Aus dem Institut für Psychopharmakologie, Zentralinstitut für Seelische Gesundheit
der medizinischen Fakultät Mannheim
(Leiter: Prof. Dr. rer. nat. Rainer Spanagel)

A meta-analysis of the sex-specific effects of psychotropic substances on acute striatal dopamine overflow measured by in vivo microdialysis in rats

Inauguraldissertation
zur Erlangung des medizinischen Doktorgrades
der
Medizinischen Fakultät Mannheim
Der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
Lisamon Mira Egenrieder

aus
Berwangen

2020

Dekan: Prof. Dr. med. Sergeij Goerdt

Referent: Prof. Dr. rer. nat. Rainer Spanagel

For my family

CONTENTS

Page

LIST OF ABBREVIATIONS

aCSF	Artificial cerebrospinal fluid
ADHD	Attention deficit hyperactivity disorder
ALICE RAP project	Addictions and Lifestyles in Contemporary Europe – Reframing Addictions Project
Ca^{2+}	Calcium
CPu	Caudate putamen
CNS	Central nervous system
DA	Dopamine
DALYs	Disability-adjusted life years
D-amphetamine	Dextroamphetamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
EU	European Union
fM	Femtomole
HPLC-EC	High performance liquid chromatography with electrochemical detection
ICD	International Classification of Diseases and Health Problems
i.p.	Intraperitoneal/-ly
i.v.	Intravenous/-ly
Kg	Kilogram
L-amphetamine	Levoamphetamine
Min	Minutes

mM	Millimole
µM	Micromole
NAc	Nucleus accumbens
Peak % BL	Peak percentage baseline
pg	Picogram
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
s.c.	Subcutaneous/-ly
sec	Second
SEM	Standard error of the mean
STR	Striatum
VTA	Ventral tegmental area
WHO	World Health Organization

LIST OF FIGURES

LIST OF TABLES

1 INTRODUCTION

1.1 Sex, drugs and addiction

‘Sex does matter’ – this is the main statement of the *Institute of Medicines* report on the state of research regarding sex differences, published already at the turn of the millennium (Pardue & Wizemann, 2001). Since then, there has been a blast of new results suggesting differences between female and male cells, animals, and humans and consequently underlining even more that sex is a ‘variable that should be considered when designing and analyzing studies in all areas’ (Pardue & Wizemann, 2001).
Furthermore, there is increasing scientific evidence indicating sex differences regarding drug use and dependence patterns. But, as stated in the publication on this thesis, how these differences ‘are manifested at a neurochemical level remains unclear‘ (Egenrieder, Mitricheva, Spanagel, & Noori, 2020).

Thus, the present thesis aims to investigate if there are sex differences in the changes of the neurotransmitter dopamine in the nucleus accumbens (NAc) and caudate putamen (CPu) after the administration of different drugs of abuse.
In the next paragraphs, a definition of the terms used in this thesis is made. Furthermore, the prevalence of addiction and the sex gap in preclinical and clinical research, from the past until now, are discussed. Hereafter, the distinct findings of sex differences – and similarities – are presented.

1.1.1 Definitions

In this section the terms ‘addiction’, ‘drugs’/’psychotropic substances’ and ‘sex’/’gender’ are described and, if needed, interpreted in the historical and sociocultural context.

The understanding of mental health and mental illness is, like the society that defines them, subject to constant change. This applies to the term ‘addiction’ and consequently as well to the term ‘drug’. Therefore, there has been a constant

development through the centuries since there are indications that humans are evolutionarily predisposed to use drugs (Anderson, Gual, & Rehm, 2018; Spanagel, 2009).
The perception of the border between culturally accepted consumption and pathological abuse depends on the surrounding society and its norms and habits. The cultural definition and attribution influence who (ab)uses which drugs in which situations and influences the risk of developing an addiction (Becker, McClellan, & Reed, 2016).

To approach a modern definition of ‘addiction’ the Diagnostic and Statistical Manual of Mental Disorders (DSM) can serve as an important tool. In its current fifth version under the category ‘addictions and related disorders’ the term ‘substance use disorder’ is established. It replaces, compared to the previous fourth DSM version, the two terms ‘substance abuse’ and ‘substance dependence’. These terms implicated that there is a separated and, by definition, milder disease of just abusing a substance without being dependent to it.
In the newest DSM version, the criteria of these two previously separated main disorders are now combined and the degree of severity can be specified by ‘mild’, ‘moderate’ or ‘severe substance use disorder’ according to the number of the criteria that are met.
This emphasizes the continuum in the development of an addiction that already begins by using a substance rather than specifying two separated diagnoses with one being less harmful than the other (Hasin et al., 2013).
The criteria that define the substance use disorder, according to the DSM-5, are the following: craving, spending a lot of time obtaining the drug, taking larger amounts and over a longer period than intended, not being able to cut down, the inability to carry out responsibilities, social impairment, drug use despite physical or psychological difficulties, risky use or signs of tolerance or withdrawal.
Another important medical classification list is the International Classification of Diseases and Health Problems (ICD-10) by the WHO. It is used worldwide for the whole spectrum of diseases, not only for mental disorders.
The term ‘dependence syndrome’ is characterized as a ‘cluster of psychological, behavioral, and cognitive phenomena in which the use of a substance or a class of

substances takes on a much higher priority for a given individual than other behaviors that once had greater value' (World Health Organization, 2018).
In this thesis the term 'addiction' will be used with reference to the heading and the definition of the DSM-5, because it is the standard classification list for psychiatric disorders, and often serves as a reference in scientific work.
Special focus lies with the aspect of considering addiction as a continuum starting by using a substance and undergoing a series of stages that spiral and escalate: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation (craving) (Koob & LeMoal, 1997).

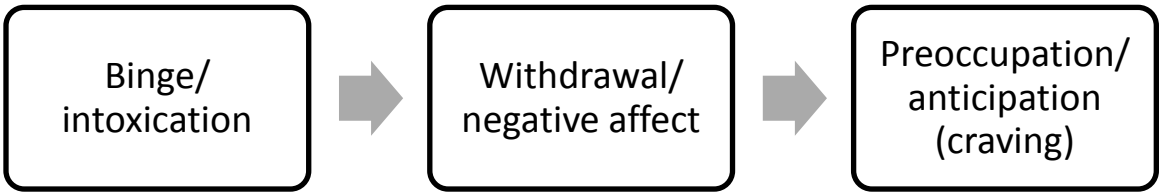


Figure 1: Stages of the development of an addiction according to Koob et al. (Koob & LeMoal, 1997)

The understanding of the term 'drug' has as well changed over the centuries and, as Jonathan Lewy states: '…the collective basket of "drugs" lacks a single definition because the idea that drugs exist as a single concept is historical' (Lewy, 2017). In addition, the line between drug and medication is not strictly drawn in English. Thus, in this work the term drug will be used meaning psychotropic substances that are thought to be habit-forming and therefore regulated by the governments of different countries (Lewy, 2017).
This definition includes the licit drugs alcohol and nicotine as well. In the present thesis morphine is the only representative of the crucial group of legally prescribed drugs, in spite of the fact that they account for a not inconsiderable part of the overall number of addicts.

This work includes only rats as subjects, and the term 'sex' will be used in the context of the biological division into females and males. In contrast, the term 'gender' refers to the socialized male and female characteristics and will only be used in regard to humans.

1.1.2 Prevalence of addiction

In this section the prevalence and some consequences of drug use and addiction are presented.

According to Anderson et al., who refer to the ALICE RAP project of the European Union (EU), there have been 10.4 million of deaths worldwide and more than one million of deaths in the EU due to alcohol, cigarettes and illicit drugs just in the year 2016. The lion's share is caused by the licit drugs alcohol and nicotine.
If morbidity is taken into account, the consequences are even greater: an estimated number of 25 million years are lost either to premature death or disability only in the EU (Anderson et al., 2018).
When it comes to sex differences the 2015 Epidemiological Survey of Substance Abuse tobacco products have been used by 28.7 % and alcohol by 72.8 % of the German respondents during the last 30 days. A clinically relevant use of alcohol could be found in 28.3 % of men and 9.6 % of women (Matos, Atzendorf, Kraus, & Piontek, 2016).
Kraus et al. compared those findings to earlier surveys: although German men drank less alcohol compared to the previous 20 years, the overall prevalence of drinking and episodic heavy drinking is still higher in men than in women. Still, the heavy drinking episodes increased as well for women.
Both sexes used less tobacco products but the smokers rate is slightly higher in Germany than in other EU countries, probably due to a relatively higher prevalence among women (Kraus, Piontek, Atzendorf, & Matos, 2016; Matos et al., 2016).
For illicit drugs Matos et al. found the highest prevalence for cannabis during the 12 months before questioning: 7.4 % of the males and 4.9 % of the females indicated consumption. One percent of the responders had consumed amphetamine. The percentages for all other illicit drugs were even under one percent each.
Generally, a cross-national survey shows the tendency that men consume more drugs than women, although females are partly closing the gap, at least for some substances and in the cohorts of younger age (Degenhardt et al., 2008).

Apart from the individual suffering, addiction generates a considerable socio-economical damage by producing direct, direct non-medical and indirect costs as

high as an estimated 65.7 million Euro in 2010 in the EU (Olesen et al., 2012). The negative balance is even worse if the millions of victims of the war on (illicit) drugs and the considerable amount of money spent by governments worldwide for incarceration would be included (Keefer, 2010; Miron & Waldock, 2010).

Summarizing the prevalence, it can be stated that substance use and addiction are frequent phenomena that occur more often in men and have a considerable impact on overall disability and mortality.

1.1.3 Sex gap in research

This section deals with the inequality in the distribution of female and male subjects in preclinical and clinical trials and the approaches that have been made to establish sex balance. The development in the US serves as an example, with special focus on the National Institutes of Health (NIH) and its recommendations as a leading institution for the setting of frameworks for research worldwide. Furthermore, the NIH's PubMed online library was used for this meta-analysis.

As Beery et al. showed, female subjects have been systemically ignored in the past for various reasons in clinical trials as well as in basic research. In part because of the assumption that the results for males do equally apply to females and partly for fear of an increased variability of the results due to the females' cycle and thus of another possible confounder (Beery & Zucker, 2011).
Moreover, in the clinical field, researchers hesitate to expose women of childbearing potential to adverse side effects (Geller, Goldstein, & Carnes, 2006).
After hints that men and women show symptoms and react to drugs differently, the approach was made to close that sex gap at least for federally supported clinical trials: the NIH Revitalization Act of 1993 required the inclusion of women in clinical trials (Freedman et al., 1995).
Since then some progress has been made regarding the inclusion of female subjects, but there is still an underrepresentation especially in studies about drugs (Geller et al., 2006; Geller, Koch, Pellettieri, & Carnes, 2011).

For basic research this development took longer. In May 2014 the director of Research on Women's Health of the NIH published a first announcement, that as well studies with animals and tissues should include both sexes (Clayton & Collins, 2014). In 2016 this was implemented into the scientific process by requiring applicants to plan the consideration of sex as a biological variable, and advising peer reviewers to focus on it (Tannenbaum, Schwarz, Clayton, de Vries, & Sullivan, 2016). Similar efforts were undertaken lately in Europe by the European commission (Klinge, 2008).

Simultaneously, there is a growing number of evidence, that females are not generally more variable than males (Becker, Prendergast, & Liang, 2016; Prendergast, Onishi, & Zucker, 2014) and thereby the pressure against the automatic exclusion of female subjects is increased.

Thus, some progress has been made but the goal of sex balance is currently still at a distance. This diminishes our understanding of the females' biology and physiopathology. More research is needed to clarify which exact differences exist between males and females regarding tissues, laboratory animals and humans.

1.1.4 Sex differences

In the following chapter, examples are given of the distinct reaction of males and females (humans as well as rats) to drugs to get a first impression of the state of research about sex differences regarding addiction. Moreover, some of the underlying mechanisms for the described differences are approached.

As the biological differences between genders/sexes are a contentious issue (Becker, McClellan, et al., 2016) it is important to emphasize that these findings should not be understood as hard-wired determinations (Becker, McClellan, & Reed, 2017). Due to the plasticity of the brain they are – regarding humans – product of an interplay between biological and sociological/behavioral influences because addiction is a phenomenon at the interface between environment and biology (Becker et al., 2017).

‘Recent clinical and preclinical studies suggest sexual dimorphisms in the entire disease dynamic of drug abuse and dependence’ (Egenrieder et al., 2020): although the prevalence of substance abuse is higher in men (Carvalho, Heilig, Perez, Probst, & Rehm, 2019), there is consistent evidence that female rats acquire drug self-administration faster (Carroll & Lynch, 2016; Lynch & Carroll, 1999) and consume in some settings more drugs than males (Carroll & Lynch, 2016; Davis, Clinton, Akil, & Becker, 2008; Priddy et al., 2017).

Also women, who are highly at risk to develop an addiction, escalate faster from first occasional use to compulsive drug intake (Becker et al., 2017; Bobzean, DeNobrega, & Perrotti, 2014; Davis et al., 2008). But this tendency is not reflected in the general US-American population (Becker et al., 2017; Keyes, Martins, Blanco, & Hasin, 2010).

Isolation influences rats of both sexes: socially housed animals show a lower intake of drugs than isolated ones (Raz & Berger, 2010; Westenbroek, Perry, Jagannathan, & Becker, 2017). Solely cocaine is an exception to this effect: the decreasing effect did only apply for females, not for males (Westenbroek, Perry, & Becker, 2013).

During withdrawal from nicotine female rats show more adverse effects associated with lower dopamine levels in the nucleus accumbens (Carcoba, Flores, Natividad, & O'Dell, 2017). Women also show more symptoms of withdrawal than men (Hogle & Curtin, 2006) and they are less likely to look for treatment, but when they do, they have similar outcomes as men (Greenfield et al., 2007).

Additionally, women have a higher relative risk excess for coronary heart disease, stroke (Hackshaw, Morris, Boniface, Tang, & Milenkovic, 2018), and lung cancer (Bjartveit & Tverdal, 2005), when they consume the same number of cigarettes as males. Nevertheless, the absolute risk is still higher in men (Bjartveit & Tverdal, 2005).

‘Similarities in animal and human studies, for instance on how patterns of drug acquisition and relapse differ between the sexes, suggest a common biological basis of sex differences in vulnerability to drug abuse’ (Egenrieder et al., 2020): the ovarian hormones, namely estrogen, appear to have an effect on the females’ brain (Becker, 2016; Becker, Perry, & Westenbroek, 2012; Bobzean et al., 2014; Lacy, Strickland, Feinstein, Robinson, & Smith, 2016; Shams, Cossette, Shizgal, & Brake, 2017). It

increases dopaminergic transmission and its overflow in response to drugs in various brain regions, including the dorsal striatum (Shams, Sanio, Quinlan, & Brake, 2016), the ventral tegmental area, and the nucleus accumbens (Bobzean et al., 2014). Furthermore, its administration aggravates addiction-like behavior (Becker, 1990; Becker & Cha, 1989; Becker & Rudick, 1999; Hu, Crombag, Robinson, & Becker, 2004).
Most of the previously described differences between the sexes are provided by studies containing only a small number of animals per trial group and meta-analyses are still missing. Therefore, 'a large-scale between-study analysis allows us *(in this thesis)* to evaluate the robustness of conclusions made by individual studies' (Egenrieder et al., 2020)

Summarized, it can be said, that there are sex differences as well as similarities in the different stages of addiction, although the current state of knowledge lacks big data approaches – as it will also be shown in the next chapter. Nevertheless, it is a major aim to understand the mechanisms in both sexes and to stress the importance of sex-specific approaches for optimal prevention and treatment strategies for addiction.

1.2 Meta-analysis

In the following passage, there is a short description of the strengths and weaknesses of meta-analyses in general, and their gaining importance in preclinical science over the course of the last years. Furthermore, specific factors of the present thesis are given.
In the clinical field, there is a long history of performing systematic reviews and meta-analyses and they have become a fundamental instrument for clinicians to imply scientific evidence into their daily practice (Gurevitch, Koricheva, Nakagawa, & Stewart, 2018).

In preclinical research, meta-analyses have been rather seldom conducted for decades; but the recent years have shown many areas in which they can provide crucial results especially in basic biology.

There has been an explosion of significant and groundbreaking meta-analyses such as the many publications based on the genome-wide association study (GWAS): in silico approaches led to the identification of a variety of genetic markers for Crohn's (Franke et al., 2010) or Alzheimer's (Lambert et al., 2013) disease. Furthermore, regarding the Covid-19 pandemic as a highly topical issue, recently a potential involvement of the ABO blood type system in the development of respiratory failure has been reported (Ellinghaus et al., 2020). Thereby, big data science supplies a first indication on the pressing matter of risk factors for the development of severe disease progression.
These scientific breakthroughs were made possible by the additional statistical power and had a massive impact on highly topical developments in the clinical field.

With the PRISMA guidelines (preferred reporting items for systematic reviews and meta-analyses), which were published in 2009, a new standard has been set to ensure the quality and comparability of reviews and meta-analyses. The work process is structured in four phases: 'identification', 'screening', 'eligibility' and 'inclusion' and can be evaluated by means of a 27-item checklist (Moher, Liberati, Tetzlaff, & Altman, 2010). PRISMA also served as a guideline for this present work.

Furthermore, there is increasing evidence that single preclinical studies often lack reproducibility, and are therefore not always as reliable as the scientific world used to assume (Arrowsmith, 2011; Begley & Ioannidis, 2015; Peers, Ceuppens, & Harbron, 2012; Prinz, Schlange, & Asadullah, 2011).
This problem was already addressed by Begley and Ellis in 2012 in *Nature*: they demanded a raise in the quality of basic research, by 'establishing large cancer cell-line collections with easy investigator access' (Begley & Ellis, 2012). In this way, they promoted another data basis for further meta-analyses in the preclinical field.

In general, big data provides a whole new spectrum of opportunities for modern life sciences in the online age. As pointed out in the corresponding publication on this thesis 'data derived from a meta-analysis are useful for textbook knowledge, provide better comparability of data given by the generalization of already existing data *(and)* should be seen within the framework of the 3R principle of animal experimentation' (Egenrieder et al., 2020). Since the sample size in animal studies is generally rather

small, they often allow only limited conclusions (Vesterinen et al., 2014). Performing a meta-analysis is a valuable tool in preventing unnecessary repeated testing and further suffering and therefore spares animal lives (Vesterinen et al., 2014).
Another important indication is when different experiments lead to contradictory results and a meta-analysis clarified the situation.
Furthermore, regarding sex differences, the available data are 'based on within-study statistics with relatively small numbers of animals and a global comparison of male-female findings of different studies is still missing' (Egenrieder et al., 2020). Thereby, the topic of this thesis is predisposed to be treated in the form of a meta-analysis, since there are few studies available with female subjects.

'In this study, we use an established (Noori, Fliegel, Brand, & Spanagel, 2012; Noori et al., 2018) hypothesis-free, global approach to statistically compare two large bodies of evidence' (Egenrieder et al., 2020). The method used was already applied before by the work group at the Institute of Psychopharmacology of the Central Institute of Mental Health (Medical Faculty Mannheim/Heidelberg University) (Brand, Fliegel, Spanagel, & Noori, 2013; Fliegel, Brand, Spanagel, & Noori, 2013; Fritze, Spanagel, & Noori, 2017; Hirth et al., 2016; Staudenmaier, 2017).
Owing to this fact, these previous results have a similar structure and can be gathered, pooled, or compared with new results of meta-analyses – as it was done in this study. They may also contribute to new results in a greater context in the future (Sena, Currie, McCann, Macleod, & Howells, 2014).

1.3 In vivo microdialysis

As microdialysis is used by the papers that are subject to this thesis, in the next chapters there will be an overview of the background and history, the single steps of conducting the experiment, and some advantages and disadvantages of the procedure.

In general, microdialysis is a minimal invasive method to measure changes of chemical agents in the extracellular fluid of different tissues and organs over time. It

is an in vivo procedure that can be conducted in awake and freely moving animals e.g. during drug administration.

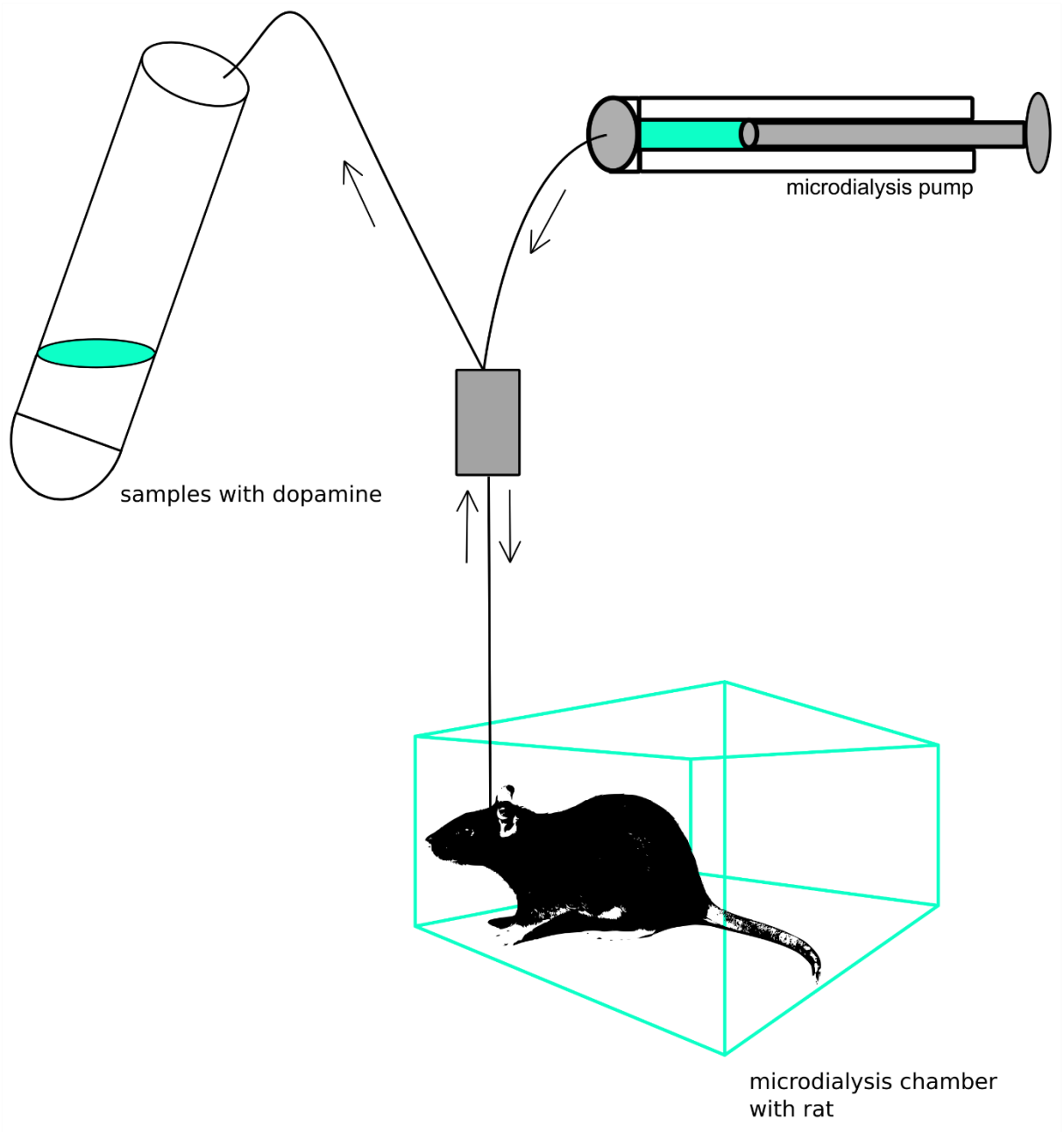


Figure 2: Experimental setup of the microdialysis procedure

In brief, a dialysis probe is placed in the rat's brain and perfused continuously with a fluid with defined contents. At its tip it has a semipermeable membrane. Due to the concentration gradient hormones, neurotransmitters, or electrolytes of the extracellular fluid can freely diffuse through this membrane into the solution of the

probe. Samples are taken at defined time intervals and analyzed for the content of interest to show its time course. For an overview of the experimental setup see Figure 2.

1.3.1 Background and history

In this paragraph, the subject is the emergence of the idea of microdialysis and its development in the last decades.

Monitoring neurochemical processes in vivo has been a challenge for scientists: On the one hand, the aim is an insight into the brain's tissue. But on the other hand, a maximum of integrity is needed, to imitate natural conditions for valid results.
Almost fifty years ago, Professor Urban Ungerstedt of the Karolinska Institute in Stockholm had the thought of mimicking a blood vessel: he built a dialysis catheter with a semipermeable membrane at its tip (Ungerstedt & Hallstrom, 1987; Ungerstedt & Pycock, 1974). This was the beginning of microdialysis and enabled the monitoring of monoamines in vivo with a reduced damage to the brain's tissue. Thus, it was possible to observe the changes of constituents in one subject.
Since then, this technique was improved and performed in a variety of studies, tissues, and animals. The majority had rats as its subject and focused on the changes of monoamines in the brain (Chefer, Thompson, Zapata, & Shippenberg, 2009). Moreover, during the last three decades, it was even adopted in clinical practice: it is used as a monitor in neurocritical care for the treatment of patients with acute brain injury (Hutchinson et al., 2015).

1.3.2 Preparation and surgery

Before the microdialysis experiment can be conducted, the animals need to undergo surgery. This passage describes each step from the preparation until the post-operative care.

Firstly, the rat is usually anesthetized and fixed in a stereotaxic apparatus to avoid the displacement of the head. The skin is shaved and cleaned, and a borehole is

drilled into the skull – either unilateral or, for some experiments, on both sides of the rat's brain. A guide cannula is placed into the hole aiming at the brain region of interest for later insertion of the microdialysis probe. The correct location (in mm, relative to the bregma), and angle of the cannula can be achieved by means of an atlas of the stereotaxic coordinates of the rat brain e.g. from Paxinos and Watson (Paxinos & Watson, 2007). The cannula is fixed to the scull with glue and covered with a plastic guard.
Sometimes, if needed, other surgical procedures are done during surgery: e.g. ovariectomy, castration, implantation of a silastic tube containing estradiol, or cannulation for following i.v.-drug-application.
In some experiments, a further cannula is implanted into another brain region to be able to administer drugs locally or to take measurements in different regions simultaneously. The animals are allowed to recover from surgery for a certain period of time and are sometimes treated with antibiotics to prevent infection.

1.3.3 Microdialysis procedure and analysis

This section contains a detailed explanation of the microdialysis experiment with its variable properties, and a short overview of the analysis of the obtained specimen.

Firstly, the microdialysis probe is inserted into the guide cannula – usually under a short anesthesia to avoid pain and stress for the animal.
There are probes at different lengths and diameters that can be chosen. The inlet and the outlet tubing of the microdialysis probe are held by a tether that can swing over the testing chamber, allowing the animal to freely move (if the rat is not anesthetized). Normally, the animals are given some time to acclimatize to the probe insertion and the new environment. Food and water may be available.
The tip of the probe extends some millimeters beyond the guide cannula into the brain region of interest. In the probe’s interior, there is a thin tubing whose inlet is connected to an infusion pump that continuously drives fluid through it. For an enlarged view of the tip of the probe see Figure 3. The flow rate and the perfusion fluid may be freely chosen, e.g. some microliters per minute and – in most of the experiments – Ringer’s solution, or artificial cerebrospinal fluid (aCSF) with a defined content of constituents.

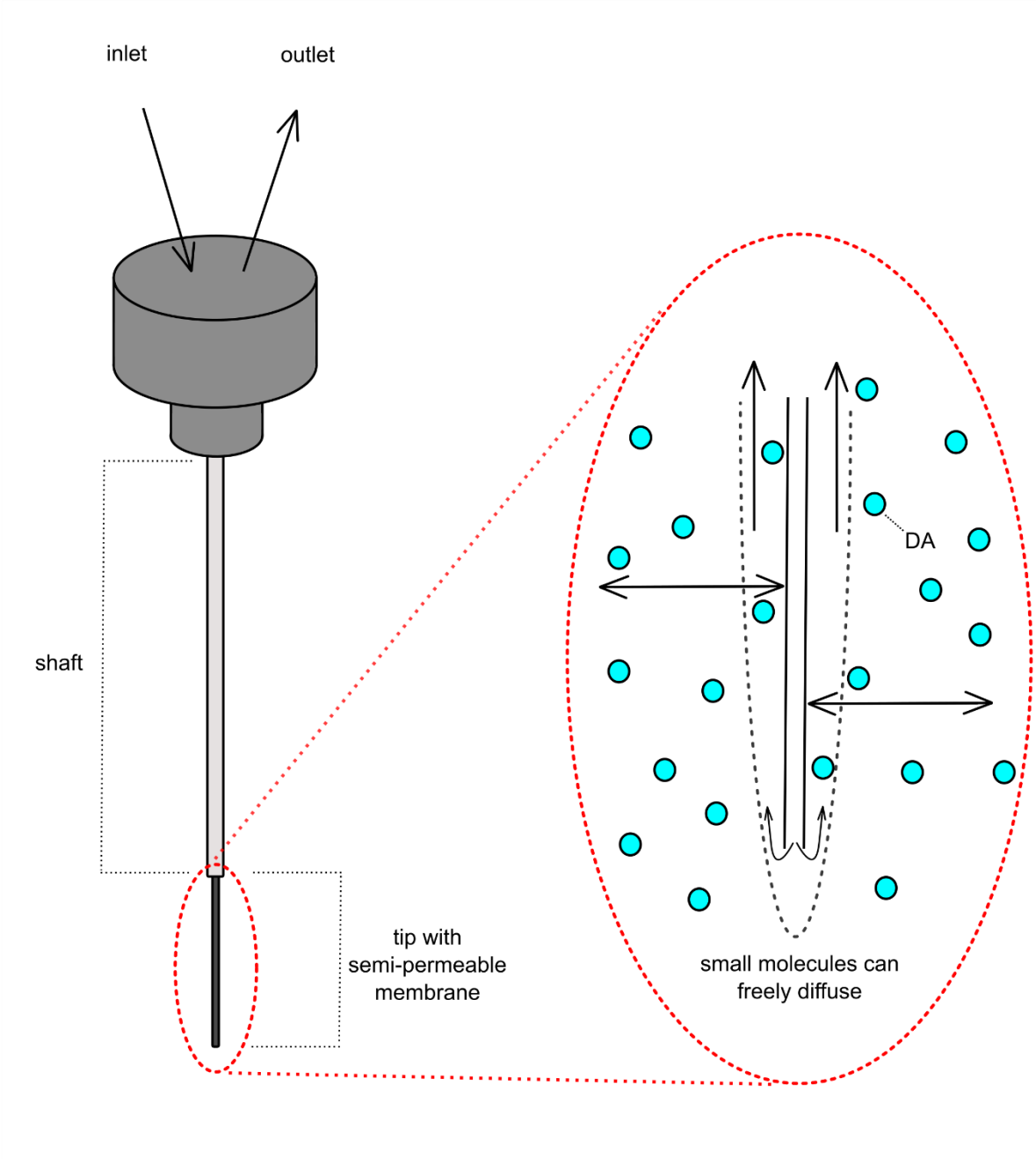


Figure 3: Schematic representation of the functioning of a microdialysis probe. DA = dopamine molecules.

At the ending of the tubing the fluid changes direction and flows back at the outer side of the probe. While passing the semipermeable membrane chemical agents can diffuse freely into the perfusate. The membrane has a specific molecular weight cut off (in Dalton) that may be chosen suitable for the analyte of interest. At the probes' outlet, samples of dialysate can be collected in specific time intervals into Eppendorf tubes. A distinct period – usually some hours – is set as a washout period allowing the concentration gradient to find an equilibrium.

At the beginning of the experiment, before the administration of the drug, some samples are taken to get an average basal value. This basal value represents 100 % and serves as a reference for the peak percentage baseline values that can be obtained after drug administration. Usually the sample time lies between five and thirty minutes. In some experiments simultaneous behavioral testing is conducted.
The obtained samples are immediately frozen – e.g. on dry ice – and analyzed afterwards. The concentration of the transmitter of interest is mostly detected via high performance liquid chromatography with electrochemical detection (HPLC-EC).
At the end of the experiment, rats are euthanized, and some microliter of dye can be injected into the probe to verify the correct placement in the brain region subjected.
There are many settings that influence the accuracy and the outcome of the microdialysis experiments: e.g. the flow rate, the perfusate, its calcium concentration, the sample time, or if the rat is anesthetized or awake.

1.3.4 Advantages and disadvantages of microdialysis

As microdialysis already exists since 1974, it is well-established and advantages as well as drawbacks of the procedure are well-known and will be shortly discussed in this section.

Compared to other techniques, microdialysis has a limited time resolution. Since it is an invasive procedure, it changes the direct environment in the tissue: the damage may cause inflammatory processes, or impair the blood-brain barrier (Plock & Kloft, 2005). Depending on the composition of the perfusion fluid, the relation of the chemical agents surrounding the probe may be altered. Anesthesia and surgery are needed, and the probe is a foreign body placed in a wound with consequences for possible group housing.
Another problem is the exact quantification of the extraction fraction i.e. the relation between the concentration reached in the fluid and the concentration in the interstitium.

Some of the advantages have been mentioned earlier: the variety of tissues, compounds and species that the microdialysis procedure can be used for, the fact

that the samples are taken directly at the region of interest, the opportunity of simultaneous measurement in different brain regions, or of directly infusing drugs.

1.4 Idea and objective of this study

Humans – like other mammals – tend to consume inebriating substances. Therefore, drug use and related disorders are worldwide phenomena with many consequences – not only for the individual, but also concerning economic and health-care issues.

The prevalence of drug-related disorders is drastically different regarding men and women: males consume drugs more often and in larger amounts than females, and notably have higher rates of drug related disorders. Nevertheless, females seem to be more prone to addiction in some phases of the development of the disease.
The biological and/or sociocultural mechanisms that are responsible for this contradiction, have still not been fully clarified. Nevertheless, some of the neurochemical reactions are known to be different in male and female laboratory animals and one of the identified underlying mechanisms appears to be the cycle – notably the altering level of estrogen – influencing the female's brain and neurotransmission.
Despite these sex differences, women and female animals were – and still are – underrepresented as subjects in research, although efforts have been made to close this sex gap. It used to originate in various reasons: partly female subjects were ignored for fear that they are more variable; partly because of the assumption that the results for males equally account for females. But none of these contradictory assumptions were well-founded.
In vivo microdialysis is a well-established method to detect neurotransmitter changes in rats during drug administration. Most of the single microdialysis experiments have small groups (e.g. about 6 animals), and therefore little generalizable informative value.

Meta-analyses are more and more conducted in basic research and have become a fundamental mean to gain groundbreaking knowledge through their additional statistical power – in particular in the field of animal studies with small trial groups.

As described in the corresponding paper on this thesis, ‘we used a well-established, hypothesis-free, global approach in order to statistically compare two large bodies of evidence, namely findings from all publications reporting on dopamine concentrations in the nucleus accumbens and the caudate putamen of male and/or female rats’ (Egenrieder et al., 2020). Therefore, systematic data mining on PubMed, the online portal of the National Library of Medicine, was performed, focusing on studies that used in vivo microdialysis and dealt with the acute administration of drugs of abuse (alcohol, amphetamine, cocaine, morphine, nicotine and tetrahydrocannabinol).
Furthermore, this thesis aims to provide an overview of the microdialysis studies that include female subjects and to investigate whether they monitor and mention the state of the estrous cycle.

The global purpose of this thesis is to set a framework for future research by providing average values for male and female rats and an analysis of the sex differences and/or similarities in the reaction to drugs of abuse.
Thereby the present work intends to diminish the unknown factors that were reason for the ignorance of female rats in both, clinical and preclinical science, and in either way – nonmatter if differences or similarities are found – raise the pressure to include humans, animals and cell lines of both sexes.

This work uses a meta-analysis approach to establish, whether microdialysis studies robustly indicate sex differences or similarities in striatal dopamine levels in rats after acute drug administration

2 METHODS

2.1 Choice of the neurotransmitter dopamine and two brain regions

The effects of drugs are mediated over various brain regions and neurotransmitters (Koob & Volkow, 2010). The role that the caudate putamen, the nucleus accumbens and dopamine play in this neuronal network is described in the following passages, in order to show why they are subject to the present thesis.

2.1.1 The neurotransmitter dopamine

The topics of this section are the effect and the occurrence of dopamine in the brain and a description of its main pathways.

Dopamine is, like noradrenalin, a catecholamine that has various effects on the body and the brain: it contributes in motivation and emotion, motor control (Bjorklund & Dunnett, 2007), and memory (Hefco et al., 2003). Furthermore, it is the key neurotransmitter for reward, and its efflux is sensitized by drugs of abuse (Berridge, 2007).
The psychostimulants cocaine and amphetamine even take their main effect in an increase of dopamine (Koob & Volkow, 2010). This mechanism is also crucial for the other three drugs of abuse of this thesis that are described in the next chapter (Di Chiara & Imperato, 1988), even though there are also other neurotransmitters involved (Koob & Volkow, 2010).

Although dopaminergic transmission can be found in a variety of brain regions (Noori, Spanagel, & Hansson, 2012), there are three main pathways that can be distinguished, anatomically and functionally: the nigrostriatal, the mesolimbic, and the mesocortical system (Bjorklund & Dunnett, 2007). In this thesis the focus lies on the caudate putamen and the nucleus accumbens because they are part of two of them: the nigrostriatal and the mesolimbic pathway. Both mediate the acutely rewarding and the habit-forming effects of drugs (Wise, 2009).

2.1.2 Striatum, caudate putamen and nucleus accumbens

In the following passage, a short overview of the striatum – that means the caudate putamen and the nucleus accumbens – is given, focusing on its function and corresponding afferents and efferences. Moreover, the anatomical nomenclature is clarified and a distinction between these brain regions is conducted in general, and for the present work in particular.

The striatum is part of the basal ganglia and plays a role in motor activity and learning processes (Kreitzer & Malenka, 2008). It is involved in the cortico-striatal-thalamic circuit which is associated with craving and obsessive-compulsive behavior (Koob & Le Moal, 2001). It can be functionally separated into a ventral and a dorsal part. In rodents the caudate putamen builds the dorsal part whereas the ventral striatum consists of the nucleus accumbens and the olfactory tubercle.
The caudate putamen, or the dorsal striatum, receives dopaminergic afferents from the substantia nigra and the ventral tegmental area and sends GABAergic and cholinergic efferences to the nucleus accumbens (Noori, Spanagel, et al., 2012). It is merely activated in the compulsive state of addiction than in the acute rewarding phase of occasional consumption (Koob & Volkow, 2010).

As it was also described in the corresponding publication (Egenrieder et al., 2020), ‘a common issue of pre-clinical studies is the inconsistent use of anatomical nomenclature. While a few studies report accurate coordinates for probe placement, the designation of the targeted brain area often differs.’
Therefore, Noori et al. developed a unified nomenclature using a cluster analysis (Noori et al., 2017; Noori, Spanagel, et al., 2012). According to the terminology established, in this thesis the following regions will be considered as caudate putamen: dorsal striatum, striatum, neostriatum. The ventral striatum and the nucleus accumbens shell and core will be grouped as nucleus accumbens.
Nevertheless, the historical inconsistent use is also reflected in this thesis: regarding the keywords for the PubMed search, the term ‘striatum’ is still present, as it used to be utilized synonymously with the caudate putamen. But, apart of that, this thesis will use ‘striatum’ for the entity of dorsal and ventral striatum (equaling caudate putamen

and nucleus accumbens) and ‘caudate putamen’ will be used meaning the dorsal striatum only.

According to the striatum and caudate putamen, the following passage deals with the function, subdivisions, afferents and efferences of the nucleus accumbens.
As mentioned before, the nucleus accumbens lies in the ventral striatum and can be divided into an inner core and an outer shell. It is functionally part of the mesolimbic system that is also referred to as the ‘reward pathway’: it originates in the ventral tegmental area that sends dopaminergic transmission to the nucleus accumbens (Koob & Le Moal, 2001; Noori, Spanagel, et al., 2012) and the olfactory tubercle.
This seems to be the correlate to the concept of incentive salience i.e. directly rewarding effects of drugs during the first state of binge and intoxication (Berridge, 2007; Koob & Volkow, 2010; Spanagel & Weiss, 1999).

Like the caudate putamen, the nucleus accumbens also receives dopaminergic afferents from the substantia nigra and the ventral tegmental area and sends GABAergic and cholinergic efferences to the caudate putamen (Noori, Spanagel, et al., 2012).

2.2 Choice of drugs of abuse

In the following, five drugs of abuse are investigated exemplarily representing the wide field of consumed and abused psychotropic substances.

Alcohol and nicotine were included because of the high prevalence of their consumption. For the same reason cannabis was included initially as a sixth drug, but no eligible microdialysis studies could be found. Therefore, it will not be further mentioned.
Morphine is the archetype opioid and, in this thesis, the only representative for the crucial group of legally prescribed drugs that is in some countries responsible for a growing number of addicts, e.g. regarding the opioid crisis in the United States. Amphetamine and cocaine were chosen as two relatively widely consumed stimulants.

In the following chapters, the definition and relevance, the origin or production process, and the effect on striatal dopamine of the five drugs will be shortly discussed, starting with those with the most harm done worldwide.

2.2.1 Nicotine

Nicotine is an alkaloid produced by many plants of the nightshades family to avert herbivores. It is the main psychotropic substance of tobacco that is thought to be motivational for the initiation and maintenance of smoking (Fiore, Smith, Jorenby, & Baker, 1994).

Tobacco is the deadliest drug worldwide (Forouzanfar, 2016), due to its negative effects including a variety of different cancers, or diseases of the respiratory and cardiovascular system. In 2016 a share of 15.1 % of deaths in the EU were attributed to tobacco – compared to 7.7 % attributed to alcohol and 1.0 % to all illicit drugs (Anderson et al., 2018). Recent findings show that even one to five cigarettes a day lead to a considerable increase of the relative risk for ischemic heart disease and dying of any other cause (Bjartveit & Tverdal, 2005).
Nicotine passes the blood brain barrier and reaches the brain within seconds after smoking (World Health Organization, 1994). It is an agonist to nicotinic acetylcholine receptors that are even named due to this fact (Koob & Le Moal, 2001).
The rewarding effect of nicotine is mediated by an increased dopamine transmission from the ventral tegmental area to the striatum (Koob & Le Moal, 2001). Moreover, there are also other neurotransmitter systems influencing the rewarding effect, and there seems to be a long-lasting increase of the sensitivity for following rewards (Kenny & Markou, 2006).

Due to the emerging phenomenon of electronic cigarettes, the question of the harmfulness of nicotine itself, without the side effects of smoking, gains more relevance.

2.2.2 Alcohol

The term alcohol usually refers to ethanol as the psychoactive ingredient in many kinds of beverages that is produced by fermentation of sugars by yeasts. In chemistry, the term describes an organic compound that carries at least one hydroxyl functional group bound to a carbon atom. It therefore includes – in its true meaning – a variety of alcohols (propanol, methanol etc.). Nevertheless, in this work, the term will be used meaning ethanol (C_2H_5OH). It is one of the oldest and most widely used drugs worldwide (World Health Organization & Unit, 2014).

Because of its toxicity and broad acceptance in many cultures, it is the drug that causes almost as much harm as nicotine: in 2012 3.3 million deaths worldwide were caused by alcohol, meaning 7.9 % of the male and 4 % of the female population died because of its adverse effects (World Health Organization & Unit, 2014). Or, regarding the burden of disease, 139 million DALYs (disability-adjusted life years) were lost due to alcohol drinking, most of them for the European region (World Health Organization & Unit, 2014).
There is a considerable amount of diseases associated with alcohol consumption that range from acute intoxication to alcohol-induced brain damage, cirrhosis or alcoholic cardiomyopathy, or the fetal alcohol syndrome after alcohol consumption during pregnancy.
Recent results show that there is no threshold for alcohol being toxic, but rather an increasing risk of harm ‘with the level of exposure’ (Anderson et al., 2018).

Alcohol interacts with various neurotransmitter systems in the brain. According to Koob et al. dopamine plays an important role for the acute effects of occasional consumption, while other neurotransmitter systems also seem involved in its reinforcing effect (Koob & Le Moal, 2001).
Acute alcohol consumption increases the dopamine concentration, preferentially in the nucleus accumbens and also in the caudate putamen (Di Chiara & Imperato, 1988).

2.2.3 Morphine

Morphine is the prototypical alkaloid of the opium poppy. Opioids were used long before in medicine as analgesics: first proofs exist from the 4th century b.c. (Köhler, 2008). Morphine is produced from the poppy seeds and was first isolated in 1804 by the German pharmacist Friedrich Wilhelm Sertürner (1783-1841) (Geschwinde, 2013).
It is an agonist to the μ-receptor, where it takes its main medical effect. Cells with this receptor are concentrated at several locations in the central nervous system (CNS) e.g. in the limbic system, the corpus striatum or the spine (Geschwinde, 2013).

Morphine is also produced in small amounts by the body itself. Therefore, it belongs, among others, to the endorphins, the group of endogen produced opioid neuropeptides. They inhibit pain in physically challenging situations, like during long runs (‘runner’s high’) and are involved in states of pleasure during laughter or food intake (Chaudhry & Bhimji, 2018).
Both, acute and chronic morphine administration increase dopamine in the nucleus accumbens (Pothos, Rada, Mark, & Hoebel, 1991) and, to a lesser extent, in the dorsal striatum (Di Chiara & Imperato, 1988).

2.2.4 Amphetamine

The term is contracted from α-methylphenethylamine and refers to a group of indirect sympathomimetic stimulants. Amphetamine exists in its two enantiomers, the less potent levoamphetamine (l-amphetamine) and the more potent dextroamphetamine (d-amphetamine). Furthermore, there is the racemase of both (d+l-amphetamine, see Figure 4).
In most of the experiments with rats d-amphetamine is administered. Therefore, for the sake of clarity, in the following tables the term amphetamine – if not further specified – refers to the more frequently used dextro-enantiomer. For the rare cases when the rats received the racemase, ‘d+l’ will be added.
There were no studies included that used levoamphetamine. Substituted amphetamines as methamphetamine or related substances like methylphenidate were not included in this thesis.

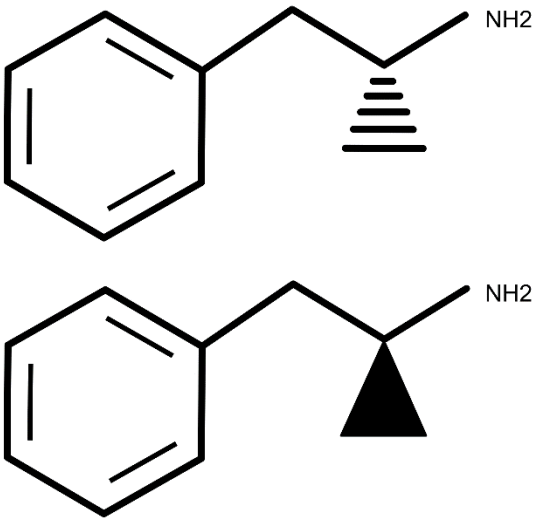


Figure 4: The two enantiomers of the amphetamine molecule: dextroamphetamine top, levoamphetamine below

The first amphetamine was synthetized in 1887 by the Romanian chemist Lazăr Edeleano (Edeleano, 1887). Today, amphetamines are in some countries prescribed for attention deficit hyperactivity disorder (ADHD) and narcolepsy (Heal, Smith, Gosden, & Nutt, 2013). They are as well misused recreationally, or to improve cognitive performance (Teter, McCabe, LaGrange, Cranford, & Boyd, 2006).
Amphetamine acts as an indirect dopamine agonist (Wise, 2009) and causes an increase of dopamine in the striatum (Di Chiara & Imperato, 1988; Sharp, Zetterstrom, Ljungberg, & Ungerstedt, 1987).

2.2.5 Cocaine

Cocaine, like amphetamine, is a potent central nervous system stimulant. It is extracted from the coca plant that is preferentially grown at the mountain ranges of South America (Geschwinde, 2013).
Seen historically, it was used in ceremonial contexts and for painful medical procedures, like trephinations, e.g. in present-day Peru (Goldstein, DesLauriers, & Burda, 2009). Until today, the leaves of the coca plant are chewed or prepared as a tea to cope with altitude or physical work.

The Austrian explorer Karl von Scherzer first brought the leaves to Europe in 1850 (Von Scherzer, 1865), and in the following decades it was established as a local anesthetic (Ruetsch, Boni, & Borgeat, 2001). Besides that, it was used to treat morphine dependence in accordance with the recommendation of Sigmund Freud (Doneith, 2008) – presumably with dubious success, from a more modern point of view. In the 1900th century it was sold without restriction for various indications and was a compound in the original receipt for Coca Cola (Goldstein et al., 2009) and therefore also used recreationally.

Acute cocaine administration dose-dependently increases dopamine in the nucleus accumbens (Frank, Krumm, & Spanagel, 2008) and the caudate putamen (Church, Justice, & Byrd, 1987; Di Chiara & Imperato, 1988). This increase is, in relation to the basal values, higher in the nucleus accumbens than in the caudate putamen (Di Chiara & Imperato, 1988).

2.3 Data-Mining

This section covers the methods applied on the online search on PubMed, the criteria for in- or exclusion, and the process of structured extraction of parameters from the selected publications. The methods used were already described in the corresponding publication on this thesis (Egenrieder et al., 2020) and may also be viewed there.

2.3.1 Search methods

In this section, the method of the literature search on PubMed and the sources of the preexisting datasets that were included are presented.

As previously reported (Brand et al., 2013; Fliegel et al., 2013; Fritze et al., 2017; Hirth et al., 2016; Noori, Fliegel, et al., 2012; Noori et al., 2018; Staudenmaier, 2017), and also described in the corresponding paper on this thesis (Egenrieder et al., 2020), a robust, standardized workflow for data-mining was developed and

established by the workgroup. ‘This approach allows an accurate extraction of *a* maximum amount of data with a minimized chance of missing critical information and was therefore applied’ (Egenrieder et al., 2020).

