic fashion. Flibanserin, the $5HT_{2A}$ antagonist and $5\text{-}HT_{1A}$ agonist, is the only medication for the treatment of HSDD in women, approved by the FDA in 2015. Even though it possesses the "ideal" pharmacological profile – it suppresses serotonin and enhances dopamine and norepinephrine in the sexual desire "hotspots" of the prefrontal cortex, its use remains controversial (Baid & Agarwal, 2018). Namely, its efficacy is low (the addition of one half of a sexually satisfactory event per month on average), while there is an increased risk of nausea, dizziness, somnolence and fatigue (Jaspers et al., 2016). Perhaps, a combined action with testosterone, as Bloemers et al. (2013) suggested, would be more efficient.

The excitatory branch of the dual control model is represented by the utilization of apomorphine and bupropion. Sublingual or nasal apomorphine is a non-selective dopaminergic agonist (D2>D1) which binds D_2 receptors of the hypothalamus and modulates nitric oxide and oxytocin signals (Tariq & Morley, 2009). Due to its ability to increase arterial blood supply (*idem*, p. 1186), it has been explored as a treatment of erectile dysfunction in men, with promising results (Hagemann et al., 2003; Montorsi et al., 2003). However, its efficacy in HSDD seems low (Caruso et al., 2004). Bupropion, another dopaminergic drug (specifically the norepinephrine-dopamine reuptake inhibitor), is efficient in reverting SSRI-induced sexual dysfunctions but shows weaker

results in non-depressed women (Bolour & Braunstein, 2005). Another molecule implicated by the dual control model, testosterone, which acts centrally via hypothalamic sites (Pfaus, 2009) and is supposed to increase sensitivity to sexual cues, is off-label and traditionally limited to menopausal/postmenopausal women, ageing men or surgically hypogonadic men (Corona et al., 2014; Achilli et al., 2017). Also, the safety of long-term use of testosterone has not been established yet (Krapf & Simon, 2009; Davis et al., 2019). Recently, a combined treatment of sublingual testosterone + 5-HT1A agonist was suggested to improve conditions where there might be a lack of sensitivity towards sexual cues and, at the same time, also the excessive inhibition upon normal sensitivity towards sexual cues (Bloemers et al., 2013) and controlled study showed promising results (Poels et al. 2014). New therapies utilizing serotonergic, dopaminergic and noradrenergic mechanisms (Stahl, 2010), or targeting melanocyte (Wikberg & Mutulis, 2008) or oxytocin receptors (Muin et al., 2015), are currently under the scope of researchers. Herbal therapies (yohimbine, ginseng, ginkgo biloba, etc.) have been shown to impart small prosexual effects too, nevertheless with the exception of yohimbin, controlled studies are scarce (Rowland, McNabney & Donarski, 2019). Interestingly, no indicated treatment of HSDD is available for men, although some authors believe that HSDD, misdiagnosed as erectile dysfunction, is even more prevalent in men than in women (Meuleman & Van Lankveld, 2005).

Our decision to test cannabis for its aphrodisiacal properties was motivated by a long track of historical and anecdotal evidence, as well as novel animal and clinical data, at least in specific samples (Androvičová et al., 2017b). With its broad accessibility, it could represent an option for patients not willing to take synthetic medication or at risk of drug-drug interactions, as cannabinoids are usually well tolerated (Alsherbiny & Li, 2019). Our naturalistic repeated measures study was designed to examine, whether cannabis may or may not increase activation in the brain reward areas in response to visual erotica. We specifically hypothesized, that the increase of activation will be seen in people who reported previous aphrodisiacal experiences upon smoking marijuana (Aphro+ group), while the opposite will be true for those who reported no aphrodisiacal experiences (Aphro- group).

We examined brain and subjective reactions of twenty-one heterosexual users of cannabis (12 men and 9 women), who administered cannabis occasionally (more than one joint a month but

less than three joints a week). We were also looking for an easy peripheral marker, which could possibly differentiate between Aphro^{+} and Aphro^{-} individuals. We chose prolactin, as a "by proxy" indicator of the central dopaminergic activity, which is known to co-fluctuate with sexual motivation (Driver-Dunckley et al., 2007; Oei, et al., 2012). Insufficient mesolimbic dopaminergic activity was also previously hypothesized to be associated with HSDD (Clayton, 2010). Further we monitored cortisol, a marker of the acute stress response (Armario, et al.,1996). In addition to monitoring basal blood levels of prolactin and cortisol, we also measured blood content of these molecules immediately prior to the visual erotic stimulation (approximately 40 minutes after intoxication) in both, intoxicated and non-intoxicated trials. In our stimulation protocol, we employed three visual conditions, pseudo-randomly ordered. Those were casual heterosexual contact (fully dressed actors of the opposite sex, in a casual office situation), erotic heterosexual contact (naked actors having intercourse) and control condition (fixation cross) (Fig. 3). The technical layout of our experiment can be seen on Fig. 4.

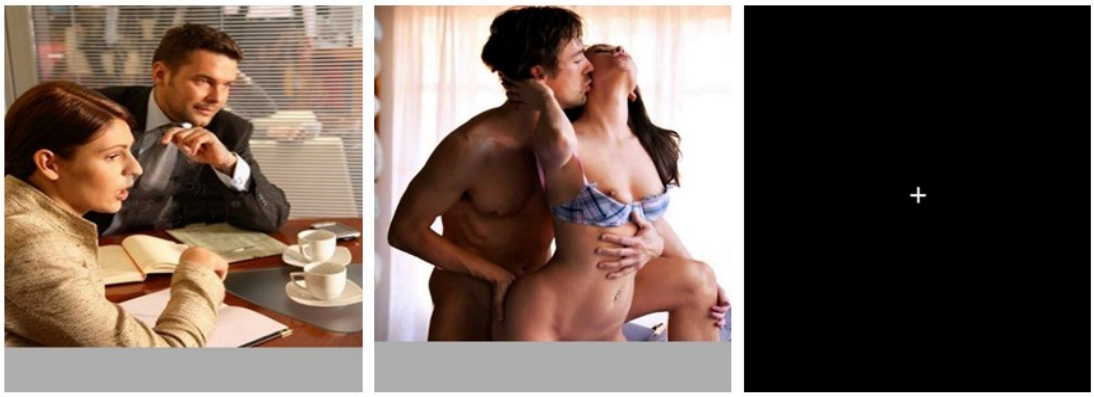

Figure 3. **Visual stimuli.**
Note. Casual heterosexual interaction, Erotic interaction, Fixation cross (left to right).