A systematic literature search was conducted on PubMed, the free, online archive of biomedical and life sciences journals at the U.S. National Institutes of Health's National Library of Medicine (https://www.ncbi.nlm.nih.gov/pubmed/). PubMed provides more than 28 million citations that were published since 1948. The search query included all articles that were released until the 31.03.2018, without any filter or preference for authors or journals.
The following combinations of keywords were applied: rat (AND) microdialysis (AND) (female (OR) sex (OR) gender) (AND (striatum (OR) nucleus accumbens) (AND) (alcohol (OR) ethanol (OR) (d,l)-amphetamine (OR) cocaine (OR) morphine (OR) nicotine (OR) tetrahydrocannabinol (OR) THC). For details see figure 5.

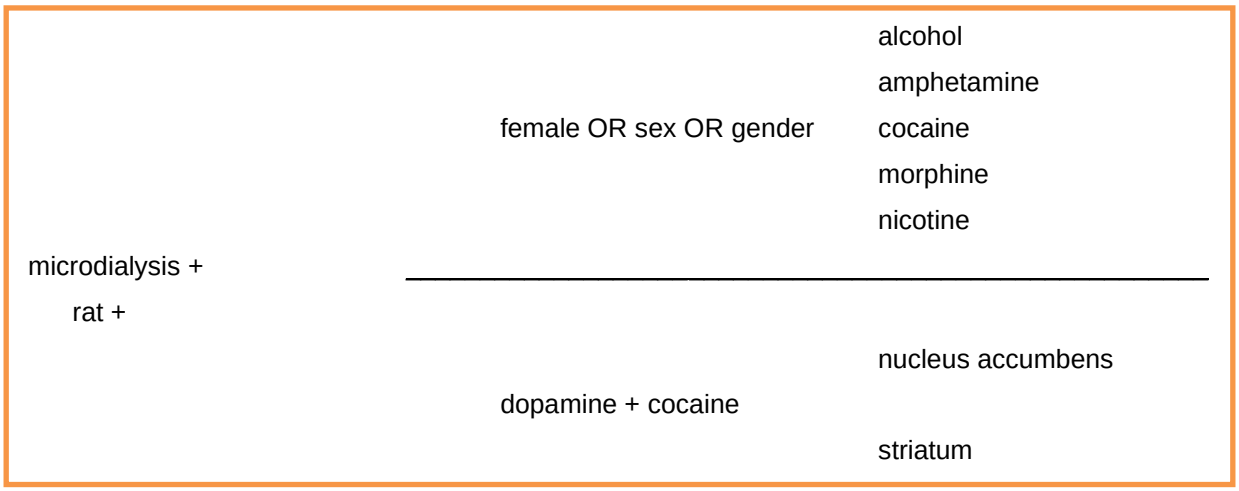


Figure 5: Keyword combinations for the conducted PubMed search

Keyword combinations for the specific search for female animals: above the line.
Search for male rats, administered with cocaine: below the line.

The same combination of keywords – apart from (female (OR) sex (OR) gender) and any other drug than cocaine – was applied to identify studies that investigated the administration of cocaine to male animals. Each dose that was found during this query was included in the further analysis, regardless if there was a matching female group.

The results for male animals administered with the other drugs of abuse could be received by preexisting meta-analyses. Data for amphetamine were kindly provided by Schabel et al. and for morphine by Gruhlke et al., respectively (neither published yet). Ethanol data were received from Brand et al. (Brand et al., 2013) and for nicotine from Staudenmaier et al. (Staudenmaier, 2017). The corresponding dosages of the drugs were extracted, matched and gathered into groups with those that were found in the female query.

The results on PubMed before any further selection were a total of 320 publications for female animals and 454 for male rats that were administered with cocaine. Apart of that the excerpted results of 187 studies were received from meta-analyses of the working group.

2.3.2 Selection criteria

This passage is about the criteria that were used to in- or exclude the papers/experiments found on PubMed by means of the search query described above. The method used was already described in the corresponding publication on this thesis (Egenrieder et al., 2020) and may also be viewed there.

Following the robust workflow, a well-defined list of in- and exclusion criteria was applied in order to maximize consistency of the included datasets: the focus was on microdialysis studies that contained a peak percentage baseline value of dopamine after a single acute administration of the respective drug of interest, i.e. alcohol, amphetamine, cocaine, morphine, or nicotine. Experiments with all other drugs were excluded. The measurements had to take place in the striatal complex, meaning the caudate putamen and the nucleus accumbens. Every other brain region examined was excluded.
Publications in English with rats as subjects were included. Papers in any other language or with primates, mice or other animals were not further taken into consideration.
All articles like reviews, comments, or meta-analyses without new experimental results were ignored, and only original research articles were further analyzed,

following the guidelines for meta-analyses of pre-clinical studies (Vesterinen et al., 2014).

The animals had to be drug naïve without any co- or pretreatment except for hormonal modifications like progesterone, estrogen, or testosterone. Therefore, studies that contained the concurrent administration of other drugs were excluded as well as those with animals that were trained to self-administer substances before the microdialysis experiment.
Furthermore, only in vivo microdialysis experiments could be taken into consideration, in vitro settings were not subject to this thesis.
Excessive other treatments like stress by isolation, prolonged food restriction, or changed environmental settings (e.g. altered temperature) were excluded likewise and were not considered further in the analysis. Moreover, animals that underwent surgery like intracerebral lesions, or were genetically modified, were excluded.
Because the keyword combination was aiming at female animals, all experiments that subjected only male animals were excluded – except for those receiving cocaine, (as there were no pre-existing data available for this subgroup, see also the described search methods).

2.3.3 Data collection

In this passage, the variables that were extracted from the included papers for further analysis are listed. The method used was already described in the corresponding publication on this thesis (Egenrieder et al., 2020) and may also be viewed there.

As previously reported (Brand et al., 2013; Fliegel et al., 2013; Fritze et al., 2017; Hirth et al., 2016; Noori, Fliegel, et al., 2012), the standardized workflow that was used included three categories of variables that were extracted (if available) from the included studies: variables of the experimental setup (i.e. microdialysis parameters), variables of the laboratory animals and variables of the outcome. This strictly defined process of data collection ensured the comparability of the dataset for female animals with those obtained from other meta-analyses. See table 1 for an overview of the three categories and the extracted variables.

The following values were extracted regarding the microdialysis experimental setup: the brain region that was examined (caudate putamen/nucleus accumbens); the administered drug (alcohol, amphetamine, cocaine, morphine, nicotine) and dose (mg/kg, g/kg, µM for local administration) and the route of administration (i.p., i.v., s.c., locally, nasally); time of the sampling rate (min), i.e. for how many minutes each sample was collected and thereby representing the temporal resolution of the experiment; the perfusion rate (µl/min); the perfusion fluid (Ringer's solution, aCSF or other fluids) and its calcium concentration (mM); and lastly the length (mm) and the outer diameter of the active microdialysis membrane.

Table 1: Categories and extracted variables

Category	Extracted variables
Experimental procedure	• brain region • drug name and applied dose • route of drug administration • sampling rate (min) • perfusion rate (µl/min) • perfusion fluide (e.g. Ringer solution) • calcium concentration in perfusate (mM) • length (mm), outer diameter of microdialysis membranes
Biological variables	• age or weight • sex • estrous cycle • ovariectomy or hormonal pre-treatment • rat strain • state of consciousness (anesthetic agent, route of administration and dosage) • housing and details of housing (size of group if group housed) • number of animals used in each experiment
Outcome	• peak % compared to baseline • the time at which the maximum occurred

The second category included all biological variables, namely the traits of the laboratory animals: the age (or, if not available, the rats' weight that was subsequently used to extrapolate the age); the sex (female/male); the estrous cycle (mentioned/not mentioned) and, if available, the exact state (proestrous, estrous, metestrous, and diestrous); if the rat was ovariectomized or hormonal pretreated (estrogen, progesterone, testosterone when males were included); the strain (e.g.

Sprague Dawley, Wistar etc.); the state of consciousness (awake/anesthetized and if so: agent, dose and route of administration of anesthetic); housing conditions (individually/group housed and if so: number and traits of other animals in group housing); and the number of animals used in each experiment.
The third category covered the outcome parameters of the experiments: the maximum drug dose effect, given as peak percentage value compared to its corresponding baseline before drug administration, and the time at which this maximum occurred. If the peak was not given in a numerical manner, the graphics were analyzed, and the peak percentage baseline value was calculated.

A standardized panel was used to collect as many variables as possible out of each publication. If the authors added a link to another experimental setup for further information, instead of listing all the variables, the referred publication was screened for further information.

2.4 Statistical analysis

This paragraph covers the description of the presentation of the PubMed findings and the statistical analysis of the included datasets. The statistical method used was already described in the corresponding publication on this thesis (Egenrieder et al., 2020) and can likewise be found there.
The method performed was used before by the work group and served as an example for this thesis. For details see again Brand et al. (2013), Fliegel et al. (2013) Staudenmaier et al. (2017), Fritze et al. (2017) and Noori et al. (Brand et al., 2013; Fliegel et al., 2013; Fritze et al., 2017; Noori et al., 2018; Staudenmaier, 2017).

Firstly, a global analysis of the conducted PubMed query was done by presenting the number of the included and excluded papers. Also, the animals obtained per drug were recorded and the distribution of their different properties (sex, strain, age, state of consciousness and route of administration of the drug) are presented in percent.
If possible, averages, standard error of the mean, median, minimum and maximum were calculated for the given parameters (e.g. microdialysis parameters like outer diameter and length of active membrane).

The peak percentage baseline value of dopamine was set as the primary outcome of this thesis, while the variety of other variables was defined as potential effect modifiers. This includes all the traits collected in the categories ‘biological’ and ‘experimental’ variables, like the animals' weight, sex, age, or the experimental settings like the flow rate, the perfusion fluid etc.
As previously reported (Noori et al., 2018), a weighted meta-analyses of the maximum drug effects was conducted with respect to the effect modifiers. Thereby the dataset was subdivided into groups, e.g. awake versus anesthetized (for a specific drug, brain region and dose, respectively). Subsequently, an analysis of variance (ANOVA) was conducted to detect statistically significant differences in the dopamine levels of the subgroups with different traits. The global level of significance was chosen as $\alpha = 0.05$.
If multiple testing was needed, Bonferroni correction was used to minimize the risk of a type I error. If there were significant differences in the peak percentage baseline values between subgroups, the weighted averages were calculated and presented separately with their respective standard error of the mean (SEM).

A correlation analysis was conducted to further examine the dopamine changes after the administration of the five drugs. Pearson's correlation coefficient was used to detect dose-dependent relationships.
Calculation was done with IBM SPSS Statistics 24 and the diagrams were created with Microsoft Excel® for office 365 MSO. The results are organized in tables and diagrams. The results of meta-analyses are often presented in forest plots (Gurevitch et al., 2018), a tool that was used also in this work.

Although the focus of the present work was on the parameters mentioned above, the context of the whole experiment was kept in mind: the results used were always averages of an experimental group, containing several animals, or even an average of several experimental groups. Thus, the data refer as well to the whole setting of the experiment as this was performed and described before (Brand et al., 2013; Fliegel et al.; Staudenmaier).

3 RESULTS

3.1 Global statistics

This section focuses on the origin and the properties of the included studies and animals and the distribution of the settings of the included microdialysis experiments. The drug specific effects and the comparison of the peak percentage baseline values will be described in a separate chapter for each drug respectively.

In sum, this thesis gathered 45 publications containing female rats (n = 842) in order to statistically compare them with data from 6402 male rats. A total amount of 459 studies with 7244 animals were included.

3.1.1 Origin of the included datasets

As described earlier, the datasets were obtained partly by a conducted PubMed search, partly by pre-existing meta-analyses about male animals. In the following passages the exact origin of the datasets is shown, and further details are given for both: the datasets received by other meta-analyses and the exact results of the PubMed search query.

For a list of the total numbers of studies and animals per source see table 2, the percentages for the included animals per source may be found in figure 6.

Table 2: Total amount of studies and animals per source

Source of data	Number of studies	Number of animals
PubMed results for female animals	45	1074
PubMed results for males/cocaine	262	3805
Preexisting data for males	187	2365
Sum of studies in analysis	459 (without duplicates)	7244

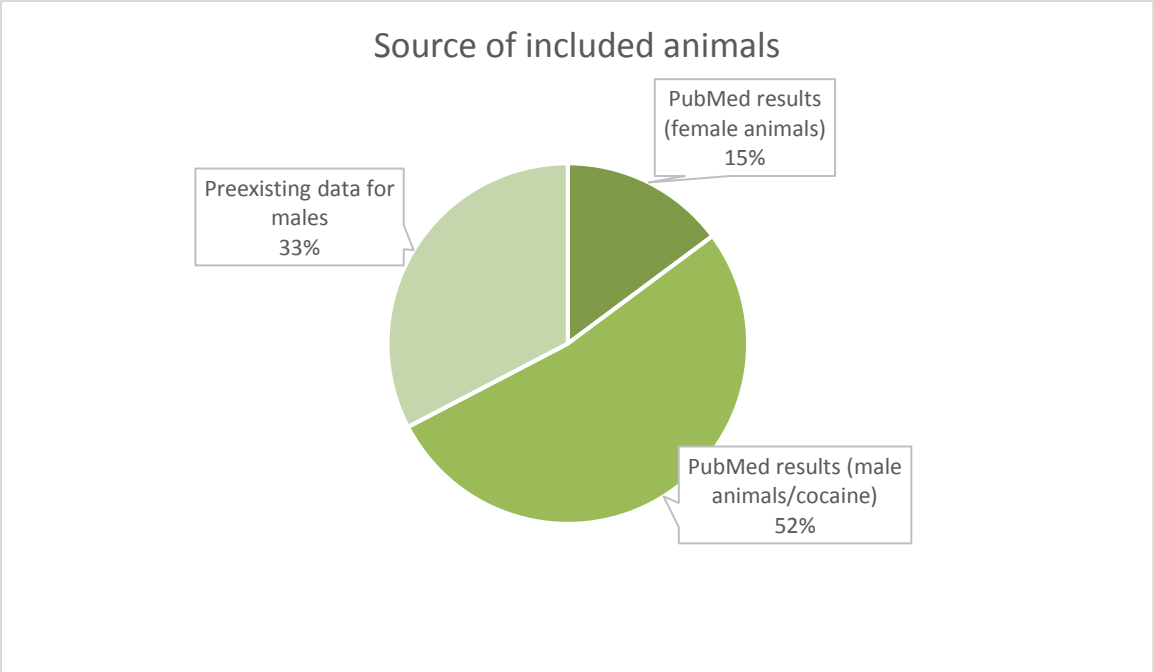


Figure 6: Included animals (n = 7244) in regard of the three different sources

All the included studies, no matter if they were received from PubMed or from other meta-analyses, provide a peak percentage baseline value of dopamine either in the nucleus accumbens or the caudate putamen.

Overall, 187 studies containing 2365 animals were extracted from other projects of the work group at the Institute of Psychopharmacology of the Central Institute of Mental Health (Medical Faculty Mannheim/Heidelberg University).

The main part of these preexisting results was the amphetamine group, containing 1831 animals out of 145 studies kindly provided by Schabel et al. Another 534 animals out of 42 studies were received from Gruhlke et al. for acute morphine administration, from Staudenmaier et al. for animals that received nicotine, and from Brand et al. for alcohol administration (for exact numbers see table 3).

Table 3: Number of studies and animals received from preexisting meta-analyses

Drug (Author)	Included studies	Number of animals
Amphetamine (Schabel et al.)	145	1831
Alcohol (Brand et al.)	11	184
Morphine (Gruhlke et al.)	16	208
Nicotine (Staudenmair et al.)	15	142
Sum	187	2365

The online search on PubMed led to 734 original publications for the two queries: female animals receiving the different drugs of abuse and male animals receiving cocaine (applying the keyword combinations described in the method section, respectively). These unfiltered search results were screened and selected according to the inclusion criteria that are described above. See the flow diagram in figure 7 for an overview of the workflow, orientated towards the PRISMA guidelines.

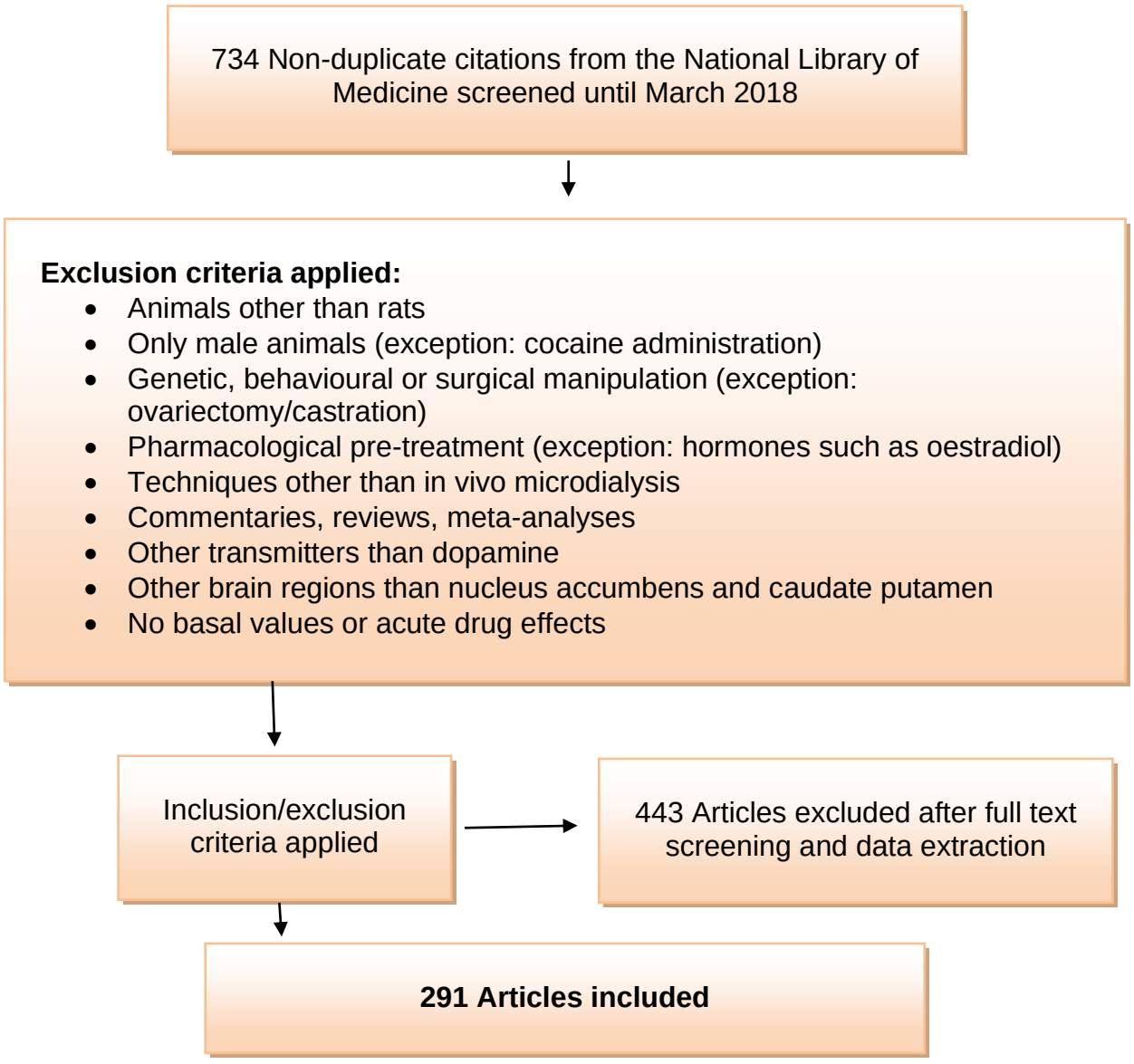


Figure 7: Flow diagram of study identification and selection process oriented towards the PRISMA guidelines

Of the 734 publications that were identified in the search query, 39.6%, equaling 291 studies, could be included for further analysis. The remaining 443 papers (60.4%) had to be excluded. Another keyword combination searching for tetrahydrocannabinol, provided only four papers of which none could be included and will therefore not be further mentioned.

The main part of the results, meaning 454 studies, were found for the search for male rats. Out of those results 257 papers (equaling 57.7%) could be included.
Much less studies were found for the specific search for female animals even though the keywords included five drugs, not only cocaine: 320 articles matched these keywords. Also, the percentage of included papers was smaller for the female query than for the male/cocaine search: 45 studies being equivalent to 14% met the inclusion criteria.

Table 4: PubMed findings per keyword and number and percentage of included and excluded studies

Keyword combination for…		Pubmed findings	Included studies	in %	Excluded studies	in %	n of studies in dataset
…females	Amphetamine	99	17	17	82	83	16
	Cocaine	48	17	35	31	65	13
	Alcohol	173	12	7	161	93	8
	Morphine	31	5	16	26	84	5
	Nicotine	24	6	25	18	75	3
Sum females (without duplicates)		320	45	14	275	86	45
….males	Cocaine	454	257	57	197	43	246
Sum females + males (without duplicates)		734	291	40	443	60	291

Viewed per drug, the query for alcohol produced most of the results. Nevertheless, relatively few papers could be included: only eight publications or 7% met the criteria. The highest percentage of included papers was reached for cocaine with 35%. For a detailed presentation of the findings for each keyword combination see the table 4.

3.1.2 Sex and estrous cycle

In the following paragraphs the distribution of the properties (sex, strain, age, consciousness, route of administration) of the overall number of animals is given and presented for each drug respectively. The impact of these effect modifiers on the dopaminergic overflow after acute administration of drugs is described later for each drug in a separate chapter.

Firstly, the sex of the rats was analyzed and presented: the online search for females provided a total amount of 45 publications containing 1074 included animals. But since sometimes the sex was not specified in these studies or both, males and females were used without explicit assignment, or the experiments contained also males, not all of those 1074 animals were actually female rats. If only those animals were taken into consideration, that were explicitly categorized as ‘female’ and half of the ‘male/female’ mixed groups, they add up to 842. Table 5 shows the distribution of the included females per drug and the corresponding percentages.
Overall, 11.6% of the animals in this thesis were females. The other 88.4% were either male animals or animals that had no labeled sex in the original publication.

Table 5: Female animals included per drug

Drug	Included animals	Percentage
Alcohol	200	24
Amphetamine	314	37
Cocaine	178	21
Morphine	102	12
Nicotine	48	6
Sum	842	100

The main part of the female animals, meaning 314, received amphetamine. This number was followed by an amount of 200 rats that were administered with alcohol and 178 with cocaine. For morphine and nicotine only 102 and 48 animals were included, respectively. In the nicotine group all measurements took place in the nucleus accumbens and there were no experiments that had the caudate putamen as brain region of interest. The results of all other drugs contained values out of both brain regions.

Secondly, an analysis of the mentioning and monitoring of the estrous cycle was conducted on the 45 studies containing female animals. The results for the keyword combination for male animals that received cocaine are not taken into consideration in this overview.

Overall, 62% of the studies did not mention the hormonal state of the animals at all. Regarding those studies that took it into account (38%) there were different levels (see figure 8): in nine of the 45 studies the females were described as ovariectomized, which amounts to a share of 20%. Another three studies (or 7%) did not measure the estrous cycle but stated that it was counterbalanced due to the experimental setup, e.g. through planning the experiments on different days for different animals.

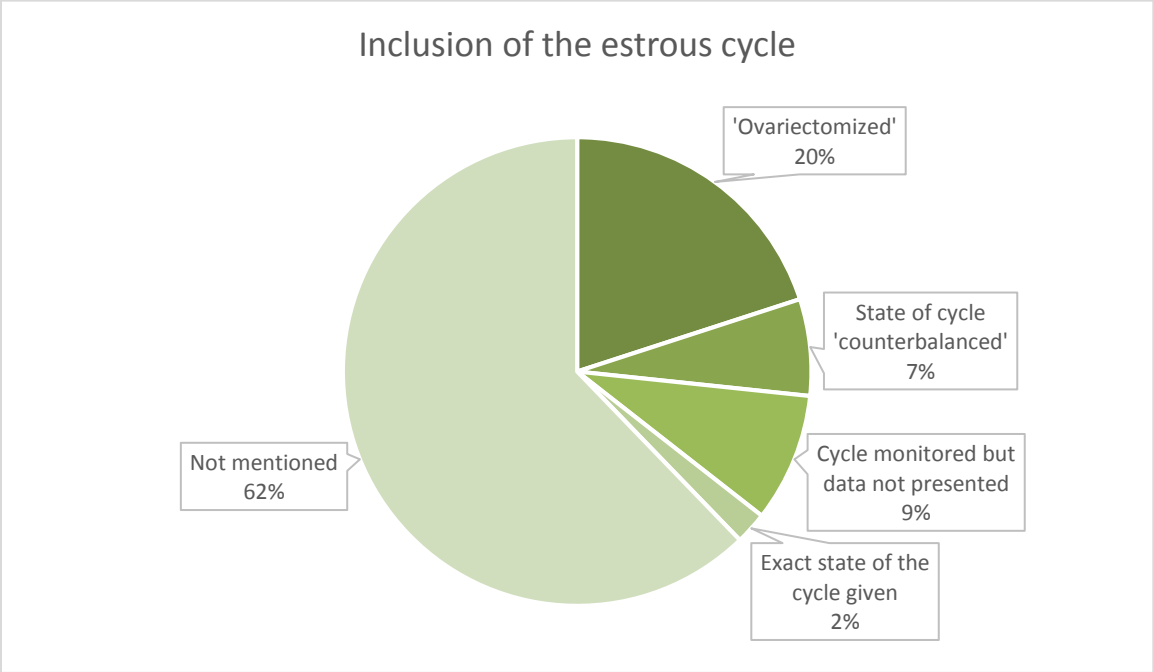


Figure 8: Percentages of the mentioning and monitoring of the estrous cycle (n = 45 studies)

In four studies (9%) the cycle was monitored but as there was no effect on the results, it was not presented. Only one study mentioned and monitored the concrete state of the estrous cycle. Therefore, a share of 2% of the included studies contained the state of the estrous cycle, which does not provide sufficient data to analyze the effect on drug-induced changes in striatal dopamine concentrations.

3.1.3 Strain

In a further step, the included studies were analyzed in regard to the other properties of the rats they used as subjects. Therefore, the total number of experimental groups (n = 512 datasets) was set as 100% as a basis for the calculation in the following chapters.

Most of the animals that were used by the included experiments were Sprague-Dawley rats with 64%. The second largest group consisted of Wistar rats with 18%. Another 16% were composed of other strains, mainly Long Evans (6%), and in 2% of the papers, the authors did not specify the strain. Special breeds like for example alcohol avoiding or obesity-prone rats were counted as ‘other strain’. For details see figure 9.

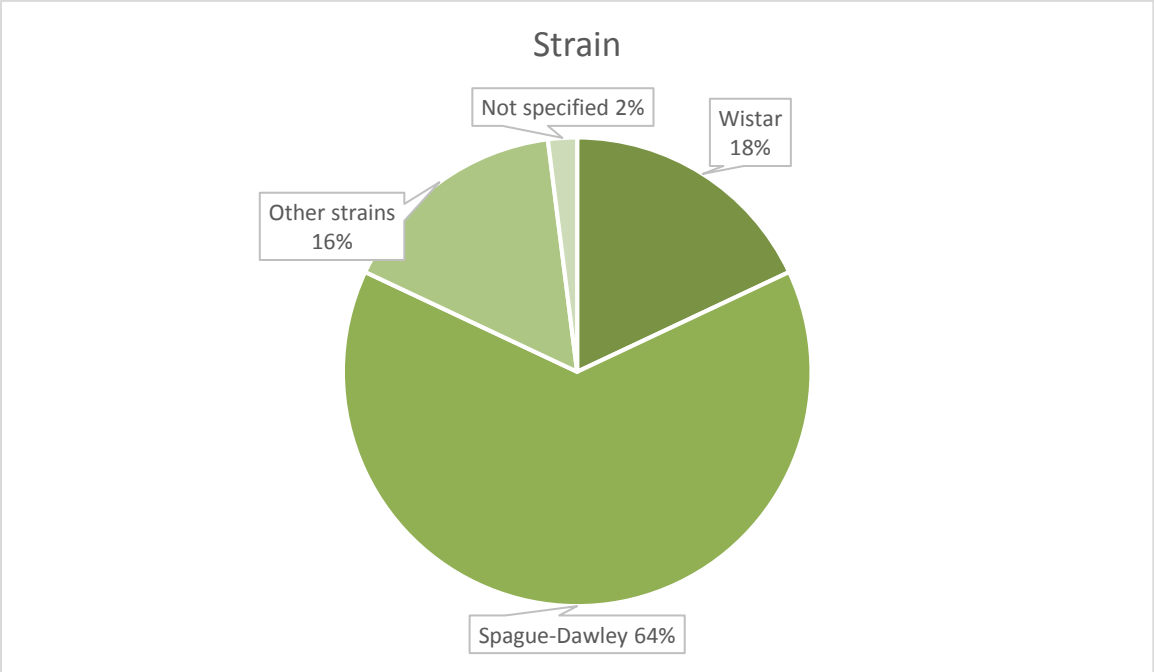


Figure 9: Percentages of the strains used by the included experiments (n of datasets = 512)

The preponderance of Sprague-Dawley and Wistar rats was found for four drugs of abuse. The only exception were studies with alcohol, probably due to the fact that in those experimental setups sometimes special breeds are used, like alcohol preferring or alcohol avoiding rats, that are contained in the section ‘other strains’. For details about the distribution of strains for the different drugs see table 6.

Table 6: Distribution of strains per drug

Drug	% Sparague-Dawley	%Wistar	% Other strains	Strain not specified
Cocaine	68	15	15	2
Amphetamine	60	21	17	2
Alcohol	20	35	45	0
Morphine	68	23	9	0
Nicotine	70	10	20	0
All Drugs	64	18	16	2

Overall, the results of this thesis should be considered referring mainly to Sprague-Dawley rats.

3.1.4 Age

Every age of subjects was included: most of the experiments (86%) were carried out in adult animals. Another 7% of the studies had adolescent subjects and again 7% did not mention the rats' age. For the distribution of the animals' age see figure 10.

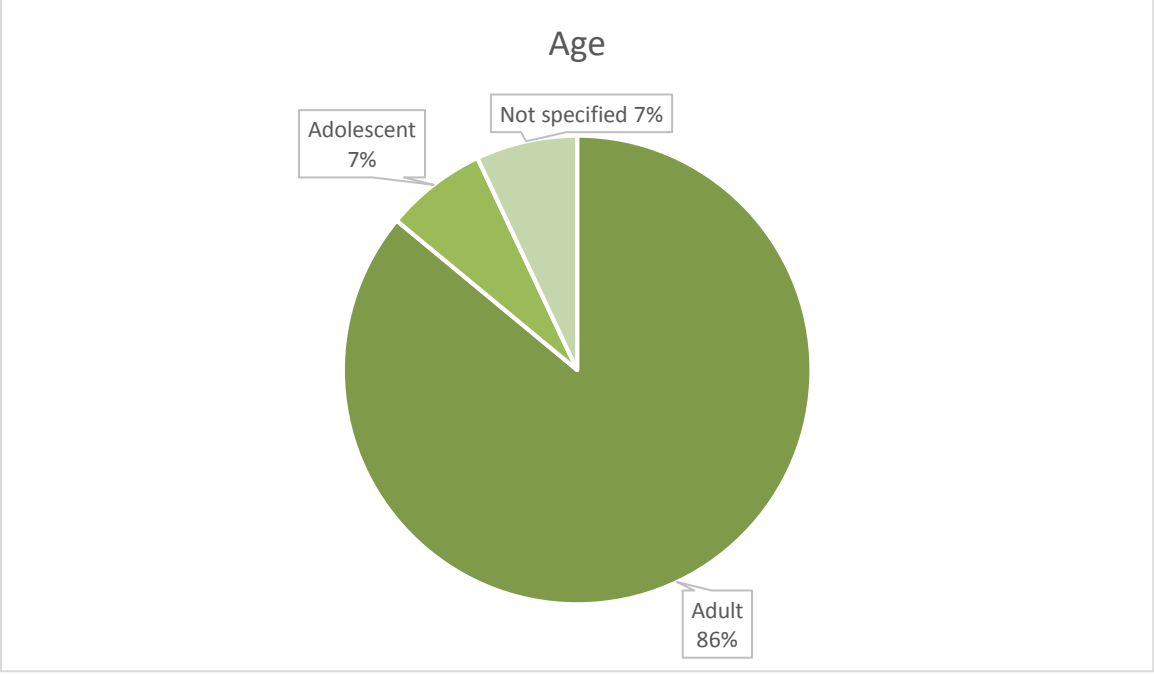


Figure 10: Percentages of the age of the animals used by the included experiments (n of datasets = 512)

A relatively high percentage of adolescent animals was present in the two smallest drug groups: among the animals that received morphine or nicotine 14%, or 25%,

respectively, were adolescent. For the three other drugs the share of adolescent animals was under 10%, or even under 5%. Therefore, the outcomes of this study relate almost exclusively to adult animals. For detailed information about the distribution of age among the included animals per drug see table 7.
Some authors did not explicitly mention the rats' age but their weight. In these cases, the age was estimated by means of standard growth curves of the respective strain.

Table 7: Distribution of age per drug

Drug	% Adult	% Adolescent	% Age not specified
Cocaine	86	7	7
Amphetamine	92	4	4
Alcohol	85	5	10
Morphine	68	14	18
Nicotine	70	25	5
All Drugs	86	7	7

3.1.5 State of consciousness

Generally, most of the microdialysis experiments are conducted on freely moving (awake) animals.

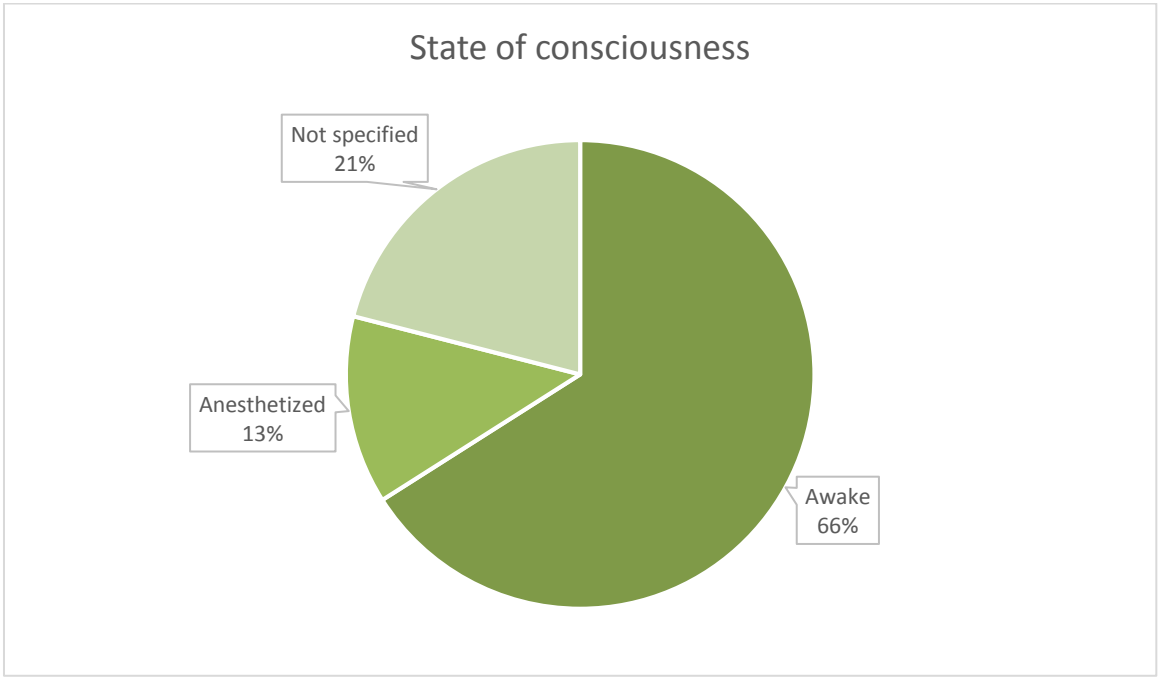


Figure 11: Percentages of the different states of consciousness of the animals used by the included experiments (n of datasets = 512)

Regarding the included studies of this meta-analysis, this tendency could also be detected: all in all, 66% of the animals were described as awake, 13% were explicitly anesthetized and in 22% of the studies the authors did not point out the state of consciousness. Most likely the animals were also awake in many of these undefined cases, as no description of any anesthetic procedure was given. When a hint on anesthesia was mentioned, the studies were counted as ‘anesthetized’. The distribution can be seen in figure 11.

Viewed for each drug separately, cocaine and amphetamine were administered to both, awake and anesthetized (11% and 19% of the experiments) animals. The remaining three drugs were only administered to awake and freely moving animals. Therefore, the present work does provide data for the effect of anesthetics on cocaine and amphetamine administration. See table 8.

Table 8: Distribution of state of consciousness per drug

Drug	% Awake	% Anesthetized	% Consciousness not specified
Cocaine	67	11	22
Amphetamine	57	19	24
Alcohol	80	0	20
Morphine	91	0	9
Nicotine	95	0	5
All Drugs	66	13	21

3.1.6 Route of administration

There were five different routes of administration in the included publications: most of the drugs were administered via the peritoneum with 64%, followed by the subcutaneous route, with 18% and the intravenous administration with 10%.
In some cases, meaning 6%, the drugs were administered via reverse microdialysis directly into different brain regions (local administration). In one experiment the rats got cocaine intranasally. For the distribution of the different routes of administration see figure 12.

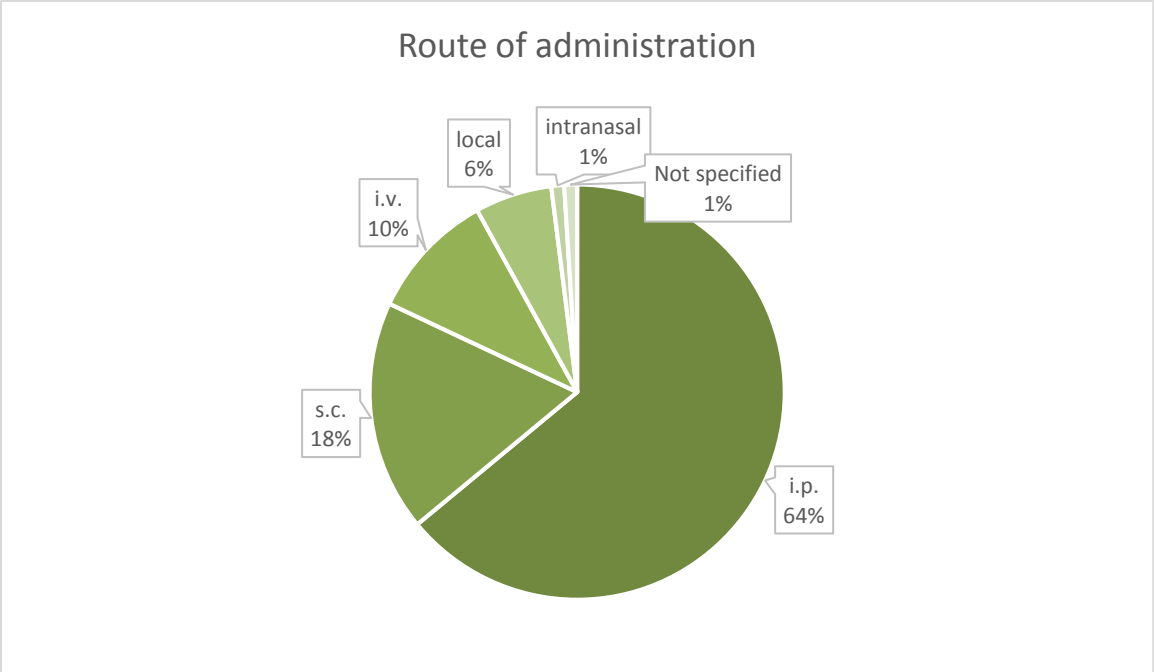


Figure 12: Distribution of the route of administration in the included experiments (n of datasets = 512)

Cocaine and alcohol were the drugs that were most frequently administered intraperitoneally and had therefore the lowest percentages of the subcutaneous route of administration (8% or 0% of the cases).

Nicotine has a relatively high share of subcutaneous administrations and therefore the lowest intraperitoneally administered cases with 5%. Local administration could be detected for alcohol, cocaine, nicotine and amphetamine.

For the distribution of the different routes of administration per drug, see table 9.

Table 9: Distribution of the route of administration

Drug	% intraperitoneal	% subcutaneous	% intravenous	% local	% intranasal	% not specified
Cocaine	75	8	14	2	1	1
Amphetamine	54	35	6	4	0	1
Alcohol	75	0	10	15	0	0
Morphine	55	41	4	0	0	0
Nicotine	5	85	0	5	0	5
All drugs	64	18	10	6	1	1

3.1.7 Microdialysis parameters

There were different solutions used as a perfusion fluid in the included publications: two thirds of the experiments used artificial cerebrospinal fluid (aCSF) or Ringer's solution. Another 16% named other fluids and 8% did not specify the selected medium. For a graphical representation see figure 13.

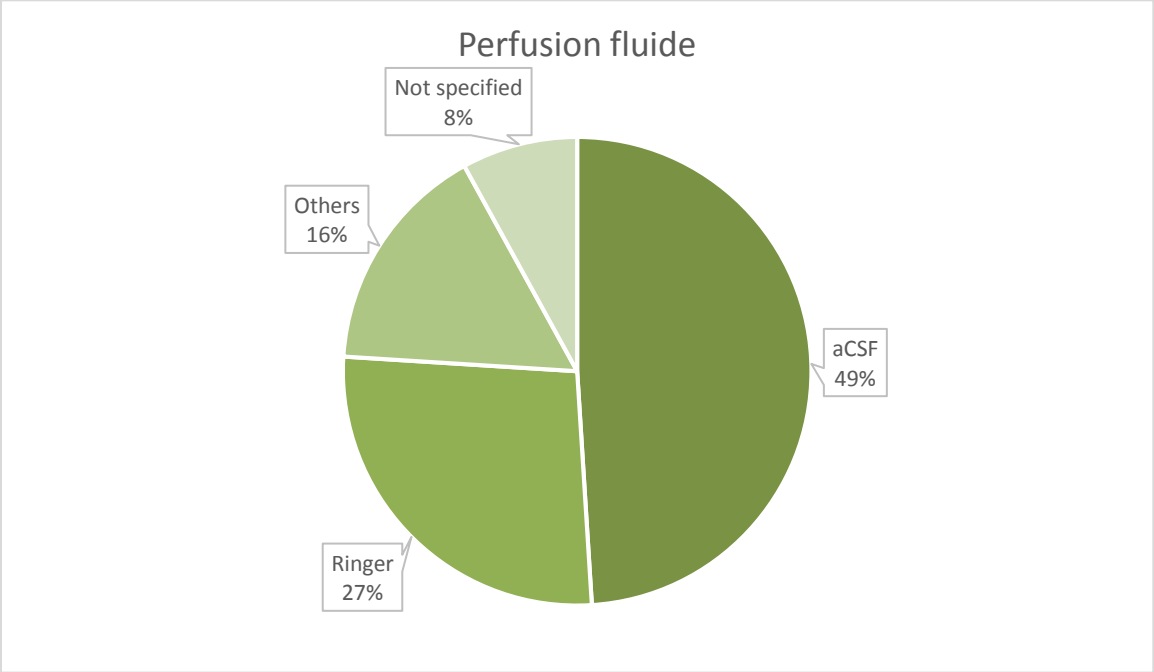


Figure 13: Percentage of the perfusion fluid used by the included experiments (n of datasets = 512)

As described above, further parameters of the microdialysis experiments were recorded: the length of the active membrane and the outer diameter of the probe, the sample time, the flowrate, and the calcium concentration of the perfusion fluid. As these parameters were the same for all experiments of one publication, the overall number of studies was set as 100% for the calculation of the following percentages.

The active membrane had an average length of 2.4 ± 0.98 mm and an outer diameter of 318 ± 110.82 µm. But not many papers mentioned the latter one: only 180 out of the total amount of 459 publications named the exact outer diameter.
The flowrate, the sample time and the calcium concentration were relatively often specified. The sample time ranged from 2 to 40 minutes and had its median at 20 minutes. The fluid was perfused at an average rate of 1.58 ± 0.75 µl/min and

contained an average of 1.51 ± 0.52 µM calcium. For the average, median, minimum, maximum, and the number of the papers without values see table 10.

Table 10: Average ± SEM, median, minimum and maximum of the different microdialysis parameters

Microdialysis parameter	Average	Median	Minimum	Maximum	Not specified (number of studies)
Length of active membrane (mm)	2.4 ± 0.98	2	1	8.5	84
Outer diameter (µm)	318 ± 110.82	300	150	600	279
Sample time (min)	18.33 ± 5.69	20	2	40	35
Flow rate (µl/min)	1.58 ± 0.75	1.5	0.16	5	35
Calcium concentration (mMol)	1.51 ± 0.52	1.2	0	1.4	78

3.2 Drug specific effects

In the following sections, the results of the statistical analysis of the peak percentage baseline values are presented. A correlation analysis was conducted per drug and brain region and one-way ANOVA was done in regard of the effect modifiers for each dosage separately. Therefore, the specific results will be presented by drug/brain region.

The references for the presented single values are in the list of appendices, for reasons of clarity. A table that gives a gathered summary of all dose-dependent effects of the five different drugs is to be found in the discussion. Forest plots were created for those dosages that contained more than 250 animals. This was the case for two groups that received amphetamine (0.5 mg/kg, nucleus accumbens and 2 mg/kg, caudate putamen) and three dosages of cocaine (5, 10, and 20 mg/kg, nucleus accumbens).

3.2.1 Alcohol

Overall, twelve studies (n = 200) contained measurements of extracellular dopamine concentrations in the striatal complex (NAc and CPu) of females after the administration of alcohol. Another eleven studies were included from Brand et al., leading to 23 publications with alcohol administration: Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993; Blanchard, Steindorf, Wang, LeFevre, et al., 1993; Bustamante et al., 2008; Campbell & McBride, 1995; Cummings, Jagannathan, Jackson, & Becker, 2014; Ding, Ingraham, Rodd, & McBride, 2016; Ding et al., 2012; Ding, Rodd, Engleman, & McBride, 2009; C. Heidbreder & De Witte, 1993; Howard, Schier, Wetzel, Duvauchelle, & Gonzales, 2008; Kohl, Katner, Chernet, & McBride, 1998; Maisonneuve & Glick, 1999; Mocsary & Bradberry, 1996; Philpot & Kirstein, 1999; D. L. Robinson, Howard, McConnell, Gonzales, & Wightman, 2009; Tobiansky et al., 2016; Yan, 1999; Yan, Zheng, Feng, & Yan, 2005; Yoon et al., 2004; Yoshimoto, Komura, & Kawamura, 1992; Yoshimoto, McBride, Lumeng, & Li, 1992a, 1992b.
Alcohol was administered in a range of 0.25 to 3 g/kg systemically and in concentrations varying between 50 to 300 mg% locally into the ventral tegmental area.

3.2.1.1 Nucleus accumbens

For measurement in the nucleus accumbens, ten different dosages (five systemically administered, five locally administered) of alcohol could be found including a total number of 403 animals, of which 156 were females.

The systemically administered dosages ranged from 0.25 to 3 g/kg (n = 347) and the local doses from 50 to 300 mg% (n = 56). Alcohol was perfused through the posterior ventral tegmental area in all experiments with local administration.
At 3 g/kg, only female rats were used as subjects. The five experiments with local administration of alcohol were also conducted on female animals only. In the remaining dose groups both sexes were present and therefore a comparison between the peak percentage values of the females and males could be conducted.

Table 11: Peak percentage baseline values in the nucleus accumbens after different dosages of ethanol, locally administrated dosages below the grey line

Dose (g/kg)	Peak% BL (weighted average) ± SEM	Sub group	n of rats	n of females (%)	P-value	Critical value (degrees of freedom)
0.25	178.45 ± 8.41	-	31	15.5 (50)	-	-
0.5	127.10 ± 1.76	Male	62	0 (0)	0,018	4.84 (1,11)
	171.74 ± 10.73	Female	28	28 (100)		
1	155.43 ± 1.93	-	139	29.5 (21)	-	-
2	151.53 ± 1.42	-	75	22.5 (30)	-	-
3	200 ± 25	-	4	4 (100)	-	-
50mg %	85 ± 4	-	7	7 (100)	-	-
100mg%	122.27 ± 4.32	-	11	11 (100)	-	-
150mg%	145 ± 12	-	7	7 (100)	-	-
200mg%	138.15 ± 4.60	-	27	27 (100)	-	-
300mg%	145 ± 10	-	4	4 (100)	-	-

However, while all doses consistently increased the level of dopamine (see table 11), only a moderate correlation (r = 0.46) between the administered dosage of ethanol and the dopaminergic overflow could be detected – at least regarding the systemic route of administration. Rats of both sexes had higher values of dopamine at the lower dosage of 0.25 g/kg systemically administered ethanol, compared to the 0.5 g/kg dose. In locally administered rats, a high linear correlation between the administered dose of alcohol and the increase of dopamine could be seen (r = 0.79). See figure 14a and b.