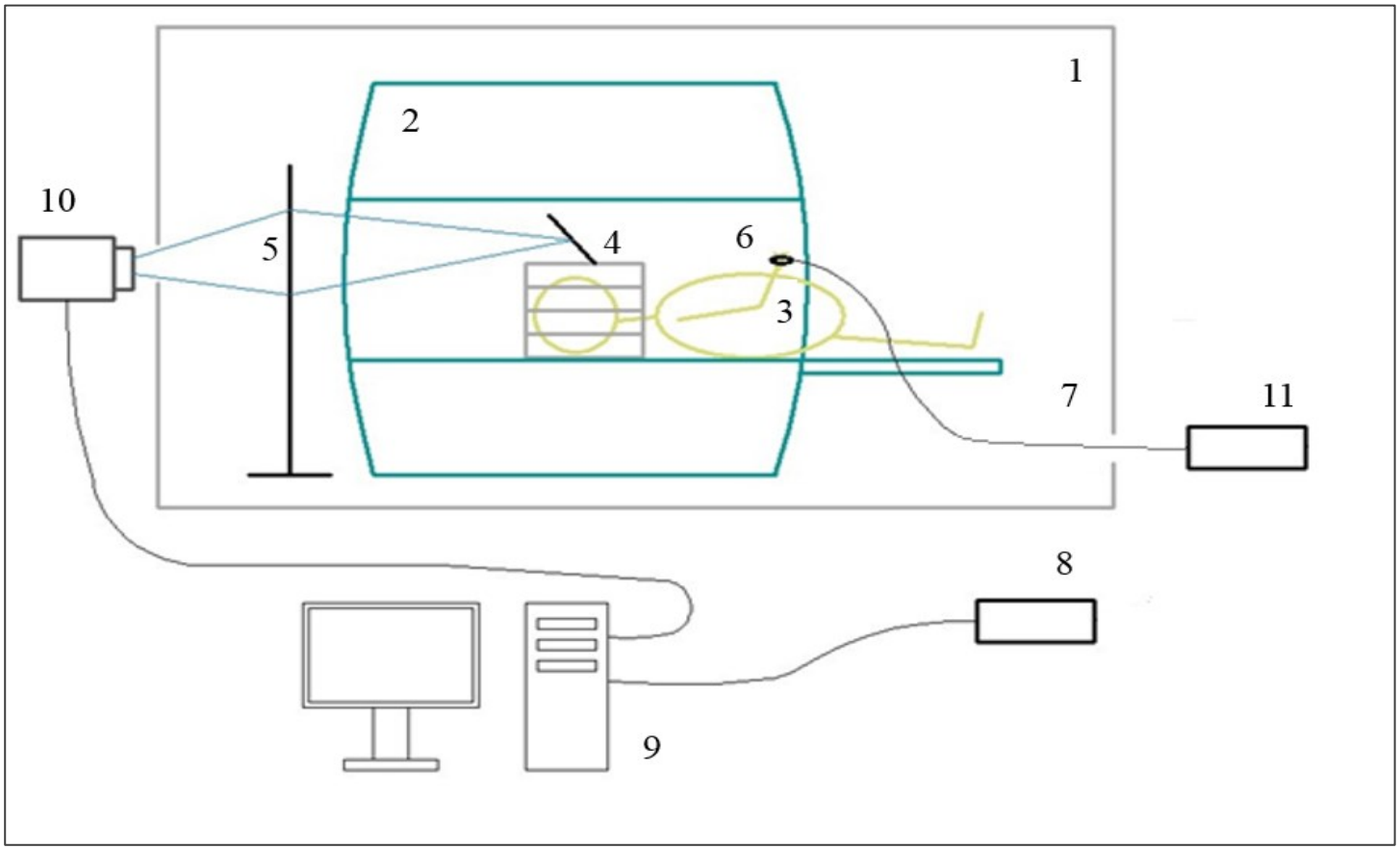

***Figure 4*. Technical layout of the experiment.**

Note. 1 = MR room. 2 = MR scanner. 3 = Volunteer. 4 = Head coil with mirror. 5 = Projection screen. 6 = Squeeze bulb (safety alarm). 7 = Cable. 8 = StimSys modul. 9 = Main computer. 10 = Projector. 11 = Intercom.

During intoxication (but not during non-intoxicated session), Aphro^{-} group showed a diminished response of the right nucleus accumbens and hypothalamus to visual erotica (Fig. 5), which was accompanied by a significantly elevated prolactinaemia (Fig. 6). In their Aphro^{+} counterparts, prolactinaemia dropped down insignificantly during intoxication (Fig. 6) and was accompanied by a heightened response of the right nucleus accumbens and hypothalamus to visual erotica (Fig. 5), irrespective of sex.

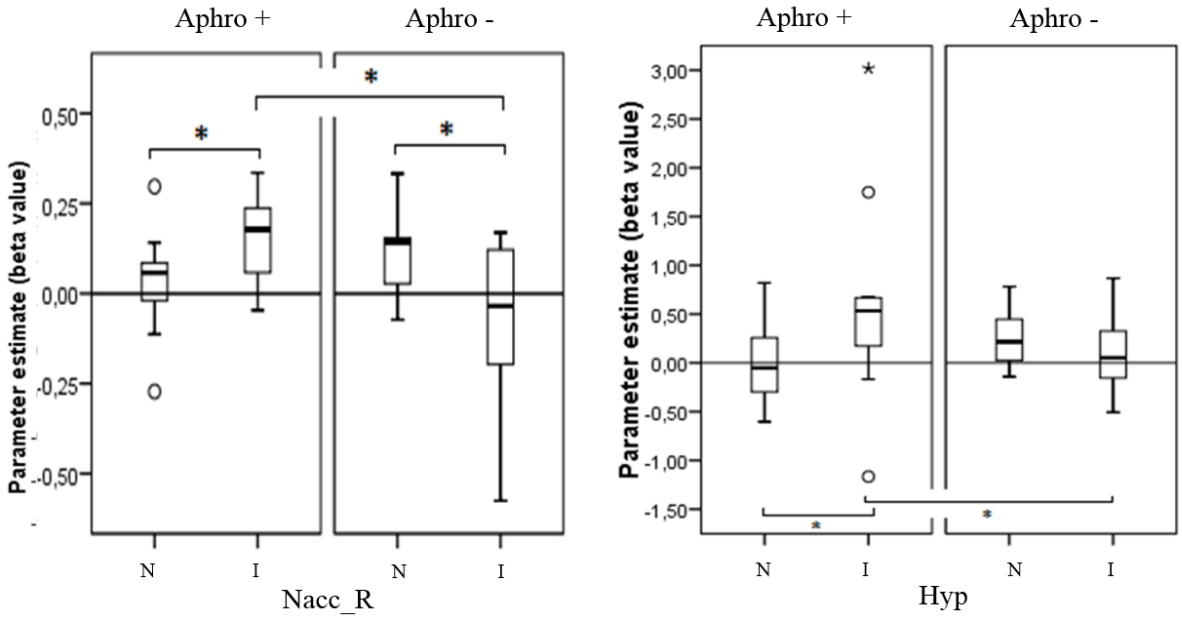

Figure 5. **Effect of intoxication in the right nucleus accumbens and hypothalamus.** *Note.* Aphro+ = group in which cannabis has aphrodisiacal properties. Aphro- = group in which cannabis does not have aphrodisiacal properties. Hyp = hypothalamus. NAcc_R = right nucleus accumbens. N = non-intoxicated trial. I = intoxicated trial. * denotes statistically significant between-group differences ($p < 0.05$). Vertical bars denote standard error of the mean. ° and star denote outliers.

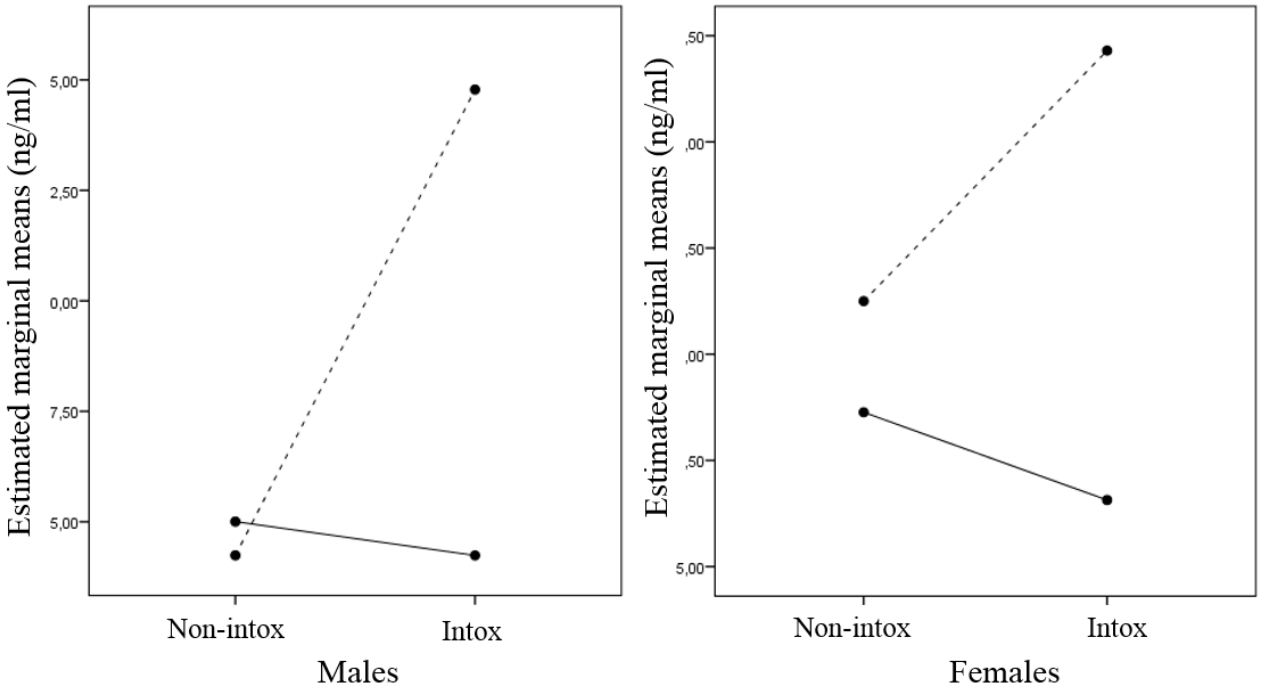

Figure 6. **Effect of intoxication on prolactin blood levels in men and women.**
Note. Solid line = Aphro+ group (i.e. the group in which cannabis has aphrodisiacal properties). Dashed line = Aphro- group (i.e. the group in which cannabis does not have aphrodisiacal properties). Non-intox = non-intoxicated trial. Intox = intoxicated trial.

Interestingly, prolactinaemia in Aphro^{-} group (i.e. $Mean_{intoxication}$ = 10.7 ng/ml, *SD* = 2.09) approached levels typical for the sexual refractory period, a period of a transitory sexual inhibition which occurs after orgasm. Normally, pre-arousal prolactin levels fluctuate commonly around 5 to 7 ng/ml, while post-orgasmic prolactin levels can reach between 15 to 25 ng/ml for at least 1 h after orgasm (Krüger et al., 2002)[9]. The mechanism of a higher peri- and post-orgasmic prolactin is not fully elucidated yet. Some consider it a side effect of a decreased dopaminergic tone, while others, a specific inhibitory signal of a biological importance (*idem*, p. 38). Similar debate exists in respect to its origin – whether prolactin signaling comes from periphery and travels to the brain or the other

[9] These fluctuations are still very different from long-lasting pathological hyperprolactinemia (prolactinaemia > 200 ng/ml) and must be considered physiological, not abnormal.

way around. Regardless of the exact mechanism, it has been documented that even slight increases in prolactin levels result in some reduction in sexual motivation (Krüger et al., 2003).

Observed differences in prolactinaemia and nucleus accumbens' response could not be accounted for by the differences in the acute stress response to intoxication, because both groups, showed significantly increased cortisol levels (irrespective of sex) (Fig. 7). Nor this could have been attributed to different baseline levels[10], because prolactinaemia (Aphro$^-$ group: $Mean_{non\text{-}intoxication}$ = 5.36 ng/ml, *SD* = 1.27; Aphro$^+$ group: $Mean_{non\text{-}intoxication}$ = 5.22 ng/ml, *SD* = 0.61) and nucleus accumbens' response were similar in both groups during the non-intoxicated state (Fig. 5 and 6). Response of the right nucleus accumbens was also negatively correlated with basal peripheral prolactin (Fig. 8).

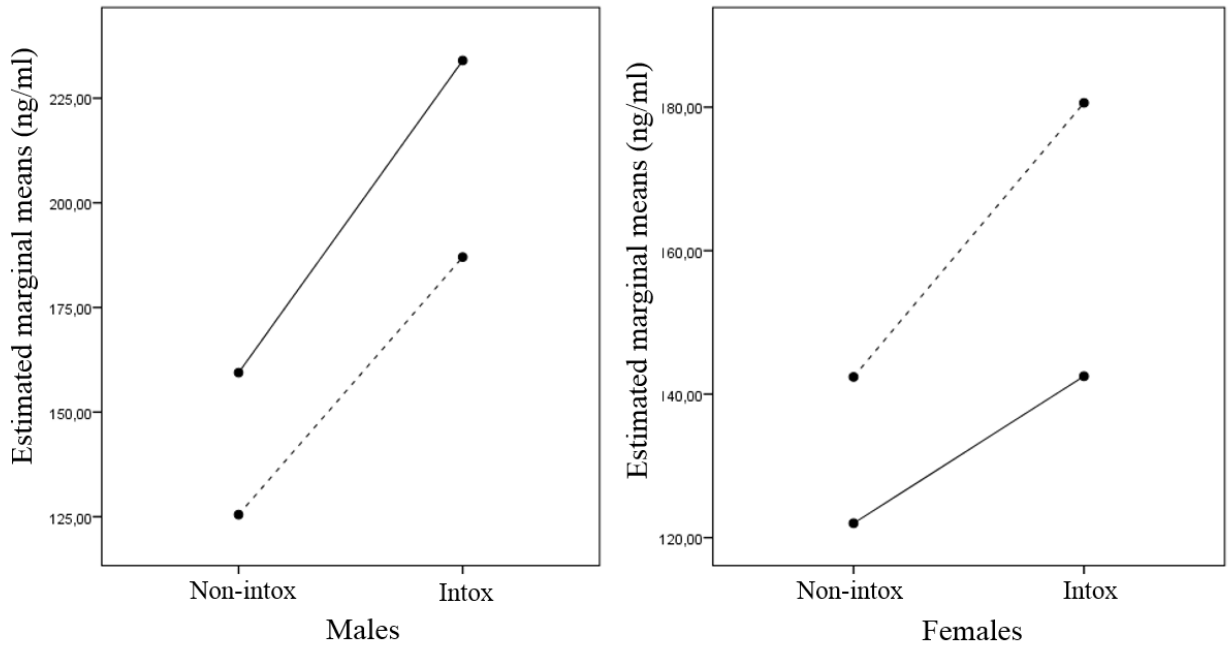

Figure 7. **Effect of intoxication on cortisol blood levels in men and women.**
Note. Solid line = Aphro+ group (i.e. the group in which cannabis has aphrodisiacal properties). Dashed line = Aphro- group (i.e. the group in which cannabis does not have aphrodisiacal properties). Non-intox = non-intoxicated trial. Intox = intoxicated trial.

[10] „Baseline" meaning native/non-intoxicated.

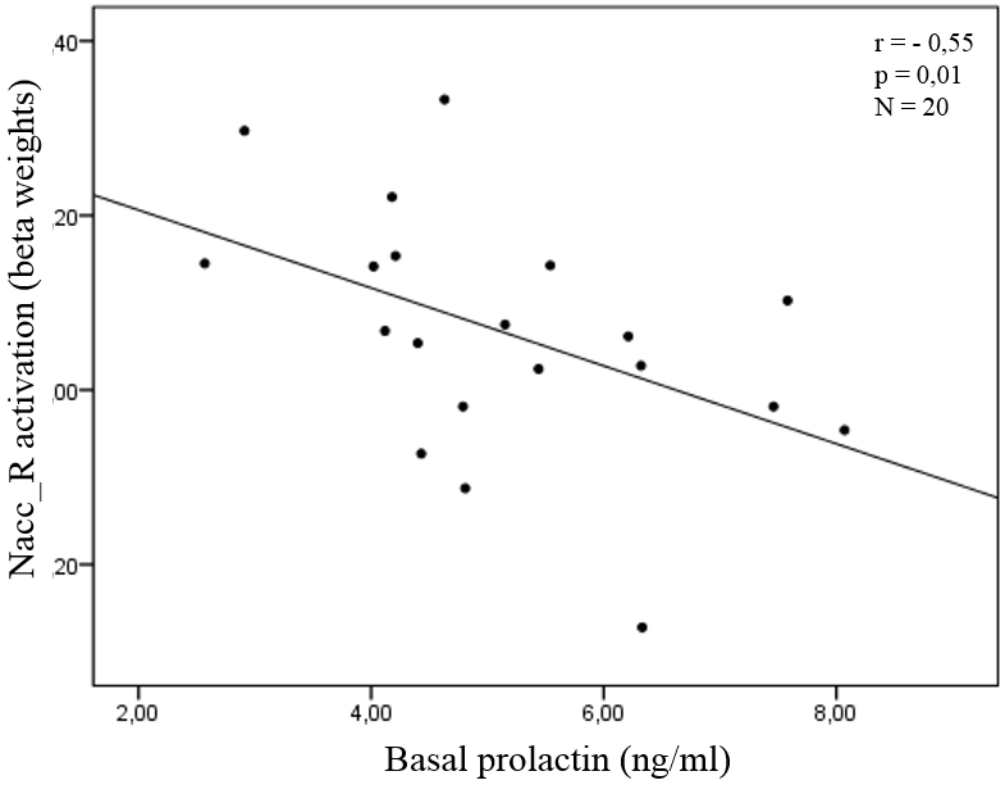

Figure 8. **Co-fluctuation of the NAcc_R activation and peripheral prolactin.**
Note. NAcc_R = the right nucleus accumbens. r = Pearson's correlation coefficient. p = statistical significance of the correlation. N = number of subjects.