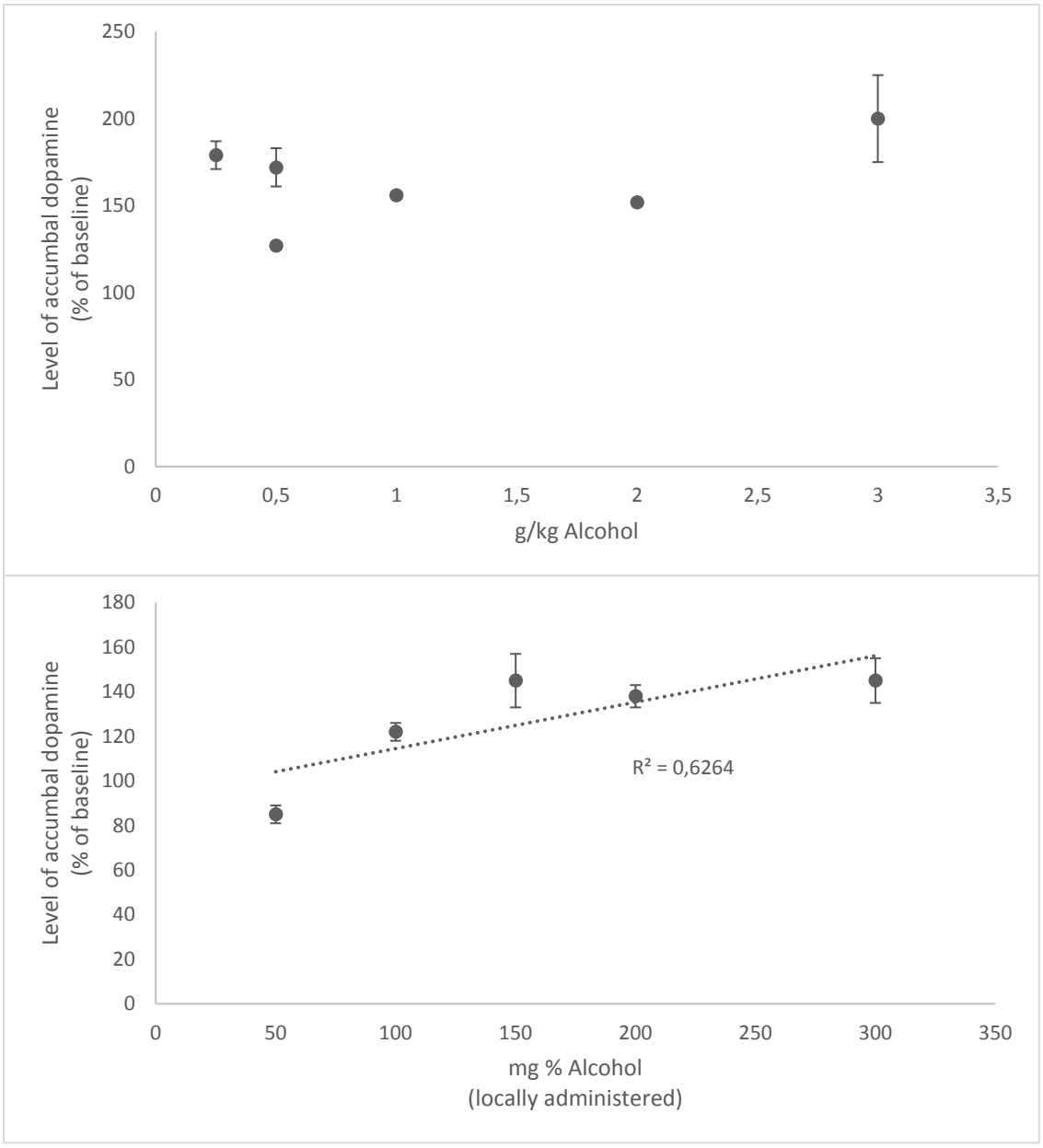


Figure 14a, b: Averages of the dose-dependent effect of ethanol on accumbal dopamine (n = 403 rats)

Systemic administration (above): n = 347 rats. R^2 = 0.22, the relationship may not be linear.

Local administration (below): n = 56 rats, perfused with different concentrations of ethanol into the posterior ventral tegmental area. R^2 = 0.63 and indicates a linear relationship.

For number of animals per dose, percentages of female rats and significant differences between groups see table above.

Only in one dose group a significant difference was detected through ANOVA: at 0.5 g/kg ethanol the peak percentage baseline value was higher in female rats, $F(1,11) = 4.84$, $p = 0.018$.

Table 12: Peak percentage baseline values of dopamine in female vs. male rats in the nucleus accumbens.

Sex	Peak percentage baseline value after 0.5 g/kg ethanol
Male	127.10 ± 1.76
Female	171.74 ± 10.73

Interestingly, in the other mixed-sex dose groups (that means 0.25, 1, and 2 g/kg) there were no significant findings regarding sex differences, whatsoever (see table 11). Detailed information including the references for the presented values and the respective peak times are set out in the appendix in chapter 7.2.

3.2.1.2 Caudate putamen

For the caudate putamen, four different dosages of ethanol could be found with a total amount of 168 rats (90 females). The query generated no results with local administration. In all included dose groups both sexes were present.

The conducted ANOVA did not show any differences between the subgroups; in particular, no sex differences could be identified. See table 13 for all peak percentage baseline values.

Table 13: Peak percentage baseline values in the caudate putamen after different dosages of ethanol.

Dose (g/kg)	Peak% BL (weighted average) ± SEM	Sub group	n of rats	n of females (%)	P-value	Critical value (degrees of freedom)
0.25	140.77 ± 4.45	-	31	15.5 (50)	-	-
0.5	160.01 ± 2.73	-	52	27.5 (53)	-	-
1	123.28 ± 2.04	-	49	27.5 (56)	-	-
2	95.54 ± 6.72	-	35	19 (55)	-	-

There was no positive dose-response relationship, but all dosages of ethanol increased dopamine levels in the caudate putamen. On the contrary, the analysis showed a negative correlation between the administered dose of ethanol and the dopamine level (r = - 0.90): the peak value of dopamine was, apart from the 0.5 g/kg value compared to the 0.25 g/kg value, inversely proportional to the administered dose of ethanol. See figure 15 and the chapter 7.2 in the appendix for more details, the respective peak times and the references for each dose group.

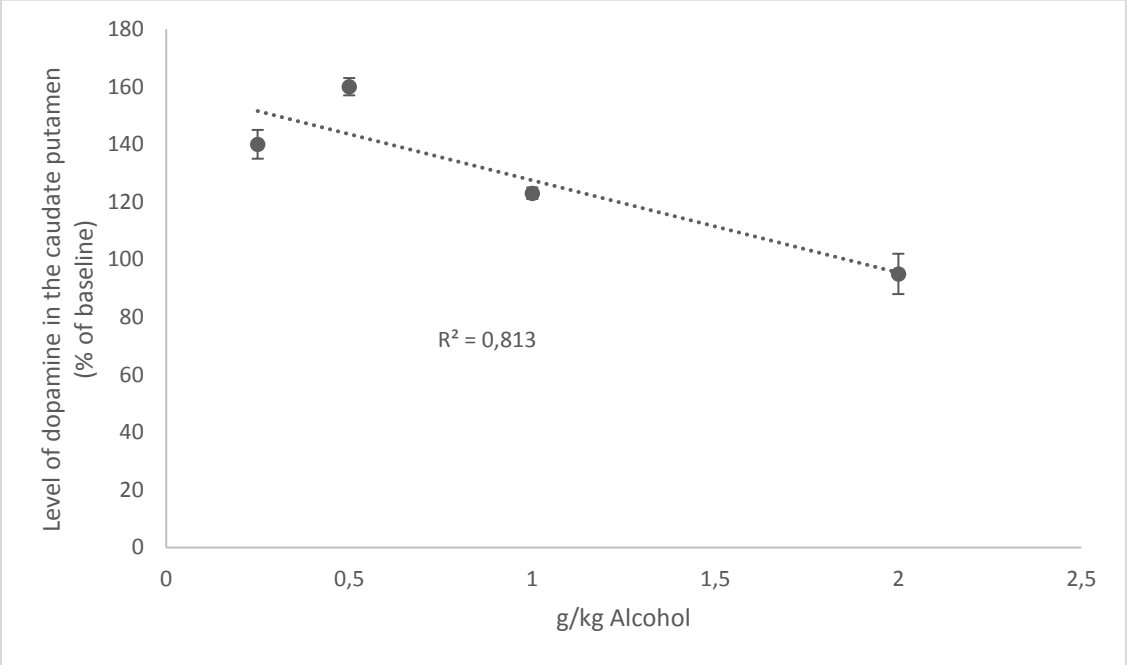


*Figure 15: Averages of the dose-dependent effect of ethanol on dopamine in the caudate putamen (*n = 167 rats)

For number of animals per dose and percentages of female rats see table above. R^2 = 0.81 and indicates a linear relationship.

3.2.2 Amphetamine

The conducted search led to data of 314 female rats excerpted from 18 original studies about the effect of amphetamine on the striatal complex: Becker & Cha, 1989; Becker & Rudick, 1999; Byun et al., 2014; Castaneda, Whishaw, Lermer, & Robinson, 1990; Castner, Xiao, & Becker, 1993; Ferguson, Flynn, Delclos, Newbold, & Gough, 2002; Geiger et al., 2009; Glick, Rossman, Wang, Dong, & Keller, 1993; Kehoe, Shoemaker, Arons, Triano, & Suresh, 1998; Kehoe, Shoemaker, Triano, Hoffman, & Arons, 1996; Maisonneuve, Keller, & Glick, 1992; McCallum, Cowe,

Lewis, & Glick, 2012; Nowak et al., 2008; T. E. Robinson & Camp, 1990, 1991; T. E. Robinson, Jurson, Bennett, & Bentgen, 1988; Shams et al., 2016; Shoblock, Sullivan, Maisonneuve, & Glick, 2003.

Another 144 studies were included from Schabel et al., adding up to an overall amount of 162 publications examining the striatal dopamine after amphetamine administration. The drug was systemically applied in a range of 0.5 to 7.5 mg/kg and there was one local dose that had a concentration of 1µM administered directly into both brain regions (NAc and CPu).

As already described in the methods, for the sake of clarity, in the following tables the term amphetamine – if not further specified – refers to the more frequently used dextro-enantiomer. For the rare cases when the rats received the racemase, ‘d+l’ will be added. There were no studies included that used levoamphetamine.

3.2.2.1 Nucleus accumbens

Amphetamine was administered at nine different dosages for measurement in the nucleus accumbens to a total amount of 1048 animals, including one local dose with 33 animals.

There were no experiments that contained the administration of the racemate or levoamphetamine. Male and female rats were available at all dosages with an overall share of 105 female animals.

Amphetamine at all dosages has a strongly enhancing impact on the dopaminergic transmission in the nucleus accumbens (table 14). However, no dose-response relationship could be identified: the correlation analysis showed no clear dose-dependent effect of amphetamine on the dopamine overflow in the nucleus accumbens ($r = - 0.12$).

Analogous to the other drugs studied, the dopaminergic response to amphetamine was examined with respect to the animals’ sex and other properties. Again, there were no significant differences in the average dopamine levels between the subgroups, notably between males and females. For further details see table 14 and chapter 7.3 in the appendix containing the references and averaged peak times of the presented results.

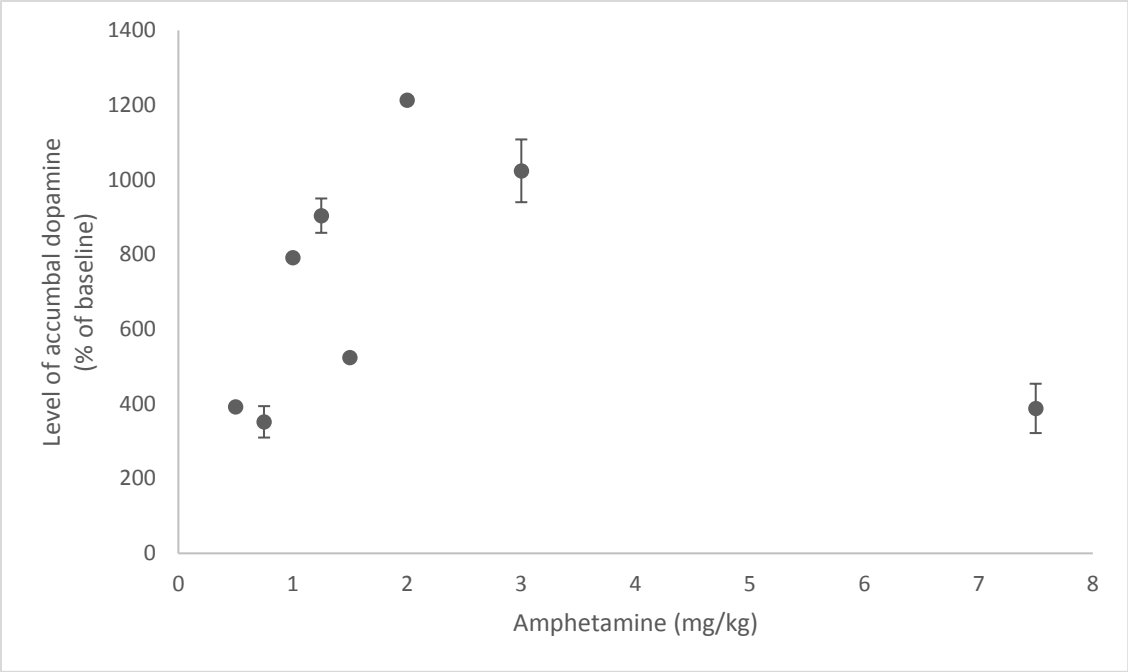


Figure 16: Averages of the dose-dependent effect of d-amphetamine on accumbal dopamine (n = 1015 rats)

For number of animals per dose and percentages of female rats see table below. $R^2 = 0.02$, the relationship may not be linear.

Table 14: Peak percentage baseline values in the nucleus accumbens after different dosages of d-amphetamine, locally administrated dosage below the grey line

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	N of rats	n of females (%)	P-value	Critical value (degrees of freedom)
0.5	392.15 ± 1.39	-	260	15.5 (6)	-	-
0.75	352.27 ± 42.05	-	11	6 (55)	-	-
1	791.46 ± 4.23	-	235	4 (2)	-	-
1.25	903.83 ± 45.88	-	30	12 (40)	-	-
1.5	523.90 ± 2.05	-	168	18 (11)	-	-
2	1213.16 ± 9.03	-	199	13 (7)	-	-
3	1024.77 ± 84.53	-	65	5 (8)	-	-
7.5	387.8 ± 65.9	-	25	12.5 (50)	-	-
1µM	342.42 ± 12.12	-	33	6 (18)	-	-

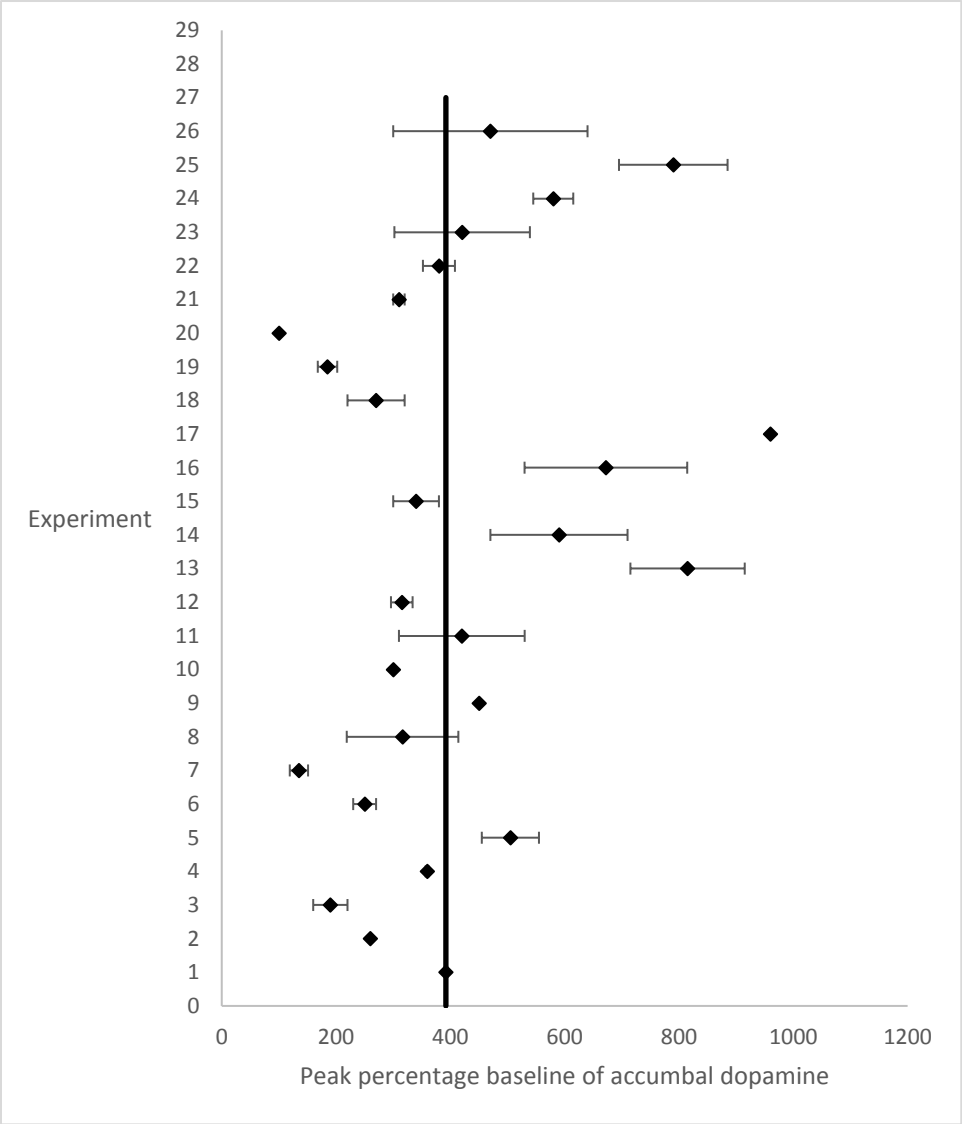


Figure 17: Averaged peak percentage baseline values of 25 publications (row 2 – 26, in chronological order) in relation to their weighted average in row 1 (0.5 mg/kg amphetamine, n = 260 rats).

The vertical line extends the weighted average. Horizontal lines represent the respective standard error of the mean (SEM). 2 Pani et al. 1990; 3 Steketee et al. 1992; 4 Di Chiara et al 1993; 5 Stewart et al. 1994; 6 Paulson et al. 1995; 7 Harmer et al. 1997; 8 Kehoe et al. 1998; 9 Darracq et al. 1998; 10 Hall et al. 1998; 11 Birrell et al. 1998; 12 Cagiano et al. 1998; 13 Ichikawa et al. 1998; 14 Hall et al. 1999; 15 Rowley et al. 2000; 16 Badiani et al. 2000; 17 Porras et al. 2002*; 18 Tronci et al. 2006; 19 Mattsson et al. 2007; 20 Pacchioni et al. 2007; 21 Rahman et al. 2008; 22 Sotty et al. 2009; 23 Sotty et al. 2009; 24 Auclair et al. 2010; 25 Fabricius et al. 2011; 26 Choi et al. 2014. *Two publications contained no SEMs.*

The forest plot (figure 17) shows the position of the single peak percentage baseline value of each experimental group in relation to the calculated weighted average.

All publications that administered 0.5 mg/kg amphetamine are listed in the chronological sequence of their publication. Row 1 shows the calculated average, the

single experiments are presented from row 2 on, each value with its respective standard error of the mean (SEM).

3.2.2.2 Caudate putamen

Ten different dosages (including one local dose) of amphetamine were administered to 1185 animals, containing 207 female animals.
There was no positive dose-response relationship in the caudate putamen (r = 0.14) for the administration of amphetamine (see figure 18). In this figure, all dose groups are included, also those that contained only males.

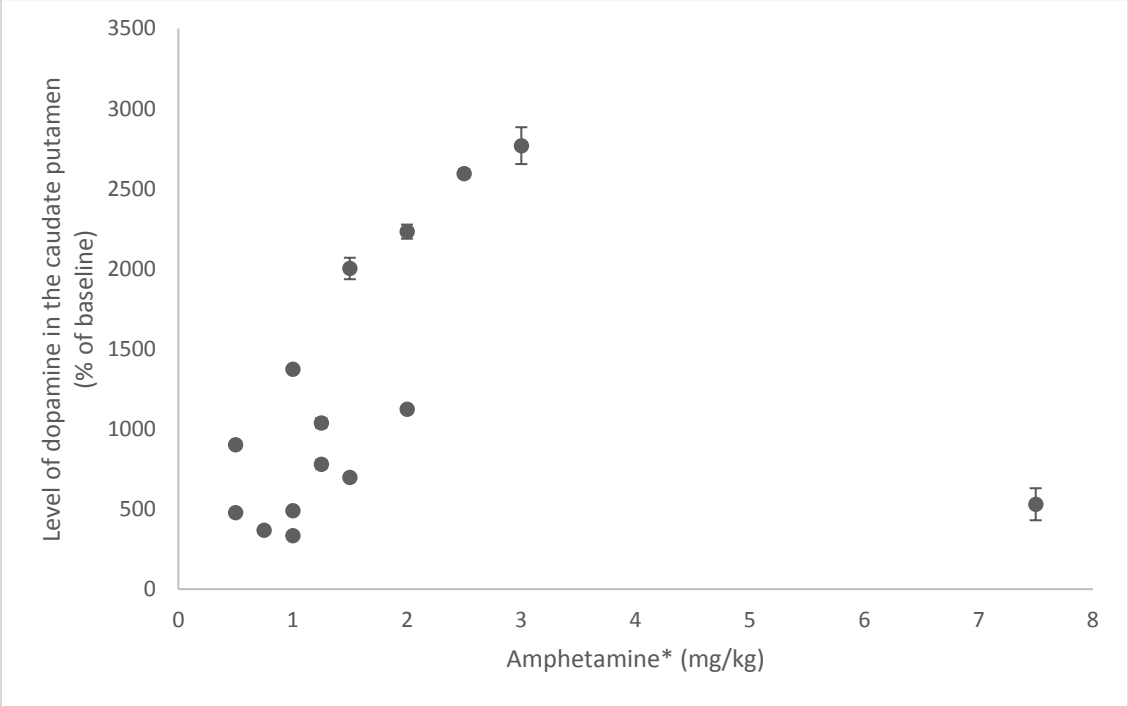


Figure 18: Averages of the dose-dependent effect of d-amphetamine and d+l-amphetamine on dopamine in the caudate putamen (*n = 1175 rats).*

For number of animals per dose, percentages of female rats and significant differences between groups see tables below and in the appendix. R^2 = 0.02, the relationship may not be linear.

**d+l-amphetamine was administered at 0.5 and 2.5 mg/kg; at 1 mg/kg both d+l- and d-amphetamine were administered, d-amphetamine at all other dosages.*

Analogous to the nucleus accumbens, all doses of amphetamine have a strongly enhancing impact on dopaminergic transmission in the caudate putamen. Interestingly, for most of the dosages, no differences between the sexes could be

identified. See table 15 (for reasons of clarity, only those dosages that contained female animals are presented).

Table 15: Peak percentage baseline values in the caudate putamen after different dosages of amphetamine (only dosages that contained female animals are presented)

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	N of rats	n of females (%)	P-value	Critical value (degrees of freedom)
0.5 d+l-amph	477.05 ± 15.24	Male	44	0 (0)	0.001	4.84 (1,11)
	901.02 ± 16.36	Female	49	49 (100)		
0.75	368.95 ± 2.98	-	19	7 (37)	-	-
1.25	780.21 ± 27.59	Male	24	0 (0)	0.039	5.50 (1,7)
	1038.25 ± 30.11	Female	24	24 (100)		
1.5	696.64 ± 4	Awake	192	8.5 (4)	0.010	4.26 (1,24)
	2001.52 ± 68.96	Anesthetized	33	0 (0)		
2	1122.92 ± 4.78	Awake	254	45 (18)	0.004	4.09 (1,40)
	2231.91 ± 44.22	Anesthetized	105	0 (0)		
2.5 d+l-amph	2595 ± 25.56	-	89	49 (55)	-	-
3	2769.21 ± 114.78	-	38	7 (18)	-	-

Two dose groups formed an exception: there were significantly higher values reached in female animals at 0.5 mg/kg ($F(1,11) = 4.84$ and $p = 0.001$) and 1.25 mg/kg ($F(1,7) = 5.5$ and $p = 0.039$), see table 16.

Table 16: Peak percentage baseline values of dopamine in female vs. male rats in the caudate putamen

Dose of administered amphetamine	Peak percentage baseline value	
0.5 mg/kg	Male	477.05 ± 15.24
	Female	901.02 ± 16.36

Dose of administered amphetamine	Peak percentage baseline value	
1.25 mg/kg	Male	780.21 ± 27.59
	Female	1038.25 ± 30.11

Further analysis of modifying factors revealed differences regarding the two enantiomers and the state of consciousness: as mentioned earlier, in most of the experiments and dosages d-amphetamine was used. The dextro-, levoamphetamine racemate was administered at 0.5 and 2.5 mg/kg.

At the dose of 1 mg/kg both, d+l-amphetamine and d-amphetamine were administered. At this concentration d-amphetamine produces, compared to the racemate, a significantly higher peak percentage baseline value of dopamine, $F(1,44) = 4.06$, $p = 0.007$. For the averages of the two types of amphetamine see table 17. Both groups contained only male animals.

Table 17: Peak percentage baseline values of dopamine in the caudate putamen of animals administered with either d-amphetamine or d+l-amphetamine (only male animals)

Administered enantiomer	Peak percentage baseline value after 1 mg/kg of amphetamine
D+l-amphetamine	489.3 ± 3.3
D-amphetamine	1060 ± 6.92

There was as well a significant difference regarding the route of administration of 1 mg/kg in the d-amphetamine subgroup. As this dose contained also only males it is not separately presented here but in the detailed list in the appendix. As already mentioned, only those seven dosages that include female animals are considered and shown from here on.

The data suggest that the dopamine level was higher in anesthetized rats. This is reflected at two dosages: in the 1.5 mg/kg group the freely moving rats had an average peak percentage baseline value of 696.64 ± 4 compared to the anesthetized animals with 2001.52 ± 68.96 (F (1,24) = 4.26, p = 0.010).

Table 18: Peak percentage baseline values of dopamine in anesthetized vs. awake rats in the caudate putamen

Dose of administered amphetamine	**Peak percentage baseline value**	
1.5 mg/kg	Awake	696.64 ± 4
	Anesthetized	2001.52 ± 68.96
2 mg/kg	Awake	1122.92 ± 4.78
	Anesthetized	2231.91 ± 44.22

The same trend showed in the 2 mg/kg amphetamine group: the conscious animals had half of the dopamine peak compared to the average anesthetized rat. 1122.92 ± 4.78 versus 2231.91 ± 44.22, F (1.40) = 4.09, p = 0.004.

For the other variables, no significant differences were found (as shown in table 15). A detailed list with all results, the corresponding references and the averaged peak times is available in the appendix, chapter 7.3.

The forest plot (figure 19) shows the position of the single peak percentage baseline value of each experimental group in relation to the calculated weighted average. All publications that administered 2 mg/kg amphetamine are listed in the chronological sequence of their publication. Row 1 shows the calculated average, the single experiments are presented from row 2 on, each value with its respective standard error of the mean (SEM).

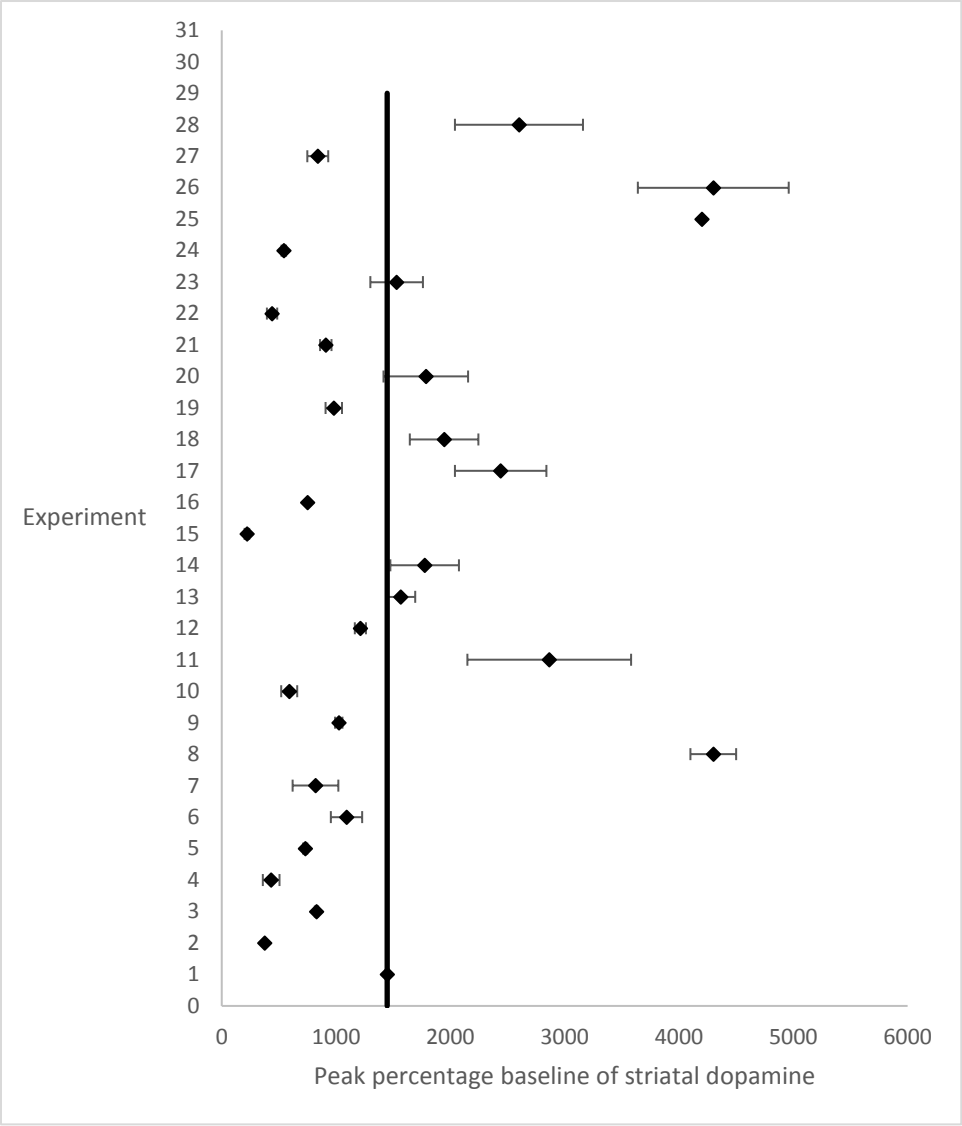


Figure 19: Averaged peak percentage baseline values of 27 publications (row 2 – 28, in chronological order) in relation to their weighted average in row 1 (2 mg/kg amphetamine, n = 359 rats).

The vertical line extends the weighted average. Horizontal lines represent the respective standard error of the mean (SEM). 2 Butcher et al. 1988; 3 Becker et al. 1989; 4 Robinson et al 1991; 5 Robertson et al. 1991; 6 Camp et al. 1992; 7 Yamamoto et al. 1992; 8 Ichikawa et al. 1992; 9 Castner et al. 1993; 10 Di Chiara et al. 1993; 11 Bjelke et al. 1994; 12 Herrera-Marschitz et al. 1994; 13 Loidl et al. 1994; 14 Dietze et al. 1994; 15 Heeringa et al. 1995; 16 Cadoni et al. 1995; 17 Kuczenski et al. 1995; 18 Miller et al. 1996; 19 Badiani et al. 1998; 20 Mc Tavish et al. 1999; 21 Miele et al. 2000; 22 Laviola et al. 2001; 23 Jaworski et al. 2001; 24 Ferguson et al. 2002; 25 Porras et al. 2002; 26 Porras et al. 2002; 27 Ferguson et al. 2003; 28 Kääriäinen et al. 2008. *Publication contained no SEM.*

3.2.3 Cocaine

Overall, the search produced data of female animals (n = 178) out of 14 studies with dosages varying between 1 and 30 mg/kg of cocaine: Chapman, See, & Bissette, 1992; Cummings, Jagannathan, Jackson, & Becker, 2014; Grotewold, Wall, Goodell, Hayter, & Bland, 2014; Holly, Shimamoto, Debold, & Miczek, 2012; Johnson, Eodice, Winterbottom, & Mokler, 2000; Kosten, Zhang, & Kehoe, 2003; Maisonneuve, Archer, & Glick, 1994; Maisonneuve & Glick, 1992; Philpot & Kirstein, 1999; T. E. Robinson & Camp, 1991; Shimamoto, Debold, Holly, & Miczek, 2011; Shimamoto, Holly, Boyson, DeBold, & Miczek, 2015; Szumlinski, McCafferty, Maisonneuve, & Glick, 2000; Tobiansky et al., 2016.
Another 246 studies were collected for male animals, adding up to an overall amount of 260 studies that examined dopamine levels in the striatal complex after cocaine administration.

3.2.3.1 Nucleus accumbens

Cocaine was administered systemically at 33 dosages and at ten dosages locally to 3433 animals in total – including 184 female rats – for measurement in the nucleus accumbens. Some of the systemic administrations were conducted in a continuous manner and are therefore presented separately.

There were six dosages with systemically administered animals of both sexes; the remaining groups contained only males. For local administration, cocaine was administered directly into the nucleus accumbens during simultaneous dopamine detection. All animals that were locally administered were males.
In the following chapter, all dosages (also those including only males) will be analyzed for a dose-response relationship; the analysis with respect to the effect modifiers will be presented afterwards with a special focus on the groups containing female rats.
In general, all doses of cocaine increase accumbal dopamine levels. For the correlation analysis, all dosages with the same unit (mg/kg or mg/kg/h for the systemic, mole for the local administration) were gathered within a separate sheet and analyzed for dose dependency: there was a moderate dose-dependent increase

of dopamine after the systemic administration of cocaine (r = 0.56) but the relationship may not be linear (R^2 = 0.31).

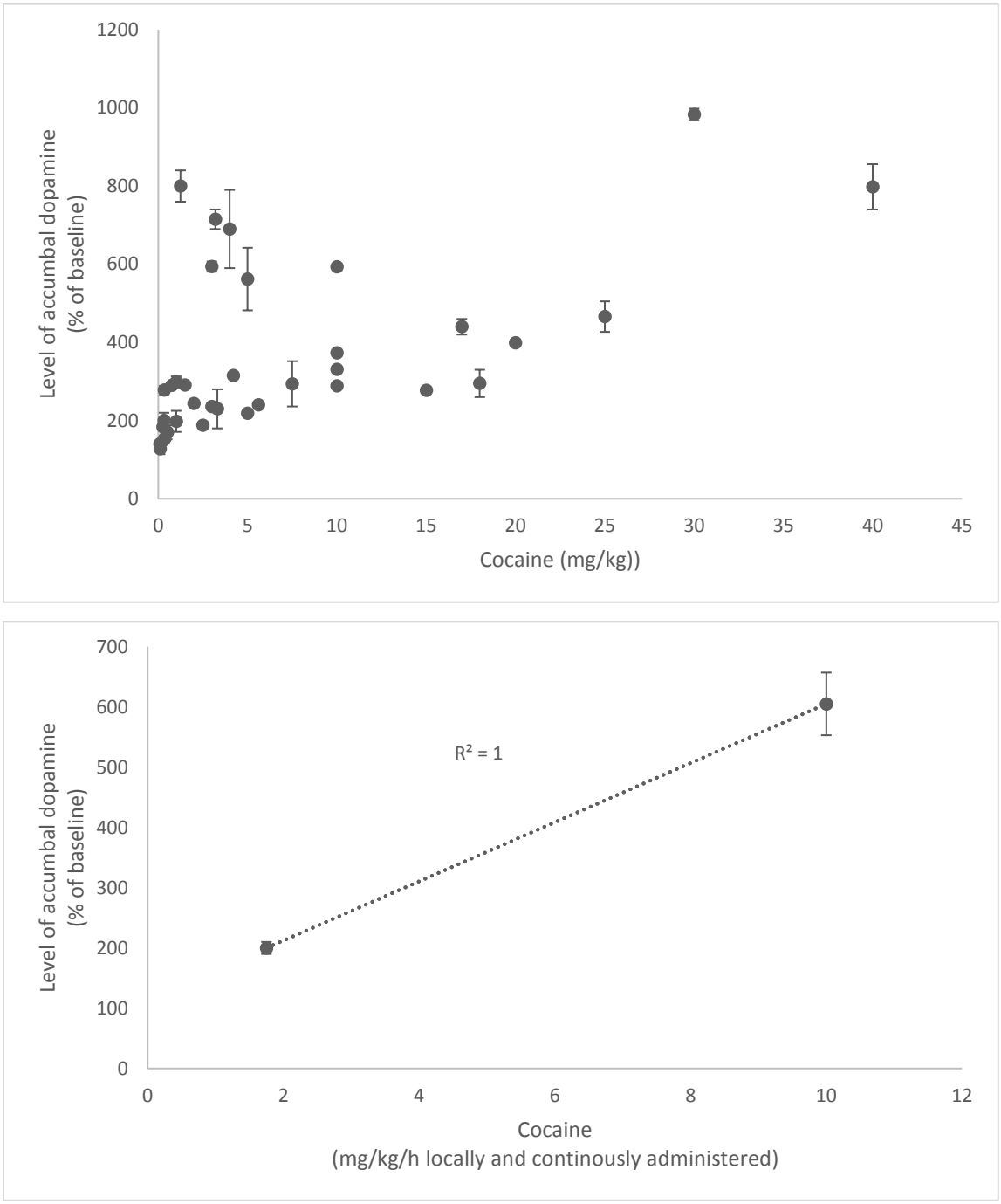


Figure 20a, b: Averages of the dose-dependent effect of systemic administration of cocaine on accumbal dopamine (n = 2702)

<u>Single, acute administration (above):</u> n = 2690 rats. R^2 = 0.31, the relationship may not be linear.

<u>Continuous perfusion (below):</u> n = 12 rats. R^2 = 1, the relationship is linear.

For number of animals per dose, percentages of female rats and significant differences between groups see tables below and the detailed table in the appendix.

When cocaine was continuously perfused, there was a strongly positive correlation with r = 1. See figure 20a, b. The correlation analysis for the locally administrated groups showed no (r = 0.21) linear relationship, see figure 21. Assembling the results of the correlation analyses, a dose-response relationship for continuously perfused, but not for systemically, or locally administered cocaine was found.

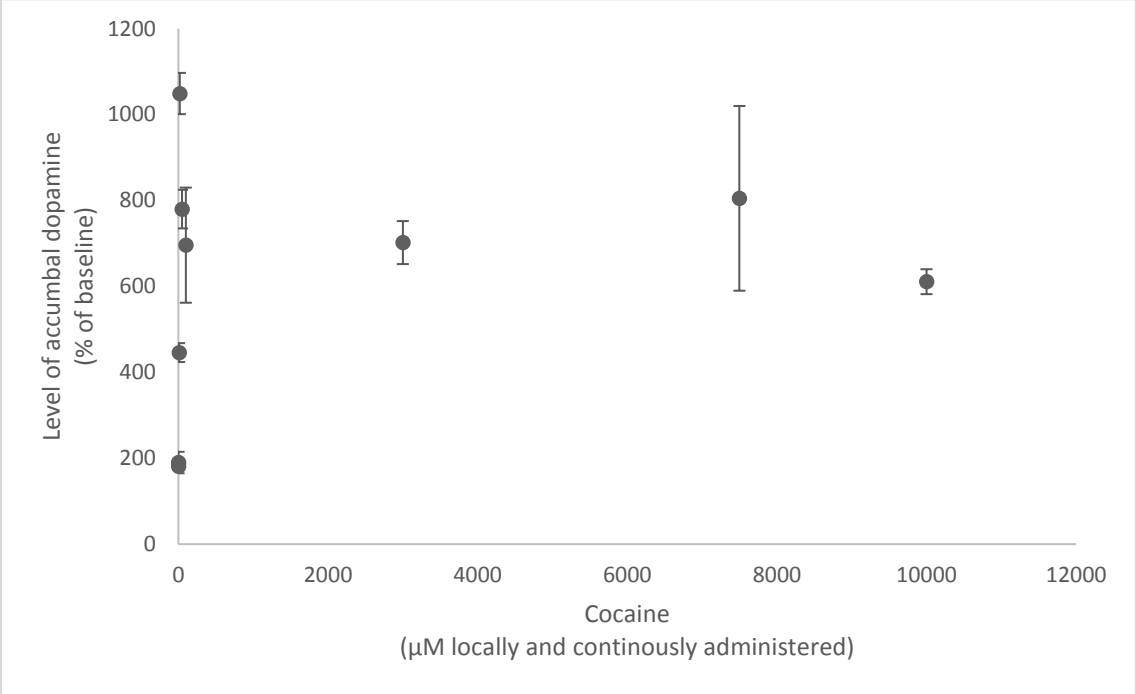


Figure 21: Averages of the dose-dependent effect of locally (nucleus accumbens) administered cocaine on accumbal dopamine (n = 155 rats, only male animals)

Animals perfused locally with fluid containing a defined amount of cocaine (in mole). R^2 = 0.04, the relationship may not be linear.

For reasons of clarity, only the six dosages that include female animals are presented from here on. For the complete results including the significant differences between male animals, the corresponding references and peak times of all results see tables in the appendix, chapter 7.4.

The animals' sex had no significant impact on the cocaine-induced dopamine alterations in the nucleus accumbens, whatsoever. Neither had the strain any effect. Differences were found regarding the animals' consciousness (at 1 and 10 mg/kg), the animals age (as well at 10mg/kg) and the route of administration (at 5 mg/kg).

The data show significant differences for the state of consciousness: at 1 mg/kg ($F(1,18) = 4.41$, $p = 0.003$) and 10 mg/kg ($F(12,79) = 3.95$, $p = 0.000$): The anesthetized animals had a higher peak percentage baseline value than those that were awake during the experiment. See table 19.

Table 19: Peak percentage baseline values of dopamine in anesthetized vs. conscious rats in the nucleus accumbens

Dose of administered cocaine	**Peak percentage baseline value**	
1 mg/kg	awake	198.25 ± 26.98
	anesthetized	299.45 ± 13.94
10 mg/kg	awake	330.72 ± 0.16
	anesthetized	593.26 ± 5.92

Table 20: Peak percentage baseline values of dopamine in adolescent vs. adult rats in the nucleus accumbens

Age	**Peak percentage baseline value after 10 mg/kg of cocaine**
Adolescent	289.33 ± 2.2
Adult	372.53 ± 0.21

In the same dose group (also at 10mg/kg), there was a significant difference regarding the rats' age, even though it was not as highly significant as the difference between awake and anesthetized rats: adult animals had a higher peak percentage baseline value than adolescent rats. $F(1,116) = 3.92$, $p= 0.027$. See table 20.

There was a significant difference regarding the route of administration at 5 mg/kg: the intraperitoneal/subcutaneous group had a lower peak than the intravenous group. F (2,36) = 3.26, p = 0.005, see table 21.

Table 21: Peak percentage baseline values of dopamine in intraperitoneally/subcutaneously vs. intravenously administered rats in the nucleus accumbens

Route of administration	Peak percentage baseline value after 5 mg/kg of cocaine
i.p./s.c.	218.69 ± 0.44
i.v.	562 ± 79.87

No other significances were found in the groups that included female animals. For further details see table 22 and the detailed list in the appendix for the groups with male subjects only.

Table 22: Peak percentage baseline values in the nucleus accumbens after different dosages of cocaine

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	N of rats	n of females (%)	P-value	Critical value (degrees of freedom)
1	198.25 ± 26.98	Awake	85	4 (5)	0.003	4.41 (1,18)
	299.45 ± 13.94	Anesthetized	29	0 (0)		
2	244.03 ± 6.02	-	36	7 (19)	-	-
2.5	187.5 ± 3.75	-	12	6 (50)	-	-
5	218.69 ± 0.44	i.p. + s.c.	252	6 (2)	0.005	3.26 (2,36)
	562 ± 79.87	i.v.	18	0 (0)		
10	330.72 ± 0.16	Awake	736	52 (7)	0.000	3.95 (12,79)
	593.26 ± 5.92	Anesthetized	90	0 (0)		
	289.33 ± 2.2	Adoles	70	6 (9)	0.027	3.92

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	N of rats	n of females (%)	P-value	Critical value (degrees of freedom)
		cent				(1,116)
	372.53 ± 0.21	Adult	713	76 (11)		
20	399.13 ± 0.63	-	416	18 (4)	-	-

Forest plots were created for those dosages that included a total amount of 250 animals or more. This was the case regarding three different doses of cocaine.
The following figures show the position of the single peak percentage baseline value of each publication in relation to the calculated weighted average. Figure 22 contains all experiments that administered 5 mg/kg cocaine. For the publications that administered 10 or 20 mg/kg cocaine see figure 23 or figure 24 respectively.

Row 1 shows the calculated average, the single experiments are presented from row 2 on, each with its respective standard error of the mean (SEM). The publications are listed in the chronological sequence of their appearance, respectively.

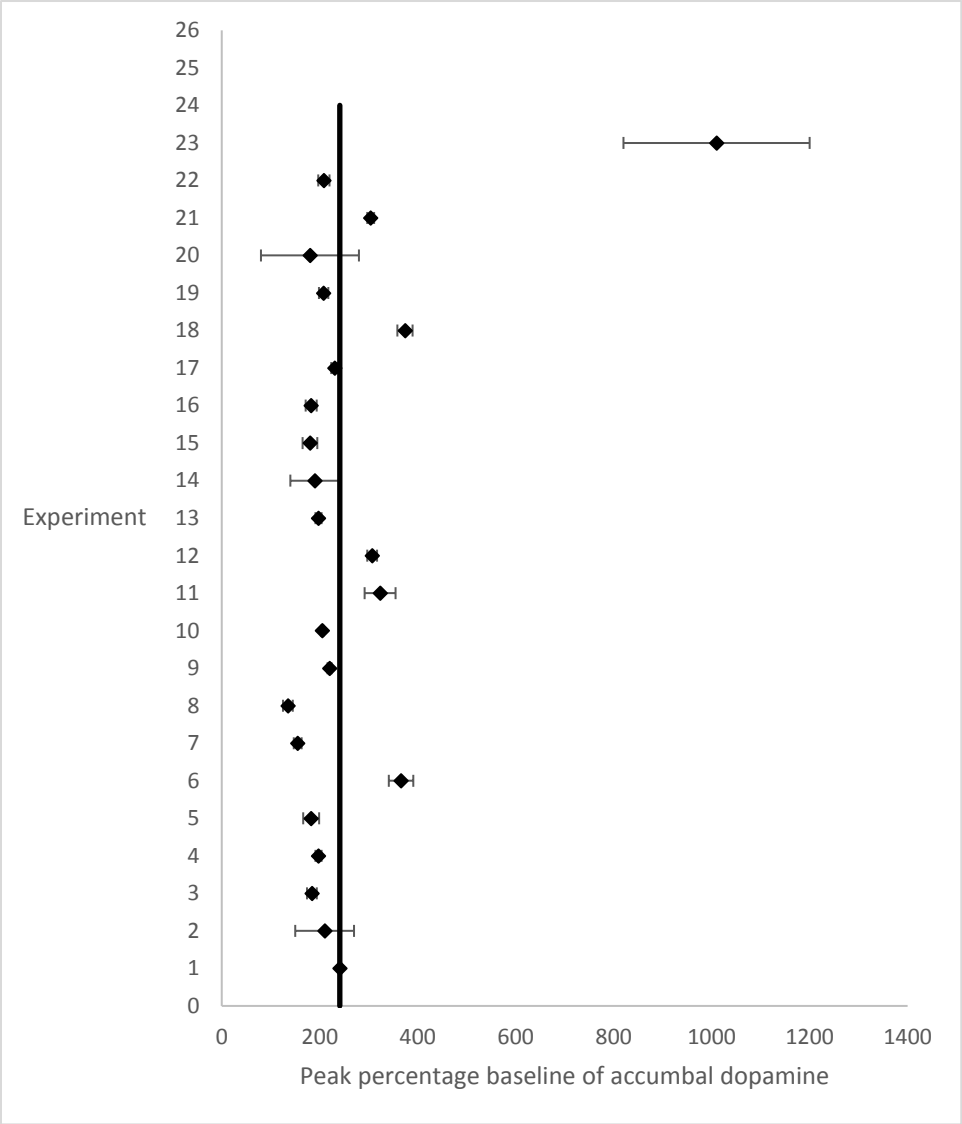


Figure 22: Averages of the peak percentage baseline values of 22 publications (row 2 – 23, in chronological order) in relation to their weighted average in row 1 (5 mg/kg cocaine, n = 270 rats).

The vertical line extends the weighted average. Horizontal lines represent the respective standard error of the mean (SEM). 2 Carboni et al. 1989; 3 Brown et al. 1991; 4 Camp et al 1994; 5 Giorgi et al. 1997; 6 Koch et al. 1997; 7 Parsons et al. 1998; 8 Gambarana et al. 1999; 9 Gambarana et al. 1999; 10 Cadoni et al. 2000; 11 Mangiavacchi et al. 2001; 12 Masi et al. 2001; 13 Mikkola et al. 2001; 14 Steketee et al. 2002; 15 Cadoni et al. 2003; 16 Kosten et al. 2003; 17 Leggio et al. 2003; 18 Nanni et al. 2003; 19 Lecca et al. 2004; 20 Kosten et al. 2005; 21 Raje et al. 2005; 22 Cadoni et al. 2007; 23 Othman et al. 2007.