These findings prompted us to look further into the differences between the groups. Groups did not differ in terms of the dosage used or the onset of use. Both groups started smoking marijuana at around the same mean age, Aphro^{+} at 19 (SD = 3.81) and Aphro^{-} at 17 years of age (SD = 2.24), not differing significantly in this variable ($t_{df(19)} = 1.52$, $p = 0.15$). Participants from the Aphro^{+} group (prolactin-stable), however, were significantly older than participants from the Aphro^{-} group (prolactin-reactive) (29 as compared to 24 years) at the time of measurement. Logically, differences in aphrodisiacal properties could therefore be connected to the longer history of use or to some age-related factors. Nevertheless, users who reported aphrodisiacal effects did not mention that the effect appeared gradually with time, but rather that it was "always there", implying that it

was a trait-like feature. A promising clue was found when we further explored both groups on their scoring on clinical scales of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Butcher et al., 2013), a standardized personality inventory, which we used to eliminate individuals with clinically relevant pathologies from the sample. The prolactin-reactive group (Aphro$^-$) scored significantly higher than the prolactin-stable group (Aphro$^+$) on three standardized clinical scales: Scale 2 – depression ($t_{(df=17)} = 3.708$, $p = 0.002$), Scale 7 – psychasthenia ($t_{(df=17)} = 4.212$, $p = 0.001$) and Scale 8 – schizophrenia ($t_{(df=17)} = 4.501$, $p < 0.001$). While the Aphro$^+$ group scored around population average on all three scales, prolactin-reactive Aphro$^-$ group reached the level of moderate elevations in scales 7 and 8 (Fig. 9**)**.

An important aspect of this study was that it was focused on skilled but not heavy users of cannabis. Our sample choice was based on several reasonings – it is known that first-time intoxication can be anxiogenic, unpleasant, associated with a loss of control, feelings of depersonalization and derealization, inability to focus attention and sometimes also with a paradoxical effect of not being able to perceive any psychotropic effect at all (Weil, 1970; Tart, 1975; Hollister, 1986). Smoking experience is therefore subject to further transformation by experience and it must be in a way "learned" to become fully appreciated. Inferences from studies on drug naïve individuals should therefore be limited to first-time-users only and not generalized. Second, in chronic users, on the other hand, neuroadaptive functional changes most likely occur, with unclear reversibility (Chang & Chronicle, 2007). They also show permanently increased blood levels of cannabinoids (Karschner et al., 2009b). Therefore, they might not be able to appreciate the intoxication as something out of normal anymore. Occasional users were, therefore, a sample which probably best reflects features of potential future users of medical cannabis – experienced, but not fully adapted to the drug.

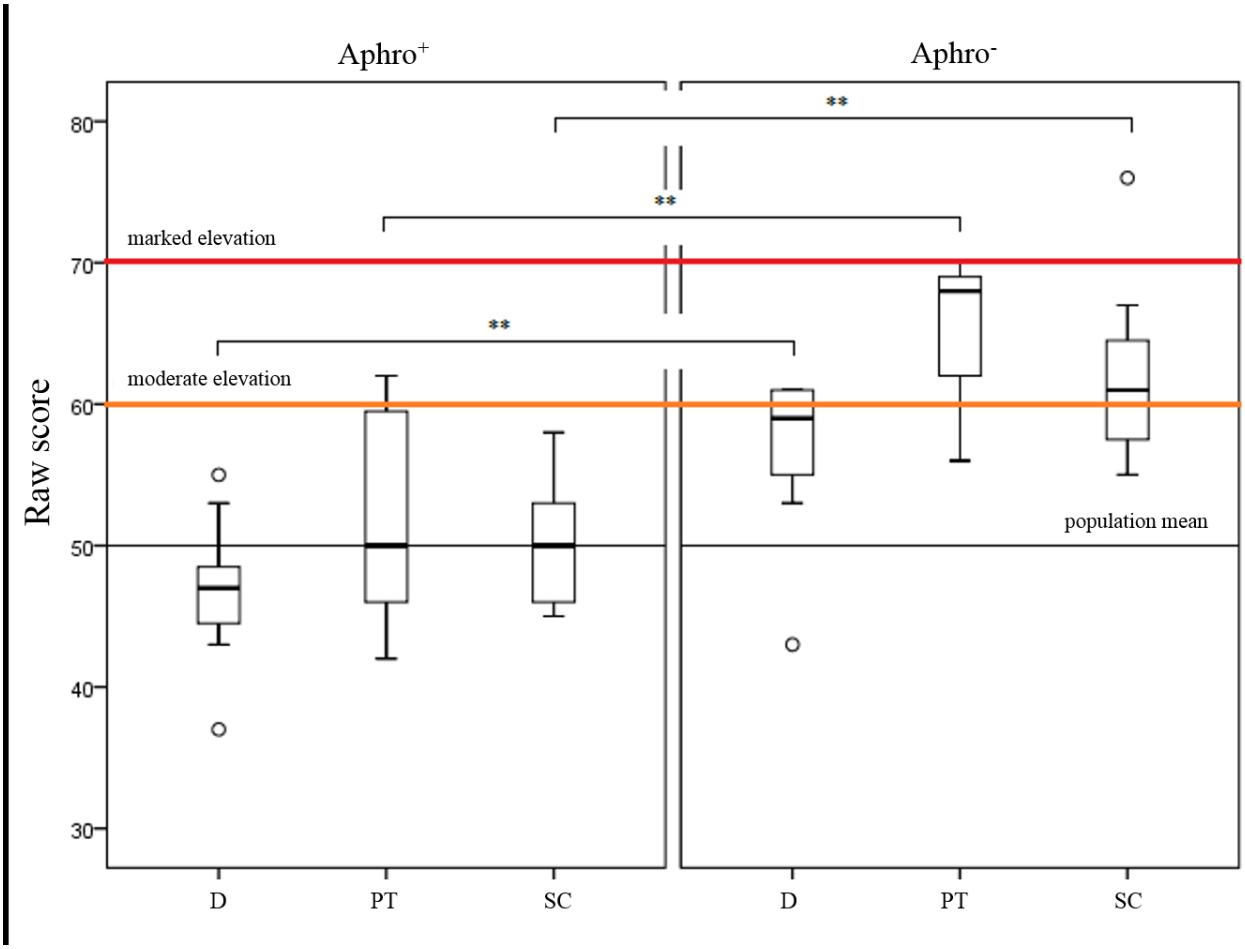

***Figure 9*. Significant differences in the clinical scales of the MMPI-2 questionnaire between Aphro+ and Aphro- group.**

Note. Aphro+ = group in which cannabis has aphrodisiacal properties. Aphro- = group in which cannabis does not have aphrodisiacal properties. D = scale 2 (depression). Pt = scale 7 (psychasthenia). Sc = scale 8 (schizophrenia). ** denotes statistically significant differences ($p < 0{,}001$). ° denotes outliers.

This work was presented at numerous conferences – local and international in the time period from 2014 through 2017. For a complete list, see Attachment IV. In 2015, it received the award for the best clinical brief communication during the Czech and Slovak Psychopharmacological Conference in Jeseník, Czech Republic. My responsibility on the project

was to i) design the study, ii) formulate a priori hypotheses, iii) manage and supervize the whole brain assessment branch of the project and data collection, iv) perform statistical analyses of the fMRI data and v) interpret the data and draft an article under the continuous supervision of my mentor. I also took care of the recruitment of participants and research assistants and oversaw the adequate administration of the research protocol. Consecutively, I supervised the data entry procedure.

The analyses included standard preprocessing and first-level analysis in the Statistical Parametric Mapping 8 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm8/, Wellcome Trust Centre for Neuroimaging, 2009), data extraction in MarsBaR version 0.43 tool for SPM (Brett et al. 2002) and further group-level analysis in SPSS (IBM Corp., 2011) and R statistical software (R Core Team, 2014). The original research paper published in the journal Psychopharmacology, was drafted by myself, except for the respective parts on the methodological procedures (cannabinoid, steroid and prolactin blood content analysis and technical parameters of MR scanning sequences). The final peer-review process was handled by myself, under the supervision of Prof. Horáček and with the help of Prof. Ježová and Dr. Hlinka, of the authorship.

III.4 General cognitive effects of acute cannabis intoxication in human users

Commentary on the original research paper:

Zaytseva, Y., Horáček, J., Hlinka, J., Fajnerová, I., Androvičová, R., Tintěra, J., Salvi V., Balíková, M., Hložek, T., Španiel, F. & Páleníček, T. (2019). Cannabis-induced altered states of consciousness are associated with specific dynamic brain connectivity states. *Journal of Psychopharmacology*, *33*(7), 811-821. https://doi.org/10.1177/0269881119849814

Cannabis induces well-known psychotropic effects, namely intensification of sensory perception, motivational changes (laughter, hunger, sleepiness, sexual desire), motor retardation,

time disintegration, incoherence of thinking, inability to focus attention, disruption of mnestic functions and psychotomimetic effects like feelings of depersonalization, disintegration, losing of control, confusion and sometimes paranoia, anxiety and anger (Mathew et al., 1993; Denier et al., 2012). These potent effects are difficult to track via standard imaging protocols (i.e. task-related brain imaging). Multiple authors who studied cannabis intoxication found only a few brain functional changes at best (Martin-Santos et al., 2010). This is confusing, given self-reports of users speak of profound psychological, physiological and motoric effects, which are even more pronounced in chronic use (Hollister, 1986). One way to think about this is to suppose, that the power of cannabis lies in the functional disintegration of the brain, rather than changing the regionally specific hemodynamic function underlying the fMRI signal *per se*. By giving a volunteer a task, a researcher might be helping to re-integrate functions back and thus in fact remove the very mental "chaos" they wanted to study.

A few years ago, the concept of *resting state* entered into neuroimaging protocols (Binder et al., 1999), enabling to study conscious mental states unburdened by external tasks (e.g. DMN). In this imaging protocol, volunteers are instructed to relax and let their minds wander freely, wherever and whenever they want to. It was reasoned, that resting state protocol would allow the observation of task-unrelated properties of basic brain organization. Earlier studies assessed neural activity by means of resting brain metabolism (PET) or cerebral blood flow (SPECT); today, mostly oxygenation dependent effects are measured (fMRI). In intoxicated occasional users, most consistent increases of neural activity were in the right hemisphere, mainly anterior cingulate, ventral frontal regions, parietal regions and insula; inconsistent results were reported for cerebellum, occipital cortex, basal ganglia, thalamus, hippocampus and amygdala (Martin-Santos et al., 2010; Van Hell, et al., 2011; Denier et al., 2012; Batalla et al., 2014). More recent studies focused, instead of local metabolic changes, on a relatively newly studied phenomenon, called functional connectivity of the brain. Functional connectivity (represented by correlations among signal time-series from various brain areas or networks) is interpreted as the measure of cooperation and competition among brain regions (Fornito et al., 2005; Fox et al., 2005; Cocchi et al., 2013) and connectivity patterns in the resting brain are considered a basic functional organization (Nekovarova et al., 2014). Positive and negative correlations are traditionally explained as mutual

excitation/cooperation or inhibition/competition among brain areas, respectively (Kelly et al., 2008). No correlation means an attenuation of the influence of one area towards the other ("de-coupling"), a strong correlation means a strong mutual cooperation (if positive) or competition/alternating activity pattern (if negative). Mostly, functional connectivity seems to correspond to anatomical connectivity, even though ideas of indirect, via-third-party connections also recently appeared (Damoiseaux & Greicius, 2009).

The above-mentioned studies made use of the concept of stationary connectivity, which is an average connectivity assessed per the whole resting state measurement. Since the advent of functional connectivity research, it has become clear that this kind of analysis implicitly works with the idea of network stability throughout the whole resting state measurement. However, neural interactions may fluctuate on a much shorter time scale (Handwerker et al., 2012). These rapid changes in the strength of functional coupling are called *dynamic connectivity*. Dynamic connectivity analysis uncovers temporal changes of connectivity during the resting state measurement and thus, might capture the effect of drugs more accurately.

Bearing this in mind, we explored dynamic fluctuations of the brain connectivity patterns caused by intoxication (Zaytseva et al., 2019). Concretely, we employed repeated measures design with 19 occasional cannabis smokers (volunteers came from the same sample as entered the studies described in previous chapters; two more male participants were excluded from the analysis, due to non-optimal resting state data quality), whose resting brain activity was recorded twice, in a normal physiological state and under intoxication. Volunteers were instructed to bring their usual sample of cannabis and administer the amount of drug as usual. This approach was employed in order to make the laboratory experiment as close to real life situations as possible and thus secure at least a partial environmental validity. Subjective evaluations of mental state were provided after each measurement via the revised version of the Abnormal Altered States of Consciousness Questionnaire (ASC) (Dittrich, 1998).

First, we identified independent functional networks (i.e. cognitive network, DMN, somatomotor, auditory subcortical and visual network) and then, we employed a method called a "sliding window approach" (Hutchison et al., 2013) and k-mean clustering (Lloyd, 1982), which eventually led to the identification of six states of network connectivity inter-changing during the

time span of the resting state measurement. These six states could be described as strong, weak and random couplings among the networks and other brain regions. The non-intoxicated resting state was abundant with connectivity patterns represented by weak mutual inhibitions between cortical and subcortical areas and weak co-facilitation within cortical and subcortical areas. States characterized by strong mutual inhibition were much less expressed. Intoxication, to the contrary, induced an equal proportion of mild and strong connectivity states. Strong connectivity states reflected mutual co-facilitation among sensory and somatosensory areas, which in turn strongly inhibited basal ganglia. We must keep in mind that these are the group results, and considerable inter-individual variability existed. For example, five individuals did not show strong connectivity patterns during intoxication at all (for further details see Fig. 10). On the other hand, half of the individuals showed a specific strong connectivity pattern which we called *State 6*, typical by high connectivity within auditory and somato-motor cortices and anticorrelation of these with subcortical structures and cerebellum. This state did not occur in any but one individual during non-intoxication. The duration of *State 6* was well correlated with THC blood levels and self-reports of the altered states of consciousness[11], and thus it does not seem artefactual but rather of a neural origin. It should be noted, that we observed extreme variability of the distribution of states across the time intra-individually. Only 4 out of 19 participants did not show thalamo-cortical anticorrelations during intoxication. Interpretation-wise, it seemed that sensory inputs were allowed to run freely without much thalamic-filtering and without translating into motivational/motoric tendencies (caudate, striatum).

My responsibility in this project was to recruit participants and research assistants, administer research protocol, manage data collection (brain data, blood collection and self-reports), supervise data entry and distribute raw data to further collaborators. Furthermore I participated in the manuscript writing and peer-review process of the drafted paper.

[11] Specifically the "oceanic boundlessness" which is a dimension from the ASC referring to the phenomena of depersonalization and derealization.