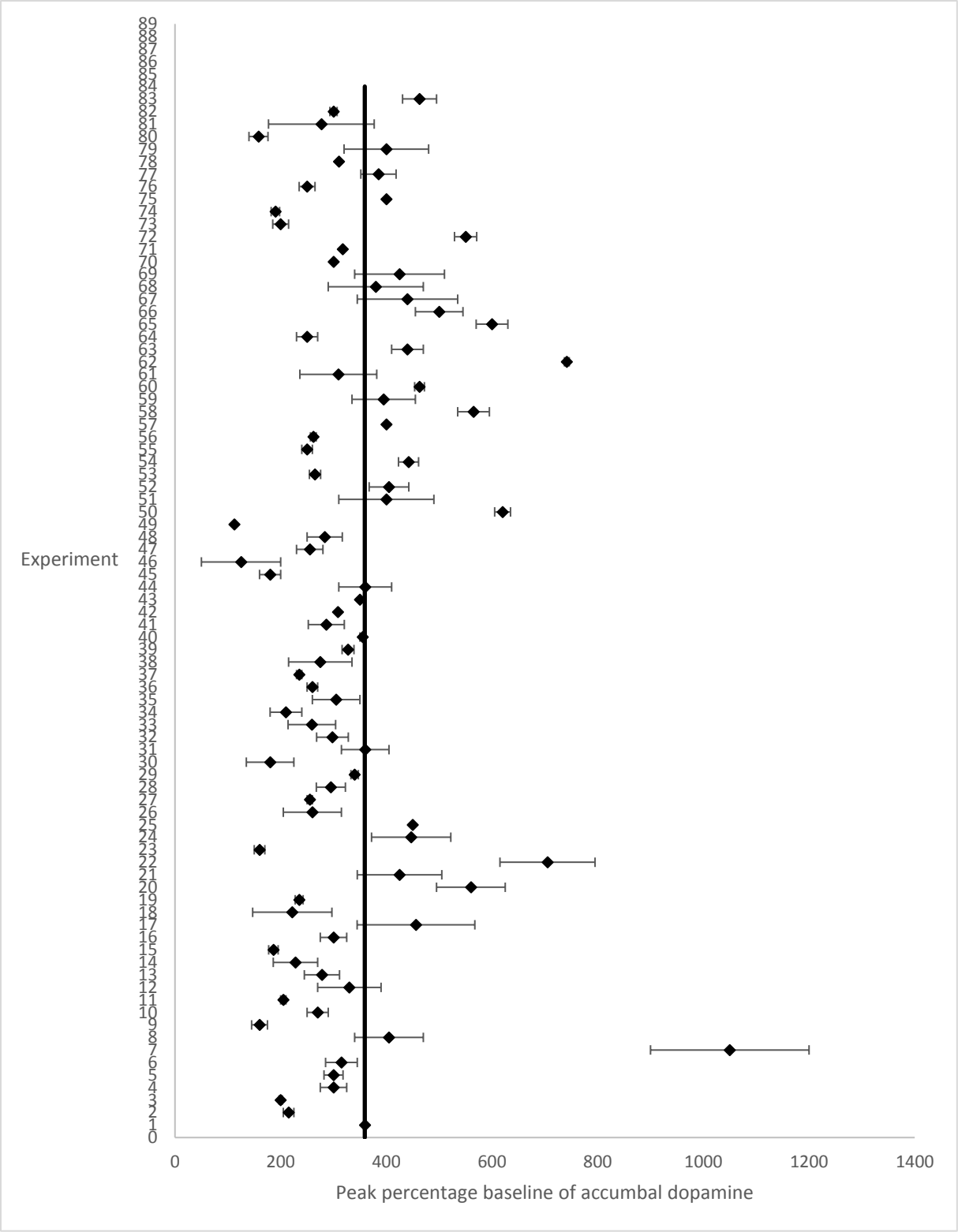


Figure 23: Averages of the peak percentage baseline values of 82 publications (row 2 – 83, in chronological order) in relation to their weighted average in row 1 (10 mg/kg cocaine, n = 825 rats).

The vertical line extends the weighted average. Horizontal lines represent the respective standard error of the mean (SEM). References are to find on the next page.

2 Pani et al. 1990; 3 Pani et al. 1990; 4 Hoger et al 1991; 5 Brown et al. 1992; 6 Rosetti et al. 1992; 7 Segal et al. 1992; 8 Weiss et al. 1992; 9 Fontana et al. 1993; 10 Kimura et al. 1993; 11 Parsons et al. 1993; 12 Essman et al 1994; 13 Maisonneuve et al. 1994; 14 Nation et al. 1994; 15 Camp et al. 1994; 16 Maisonneuve et al. 1995; 17 Pap et al. 1995; 18 Rouge-Pont et al. 1995; 19 Strecker et al. 1995; 20 Cervo et al 1996; 21 Clark et al. 1996; 22 Kankaanpaa et al. 1996; 23 Martin-Fardon et al. 1996; 24 Neisewander et al. 1996; 25 Shimda et al. 1996; 26 Willins et al. 1998; 27 Parsons et al. 1998; 28 Cadoni et al. 1999; 29 Parsons et al. 1999; 30 Tolliver et al. 1999; 31 Cadoni et al. 2000; 32 Johnson et al. 2000; 33 Lutfy et al. 2001; 34 Alvarez Fischer et al. 2001; 35 Andrews et al. 2001; 36 Mikkola et al. 2001; 37 Muller et al. 2002; 38 Steketee et al. 2002; 39 Kosten et al. 2003; 40 Bubar et al. 2003; 41 Cadoni et al. 2003; 42 Mc Farland et al. 2003; 43 Navailles et al. 2004; 44 O'Dell et al. 2004; 45 De Deurwaerdere et al. 2005; 46 Kosten et al. 2005; 47 Lodge et al. 2005; 48 Tanda et al. 2005; 49 Valdomero et al. 2005; 50 Caille et al. 2006; 51 Izawa et al. 2006; 52 Jocham et al. 2006; 53 Cadoni et al. 2007; 54 Jocham et al. 2007; 55 Leri et al. 2007; 56 Tanda et al. 2007; 57 Xi et al. 2007*; 58 Navailles et al. 2008; 59 Peng et al. 2008; 60 Peng et al. 2008; 61 Nelson et al. 2009; 62 Leggio et al. 2009; 63 Espana et al. 2010; 64 Panos et al. 2010; 65 Xi et al. 2010; 66 Xi et al. 2010; 67 Espana et al. 2011; 68 Miczek et al. 2011; 69 Shimamoto et al. 2011; 70 Devoto et al. 2012; 71 Holly et al. 2012; 72 Pan et al. 2012; 73 Tanda et al. 2013; 74 Thongsaard et al. 2013; 75 Devoto et al. 2014; 76 Boyson et al. 2014; 77 Cummings et al. 2014; 78 Kohut et al. 2014; 79 Verheij et al. 2014; 80 Ogbonmwan et al. 2015; 81 Shimamoto et al. 2015; 82 Tanda et al. 2016; 83 Tobiansky et al. 2016. *Two publications contained no SEMs.*

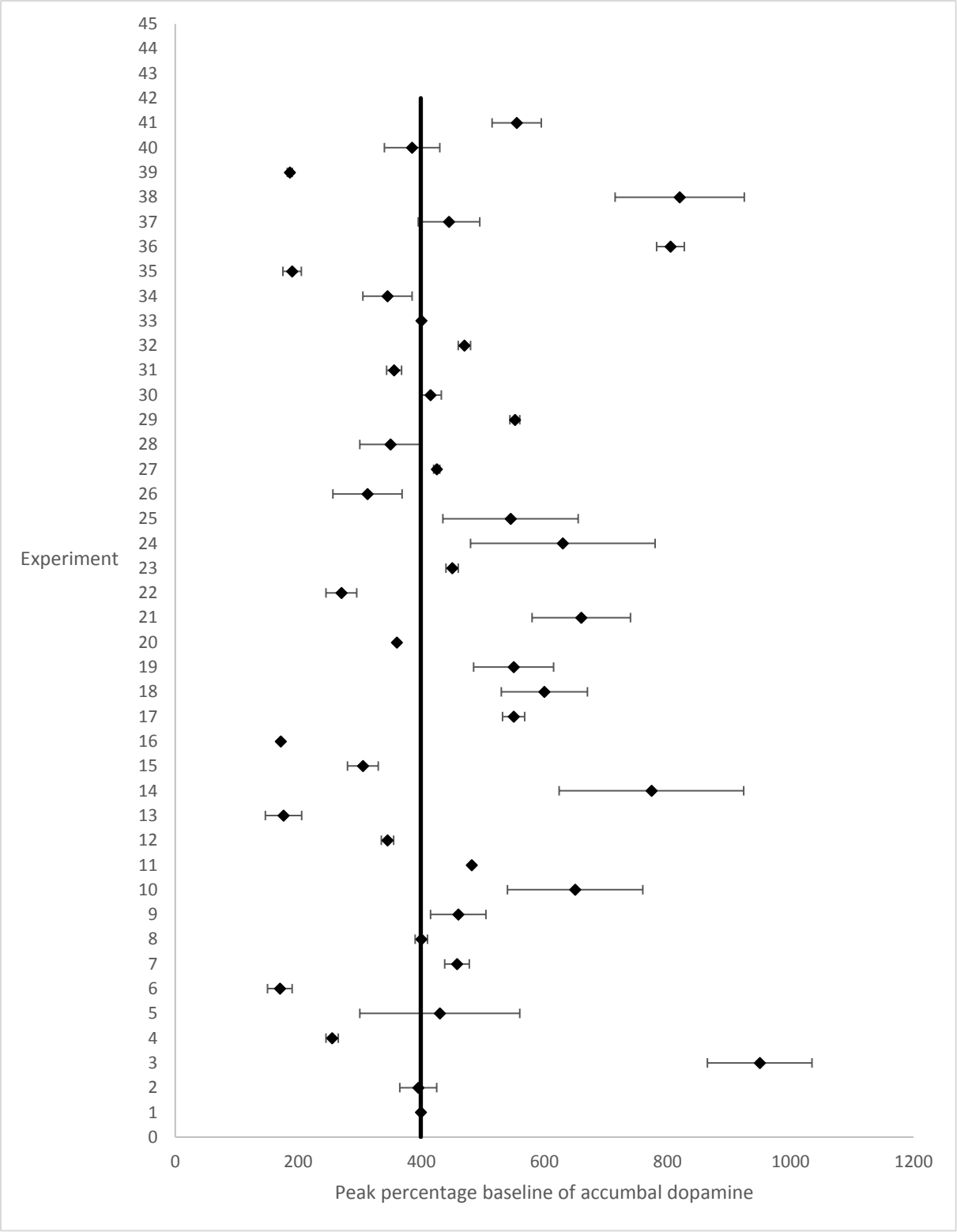


Figure 24: Averages of the peak percentage baseline values of 40 publications (row 2 – 41, in chronological order) in relation to their weighted average in row 1 (20 mg/kg cocaine, n = 416 rats).

The vertical line extends the weighted average. Horizontal lines represent the respective standard error of the mean (SEM). References are to find on the next page.

2 Maisonneuve et al. 1992; 3 Maisonneuve et al. 1994; 4 Chen et al 1996; 5 Heidbreder et al. 1996; 6 Martin-Fardon et al. 1996; 7 Morgan et al. 1997; 8 Morgan et al. 1997; 9 Reith et al. 1997; 10 Heidbreder et al.1998; 11 Morgan et al. 1998; 12 Parsons et al. 1998; 13 Hedou et al. 1999; 14 Kuczenski et al. 1999; 15 Philpot et al. 1999; 16 Ferraro et al. 2000; 17 Gerasimov et al. 2000; 18 Szumlinski et al. 2000; 19 Schiffer et al. 2000; 20 Martin-Fardon et al. 2001; 21 Molina et al. 2001; 22 Chefer et al. 2002; 23 Gerasimov et al. 2002; 24 Kankaanpaa et al. 2002; 25 Steketee et al. 2002; 26 Chefer et al. 2003; 27 Leri et al. 2003; 28 Schiffer et al. 2003; 29 Schiffer et al. 2003; 30 De Deurwaerdere et al. 2005; 31 Cadoni et al. 2007; 32 Frantz et al. 2007; 33 Leri et al. 2007; 34 Jang et al. 2008; 35 Mc Dougall et al. 2008; 36 Kurling-Kailanto et al. 2010; 37 Panos et al. 2010; 38 Kailanto et al. 2011; 39 Puig et al. 2012; 40 Vazquez-DeRose et al. 2013; 41 Tanda et al. 2016. *Publication contained no SEM.*

3.2.3.2 Caudate putamen

In total 20 different dosages of cocaine (13 systemically and 7 locally administered) were included that took measurements in the caudate putamen of 858 animals. All in all, 44 animals were female.

In the experiments with local administration, cocaine was perfused directly into the caudate putamen during concurrent dopamine detection. Only in one experimental group at the dose of 1000 µM the drug was perfused into the substantia nigra.
Three of the 13 systemic dosages contained female subjects, the remaining groups consisted of males. All locally administered animals were also male rats. In those groups no comparison between the sexes could be conducted.

All doses of cocaine increased the level of dopamine in the caudate putamen, in analogy to the nucleus accumbens. For the correlation analyses, all animals that received corresponding dosages – meaning that they were given in the same unit – were considered: there is neither a dose-dependent effect of systemically administered cocaine ($r = 0.22$), nor for local administration ($r = 0.30$). See figure 25a, b. In summary, no dose-response relationship was identified for the dopaminergic transmission in the caudate putamen, whatsoever.

For clarity reasons, the following presentation of the significant results is focused on the mixed-sex groups. There were 17 groups that contained only male subjects that will not be further mentioned. The complete results for all dosages can be found in the appendix in chapter 7.4.

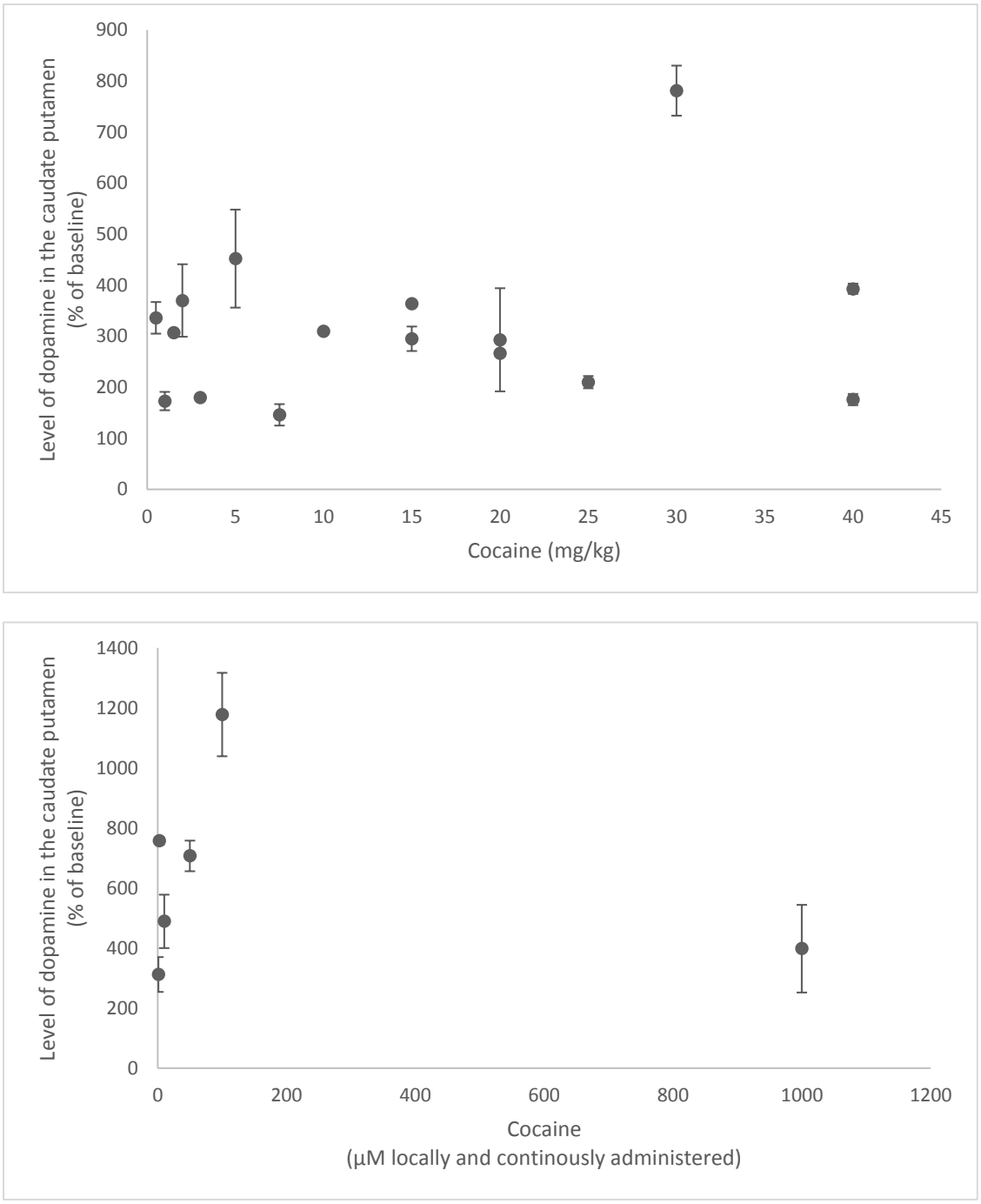


Figure 25a, b: Averages of the dose-dependent effect of cocaine on dopamine in the caudate putamen (n = 704 rats)

<u>Systemic administration (above):</u> (n = 635 rats). R^2 = 0.05, the relationship may not be linear. <u>Local administration (below):</u> (n = 69 rats), all administered via the caudate putamen, except for one experiment at the 1000 µM group that administered cocaine into the substantia nigra. For number of animals per dose, percentages of female rats and significant differences between groups see tables below. R^2 = 0.09, the relationship may not be linear.

Analogous to the other drugs studied, dopaminergic response to cocaine was examined with respect to the animals' sex. There is only a limited number of studies on cocaine-induced effects on the caudate putamen. Nevertheless, there were significant differences for one dose group only: male animals had a significantly higher dopamine value at 15 mg/kg cocaine than females (table 23). F (1,8) = 5.32, p = 0.009.

Table 23: Peak percentage baseline values of dopamine in female vs. male rats in the caudate putamen

Sex	Peak percentage baseline value after 15 mg/kg cocaine
Female	295.22 ± 24.06
Male	364.21 ± 3.03

Table 24: Peak percentage baseline values in the caudate putamen after different dosages of cocaine

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	N of rats	n of females (%)	P-value	Critical value (degrees of freedom)
10	309.89 ± 0.89	-	213	22 (10)	-	-
15	295.22 ± 24.06	Female	9	9 (100)	0.009	5.32 (1,8)
	364.21 ± 3.03	Male	57	0 (0)		
20	267.14 ± 1.56	Other strains	122	6 (5)	0.008	4.35 (3,18)
	392.5 ± 101.25	Long Evans	24	0 (0)		

Regarding the other effect modifiers, no significant differences were detected, except for the rats' strain: at 20 mg/kg ANOVA showed a higher peak percentage baseline value in Long Evans. F (3,18) = 4.35, p = 0.008. See table 25.

Table 25: Peak percentage baseline values of dopamine in female vs. male rats in the caudate putamen

**Sprague-Dawley, Wistar and spontaneously hypertensive rats*

Strain	Peak percentage baseline value after 20 mg/kg cocaine
Other strains*	267.14 ± 1.56
Long Evans	392.5 ± 101.25

3.2.4 Morphine

The online search led to data of 102 female rats, provided by 5 original publications. Another 16 studies were included from Gruhlke et al., leading to an overall amount of 21 publications with measurements in the striatal complex after acute morphine administration: Borg & Taylor, 1997; Cadoni & Di Chiara, 2007; Di Giannuario, Pieretti, Catalani, & Loizzo, 1999; Fadda, Scherma, Fresu, Collu, & Fratta, 2003; Johnson & Glick, 1993, 1994; Jonsson, Adermark, Ericson, & Soderpalm, 2014; M. R. Kim et al., 2005; Maisonneuve & Glick, 1999; Maisonneuve, Keller, & Glick, 1991; Pearl, Maisonneuve, & Glick, 1996; Pothos et al., 1991; E. N. Pothos, Creese, & Hoebel, 1995; Pozzi, Trabace, Invernizzi, & Samanin, 1995; Rada, Mark, Pothos, & Hoebel, 1991; Steinmiller, Maisonneuve, & Glick, 2003; Sustkova-Fiserova, Jerabek, Havlickova, Kacer, & Krsiak, 2014; Szumlinski, Maisonneuve, & Glick, 2000; Tanda & Di Chiara, 1998; Willins & Meltzer, 1998; Yong et al., 2012.

In this passage, the results for both brain regions will be presented together.
Regarding the nucleus accumbens, three different dosages (5, 20 and 30 mg/kg) of morphine were administered, with a total amount of 229 animals, including 77 female rats. Some of the animals had concurrent measurements in both brain regions.
Concerning the caudate putamen, only two dosages (5 and 30 mg/kg), which included 62 animals (54 females), were administered.
There were no studies with local administration.

At the dosage of 30 mg/kg, only female rats were present – for both brain regions. The other two dosages contained animals of both sexes and therefor made a comparison between females and males possible.

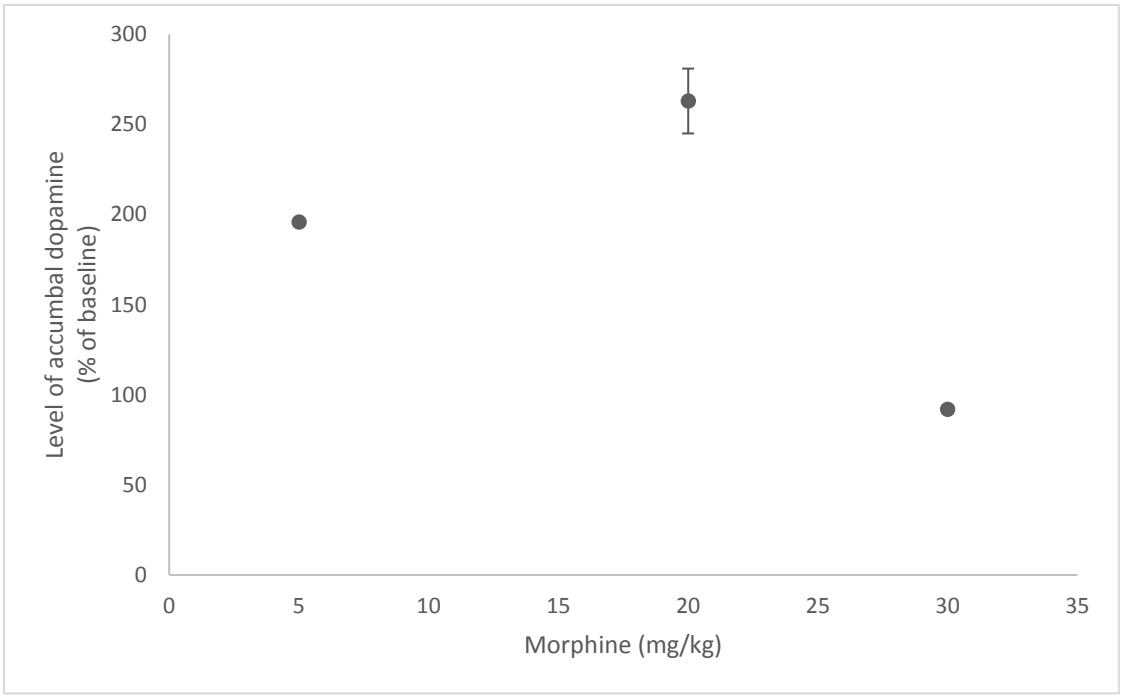
At the dose of 5 mg/kg, dopamine levels in both brain regions were increased. Moreover, also the 20 mg/kg dose led to an enhancement in the nucleus accumbens. There were no sex differences regarding the peak percentage baseline levels of dopamine at these dosages, see table 26.

Table 26: Peak percentage baseline values of striatal dopamine after different dosages of morphine, NAc above, CPu below the grey line

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	N of rats	n of females (%)	P-value	Critical value (degrees of freedom)
5	195.09 ± 0.73	-	138	23 (17)	-	-
20	262.49 ± 17.48	-	55	18 (33)	-	-
30	92 ± 1.6	-	30	30 (100)	-	-
5	165.46 ± 2.87	-	26	18 (58)	-	-
30	92 ± 1.6	-	30	30 (100)	-	-

Surprisingly, at the highest dosage of 30 mg/kg, there was a reduction of dopamine to about 90% of the baseline concentration of both brain regions. The data for both groups came from the same three studies (Johnson & Glick, 1993, 1994; Maisonneuve, Keller, & Glick, 1991). Regarding the low number of studies in these dose groups, more data is needed for a reliable conclusion.

Consequently, the correlation analyses showed no positive dose-response relationship for neither brain region: in the nucleus accumbens, the highest dose of 30 mg/kg produced the lowest average peak percentage baseline and there was no dose-dependent effect, whatsoever (r = -0.51).
In the caudate putamen there was a negative dose-dependent correlation (r = -1). See figure 26a and b for a graphical representation and for the respective references and peak time see chapter 7.5 in the appendix.



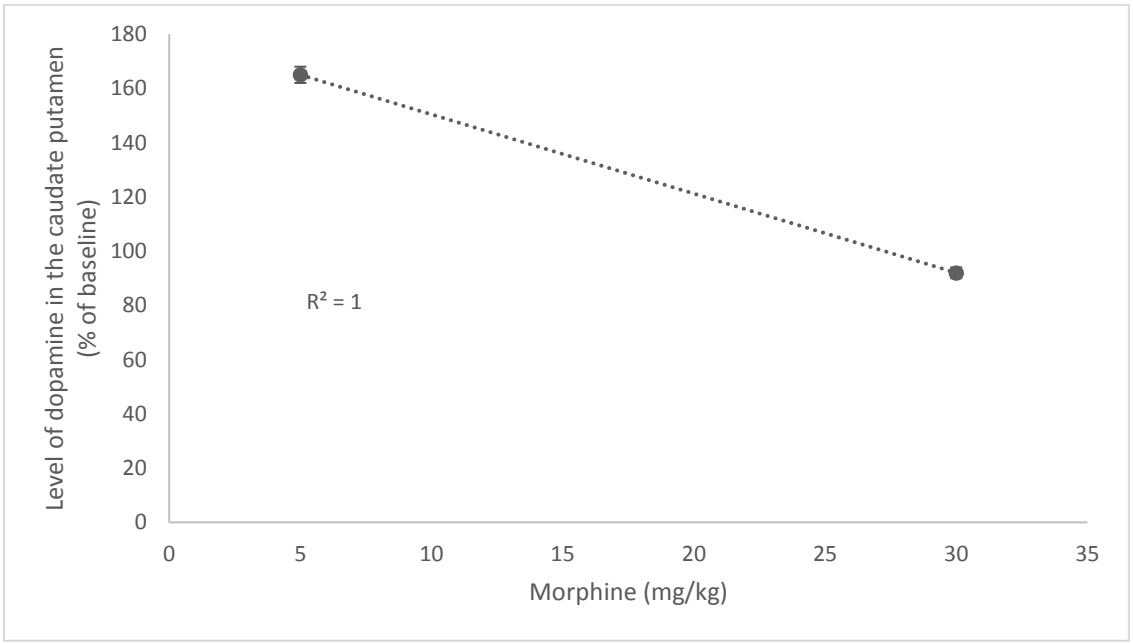


Figure 26a, b: Averages of the dose-dependent effect of morphine on striatal dopamine (n = 291 rats)

<u>NAc above:</u> n = 229 animals. R^2 = 0.26, the relationship may not be linear.

CPu <u>below:</u> n = 62 animals. There is a linear relationship, R^2 = 1.

For number of animals per dose and percentages of female rats see table above

3.2.5 Nicotine

There was only data for measurement in the nucleus accumbens of 48 female rats, obtained by six studies. Another 15 studies have been provided by Staudenmaier et al., adding up to 21 included studies in total: Balfour, Birrell, Moran, & Benwell, 1996; Bassareo, De Luca, & Di Chiara, 2007; Benwell, Balfour, & Birrell, 1995; Birrell & Balfour, 1998; Cadoni & Di Chiara, 2000; Cadoni, Muto, & Di Chiara, 2009; Cadoni, Solinas, Valentini, & Di Chiara, 2003; Carboni, Silvagni, Rolando, & Di Chiara, 2000; Dewey et al., 1999; Ding et al., 2012; Eggan & McCallum, 2016, 2017; Ferrari, Le Novere, Picciotto, Changeux, & Zoli, 2002; Iyaniwura, Wright, & Balfour, 2001; Jonsson, Adermark, Ericson, & Soderpalm, 2014; Maisonneuve & Glick, 1999; McCallum, Cowe, Lewis, & Glick, 2012; Mirza, Pei, Stolerman, & Zetterstrom, 1996; Shoaib & Shippenberg, 1996; Steinmiller, Maisonneuve, & Glick, 2003; Wang et al., 2015.

Nicotine was administered at 0.4 mg/kg systemically, and locally at 200 µM to a total amount of 190 animals. For local administration nicotine was perfused directly into the posterior ventral tegmental area. There were no male rats found that were administered locally. Therefore, the data allowed no comparison in this group. In the bigger 0.4 mg/kg group, both sexes were present, and therefore a male-female comparison was possible.

Table 27: Peak percentage baseline values in the nucleus accumbens after different dosages of nicotine

Dose (mg/kg)	Peak% BL (weighted average) ± SEM	Sub group	n of rats	n of females (%)	P-value	Critical value (degrees of freedom)
0.4	157.73 ± 0.36	-	175	32.5 (19)	-	-
200 µM	125 ± 15	-	9	9 (100)	-	-

At a dose of 0.4mg/kg, systemically administered nicotine increased dopamine levels without any difference between male and female animals. In analogy to the systemic administration, locally administered nicotine also enhanced dopamine transmission in

the nucleus accumbens. See table 27 and chapter 7.6 in the appendix for the corresponding references and peak times.

As the results provided only one dose for systemic and one for local administration, the dose-dependent effect of nicotine could not be studied through a correlation analysis.

4 DISCUSSION

In this section, the results are interpreted in the order they were presented earlier and put in the context of previous findings. Moreover, some limitations of this thesis, a conclusion and a short outlook are given.

In recent years, the topic of sex differences has rightfully become a focus of scientific research (Bangasser & Valentino, 2014; Bobzean et al., 2014; Kaczkurkin, Raznahan, & Satterthwaite, 2019; Rubinow & Schmidt, 2019) and current findings suggest sexual dimorphisms in the neurophysiological brain pathways that are crucial for drug intake and addictive behavior (Becker & Chartoff, 2018). ‘Yet, how potential sex differences are manifested at a neurochemical level remains unclear’ (Egenrieder et al., 2020).
Nevertheless, female subjects have been systemically ignored for decades in the field of microdialysis experiments and therefore, most of the studies using female animals provide only small numbers. Moreover, there is increasing evidence that single preclinical studies often lack reproducibility (Arrowsmith, 2011; Begley & Ioannidis, 2015; Peers et al., 2012; Prinz et al., 2011). Therefore, this thesis used a hypothesis-free meta-analysis approach that provides adequate statistical power for this subject area.

Microdialysis is a well-established method to detect neurotransmitter concentrations in rats. Although it has existed for several decades there are neither standardized procedures nor generally accepted basal values.
Therefore, the main aim of this meta-analysis was to screen the online library PubMed for microdialysis experiments with female rats, in order to analyze whether the data indicate a difference in the dopaminergic overflow in reaction to drugs of abuse in male and female rats. The search query focused on studies containing the acute administration of alcohol, amphetamine, cocaine, morphine or nicotine (and tetrahydrocannabinol), and the following detection of dopamine (DA) in the striatal complex – that is the nucleus accumbens (NAc) and the caudate putamen (CPu).

Hence, this thesis provides a wide overview of the distribution of female rats in microdialysis studies in the field of addiction research. Additionally, it presents a variety of averages of the peak percentage baseline value of striatal dopamine after the acute administration of five different drugs of abuse for both, male and female rats. It therefore offers a universal framework for preclinical experimental designs.

4.1 Global statistics: included animals and microdialysis settings

The included experiments were analyzed globally: the main part of the distribution of the rats' properties was similar to previous meta-analyses by the work group. Regarding the animals' sex, the share of female rats was relatively low, even though the specific aim of this thesis was to find datasets of females: 11.6% (n = 842) of the animals were female. But, as expected, this sex gap was smaller than in previous meta-analyses on microdialysis studies that did not put their focus on female animals (Fliegel et al., 2013; Fritze et al., 2017; Noori, Fliegel, et al., 2012).
Overall, this thesis provides the peak percentage baseline values of DA of 7244 rats out of 459 publications and 103 different administered dosages of the five drugs of abuse. Some of the dosages of administered cocaine and amphetamine did not contain females at all. Some other dosages (3 g/kg alcohol, all local dosages of alcohol, morphine at 30 mg/kg in the nucleus accumbens and the caudate putamen and nicotine, locally administered) did only contain females and therefore allowed no comparison.

Regarding the other properties of the included animals, the preponderance of Sprague-Dawley is consistent with other meta-analyses on microdialysis experiments (Fliegel et al., 2013; Frank et al., 2008; Fritze et al., 2017; Noori, Fliegel, et al., 2012). Also, the fact that most of the included animals were adult (Fritze et al., 2017), administered via the peritoneum (Fliegel et al., 2013; Frank et al., 2008; Fritze et al., 2017) and awake (Fliegel et al., 2013; Fritze et al., 2017) is concordant with other authors.

There is a variety of different settings for a microdialysis experiment. The distribution found in this study is also mostly consistent with the findings of previous analyses (Fliegel et al., 2013; Frank et al., 2008; Fritze et al., 2017; Noori, Fliegel, et al., 2012).

In conclusion, this means that even though there are no standardized procedures for microdialysis experiments yet, at least the sum of the single settings of the studies is quite similar in different meta-analyses. Therefore, comparability is given and the concept of this work to combine the obtained results with data of other meta-analyses seems to be reasonable.

4.2 Comparison of the level of dopamine

For the further analysis of the dopamine levels regarding the animals' sex, one-way ANOVA was conducted on the different dosages of the five drugs of abuse.

Overall, no sex differences were found regarding the variety of drugs and doses, except for some single dosages. Females had higher levels of DA at two dosages of amphetamine in the CPu and at one dose of ethanol in the NAc. For one dose of cocaine an opposing tendency was found in the CPu. Analyzing all other drugs and dosages, there were no significant differences in the dopamine overflow of males and females, whatsoever.

Interestingly, further calculations in the published paper on this thesis (Egenrieder et al., 2020), that included also the basal values of dopamine, showed that 'the most critical effect modifier was ovariectomy (OVX)'. Hence, as female rats are often ovariectomized and 'OVX leads to a significant reduction of basal DA levels in caudate putamen but not in nucleus accumbens' (Egenrieder et al., 2020) this may be one explanation for previous results suggesting sex differences in CPu.

Thereby, as stated in the paper 'consequently, a procedure such as OVX that leads to a significant change in basal levels in comparison to non-ovariectomized females will affect all following pharmacological manipulations. Therefore, statistical tests of drug response in OVX and male rats are objectively not optimal to address sex differences, even when a hormonal pre-treatment was applied' (Egenrieder et al., 2020).

In this thesis, 20% of the studies that included female animals described the subjects explicitly as ovariectomized. Another 62% did not mention the hormonal state of the subjects at all, indicating that some of those may as well have been OVX. Only in five experiments (equaling 18% of all included studies with females) the estrous cycle was mentioned, and the exact state was only given in one study, which equals 2% of

the included studies. Therefore, the dataset of this thesis did not provide sufficient data for a further analysis of the impact of the females' cycle on drug-dependent effects and did therefore not allow any conclusion. This clearly is both, an important outcome and a limitation of the present work.

Although no sex differences were found, the data suggest that almost all dosages of the five drugs of abuse consistently increase the extracellular level of dopamine in the CPu and the NAc. This is in accordance with the other publication on this work that put the data in a greater context by combining the results of this thesis with those of several datasets of the work group at the Institute of Psychopharmacology of the Central Institute of Mental Health (Noori et al., 2018). Thereby, Noori et al. show an interaction of about 260 neuropsychiatric drugs with the dopaminergic system and raise the question 'if dopamine possesses the necessary specificity to be considered as a reliable marker for drug effects' (Egenrieder et al., 2020).

Concerning the state of consciousness, as mentioned earlier, only cocaine and amphetamine were administered to anesthetized animals. Therefore, this work can only draw conclusions regarding these two drugs. Almost all dose groups showed no significant difference when the rats were anesthetized, consistent with earlier findings described by other authors (Fink-Jensen et al., 1994; Hamilton, Mele, & Pert, 1992). The only significances found by the present work indicated that anesthetized animals had a higher peak percentage baseline value in the CPu at two doses of amphetamine, or in the NAc at two doses of cocaine.

The route of administration affected in some cases of amphetamine or cocaine administration the dopaminergic overflow. As might be expected, it was highest when the rats received the drugs intravenously. The subcutaneous or intraperitoneal route of administration led to lower peak percentage baseline values.

The peak percentage baseline values were consistently stable for almost all drugs and dosages with respect to the animals' age and strain.

Unsurprisingly, there was a significantly higher dopamine overflow in the CPu when d-amphetamine was administered, compared to the dextro-, levoamphetamine racemate, as d-amphetamine is known to be the enantiomer with a higher potency.

4.3 Dose-dependent effects of the drugs of abuse

A correlation analysis was done for each drug and brain region to detect linear relationships. Local and systemic administration were distinguished and calculated separately. For a systematic overview of the dose-dependent effects of the drugs see table 28.

A dose-dependent increase of dopamine (↑) in the nucleus accumbens was found for systemically and locally administered alcohol and systemically administered cocaine.

In the caudate putamen higher levels of systemically administered alcohol or locally administered cocaine had a decreasing effect (↓) on the dopamine overflow. A dose-dependent decrease was also found for morphine in both brain regions, but as mentioned earlier, regarding the low number of studies in these dose groups, more data is needed for a reliable conclusion.

Amphetamine had no dose-dependent effects (↔). Neither was there a correlation between the local administration of cocaine and the accumbal dopamine overflow.

For nicotine the results did not provide enough datasets for a correlation analysis.

Table 28: dose-dependent effect of the five drugs of abuse: systemic administration above, local administration below the grey line

(↑ = increase, ↓ = decrease, ↔ = no dose-dependent effect on DA overflow)

Cocaine was administered either once or continuously perfused. Tendency for the latter one is given in parenthesis.

For nicotine there were only single doses with measurement in the nucleus accumbens and no measurements in the caudate putamen. Therefore, no tendency could be detected

Drug	Brain region	Effect
Alcohol	nucleus accumbens	↑
	caudate putamen	↓↓↓
Amphetamine	nucleus accumbens	↔
	caudate putamen	↔
Cocaine	nucleus accumbens	↑↑ (↑↑↑)
	caudate putamen	↔

Drug	Brain region	Effect
Morphine	nucleus accumbens	↓↓
	caudate putamen	↓↓↓
Nicotine	nucleus accumbens	-
	caudate putamen	-
Alcohol	nucleus accumbens	↑↑↑
Cocaine	nucleus accumbens	↔
	caudate putamen	↓

This lack of a positive dose-dependent relation for some drugs could be explained by the fact that the focus was only on those dosages that included female rats. Therefore, some dosages contained rather small groups of animals that led to an overrepresentation of single experiments and a disrupting effect with regard to the correlation analysis.
Due to the search method, only cocaine provided each dosage without the focus on those containing female animals. The dose-dependent relationship is in accordance with previous studies (Frank et al., 2008).

4.4 Drawbacks and limitations

The focus of this thesis lied on the imitated situation of single acute drug intake. But this is, as Koob et al. showed, far from the complex evolution of an addiction and ignores the crucial long-term neuroadaptive changes that finally result in the disease (Koob & Volkow, 2010). Neither does this work pay attention to the essential environment-individual interactions that are an important part of the disease. In consequence, there is a limited transferability of the results to humans and the clinical field.

As mentioned before, big data approaches are valuable and powerful means in modern life science and notably in evidence-based medicine and have recently demonstrated their importance regarding basic research. Nevertheless, although this is the particular strength of this thesis, it implies also drawbacks: as mentioned earlier, until today, there are no standardized procedures that guarantee a comparability of the different studies. For instance, laboratory methods can differ between the work groups and over the course of time. For the included studies the years of publication range from 1986 to 2017, equaling more than three decades. 'In addition, the accuracy of the outcomes of a meta-analysis strongly depends on the quality of the experimental procedures and reporting of the studies that it integrates' (Egenrieder et al., 2020).

Moreover, the fact that a part of the data was received by other meta-analyses, could be a weakness: other authors may have slightly varying interpretation of the in- and exclusion criteria.

Another possible limitation is inherent to the specific question of this thesis: the lack of studies with female subjects leads to small numbers and therefore made it, as mentioned earlier, in some cases difficult to draw conclusions or to establish generalizations based on the dataset.

Another example for the lack of standardized procedures are the distinct experimental settings, e.g. the basal level of dopamine: each laboratory defines its own baseline, depending on the first few samples of the experiment. That can lead to differing underlying values and therefore produce calculated peaks of varying highs. Furthermore, 'there is large variability in perfusion rates, exact positioning of microdialysis probe, age of the animals and even in how the results are reported that may affect the overall findings' (Egenrieder et al., 2020).

Apart of that, during the PubMed query, no difference was made in the quality of the included papers. Therefore, as Sena et al. stated: 'Empirical evidence suggests that too many preclinical experiments lack methodological rigor, and this leads to inflated treatment effects' (Sena et al., 2014).

Another limitation is the choice of drugs that necessarily excludes other important substances and diseases. For example, all the legally prescribed drugs (apart of morphine) or the substance-independent addictions (gambling and others).

Furthermore, there could be sex differences in other neuro-circuits, brain regions and neurotransmitter systems that were not subject to this present thesis.

Keeping these limitations in mind, the present thesis aims to present a variety of averages of the peak percentage baseline value of dopamine (DA) in the nucleus accumbens (NAc) or the caudate putamen (CPu) after acute drug administration.
Its purpose is to offer a universal framework for preclinical experimental designs.

4.5 Conclusion and outlook

There are two contrary paradigms that have been stated as reasons for the exclusion of females: they were thought to be either more variable or to react exactly like male subjects (and therefore have not to be further considered). These two hypotheses must be either verified or falsified before they can further serve as a basis to systemically exclude female animals.

In conclusion, this thesis found no overall differences in the drug induced overflow of male and female rats within the striatal complex. However, the few differences that were found seem to be due to small sample sizes and may as well be affected by the fact that a share of the female animals were ovariectomized. Because, as the corresponding publication on this thesis showed, ‘the most critical effect modifier was ovariectomy’ (Egenrieder et al., 2020). And moreover, ‘an impact of ovariectomie on basal levels was found’ (Egenrieder et al., 2020). Therefore, pharmaceutical interventions on ovariectomized females lead to biased results, compared to females without previous operation. For the females that were not ovariectomized, the frequency of the monitoring of the estrous cycle was analyzed: the exact state was mentioned by one author only.

Besides, all drugs under investigation enhanced the dopaminergic transmission in the striatal complex, i.e. the caudate putamen and the nucleus accumbens. The enhancement accounted for both sexes equally.
Correlation analysis showed a positive dose-response relationship for some drugs but not for all. Alcohol and cocaine had a positive correlation regarding the administered dose and the accumbal dopamine overflow. In the caudate putamen the

magnitude of the administered dose had no (amphetamine and cocaine) or even a negative (alcohol and morphine) dose-dependent effect.
The dataset showed robustness of the traits strain, age, stage of consciousness and route of administration, which is concordant with previous findings of the work group.

Overall, the neglect of female subjects in basic research, which had lasted for decades and is far from defeated, was a phenomenon well reflected in the search query and the results of this thesis: there were few studies that included female animals compared to the amount of male-focused experiments.
Therefore, as soon as both sexes will equally be used as subjects, a whole new aspect of research will emerge in general and for the reward circuit. For example, there will be new possibilities for the analysis of different housing conditions. Regarding single-sex experiments, it is already known that the fact if an animal is either group or individually housed influences the dopamine neurotransmission as well as the amount of drug self-administration (Engleman, Ingraham, O'Brien, McBride, & Murphy, 2004; Westenbroek et al., 2017). If both sexes are included, it is possible that the housing condition has an even greater effect: a more naturalistic setting could be established by studying the influence of mixed-sex pair or group housing.
Even more potential lies in the exact monitoring of the state of the estrous cycle, since this is often named as a reason for the exclusion of female subjects. Since (as shown also in this work) the cycle is seldom monitored, there are insufficient data on the subject which impact it has on dopaminergic transmission.
It can be also stated that standardized procedures for the microdialysis technique seem to be overdue but at least the sum of the single settings of the studies is quite similar in different meta-analyses and thereby, comparability is given.
The present work aims to provide a framework for both: for the standardization of microdialysis studies in general and for the inclusion of females in studies about the neurobiological mechanisms of addiction.

5 SUMMARY

In recent years, the topic of sex differences has rightfully become a focus of scientific research. Current findings suggest sexual dimorphism in the neurophysiological brain pathways that are crucial for drug-seeking and addictive behavior, but how this affects the underlying neurochemical processes, is still widely unexplored.
Nevertheless, female subjects have been systemically ignored for decades in the field of microdialysis experiments and the few existing studies using female animals provide only small numbers. Moreover, there is increasing evidence that single preclinical studies often lack reproducibility.
Therefore, a hypothesis-free meta-analysis approach was used that provides adequate statistical power for this subject area. The main question of this thesis was whether data of microdialysis experiments indicate a difference in the dopaminergic overflow in reaction to drugs of abuse in male and female rats.
Thereby, systematic data mining was performed on the PubMed online library (https://www.ncbi.nlm.nih.gov/pubmed/) focusing on studies measuring extracellular dopamine concentrations in the striatal complex. The focused lied on six drugs of abuse (alcohol, amphetamine, cocaine, nicotine, morphine and tetrahydrocannabinol) and two brain regions (caudate putamen and nucleus accumbens).

Data from 45 microdialysis experiments on female rats (number of animals = 842) were extracted and statistically compared with data from 6402 male rats. Overall, 291 studies were included, providing averages of the peak percentage baseline value of dopamine for 103 different dosages. All drugs under investigation notably increased the dopaminergic transmission in the striatal complex. For some drugs, a positive dose-response relationship was detected.
Regarding the entity of dose groups, no sex differences in the dopaminergic response to drugs of abuse were found, but for some small subgroups. Neither did the rats' age, strain, stage of consciousness or the route of administration have an impact on the overall peak percentage baseline values, suggesting robustness of these parameters. Attempts were also made to extract the rats' estrous cycle as a variable, but only one study monitored it.

Overall, the neglect of female subjects in basic research, which had lasted for decades and is far from defeated, was a phenomenon well reflected in the results of the search query in this thesis.

What can be therefore concluded, is that future research should intensify its efforts to include female subjects and to close the sex-gap in preclinical as well as in clinical research. This will provide more data that are crucial to get valid results about sex similarities or differences, as this thesis only shed light on a small subdivision.

6 REFERENCES

Afanas'ev, I., Ferger, B., & Kuschinsky, K. (2000). The associative type of sensitization to d-amphetamine is expressed as an NO-dependent dramatic increase in extracellular dopamine in the nucleus accumbens. *Naunyn Schmiedebergs Arch Pharmacol, 362*(3), 232-237.

al-Tajir, G., & Starr, M. S. (1993). Disordered dopamine neurotransmission in the striatum of rats undergoing pilocarpine-induced generalized seizures, as revealed by microdialysis. *J Neural Transm Park Dis Dement Sect, 5*(2), 89-100.

Alvarez Fischer, D., Schafer, M. K., Ferger, B., Gross, S., Westermann, R., Weihe, E., & Kuschinsky, K. (2001). Sensitization to the behavioural effects of cocaine: alterations in tyrosine hydroxylase or endogenous opioid mRNAs are not necessarily involved. *Naunyn Schmiedebergs Arch Pharmacol, 363*(3), 288-294. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11284443

Anderson, P., Gual, A., & Rehm, J. (2018). Reducing the health risks derived from exposure to addictive substances. *Curr Opin Psychiatry*. doi:10.1097/yco.0000000000000432

Andrews, C. M., Kung, H. F., & Lucki, I. (2005). The 5-HT1A receptor modulates the effects of cocaine on extracellular serotonin and dopamine levels in the nucleus accumbens. *Eur J Pharmacol, 508*(1-3), 123-130. doi:10.1016/j.ejphar.2004.12.033

Andrews, C. M., & Lucki, I. (2001). Effects of cocaine on extracellular dopamine and serotonin levels in the nucleus accumbens. *Psychopharmacology (Berl), 155*(3), 221-229. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11432683

Arnold, H. M., Nelson, C. L., Neigh, G. N., Sarter, M., & Bruno, J. P. (2000). Systemic and intra-accumbens administration of amphetamine differentially affects cortical acetylcholine release. *Neuroscience, 96*(4), 675-685.

Arrowsmith, J. (2011). Phase II failures: 2008-2010. *Nature Reviews Drug Discovery, 10*(5), 1-1. doi:10.1038/nrd3439

Auclair, A., Blanc, G., Glowinski, J., & Tassin, J. P. (2004). Role of serotonin 2A receptors in the D-amphetamine-induced release of dopamine: comparison with previous data on alpha1b-adrenergic receptors. *J Neurochem, 91*(2), 318-326. doi:10.1111/j.1471-4159.2004.02714.x

Auclair, A. L., Cathala, A., Sarrazin, F., Depoortere, R., Piazza, P. V., Newman-Tancredi, A., & Spampinato, U. (2010). The central serotonin 2B receptor: a new pharmacological target to modulate the mesoaccumbens dopaminergic pathway activity. *J Neurochem, 114*(5), 1323-1332. doi:10.1111/j.1471-4159.2010.06848.x

Badiani, A., Oates, M. M., Day, H. E., Watson, S. J., Akil, H., & Robinson, T. E. (1998). Amphetamine-induced behavior, dopamine release, and c-fos mRNA expression: modulation by environmental novelty. *J Neurosci, 18*(24), 10579-10593. Retrieved from http://www.jneurosci.org/content/jneuro/18/24/10579.full.pdf

Badiani, A., Oates, M. M., Fraioli, S., Browman, K. E., Ostrander, M. M., Xue, C. J., . . . Robinson, T. E. (2000). Environmental modulation of the response to amphetamine: dissociation between changes in behavior and changes in

dopamine and glutamate overflow in the rat striatal complex. *Psychopharmacology (Berl), 151*(2-3), 166-174. Retrieved from https://deepblue.lib.umich.edu/bitstream/handle/2027.42/41971/213-151-2-3-166_01510166.pdf?sequence=1

Balcioglu, A., Zhang, K., & Tarazi, F. I. (2003). Dopamine depletion abolishes apomorphine- and amphetamine-induced increases in extracellular serotonin levels in the striatum of conscious rats: a microdialysis study. *Neuroscience, 119*(4), 1045-1053.

Balfour, D. J., Birrell, C. E., Moran, R. J., & Benwell, M. E. (1996). Effects of acute D-CPPene on mesoaccumbens dopamine responses to nicotine in the rat. *Eur J Pharmacol, 316*(2-3), 153-156.