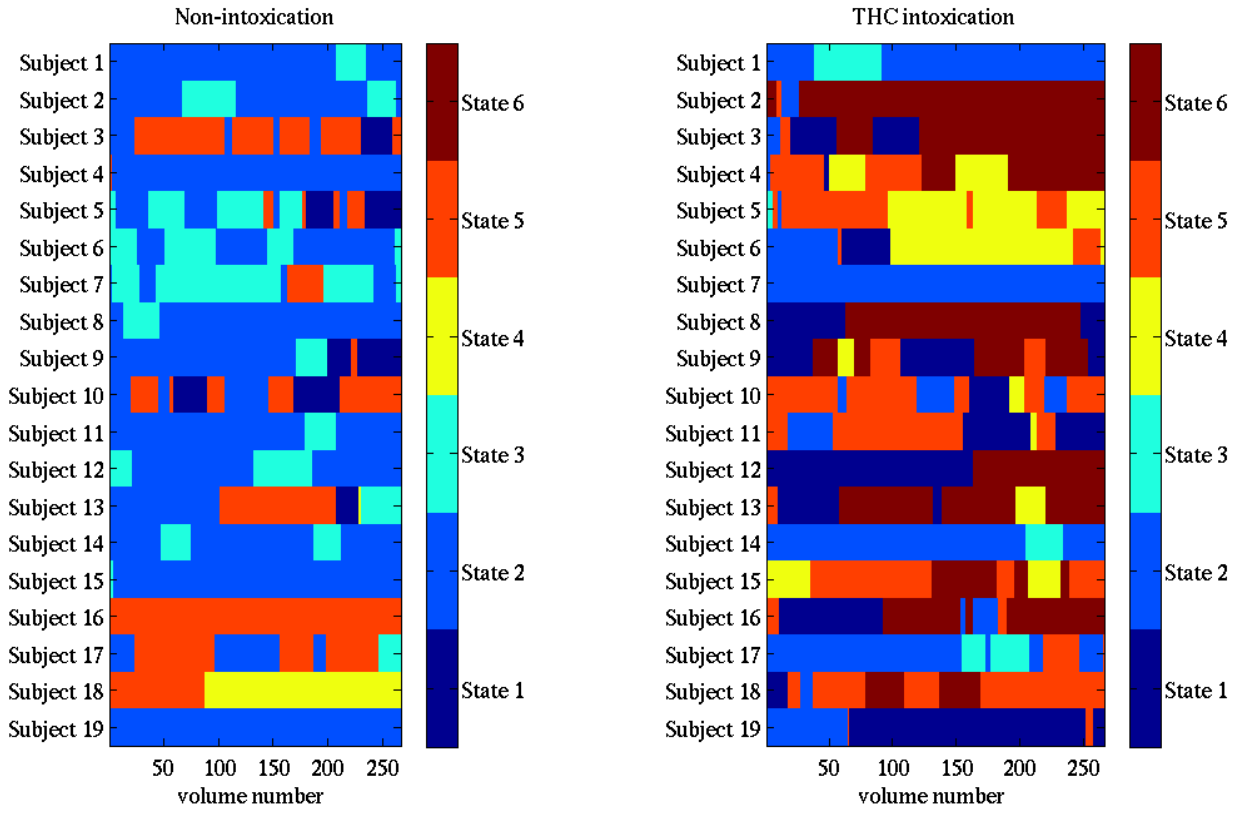

***Figure 10*. Individual time courses of various connectivity patterns.**

Note. State 1 = strong positive correlations (correlation coefficient above 0.5) among auditory, visual and somatomotor cortices and anticorrelations (negative correlations) of these sensory areas with subcortical structures, insular cortex and cerebellum. *State 2* = weak correlations (correlation coefficient in the range from −0.2 to +0.2) between and within each identified network. *State 3* = random correlations plus. *State 4* = strong positive correlations (correlation coefficient above 0.5) among auditory, visual and somatomotor cortices and posterior cingulate cortex and anticorrelations (negative correlations) with subcortical structures. *State 5* = similar to State 2, but connectivity within auditory and visual cortices and anticorrelations with subcortical structures, did not reach the statistical threshold. *State 6* = strong connections within auditory and somatomotor cortices and anticorrelation of sensory networks with subcortical structures, specifically with the caudate nucleus.

IV. Discussion

The main argument of this thesis, i.e. a hypothetical enhancement of the brain response to sexual stimuli by cannabis intoxication, was supported by empirical data. In a portion of occasional users (approx. 50%), characterized by stable peripheral prolactin, hypothalamus and nucleus accumbens increased their responsivity specifically to visual erotica, upon smoking cannabis. In prolactin-reactive individuals, in contrast, we observed opposite reactions, i.e. the decrease in the limbic response to sexual stimuli. These phenomena were independent of the general stress response (cortisol increased in both groups upon intoxication) and independent of sex (occurred in both sexes alike), but they were associated with elevated score in three clinical scales of the MMPI-2 questionnaire in prolactin-reactive individuals. On the level of brain connectivity, we observed a marked intoxication-related shift from weak to strong coupling (in either direction, positive or negative) among various networks. Most notably, intoxication enhanced co-facilitation among and within sensory cortex and anti-correlation of sensory cortex to basal ganglia and portions of the DMN. Interestingly, the occurrence of a specific connectivity state (*"State 6"),* marked by a very strong coupling among networks and associated with the experience of altered state of consciousness, was directly dependent on Δ^9-THC blood content. Pharmacokinetics informed us, that a time window of approximately four hours is needed in order for psychoactive molecules to clear out from the system in occasional, non-chronic users. In conclusion, the cannabis-intoxication related enhancement of limbic activity and cross talk among sensory cortices may present an opportunity for the treatment of HSDD, at least in a portion of users.

Current models of HSDD are inspired largely by the dual control model hypothesis (Janssen & Bancroft, 2007), which stresses mainly two etiological mechanisms: a "relative insensitive brain system for sexual cues or … enhanced activity of sexual inhibitory mechanisms" (Bloemers et al., 2013, p. 791). In relation to the drug development efforts, this reasoning translates into targeting androgen and serotonin receptors in the brain, as the main players in sexual desire establishment. It is little wonder, because therapies based on SSRIs or antiandrogens often lead to sexual desire and arousal deterioration (Lorenz, Rullo & Faubion, 2016; Donovan et al., 2018; Olivier et al., 2019), which sometimes perpetuate beyond the period of immediate use (Bala, Nguyen &

Hellstrom, 2018). Motivational processes, though, comprise of other important aspects, such as a) the active seeking out of salient stimuli (Falkner et al., 2016) and b) the translation of sensory excitation into motivated behavioral action (Duffy, 1997), Although, conceptually, behavioral output is beyond the topic of the desire establishment, the translation of excitation into the real behavior is commonly used as the measure of efficacy of aphrodisiacal medicine (Jaspers et al., 2016). In this respect, dopaminergic transmission is known to critically affect human sexual behavior (Pfaus, 2009), possibly via connections from medial prefrontal cortex to basal ganglia (Spinella, 2007). The enhancement of central dopamine levels was shown to lead to multiple sexual effects, from the increased response of nucleus accumbens to sexual stimuli in healthy subjects (Oei et al., 2012), through normalization of brain activation to erotic stimuli in men with erectile dysfunction (Montorsi et al., 2003), to hypersexuality and compulsive sexual behaviors in Parkinsonian patients treated with 3,4-dihydroxy-Lphenylalanine (L-DOPA) (Kraus, Voon & Potenza, 2016; Barbosa et al., 2018). In this respect, cannabis (or synthetic CB1 agonists) represents an outstanding opportunity, because it seems to combine two effects crucial to the establishment and behavioral translation of sexual desire – i.e. central dopaminergic enhancement and heightened sensuousness (via modification of inter- and intra-regional sensory brain connectivity).

However, cannabis does not seem to affect dopaminergic transmition universally in the same direction. Differences in prolactin response we observed were remarkable but not easily explained by the dosage, onset of cannabis use, or content of phytocannabinoids in the samples provided[12]. They seemed to be, however, related to the specific personality differences. Aphro- group (prolactine-reactive) scored significantly higher than Aphro+ group (prolactin stable) on three clinical scales in MMPI-2 inventory: Scale 2 (D, depression); Scale 7 (Pt, psychasthenia) and Scale 8 (Sc, schizophrenia). In Scales 7 and 8, Aphro- group even reached a subclinical moderate elevation range. Aphro+ group scored around population average on all nine clinical scales. Markedly, Aphro- group was slightly but significantly younger than Aphro+ group (24 vs. 29 years) and 77% of Aphro- subjects were still attending college (as compared to the Aphro$^+$ group with

[12] Samples used in our study were remarkable by high Δ^9-THC and very low CBD content (Balikova et al., 2014).

38% of subjects still attending school). MMPI-2 code type 2-7-8[13] is a three-point pattern indicative of depression, anxiety, feelings of the lack of control and possibly of bizarre experiences (Sellbom, Graham & Schenk, 2005). It is commonly found in young people seeking outpatient psychiatric care, particularly in college students (Lachar, 1974; Kelley & King, 1979). Therefore, our results might be linked to the situation of high school/college attendance, possibly through a variety of stressors connected to the pursuing of higher studies. Bearing this in mind, the high prolactin reactivity to cannabis smoking could have been a function of age or of a specific life situation (university studies) or a combination of both and not a trait like feature. In this respect some findings in cannabis use could be a residue of research with a sample bias (centered on student populations).

Apart from the tentative dopaminergic effect in the limbic brain, our findings of the facilitation of cross-talk among sensory cortices seem to offer a mechanism of unrestrained sensuousness often reported by users (Green, Kavanagh & Young, 2003). While non-intoxicated conscious mind was, in our study, characterized by weak to mild mutual inhibitions among sensory, executive and motor brain networks, likely to ensure flexibility of the system, intoxication brought massive mutual inhibitions among networks and mutual facilitations within networks (especially in the sensory cortex). Thus, if, for example, sensory processing takes prime in overall mental engagement, it may block regulatory actions from executive areas and inhibit motor areas (hence slowness of movement). Similar findings of facilitated connectivity in sensorimotor cortices and dorsal visual streams were brought by Klumpers et al. (2012). Increased negative connectivity was, in turn, reported by Whitfield- Gabrieli et al. (2018), for the DMN and executive control network (mutual inhibition) and by Fischer et al. (2014), who found heightened connectivity of the nucleus accumbens to the frontal reward regions (orbital cortex, anterior cingulate, frontal pole). The significance of the enhancement of sensory processing in HSDD could be enormous – majority of available psychotherapies are focused on the training of the so called "sensate focus" (Pereira et al., 2013), i.e. the ability to allocate one's attention fully to the sensuous perception.

It should be noted here, that there are studies which stress opposite effects in cannabis use

[13] Code 2-7-8 means increased scoring on Scales 2, 7 and 8.

– namely the loss of functional coupling among areas. For example, Blanco-Hinojo et al. (2017) reported reduced input from frontal and sensory cortices to basal ganglia, suggesting a mechanism for the diminished responsiveness to both internal and external motivation signals in chronic cannabis use; Pujol et al. (2014) found attenuation of competition between the DMN and executive control network, which offers a mechanism for the decreased self-awareness and memory impairment; Ramaekers et al. (2016) observed reduced connectivity between nucleus accumbens and frontal midline structures like cingulate gyrus (middle part), superior frontal gyrus medial part and temporal, parietal and occipital areas, suggesting a mechanism for cognitive impulsivity. The loss of connectivity alongside short axons was reported for the hippocampus and caudate (Kim et al., 2019) and inter-hemispherally (Orr et al., 2013), with possible implications for habit-formation, learning and substance dependence (Patel & Marwaha, 2019). These findings are supported by the detection of impaired axonal pathways in fornix, corpus callosum and commissural fibers as revealed by the diffusion tensor imaging (Zalesky et al., 2012). Even if the dis-coupling among regions is not a "pathology" in itself and occurs regularly as a transient state of cross-communication among various brain networks (Honey et al., 2007; Sneve et al., 2017), there are concerns about the longevity of such "dis-coupling" effects and consequently, about the loss of cognitive flexibility in drug users (Ma et al., 2011; Sutherland et al., 2012; Ding & Lee, 2013; Zaytseva et al., 2019). Apart from the potential long-term effects of the connectivity loss, there are also other aspects of cannabis use which should be approached with caution. Cannabis use was previously linked to high-risk behaviors (Charrier et al., 2019), male infertility (Rajanahally et al., 2019), or to the development of psychosis (Kuepper et al., 2011; Radhakrishnan, Wilkinson & D'Souza, 2014). In this respect, our finding that the dopaminergic system (as indicated by prolactin reactivity) could be easily disrupted in a specific portion of users is valuable. Further, use during pregnancy and post-partum would be contraindicated - due to high liposolubility and small molecular size, cannabinoids can easily cross placenta (Boskovic et al., 2010) or enter breast milk (Garry et al., 2009) and might be harmful to fetus and newborn children.

In conclusion, caution should be exercised regarding potential harmful effects of cannabis and pros and cons of cannabinoid medication should be carefully weighed. Hopefully, current diagnostic options including neuroimaging methods and biomarkers should eventually make

possible to determine whether a person would or would not benefit from the cannabis-derived medication. Various subgroups of users exist, using cannabis for different purposes and at different risks of developing mental health problems. These inter-individual differences should not be discarded as inconvenient complications which make statistics less powerful but rather as useful leads towards personalized and differentiated medical use of cannabis.

V. Summary and conclusions

We have brought new insights into the potential usefulness of cannabis treatment of HSDD, by reviewing available human and animal evidence and by conducting our own naturalistic experiment. In this experiment, we demonstrated that intoxication can increase the response of nucleus accumbens and hypothalamus, key motivational areas, to visual erotica, in a portion of users. We also identified a possible dopaminergic mechanism (as indicated *by proxy* by peripheral prolactin) responsible for these interindividual differences. Peripheral prolactin can thus serve as a simple marker predicting the direction of activation change in the pertinent limbic areas. These results were further informed by our additional studies mapping pharmacokinetics of phytocannabinoids and the dynamic brain connectivity patterns during intoxication. The dynamic brain connectivity study revealed strong connectivity patterns within sensory cortices, which could be a basis of heightened sensuousness experienced during intoxication. The pharmacokinetic study showed that peak blood concentration of Δ9-THC is to be encountered within 30 minutes of inhalation and with a controlled regular use, not exceeding several joints a month; no residual levels of Δ9-THC are detectable after 4 hours of inhalation in occasional users.

There are several limitations as to the definitive conclusions about the potential of cannabis in the treatment of HSDD. First, the enhancement of limbic activation to sexual stimuli does not seem to be a universal feature of cannabis intoxication. Therefore, more research into individual parameters (e.g. prolactin reactivity) which may interfere with the desired effects is necessary. Second, brain activational changes might not necessarily translate into behavioral effects and further investigation into this matter should be granted. Last, pharmacokinetics of cannabinoids are rather complex. Apart from some "knowns" like rapid crossing of the blood-brain barrier and a relatively short latency to the onset of central effects, there are also "unknowns" – e.g. the establishment of blood levels necessary to attain the desired effects, the deposition of cannabinoids in the fat tissue and variable inter-individual metabolic idiosyncrasies.

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Attachment I (Quantification of cannabinoids)

The sample preparation procedure was briefly as follows: 1) a total of 10 µl of deuterated CBD-d3/THC-d3/ 11-OH-THC-d3 (5 ng/µl) internal standard solution was added to each 1.0 ml sample of serum, 2) serum extracts were diluted with 4 ml sodium acetate buffer with pH of 4.0 (0.01 mol/l) and 3) cannabinoids were extracted with SPE columns (Bond-ELUT, 130 mg, Agilent Technologies), eluted with hexan/ethyl acetate (1:4 v/v) and dried under a nitrogen gas stream in 400 µl glass insert placed in 1.5 glass vial, 4) derivatized with 100 µl N-Methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) for 20 min at 80ºC. Quantification of extracted cannabinoids was performed by gas chromatography-mass spectrometry (GC-MS, Agilent Technologies) using electron impact ionization in selective ion mode (CBD: m/z 391; CBD-d3: m/z 394; THC: m/z 386; THC-d3: m/z 389; 11-OH-THC: m/z 371; 11-OH- THC-d3: m/z 374). Calibration curve ranges were prepared by spiking drug-free bovine serum for analysis at concentrations of (i) 2 – 100 ng/ml CBD, THC and 11-OH-THC; (ii) 100 – 1 000 ng/ml CBD, THC and 11-OH-THC. The standards were vortexed and treated identically as real samples. The lower limit of quantification (LOQ) was 2 ng/ml, the limit of detection (LOD) was 1 ng/ml.

Attachment II (Articles in extenso)

Journal articles with IF related to the thesis

Androvicova, R., Horacek, J., Stark, T., Drago, F., & Micale, V. (2017). Endocannabinoid system in sexual motivational processes: Is it a novel therapeutic horizon? *Pharmacological Research*, *115*, 200-208. **IF 4.897** (invited review).

Androvicova, R., Horacek, J., Tintera, J., Hlinka, J., Rydlo, J., Jezova, D., Balikova, M., Hlozek, T., Miksatkova, P., Kuchar, M., Roman, M., Tomicek, P., Tyls, F., Viktorinova, M. & Palenicek, T. (2017). Individual prolactin reactivity modulates response of nucleus accumbens to erotic stimuli during acute cannabis intoxication: an fMRI pilot study. *Psychopharmacology, 234*(13), 1933-1943. **IF 3.308** (original research).

Zaytseva, Y., Horáček, J., Hlinka, J., Fajnerová, I., **Androvičová, R.**, Tintěra, J., Salvi, V., Balíková, M., Hložek, T., Španiel, F. & Páleníček, T. (2019). Cannabis-induced altered states of consciousness are associated with specific dynamic brain connectivity states. *Journal of Psychopharmacology, 33*(7), 811–821. **IF 4.738** (original research).

Articles in peer-reviewed journals without IF related to the thesis

Balíková, M., Hložek, T., Páleníček, T., Tylš, F., Viktorinová, M., Melicher, T., **Androvičová, R.**, Tomíček, P., Roman, M. & Horáček, J. (2014). Časový profil hladin THC v krevním séru u rekreačních a chronických kuřáků marihuany po akutním užití drogy – implikace pro řízení motorových vozidel. [Time profile of serum THC levels in occasional and chronic marihuana smokers after acute drug use-implication for driving motor vehicles.]. *Soudní lékařství [Forensic Medicine], 59*(1), 2-6.