Balla, A., Koneru, R., Smiley, J., Sershen, H., & Javitt, D. C. (2001). Continuous phencyclidine treatment induces schizophrenia-like hyperreactivity of striatal dopamine release. *Neuropsychopharmacology, 25*(2), 157-164. doi:10.1016/s0893-133x(01)00230-5

Bangasser, D. A., & Valentino, R. J. (2014). Sex differences in stress-related psychiatric disorders: Neurobiological perspectives. *Frontiers in Neuroendocrinology, 35*(3), 303-319. doi:10.1016/j.yfrne.2014.03.008

Baptista, T., Weiss, S. R., & Post, R. M. (1993). Carbamazepine attenuates cocaine-induced increases in dopamine in the nucleus accumbens: an in vivo dialysis study. *Eur J Pharmacol, 236*(1), 39-42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8319744

Barr, J. L., Rasmussen, B. A., Tallarida, C. S., Scholl, J. L., Forster, G. L., Unterwald, E. M., & Rawls, S. M. (2015). Ceftriaxone attenuates acute cocaine-evoked dopaminergic neurotransmission in the nucleus accumbens of the rat. *Br J Pharmacol*. doi:10.1111/bph.13330

Barrot, M., Abrous, D. N., Marinelli, M., Rouge-Pont, F., Le Moal, M., & Piazza, P. V. (2001). Influence of glucocorticoids on dopaminergic transmission in the rat dorsolateral striatum. *Eur J Neurosci, 13*(4), 812-818. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11207816

Barrot, M., Marinelli, M., Abrous, D. N., Rouge-Pont, F., Le Moal, M., & Piazza, P. V. (2000). The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. *Eur J Neurosci, 12*(3), 973-979. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10762327

Barrot, M., Rettori, M. C., Guardiola-Lemaitre, B., Jarry, C., Le Moal, M., & Piazza, P. V. (2000). Interactions between imidazoline binding sites and dopamine levels in the rat nucleus accumbens. *Eur J Neurosci, 12*(12), 4547-4551. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11122366

Bassareo, V., De Luca, M. A., & Di Chiara, G. (2007). Differential impact of pavlovian drug conditioned stimuli on in vivo dopamine transmission in the rat accumbens shell and core and in the prefrontal cortex. *Psychopharmacology (Berl), 191*(3), 689-703. doi:10.1007/s00213-006-0560-7

Baumann, M. H., Char, G. U., De Costa, B. R., Rice, K. C., & Rothman, R. B. (1994). GBR12909 attenuates cocaine-induced activation of mesolimbic dopamine neurons in the rat. *J Pharmacol Exp Ther, 271*(3), 1216-1222. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7996429

Becker, J. B. (1990). Direct effect of 17 beta-estradiol on striatum: sex differences in dopamine release. *Synapse, 5*(2), 157-164. doi:10.1002/syn.890050211

Becker, J. B. (2016). Sex differences in addiction. *Dialogues Clin Neurosci, 18*(4), 395-402.

Becker, J. B., & Cha, J. H. (1989). Estrous cycle-dependent variation in amphetamine-induced behaviors and striatal dopamine release assessed with microdialysis. *Behav Brain Res, 35*(2), 117-125. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2818831

Becker, J. B., & Chartoff, E. (2018). Sex differences in neural mechanisms mediating reward and addiction. *Neuropsychopharmacology*. doi:10.1038/s41386-018-0125-6

Becker, J. B., McClellan, M., & Reed, B. G. (2016). Sociocultural context for sex differences in addiction. *Addict Biol, 21*(5), 1052-1059. doi:10.1111/adb.12383

Becker, J. B., McClellan, M. L., & Reed, B. G. (2017). Sex differences, gender and addiction. *J Neurosci Res, 95*(1-2), 136-147. doi:10.1002/jnr.23963

Becker, J. B., Perry, A. N., & Westenbroek, C. (2012). Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. *Biol Sex Differ, 3*(1), 14. doi:10.1186/2042-6410-3-14

Becker, J. B., Prendergast, B. J., & Liang, J. W. (2016). Female rats are not more variable than male rats: a meta-analysis of neuroscience studies. *Biol Sex Differ, 7*, 34. doi:10.1186/s13293-016-0087-5

Becker, J. B., & Rudick, C. N. (1999). Rapid effects of estrogen or progesterone on the amphetamine-induced increase in striatal dopamine are enhanced by estrogen priming: a microdialysis study. *Pharmacol Biochem Behav, 64*(1), 53-57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10494997

Beery, A. K., & Zucker, I. (2011). Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev, 35*(3), 565-572. doi:10.1016/j.neubiorev.2010.07.002

Begley, C. G., & Ellis, L. M. (2012). Raise standards for preclinical cancer research. *Nature, 483*(7391), 531-533. doi:10.1038/483531a

Begley, C. G., & Ioannidis, J. P. A. (2015). Reproducibility in Science Improving the Standard for Basic and Preclinical Research. *Circulation Research, 116*(1), 116-126. doi:10.1161/circresaha.114.303819

Benwell, M. E., Balfour, D. J., & Birrell, C. E. (1995). Desensitization of the nicotine-induced mesolimbic dopamine responses during constant infusion with nicotine. *Br J Pharmacol, 114*(2), 454-460.

Benwell, M. E., Balfour, D. J., & Lucchi, H. M. (1993). Influence of tetrodotoxin and calcium on changes in extracellular dopamine levels evoked by systemic nicotine. *Psychopharmacology (Berl), 112*(4), 467-474. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7871059

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl), 191*(3), 391-431. doi:10.1007/s00213-006-0578-x

Beyer, C. E., & Steketee, J. D. (1999). Dopamine depletion in the medial prefrontal cortex induces sensitized-like behavioral and neurochemical responses to cocaine. *Brain Res, 833*(2), 133-141. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10375688

Beyer, C. E., & Steketee, J. D. (2000). Intra-medial prefrontal cortex injection of quinpirole, but not SKF 38393, blocks the acute motor-stimulant response to cocaine in the rat. *Psychopharmacology (Berl), 151*(2-3), 211-218. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10972467

Beyer, C. E., & Steketee, J. D. (2002). Cocaine sensitization: modulation by dopamine D2 receptors. *Cereb Cortex, 12*(5), 526-535. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11950770

Birrell, C. E., & Balfour, D. J. (1998). The influence of nicotine pretreatment on mesoaccumbens dopamine overflow and locomotor responses to D-amphetamine. *Psychopharmacology (Berl), 140*(2), 142-149. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9860104

Bjartveit, K., & Tverdal, A. (2005). Health consequences of smoking 1-4 cigarettes per day. *Tobacco Control, 14*(5), 315-320. doi:10.1136/tc.2005.011932

Bjelke, B., Stromberg, I., O'Connor, W. T., Andbjer, B., Agnati, L. F., & Fuxe, K. (1994). Evidence for volume transmission in the dopamine denervated neostriatum of the rat after a unilateral nigral 6-OHDA microinjection. Studies with systemic D-amphetamine treatment. *Brain Res, 662*(1-2), 11-24.

Bjorklund, A., & Dunnett, S. B. (2007). Dopamine neuron systems in the brain: an update. *Trends Neurosci, 30*(5), 194-202. doi:10.1016/j.tins.2007.03.006

Blanchard, B. A., & Glick, S. D. (1995). Sex differences in mesolimbic dopamine responses to ethanol and relationship to ethanol intake in rats. *Recent Dev Alcohol, 12*, 231-241. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7624545

Blanchard, B. A., Steindorf, S., Wang, S., & Glick, S. D. (1993). Sex differences in ethanol-induced dopamine release in nucleus accumbens and in ethanol consumption in rats. *Alcohol Clin Exp Res, 17*(5), 968-973. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8279683

Blanchard, B. A., Steindorf, S., Wang, S., LeFevre, R., Mankes, R. F., & Glick, S. D. (1993). Prenatal ethanol exposure alters ethanol-induced dopamine release in nucleus accumbens and striatum in male and female rats. *Alcohol Clin Exp Res, 17*(5), 974-981. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8279684

Bobzean, S. A., DeNobrega, A. K., & Perrotti, L. I. (2014). Sex differences in the neurobiology of drug addiction. *Exp Neurol, 259*, 64-74. doi:10.1016/j.expneurol.2014.01.022

Borg, P. J., & Taylor, D. A. (1997). Involvement of mu- and delta-opioid receptors in the effects of systemic and locally perfused morphine on extracellular levels of dopamine, DOPAC and HVA in the nucleus accumbens of the halothane-anaesthetized rat. *Naunyn Schmiedebergs Arch Pharmacol, 355*(5), 582-588.

Boyson, C. O., Holly, E. N., Shimamoto, A., Albrechet-Souza, L., Weiner, L. A., DeBold, J. F., & Miczek, K. A. (2014). Social stress and CRF-dopamine interactions in the VTA: role in long-term escalation of cocaine self-administration. *J Neurosci, 34*(19), 6659-6667. doi:10.1523/JNEUROSCI.3942-13.2014

Bradberry, C. W., Gruen, R. J., Berridge, C. W., & Roth, R. H. (1991). Individual differences in behavioral measures: correlations with nucleus accumbens dopamine measured by microdialysis. *Pharmacol Biochem Behav, 39*(4), 877-882.

Bradberry, C. W., Lee, T., & Jatlow, P. (1999). Rapid induction of behavioral and neurochemical tolerance to cocaethylene, a model compound for agonist therapy of cocaine dependence. *Psychopharmacology (Berl), 146*(1), 87-92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10485969

Bradberry, C. W., Nobiletti, J. B., Elsworth, J. D., Murphy, B., Jatlow, P., & Roth, R. H. (1993). Cocaine and cocaethylene: microdialysis comparison of brain drug levels and effects on dopamine and serotonin. *J Neurochem, 60*(4), 1429-1435. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8455033

Bradberry, C. W., & Roth, R. H. (1989). Cocaine increases extracellular dopamine in rat nucleus accumbens and ventral tegmental area as shown by in vivo microdialysis. *Neurosci Lett, 103*(1), 97-102. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2779859

Brand, I., Fliegel, S., Spanagel, R., & Noori, H. R. (2013). Global ethanol-induced enhancements of monoaminergic neurotransmission: a meta-analysis study. *Alcohol Clin Exp Res, 37*(12), 2048-2057. doi:10.1111/acer.12207

Bredeloux, P., Dubuc, I., & Costentin, J. (2007). Comparisons between bupropion and dexamphetamine in a range of in vivo tests exploring dopaminergic transmission. *Br J Pharmacol, 150*(6), 711-719. doi:10.1038/sj.bjp.0707151

Brown, E. E., & Fibiger, H. C. (1992). Cocaine-induced conditioned locomotion: absence of associated increases in dopamine release. *Neuroscience, 48*(3), 621-629. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1603333

Brown, E. E., Finlay, J. M., Wong, J. T., Damsma, G., & Fibiger, H. C. (1991). Behavioral and neurochemical interactions between cocaine and buprenorphine: implications for the pharmacotherapy of cocaine abuse. *J Pharmacol Exp Ther, 256*(1), 119-126. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1988653

Brown, E. E., Nomikos, G. G., Wilson, C., & Fibiger, H. C. (1991). Chronic desipramine enhances the effect of locally applied amphetamine on interstitial concentrations of dopamine in the nucleus accumbens. *Eur J Pharmacol, 202*(1), 125-127.

Bubar, M. J., McMahon, L. R., De Deurwaerdere, P., Spampinato, U., & Cunningham, K. A. (2003). Selective serotonin reuptake inhibitors enhance cocaine-induced locomotor activity and dopamine release in the nucleus accumbens. *Neuropharmacology, 44*(3), 342-353. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12604093

Bustamante, D., Quintanilla, M. E., Tampier, L., Gonzalez-Lira, V., Israel, Y., & Herrera-Marschitz, M. (2008). Ethanol induces stronger dopamine release in nucleus accumbens (shell) of alcohol-preferring (bibulous) than in alcohol-avoiding (abstainer) rats. *Eur J Pharmacol, 591*(1-3), 153-158. doi:10.1016/j.ejphar.2008.06.069

Butcher, S. P., Fairbrother, I. S., Kelly, J. S., & Arbuthnott, G. W. (1988). Amphetamine-induced dopamine release in the rat striatum: an in vivo microdialysis study. *J Neurochem, 50*(2), 346-355. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-4159.1988.tb02919.x

Byun, N. E., Grannan, M., Bubser, M., Barry, R. L., Thompson, A., Rosanelli, J., . . . Jones, C. K. (2014). Antipsychotic drug-like effects of the selective M4 muscarinic acetylcholine receptor positive allosteric modulator VU0152100. *Neuropsychopharmacology, 39*(7), 1578-1593. doi:10.1038/npp.2014.2

Cadoni, C., & Di Chiara, G. (1999). Reciprocal changes in dopamine responsiveness in the nucleus accumbens shell and core and in the dorsal caudate-putamen in rats sensitized to morphine. *Neuroscience, 90*(2), 447-455. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10215150

Cadoni, C., & Di Chiara, G. (2000). Differential changes in accumbens shell and core dopamine in behavioral sensitization to nicotine. *Eur J Pharmacol, 387*(3), R23-25.

Cadoni, C., & Di Chiara, G. (2007). Differences in dopamine responsiveness to drugs of abuse in the nucleus accumbens shell and core of Lewis and Fischer 344 rats. *J Neurochem, 103*(2), 487-499. doi:10.1111/j.1471-4159.2007.04795.x

Cadoni, C., Muto, T., & Di Chiara, G. (2009). Nicotine differentially affects dopamine transmission in the nucleus accumbens shell and core of Lewis and Fischer 344 rats. *Neuropharmacology, 57*(5-6), 496-501. doi:10.1016/j.neuropharm.2009.07.033

Cadoni, C., Pinna, A., Russi, G., Consolo, S., & Di Chiara, G. (1995). Role of vesicular dopamine in the in vivo stimulation of striatal dopamine transmission by amphetamine: evidence from microdialysis and Fos immunohistochemistry. *Neuroscience, 65*(4), 1027-1039.

Cadoni, C., Solinas, M., & Di Chiara, G. (2000). Psychostimulant sensitization: differential changes in accumbal shell and core dopamine. *Eur J Pharmacol, 388*(1), 69-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10657548

Cadoni, C., Solinas, M., Valentini, V., & Di Chiara, G. (2003). Selective psychostimulant sensitization by food restriction: differential changes in accumbens shell and core dopamine. *Eur J Neurosci, 18*(8), 2326-2334. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14622194

Cagiano, R., Ancona, D., Cassano, T., Tattoli, M., Trabace, L., & Cuomo, V. (1998). Effects of prenatal exposure to low concentrations of carbon monoxide on sexual behaviour and mesolimbic dopaminergic function in rat offspring. *Br J Pharmacol, 125*(4), 909-915. doi:10.1038/sj.bjp.0702143

Caille, S., & Parsons, L. H. (2006). Cannabinoid modulation of opiate reinforcement through the ventral striatopallidal pathway. *Neuropsychopharmacology, 31*(4), 804-813. doi:10.1038/sj.npp.1300848

Camp, D. M., Browman, K. E., & Robinson, T. E. (1994). The effects of methamphetamine and cocaine on motor behavior and extracellular dopamine in the ventral striatum of Lewis versus Fischer 344 rats. *Brain Res, 668*(1-2), 180-193. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7704604

Camp, D. M., & Robinson, T. E. (1992). On the use of multiple probe insertions at the same site for repeated intracerebral microdialysis experiments in the nigrostriatal dopamine system of rats. *J Neurochem, 58*(5), 1706-1715. Retrieved from https://deepblue.lib.umich.edu/bitstream/handle/2027.42/65235/j.1471-4159.1992.tb10044.x.pdf?sequence=1

Campbell, A. D., & McBride, W. J. (1995). Serotonin-3 receptor and ethanol-stimulated dopamine release in the nucleus accumbens. *Pharmacol Biochem Behav, 51*(4), 835-842. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7675866

Cao, J., Lotfipour, S., Loughlin, S. E., & Leslie, F. M. (2007). Adolescent maturation of cocaine-sensitive neural mechanisms. *Neuropsychopharmacology, 32*(11), 2279-2289. doi:10.1038/sj.npp.1301349

Carboni, E., Imperato, A., Perezzani, L., & Di Chiara, G. (1989). Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. *Neuroscience, 28*(3), 653-661. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2710338

Carboni, E., Silvagni, A., Rolando, M. T., & Di Chiara, G. (2000). Stimulation of in vivo dopamine transmission in the bed nucleus of stria terminalis by reinforcing drugs. *J Neurosci, 20*(20), RC102. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11027253

Carcoba, L. M., Flores, R. J., Natividad, L. A., & O'Dell, L. E. (2017). Amino acid modulation of dopamine in the nucleus accumbens mediates sex differences in nicotine withdrawal. *Addict Biol*. doi:10.1111/adb.12556

Carroll, M. E., & Lynch, W. J. (2016). How to study sex differences in addiction using animal models. *Addict Biol, 21*(5), 1007-1029. doi:10.1111/adb.12400

Carvalho, A. F., Heilig, M., Perez, A., Probst, C., & Rehm, J. (2019). Alcohol use disorders. *Lancet, 394*(10200), 781-792. doi:10.1016/s0140-6736(19)31775-1

Cass, W. A., Manning, M. W., & Dugan, M. T. (1998). Effects of neurotoxic doses of methamphetamine on potassium and amphetamine evoked overflow of dopamine in the striatum of awake rats. *Neurosci Lett, 248*(3), 175-178.

Castaneda, E., Moss, D. E., Oddie, S. D., & Whishaw, I. Q. (1991). THC does not affect striatal dopamine release: microdialysis in freely moving rats. *Pharmacol Biochem Behav, 40*(3), 587-591.

Castaneda, E., Whishaw, I. Q., Lermer, L., & Robinson, T. E. (1990). Dopamine depletion in neonatal rats: effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood. *Brain Res, 508*(1), 30-39. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1692503

Castaneda, E., Whishaw, I. Q., & Robinson, T. E. (1990). Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a bilateral 6-OHDA lesion: variation as a function of lesion size. *J Neurosci, 10*(6), 1847-1854.

Castaneda, E., Whishaw, I. Q., & Robinson, T. E. (1992). Recovery from lateralized neocortical damage: dissociation between amphetamine-induced asymmetry in behavior and striatal dopamine neurotransmission in vivo. *Brain Res, 571*(2), 248-259.

Castner, S. A., Xiao, L., & Becker, J. B. (1993). Sex differences in striatal dopamine: in vivo microdialysis and behavioral studies. *Brain Res, 610*(1), 127-134. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8518920

Cervo, L., Pozzi, L., & Samanin, R. (1996). 5-HT3 receptor antagonists do not modify cocaine place conditioning or the rise in extracellular dopamine in the nucleus accumbens of rats. *Pharmacol Biochem Behav, 55*(1), 33-37. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8870035

Chambers, R. A., Sentir, A. M., & Engleman, E. A. (2010). Ventral and dorsal striatal dopamine efflux and behavior in rats with simple vs. co-morbid histories of cocaine sensitization and neonatal ventral hippocampal lesions. *Psychopharmacology (Berl), 212*(1), 73-83. doi:10.1007/s00213-010-1929-1

Chapman, M. A., See, R. E., & Bissette, G. (1992). Neurotensin increases extracellular striatal dopamine levels in vivo. *Neuropeptides, 22*(3), 175-183. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1436404

Chaudhry, S. R., & Bhimji, S. S. (2018). Biochemistry, Endorphin. In *StatPearls*. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC. (Reprinted from: Abstract only, endorphines).

Chefer, V. I., & Shippenberg, T. S. (2002). Changes in basal and cocaine-evoked extracellular dopamine uptake and release in the rat nucleus accumbens during early abstinence from cocaine: quantitative determination under transient conditions. *Neuroscience, 112*(4), 907-919. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12088750

Chefer, V. I., Thompson, A. C., Zapata, A., & Shippenberg, T. S. (2009). Overview of brain microdialysis. *Curr Protoc Neurosci, Chapter 7*, Unit7.1. doi:10.1002/0471142301.ns0701s47

Chefer, V. I., Zakharova, I., & Shippenberg, T. S. (2003). Enhanced responsiveness to novelty and cocaine is associated with decreased basal dopamine uptake and release in the nucleus accumbens: quantitative microdialysis in rats under transient conditions. *J Neurosci, 23*(7), 3076-3084. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12684494

Chen, J., Marmur, R., Paredes, W., Pulles, A., & Gardner, E. L. (1996). Systemic cocaine challenge after chronic cocaine treatment reveals sensitization of extracellular dopamine levels in nucleus accumbens but direct cocaine perfusion into nucleus accumbens does not: implications for the neural locus of cocaine sensitization. *Life Sci, 58*(8), PL139-146. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8594313

Chen, Y. C., Choi, J. K., Andersen, S. L., Rosen, B. R., & Jenkins, B. G. (2005). Mapping dopamine D2/D3 receptor function using pharmacological magnetic resonance imaging. *Psychopharmacology (Berl), 180*(4), 705-715. doi:10.1007/s00213-004-2034-0

Chen, Y. I., Choi, J. K., Xu, H., Ren, J., Andersen, S. L., & Jenkins, B. G. (2010). Pharmacologic neuroimaging of the ontogeny of dopamine receptor function. *Dev Neurosci, 32*(2), 125-138. doi:10.1159/000286215

Chen, Y. I., Ren, J., Wang, F. N., Xu, H., Mandeville, J. B., Kim, Y., . . . Kwong, K. K. (2008). Inhibition of stimulated dopamine release and hemodynamic response in the brain through electrical stimulation of rat forepaw. *Neurosci Lett, 431*(3), 231-235. doi:10.1016/j.neulet.2007.11.063

Choi, F. Y., Ahn, S., Wang, Y. T., & Phillips, A. G. (2014). Interference with AMPA receptor endocytosis: effects on behavioural and neurochemical correlates of amphetamine sensitization in male rats. *J Psychiatry Neurosci, 39*(3), 189-199. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997604/pdf/jpn-39-189.pdf

Church, W. H., Justice, J. B., Jr., & Byrd, L. D. (1987). Extracellular dopamine in rat striatum following uptake inhibition by cocaine, nomifensine and benztropine. *Eur J Pharmacol, 139*(3), 345-348. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3666010

Clark, R. N., Ashby, C. R., Jr., Dewey, S. L., Ramachandran, P. V., & Strecker, R. E. (1996). Effect of acute and chronic fluoxetine on extracellular dopamine levels in the caudate-putamen and nucleus accumbens of rat. *Synapse, 23*(3), 125-131. doi:10.1002/(SICI)1098-2396(199607)23:3<125::AID-SYN1>3.0.CO;2-A

Clayton, J. A., & Collins, F. S. (2014). Policy: NIH to balance sex in cell and animal studies. *Nature, 509*(7500), 282-283. Retrieved from http://www.nature.com:80/polopoly_fs/1.15195!/menu/main/topColumns/topLeftColumn/pdf/509282a.pdf

Cortez, A. M., Charntikov, S., Der-Ghazarian, T., Horn, L. R., Crawford, C. A., & McDougall, S. A. (2010). Age-dependent effects of kappa-opioid receptor stimulation on cocaine-induced stereotyped behaviors and dopamine overflow in the caudate-putamen: an in vivo microdialysis study. *Neuroscience, 169*(1), 203-213. doi:10.1016/j.neuroscience.2010.04.052

Coury, A., Blaha, C. D., Atkinson, L. J., & Phillips, A. G. (1992). Cocaine-induced changes in extracellular levels of striatal dopamine measured concurrently by microdialysis with HPLC-EC and chronoamperometry. *Ann N Y Acad Sci, 654*, 424-427. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1632594

Coutureau, E., Lena, I., Dauge, V., & Di Scala, G. (2002). The entorhinal cortex-nucleus accumbens pathway and latent inhibition: a behavioral and neurochemical study in rats. *Behav Neurosci, 116*(1), 95-104.

Crespo, J. A., Sturm, K., Saria, A., & Zernig, G. (2006). Activation of muscarinic and nicotinic acetylcholine receptors in the nucleus accumbens core is necessary for the acquisition of drug reinforcement. *J Neurosci, 26*(22), 6004-6010. doi:10.1523/JNEUROSCI.4494-05.2006

Cummings, J. A., Jagannathan, L., Jackson, L. R., & Becker, J. B. (2014). Sex differences in the effects of estradiol in the nucleus accumbens and striatum on the response to cocaine: neurochemistry and behavior. *Drug Alcohol Depend, 135*, 22-28. doi:10.1016/j.drugalcdep.2013.09.009

D'Souza, M. S., & Duvauchelle, C. L. (2006). Comparing nucleus accumbens and dorsal striatal dopamine responses to self-administered cocaine in naive rats. *Neurosci Lett, 408*(2), 146-150. doi:10.1016/j.neulet.2006.08.076

Darracq, L., Blanc, G., Glowinski, J., & Tassin, J. P. (1998). Importance of the noradrenaline-dopamine coupling in the locomotor activating effects of D-amphetamine. *J Neurosci, 18*(7), 2729-2739. Retrieved from http://www.jneurosci.org/content/jneuro/18/7/2729.full.pdf

Davis, B. A., Clinton, S. M., Akil, H., & Becker, J. B. (2008). The effects of novelty-seeking phenotypes and sex differences on acquisition of cocaine self-administration in selectively bred High-Responder and Low-Responder rats. *Pharmacol Biochem Behav, 90*(3), 331-338. doi:10.1016/j.pbb.2008.03.008

De Deurwaerdere, P., Moison, D., Navailles, S., Porras, G., & Spampinato, U. (2005). Regionally and functionally distinct serotonin3 receptors control in vivo dopamine outflow in the rat nucleus accumbens. *J Neurochem, 94*(1), 140-149. doi:10.1111/j.1471-4159.2005.03174.x

De Souza Silva, M. A., Mattern, C., Hacker, R., Nogueira, P. J., Huston, J. P., & Schwarting, R. K. (1997). Intranasal administration of the dopaminergic agonists L-DOPA, amphetamine, and cocaine increases dopamine activity in the neostriatum: a microdialysis study in the rat. *J Neurochem, 68*(1), 233-239. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8978730

Degenhardt, L., Chiu, W. T., Sampson, N., Kessler, R. C., Anthony, J. C., Angermeyer, M., . . . Wells, J. E. (2008). Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO World Mental Health Surveys. *Plos Medicine, 5*(7), 1053-1067. doi:10.1371/journal.pmed.0050141

Desai, R. I., Paronis, C. A., Martin, J., Desai, R., & Bergman, J. (2010). Monoaminergic psychomotor stimulants: discriminative stimulus effects and dopamine efflux. *J Pharmacol Exp Ther, 333*(3), 834-843. doi:10.1124/jpet.110.165746

Devoto, P., Flore, G., Ibba, A., Fratta, W., & Pani, L. (2001). Lead intoxication during intrauterine life and lactation but not during adulthood reduces nucleus accumbens dopamine release as studied by brain microdialysis. *Toxicol Lett, 121*(3), 199-206. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11369474

Devoto, P., Flore, G., Saba, P., Cadeddu, R., & Gessa, G. L. (2012). Disulfiram stimulates dopamine release from noradrenergic terminals and potentiates cocaine-induced dopamine release in the prefrontal cortex. *Psychopharmacology (Berl), 219*(4), 1153-1164. doi:10.1007/s00213-011-2447-5

Devroye, C., Cathala, A., Maitre, M., Piazza, P. V., Abrous, D. N., Revest, J. M., & Spampinato, U. (2015). Serotonin2C receptor stimulation inhibits cocaine-induced Fos expression and DARPP-32 phosphorylation in the rat striatum independently of dopamine outflow. *Neuropharmacology, 89*, 375-381. doi:10.1016/j.neuropharm.2014.10.016

Dewey, S. L., Brodie, J. D., Gerasimov, M., Horan, B., Gardner, E. L., & Ashby, C. R., Jr. (1999). A pharmacologic strategy for the treatment of nicotine addiction. *Synapse, 31*(1), 76-86. doi:10.1002/(SICI)1098-2396(199901)31:1<76::AID-SYN10>3.0.CO;2-Y

Dewey, S. L., Chaurasia, C. S., Chen, C. E., Volkow, N. D., Clarkson, F. A., Porter, S. P., . . . Brodie, J. D. (1997). GABAergic attenuation of cocaine-induced dopamine release and locomotor activity. *Synapse, 25*(4), 393-398. doi:10.1002/(SICI)1098-2396(199704)25:4<393::AID-SYN11>3.0.CO;2-W

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A, 85*(14), 5274-5278. Retrieved from http://www.pnas.org/content/pnas/85/14/5274.full.pdf

Di Chiara, G., Tanda, G., Frau, R., & Carboni, E. (1993). On the preferential release of dopamine in the nucleus accumbens by amphetamine: further evidence obtained by vertically implanted concentric dialysis probes. *Psychopharmacology (Berl), 112*(2-3), 398-402.

Di Giannuario, A., Pieretti, S., Catalani, A., & Loizzo, A. (1999). Orphanin FQ reduces morphine-induced dopamine release in the nucleus accumbens: a microdialysis study in rats. *Neurosci Lett, 272*(3), 183-186.

Di Paolo, T., Rouillard, C., Morissette, M., Levesque, D., & Bedard, P. J. (1989). Endocrine and neurochemical actions of cocaine. *Can J Physiol Pharmacol, 67*(9), 1177-1181. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2688866

Dietze, S., & Kuschinsky, K. (1994). Effect of conditioning with d-amphetamine on the extracellular concentration of dopamine and its metabolites in the striatum of behaving rats. *Naunyn Schmiedebergs Arch Pharmacol, 350*(1), 22-27.

Ding, Z. M., Ingraham, C. M., Rodd, Z. A., & McBride, W. J. (2016). Alcohol drinking increases the dopamine-stimulating effects of ethanol and reduces D2 auto-receptor and group II metabotropic glutamate receptor function within the posterior ventral tegmental area of alcohol preferring (P) rats. *Neuropharmacology, 109*, 41-48. doi:10.1016/j.neuropharm.2016.05.023

Ding, Z. M., Katner, S. N., Rodd, Z. A., Truitt, W., Hauser, S. R., Deehan, G. A., Jr., . . . McBride, W. J. (2012). Repeated exposure of the posterior ventral tegmental area to nicotine increases the sensitivity of local dopamine neurons to the stimulating effects of ethanol. *Alcohol, 46*(3), 217-223. doi:10.1016/j.alcohol.2011.11.007

Ding, Z. M., Rodd, Z. A., Engleman, E. A., & McBride, W. J. (2009). Sensitization of ventral tegmental area dopamine neurons to the stimulating effects of ethanol. *Alcohol Clin Exp Res, 33*(9), 1571-1581. doi:10.1111/j.1530-0277.2009.00985.x

Doneith, K. G. (2008). *Binswangers Privatklinik Bellevue 1881 - 1885*.

Druhan, J. P., Rajabi, H., & Stewart, J. (1996). MK-801 increases locomotor activity without elevating extracellular dopamine levels in the nucleus accumbens. *Synapse, 24*(2), 135-146. doi:10.1002/(SICI)1098-2396(199610)24:2<135::AID-SYN5>3.0.CO;2-G

Duvauchelle, C. L., Ikegami, A., Asami, S., Robens, J., Kressin, K., & Castaneda, E. (2000). Effects of cocaine context on NAcc dopamine and behavioral activity after repeated intravenous cocaine administration. *Brain Res, 862*(1-2), 49-58. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10799668

Duvauchelle, C. L., Ikegami, A., & Castaneda, E. (2000). Conditioned increases in behavioral activity and accumbens dopamine levels produced by intravenous cocaine. *Behav Neurosci, 114*(6), 1156-1166. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11142647

Edeleano, L. (1887). Ueber einige Derivate der Phenylmethacrylsäure und der Phenylisobuttersäure. *European Journal of Inorganic Chemistry, 20*(1), 616-622.

Egenrieder, L., Mitricheva, E., Spanagel, R., & Noori, H. R. (2020). No basal or drug-induced sex differences in striatal dopaminergic levels: a cluster and meta-analysis of rat microdialysis studies. *J Neurochem, 152*(4), 482-492. doi:10.1111/jnc.14911

Eggan, B. L., & McCallum, S. E. (2016). 18-Methoxycoronaridine acts in the medial habenula to attenuate behavioral and neurochemical sensitization to nicotine. *Behav Brain Res, 307*, 186-193. doi:10.1016/j.bbr.2016.04.008

Eggan, B. L., & McCallum, S. E. (2017). alpha3beta4 nicotinic receptors in the medial habenula and substance P transmission in the interpeduncular nucleus modulate nicotine sensitization. *Behav Brain Res, 316*, 94-103. doi:10.1016/j.bbr.2016.08.028

Ellinghaus, D., Degenhardt, F., Bujanda, L., Buti, M., Albillos, A., Invernizzi, P., . . . Karlsen, T. H. (2020). Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med*. doi:10.1056/NEJMoa2020283

Engleman, E. A., Ingraham, C. M., O'Brien, C. E., McBride, W. J., & Murphy, J. M. (2004). Effect of housing conditions on sulpiride-induced increases in extracellular dopamine (DA) levels in the nucleus accumbens of alcohol-preferring (P) rats. *Brain Res, 1022*(1-2), 247-250. doi:10.1016/j.brainres.2004.06.069

Espana, R. A., Melchior, J. R., Roberts, D. C., & Jones, S. R. (2011). Hypocretin 1/orexin A in the ventral tegmental area enhances dopamine responses to cocaine and promotes cocaine self-administration. *Psychopharmacology (Berl), 214*(2), 415-426. doi:10.1007/s00213-010-2048-8

Espana, R. A., Oleson, E. B., Locke, J. L., Brookshire, B. R., Roberts, D. C., & Jones, S. R. (2010). The hypocretin-orexin system regulates cocaine self-administration via actions on the mesolimbic dopamine system. *Eur J Neurosci, 31*(2), 336-348. doi:10.1111/j.1460-9568.2009.07065.x

Essman, W. D., Singh, A., & Lucki, I. (1994). Serotonergic properties of cocaine: effects on a 5-HT2 receptor-mediated behavior and on extracellular concentrations of serotonin and dopamine. *Pharmacol Biochem Behav, 49*(1), 107-113. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7816859

Fabricius, K., Steiniger-Brach, B., Helboe, L., Fink-Jensen, A., & Wortwein, G. (2011). Socially isolated rats exhibit changes in dopamine homeostasis pertinent to schizophrenia. *Int J Dev Neurosci, 29*(3), 347-350. doi:10.1016/j.ijdevneu.2010.09.003

Fadda, P., Scherma, M., Fresu, A., Collu, M., & Fratta, W. (2003). Baclofen antagonizes nicotine-, cocaine-, and morphine-induced dopamine release in the nucleus accumbens of rat. *Synapse, 50*(1), 1-6. doi:10.1002/syn.10238

Feifel, D., Shilling, P. D., Kuczenski, R., & Segal, D. S. (2003). Altered extracellular dopamine concentration in the brains of cholecystokinin-A receptor deficient rats. *Neurosci Lett, 348*(3), 147-150. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12932815

Feigenbaum, J. J., & Howard, S. G. (1997). Effects of naloxone on amphetamine induced striatal dopamine release in vivo: a microdialysis study. *Life Sci, 60*(19), 1659-1668.

Ferguson, S. A., Flynn, K. M., Delclos, K. B., Newbold, R. R., & Gough, B. J. (2002). Effects of lifelong dietary exposure to genistein or nonylphenol on amphetamine-stimulated striatal dopamine release in male and female rats. *Neurotoxicol Teratol, 24*(1), 37-45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11836070

Ferguson, S. A., Gough, B. J., & Cada, A. M. (2003). In vivo basal and amphetamine-induced striatal dopamine and metabolite levels are similar in the spontaneously hypertensive, Wistar-Kyoto and Sprague-Dawley male rats. *Physiol Behav, 80*(1), 109-114.

Ferrari, R., Le Novere, N., Picciotto, M. R., Changeux, J. P., & Zoli, M. (2002). Acute and long-term changes in the mesolimbic dopamine pathway after systemic or local single nicotine injections. *Eur J Neurosci, 15*(11), 1810-1818.

Ferraro, T. N., Golden, G. T., Berrettini, W. H., Gottheil, E., Yang, C. H., Cuppels, G. R., & Vogel, W. H. (2000). Cocaine intake by rats correlates with cocaine-induced dopamine changes in the nucleus accumbens shell. *Pharmacol Biochem Behav, 66*(2), 397-401. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10880696

Ferris, M. J., Mateo, Y., Roberts, D. C., & Jones, S. R. (2011). Cocaine-insensitive dopamine transporters with intact substrate transport produced by self-administration. *Biol Psychiatry, 69*(3), 201-207. doi:10.1016/j.biopsych.2010.06.026

Fink-Jensen, A., Ingwersen, S. H., Nielsen, P. G., Hansen, L., Nielsen, E. B., & Hansen, A. J. (1994). Halothane anesthesia enhances the effect of dopamine uptake inhibition on interstitial levels of striatal dopamine. *Naunyn Schmiedebergs Arch Pharmacol, 350*(3), 239-244. Retrieved from https://link-springer-com.ezproxy.medma.uni-heidelberg.de/content/pdf/10.1007%2FBF00175028.pdf

Fiore, M. C., Smith, S. S., Jorenby, D. E., & Baker, T. B. (1994). The effectiveness of the nicotine patch for smoking cessation: A meta-analysis. *JAMA, 271*(24), 1940-1947. doi:10.1001/jama.1994.03510480064036

Fiorino, D. F., & Phillips, A. G. (1999). Facilitation of sexual behavior and enhanced dopamine efflux in the nucleus accumbens of male rats after D-amphetamine-induced behavioral sensitization. *J Neurosci, 19*(1), 456-463. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9870973

Flagstad, P., Mork, A., Glenthoj, B. Y., van Beek, J., Michael-Titus, A. T., & Didriksen, M. (2004). Disruption of neurogenesis on gestational day 17 in the rat causes behavioral changes relevant to positive and negative schizophrenia symptoms and alters amphetamine-induced dopamine release in nucleus accumbens. *Neuropsychopharmacology, 29*(11), 2052-2064. doi:10.1038/sj.npp.1300516

Fliegel, S., Brand, I., Spanagel, R., & Noori, H. R. (2013). Ethanol-induced alterations of amino acids measured by in vivo microdialysis in rats: a meta-analysis. *In Silico Pharmacol, 1*, 7. doi:10.1186/2193-9616-1-7

Florin, S. M., Kuczenski, R., & Segal, D. S. (1994). Regional extracellular norepinephrine responses to amphetamine and cocaine and effects of clonidine pretreatment. *Brain Res, 654*(1), 53-62.

Florin, S. M., Kuczenski, R., & Segal, D. S. (1995). Effects of reserpine on extracellular caudate dopamine and hippocampus norepinephrine responses to amphetamine and cocaine: mechanistic and behavioral considerations. *J Pharmacol Exp Ther, 274*(1), 231-241. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7616403

Fontana, D. J., Post, R. M., & Pert, A. (1993). Conditioned increases in mesolimbic dopamine overflow by stimuli associated with cocaine. *Brain Res, 629*(1), 31-39. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8287278

Forouzanfar, M. (2016). Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet, 388*(10053), 1659-1724. doi:10.1016/s0140-6736(16)31679-8

Frank, S. T., Krumm, B., & Spanagel, R. (2008). Cocaine-induced dopamine overflow within the nucleus accumbens measured by in vivo microdialysis: a meta-analysis. *Synapse, 62*(4), 243-252. doi:10.1002/syn.20489

Franke, A., McGovern, D. P. B., Barrett, J. C., Wang, K., Radford-Smith, G. L., Ahmad, T., . . . Parkes, M. (2010). Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nature Genetics, 42*(12), 1118-+. doi:10.1038/ng.717

Frantz, K. J., Hansson, K. J., Stouffer, D. G., & Parsons, L. H. (2002). 5-HT(6) receptor antagonism potentiates the behavioral and neurochemical effects of amphetamine but not cocaine. *Neuropharmacology, 42*(2), 170-180. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11804613

Frantz, K. J., O'Dell, L. E., & Parsons, L. H. (2007). Behavioral and neurochemical responses to cocaine in periadolescent and adult rats. *Neuropsychopharmacology, 32*(3), 625-637. doi:10.1038/sj.npp.1301130

Freedman, L. S., Simon, R., Foulkes, M. A., Friedman, L., Geller, N. L., Gordon, D. J., & Mowery, R. (1995). Inclusion of women and minorities in clinical trials and the NIH Revitalization Act of 1993--the perspective of NIH clinical trialists. *Control Clin Trials, 16*(5), 277-285; discussion 286-279, 293-309.

Fritze, S., Spanagel, R., & Noori, H. R. (2017). Adaptive dynamics of the 5-HT systems following chronic administration of selective serotonin reuptake inhibitors: a meta-analysis. *J Neurochem, 142*(5), 747-755. doi:10.1111/jnc.14114

Gabriele, A., Pacchioni, A. M., & See, R. E. (2012). Dopamine and glutamate release in the dorsolateral caudate putamen following withdrawal from cocaine self-administration in rats. *Pharmacol Biochem Behav, 103*(2), 373-379. doi:10.1016/j.pbb.2012.09.015

Gambarana, C., Ghiglieri, O., Masi, F., Scheggi, S., Tagliamonte, A., & De Montis, M. G. (1999). The effects of long-term administration of rubidium or lithium on reactivity to stress and on dopamine output in the nucleus accumbens in rats. *Brain Res, 826*(2), 200-209. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10224297

Gambarana, C., Masi, F., Tagliamonte, A., Scheggi, S., Ghiglieri, O., & De Montis, M. G. (1999). A chronic stress that impairs reactivity in rats also decreases dopaminergic transmission in the nucleus accumbens: a microdialysis study. *J*

Neurochem, 72(5), 2039-2046. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10217282

Garces-Ramirez, L., Green, J. L., Hiranita, T., Kopajtic, T. A., Mereu, M., Thomas, A. M., . . . Tanda, G. (2011). Sigma receptor agonists: receptor binding and effects on mesolimbic dopamine neurotransmission assessed by microdialysis. *Biol Psychiatry, 69*(3), 208-217. doi:10.1016/j.biopsych.2010.07.026

Garcia-Keller, C., Martinez, S. A., Esparza, M. A., Bollati, F., Kalivas, P. W., & Cancela, L. M. (2013). Cross-sensitization between cocaine and acute restraint stress is associated with sensitized dopamine but not glutamate release in the nucleus accumbens. *Eur J Neurosci, 37*(6), 982-995. doi:10.1111/ejn.12121

Gatley, S. J., Meehan, S. M., Chen, R., Pan, D. F., Schechter, M. D., & Dewey, S. L. (1996). Place preference and microdialysis studies with two derivatives of methylphenidate. *Life Sci, 58*(24), PL345-352. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8649202

Gehrke, B. J., Chefer, V. I., & Shippenberg, T. S. (2008). Effects of acute and repeated administration of salvinorin A on dopamine function in the rat dorsal striatum. *Psychopharmacology (Berl), 197*(3), 509-517. doi:10.1007/s00213-007-1067-6

Geiger, B. M., Haburcak, M., Avena, N. M., Moyer, M. C., Hoebel, B. G., & Pothos, E. N. (2009). Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. *Neuroscience, 159*(4), 1193-1199. doi:10.1016/j.neuroscience.2009.02.007

Geller, S. E., Goldstein, M., & Carnes, M. (2006). Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. *Journal of Womens Health, 15*(10), 1123-1131. doi:10.1089/jwh.2006.15.1123

Geller, S. E., Koch, A., Pellettieri, B., & Carnes, M. (2011). Inclusion, Analysis, and Reporting of Sex and Race/Ethnicity in Clinical Trials: Have We Made Progress? *Journal of Womens Health, 20*(3), 315-320. doi:10.1089/jwh.2010.2469

Gerasimov, M. R., Schiffer, W. K., Brodie, J. D., Lennon, I. C., Taylor, S. J., & Dewey, S. L. (2000). gamma-aminobutyric acid mimetic drugs differentially inhibit the dopaminergic response to cocaine. *Eur J Pharmacol, 395*(2), 129-135. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10794818

Gerasimov, M. R., Schiffer, W. K., Marstellar, D., Ferrieri, R., Alexoff, D., & Dewey, S. L. (2002). Toluene inhalation produces regionally specific changes in extracellular dopamine. *Drug Alcohol Depend, 65*(3), 243-251. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11841896

Geschwinde, T. (2013). *Rauschdrogen : Marktformen und Wirkungsweisen* (7. Aufl. 2013. 7., vollst. überarb. u. erw. Aufl ed.). Berlin, Heidelberg: Springer.

Giorgi, O., Corda, M. G., Carboni, G., Frau, V., Valentini, V., & Di Chiara, G. (1997). Effects of cocaine and morphine in rats from two psychogenetically selected lines: a behavioral and brain dialysis study. *Behav Genet, 27*(6), 537-546. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9476362

Giustino, A., Cuomo, V., & Marsden, C. A. (1998). Maternal cocaine exposure alters mesolimbic dopaminergic function in rat offspring. *Eur J Pharmacol, 345*(2), 175-180. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9600634

Glick, S. D., Rossman, K., Wang, S., Dong, N., & Keller, R. W., Jr. (1993). Local effects of ibogaine on extracellular levels of dopamine and its metabolites in

nucleus accumbens and striatum: interactions with D-amphetamine. *Brain Res, 628*(1-2), 201-208. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8313148

Goldstein, R. A., DesLauriers, C., & Burda, A. M. (2009). Cocaine: history, social implications, and toxicity--a review. *Dis Mon, 55*(1), 6-38. doi:10.1016/j.disamonth.2008.10.002

Greenfield, S. F., Brooks, A. J., Gordon, S. M., Green, C. A., Kropp, F., McHugh, R. K., . . . Miele, G. M. (2007). Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug Alcohol Depend, 86*(1), 1-21. doi:10.1016/j.drugalcdep.2006.05.012

Grotewold, S. K., Wall, V. L., Goodell, D. J., Hayter, C., & Bland, S. T. (2014). Effects of cocaine combined with a social cue on conditioned place preference and nucleus accumbens monoamines after isolation rearing in rats. *Psychopharmacology (Berl), 231*(15), 3041-3053. doi:10.1007/s00213-014-3470-0

Gurevitch, J., Koricheva, J., Nakagawa, S., & Stewart, G. (2018). Meta-analysis and the science of research synthesis. *Nature, 555*, 175. doi:10.1038/nature25753

Gurkovskaya, O. V., Palamarchouk, V., Smagin, G., & Goeders, N. E. (2005). Effects of corticotropin-releasing hormone receptor antagonists on cocaine-induced dopamine overflow in the medial prefrontal cortex and nucleus accumbens of rats. *Synapse, 57*(4), 202-212. doi:10.1002/syn.20172

Hackshaw, A., Morris, J. K., Boniface, S., Tang, J. L., & Milenkovic, D. (2018). Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *Bmj-British Medical Journal, 360*, 15. doi:10.1136/bmj.j5855

Hall, F. S., Wilkinson, L. S., Humby, T., Inglis, W., Kendall, D. A., Marsden, C. A., & Robbins, T. W. (1998). Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. *Pharmacol Biochem Behav, 59*(4), 859-872.

Hall, F. S., Wilkinson, L. S., Humby, T., & Robbins, T. W. (1999). Maternal deprivation of neonatal rats produces enduring changes in dopamine function. *Synapse, 32*(1), 37-43. doi:10.1002/(sici)1098-2396(199904)32:1<37::Aid-syn5>3.0.Co;2-4

Hamilton, M. E., Mele, A., & Pert, A. (1992). Striatal extracellular dopamine in conscious vs. anesthetized rats: effects of chloral hydrate anesthetic on responses to drugs of different classes. *Brain Res, 597*(1), 1-7.

Hamilton, M. E., Redondo, J. L., & Freeman, A. S. (2000). Overflow of dopamine and cholecystokinin in rat nucleus accumbens in response to acute drug administration. *Synapse, 38*(3), 238-242. doi:10.1002/1098-2396(20001201)38:3<238::Aid-syn2>3.0.Co;2-5

Harmer, C. J., Hitchcott, P. K., Morutto, S. L., & Phillips, G. D. (1997). Repeated d-amphetamine enhances stimulated mesoamygdaloid dopamine transmission. *Psychopharmacology (Berl), 132*(3), 247-254. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9292624

Harsing, L. G., Jr., Sershen, H., Toth, E., Hashim, A., Ramacci, M. T., & Lajtha, A. (1992). Acetyl-L-carnitine releases dopamine in rat corpus striatum: an in vivo microdialysis study. *Eur J Pharmacol, 218*(1), 117-121.

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., . . . Grant, B. F. (2013). DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry, 170*(8), 834-851. doi:10.1176/appi.ajp.2013.12060782

Heal, D. J., Smith, S. L., Gosden, J., & Nutt, D. J. (2013). Amphetamine, past and present--a pharmacological and clinical perspective. *J Psychopharmacol, 27*(6), 479-496. doi:10.1177/0269881113482532

Hedou, G., Feldon, J., & Heidbreder, C. A. (1999). Effects of cocaine on dopamine in subregions of the rat prefrontal cortex and their efferents to subterritories of the nucleus accumbens. *Eur J Pharmacol, 372*(2), 143-155. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10395094

Heeringa, M. J., & Abercrombie, E. D. (1995). Biochemistry of somatodendritic dopamine release in substantia nigra: an in vivo comparison with striatal dopamine release. *J Neurochem, 65*(1), 192-200. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1471-4159.1995.65010192.x

Hefco, V., Yamada, K., Hefco, A., Hritcu, L., Tiron, A., & Nabeshima, T. (2003). Role of the mesotelencephalic dopamine system in learning and memory processes in the rat. *Eur J Pharmacol, 475*(1-3), 55-60. Retrieved from https://www.sciencedirect.com/science/article/pii/S0014299903021150?via%3Dihub

Heidbreder, C., & De Witte, P. (1993). Ethanol differentially affects extracellular monoamines and GABA in the nucleus accumbens. *Pharmacol Biochem Behav, 46*(2), 477-481.