Journal articles with IF unrelated to the thesis

Tomecek, D., **Androvičová, R.**, Fajnerova, I., Děchtěrenko, F., Rydlo, J., Horáček, J., … Hlinka, J. (2019). *Personality Reflection in the Brain's Intrinsic Functional Architecture Remains Elusive.* Manuscript submitted for publication.

Bravermanová, A., Viktorinová, M., Tylš, F., Novák, T., **Androvičová, R.**, Korčák, J., Horáček, J., Balíková, M., Grišková-Bulanová, I., Danielová, D., Vlček, P., Mohr, P., Brunovský, M., Koudelka, V. & Páleníček, T. (2018). Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing—study on P300 and mismatch negativity in healthy volunteers. *Psychopharmacology, 235*(2), 491-503. **IF 3.308** (original research).

Articles in peer-reviewed journals without IF unrelated to the thesis

Klapilová, K., Varella-Valentová, J., Lindová, J., **Androvičová, R.**, Krejčová, L., Zikánová, T., Binter, J. & Bártová, K. (2017) Poruchy sexuální preference pohledem evoluční sexuologie. [Disorders of sexual preference from the perspective of evolutionary sexology.]. *Sexuológia [Sexology]*, *2017*(1), 26-32. ISSN 1335-8820.

Attachment III (Articles in books):

Klapilová, K., **Androvičová, R.**, Bártová, K., Binter, J., Krejčová, L., Lindová, J., Průšová, D., Wells, T. J., Zikánová, T. & Varella Valentová, J. (2016) (R)evoluce ve výzkumu lidské sexuality. [(R)evolution in the research of human sexuality.] In: J. Horáček, L. Kesner, C. Höschl & F. Španiel (Eds.) *Mozek a jeho člověk, mysl a její nemoc*. *[Brain and its man, mind and her disease.]* Prague: Galén. 117-129. ISBN: 978-80-7492-283-1.

Binter, J., Klapilová, K., Zikánová, T., Nilsson, T., Bártová, K., Krejčová, L., **Androvičová, R.**, Lindová, J., Průšová, D., Wells, T. J., & Říha, D. (2016) Exploring the pathways of adaptation: avatar 3D animation procedures and virtual reality arenas in research of human courtship behaviour and sexual reactivity in psychological research. In: P. Jerry & N. Tavares-Jones (Eds.) *Virtual Worlds: The Virtual Reality and Augmented Reality Intersections*. Oxford: Inter-Disciplinary Press. 35-44. ISBN: 978-1-84888-384-0.

Attachment IV (Conferences, presenting author):

Abstracts in journals with IF:

Androvičová, **R**., Krejčová, L., Bártová, K., Weiss, P. & Klapilová, K. (2018) Preferences for non-consensual sexual activities in the general population of Czech males (a representative survey). Lisbon, Portugal, 28.2.2018 - 3.3.2018. *Journal of Sexual Medicine, 15*(7, Suppl. 3), "S246". ISSN: 1743-6095. **IF 2.93**

Androvičová, **R**., Hůla, M., Novák, O., Tomeček, D., Weiss, P. & Klapilová, K. (2018) Is stranger rape a strategy to avoid female courtship behaviour?: a parallel fMRI and penile plethysmography study. Lisbon, Portugal, 28.2.2018 - 3.3.2018. *Journal of Sexual Medicine*, *15*(7, Suppl. 3), "S246–S247". ISSN: 1743-6095. **IF 2.93**

Androvičová, **R**., Horáček, J., Tintěra, J., Rydlo, J., Ježová, D., Balíková, M., Hložek, T., Mikšátková, P., Kuchař, M., Hlinka, J., Roman, M., Tomíček, P., Viktorinová, M., Tylš, F. & Páleníček, T. (2017) Acute cannabis intoxication and the brain's response to visual erotica: an fMRI study. Prague, Czechia, 28.5.2017 - 31.5.2017. *Journal of Sexual Medicine*, *14*(5, Suppl. 4), "e253". ISSN: 1743-6095. **IF 2.93**

Abstracts in journals without IF:

Androvičová, **R**., Horáček, J., Štárk, T., Drago, F. & Micale, V. (2017) Endokanabinoidní systém a sexualita: preklinická a klinická evidence. [Endocannabinoid system and sexuality: preclinical and clinical evidence.] Jeseník, Czechia, 4.1.2017 - 8.1.2017. *Psychiatrie [Psychiatry]*. *21*(Suppl. 1), 24. ISSN: 1211-7579.

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Androvičová, R., Horáček, J., Páleníček, T., Tintěra, J. & Rydlo, J. (2014) Jak kanabis ovlivňuje odpověď mozku při sledování vizuální intimní erotiky: fMRI studie. [How cannabis affects brain response to visual erotica: fMRI study.] Průhonice, Czechia, 11.10.2014. *II. Celostátní konference gynekologické sexuologie. [II. National Conference of Gynecological Sexology.]*

Androvičová, **R**., Horáček, J., Páleníček, T., Tintěra, J. & Rydlo, J. (2013) Efekt kanabisu na aktivaci mozku vizuálními sexuálními stimuly: fMRI studie. [The effect of cannabis on the brain activation to visual sexual stimuli.] Olomouc, Czechia, 27.3.2013 - 28.3.2013. *10. Mezinárodní workshop funkční magnetické resonance. [10th International workshop of functional magnetic resonance.]*

Attachment V (Conferences, non-presenting author):

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Páleníček, T., Tylš, F., Viktorinová, M., **Androvičová, R.**, Brunovský, M., Zach, P., Bravermanová, A., Korčák, J. & Horáček, J. (2018) The effects of psilocybin on brain EEG activity and connectivity in healthy volunteers - focus on the dynamics of the psychedelic state. Nice, France, 3.4.2018 - 6.4.2018. *European Psychiatry, the Journal of the European Psychiatric Association*, *48*(Suppl. 1), "S130". ISSN: 0924-9338. **IF 3.912**

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Binter, J., Leongómez, JD., Šebesta, P., Bártová, K., Krejčová, L., Zikánová, T., Wells, TJ., Mueller, S., **Androvičová**, R., Ježková, K., Lindová, J. & Klapilová, K. (2015) Změna hladiny steroidních hormonů a hlasového projevu u dospívajících mužů v průběhu kompetice o patrnerku. [Fluctuations in the steroid hormone content and vocal expression in adolescent

males during the competition for a mate.] České Budějovice, Czechia, 4.11.2015 - 7.11.2015. *42. Etologická konference České a Slovenské etologická společnosti [42nd ethological conference of the Czech and Slovak Ethological Society]*, p. 16.

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Attachment VI (The four original papers underlying this doctoral thesis)

1) **Androvicova, R**., Horacek, J., Stark, T., Drago, F., & Micale, V. (2017). Endocannabinoid system in sexual motivational processes: Is it a novel therapeutic horizon? *Pharmacological Research*, *115*, 200-208. https://doi.org/10.1016/j.phrs.2016.11.021 **IF 4.897**

2) Balíková, M., Hložek, T., Páleníček, T., Tylš, F., Viktorinová, M., Melicher, T., **Androvičová, R.**, Tomíček, P., Roman, M., & Horáček, J. (2014). Časový profil hladin THC v krevním séru u rekreačních a chronických kuřáků marihuany po akutním užití drogy – implikace pro řízení motorových vozidel [Time profile of serum THC levels in occasional and chronic marihuana smokers after acute drug use - implication for driving motor vehicles]. *Soudní lékařství [Forensic medicine], 59*(1), 2-6.

3) **Androvicova, R.**, Horacek, J., Tintera, J., Hlinka, J., Rydlo, J., Jezova, D., Balikova, M., Hlozek, T., Miksátkova, P., Kuchar, M., Roman, M., Tomicek, P., Tyls, F., Viktorinova, M. & Palenicek, T. (2017). Individual prolactin reactivity modulates response of nucleus accumbens to erotic stimuli during acute cannabis intoxication: an fMRI pilot study. *Psychopharmacology*, *234*(13), 1933-1943. https://doi.org/10.1007/s00213-017-4601-1 **IF 3.222**

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