Heidbreder, C. A., Schenk, S., Partridge, B., & Shippenberg, T. S. (1998). Increased responsiveness of mesolimbic and mesostriatal dopamine neurons to cocaine following repeated administration of a selective kappa-opioid receptor agonist. *Synapse, 30*(3), 255-262. doi:10.1002/(SICI)1098-2396(199811)30:3<255::AID-SYN3>3.0.CO;2-A

Heidbreder, C. A., Thompson, A. C., & Shippenberg, T. S. (1996). Role of extracellular dopamine in the initiation and long-term expression of behavioral sensitization to cocaine. *J Pharmacol Exp Ther, 278*(2), 490-502. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8768696

Hemby, S. E., Co, C., Reboussin, D., Davies, H. M., Dworkin, S. I., & Smith, J. E. (1995). Comparison of a novel tropane analog of cocaine, 2 beta-propanoyl-3 beta-(4-tolyl) tropane with cocaine HCl in rats: nucleus accumbens extracellular dopamine concentration and motor activity. *J Pharmacol Exp Ther, 273*(2), 656-666. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7752068

Hernandez, G., Haines, E., & Shizgal, P. (2008). Potentiation of intracranial self-stimulation during prolonged subcutaneous infusion of cocaine. *J Neurosci Methods, 175*(1), 79-87. doi:10.1016/j.jneumeth.2008.08.005

Hernandez, G., Trujillo-Pisanty, I., Cossette, M. P., Conover, K., & Shizgal, P. (2012). Role of dopamine tone in the pursuit of brain stimulation reward. *J Neurosci, 32*(32), 11032-11041. doi:10.1523/JNEUROSCI.1051-12.2012

Hernandez, L., Gonzalez, L., Murzi, E., Paez, X., Gottberg, E., & Baptista, T. (1994). Testosterone modulates mesolimbic dopaminergic activity in male rats. *Neurosci Lett, 171*(1-2), 172-174.

Hernandez, L., Guzman, N. A., & Hoebel, B. G. (1991). Bidirectional microdialysis in vivo shows differential dopaminergic potency of cocaine, procaine and lidocaine in the nucleus accumbens using capillary electrophoresis for calibration of drug outward diffusion. *Psychopharmacology (Berl), 105*(2), 264-268. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1796132

Hernandez, L., & Hoebel, B. G. (1988). Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by

microdialysis. *Life Sci, 42*(18), 1705-1712. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3362036

Hernandez, L., Stanley, B. G., & Hoebel, B. G. (1986). A small, removable microdialysis probe. *Life Sci, 39*(26), 2629-2637.

Herrera-Marschitz, M., Luthman, J., & Ferre, S. (1994). Unilateral neonatal intracerebroventricular 6-hydroxydopamine administration in rats: II. Effects on extracellular monoamine, acetylcholine and adenosine levels monitored with in vivo microdialysis. *Psychopharmacology (Berl), 116*(4), 451-456.

Hertel, P., Mathe, J. M., Nomikos, G. G., Iurlo, M., Mathe, A. A., & Svensson, T. H. (1995). Effects of D-amphetamine and phencyclidine on behavior and extracellular concentrations of neurotensin and dopamine in the ventral striatum and the medial prefrontal cortex of the rat. *Behav Brain Res, 72*(1-2), 103-114.

Hirth, N., Meinhardt, M. W., Noori, H. R., Salgado, H., Torres-Ramirez, O., Uhrig, S., . . . Hansson, A. C. (2016). Convergent evidence from alcohol-dependent humans and rats for a hyperdopaminergic state in protracted abstinence. *Proc Natl Acad Sci U S A, 113*(11), 3024-3029. doi:10.1073/pnas.1506012113

Hogle, J. M., & Curtin, J. J. (2006). Sex differences in negative affective response during nicotine withdrawal. *Psychophysiology, 43*(4), 344-356. doi:10.1111/j.1469-8986.2006.00406.x

Holly, E. N., Shimamoto, A., Debold, J. F., & Miczek, K. A. (2012). Sex differences in behavioral and neural cross-sensitization and escalated cocaine taking as a result of episodic social defeat stress in rats. *Psychopharmacology (Berl), 224*(1), 179-188. doi:10.1007/s00213-012-2846-2

Hooks, M. S., Colvin, A. C., Juncos, J. L., & Justice, J. B., Jr. (1992). Individual differences in basal and cocaine-stimulated extracellular dopamine in the nucleus accumbens using quantitative microdialysis. *Brain Res, 587*(2), 306-312. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1525663

Hooks, M. S., Duffy, P., Striplin, C., & Kalivas, P. W. (1994). Behavioral and neurochemical sensitization following cocaine self-administration. *Psychopharmacology (Berl), 115*(1-2), 265-272. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7862906

Hooks, M. S., Jones, G. H., Smith, A. D., Neill, D. B., & Justice, J. B., Jr. (1991). Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. *Synapse, 9*(2), 121-128. doi:10.1002/syn.890090206

Horger, B. A., Valadez, A., Wellman, P. J., & Schenk, S. (1994). Augmentation of the neurochemical effects of cocaine in the ventral striatum and medial prefrontal cortex following preexposure to amphetamine, but not nicotine: an in vivo microdialysis study. *Life Sci, 55*(15), 1245-1251. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7934622

Horger, B. A., Wellman, P. J., Morien, A., Davies, B. T., & Schenk, S. (1991). Caffeine exposure sensitizes rats to the reinforcing effects of cocaine. *Neuroreport, 2*(1), 53-56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1768850

Howard, E. C., Schier, C. J., Wetzel, J. S., Duvauchelle, C. L., & Gonzales, R. A. (2008). The shell of the nucleus accumbens has a higher dopamine response compared with the core after non-contingent intravenous ethanol administration. *Neuroscience, 154*(3), 1042-1053. doi:10.1016/j.neuroscience.2008.04.014

Howes, S. R., Dalley, J. W., Morrison, C. H., Robbins, T. W., & Everitt, B. J. (2000). Leftward shift in the acquisition of cocaine self-administration in isolation-reared rats: relationship to extracellular levels of dopamine, serotonin and glutamate in the nucleus accumbens and amygdala-striatal FOS expression. *Psychopharmacology (Berl), 151*(1), 55-63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10958117

Hu, M., Crombag, H. S., Robinson, T. E., & Becker, J. B. (2004). Biological basis of sex differences in the propensity to self-administer cocaine. *Neuropsychopharmacology, 29*(1), 81-85. doi:10.1038/sj.npp.1300301

Huang, R. L., Wang, C. T., Tai, M. Y., Tsai, Y. F., & Peng, M. T. (1995). Effects of age on dopamine release in the nucleus accumbens and amphetamine-induced locomotor activity in rats. *Neurosci Lett, 200*(1), 61-64.

Humby, T., Wilkinson, L. S., Robbins, T. W., & Geyer, M. A. (1996). Prepulses inhibit startle-induced reductions of extracellular dopamine in the nucleus accumbens of rat. *J Neurosci, 16*(6), 2149-2156.

Hurd, Y. L., Kehr, J., & Ungerstedt, U. (1988). In vivo microdialysis as a technique to monitor drug transport: correlation of extracellular cocaine levels and dopamine overflow in the rat brain. *J Neurochem, 51*(4), 1314-1316. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3418351

Hurd, Y. L., & Ungerstedt, U. (1989a). Ca2+ dependence of the amphetamine, nomifensine, and Lu 19-005 effect on in vivo dopamine transmission. *Eur J Pharmacol, 166*(2), 261-269.

Hurd, Y. L., & Ungerstedt, U. (1989b). Cocaine: an in vivo microdialysis evaluation of its acute action on dopamine transmission in rat striatum. *Synapse, 3*(1), 48-54. doi:10.1002/syn.890030107

Hurd, Y. L., & Ungerstedt, U. (1989c). In vivo neurochemical profile of dopamine uptake inhibitors and releasers in rat caudate-putamen. *Eur J Pharmacol, 166*(2), 251-260.

Hutchinson, P. J., Jalloh, I., Helmy, A., Carpenter, K. L., Rostami, E., Bellander, B. M., . . . Ungerstedt, U. (2015). Consensus statement from the 2014 International Microdialysis Forum. *Intensive Care Med, 41*(9), 1517-1528. doi:10.1007/s00134-015-3930-y

Ichikawa, J., Kuroki, T., Kitchen, M. T., & Meltzer, H. Y. (1995). R(+)-8-OH-DPAT, a 5-HT1A receptor agonist, inhibits amphetamine-induced dopamine release in rat striatum and nucleus accumbens. *Eur J Pharmacol, 287*(2), 179-184.

Ichikawa, J., Kuroki, T., & Meltzer, H. Y. (1998). Differential effects of chronic imipramine and fluoxetine on basal and amphetamine-induced extracellular dopamine levels in rat nucleus accumbens. *Eur J Pharmacol, 350*(2-3), 159-164.

Ichikawa, J., & Meltzer, H. Y. (1992a). Amperozide, a novel antipsychotic drug, inhibits the ability of d-amphetamine to increase dopamine release in vivo in rat striatum and nucleus accumbens. *J Neurochem, 58*(6), 2285-2291. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-4159.1992.tb10975.x

Ichikawa, J., & Meltzer, H. Y. (1992b). The effect of chronic atypical antipsychotic drugs and haloperidol on amphetamine-induced dopamine release in vivo. *Brain Res, 574*(1-2), 98-104.

Ichikawa, J., & Meltzer, H. Y. (1995). DOI, a 5-HT2A/2C receptor agonist, potentiates amphetamine-induced dopamine release in rat striatum. *Brain Res, 698*(1-2), 204-208.

Ikegami, A., & Duvauchelle, C. L. (2004). Nucleus accumbens and medial prefrontal cortex dopaminergic response to self-administered cocaine in naive rats. *Neurosci Lett, 354*(3), 205-208. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14700732

Imperato, A., Obinu, M. C., Carta, G., Mascia, M. S., Casu, M. A., & Gessa, G. L. (1996). Reduction of dopamine release and synthesis by repeated amphetamine treatment: role in behavioral sensitization. *Eur J Pharmacol, 317*(2-3), 231-237.

Inada, T., Polk, K., Jin, C., Purser, C., Hume, A., Hoskins, B., . . . Rockhold, R. W. (1992). Cocaine elevates striatal dopamine efflux in spontaneously hypertensive and Wistar-Kyoto rats. *Brain Res Bull, 28*(2), 227-231. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1596742

Inada, T., Polk, K., Purser, C., Hume, A., Hoskins, B., Ho, I. K., & Rockhold, R. W. (1992). Behavioral and neurochemical effects of continuous infusion of cocaine in rats. *Neuropharmacology, 31*(7), 701-708. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1407406

Ivens, I. A., Janak, P. H., & Martinez, J. L., Jr. (1992). Microdialysis measurement of striatal dopamine levels in freely moving rats after cocaine or amphetamine treatment. *Proc West Pharmacol Soc, 35*, 165-169. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1502217

Iyaniwura, T. T., Wright, A. E., & Balfour, D. J. (2001). Evidence that mesoaccumbens dopamine and locomotor responses to nicotine in the rat are influenced by pretreatment dose and strain. *Psychopharmacology (Berl), 158*(1), 73-79. doi:10.1007/s002130100852

Izawa, J., Yamanashi, K., Asakura, T., Misu, Y., & Goshima, Y. (2006). Differential effects of methamphetamine and cocaine on behavior and extracellular levels of dopamine and 3,4-dihydroxyphenylalanine in the nucleus accumbens of conscious rats. *Eur J Pharmacol, 549*(1-3), 84-90. doi:10.1016/j.ejphar.2006.08.031

Jang, E. Y., Choe, E. S., Hwang, M., Kim, S. C., Lee, J. R., Kim, S. G., . . . Yang, C. H. (2008). Isoliquiritigenin suppresses cocaine-induced extracellular dopamine release in rat brain through GABA(B) receptor. *Eur J Pharmacol, 587*(1-3), 124-128. doi:10.1016/j.ejphar.2008.03.054

Javitt, D. C., Balla, A., Burch, S., Suckow, R., Xie, S., & Sershen, H. (2004). Reversal of phencyclidine-induced dopaminergic dysregulation by N-methyl-D-aspartate receptor/glycine-site agonists. *Neuropsychopharmacology, 29*(2), 300-307. doi:10.1038/sj.npp.1300313

Jaworski, J. N., Gonzales, R. A., & Randall, P. K. (2001). Effect of dopamine D2/D3 receptor antagonist sulpiride on amphetamine-induced changes in striatal extracellular dopamine. *Eur J Pharmacol, 418*(3), 201-206.

Jin, W., Kim, M. S., Jang, E. Y., Lee, J. Y., Lee, J. G., Kim, H. Y., . . . Yang, C. H. (2017). Acupuncture reduces relapse to cocaine-seeking behavior via activation of GABA neurons in the ventral tegmental area. *Addict Biol*. doi:10.1111/adb.12499

Jocham, G., Lauber, A. C., Muller, C. P., Huston, J. P., & de Souza Silva, M. A. (2007). Neurokinin 3 receptor activation potentiates the psychomotor and nucleus accumbens dopamine response to cocaine, but not its place conditioning effects. *Eur J Neurosci, 25*(8), 2457-2472. doi:10.1111/j.1460-9568.2007.05491.x

Jocham, G., Lezoch, K., Muller, C. P., Kart-Teke, E., Huston, J. P., & de Souza Silva, M. A. (2006). Neurokinin receptor antagonism attenuates cocaine's behavioural activating effects yet potentiates its dopamine-enhancing action in the nucleus accumbens core. *Eur J Neurosci, 24*(6), 1721-1732. doi:10.1111/j.1460-9568.2006.05041.x

Johnson, D. W., Eodice, P., Winterbottom, H., & Mokler, D. J. (2000). Decreased accumbens dopamine release after cocaine challenge in behaviorally sensitized female rats. *Pharmacol Biochem Behav, 65*(4), 659-664. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10764919

Johnson, D. W., & Glick, S. D. (1993). Dopamine release and metabolism in nucleus accumbens and striatum of morphine-tolerant and nontolerant rats. *Pharmacol Biochem Behav, 46*(2), 341-347. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8265688

Johnson, D. W., & Glick, S. D. (1994). Handling and/or saline injections alter basal and morphine-evoked changes in dopamine metabolites in the striatum and nucleus accumbens of rats. *Pharmacol Biochem Behav, 47*(3), 765-768. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8208798

Jonsson, S., Adermark, L., Ericson, M., & Soderpalm, B. (2014). The involvement of accumbal glycine receptors in the dopamine-elevating effects of addictive drugs. *Neuropharmacology, 82*, 69-75. doi:10.1016/j.neuropharm.2014.03.010

Justinova, Z., Ferre, S., Redhi, G. H., Mascia, P., Stroik, J., Quarta, D., . . . Goldberg, S. R. (2011). Reinforcing and neurochemical effects of cannabinoid CB1 receptor agonists, but not cocaine, are altered by an adenosine A2A receptor antagonist. *Addict Biol, 16*(3), 405-415. doi:10.1111/j.1369-1600.2010.00258.x

Kaariainen, T. M., Lehtonen, M., Forsberg, M. M., Savolainen, J., Kaenmaki, M., & Mannisto, P. T. (2008). Comparison of the effects of deramciclane, ritanserin and buspirone on extracellular dopamine and its metabolites in striatum and nucleus accumbens of freely moving rats. *Basic Clin Pharmacol Toxicol, 102*(1), 50-58. doi:10.1111/j.1742-7843.2007.00145.x

Kaczkurkin, A. N., Raznahan, A., & Satterthwaite, T. D. (2019). Sex differences in the developing brain: insights from multimodal neuroimaging. *Neuropsychopharmacology, 44*(1), 71-85. doi:10.1038/s41386-018-0111-z

Kailanto, S., Kankaanpaa, A., & Seppala, T. (2011). Subchronic steroid administration induces long lasting changes in neurochemical and behavioral response to cocaine in rats. *Steroids, 76*(12), 1310-1316. doi:10.1016/j.steroids.2011.06.011

Kalivas, P. W., & Duffy, P. (1993). Time course of extracellular dopamine and behavioral sensitization to cocaine. I. Dopamine axon terminals. *J Neurosci, 13*(1), 266-275. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8423473

Kalivas, P. W., Duffy, P., & Mackler, S. A. (1999). Interrupted expression of NAC-1 augments the behavioral responses to cocaine. *Synapse, 33*(2), 153-159. doi:10.1002/(SICI)1098-2396(199908)33:2<153::AID-SYN5>3.0.CO;2-N

Kankaanpaa, A., Lillsunde, P., Ruotsalainen, M., Ahtee, L., & Seppala, T. (1996). 5-HT3 receptor antagonist MDL 72222 dose-dependently attenuates cocaine- and amphetamine-induced elevations of extracellular dopamine in the nucleus accumbens and the dorsal striatum. *Pharmacol Toxicol, 78*(5), 317-321. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8737967

Kankaanpaa, A., Meririnne, E., & Seppala, T. (2002). 5-HT3 receptor antagonist MDL 72222 attenuates cocaine- and mazindol-, but not methylphenidate-induced

neurochemical and behavioral effects in the rat. *Psychopharmacology (Berl), 159*(4), 341-350. doi:10.1007/s00213-001-0939-4

Kashiwagi, Y., Rokugawa, T., Yamada, T., Obata, A., Watabe, H., Yoshioka, Y., & Abe, K. (2015). Pharmacological MRI response to a selective dopamine transporter inhibitor, GBR12909, in awake and anesthetized rats. *Synapse, 69*(4), 203-212. doi:10.1002/syn.21803

Keefer, P. L., Norman. (2010). *Innocent Bystanders*.

Kehoe, P., Shoemaker, W. J., Arons, C., Triano, L., & Suresh, G. (1998). Repeated isolation stress in the neonatal rat: relation to brain dopamine systems in the 10-day-old rat. *Behav Neurosci, 112*(6), 1466-1474. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9926829

Kehoe, P., Shoemaker, W. J., Triano, L., Hoffman, J., & Arons, C. (1996). Repeated isolation in the neonatal rat produces alterations in behavior and ventral striatal dopamine release in the juvenile after amphetamine challenge. *Behav Neurosci, 110*(6), 1435-1444. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8986344

Keller, R. W., Jr., Maisonneuve, I. M., Carlson, J. N., & Glick, S. D. (1992). Within-subject sensitization of striatal dopamine release after a single injection of cocaine: an in vivo microdialysis study. *Synapse, 11*(1), 28-34. doi:10.1002/syn.890110105

Kenny, P. J., & Markou, A. (2006). Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology, 31*(6), 1203-1211. doi:10.1038/sj.npp.1300905

Keyes, K. M., Martins, S. S., Blanco, C., & Hasin, D. S. (2010). Telescoping and gender differences in alcohol dependence: new evidence from two national surveys. *Am J Psychiatry, 167*(8), 969-976. doi:10.1176/appi.ajp.2009.09081161

Kihara, T., Ikeda, M., Matsubara, K., & Matsushita, A. (1993). Differential effects of ceruletide on amphetamine-induced behaviors and regional dopamine release in the rat. *Eur J Pharmacol, 230*(3), 271-277.

Kim, J. H., Austin, J. D., Tanabe, L., Creekmore, E., & Vezina, P. (2005). Activation of group II mGlu receptors blocks the enhanced drug taking induced by previous exposure to amphetamine. *Eur J Neurosci, 21*(1), 295-300. doi:10.1111/j.1460-9568.2004.03822.x

Kim, M. R., Kim, S. J., Lyu, Y. S., Kim, S. H., Lee, Y., Kim, T. H., . . . Yang, C. H. (2005). Effect of acupuncture on behavioral hyperactivity and dopamine release in the nucleus accumbens in rats sensitized to morphine. *Neurosci Lett, 387*(1), 17-21. doi:10.1016/j.neulet.2005.07.007

Kimmel, H. L., Justice, J. B., Jr., & Holtzman, S. G. (1998). Dissociation of morphine-induced potentiation of turning and striatal dopamine release by amphetamine in the nigrally-lesioned rat. *Eur J Pharmacol, 346*(2-3), 203-208.

Kimura, K., Nomikos, G. G., & Svensson, T. H. (1993). Effects of amperozide on psychostimulant-induced hyperlocomotion and dopamine release in the nucleus accumbens. *Pharmacol Biochem Behav, 44*(1), 27-36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7679220

King, D., & Finlay, J. M. (1995). Effects of selective dopamine depletion in medial prefrontal cortex on basal and evoked extracellular dopamine in neostriatum. *Brain Res, 685*(1-2), 117-128.

King, D., Zigmond, M. J., & Finlay, J. M. (1997). Effects of dopamine depletion in the medial prefrontal cortex on the stress-induced increase in extracellular

dopamine in the nucleus accumbens core and shell. *Neuroscience, 77*(1), 141-153.

Klinge, I. (2008). Gender perspectives in European research. *Pharmacol Res, 58*(3-4), 183-189. doi:10.1016/j.phrs.2008.07.011

Koch, S., Piercey, M. F., Galloway, M. P., & Svensson, K. A. (1997). Interactions between cocaine and (-)-DS 121: studies with 2-deoxyglucose autoradiography and microdialysis in the rat brain. *Eur J Pharmacol, 319*(2-3), 173-180. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9042588

Kohl, R. R., Katner, J. S., Chernet, E., & McBride, W. J. (1998). Ethanol and negative feedback regulation of mesolimbic dopamine release in rats. *Psychopharmacology (Berl), 139*(1-2), 79-85. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9768545

Köhler, T. (2008). *Rauschdrogen : Geschichte, Substanzen, Wirkung* (Orig.-Ausg. ed. Vol. 2445 : C.-H.-Beck-Wissen). München.

Kohut, S. J., Hiranita, T., Hong, S. K., Ebbs, A. L., Tronci, V., Green, J., . . . Tanda, G. (2014). Preference for distinct functional conformations of the dopamine transporter alters the relationship between subjective effects of cocaine and stimulation of mesolimbic dopamine. *Biol Psychiatry, 76*(10), 802-809. doi:10.1016/j.biopsych.2014.03.031

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology, 24*(2), 97-129. doi:10.1016/s0893-133x(00)00195-0

Koob, G. F., & LeMoal, M. (1997). Drug abuse: Hedonic homeostatic dysregulation. *Science, 278*(5335), 52-58. doi:10.1126/science.278.5335.52

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of Addiction. *Neuropsychopharmacology, 35*(1), 217-238. doi:10.1038/npp.2009.110

Kosten, T. A., Zhang, X. Y., & Kehoe, P. (2003). Chronic neonatal isolation stress enhances cocaine-induced increases in ventral striatal dopamine levels in rat pups. *Brain Res Dev Brain Res, 141*(1-2), 109-116. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12644254

Kosten, T. A., Zhang, X. Y., & Kehoe, P. (2005). Neurochemical and behavioral responses to cocaine in adult male rats with neonatal isolation experience. *J Pharmacol Exp Ther, 314*(2), 661-667. doi:10.1124/jpet.104.081216

Kraft, M., Noailles, P., & Angulo, J. A. (2001). Substance P modulates cocaine-evoked dopamine overflow in the striatum of the rat brain. *Ann N Y Acad Sci, 937*, 121-131. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11458533

Kraus, L., Piontek, D., Atzendorf, J., & Matos, E. G. d. (2016). Zeitliche Entwicklungen im Substanzkonsum in der deutschen Allgemeinbevölkerung : Ein Rückblick auf zwei Dekaden. *SUCHT, 62*, 283-294.

Kreitzer, A. C., & Malenka, R. C. (2008). Striatal Plasticity and Basal Ganglia Circuit Function. *Neuron, 60*(4), 543-554. doi:10.1016/j.neuron.2008.11.005

Kreuter, J. D., Mattson, B. J., Wang, B., You, Z. B., & Hope, B. T. (2004). Cocaine-induced Fos expression in rat striatum is blocked by chloral hydrate or urethane. *Neuroscience, 127*(1), 233-242. doi:10.1016/j.neuroscience.2004.04.047

Kuczenski, R., & Segal, D. (1989). Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. *J Neurosci, 9*(6), 2051-2065. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2566664

Kuczenski, R., & Segal, D. S. (1990). In vivo measures of monoamines during amphetamine-induced behaviors in rats. *Prog Neuropsychopharmacol Biol Psychiatry, 14 Suppl*, S37-50.

Kuczenski, R., & Segal, D. S. (1997). Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem, 68*(5), 2032-2037.

Kuczenski, R., & Segal, D. S. (1999). Dynamic changes in sensitivity occur during the acute response to cocaine and methylphenidate. *Psychopharmacology (Berl), 147*(1), 96-103. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10591874

Kuczenski, R., Segal, D. S., & Aizenstein, M. L. (1991). Amphetamine, cocaine, and fencamfamine: relationship between locomotor and stereotypy response profiles and caudate and accumbens dopamine dynamics. *J Neurosci, 11*(9), 2703-2712. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1715389

Kuczenski, R., Segal, D. S., Cho, A. K., & Melega, W. (1995). Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. *J Neurosci, 15*(2), 1308-1317. Retrieved from http://www.jneurosci.org/content/jneuro/15/2/1308.full.pdf

Kurling-Kailanto, S., Kankaanpaa, A., & Seppala, T. (2010). Subchronic nandrolone administration reduces cocaine-induced dopamine and 5-hydroxytryptamine outflow in the rat nucleus accumbens. *Psychopharmacology (Berl), 209*(3), 271-281. doi:10.1007/s00213-010-1796-9

Lack, C. M., Jones, S. R., & Roberts, D. C. (2008). Increased breakpoints on a progressive ratio schedule reinforced by IV cocaine are associated with reduced locomotor activation and reduced dopamine efflux in nucleus accumbens shell in rats. *Psychopharmacology (Berl), 195*(4), 517-525. doi:10.1007/s00213-007-0919-4

Lacy, R. T., Strickland, J. C., Feinstein, M. A., Robinson, A. M., & Smith, M. A. (2016). The effects of sex, estrous cycle, and social contact on cocaine and heroin self-administration in rats. *Psychopharmacology (Berl), 233*(17), 3201-3210. doi:10.1007/s00213-016-4368-9

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., . . . Charge. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics, 45*(12), 1452-U1206. doi:10.1038/ng.2802

Lategan, A. J., Marien, M. R., & Colpaert, F. C. (1990). Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis. *Brain Res, 523*(1), 134-138.

Laviola, G., Pascucci, T., & Pieretti, S. (2001). Striatal dopamine sensitization to D-amphetamine in periadolescent but not in adult rats. *Pharmacol Biochem Behav, 68*(1), 115-124. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11274716

Lecca, D., Piras, G., Driscoll, P., Giorgi, O., & Corda, M. G. (2004). A differential activation of dopamine output in the shell and core of the nucleus accumbens is associated with the motor responses to addictive drugs: a brain dialysis study in Roman high- and low-avoidance rats. *Neuropharmacology, 46*(5), 688-699. doi:10.1016/j.neuropharm.2003.11.011

Lee, B., Yang, C. H., Hahm, D. H., Lee, H. J., Han, S. M., Kim, K. S., & Shim, I. (2008). Inhibitory effects of ginseng total saponins on behavioral sensitization

and dopamine release induced by cocaine. *Biol Pharm Bull, 31*(3), 436-441. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18310906

Leggio, B., Masi, F., Grappi, S., Nanni, G., Gambarana, C., Colombo, G., & de Montis, M. G. (2003). Sardinian alcohol-preferring and non-preferring rats show different reactivity to aversive stimuli and a similar response to a natural reward. *Brain Res, 973*(2), 275-284. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12738071

Leggio, G. M., Cathala, A., Moison, D., Cunningham, K. A., Piazza, P. V., & Spampinato, U. (2009). Serotonin2C receptors in the medial prefrontal cortex facilitate cocaine-induced dopamine release in the rat nucleus accumbens. *Neuropharmacology, 56*(2), 507-513. doi:10.1016/j.neuropharm.2008.10.005

Leri, F., Flores, J., Rajabi, H., & Stewart, J. (2003). Effects of cocaine in rats exposed to heroin. *Neuropsychopharmacology, 28*(12), 2102-2116. doi:10.1038/sj.npp.1300284

Leri, F., Sorge, R. E., Cummins, E., Woehrling, D., Pfaus, J. G., & Stewart, J. (2007). High-dose methadone maintenance in rats: effects on cocaine self-administration and behavioral side effects. *Neuropsychopharmacology, 32*(11), 2290-2300. doi:10.1038/sj.npp.1301357

Lewy, J. (2017). *Drugs in Germany and the United States, 1819-1945 : the birth of two addictions.* Nomos

Dissertation, Hebrew University Jerusalem, 2011, Baden-Baden.

Lienau, A. K., & Kuschinsky, K. (1997). Sensitization phenomena after repeated administration of cocaine or D-amphetamine in rats: associative and non-associative mechanisms and the role of dopamine in the striatum. *Naunyn Schmiedebergs Arch Pharmacol, 355*(4), 531-537. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9109371

Lodge, D. J., & Grace, A. A. (2005). Acute and chronic corticotropin-releasing factor 1 receptor blockade inhibits cocaine-induced dopamine release: correlation with dopamine neuron activity. *J Pharmacol Exp Ther, 314*(1), 201-206. doi:10.1124/jpet.105.084913

Loidl, C. F., Herrera-Marschitz, M., Andersson, K., You, Z. B., Goiny, M., O'Connor, W. T., . . . et al. (1994). Long-term effects of perinatal asphyxia on basal ganglia neurotransmitter systems studied with microdialysis in rat. *Neurosci Lett, 175*(1-2), 9-12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7970219

Loonam, T. M., Noailles, P. A., Yu, J., Zhu, J. P., & Angulo, J. A. (2003). Substance P and cholecystokinin regulate neurochemical responses to cocaine and methamphetamine in the striatum. *Life Sci, 73*(6), 727-739. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12801594

Lu, L., Liu, Z., Huang, M., & Zhang, Z. (2003). Dopamine-dependent responses to cocaine depend on corticotropin-releasing factor receptor subtypes. *J Neurochem, 84*(6), 1378-1386. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12614338

Lutfy, K., Do, T., & Maidment, N. T. (2001). Orphanin FQ/nociceptin attenuates motor stimulation and changes in nucleus accumbens extracellular dopamine induced by cocaine in rats. *Psychopharmacology (Berl), 154*(1), 1-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11291998

Lynch, W. J., & Carroll, M. E. (1999). Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. *Psychopharmacology (Berl), 144*(1), 77-82.

Mabrouk, O. S., Han, J. L., Wong, J. T., Akil, H., Kennedy, R. T., & Flagel, S. B. (2017). The in Vivo Neurochemical Profile of Selectively Bred High-Responder and Low-Responder Rats Reveals Baseline, Cocaine-Evoked, and Novelty-Evoked Differences in Monoaminergic Systems. *ACS Chem Neurosci*. doi:10.1021/acschemneuro.7b00294

Maier, E. Y., Ledesma, R. T., Seiwell, A. P., & Duvauchelle, C. L. (2008). Diazepam alters cocaine self-administration, but not cocaine-stimulated locomotion or nucleus accumbens dopamine. *Pharmacol Biochem Behav, 91*(1), 202-207. doi:10.1016/j.pbb.2008.07.008

Maisonneuve, I. M., Archer, S., & Glick, S. D. (1994). U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. *Neurosci Lett, 181*(1-2), 57-60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7898771

Maisonneuve, I. M., & Glick, S. D. (1992). Interactions between ibogaine and cocaine in rats: in vivo microdialysis and motor behavior. *Eur J Pharmacol, 212*(2-3), 263-266. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1601069

Maisonneuve, I. M., & Glick, S. D. (1999). Attenuation of the reinforcing efficacy of morphine by 18-methoxycoronaridine. *Eur J Pharmacol, 383*(1), 15-21. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10556676

Maisonneuve, I. M., Ho, A., & Kreek, M. J. (1995). Chronic administration of a cocaine "binge" alters basal extracellular levels in male rats: an in vivo microdialysis study. *J Pharmacol Exp Ther, 272*(2), 652-657. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7853178

Maisonneuve, I. M., Keller, R. W., Jr., & Glick, S. D. (1991). Interactions between ibogaine, a potential anti-addictive agent, and morphine: an in vivo microdialysis study. *Eur J Pharmacol, 199*(1), 35-42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1893925

Maisonneuve, I. M., Keller, R. W., Jr., & Glick, S. D. (1992). Interactions of ibogaine and D-amphetamine: in vivo microdialysis and motor behavior in rats. *Brain Res, 579*(1), 87-92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1623410

Maisonneuve, I. M., & Kreek, M. J. (1994). Acute tolerance to the dopamine response induced by a binge pattern of cocaine administration in male rats: an in vivo microdialysis study. *J Pharmacol Exp Ther, 268*(2), 916-921. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8114005

Mangiavacchi, S., Masi, F., Scheggi, S., Leggio, B., De Montis, M. G., & Gambarana, C. (2001). Long-term behavioral and neurochemical effects of chronic stress exposure in rats. *J Neurochem, 79*(6), 1113-1121. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11752052

Manley, L. D., Kuczenski, R., Segal, D. S., Young, S. J., & Groves, P. M. (1992). Effects of frequency and pattern of medial forebrain bundle stimulation on caudate dialysate dopamine and serotonin. *J Neurochem, 58*(4), 1491-1498. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1548482

Martin-Fardon, R., Arnaud, M., Rousseau, E., Kamenka, J. M., Privat, A., & Vignon, J. (1996). N-[1-(2-Benzo(b)thiophenyl)cyclohexyl]piperidine (BTCP) and cocaine induce similar effects on striatal dopamine: a microdialysis study in freely moving rats. *Neurosci Lett, 211*(3), 179-182. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8817570

Martin-Fardon, R., Kerr, T. M., Deleuze-Masquefa, C., Kamenka, J. M., & Weiss, F. (2001). Behavioral and neurochemical effects of 3-OH-pip-BTCP, an active

metabolite of BTCP in rats. *Neuroreport, 12*(18), 4165-4169. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11742258

Mascia, P., Pistis, M., Justinova, Z., Panlilio, L. V., Luchicchi, A., Lecca, S., . . . Goldberg, S. R. (2011). Blockade of nicotine reward and reinstatement by activation of alpha-type peroxisome proliferator-activated receptors. *Biol Psychiatry, 69*(7), 633-641. doi:10.1016/j.biopsych.2010.07.009

Masi, F., Scheggi, S., Mangiavacchi, S., Tolu, P., Tagliamonte, A., De Montis, M. G., & Gambarana, C. (2001). Dopamine output in the nucleus accumbens shell is related to the acquisition and the retention of a motivated appetitive behavior in rats. *Brain Res, 903*(1-2), 102-109. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11382393

Mateo, Y., Lack, C. M., Morgan, D., Roberts, D. C., & Jones, S. R. (2005). Reduced dopamine terminal function and insensitivity to cocaine following cocaine binge self-administration and deprivation. *Neuropsychopharmacology, 30*(8), 1455-1463. doi:10.1038/sj.npp.1300687

Matos, E. G. d., Atzendorf, J., Kraus, L., & Piontek, D. (2016). Substanzkonsum in der Allgemeinbevölkerung in Deutschland : Ergebnisse des Epidemiologischen Suchtsurveys 2015. *SUCHT, 62*, 271-281.

Mattsson, A., Olson, L., Svensson, T. H., & Schilstrom, B. (2007). Cortical cholinergic deficiency enhances amphetamine-induced dopamine release in the accumbens but not striatum. *Exp Neurol, 208*(1), 73-79. doi:10.1016/j.expneurol.2007.07.012

McCallum, S. E., Cowe, M. A., Lewis, S. W., & Glick, S. D. (2012). alpha3beta4 nicotinic acetylcholine receptors in the medial habenula modulate the mesolimbic dopaminergic response to acute nicotine in vivo. *Neuropharmacology, 63*(3), 434-440. doi:10.1016/j.neuropharm.2012.04.015

McDougall, S. A., Reichel, C. M., Farley, C. M., Flesher, M. M., Der-Ghazarian, T., Cortez, A. M., . . . Crawford, C. A. (2008). Postnatal manganese exposure alters dopamine transporter function in adult rats: Potential impact on nonassociative and associative processes. *Neuroscience, 154*(2), 848-860. doi:10.1016/j.neuroscience.2008.03.070

McFarland, K., Lapish, C. C., & Kalivas, P. W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci, 23*(8), 3531-3537. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12716962

McKittrick, C. R., & Abercrombie, E. D. (2007). Catecholamine mapping within nucleus accumbens: differences in basal and amphetamine-stimulated efflux of norepinephrine and dopamine in shell and core. *J Neurochem, 100*(5), 1247-1256. doi:10.1111/j.1471-4159.2006.04300.x

McNeish, C. S., Svingos, A. L., Hitzemann, R., & Strecker, R. E. (1993). The 5-HT3 antagonist zacopride attenuates cocaine-induced increases in extracellular dopamine in rat nucleus accumbens. *Pharmacol Biochem Behav, 45*(4), 759-763. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8415815

McTavish, S. F., Cowen, P. J., & Sharp, T. (1999). Effect of a tyrosine-free amino acid mixture on regional brain catecholamine synthesis and release. *Psychopharmacology (Berl), 141*(2), 182-188.

Mele, A., Fontana, D., & Pert, A. (1997). Alterations in striatal dopamine overflow during rotational behavior induced by amphetamine, phencyclidine, and MK-801. *Synapse, 26*(3), 218-224. doi:10.1002/(sici)1098-2396(199707)26:3<218::Aid-syn3>3.0.Co;2-a

Melega, W. P., Williams, A. E., Schmitz, D. A., DiStefano, E. W., & Cho, A. K. (1995). Pharmacokinetic and pharmacodynamic analysis of the actions of D-amphetamine and D-methamphetamine on the dopamine terminal. *J Pharmacol Exp Ther, 274*(1), 90-96.

Meyer, A. C., & Bardo, M. T. (2015). Amphetamine self-administration and dopamine function: assessment of gene x environment interactions in Lewis and Fischer 344 rats. *Psychopharmacology (Berl), 232*(13), 2275-2285. doi:10.1007/s00213-014-3854-1

Miczek, K. A., Nikulina, E. M., Shimamoto, A., & Covington, H. E., 3rd. (2011). Escalated or suppressed cocaine reward, tegmental BDNF, and accumbal dopamine caused by episodic versus continuous social stress in rats. *J Neurosci, 31*(27), 9848-9857. doi:10.1523/JNEUROSCI.0637-11.2011

Miele, M., Mura, M. A., Enrico, P., Esposito, G., Serra, P. A., Migheli, R., . . . Desole, M. S. (2000). On the mechanism of d-amphetamine-induced changes in glutamate, ascorbic acid and uric acid release in the striatum of freely moving rats. *Br J Pharmacol, 129*(3), 582-588. doi:10.1038/sj.bjp.0703066

Mikkola, J. A., Honkanen, A., Piepponen, T. P., Kiianmaa, K., & Ahtee, L. (2001). Effects of repeated cocaine treatment on striatal dopamine release in alcohol-preferring AA and alcohol-avoiding ANA rats. *Naunyn Schmiedebergs Arch Pharmacol, 363*(2), 209-214. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11218073

Miller, D. W., & Abercrombie, E. D. (1996). Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. *Brain Res Bull, 40*(1), 57-62.

Miron, J., & Waldock, K. (2010). The budgetary impact of ending drug prohibition.

Mirza, N. R., Pei, Q., Stolerman, I. P., & Zetterstrom, T. S. (1996). The nicotinic receptor agonists (-)-nicotine and isoarecolone differ in their effects on dopamine release in the nucleus accumbens. *Eur J Pharmacol, 295*(2-3), 207-210.

Mitrano, D. A., Schroeder, J. P., Smith, Y., Cortright, J. J., Bubula, N., Vezina, P., & Weinshenker, D. (2012). alpha-1 Adrenergic receptors are localized on presynaptic elements in the nucleus accumbens and regulate mesolimbic dopamine transmission. *Neuropsychopharmacology, 37*(9), 2161-2172. doi:10.1038/npp.2012.68

Mocsary, Z., & Bradberry, C. W. (1996). Effect of ethanol on extracellular dopamine in nucleus accumbens: comparison between Lewis and Fischer 344 rat strains. *Brain Res, 706*(2), 194-198.

Moghaddam, B., & Bolinao, M. L. (1994). Glutamatergic antagonists attenuate ability of dopamine uptake blockers to increase extracellular levels of dopamine: implications for tonic influence of glutamate on dopamine release. *Synapse, 18*(4), 337-342. doi:10.1002/syn.890180409

Moghaddam, B., & Bunney, B. S. (1989). Differential effect of cocaine on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens: comparison to amphetamine. *Synapse, 4*(2), 156-161. doi:10.1002/syn.890040209

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg, 8*(5), 336-341. doi:10.1016/j.ijsu.2010.02.007

Molina, P. E., Ahmed, N., Gatley, J., Volkow, N. D., & Abumrad, N. N. (2001). L-tryptophan attenuation of the dopaminergic and behavioral responses to

cocaine. *Life Sci, 69*(16), 1897-1906. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11693270

Morgan, A. E., & Dewey, S. L. (1998). Effects of pharmacologic increases in brain GABA levels on cocaine-induced changes in extracellular dopamine. *Synapse, 28*(1), 60-65. doi:10.1002/(SICI)1098-2396(199801)28:1<60::AID-SYN7>3.0.CO;2-A

Morgan, A. E., Horan, B., Dewey, S. L., & Ashby, C. R., Jr. (1997). Repeated administration of 3,4-methylenedioxymethamphetamine augments cocaine's action on dopamine in the nucleus accumbens: a microdialysis study. *Eur J Pharmacol, 331*(1), R1-3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9274936

Morgan, A. E., Porter, S. P., Clarkson, F. A., Volkow, N. D., Fowler, J. S., & Dewey, S. L. (1997). Direct approach for attenuating cocaine's effects on extracellular dopamine: targeting the dopamine transporter. *Synapse, 26*(4), 423-427. doi:10.1002/(SICI)1098-2396(199708)26:4<423::AID-SYN10>3.0.CO;2-U

Muller, C. P., De Souza Silva, M. A., DePalma, G., Tomaz, C., Carey, R. J., & Huston, J. P. (2002). The selective serotonin(1A)-receptor antagonist WAY 100635 blocks behavioral stimulating effects of cocaine but not ventral striatal dopamine increase. *Behav Brain Res, 134*(1-2), 337-346. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12191821

Murzi, E., Contreras, Q., Teneud, L., Valecillos, B., Parada, M. A., De Parada, M. P., & Hernandez, L. (1996). Diabetes decreases limbic extracellular dopamine in rats. *Neurosci Lett, 202*(3), 141-144.

Naef, L., Moquin, L., Dal Bo, G., Giros, B., Gratton, A., & Walker, C. D. (2011). Maternal high-fat intake alters presynaptic regulation of dopamine in the nucleus accumbens and increases motivation for fat rewards in the offspring. *Neuroscience, 176*, 225-236. doi:10.1016/j.neuroscience.2010.12.037

Nanni, G., Scheggi, S., Leggio, B., Grappi, S., Masi, F., Rauggi, R., & De Montis, M. G. (2003). Acquisition of an appetitive behavior prevents development of stress-induced neurochemical modifications in rat nucleus accumbens. *J Neurosci Res, 73*(4), 573-580. doi:10.1002/jnr.10685

Nation, J. R., & Burkey, R. T. (1994). Attenuation of cocaine-induced elevation of nucleus accumbens dopamine in lead-exposed rats. *Brain Res Bull, 35*(1), 101-105. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7953752

Navailles, S., De Deurwaerdere, P., Porras, G., & Spampinato, U. (2004). In vivo evidence that 5-HT2C receptor antagonist but not agonist modulates cocaine-induced dopamine outflow in the rat nucleus accumbens and striatum. *Neuropsychopharmacology, 29*(2), 319-326. doi:10.1038/sj.npp.1300329

Navailles, S., Moison, D., Cunningham, K. A., & Spampinato, U. (2008). Differential regulation of the mesoaccumbens dopamine circuit by serotonin2C receptors in the ventral tegmental area and the nucleus accumbens: an in vivo microdialysis study with cocaine. *Neuropsychopharmacology, 33*(2), 237-246. doi:10.1038/sj.npp.1301414

Neisewander, J. L., O'Dell, L. E., Tran-Nguyen, L. T., Castaneda, E., & Fuchs, R. A. (1996). Dopamine overflow in the nucleus accumbens during extinction and reinstatement of cocaine self-administration behavior. *Neuropsychopharmacology, 15*(5), 506-514. doi:10.1016/S0893-133X(96)00097-8

Nelson, A. M., Larson, G. A., & Zahniser, N. R. (2009). Low or high cocaine responding rats differ in striatal extracellular dopamine levels and dopamine

transporter number. *J Pharmacol Exp Ther, 331*(3), 985-997. doi:10.1124/jpet.109.159897

Nelson, C. L., Sarter, M., & Bruno, J. P. (2000). Repeated pretreatment with amphetamine sensitizes increases in cortical acetylcholine release. *Psychopharmacology (Berl), 151*(4), 406-415.

Nicholson, K. L., Balster, R. L., Golembiowska, K., Kowalska, M., Tizzano, J. P., Skolnick, P., & Basile, A. S. (2009). Preclinical evaluation of the abuse potential of the analgesic bicifadine. *J Pharmacol Exp Ther, 330*(1), 236-248. doi:10.1124/jpet.109.150540

Noailles, P. A., & Angulo, J. A. (2002). Neurokinin receptors modulate the neurochemical actions of cocaine. *Ann N Y Acad Sci, 965*, 267-273. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12105102

Nomikos, G. G., Damsma, G., Wenkstern, D., & Fibiger, H. C. (1990). In vivo characterization of locally applied dopamine uptake inhibitors by striatal microdialysis. *Synapse, 6*(1), 106-112. doi:10.1002/syn.890060113

Nomikos, G. G., Damsma, G., Wenkstern, D., & Fibiger, H. C. (1991). Chronic desipramine enhances amphetamine-induced increases in interstitial concentrations of dopamine in the nucleus accumbens. *Eur J Pharmacol, 195*(1), 63-73.

Nomikos, G. G., Zis, A. P., Damsma, G., & Fibiger, H. C. (1991). Effects of chronic electroconvulsive shock on interstitial concentrations of dopamine in the nucleus accumbens. *Psychopharmacology (Berl), 105*(2), 230-238.

Noori, H. R., Fliegel, S., Brand, I., & Spanagel, R. (2012). The impact of acetylcholinesterase inhibitors on the extracellular acetylcholine concentrations in the adult rat brain: a meta-analysis. *Synapse, 66*(10), 893-901. doi:10.1002/syn.21581

Noori, H. R., Mervin, L. H., Bokharaie, V., Durmus, O., Egenrieder, L., Fritze, S., . . . Spanagel, R. (2018). Systemic neurotransmitter responses to clinically approved and experimental neuropsychiatric drugs. *Nat Commun, 9*(1), 4699. doi:10.1038/s41467-018-07239-1

Noori, H. R., Schöttler, J., Ercsey-Ravasz, M., Cosa-Linan, A., Varga, M., Toroczkai, Z., & Spanagel, R. (2017). A multiscale cerebral neurochemical connectome of the rat brain. *PLoS Biol, 15*(7), e2002612. doi:10.1371/journal.pbio.2002612

Noori, H. R., Spanagel, R., & Hansson, A. C. (2012). Neurocircuitry for modeling drug effects. *Addict Biol, 17*(5), 827-864. doi:10.1111/j.1369-1600.2012.00485.x

Nowak, P., Bortel, A., Dabrowska, J., Oswiecimska, J., Drosik, M., Kwiecinski, A., . . . Brus, R. (2007). Amphetamine and mCPP effects on dopamine and serotonin striatal in vivo microdialysates in an animal model of hyperactivity. *Neurotox Res, 11*(2), 131-144. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17449455

Nowak, P., Brus, R., & Kostrzewa, R. M. (2001). Amphetamine-induced enhancement of neostriatal in vivo microdialysate dopamine content in rats, quinpirole-primed as neonates. *Pol J Pharmacol, 53*(4), 319-329. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11990078

Nowak, P., Brus, R., Oswiecimska, J., Sokola, A., & Kostrzewa, R. M. (2002). 7-Nitroindazole enhances amphetamine-evoked dopamine release in rat striatum. an in vivo microdialysis and voltammetric study. *J Physiol Pharmacol, 53*(2), 251-263.

Nowak, P., Szczerbak, G., Biedka, I., Drosik, M., Kostrzewa, R. M., & Brus, R. (2006). Effect of ketanserin and amphetamine on nigrostriatal

neurotransmission and reactive oxygen species in Parkinsonian rats. In vivo microdialysis study. *J Physiol Pharmacol, 57*(4), 583-597.

Nowak, P., Szczerbak, G., Nitka, D., Kostrzewa, R. M., Sitkiewicz, T., & Brus, R. (2008). Effect of prenatal lead exposure on nigrostriatal neurotransmission and hydroxyl radical formation in rat neostriatum: dopaminergic-nitrergic interaction. *Toxicology, 246*(1), 83-89. doi:10.1016/j.tox.2007.12.026

O'Dell, L. E., & Parsons, L. H. (2004). Serotonin1B receptors in the ventral tegmental area modulate cocaine-induced increases in nucleus accumbens dopamine levels. *J Pharmacol Exp Ther, 311*(2), 711-719. doi:10.1124/jpet.104.069278

Ogbonmwan, Y. E., Sciolino, N. R., Groves-Chapman, J. L., Freeman, K. G., Schroeder, J. P., Edwards, G. L., . . . Weinshenker, D. (2015). The galanin receptor agonist, galnon, attenuates cocaine-induced reinstatement and dopamine overflow in the frontal cortex. *Addict Biol, 20*(4), 701-713. doi:10.1111/adb.12166

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., Jonsson, B., Grp, C. S., & European Brain, C. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology, 19*(1), 155-162. doi:10.1111/j.1468-1331.2011.03590.x

Olson, R. J., & Justice, J. B., Jr. (1993). Quantitative microdialysis under transient conditions. *Anal Chem, 65*(8), 1017-1022.

Olsson, S. K., Andersson, A. S., Linderholm, K. R., Holtze, M., Nilsson-Todd, L. K., Schwieler, L., . . . Erhardt, S. (2009). Elevated levels of kynurenic acid change the dopaminergic response to amphetamine: implications for schizophrenia. *Int J Neuropsychopharmacol, 12*(4), 501-512. doi:10.1017/s1461145708009383

Othman, A. A., Newman, A. H., & Eddington, N. D. (2007). Applicability of the dopamine and rate hypotheses in explaining the differences in behavioral pharmacology of the chloro-benztropine analogs: studies conducted using intracerebral microdialysis and population pharmacodynamic modeling. *J Pharmacol Exp Ther, 322*(2), 760-769. doi:10.1124/jpet.107.123315

Pacchioni, A. M., Cador, M., Bregonzio, C., & Cancela, L. M. (2007). A glutamate-dopamine interaction in the persistent enhanced response to amphetamine in nucleus accumbens core but not shell following a single restraint stress. *Neuropsychopharmacology, 32*(3), 682-692. doi:10.1038/sj.npp.1301080

Pacchioni, A. M., Gioino, G., Assis, A., & Cancela, L. M. (2002). A single exposure to restraint stress induces behavioral and neurochemical sensitization to stimulating effects of amphetamine: involvement of NMDA receptors. *Ann N Y Acad Sci, 965*, 233-246.

Pan, Y., Gerasimov, M. R., Kvist, T., Wellendorph, P., Madsen, K. K., Pera, E., . . . Silverman, R. B. (2012). (1S, 3S)-3-amino-4-difluoromethylenyl-1-cyclopentanoic acid (CPP-115), a potent gamma-aminobutyric acid aminotransferase inactivator for the treatment of cocaine addiction. *J Med Chem, 55*(1), 357-366. doi:10.1021/jm201231w

Pani, L., Kuzmin, A., Diana, M., De Montis, G., Gessa, G. L., & Rossetti, Z. L. (1990). Calcium receptor antagonists modify cocaine effects in the central nervous system differently. *Eur J Pharmacol, 190*(1-2), 217-221. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2076753

Pani, L., Kuzmin, A., Stefanini, E., Gessa, G. L., & Rossetti, Z. L. (1990). Flunarizine potentiates cocaine-induced dopamine release and motor stimulation in rats.

Eur J Pharmacol, 190(1-2), 223-227. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2076754

Panin, F., Cathala, A., Piazza, P. V., & Spampinato, U. (2012). Coupled intracerebral microdialysis and electrophysiology for the assessment of dopamine neuron function in vivo. *J Pharmacol Toxicol Methods, 65*(2), 83-92. doi:10.1016/j.vascn.2012.01.003

Panos, J. J., & Baker, L. E. (2010). An in vivo microdialysis assessment of concurrent MDMA and cocaine administration in Sprague-Dawley rats. *Psychopharmacology (Berl), 209*(1), 95-102. doi:10.1007/s00213-009-1774-2

Pap, A., & Bradberry, C. W. (1995). Excitatory amino acid antagonists attenuate the effects of cocaine on extracellular dopamine in the nucleus accumbens. *J Pharmacol Exp Ther, 274*(1), 127-133. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7616389

Pardue, M.-L., & Wizemann, T. M. (2001). *Exploring the biological contributions to human health: does sex matter?* : National Academies Press.

Parsons, L. H., & Justice, J. B., Jr. (1993). Serotonin and dopamine sensitization in the nucleus accumbens, ventral tegmental area, and dorsal raphe nucleus following repeated cocaine administration. *J Neurochem, 61*(5), 1611-1619. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7693863

Parsons, L. H., Kerr, T. M., & Weiss, F. (1998). Simple microbore high-performance liquid chromatographic method for the determination of dopamine and cocaine from a single in vivo brain microdialysis sample. *J Chromatogr B Biomed Sci Appl, 709*(1), 35-45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9653924

Parsons, L. H., Koob, G. F., & Weiss, F. (1999). RU 24969, a 5-HT1B/1A receptor agonist, potentiates cocaine-induced increases in nucleus accumbens dopamine. *Synapse, 32*(2), 132-135. doi:10.1002/(SICI)1098-2396(199905)32:2<132::AID-SYN6>3.0.CO;2-V

Paulson, P. E., & Robinson, T. E. (1995). Amphetamine-induced time-dependent sensitization of dopamine neurotransmission in the dorsal and ventral striatum: a microdialysis study in behaving rats. *Synapse, 19*(1), 56-65. doi:10.1002/syn.890190108

Paxinos, G., & Watson, C. (2007). *The rat brain in stereotaxic coordinates* (6. ed. ed.). Amsterdam ; Heidelberg[u.a.]: Academic Press; Elsevier.

Pearl, S. M., Maisonneuve, I. M., & Glick, S. D. (1996). Prior morphine exposure enhances ibogaine antagonism of morphine-induced dopamine release in rats. *Neuropharmacology, 35*(12), 1779-1784. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9076757

Peers, I. S., Ceuppens, P. R., & Harbron, C. (2012). In search of preclinical robustness. *Nature Reviews Drug Discovery, 11*(10), 733-734. doi:10.1038/nrd3849

Pehek, E. A. (1999). Comparison of effects of haloperidol administration on amphetamine-stimulated dopamine release in the rat medial prefrontal cortex and dorsal striatum. *J Pharmacol Exp Ther, 289*(1), 14-23.

Pehrson, A. L., & Moghaddam, B. (2010). Impact of metabotropic glutamate 2/3 receptor stimulation on activated dopamine release and locomotion. *Psychopharmacology (Berl), 211*(4), 443-455. doi:10.1007/s00213-010-1914-8

Peleg-Raibstein, D., & Feldon, J. (2006). Effects of dorsal and ventral hippocampal NMDA stimulation on nucleus accumbens core and shell dopamine release. *Neuropharmacology, 51*(5), 947-957. doi:10.1016/j.neuropharm.2006.06.002

Peng, X. Q., Li, X., Gilbert, J. G., Pak, A. C., Ashby, C. R., Jr., Brodie, J. D., . . . Xi, Z. X. (2008). Gamma-vinyl GABA inhibits cocaine-triggered reinstatement of drug-seeking behavior in rats by a non-dopaminergic mechanism. *Drug Alcohol Depend, 97*(3), 216-225. doi:10.1016/j.drugalcdep.2007.10.004

Peng, X. Q., Li, X., Li, J., Ramachandran, P. V., Gagare, P. D., Pratihar, D., . . . Xi, Z. X. (2008). Effects of gabapentin on cocaine self-administration, cocaine-triggered relapse and cocaine-enhanced nucleus accumbens dopamine in rats. *Drug Alcohol Depend, 97*(3), 207-215. doi:10.1016/j.drugalcdep.2007.09.019

Pepper, J. P., Baumann, M. H., Ayestas, M., & Rothman, R. B. (2001). Inhibition of MAO-A fails to alter cocaine-induced increases in extracellular dopamine and norepinephrine in rat nucleus accumbens. *Brain Res Mol Brain Res, 87*(2), 184-189. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11245920

Pettit, H. O., & Justice, J. B., Jr. (1989). Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. *Pharmacol Biochem Behav, 34*(4), 899-904. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2623043

Pettit, H. O., Pan, H. T., Parsons, L. H., & Justice, J. B., Jr. (1990). Extracellular concentrations of cocaine and dopamine are enhanced during chronic cocaine administration. *J Neurochem, 55*(3), 798-804. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2384752

Philpot, R. M., & Kirstein, C. L. (1999). Repeated cocaine exposure: effects on catecholamines in the nucleus accumbens septi of periadolescent animals. *Pharmacol Biochem Behav, 62*(3), 465-472. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10080238

Pierce, R. C., Born, B., Adams, M., & Kalivas, P. W. (1996). Repeated intra-ventral tegmental area administration of SKF-38393 induces behavioral and neurochemical sensitization to a subsequent cocaine challenge. *J Pharmacol Exp Ther, 278*(1), 384-392. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8764374

Pierce, R. C., Meil, W. M., & Kalivas, P. W. (1997). The NMDA antagonist, dizocilpine, enhances cocaine reinforcement without influencing mesoaccumbens dopamine transmission. *Psychopharmacology (Berl), 133*(2), 188-195. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9342786

Placenza, F. M., Rajabi, H., & Stewart, J. (2008). Effects of chronic buprenorphine treatment on levels of nucleus accumbens glutamate and on the expression of cocaine-induced behavioral sensitization in rats. *Psychopharmacology (Berl), 200*(3), 347-355. doi:10.1007/s00213-008-1210-z

Plock, N., & Kloft, C. (2005). Microdialysis--theoretical background and recent implementation in applied life-sciences. *Eur J Pharm Sci, 25*(1), 1-24. doi:10.1016/j.ejps.2005.01.017

Polissidis, A., Chouliara, O., Galanopoulos, A., Naxakis, G., Papahatjis, D., Papadopoulou-Daifoti, Z., & Antoniou, K. (2014). Cannabinoids negatively modulate striatal glutamate and dopamine release and behavioural output of acute D-amphetamine. *Behav Brain Res, 270*, 261-269. doi:10.1016/j.bbr.2014.05.029

Pontieri, F. E., Tanda, G., & Di Chiara, G. (1995). Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. *Proc Natl Acad Sci*

U S A, 92(26), 12304-12308. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8618890

Porras, G., De Deurwaerdere, P., Moison, D., & Spampinato, U. (2003). Conditional involvement of striatal serotonin3 receptors in the control of in vivo dopamine outflow in the rat striatum. *Eur J Neurosci, 17*(4), 771-781. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12603267

Porras, G., Di Matteo, V., De Deurwaerdere, P., Esposito, E., & Spampinato, U. (2002). Central serotonin4 receptors selectively regulate the impulse-dependent exocytosis of dopamine in the rat striatum: in vivo studies with morphine, amphetamine and cocaine. *Neuropharmacology, 43*(7), 1099-1109. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12504916

Porras, G., Di Matteo, V., Fracasso, C., Lucas, G., De Deurwaerdere, P., Caccia, S., . . . Spampinato, U. (2002). 5-HT2A and 5-HT2C/2B receptor subtypes modulate dopamine release induced in vivo by amphetamine and morphine in both the rat nucleus accumbens and striatum. *Neuropsychopharmacology, 26*(3), 311-324. doi:10.1016/s0893-133x(01)00333-5

Pothos, Rada, P., Mark, G. P., & Hoebel, B. G. (1991). Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. *Brain Res, 566*(1-2), 348-350. Retrieved from https://www.sciencedirect.com/science/article/pii/000689939191724F?via%3Dihub

Pothos, E. N., Creese, I., & Hoebel, B. G. (1995). Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. *J Neurosci, 15*(10), 6640-6650.

Pozzi, L., Trabace, L., Invernizzi, R., & Samanin, R. (1995). Intranigral GR-113808, a selective 5-HT4 receptor antagonist, attenuates morphine-stimulated dopamine release in the rat striatum. *Brain Res, 692*(1-2), 265-268.

Prendergast, B. J., Onishi, K. G., & Zucker, I. (2014). Female mice liberated for inclusion in neuroscience and biomedical research. *Neurosci Biobehav Rev, 40*, 1-5. doi:10.1016/j.neubiorev.2014.01.001

Priddy, B. M., Carmack, S. A., Thomas, L. C., Vendruscolo, J. C., Koob, G. F., & Vendruscolo, L. F. (2017). Sex, strain, and estrous cycle influences on alcohol drinking in rats. *Pharmacol Biochem Behav, 152*, 61-67. doi:10.1016/j.pbb.2016.08.001

Prinz, F., Schlange, T., & Asadullah, K. (2011). Believe it or not: how much can we rely on published data on potential drug targets? *Nature Reviews Drug Discovery, 10*(9), 712-U781. doi:10.1038/nrd3439-c1

Puig, S., Noble, F., & Benturquia, N. (2012). Short- and long-lasting behavioral and neurochemical adaptations: relationship with patterns of cocaine administration and expectation of drug effects in rats. *Transl Psychiatry, 2*, e175. doi:10.1038/tp.2012.103

Rada, P., Mark, G. P., Pothos, E., & Hoebel, B. G. (1991). Systemic morphine simultaneously decreases extracellular acetylcholine and increases dopamine in the nucleus accumbens of freely moving rats. *Neuropharmacology, 30*(10), 1133-1136.

Rahman, S., Zhang, Z., Papke, R. L., Crooks, P. A., Dwoskin, L. P., & Bardo, M. T. (2008). Region-specific effects of N,N'-dodecane-1,12-diyl-bis-3-picolinium

dibromide on nicotine-induced increase in extracellular dopamine in vivo. *Br J Pharmacol, 153*(4), 792-804. doi:10.1038/sj.bjp.0707612

Raje, S., Cornish, J., Newman, A. H., Cao, J., Katz, J. L., & Eddington, N. D. (2005). Pharmacodynamic assessment of the benztropine analogues AHN-1055 and AHN-2005 using intracerebral microdialysis to evaluate brain dopamine levels and pharmacokinetic/pharmacodynamic modeling. *Pharm Res, 22*(4), 603-612. doi:10.1007/s11095-005-2488-8

Raz, S., & Berger, B. D. (2010). Social isolation increases morphine intake: behavioral and psychopharmacological aspects. *Behav Pharmacol, 21*(1), 39-46. doi:10.1097/FBP.0b013e32833470bd

Reid, M. S., & Berger, S. P. (1996). Evidence for sensitization of cocaine-induced nucleus accumbens glutamate release. *Neuroreport, 7*(7), 1325-1329. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8817559

Reid, M. S., Herrera-Marschitz, M., & Ungerstedt, U. (1991). Effects of intranigral substance P and neurokinin A injections on extracellular dopamine levels measured with microdialysis in the striatum and frontoparietal cortex of rats. *J Neurochem, 57*(3), 970-974.

Reid, M. S., Ho, L. B., Tolliver, B. K., Wolkowitz, O. M., & Berger, S. P. (1998). Partial reversal of stress-induced behavioral sensitization to amphetamine following metyrapone treatment. *Brain Res, 783*(1), 133-142.

Reith, M. E., Li, M. Y., & Yan, Q. S. (1997). Extracellular dopamine, norepinephrine, and serotonin in the ventral tegmental area and nucleus accumbens of freely moving rats during intracerebral dialysis following systemic administration of cocaine and other uptake blockers. *Psychopharmacology (Berl), 134*(3), 309-317. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9438681

Ren, J., Xu, H., Choi, J. K., Jenkins, B. G., & Chen, Y. I. (2009). Dopaminergic response to graded dopamine concentration elicited by four amphetamine doses. *Synapse, 63*(9), 764-772. doi:10.1002/syn.20659

Robertson, G. S., Damsma, G., & Fibiger, H. C. (1991). Characterization of dopamine release in the substantia nigra by in vivo microdialysis in freely moving rats. *J Neurosci, 11*(7), 2209-2216. Retrieved from http://www.jneurosci.org/content/jneuro/11/7/2209.full.pdf

Robertson, M. W., Leslie, C. A., & Bennett, J. P., Jr. (1991). Apparent synaptic dopamine deficiency induced by withdrawal from chronic cocaine treatment. *Brain Res, 538*(2), 337-339. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2012975

Robinson, D. L., Howard, E. C., McConnell, S., Gonzales, R. A., & Wightman, R. M. (2009). Disparity between tonic and phasic ethanol-induced dopamine increases in the nucleus accumbens of rats. *Alcohol Clin Exp Res, 33*(7), 1187-1196. doi:10.1111/j.1530-0277.2009.00942.x

Robinson, T. E., & Camp, D. M. (1990). Does amphetamine preferentially increase the extracellular concentration of dopamine in the mesolimbic system of freely moving rats? *Neuropsychopharmacology, 3*(3), 163-173. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1694669

Robinson, T. E., & Camp, D. M. (1991). The effects of four days of continuous striatal microdialysis on indices of dopamine and serotonin neurotransmission in rats. *J Neurosci Methods, 40*(2-3), 211-222. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1724788

Robinson, T. E., Jurson, P. A., Bennett, J. A., & Bentgen, K. M. (1988). Persistent sensitization of dopamine neurotransmission in ventral striatum (nucleus

accumbens) produced by prior experience with (+)-amphetamine: a microdialysis study in freely moving rats. *Brain Res, 462*(2), 211-222. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2847849

Robinson, T. E., Yew, J., Paulson, P. E., & Camp, D. M. (1990). The long-term effects of neurotoxic doses of methamphetamine on the extracellular concentration of dopamine measured with microdialysis in striatum. *Neurosci Lett, 110*(1-2), 193-198.

Rossetti, Z. L., Hmaidan, Y., & Gessa, G. L. (1992). Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. *Eur J Pharmacol, 221*(2-3), 227-234. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1426002

Roth-Deri, I., Friedman, A., Abraham, L., Lax, E., Flaumenhaft, Y., Dikshtein, Y., & Yadid, G. (2009). Antidepressant treatment facilitates dopamine release and drug seeking behavior in a genetic animal model of depression. *Eur J Neurosci, 30*(3), 485-492. doi:10.1111/j.1460-9568.2009.06840.x

Rothman, R. B., Ayestas, M., & Baumann, M. H. (1996). Phentermine pretreatment antagonizes the cocaine-induced rise in mesolimbic dopamine. *Neuroreport, 8*(1), 7-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9051742

Rothman, R. B., Mele, A., Reid, A. A., Akunne, H., Greig, N., Thurkauf, A., . . . Pert, A. (1989). Tight binding dopamine reuptake inhibitors as cocaine antagonists. A strategy for drug development. *FEBS Lett, 257*(2), 341-344. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2583282

Rothman, R. B., Mele, A., Reid, A. A., Akunne, H. C., Greig, N., Thurkauf, A., . . . Pert, A. (1991). GBR12909 antagonizes the ability of cocaine to elevate extracellular levels of dopamine. *Pharmacol Biochem Behav, 40*(2), 387-397. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1839568

Rouge-Pont, F., Marinelli, M., Le Moal, M., Simon, H., & Piazza, P. V. (1995). Stress-induced sensitization and glucocorticoids. II. Sensitization of the increase in extracellular dopamine induced by cocaine depends on stress-induced corticosterone secretion. *J Neurosci, 15*(11), 7189-7195. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7472473

Rowley, H. L., Butler, S. A., Prow, M. R., Dykes, S. G., Aspley, S., Kilpatrick, I. C., & Heal, D. J. (2000). Comparison of the effects of sibutramine and other weight-modifying drugs on extracellular dopamine in the nucleus accumbens of freely moving rats. *Synapse, 38*(2), 167-176. doi:10.1002/1098-2396(200011)38:2<167::Aid-syn8>3.0.Co;2-w

Rowley, H. L., Kulkarni, R., Gosden, J., Brammer, R., Hackett, D., & Heal, D. J. (2012). Lisdexamfetamine and immediate release d-amfetamine - differences in pharmacokinetic/pharmacodynamic relationships revealed by striatal microdialysis in freely-moving rats with simultaneous determination of plasma drug concentrations and locomotor activity. *Neuropharmacology, 63*(6), 1064-1074. doi:10.1016/j.neuropharm.2012.07.008

Rubinow, D. R., & Schmidt, P. J. (2019). Sex differences and the neurobiology of affective disorders. *Neuropsychopharmacology, 44*(1), 111-128. doi:10.1038/s41386-018-0148-z

Ruetsch, Y. A., Boni, T., & Borgeat, A. (2001). From cocaine to ropivacaine: the history of local anesthetic drugs. *Curr Top Med Chem, 1*(3), 175-182. Retrieved from http://www.eurekaselect.com/81581/article

Schad, C. A., Justice, J. B., Jr., & Holtzman, S. G. (1995). Naloxone reduces the neurochemical and behavioral effects of amphetamine but not those of

cocaine. *Eur J Pharmacol, 275*(1), 9-16. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7774666

Schad, C. A., Justice, J. B., Jr., & Holtzman, S. G. (2002). Endogenous opioids in dopaminergic cell body regions modulate amphetamine-induced increases in extracellular dopamine levels in the terminal regions. *J Pharmacol Exp Ther, 300*(3), 932-938. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11861800

Schiffer, W. K., Azmoodeh, M., Gerasimov, M., Volkow, N. D., Fowler, J. S., & Dewey, S. L. (2003). Selegiline potentiates cocaine-induced increases in rodent nucleus accumbens dopamine. *Synapse, 48*(1), 35-38. doi:10.1002/syn.10183

Schiffer, W. K., Gerasimov, M. R., Bermel, R. A., Brodie, J. D., & Dewey, S. L. (2000). Stereoselective inhibition of dopaminergic activity by gamma vinyl-GABA following a nicotine or cocaine challenge: a PET/microdialysis study. *Life Sci, 66*(13), PL169-173. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10737423

Schiffer, W. K., Marsteller, D., & Dewey, S. L. (2003). Sub-chronic low dose gamma-vinyl GABA (vigabatrin) inhibits cocaine-induced increases in nucleus accumbens dopamine. *Psychopharmacology (Berl), 168*(3), 339-343. doi:10.1007/s00213-003-1446-6

Schwarz, A. J., Zocchi, A., Reese, T., Gozzi, A., Garzotti, M., Varnier, G., . . . Bifone, A. (2004). Concurrent pharmacological MRI and in situ microdialysis of cocaine reveal a complex relationship between the central hemodynamic response and local dopamine concentration. *Neuroimage, 23*(1), 296-304. doi:10.1016/j.neuroimage.2004.05.001

Segal, D. S., & Kuczenski, R. (1992). Repeated cocaine administration induces behavioral sensitization and corresponding decreased extracellular dopamine responses in caudate and accumbens. *Brain Res, 577*(2), 351-355. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1606506

Segal, D. S., & Kuczenski, R. (1999). Escalating dose-binge stimulant exposure: relationship between emergent behavioral profile and differential caudate-putamen and nucleus accumbens dopamine responses. *Psychopharmacology (Berl), 142*(2), 182-192.

Sena, E. S., Currie, G. L., McCann, S. K., Macleod, M. R., & Howells, D. W. (2014). Systematic reviews and meta-analysis of preclinical studies: why perform them and how to appraise them critically. *J Cereb Blood Flow Metab, 34*(5), 737-742. doi:10.1038/jcbfm.2014.28

Sershen, H., Balla, A., Aspromonte, J. M., Xie, S., Cooper, T. B., & Javitt, D. C. (2008). Characterization of interactions between phencyclidine and amphetamine in rodent prefrontal cortex and striatum: implications in NMDA/glycine-site-mediated dopaminergic dysregulation and dopamine transporter function. *Neurochem Int, 52*(1-2), 119-129. doi:10.1016/j.neuint.2007.07.011

Shams, W. M., Cossette, M. P., Shizgal, P., & Brake, W. G. (2017). 17beta-estradiol locally increases phasic dopamine release in the dorsal striatum. *Neurosci Lett, 665*, 29-32. doi:10.1016/j.neulet.2017.11.039

Shams, W. M., Sanio, C., Quinlan, M. G., & Brake, W. G. (2016). 17beta-Estradiol infusions into the dorsal striatum rapidly increase dorsal striatal dopamine release in vivo. *Neuroscience, 330*, 162-170. doi:10.1016/j.neuroscience.2016.05.049

Sharp, T., Zetterstrom, T., Ljungberg, T., & Ungerstedt, U. (1987). A direct comparison of amphetamine-induced behaviours and regional brain dopamine release in the rat using intracerebral dialysis. *Brain Res, 401*(2), 322-330. Retrieved from https://www.sciencedirect.com/science/article/pii/0006899387914168?via%3Dihub

Shimada, A., Yamaguchi, K., & Yanagita, T. (1996). Neurochemical analysis of the psychotoxicity of methamphetamine and cocaine by microdialysis in the rat brain. *Ann N Y Acad Sci, 801*, 361-370. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8959048

Shimamoto, A., Debold, J. F., Holly, E. N., & Miczek, K. A. (2011). Blunted accumbal dopamine response to cocaine following chronic social stress in female rats: exploring a link between depression and drug abuse. *Psychopharmacology (Berl), 218*(1), 271-279. doi:10.1007/s00213-011-2364-7

Shimamoto, A., Holly, E. N., Boyson, C. O., DeBold, J. F., & Miczek, K. A. (2015). Individual differences in anhedonic and accumbal dopamine responses to chronic social stress and their link to cocaine self-administration in female rats. *Psychopharmacology (Berl), 232*(4), 825-834. doi:10.1007/s00213-014-3725-9

Shimizu, N., Duan, S. M., Hori, T., & Oomura, Y. (1990). Glutamate modulates dopamine release in the striatum as measured by brain microdialysis. *Brain Res Bull, 25*(1), 99-102. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1976424

Shoaib, M., & Shippenberg, T. S. (1996). Adrenalectomy attenuates nicotine-induced dopamine release and locomotor activity in rats. *Psychopharmacology (Berl), 128*(4), 343-350.

Shoblock, J. R., Sullivan, E. B., Maisonneuve, I. M., & Glick, S. D. (2003). Neurochemical and behavioral differences between d-methamphetamine and d-amphetamine in rats. *Psychopharmacology (Berl), 165*(4), 359-369. doi:10.1007/s00213-002-1288-7

Shou, M., Ferrario, C. R., Schultz, K. N., Robinson, T. E., & Kennedy, R. T. (2006). Monitoring dopamine in vivo by microdialysis sampling and on-line CE-laser-induced fluorescence. *Anal Chem, 78*(19), 6717-6725. doi:10.1021/ac0608218

Skutella, T., Schwarting, R. K., Huston, J. P., Sillaber, I., Probst, J. C., Holsboer, F., & Spanagel, R. (1997). Infusions of tyrosine hydroxylase antisense oligodeoxynucleotide into substantia nigra of the rat: effects on tyrosine hydroxylase mRNA and protein content, striatal dopamine release and behaviour. *Eur J Neurosci, 9*(2), 210-220.

Smith, A. D., & Justice, J. B. (1994). The effect of inhibition of synthesis, release, metabolism and uptake on the microdialysis extraction fraction of dopamine. *J Neurosci Methods, 54*(1), 75-82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7815821

Sood, P., Cole, S., Fraier, D., & Young, A. M. (2009). Evaluation of metaquant microdialysis for measurement of absolute concentrations of amphetamine and dopamine in brain: a viable method for assessing pharmacokinetic profile of drugs in the brain. *J Neurosci Methods, 185*(1), 39-44. doi:10.1016/j.jneumeth.2009.09.004

Sorg, B. A., & Kalivas, P. W. (1991). Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. *Brain Res, 559*(1), 29-36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1782559

Sotty, F., Damgaard, T., Montezinho, L. P., Mork, A., Olsen, C. K., Bundgaard, C., & Husum, H. (2009). Antipsychotic-like effect of retigabine [N-(2-Amino-4-(fluorobenzylamino)-phenyl)carbamic acid ester], a KCNQ potassium channel opener, via modulation of mesolimbic dopaminergic neurotransmission. *J Pharmacol Exp Ther, 328*(3), 951-962. doi:10.1124/jpet.108.146944

Sotty, F., Montezinho, L. P., Steiniger-Brach, B., & Nielsen, J. (2009). Phosphodiesterase 10A inhibition modulates the sensitivity of the mesolimbic dopaminergic system to D-amphetamine: involvement of the D1-regulated feedback control of midbrain dopamine neurons. *J Neurochem, 109*(3), 766-775. doi:10.1111/j.1471-4159.2009.06004.x

Spanagel, R. (2009). Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol Rev, 89*(2), 649-705. doi:10.1152/physrev.00013.2008

Spanagel, R., & Weiss, F. (1999). The dopamine hypothesis of reward: past and current status. *Trends Neurosci, 22*(11), 521-527. doi:10.1016/s0166-2236(99)01447-2

Staudenmaier, S. M. (2017). *Metaanalyse der durch Nikotin hervorgerufenen Konzentrationsänderungen von Neurotransmittern im Säugetiergehirn und der speziesübergreifenden Verhaltensänderungen.* Dissertation, Ruprecht-Karls-Universität Heidelberg, 2017, Heidelberg.

Steinmiller, C. L., Maisonneuve, I. M., & Glick, S. D. (2003). Effects of dextromethorphan on dopamine release in the nucleus accumbens: Interactions with morphine. *Pharmacol Biochem Behav, 74*(4), 803-810. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12667894

Steketee, J. D. (1993). Injection of the protein kinase inhibitor H7 into the A10 dopamine region blocks the acute responses to cocaine: behavioral and in vivo microdialysis studies. *Neuropharmacology, 32*(12), 1289-1297. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8152520

Steketee, J. D. (1997). Intra-ventral tegmental area administration of H7 delays, but does not prevent the development of cocaine-induced sensitization. *Brain Res Bull, 43*(6), 565-571. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9254028

Steketee, J. D. (1998a). Injection of SCH 23390 into the ventral tegmental area blocks the development of neurochemical but not behavioral sensitization to cocaine. *Behav Pharmacol, 9*(1), 69-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9832950

Steketee, J. D. (1998b). Repeated injection of GBR 12909, but not cocaine or WIN 35,065-2, into the ventral tegmental area induces behavioral sensitization. *Behav Brain Res, 97*(1-2), 39-48. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9867229

Steketee, J. D., & Goeders, N. E. (2002). Pretreatment with corticosterone attenuates the nucleus accumbens dopamine response but not the stimulant response to cocaine in rats. *Behav Pharmacol, 13*(7), 593-601. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12409997

Steketee, J. D., & Kalivas, P. W. (1991). Sensitization to psychostimulants and stress after injection of pertussis toxin into the A10 dopamine region. *J Pharmacol Exp Ther, 259*(2), 916-924. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1941636

Steketee, J. D., & Kalivas, P. W. (1992). Microinjection of the D2 agonist quinpirole into the A10 dopamine region blocks amphetamine-, but not cocaine-

stimulated motor activity. *J Pharmacol Exp Ther, 261*(2), 811-818. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1349649

Steketee, J. D., Sorg, B. A., & Kalivas, P. W. (1992). The role of the nucleus accumbens in sensitization to drugs of abuse. *Prog Neuropsychopharmacol Biol Psychiatry, 16*(2), 237-246. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1579639

Steketee, J. D., & Walsh, T. J. (2005). Repeated injections of sulpiride into the medial prefrontal cortex induces sensitization to cocaine in rats. *Psychopharmacology (Berl), 179*(4), 753-760. doi:10.1007/s00213-004-2102-5

Stewart, J., Deschamps, S. E., & Amir, S. (1994). Inhibition of nitric oxide synthase does not block the development of sensitization to the behavioral activating effects of amphetamine. *Brain Res, 641*(1), 141-144.

Stewart, J., & Rajabi, H. (1996). Initial increases in extracellular dopamine in the ventral tegmental area provide a mechanism for the development of desipramine-induced sensitization within the midbrain dopamine system. *Synapse, 23*(4), 258-264. doi:10.1002/(SICI)1098-2396(199608)23:4<258::AID-SYN3>3.0.CO;2-6

Strecker, R. E., Eberle, W. F., & Ashby, C. R., Jr. (1995). Extracellular dopamine and its metabolites in the nucleus accumbens of Fischer and Lewis rats: basal levels and cocaine-induced changes. *Life Sci, 56*(6), PL135-141. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7530315

Sustkova-Fiserova, M., Jerabek, P., Havlickova, T., Kacer, P., & Krsiak, M. (2014). Ghrelin receptor antagonism of morphine-induced accumbens dopamine release and behavioral stimulation in rats. *Psychopharmacology (Berl), 231*(14), 2899-2908. doi:10.1007/s00213-014-3466-9

Sziraki, I., Sershen, H., Benuck, M., Hashim, A., & Lajtha, A. (1998). Receptor systems participating in nicotine-specific effects. *Neurochem Int, 33*(5), 445-457. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9874095

Szumlinski, K. K., Frys, K. A., & Kalivas, P. W. (2004). Dissociable roles for the dorsal and median raphe in the facilitatory effect of 5-HT1A receptor stimulation upon cocaine-induced locomotion and sensitization. *Neuropsychopharmacology, 29*(9), 1675-1687. doi:10.1038/sj.npp.1300473

Szumlinski, K. K., Maisonneuve, I. M., & Glick, S. D. (2000). The potential anti-addictive agent, 18-methoxycoronaridine, blocks the sensitized locomotor and dopamine responses produced by repeated morphine treatment. *Brain Res, 864*(1), 13-23. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10793182

Szumlinski, K. K., McCafferty, C. A., Maisonneuve, I. M., & Glick, S. D. (2000). Interactions between 18-methoxycoronaridine (18-MC) and cocaine: dissociation of behavioural and neurochemical sensitization. *Brain Res, 871*(2), 245-258. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10899291

Tanda, G., & Di Chiara, G. (1998). A dopamine-mu1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse. *Eur J Neurosci, 10*(3), 1179-1187.

Tanda, G., Ebbs, A., Newman, A. H., & Katz, J. L. (2005). Effects of 4'-chloro-3 alpha-(diphenylmethoxy)-tropane on mesostriatal, mesocortical, and mesolimbic dopamine transmission: comparison with effects of cocaine. *J Pharmacol Exp Ther, 313*(2), 613-620. doi:10.1124/jpet.104.080465

Tanda, G., Ebbs, A. L., Kopajtic, T. A., Elias, L. M., Campbell, B. L., Newman, A. H., & Katz, J. L. (2007). Effects of muscarinic M1 receptor blockade on cocaine-

induced elevations of brain dopamine levels and locomotor behavior in rats. *J Pharmacol Exp Ther, 321*(1), 334-344. doi:10.1124/jpet.106.118067

Tanda, G., Li, S. M., Mereu, M., Thomas, A. M., Ebbs, A. L., Chun, L. E., . . . Katz, J. L. (2013). Relations between stimulation of mesolimbic dopamine and place conditioning in rats produced by cocaine or drugs that are tolerant to dopamine transporter conformational change. *Psychopharmacology (Berl), 229*(2), 307-321. doi:10.1007/s00213-013-3109-6

Tanda, G., Mereu, M., Hiranita, T., Quarterman, J. C., Coggiano, M., & Katz, J. L. (2016). Lack of Specific Involvement of (+)-Naloxone and (+)-Naltrexone on the Reinforcing and Neurochemical Effects of Cocaine and Opioids. *Neuropsychopharmacology, 41*(11), 2772-2781. doi:10.1038/npp.2016.91

Tannenbaum, C., Schwarz, J. M., Clayton, J. A., de Vries, G. J., & Sullivan, C. (2016). Evaluating sex as a biological variable in preclinical research: the devil in the details. *Biol Sex Differ, 7*, 4. doi:10.1186/s13293-016-0066-x

Tateyama, M., Ohta, S., Nagao, T., Hirobe, M., & Ono, H. (1993). Inhibitory effect of 4-phenyltetrahydroisoquinoline on locomotion and dopamine release induced by micro-injection of methamphetamine into the nucleus accumbens of the rat. *Neuropharmacology, 32*(8), 761-766. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8413840

Tepper, J. M., Creese, I., & Schwartz, D. H. (1991). Stimulus-evoked changes in neostriatal dopamine levels in awake and anesthetized rats as measured by microdialysis. *Brain Res, 559*(2), 283-292. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1794102

Teter, C. J., McCabe, S. E., LaGrange, K., Cranford, J. A., & Boyd, C. J. (2006). Illicit use of specific prescription stimulants among college students: Prevalence, motives, and routes of administration. *Pharmacotherapy, 26*(10), 1501-1510. doi:10.1592/phco.26.10.1501

Thiriet, N., Jouvert, P., Gobaille, S., Solov'eva, O., Gough, B., Aunis, D., . . . Zwiller, J. (2001). C-type natriuretic peptide (CNP) regulates cocaine-induced dopamine increase and immediate early gene expression in rat brain. *Eur J Neurosci, 14*(10), 1702-1708. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11860464

Thongsaard, W., & Marsden, C. (2013). Effect of Thunbergia laurifolia extract on extracellular dopamine level in rat nucleus accumbens. *J Med Assoc Thai, 96 Suppl 1*, S85-89. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23724461

Tobiansky, D. J., Will, R. G., Lominac, K. D., Turner, J. M., Hattori, T., Krishnan, K., . . . Dominguez, J. M. (2016). Estradiol in the Preoptic Area Regulates the Dopaminergic Response to Cocaine in the Nucleus Accumbens. *Neuropsychopharmacology, 41*(7), 1897-1906. doi:10.1038/npp.2015.360

Tolliver, B. K., Ho, L. B., Reid, M. S., & Berger, S. P. (1996). Evidence for involvement of ventral tegmental area cyclic AMP systems in behavioral sensitization to psychostimulants. *J Pharmacol Exp Ther, 278*(1), 411-420. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8764377

Tolliver, B. K., Newman, A. H., Katz, J. L., Ho, L. B., Fox, L. M., Hsu, K., Jr., & Berger, S. P. (1999). Behavioral and neurochemical effects of the dopamine transporter ligand 4-chlorobenztropine alone and in combination with cocaine in vivo. *J Pharmacol Exp Ther, 289*(1), 110-122. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10086994

Torres, G., Rivier, C., & Weiss, F. (1994). A ketamine mixture anesthetic inhibits neuroendocrine and behavioral consequences of cocaine administration. *Brain Res, 656*(1), 33-42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7804843

Tran-Nguyen, L. T., Castaneda, E., & MacBeth, T. (1996). Changes in behavior and monoamine levels in microdialysate from dorsal striatum after 6-OHDA infusions into ventral striatum. *Pharmacol Biochem Behav, 55*(1), 141-150.

Tronci, E., Simola, N., Carta, A. R., De Luca, M. A., & Morelli, M. (2006). Potentiation of amphetamine-mediated responses in caffeine-sensitized rats involves modifications in A2A receptors and zif-268 mRNAs in striatal neurons. *J Neurochem, 98*(4), 1078-1089. doi:10.1111/j.1471-4159.2006.03943.x

Ungerstedt, U., & Hallstrom, A. (1987). In vivo microdialysis--a new approach to the analysis of neurotransmitters in the brain. *Life Sci, 41*(7), 861-864.

Ungerstedt, U., & Pycock, C. (1974). Functional correlates of dopamine neurotransmission. *Bull Schweiz Akad Med Wiss, 30*(1-3), 44-55.

Valdomero, A., Isoardi, N. A., Orsingher, O. A., & Cuadra, G. R. (2005). Pharmacological reactivity to cocaine in adult rats undernourished at perinatal age: behavioral and neurochemical correlates. *Neuropharmacology, 48*(4), 538-546. doi:10.1016/j.neuropharm.2004.11.011

Vazquez-DeRose, J., Stauber, G., Khroyan, T. V., Xie, X. S., Zaveri, N. T., & Toll, L. (2013). Retrodialysis of N/OFQ into the nucleus accumbens shell blocks cocaine-induced increases in extracellular dopamine and locomotor activity. *Eur J Pharmacol, 699*(1-3), 200-206. doi:10.1016/j.ejphar.2012.11.050

Verheij, M. M., Karel, P., Cools, A. R., & Homberg, J. R. (2014). Reduced cocaine-induced serotonin, but not dopamine and noradrenaline, release in rats with a genetic deletion of serotonin transporters. *Eur Neuropsychopharmacol, 24*(11), 1850-1854. doi:10.1016/j.euroneuro.2014.09.004

Vesterinen, H. M., Sena, E. S., Egan, K. J., Hirst, T. C., Churolov, L., Currie, G. L., . . . Macleod, M. R. (2014). Meta-analysis of data from animal studies: a practical guide. *J Neurosci Methods, 221*, 92-102. doi:10.1016/j.jneumeth.2013.09.010

Vezina, P. (1993). Amphetamine injected into the ventral tegmental area sensitizes the nucleus accumbens dopaminergic response to systemic amphetamine: an in vivo microdialysis study in the rat. *Brain Res, 605*(2), 332-337.

Vollbrecht, P. J., Mabrouk, O. S., Nelson, A. D., Kennedy, R. T., & Ferrario, C. R. (2016). Pre-existing differences and diet-induced alterations in striatal dopamine systems of obesity-prone rats. *Obesity (Silver Spring), 24*(3), 670-677. doi:10.1002/oby.21411

Von Scherzer, K. (1865). Reise der österreichischen Fregatte Novara um die Erde. Statistischcommercieller Theil von Dr. Karl von Scherzer. Erster Band. Wien 1864. *Zeitschrift der Gesellschaft für Erdkunde zu Berlin, 19*, 156.

Wan, R. Q., Giovanni, A., Kafka, S. H., & Corbett, R. (1996). Neonatal hippocampal lesions induced hyperresponsiveness to amphetamine: behavioral and in vivo microdialysis studies. *Behav Brain Res, 78*(2), 211-223. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8864054

Wang, X. F., Bi, G. H., He, Y., Yang, H. J., Gao, J. T., Okunola-Bakare, O. M., . . . Newman, A. H. (2015). R-modafinil attenuates nicotine-taking and nicotine-seeking behavior in alcohol-preferring rats. *Neuropsychopharmacology, 40*(7), 1762-1771. doi:10.1038/npp.2015.24

Warburton, E. C., Mitchell, S. N., & Joseph, M. H. (1996). Calcium dependence of sensitised dopamine release in rat nucleus accumbens following amphetamine

challenge: implications for the disruption of latent inhibition. *Behav Pharmacol, 7*(2), 119-129.

Wasik, A., Romanska, I., & Antkiewicz-Michaluk, L. (2010). Important role of 3-methoxytyramine in the inhibition of cocaine sensitization by 1-methyl-1,2,3,4-tetrahydroisoquinoline: an in vivo microdialysis study. *Pharmacol Rep, 62*(6), 983-997. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21273655

Weikop, P., Egestad, B., & Kehr, J. (2004). Application of triple-probe microdialysis for fast pharmacokinetic/pharmacodynamic evaluation of dopamimetic activity of drug candidates in the rat brain. *J Neurosci Methods, 140*(1-2), 59-65. doi:10.1016/j.jneumeth.2004.06.017

Weiss, F., Paulus, M. P., Lorang, M. T., & Koob, G. F. (1992). Increases in extracellular dopamine in the nucleus accumbens by cocaine are inversely related to basal levels: effects of acute and repeated administration. *J Neurosci, 12*(11), 4372-4380. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1432099

Westenbroek, C., Perry, A. N., & Becker, J. B. (2013). Pair housing differentially affects motivation to self-administer cocaine in male and female rats. *Behav Brain Res, 252*, 68-71. doi:10.1016/j.bbr.2013.05.040

Westenbroek, C., Perry, A. N., Jagannathan, L., & Becker, J. B. (2017). Effect of social housing and oxytocin on the motivation to self-administer methamphetamine in female rats. *Physiol Behav*. doi:10.1016/j.physbeh.2017.10.020

Whishaw, I. Q., Fiorino, D., Mittleman, G., & Castaneda, E. (1992). Do forebrain structures compete for behavioral expression? Evidence from amphetamine-induced behavior, microdialysis, and caudate-accumbens lesions in medial frontal cortex damaged rats. *Brain Res, 576*(1), 1-11.

Whittington, R. A., Virag, L., Vulliemoz, Y., Cooper, T. B., & Morishima, H. O. (2002). Dexmedetomidine increases the cocaine seizure threshold in rats. *Anesthesiology, 97*(3), 693-700. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12218537

Wilkinson, L. S., Killcross, S. S., Humby, T., Hall, F. S., Geyer, M. A., & Robbins, T. W. (1994). Social isolation in the rat produces developmentally specific deficits in prepulse inhibition of the acoustic startle response without disrupting latent inhibition. *Neuropsychopharmacology, 10*(1), 61-72. doi:10.1038/npp.1994.8

Wilkinson, L. S., Mittleman, G., Torres, E., Humby, T., Hall, F. S., & Robbins, T. W. (1993). Enhancement of amphetamine-induced locomotor activity and dopamine release in nucleus accumbens following excitotoxic lesions of the hippocampus. *Behav Brain Res, 55*(2), 143-150.

Willins, D. L., & Meltzer, H. Y. (1998). Serotonin 5-HT2C agonists selectively inhibit morphine-induced dopamine efflux in the nucleus accumbens. *Brain Res, 781*(1-2), 291-299. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9507167

Wise, R. A. (2009). Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. *Trends Neurosci, 32*(10), 517-524. doi:10.1016/j.tins.2009.06.004

Wolf, M. E., Xue, C. J., White, F. J., & Dahlin, S. L. (1994). MK-801 does not prevent acute stimulatory effects of amphetamine or cocaine on locomotor activity or extracellular dopamine levels in rat nucleus accumbens. *Brain Res, 666*(2), 223-231. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7882032

Woodward, J. J., Compton, D. M., Balster, R. L., & Martin, B. R. (1995). In vitro and in vivo effects of cocaine and selected local anesthetics on the dopamine transporter. *Eur J Pharmacol, 277*(1), 7-13. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7635175

World Health Organization. (1994). Lexicon of alcohol and drug terms.

World Health Organization. (2018, May 17, 2018). Dependence syndrome. Retrieved from http://www.who.int/substance_abuse/terminology/definition1/en/

World Health Organization, & Unit, W. H. O. M. o. S. A. (2014). *Global status report on alcohol and health, 2014*: World Health Organization.

Xi, Z. X., Kiyatkin, M., Li, X., Peng, X. Q., Wiggins, A., Spiller, K., . . . Gardner, E. L. (2010). N-acetylaspartylglutamate (NAAG) inhibits intravenous cocaine self-administration and cocaine-enhanced brain-stimulation reward in rats. *Neuropharmacology, 58*(1), 304-313. doi:10.1016/j.neuropharm.2009.06.016

Xi, Z. X., Li, X., Peng, X. Q., Li, J., Chun, L., Gardner, E. L., . . . Ashby, C. R., Jr. (2010). Inhibition of NAALADase by 2-PMPA attenuates cocaine-induced relapse in rats: a NAAG-mGluR2/3-mediated mechanism. *J Neurochem, 112*(2), 564-576. doi:10.1111/j.1471-4159.2009.06478.x

Xi, Z. X., Yang, Z., Li, S. J., Li, X., Dillon, C., Peng, X. Q., . . . Gardner, E. L. (2007). Levo-tetrahydropalmatine inhibits cocaine's rewarding effects: experiments with self-administration and brain-stimulation reward in rats. *Neuropharmacology, 53*(6), 771-782. doi:10.1016/j.neuropharm.2007.08.004

Xie, X., & Steketee, J. D. (2009). Effects of repeated exposure to cocaine on group II metabotropic glutamate receptor function in the rat medial prefrontal cortex: behavioral and neurochemical studies. *Psychopharmacology (Berl), 203*(3), 501-510. doi:10.1007/s00213-008-1392-4

Yamamoto, B. K., & Meltzer, H. Y. (1992). The effect of the atypical antipsychotic drug, amperozide, on carrier-mediated striatal dopamine release measured in vivo. *J Pharmacol Exp Ther, 263*(1), 180-185. Retrieved from http://jpet.aspetjournals.org/content/263/1/180.long

Yan, Q. S. (1999). Extracellular dopamine and serotonin after ethanol monitored with 5-minute microdialysis. *Alcohol, 19*(1), 1-7.

Yan, Q. S. (2003). Involvement of non-exocytotic mechanisms in ethanol-induced in vivo dopamine release: comparisons with cocaine. *Eur J Pharmacol, 477*(1), 37-44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14512096

Yan, Q. S., Zheng, S. Z., Feng, M. J., & Yan, S. E. (2005). Involvement of 5-HT1B receptors within the ventral tegmental area in ethanol-induced increases in mesolimbic dopaminergic transmission. *Brain Res, 1060*(1-2), 126-137. doi:10.1016/j.brainres.2005.08.051

Yong, Z., Yan, L., Zhou, P., Yu, G., Dong, H., & Gong, Z. (2012). Effects of thienorphine on release of dopamine and noradrenalin: an in vivo microdialysis study in rats. *Neurosci Lett, 513*(2), 132-136. doi:10.1016/j.neulet.2012.02.013

Yoon, S. S., Kwon, Y. K., Kim, M. R., Shim, I., Kim, K. J., Lee, M. H., . . . Yang, C. H. (2004). Acupuncture-mediated inhibition of ethanol-induced dopamine release in the rat nucleus accumbens through the GABAB receptor. *Neurosci Lett, 369*(3), 234-238. doi:10.1016/j.neulet.2004.07.095

Yoshimoto, K., Kato, B., Ueda, S., Noritake, K., Sakai, K., Shibata, M., . . . Yasuhara, M. (2001). Dopamine and serotonin uptake inhibitors on the release of dopamine and serotonin in the nucleus accumbens of young and aged rats. *Mech Ageing Dev, 122*(15), 1707-1721. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11557275

Yoshimoto, K., Komura, S., & Kawamura, K. (1992). Occurrence in vivo of 5-hydroxytryptophol in the brain of rats treated with ethanol. *Alcohol Alcohol, 27*(2), 131-136.

Yoshimoto, K., McBride, W. J., Lumeng, L., & Li, T. K. (1992a). Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. *Alcohol, 9*(1), 17-22.

Yoshimoto, K., McBride, W. J., Lumeng, L., & Li, T. K. (1992b). Ethanol enhances the release of dopamine and serotonin in the nucleus accumbens of HAD and LAD lines of rats. *Alcohol Clin Exp Res, 16*(4), 781-785. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1530-0277.1992.tb00678.x

Yoshimoto, K., Ueda, S., Nishi, M., Yang, Y., Matsushita, H., Takeuchi, Y., . . . Yasuhara, M. (2000). Changes in dopamine transporter and c-Fos expression in the nucleus accumbens of alcohol-tolerant rats. *Alcohol Clin Exp Res, 24*(3), 361-365. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10776677

Zayara, A. E., McIver, G., Valdivia, P. N., Lominac, K. D., McCreary, A. C., & Szumlinski, K. K. (2011). Blockade of nucleus accumbens 5-HT2A and 5-HT2C receptors prevents the expression of cocaine-induced behavioral and neurochemical sensitization in rats. *Psychopharmacology (Berl), 213*(2-3), 321-335. doi:10.1007/s00213-010-1996-3

Zernig, G., O'Laughlin, I. A., & Fibiger, H. C. (1997). Nicotine and heroin augment cocaine-induced dopamine overflow in nucleus accumbens. *Eur J Pharmacol, 337*(1), 1-10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9389374

Zhu, D. X., Sullivan, J. P., & Brioni, J. D. (1999). ATP-sensitive potassium channels regulate in vivo dopamine release in rat striatum. *Jpn J Pharmacol, 79*(1), 59-64.

Own publications

I. Noori, H.R., Mervin, L.H., Bokharaie, V., Durmus, O., Egenrieder, L., Fritze, S., Gruhlke, B., Reinhardt, G., Schabel, H., Staudenmaier, S., Logothetis, N.K., Bender, A., Spanagel, R. (2018). Systemic neurotransmitter responses to clinically approved and experimental neuropsychiatric drugs. *Nat Commun, 9*(1), 4699. doi: 10.1038/s41467-018-07239-1

II. Egenrieder, L., Mitricheva, E., Spanagel, R., Noori, H.R. (2019). No basal or drug-induced sex differences in striatal dopaminergic levels: a cluster and meta-analysis of rat microdialysis studies. *J Neurochem*, *152, 482–492.,* https://doi.org/10.1111/jnc.14911

7 LIST OF APPENDICES

7.1 Global statistics

Table 29: Number of animals per drug/ keyword combination

Drug	Number of included animals
Amphetamine	402
Cocaine females (male rats)	282 (3805)
Alcohol	289
Morphine	54
Nicotine	48
SUM	4879

Table 30: Used perfusion solutions in percent

% aCSF	% Ringer	% Others	% Not specified
49	27	16	8

7.2 Alcohol

7.2.1 Nucleus accumbens

Table 31: Peak percentage baseline values of accumbal dopamine after the administration of different doses of alcohol

Dose (g/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.25	178.45	± 8.41 (82.26)	-	31	50	-	-	(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993)
0.5	171.74	± 10.73 (100)	female	28	100	0,018	4.84 (1,11)	(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993; Blanchard, Steindorf, Wang, LeFevre, et al., 1993)
	127.10	± 1.76	male	62	0			(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993; Blanchard, Steindorf, Wang, LeFevre, et al., 1993; Howard,

Dose (g/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
		(32.37)						Schier, Wetzel, Duvauchelle, & Gonzales, 2008; Mocsary & Bradberry, 1996; Yan, 1999; Yoshimoto, McBride, Lumeng, & Li, 1992a, 1992b)
1	155.43	± 1.93 (53.09)	-	139	21	-	-	(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993; Blanchard, Steindorf, Wang, LeFevre, et al., 1993; Bustamante et al., 2008; Campbell & McBride, 1995; C. Heidbreder & De Witte, 1993; Howard et al., 2008; Mocsary & Bradberry, 1996; D. L. Robinson, Howard, McConnell, Gonzales, & Wightman, 2009; Yan, 1999; Yan, Zheng, Feng, & Yan, 2005; Yoon et al., 2004; Yoshimoto, McBride, et al., 1992a, 1992b)
2	151.53	± 1.42 (51.23)	-	75	15	-	-	(Blanchard, Steindorf, Wang, & Glick, 1993; Campbell & McBride, 1995; Kohl, Katner, Chernet, & McBride, 1998; Mocsary & Bradberry, 1996; D. L. Robinson et al., 2009; Yan, 1999; Yan et al., 2005; Yoshimoto, McBride, et al., 1992a, 1992b)
3	200	± 25 (40)	-	4	100	-	-	(Kohl et al., 1998)
50mg%	85	± 4 (20)	-	7	100	-	-	(Ding, Ingraham, Rodd, & McBride, 2016)
100mg%	122.27	± 4.32 (47.27)	-	11	100	-	-	(Ding et al., 2012; Ding, Rodd, Engleman, & McBride, 2009)
150mg%	145	± 12 (20)	-	7	100	-	-	(Ding et al., 2016)
200mg%	138.15	± 4.60 (44.44)	-	27	100	-	-	(Ding et al., 2012; Ding et al., 2009)
300mg%	145	± 10 (40)	-	4	100	-	-	(Ding et al., 2009)

7.2.2 Caudate putamen

Table 32: Peak percentage baseline values of dopamine in caudate putamen after the administration of different doses of alcohol

Dose (g/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.25	140.77	± 4.45 (93.87)	-	31	50	-	-	(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993)
0.5	160.01	± 2.73 (40)	-	52	53	-	-	(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993; Blanchard, Steindorf, Wang, LeFevre, et al., 1993)
1	123.28	± 2.04 (41.02)	-	49	22	-	-	(Blanchard & Glick, 1995; Blanchard, Steindorf, Wang, & Glick, 1993; Blanchard, Steindorf, Wang, LeFevre, et al., 1993)
2	95.54	± 6.72 (68)	-	35	55	-	-	(Blanchard, Steindorf, Wang, & Glick, 1993; Yoshimoto, Komura, & Kawamura, 1992)

7.3 Amphetamine

7.3.1 Nucleus accumbens

Table 33: Peak percentage baseline values of accumbal dopamine after the administration of different doses of amphetamine

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.5	392.15	± 1.39 (45.86)	-	260	6	-	-	(A. L. Auclair et al., 2010; Badiani et al., 2000; Birrell & Balfour, 1998; Cagiano et al., 1998; Choi, Ahn, Wang, & Phillips, 2014; Darracq, Blanc, Glowinski, & Tassin, 1998; Di Chiara, Tanda, Frau, & Carboni, 1993; Fabricius, Steiniger-Brach, Helboe, Fink-Jensen, & Wortwein, 2011; Hall et al., 1998; Hall, Wilkinson, Humby, & Robbins, 1999; Harmer, Hitchcott, Morutto, & Phillips, 1997; Ichikawa, Kuroki, & Meltzer, 1998; Kehoe, Shoemaker, Arons, Triano, & Suresh, 1998; Mattsson, Olson, Svensson,

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
								& Schilstrom, 2007; Pacchioni, Cador, Bregonzio, & Cancela, 2007; Pani, Kuzmin, Diana, et al., 1990; Paulson & Robinson, 1995; Porras, Di Matteo, Fracasso, et al., 2002; Rahman et al., 2008; Rowley et al., 2000; Sotty, Damgaard, et al., 2009; Sotty, Montezinho, Steiniger-Brach, & Nielsen, 2009; Steketee & Kalivas, 1992; Stewart, Deschamps, & Amir, 1994; Tronci, Simola, Carta, De Luca, & Morelli, 2006)
0.75	352.27	± 42.05 (31.36)	-	11	55	-	-	(A. Auclair, Blanc, Glowinski, & Tassin, 2004; T. E. Robinson & Camp, 1990)
1	791.46	± 4.23 (39)	-	235	2	-	-	(Afanas'ev, Ferger, & Kuschinsky, 2000; Byun et al., 2014; Carboni, Imperato, Perezzani, & Di Chiara, 1989; Choi et al., 2014; Coutureau, Lena, Dauge, & Di Scala, 2002; De Deurwaerdere, Moison, Navailles, Porras, & Spampinato, 2005; Di Chiara et al., 1993; Frantz, Hansson, Stouffer, & Parsons, 2002; Hall et al., 1998; Hamilton, Redondo, & Freeman, 2000; Ichikawa, Kuroki, Kitchen, & Meltzer, 1995; Ichikawa & Meltzer, 1992b, 1995; Kim, Austin, Tanabe, Creekmore, & Vezina, 2005; Kimura, Nomikos, & Svensson, 1993; McCallum, Cowe, Lewis, & Glick, 2012; Meyer & Bardo, 2015; Moghaddam & Bunney, 1989; Nicholson et al., 2009; Peleg-Raibstein & Feldon, 2006; T. E. Robinson & Camp, 1990; Vezina, 1993; Warburton, Mitchell, & Joseph, 1996)
1.25	903.83	± 45.88 (40)	-	30	40	-	-	(Glick, Rossman, Wang, Dong, & Keller, 1993; Lategan, Marien, & Colpaert, 1990; Maisonneuve, Keller, & Glick, 1992; Olson & Justice, 1993)
1.5	523.90	± 2.05 (40.05)	-	168	11	-	-	(Castaneda, Moss, Oddie, & Whishaw, 1991; Druhan, Rajabi, & Stewart, 1996; Fiorino & Phillips, 1999; Geiger et al., 2009; Hertel et al., 1995; Huang, Wang, Tai, Tsai, & Peng, 1995; Humby, Wilkinson, Robbins, & Geyer, 1996; Imperato et al., 1996; King, Zigmond, & Finlay, 1997; Naef et al., 2011; Nomikos, Damsma, Wenkstern, & Fibiger, 1991; Nomikos, Zis, Damsma, & Fibiger, 1991; E. N. Pothos, Creese, & Hoebel, 1995; Reid, Ho, Tolliver, Wolkowitz, & Berger, 1998; T. E. Robinson & Camp, 1990; Rowley et al., 2000; Stewart & Rajabi, 1996; Tolliver, Ho, Reid, & Berger, 1996; Wan, Giovanni, Kafka, & Corbett, 1996; Whishaw, Fiorino, Mittleman, & Castaneda, 1992; Wilkinson et al., 1993)
2	1213.16	± 9.03 (47.93)	-	199	7	-	-	(Arnold, Nelson, Neigh, Sarter, & Bruno, 2000; A. Auclair et al., 2004; Badiani et al., 1998; Darracq et al., 1998; Di Chiara et al., 1993; Flagstad et al., 2004; Hall et al., 1998; L. Hernandez, Stanley, & Hoebel, 1986; Ichikawa & Meltzer, 1992a; Kaariainen et al., 2008; McKittrick & Abercrombie, 2007; C. L. Nelson, Sarter, & Bruno, 2000; Olsson et al., 2009; Porras, Di Matteo, De Deurwaerdere, Esposito, & Spampinato, 2002; Porras, Di Matteo, Fracasso, et al., 2002; Reid, Herrera-Marschitz, & Ungerstedt, 1991; T. E. Robinson, Jurson, Bennett, & Bentgen, 1988; Shoblock, Sullivan, Maisonneuve, & Glick, 2003; Wilkinson et al., 1994)
3	1024.77	± 84.53 (29.47)	-	65	8	-	-	(Bradberry, Gruen, Berridge, & Roth, 1991; Y. C. Chen, Choi, Andersen, Rosen, & Jenkins, 2005; Nicholson et al., 2009; T. E. Robinson & Camp, 1990)
7.5	387.8	± 65.9	-	25	50	-	-	(Kehoe, Shoemaker, Triano, Hoffman, & Arons, 1996)

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
		(30)						
1µM	342.42	± 12.12 (53.94)	-	33	18	-	-	(Birrell & Balfour, 1998; Brown, Nomikos, Wilson, & Fibiger, 1991; Glick et al., 1993; Huang et al., 1995)

7.3.2 Caudate putamen

Table 34: peak percentage baseline values of dopamine in caudate putamen of intraperitoneally vs. intravenously and subcutaneously administered animals

Route of administration	Peak percentage baseline value after 1 mg/kg of d-amphetamine
i.p.	334.05 ± 6.46
i.v. + s.c.	1372.82 ± 12.35

Table 35: Peak percentage baseline values of dopamine in caudate putamen after the administration of different doses of amphetamine

Dosages with female animals in bold characters

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.5 d+l-amph	901.02	± 16.36 (39.18)	Female	49	100	0.001	4.84 (1,11)	(Feifel, Shilling, Kuczenski, & Segal, 2003; Florin, Kuczenski, & Segal, 1994; Kuczenski & Segal, 1989; Nowak et al., 2007; Sershen et al., 2008; Shams et al., 2016; Sharp et al., 1987; Tepper, Creese, & Schwartz, 1991)
	477.05	± 15.24 (30.73)	Male	44	0			

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.75	368.95	± 2.98 (64.21)	-	19	36	-	-	(T. E. Robinson & Camp, 1990; Zhu, Sullivan, & Brioni, 1999)
1 d+l-amph	489.3	± 3.3 (46.39)	d+l-amph	149	0	0.007	4.06 (1,44)	(al-Tajir & Starr, 1993; Balla, Koneru, Smiley, Sershen, & Javitt, 2001; L. Hernandez et al., 1994; Javitt et al., 2004; Kankaanpaa, Lillsunde, Ruotsalainen, Ahtee, & Seppala, 1996; Kihara, Ikeda, Matsubara, & Matsushita, 1993; Kuczenski & Segal, 1989; Melega, Williams, Schmitz, DiStefano, & Cho, 1995; Murzi et al., 1996; Nowak, Brus, & Kostrzewa, 2001; Nowak, Brus, Oswiecimska, Sokola, & Kostrzewa, 2002; Nowak et al., 2006; Nowak et al., 2008; Pehrson & Moghaddam, 2010; Sershen et al., 2008; Sood, Cole, Fraier, & Young, 2009)
1 d-amph	1372.82	± 12.35 (32.23)	i.v. + s.c.	103	0	0.006	3.44 (2,22)	(Balcioglu, Zhang, & Tarazi, 2003; Bredeloux, Dubuc, & Costentin, 2007; Byun et al., 2014; Carboni et al., 1989; Di Chiara et al., 1993; Fink-Jensen et al., 1994; Hamilton et al., 1992; Ichikawa et al., 1995; Ichikawa & Meltzer, 1992b, 1995; Kimmel, Justice, & Holtzman, 1998; Ren, Xu, Choi, Jenkins, & Chen, 2009; T. E. Robinson & Camp, 1990)
	334.05	± 6.46 (30.84)	i.p.	42	0			(Harsing et al., 1992; Kashiwagi et al., 2015; Mele, Fontana, & Pert, 1997; Nicholson et al., 2009; Polissidis et al., 2014)
1.25	1038.25	± 30.11 (50)	female	24	100	0.039	5.50 (1,7)	(Castner, Xiao, & Becker, 1993; Glick et al., 1993; Maisonneuve et al., 1992)
	780.21	± 27.59 (43)	Male	24	0			(Castner et al., 1993; Lategan et al., 1990; Pehek, 1999)
1.5	696.64	± 4 (40.76)	Awake	192	5	0.010	4.26 (1,24)	(Cass, Manning, & Dugan, 1998; Castaneda et al., 1991; Castaneda, Whishaw, Lermer, & Robinson, 1990; Castaneda, Whishaw, & Robinson, 1990, 1992; King & Finlay, 1995; Lienau & Kuschinsky, 1997; Nomikos, Damsma, et al., 1991; Pacchioni, Gioino, Assis, & Cancela, 2002; E. N. Pothos et al., 1995; T. E. Robinson & Camp, 1990; T. E. Robinson, Yew, Paulson, & Camp, 1990; Rowley et al., 2012; Skutella et al., 1997; Tran-Nguyen, Castaneda, & MacBeth, 1996; Whishaw et al., 1992; Zhu et al., 1999)
	2001.52	± 68.96 (38.79)	Anesthetized	33	0			(Feigenbaum & Howard, 1997; Hurd & Ungerstedt, 1989a, 1989c)
2	1122.92	± 4.78 (41.34)	Awake	254	22	0.004	4.09 (1,40)	(Badiani et al., 1998; Becker & Cha, 1989; Bjelke et al., 1994; Cadoni, Pinna, Russi, Consolo, & Di Chiara, 1995; Camp & Robinson, 1992; Castner et al., 1993; Di Chiara et al., 1993; Dietze & Kuschinsky, 1994; Ferguson, Flynn, Delclos, Newbold, & Gough, 2002; Ferguson, Gough, & Cada, 2003; Heeringa & Abercrombie, 1995; Ichikawa & Meltzer, 1992a; Jaworski, Gonzales, & Randall, 2001; Kaariainen et al., 2008; Kuczenski, Segal, Cho, & Melega, 1995; Laviola, Pascucci, & Pieretti, 2001; Miele et al., 2000; Miller & Abercrombie, 1996; G. S. Robertson, Damsma, & Fibiger, 1991; Yamamoto & Meltzer, 1992)

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
	2231.91	± 44.22 (40.92)	Anesthetized	105	0			(Butcher, Fairbrother, Kelly, & Arbuthnott, 1988; Herrera-Marschitz, Luthman, & Ferre, 1994; Loidl et al., 1994; McTavish, Cowen, & Sharp, 1999; Porras, Di Matteo, De Deurwaerdere, et al., 2002; Porras, Di Matteo, Fracasso, et al., 2002)
2.5 d+l-amph	2595	± 25.56 (32.08)	-	89	55	-	-	(Becker & Rudick, 1999; Kuczenski & Segal, 1989; Kuczenski & Segal, 1990, 1997; Melega et al., 1995; Segal & Kuczenski, 1999)
3	2769.21	± 114.78 (24.69)	-	38	18	-	-	(Y. C. Chen et al., 2005; Y. I. Chen et al., 2008; Feigenbaum & Howard, 1997; Fink-Jensen et al., 1994; Nicholson et al., 2009; Ren et al., 2009; T. E. Robinson & Camp, 1990)
7.5	530	± 100 (60)	-	6	0	-	-	(Bredeloux et al., 2007)
1µM	364	± 58 (48)	-	10	60	-	-	(Glick et al., 1993; Nomikos, Damsma, Wenkstern, & Fibiger, 1990)

7.4 Cocaine

7.4.1 Nucleus accumbens

Table 36: Peak percentage baseline values of dopamine in the nucleus accumbens in intraperitoneally and subcutaneously vs. intravenously administered animals, no females included

Route of administration	Peak percentage baseline value after 3 mg/kg cocaine
i.p. + s.c.	235.32 ± 2
i.v.	594.07 ± 13.36

Table 37: Peak percentage baseline values of accumbal dopamine after the administration of different doses of cocaine

Dosages with female animals in bold characters

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.083	140	± 6.5 (37.5)	-	14	0	-	-	(Howes, Dalley, Morrison, Robbins, & Everitt, 2000)
0.1	128	± 14 (10)	-	10	0	-	-	(Garces-Ramirez et al., 2011; Tanda et al., 2016)
0.25	183.63	± 9.43 (25)	-	8	0	-	-	(Pettit & Justice, 1989; Sziraki, Sershen, Benuck, Hashim, & Lajtha, 1998)
0.3	150	± 7 (20)	-	5	0	-	-	(Baumann, Char, De Costa, Rice, & Rothman, 1994)
0.32	200	± 20 (10)	-	8	0	-	-	(Garces-Ramirez et al., 2011)
0.33	278	± 11.25 (10)	-	12	0	-	-	(Crespo, Sturm, Saria, & Zernig, 2006)
0.37	155	± 2.5 (10)	-	18	0	-	-	(Frantz, O'Dell, & Parsons, 2007)
0.5	170	± 18 (10)	-	8	0	-	-	(Pontieri, Tanda, & Di Chiara, 1995)
0.75	290	± 5 (10)	-	5	0	-	-	(Pettit & Justice, 1989)
1	198.25	± 26.98 (26.98)	Awake	85	5	0.003	4.41 (1,18)	(Baumann et al., 1994; Bradberry, Lee, & Jatlow, 1999; Carboni et al., 1989; Garces-Ramirez et al., 2011; Kohut et al., 2014; Maisonneuve, Archer, & Glick, 1994; Pepper, Baumann, Ayestas, & Rothman, 2001; Pontieri et al., 1995; Roth-Deri et al., 2009; Tanda, Ebbs, Newman, & Katz, 2005; Tanda et al., 2007)
	299.45	± 13.94 (24.14)	Anesthetized	29	0			(Baptista, Weiss, & Post, 1993; Bradberry et al., 1993; Bradberry & Roth, 1989; Moghaddam & Bunney, 1989)
1.25	800	± 40 (10)	-	3	0	-	-	(Pettit & Justice, 1989)
1.5	291.09	± 6.65 (13.44)	-	32	0	-	-	(D'Souza & Duvauchelle, 2006; Espana et al., 2010; Ferris, Mateo, Roberts, & Jones, 2011; Maier, Ledesma, Seiwell, & Duvauchelle, 2008; Mateo, Lack, Morgan, Roberts, & Jones, 2005)

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
2	244.03	± 6.02 (25.28)	-	36	19	-	-	(Grotewold, Wall, Goodell, Hayter, & Bland, 2014; Moghaddam & Bunney, 1989; Philpot & Kirstein, 1999; Roth-Deri et al., 2009)
2.5	187.5	± 3.75 (97.5)	-	12	50	-	-	(Kosten, Zhang, & Kehoe, 2003)
3	235.32	± 2 (22.86)	i.p. + s.c.	98	0	0.005	4.38 (1,20)	(Hemby et al., 1995; Izawa, Yamanashi, Asakura, Misu, & Goshima, 2006; Justinova et al., 2011; Kohut et al., 2014; Mascia et al., 2011; Schad, Justice, & Holtzman, 1995; Strecker, Eberle, & Ashby, 1995; Tanda et al., 2005; Tanda et al., 2007; Tanda et al., 2013; Zernig, O'Laughlin, & Fibiger, 1997)
	594.07	± 13.36 (22.15)	i.v.	33	0			(Baumann et al., 1994; Ikegami & Duvauchelle, 2004; Roth-Deri et al., 2009; Rothman, Ayestas, & Baumann, 1996)
3.19	715	± 25 (15)	-	5	0	-	-	(Panin, Cathala, Piazza, & Spampinato, 2012)
3.3	230	± 50 (20)	-	6	0	-	-	(Desai, Paronis, Martin, Desai, & Bergman, 2010)
4	690	± 100 (20)	-	13	0	-	-	(Baptista et al., 1993)
4.2	315	± 2.5 (10)	-	8	0	-	-	(Duvauchelle, Ikegami, Asami, et al., 2000; Duvauchelle, Ikegami, & Castaneda, 2000)
5	218.69	± 0.44 (34.09)	i.p. + s.c.	252	2	0.005	3.26 (2,36)	(Brown, Finlay, Wong, Damsma, & Fibiger, 1991; Cadoni, Solinas, & Di Chiara, 2000; Cadoni, Solinas, Valentini, & Di Chiara, 2003; Camp, Browman, & Robinson, 1994; Carboni et al., 1989; Gambarana, Ghiglieri, et al., 1999; Gambarana, Masi, et al., 1999; Giorgi et al., 1997; Kosten et al., 2003; Lecca, Piras, Driscoll, Giorgi, & Corda, 2004; B. Leggio et al., 2003; Mangiavacchi et al., 2001; Masi et al., 2001; Mikkola, Honkanen, Piepponen, Kiianmaa, & Ahtee, 2001; Nanni et al., 2003; Parsons, Kerr, & Weiss, 1998; Steketee & Goeders, 2002)
	562	± 79.87 (38.29)	i.v.	18	0			(Koch, Piercey, Galloway, & Svensson, 1997; Othman, Newman, & Eddington, 2007; Raje et al., 2005)
5.6	240	± 4 (20)	-	6	0	-	-	(Desai et al., 2010)
7.5	294.44	± 58.33 (20)	-	9	0	-	-	(Fadda, Scherma, Fresu, Collu, & Fratta, 2003; Pap & Bradberry, 1995)(Fadda, Scherma, Fresu, Collu, & Fratta, 2003; Pap & Bradberry, 1995)
10	330.72	± 0.16 (32.37)	Awake	736	11	0.000	3.95 (12,79)	(Alvarez Fischer et al., 2001; Andrews & Lucki, 2001; Boyson et al., 2014; Brown & Fibiger, 1992; Bubar, McMahon, De Deurwaerdere, Spampinato, & Cunningham, 2003; Cadoni & Di Chiara, 1999, 2007; Cadoni et al., 2000; Cadoni et al., 2003; Caille & Parsons, 2006; Camp et

								al., 1994; Cervo, Pozzi, & Samanin, 1996; Clark, Ashby, Dewey, Ramachandran, & Strecker, 1996; Cummings, Jagannathan, Jackson, & Becker, 2014; De Deurwaerdere et al., 2005; Devoto, Flore, Saba, Cadeddu, & Gessa, 2012; Espana, Melchior, Roberts, & Jones, 2011; Espana et al., 2010; Fontana, Post, & Pert, 1993; Holly, Shimamoto, Debold, & Miczek, 2012; Horger, Wellman, Morien, Davies, & Schenk, 1991; Izawa et al., 2006; Jocham, Lauber, Muller, Huston, & de Souza Silva, 2007; Jocham et al., 2006; Johnson, Eodice, Winterbottom, & Mokler, 2000; Kimura et al., 1993; Kohut et al., 2014; Kosten et al., 2003; Kosten, Zhang, & Kehoe, 2005; Leri et al., 2007; Lodge & Grace, 2005; Maisonneuve, Ho, & Kreek, 1995; Maisonneuve & Kreek, 1994; Martin-Fardon et al., 1996; McFarland, Lapish, & Kalivas, 2003; Miczek, Nikulina, Shimamoto, & Covington, 2011; Mikkola et al., 2001; Muller et al., 2002; Nation & Burkey, 1994; Neisewander, O'Dell, Tran-Nguyen, Castaneda, & Fuchs, 1996; A. M. Nelson, Larson, & Zahniser, 2009; O'Dell & Parsons, 2004; Ogbonmwan et al., 2015; Pan et al., 2012; Pani, Kuzmin, Diana, et al., 1990; Pani, Kuzmin, Stefanini, Gessa, & Rossetti, 1990; Panos & Baker, 2010; Pap & Bradberry, 1995; Parsons & Justice, 1993; Parsons et al., 1998; Parsons, Koob, & Weiss, 1999; Peng, Li, Gilbert, et al., 2008; Peng, Li, Li, et al., 2008; Rossetti, Hmaidan, & Gessa, 1992; Rouge-Pont, Marinelli, Le Moal, Simon, & Piazza, 1995; Segal & Kuczenski, 1992; Shimada, Yamaguchi, & Yanagita, 1996; Shimamoto, Debold, Holly, & Miczek, 2011; Shimamoto, Holly, Boyson, DeBold, & Miczek, 2015; Steketee & Goeders, 2002; Strecker et al., 1995; Tanda et al., 2005; Tanda et al., 2007; Tanda et al., 2013; Tanda et al., 2016; Thongsaard & Marsden, 2013; Tobiansky et al., 2016; Tolliver et al., 1999; Valdomero, Isoardi, Orsingher, & Cuadra, 2005; Verheij, Karel, Cools, & Homberg, 2014; Willins & Meltzer, 1998; Xi, Kiyatkin, et al., 2010; Xi, Li, et al., 2010; Xi et al., 2007)
	593.26	± 5.92 (31.23)	Anesthetized	90	0			(Essman, Singh, & Lucki, 1994; Kankaanpaa et al., 1996; G. M. Leggio et al., 2009; Lutfy, Do, & Maidment, 2001; Navailles, De Deurwaerdere, Porras, & Spampinato, 2004; Navailles, Moison, Cunningham, & Spampinato, 2008; Weiss, Paulus, Lorang, & Koob, 1992)
	289.33	± 2.2 (31)	Adolescent	70	9	0.027	3.92 (1,116)	(Boyson et al., 2014; Cervo et al., 1996; Devoto, Flore, Ibba, Fratta, & Pani, 2001; Devoto et al., 2012; Kosten et al., 2003; Lutfy et al., 2001; A. M. Nelson et al., 2009; Ogbonmwan et al., 2015; Pani, Kuzmin, Diana, et al., 1990; Pani, Kuzmin, Stefanini, et al., 1990; Willins & Meltzer, 1998)
	372.53	± 0.21	Adult	713	11			(Alvarez Fischer et al., 2001; Andrews & Lucki, 2001; Brown & Fibiger, 1992; Bubar et al., 2003; Cadoni & Di Chiara, 1999, 2007; Cadoni et al., 2000; Cadoni et al., 2003; Caille & Parsons, 2006; Clark et al., 1996; Cummings et al., 2014; De Deurwaerdere et al., 2005; Espana et al., 2011; Espana et al., 2010; Essman et al., 1994; Fontana et al., 1993; Holly et al., 2012; Horger et al., 1991; Izawa et al., 2006; Jocham et al., 2007; Jocham et al., 2006; Johnson et al., 2000; Kankaanpaa et al., 1996; Kimura et al., 1993; Kohut et al., 2014; Kosten et al., 2005; G. M. Leggio et al., 2009Navailles, 2004 #2133; Leri et al., 2007; Lodge & Grace, 2005; Maisonneuve et al., 1995; Maisonneuve & Kreek, 1994; Martin-Fardon et al., 1996; Miczek et al., 2011; Mikkola et al., 2001; Muller et al., 2002; Nation & Burkey, 1994; Navailles et al., 2008; Neisewander et al., 1996; O'Dell & Parsons, 2004; Pan et al., 2012; Panos & Baker, 2010; Pap & Bradberry, 1995; Parsons & Justice, 1993; Parsons et al., 1998; Parsons et al., 1999; Peng, Li, Gilbert, et al., 2008; Peng, Li, Li, et al., 2008; Rossetti et al., 1992; Rouge-Pont et al., 1995; Segal & Kuczenski, 1992; Shimada et al., 1996; Shimamoto et al., 2011; Shimamoto et al., 2015; Steketee & Goeders, 2002; Strecker et al., 1995; Tanda et al., 2005; Tanda et al., 2007; Tanda et al., 2013; Tanda et al., 2016; Thongsaard & Marsden, 2013; Tobiansky et al., 2016;

								Tolliver et al., 1999; Valdomero et al., 2005; Weiss et al., 1992; Xi, Kiyatkin, et al., 2010; Xi, Li, et al., 2010; Xi et al., 2007)
15	277.17	± 0.25 (35.20)	-	579	0	-	-	(Barr et al., 2015; Barrot, Marinelli, et al., 2000; Barrot, Rettori, et al., 2000; Benwell, Balfour, & Lucchi, 1993; Beyer & Steketee, 1999, 2000, 2002; Birrell & Balfour, 1998; Bradberry et al., 1993; Chambers, Sentir, & Engleman, 2010; De Souza Silva et al., 1997; Feifel et al., 2003; Garcia-Keller et al., 2013; Giustino, Cuomo, & Marsden, 1998; Gurkovskaya, Palamarchouk, Smagin, & Goeders, 2005; Hooks, Colvin, Juncos, & Justice, 1992; Hooks, Duffy, Striplin, & Kalivas, 1994; Hooks, Jones, Smith, Neill, & Justice, 1991; Horger, Valadez, Wellman, & Schenk, 1994; Jin et al., 2017; Jonsson, Adermark, Ericson, & Soderpalm, 2014; Kalivas & Duffy, 1993; Kalivas, Duffy, & Mackler, 1999; Lack, Jones, & Roberts, 2008; Lee et al., 2008; Lu, Liu, Huang, & Zhang, 2003; Mabrouk et al., 2017; Maisonneuve et al., 1995; Maisonneuve & Kreek, 1994; Mitrano et al., 2012; Navailles et al., 2004; Pierce, Born, Adams, & Kalivas, 1996; Pierce, Meil, & Kalivas, 1997; Placenza, Rajabi, & Stewart, 2008; Porras, Di Matteo, De Deurwaerdere, et al., 2002; Reid & Berger, 1996; Sorg & Kalivas, 1991; Steketee, 1993, 1997, 1998a, 1998b; Steketee & Kalivas, 1991; Steketee, Sorg, & Kalivas, 1992; Steketee & Walsh, 2005; Szumlinski, Frys, & Kalivas, 2004; Torres, Rivier, & Weiss, 1994; Vollbrecht, Mabrouk, Nelson, Kennedy, & Ferrario, 2016; Wolf, Xue, White, & Dahlin, 1994; Xie & Steketee, 2009; Zayara et al., 2011)
17	440	± 20 (20)	-	6	0	-	-	(Kohut et al., 2014)
18	295	± 35 (40)	-	11	0	-	-	(Andrews & Lucki, 2001)
20	399.13	± 0.63 (51.12)	-	416	5	-	-	(Cadoni & Di Chiara, 2007; Chefer & Shippenberg, 2002; Chefer, Zakharova, & Shippenberg, 2003; J. Chen, Marmur, Paredes, Pulles, & Gardner, 1996; De Deurwaerdere et al., 2005; Ferraro et al., 2000; Frantz et al., 2007; Gerasimov et al., 2000; Gerasimov et al., 2002; Hedou, Feldon, & Heidbreder, 1999; C. A. Heidbreder, Schenk, Partridge, & Shippenberg, 1998; C. A. Heidbreder, Thompson, & Shippenberg, 1996; Jang et al., 2008; Kailanto, Kankaanpaa, & Seppala, 2011; Kankaanpaa, Meririnne, & Seppala, 2002; Kuczenski & Segal, 1999; Kurling-Kailanto, Kankaanpaa, & Seppala, 2010; Leri, Flores, Rajabi, & Stewart, 2003; Leri et al., 2007; Maisonneuve et al., 1994; Maisonneuve & Glick, 1992; Martin-Fardon et al., 1996; Martin-Fardon, Kerr, Deleuze-Masquefa, Kamenka, & Weiss, 2001; McDougall et al., 2008; Molina, Ahmed, Gatley, Volkow, & Abumrad, 2001; Morgan & Dewey, 1998; Morgan, Horan, Dewey, & Ashby, 1997; Morgan, Porter, et al., 1997; Panos & Baker, 2010; Parsons et al., 1998; Philpot & Kirstein, 1999; Puig, Noble, & Benturquia, 2012; Reith, Li, & Yan, 1997; Schiffer, Azmoodeh, et al., 2003; Schiffer, Gerasimov, Bermel, Brodie, & Dewey, 2000; Schiffer, Marsteller, & Dewey, 2003; Steketee & Goeders, 2002; Szumlinski, McCafferty, Maisonneuve, & Glick, 2000; Tanda et al., 2016; Vazquez-DeRose et al., 2013)
25	465.79	± 39.21 (40)	-	19	0	-	-	(Andrews, Kung, & Lucki, 2005; Andrews & Lucki, 2001)
30	983.24	± 14.75 (28.83)	-	73	0	-	-	(Barrot, Rettori, et al., 2000; Kohut et al., 2014; Leri et al., 2007; Navailles et al., 2004; Pettit, Pan, Parsons, & Justice, 1990; Pierce et al., 1997; M. W. Robertson, Leslie, & Bennett, 1991; Strecker et al., 1995; Tanda et al., 2005)
40	798.19	± 57.81	-	27	0	-	-	(Kuczenski & Segal, 1999; Kuczenski, Segal, & Aizenstein, 1991; Tolliver et al.,

		(35.76)						1999)
1.25 mg/kg /min	3000	± 210 (30)	-	8	0	-	-	(Whittington, Virag, Vulliemoz, Cooper, & Morishima, 2002)
1.75 mg/kg /h	200	± 10 (240)	-	5	0	-	-	(G. Hernandez, Trujillo-Pisanty, Cossette, Conover, & Shizgal, 2012)
10 mg/kg /h	605	± 52 (260)	-	7	0	-	-	(G. Hernandez, Haines, & Shizgal, 2008)
1 µM	181.4	± 3.7 (84)	-	10	0	-	-	(Smith & Justice, 1994; Tolliver et al., 1999)
3 µM	190	± 25 (20)	-	4	0	-	-	(Tateyama, Ohta, Nagao, Hirobe, & Ono, 1993)
10 µM	446.05	± 21.71 (37.30)	-	37	0	-	-	(J. Chen et al., 1996; Tolliver et al., 1999; Yan, 2003; Yoshimoto et al., 2000)
20 µM	1049	± 47.78 (55.56)	-	18	0	-	-	(Smith & Justice, 1994; Yoshimoto et al., 2001)
50 µM	780	± 45 (20)	-	7	0	-	-	(J. Chen et al., 1996)
100 µM	696.19	± 134.29 (65.24)	-	21	0	-	-	(Andrews & Lucki, 2001; J. Chen et al., 1996; Tolliver et al., 1999)
3 mM	702.22	± 50.37 (137.78)	-	27	0	-	-	(Andrews et al., 2005; Andrews & Lucki, 2001)
7.5 mM	805	± 215 (40)	-	18	0	-	-	(L. Hernandez, Guzman, & Hoebel, 1991)
10 mM	610.77	± 28.46 (98.46)	-	13	0	-	-	(Andrews & Lucki, 2001)
20 µg	3444	± 1472 (20)	-	12	0	-	-	(L. Hernandez & Hoebel, 1988; Tateyama et al., 1993)

7.4.2 Caudate putamen

Table 38: Peak percentage baseline values of dopamine in caudate putamen after the administration of different doses of cocaine

Dosages with female animals in bold characters

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	N of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.5	335.59	± 30.72 (12.94)	-	17	0	-	-	(Y. I. Chen et al., 2010; Schwarz et al., 2004)
1	173.33	± 17.88 (30)	-	30	0	-	-	(Carboni et al., 1989; Hurd & Ungerstedt, 1989b; Tanda et al., 2005)
1.5	307.05	± 4.50 (13.92)	-	41	0	-	-	(Cao, Lotfipour, Loughlin, & Leslie, 2007; D'Souza & Duvauchelle, 2006; Hurd, Kehr, & Ungerstedt, 1988; Hurd & Ungerstedt, 1989b)
2	370.63	± 70.94 (7.75)	-	8	0	-	-	(Hurd & Ungerstedt, 1989b; Shou, Ferrario, Schultz, Robinson, & Kennedy, 2006)
3	179.48	± 3.73 (17.17)	-	23	0	-	-	(Church et al., 1987; Schad et al., 1995; Schad, Justice, & Holtzman, 2002; Tanda et al., 2005)
5	452.27	± 95.61 (51.52)	-	17	0	-	-	(Carboni et al., 1989; Martin-Fardon et al., 1996; Weikop, Egestad, & Kehr, 2004)
7.5	146	± 21 (40)	-	4	0	-	-	(Ivens, Janak, & Martinez, 1992)
10	309.89	± 0.89 (31.48)	-	213	10	-	-	(Chapman, See, & Bissette, 1992; Church et al., 1987; Coury, Blaha, Atkinson, & Phillips, 1992; Cummings et al., 2014; Ivens et al., 1992; Kankaanpaa et al., 1996; Kraft, Noailles, & Angulo, 2001; Kuczenski et al., 1991; Lienau & Kuschinsky, 1997; Loonam, Noailles, Yu, Zhu, & Angulo, 2003; Maisonneuve et al., 1995; Maisonneuve & Kreek, 1994; Martin-Fardon et al., 1996; McNeish, Svingos, Hitzemann, & Strecker, 1993; Mikkola et al., 2001; Navailles et al., 2004; A. M. Nelson et al., 2009; Noailles & Angulo, 2002; Porras, De Deurwaerdere, Moison, & Spampinato, 2003; Segal & Kuczenski, 1992; Tanda et al., 2005; Valdomero et al., 2005)
15	295.22	± 24.06 (20)	Female	9	100	0.009	5.32 (1,8)	(T. E. Robinson & Camp, 1991)
	364.21	± 3.03 (34.21)	Male	57	0			(Barrot et al., 2001; Chambers et al., 2010; Devroye et al., 2015; Maisonneuve et al., 1995; Maisonneuve & Kreek, 1994; Navailles et al., 2004; Porras et al., 2003; Wasik, Romanska, & Antkiewicz-Michaluk, 2010)
20	267.14	± 1.56	Other strains	122		0.008	(3,18)	(Dewey et al., 1997; Florin, Kuczenski, & Segal, 1995; Gabriele, Pacchioni, & See, 2012; Gatley et al., 1996; Gehrke, Chefer, & Shippenberg, 2008; C. A. Heidbreder et al., 1998; Inada, Polk, Jin, et al., 1992; Inada,

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	N of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
		(40.66)						Polk, Purser, et al., 1992; Kreuter, Mattson, Wang, You, & Hope, 2004; Kuczenski & Segal, 1999; Maisonneuve & Glick, 1992; Martin-Fardon et al., 1996; McDougall et al., 2008; Porras et al., 2003)
	392.5	± 101.25 (50)	Long Evans	24	0			(Keller, Maisonneuve, Carlson, & Glick, 1992)
25	210	± 11.67 (50.67)	-	15	27	-	-	(Cortez et al., 2010)
30	781.94	± 48.55 (31.79)	-	34	21	-	-	(Chapman et al., 1992; Church et al., 1987; Dewey et al., 1997; Di Paolo, Rouillard, Morissette, Levesque, & Bedard, 1989; Navailles et al., 2004; Tanda et al., 2005)
40	176.22	± 10.78 (30)	Anesthetized	9	0	0.010	18.51 (1,2)	(Inada, Polk, Jin, et al., 1992)
	393.12	± 10.04 (49.57)	Awake	12	0			(Kuczenski & Segal, 1999; Martin-Fardon et al., 1996)
1 µM	311.54	± 57.69 (46.15)	-	13	0	-	-	(Hurd & Ungerstedt, 1989b; Nomikos et al., 1990; Woodward, Compton, Balster, & Martin, 1995)
2.5 µM	757	± 13.3 (n.g.)	-	6	0	-	-	(Manley, Kuczenski, Segal, Young, & Groves, 1992)
10 µM	488.89	± 88.89 (17.78)	-	9	0	-	-	(Hurd & Ungerstedt, 1989b; Woodward et al., 1995)
50 µM	706.45	± 51.29 (27.74)	-	16	0	-	-	(Moghaddam & Bolinao, 1994; Shimizu, Duan, Hori, & Oomura, 1990)
100 µM	1178.28	± 139.74 (22.76)	-	15	0	-	-	(Hurd & Ungerstedt, 1989b; Rothman et al., 1991; Woodward et al., 1995)
1 mM (1000 µM)	397.5	± 146.25 (35)	-	10	0	-	-	(Hurd & Ungerstedt, 1989b; Rothman et al., 1989)
1 mg/kg	1000	± 200 (20)	-	7	0	-	-	(Thiriet et al., 2001)

Table 39: Peak percentage baseline values of dopamine in anesthetized vs. awake rats in the caudate putamen, no females included

State of consciousness	Peak percentage baseline value after 40 mg/kg cocaine
Anesthetized	176.22 ± 10.78
Awake	393.12 ± 10.04

7.5 Morphine

7.5.1 Nucleus accumbens

Table 40: Peak percentage baseline values of accumbal dopamine after the administration of different doses of morphine

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
5	195.09	0.73 (138)	-	138	17	-	-	(Borg & Taylor, 1997; Cadoni & Di Chiara, 2007; Di Giannuario, Pieretti, Catalani, & Loizzo, 1999; Fadda et al., 2003; Jonsson et al., 2014; M. R. Kim et al., 2005; Maisonneuve & Glick, 1999; Maisonneuve et al., 1991; Pearl, Maisonneuve, & Glick, 1996; Pozzi, Trabace, Invernizzi, & Samanin, 1995; Steinmiller, Maisonneuve, & Glick, 2003; Sustkova-Fiserova, Jerabek, Havlickova, Kacer, & Krsiak, 2014; Tanda & Di Chiara, 1998; Willins & Meltzer, 1998)
20	262.49	17.48 (88)	-	55	33	-	-	(Pothos et al., 1991; E. N. Pothos et al., 1995; Rada, Mark, Pothos, & Hoebel, 1991; Steinmiller et al., 2003; Szumlinski, Maisonneuve, & Glick, 2000; Yong et al., 2012)
30	92	1.6 (160)	-	32	100	-	-	(Johnson & Glick, 1993, 1994; Maisonneuve et al., 1991)

7.5.2 Caudate putamen

Table 41: Peak percentage baseline values of dopamine in caudate putamen after the administration of different doses of morphine

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
5	165.46	2.87 (74)	-	26	58	-	-	(Maisonneuve & Glick, 1999; Maisonneuve et al., 1991; Pearl et al., 1996; Pozzi et al., 1995)
30	92	1.6 (120)	-	30	100	-	-	(Johnson & Glick, 1993, 1994; Maisonneuve et al., 1991)

7.6 Nicotine

Table 42: Peak percentage baseline values of accumbal dopamine after the administration of different doses of nicotine

Dose (mg/kg)	Peak% BL (weighted average)	± SEM (peak time[min])	Sub group	n of rats	% of rats female	P-value	Critical value (degrees of freedom)	References
0.4	157.73	0.36 (50.03)	-	175	19	-	-	(Balfour, Birrell, Moran, & Benwell, 1996; Bassareo, De Luca, & Di Chiara, 2007; Benwell, Balfour, & Birrell, 1995; Birrell & Balfour, 1998; Cadoni & Di Chiara, 2000; Cadoni, Muto, & Di Chiara, 2009; Cadoni et al., 2003; Carboni, Silvagni, Rolando, & Di Chiara, 2000; Dewey et al., 1999; Eggan & McCallum, 2016, 2017; Ferrari, Le Novere, Picciotto, Changeux, & Zoli, 2002; Iyaniwura, Wright, & Balfour, 2001; Jonsson et al., 2014; Maisonneuve & Glick, 1999; McCallum et al., 2012; Mirza, Pei, Stolerman, & Zetterstrom, 1996; Shoaib & Shippenberg, 1996; Steinmiller et al., 2003; Wang et al., 2015)
200 µM	125	15 (20)	-	9	100	-	-	(Ding et al., 2012)

8 CURRICULUM VITAE

PERSONAL DATA

Surname and name:	Egenrieder, Lisamon Mira
Date of birth:	09.02.1986
Place of birth:	Berwangen/Kirchardt
Family status:	Married
Father:	Lutz Adomeit-Egenrieder, registered nurse
Mother:	Dorothea Egenrieder, graduate biologist

EDUCATION

1992 – 2005	Freie Waldorfschule Kempten (Allgäu)
06.2005	Abitur

VOCATIONAL TRAINING

2006 – 2009	Integrated training as a registered nurse and geriatric nurse at the vocational school at the *Bezirkskrankenhaus Kaufbeuren*
10.2009 – 09.2010 09.2012 & 09.2013	Working as a nurse at the department of psychotherapy at the *Bezirkskrankenhaus Kempten*

UNIVERSITARY CAREER

10.2011	Start of medical studies at the University of Heidelberg, Fakultät Mannheim (Ruprecht Karls Universität Heidelberg)
09.2013	First part of the medical examinations (M1)
2013 – 2017	Main course of the medical studies
11.2016	Second part of the medical examinations (M2)

	Practical year:
2016 – 2017	Surgery: acute care surgery at the *University Teaching Hospital of Butare* (Ruanda) Internal Medicine: emergency medicine and cardiology at the *Klinikum Offenbach* Anesthesiology: *Theresienkrankenhaus Mannheim* Psychosomatics: *Central Institute of Mental Health Mannheim*
11.2017	Third part of the medical examinations (M3)
2014 – 2020	Working on the thesis: *'A meta-analysis of the sex-specific effects of psychotropic substances on acute striatal dopamine overflow measured by in vivo microdialysis in rats'* at the Central Institute of Mental Health (ZI) Mannheim, Prof. Dr. rer. nat. Rainer Spanagel

PROFESSIONAL CAREER

12.2018 – 02.2019	Assistant doctor at the department of internal medicine at the *Klinikverbund Kempten-Oberallgäu, Klinikum Immenstadt*
03.2019 - 04.2020	Assistant doctor at the department of anesthesiology, emergency medicine, intensive care and pain therapy at the *Klinikverbund Kaufbeuren-Ostallgäu, Klinikum Kaufbeuren and Füssen*
05.2020 – now	Assistant doctor at intensive care unit, at the *Klinikverbund Kaufbeuren-Ostallgäu, Klinikum Kaufbeuren*

9 ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my supervisor Prof. Dr. rer. nat. Rainer Spanagel for the given opportunity and the framework for this project.
I am particularly grateful for his guidance and expertise as well as his thorough review of this thesis and the valuable comments he shared. Through him the results and the quality of their presentation in this thesis were immensely enhanced.
Thanks to him the idea was born to create a paper about the main results of this thesis. His input was also crucial for the process of writing, reviewing and finally the publication of the manuscript, that would not exist without him. This also applies for the first publication, in which the results of our whole work group at the Institute of Psychopharmacology of the Central Institute of Mental Health were put together and published.

As well as to my supervisor, I am deeply grateful to my advisor PD Dr. Dr. Hamid R. Noori, without whom this thesis would neither have been commenced nor finished.
I am truly thankful for his continuous support right from the beginning by providing a topic and title, his patience and motivation, countless explanations during the whole process of data mining and hundreds of helpful emails over the course of the last seven years.
He supervised and guided me throughout the whole process of developing this thesis with his endless knowledge and immense theoretical and practical scientific experience, culminating in the authoring of the two outstanding publications surrounding this work. Additionally, he mastered the advanced calculations and following analysis of the results for our publication that supported the main statement of this present work. I can not emphasize his contribution enough!
Again, this also applies for our first publication with the gathered results of the work group: PD Dr. Dr. Hamid R. Noori was the main actor and the driving force for the outstanding manuscript.

A special word of thank you goes to Ekaterina Mitricheva who also went through the whole process of datamining for our publication by screening the titles and abstracts of research articles. Subsequently, she reviewed the full text of any potentially eligible

title and abstract and therefore made an important contribution to the published paper.
Regarding this second publication I profoundly appreciate the fact that Prof. Dr. rer. nat. Christian P. Müller wrote an editorial referring to our work and thereby underlining the importance and currency of the topic (*'everything you always wanted to know about sex and dopamine but were afraid to ask'*).
Also, I want to thank Ph.D. Jill Becker, who enriched the early phase of this thesis with insightful comments and encouragement due to her immense knowledge in the field of sex differences in basic research.
Not to forget my colleagues from the work group at the Institute of Psychopharmacology of the Central Institute of Mental Health: Britta Gruhlke, Hans-Hendrik Schabel, Dr. Sabine Staudenmaier and Dr. Ines Brand who kindly provided their results for comparison.

My sincere thanks also go to Lukas Dürr (diploma of fine arts) who created the schematic figures of the microdialysis experiment and the amphetamine molecule and advised me on graphics, Alexander Scherf for statistical support and BA Lydia Ernst, Elena Egenrieder and Aurelia Vollstedt for many days and afternoons including coffee and lots of motivation.
A very special word of thanks goes to the Cantia team i.e. Dipl. Psych. Eva Leutz, Amanda Beckers-Wilkinson and Huub Beckers for repeated proofreading and corrections and many pieces of advice.
I'm also deeply grateful that Antoio Fallu, MA Franziska Reich and my husband Aaron Leutz did thorough proofreading and added the last corrections.

Last but not least, I would like to thank my family, including my parents, brothers and sisters and again my husband for providing the financial framework as well as the emotional support during the whole course of my study and during the process of writing and finishing this thesis afterwards – parallel to the challenging start of my career as a doctor. None of this would have been possible without you!
I also want to thank all those friends, who could not be named individually here (but hopefully know who they are), for being there, reading and correcting, checking grammar rules, housing, feeding and consoling me and supporting me spiritually through writing this thesis and in my life in general.

I would also like to emphasize that I am particularly grateful for the opportunity to study basically for free in Europe and for the financial support by the German society through the Bundesausbildungsförderungsgesetz (BAföG), that enabled me to start and to continue my training as a doctor in the first place.