Aus der psychiatrischen Universitätsklinik der Charité im St. Hedwig-Krankenhaus und der Medizinischen Fakultät der Charité – Universitätsmedizin Berlin

DISSERTATION

The Significance of Dopamine and Glutamate for Neuronal Reward Processing over the Lifespan

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Content

Summary

Rewards are considered as crucial factor for adaptive behavior of the human being. Further, behavioral and neuronal processing of rewards may be influenced by developmental changes. Interestingly, dopaminergic and glutamatergic factors in the striatum may also change during the lifespan, and are involved in learning processes. Therefore, we investigated adolescents, younger adults, and older adults by mean of a reward task during functional magnetic resonance imaging (fMRI). Core reward areas like the ventral striatum (VS) were characterized by a hyperactivation in adolescents compared with both adult groups. We interpreted these findings as the result of an asymmetric (protracted) development of the "frontal inhibition system" in comparison to the (faster) development of the VS in adolescents. Further, frontal areas showed hyperactivation in older adults compared with younger groups. These findings were interpreted as compensatory age-specific effects in fronto-parietal regions.

In a second study, we additionally focused on the impact of frontal glutamate concentrations on reward processing in healthy adolescents and observed an inverse coupling of glutamate concentrations in the anterior cingulate cortex (ACC) and neuronal activation of the VS. This finding demonstrates the important role of glutamate in reward processing and as a potential vulnerability factor for mental disorders starting in adolescence.

The striatum may also be involved in reward associated response inhibition modulated by dopamine. Therefore, in a trimodal imaging approach [using F18-DOPA positron emission tomography, magnetic resonance spectroscopy (MRS) and fMRI] we investigated a response inhibition task in healthy participants between 20 and 80 years of age. We observed a positive association between dopamine synthesis capacity and inhibition-related neural activity in the caudate nucleus. This relationship was further mediated by striatal glutamate. However, age did not affect response inhibition-related neurofunctional or neurochemical parameters.

Taken together, in the present dissertation I demonstrate the importance of dopamine-glutamate interactions with regard to reward processing in striatal areas in aging. Further, glutamatergic factor in fronto-limbic networks may also be related to increased risk and onset of psychiatric diseases (e.g. schizophrenia) during adolescence. Additionally, neuronal factors of response inhibition seem to be associated to striatal dopamine and glutamate, but those findings may not be associated to aging. Globally, the present results add to the understanding of reward processing and associated inhibition processing as well as associated neurochemical and neurofunctional properties in the eyes of lifelong changes. The present findings may further stimulate age related research on neurochemical and neurofunctional characteristics of mental disease like schizophrenia or addiction.

Zusammenfassung

Belohnungen sind ein wichtiger und basaler Faktor für Anpassungsverhalten bei Menschen. Weiterhin scheinen Verhalten und neuronale Verarbeitung von Belohnungen durch entwicklungsspezifische Aspekte beeinflusst zu sein. Die Neurotransmitter Dopamin und Glutamat sind eng mit Belohnungsverarbeitung assoziiert und durchlaufen altersabhängige Veränderungen. Aus diesem Grund wurden in den hier durchgeführten Studien gesunde Adoleszente, junge Erwachsene und ältere Erwachsene während der Durchführung einer Belohnungsaufgabe mittels funktioneller Kernspintomographie (fMRT) untersucht. Die Ergebnisse zeigten eine erhöhte Aktivierung der Kern-Belohnungszentren [z.B. das ventrale Striatum (VS)] bei Adoleszenten im Vergleich zu jungen und älteren Erwachsenen. Diese Ergebnisse wurden interpretiert als Resultat einer verzögerten Entwicklung des „frontalen Inhibitionssystems“ im Verhältnis zum (sich schneller entwickelnden) VS. Weiterhin beobachteten wir eine erhöhte Aktivierung in frontalen Gebieten bei älteren Erwachsenen im Vergleich zu den beiden jüngeren Gruppen. Diese Ergebnisse sprechen für einen kompensatorischen, altersspezifischen Effekt in frontal-parietalen Regionen.

In einer zweiten Studie konzentrierten wir uns zusätzlich auf die Bedeutung von frontalem Glutamat-Konzentrationen für Belohnungsverarbeitung bei gesunden Adoleszenten und beobachteten einen negativen Zusammenhang zwischen Glutamat-Konzentrationen im anterioren Zingulum (ACC) und neuronaler Verarbeitung im VS bei Adoleszenten. Diese Ergebnisse zeigen welche wichtige Rolle Glutamat während neuronaler Belohnungsverarbeitung spielt. Außerdem könnten die Ergebnisse eine entwicklungsspezifische Vulnerabilität für geistige Krankheiten wiederspiegeln.

Das Striatum scheint weiterhin mit der Inhibition von belohnungsabhängigem Verhalten („response inhibition“) verknüpft zu sein, welche von dem Neurotransmitter Dopamin moduliert wird. Aus diesem Grund wurde in einem trimodalen Bildgebungsprojekt [F18-DOPA Positronen-Emissions-Tomographie, Magnetresonanzspektroskopie (MRS) und fMRT] eine „response inhibition“ Aufgabe von Personen zwischen 20 und 80 Jahren durchgeführt. Wir beobachteten einen positiven Zusammenhang zwischen Dopamin-Synthese-Kapazität und neuronaler Aktivität im Nucleus caudatus während Inhibitionsprozesse aktiv waren. Dieser Zusammenhang war auch assoziiert mit striataler Glutamat-Konzentration. Altersfaktoren schienen diese Prozesse jedoch nicht zu beeinflussen.

In der gegenwärtigen Dissertation untersuche und beschreibe ich die Relevanz von Dopamin-Glutamat Interaktionen in Verbindung mit Belohnungsverarbeitung in striatalen Gebieten in Abhängigkeit des Alters der Probanden. Die Ergebnisse liefern Hinweise dass Dopamin-Glutamat Interaktionen mit der erhöhten Vulnerabilität für geistige Krankheiten (z.B. Schizophrenie) während der Adoleszenz in Verbindung stehen könnten. Zusätzlich scheint die neuronale Verarbeitung von Inhibition mit Dopamin und Glutamat in Verbindung zu stehen, diese Zusammenhänge scheinen jedoch unabhängig von Altersprozessen zu sein. Die hier gezeigten Ergebnisse erweitern das Verständnis von Belohnungsverarbeitung und Inhibitionsprozessen, sowie die damit assoziierten neurofunktionale und neurochemischen Veränderungen, insbesondere im Rahmen von Veränderungen über die Lebensspanne. Weiterhin könnten die hier gezeigten Ergebnisse die Erforschung von neurochemischen und neurofunktionalen Aspekten von geistigen Krankheiten (z.B. Schizophrenie oder Sucht) im Rahmen von Altersprozessen weiter stimulieren.

1. Introduction

1.1 Short History of Reward Related Research

The psychologists Edward Lee Thorndike can be seen as a pioneer in reinforcement learning related research. He got most famous for his so called "Law of Effect", describing stimulus-reward contingencies in animals:

"Of several responses made to the same situation, those which are accompanied or closely followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it [the situation] recurs, they [the responses] will be more likely to recur; those which are accompanied or closely followed by discomfort to the animal will, other things being equal, have their connections with that situation weakened, so that, when it recurs, they will be less likely to occur. The greater the satisfaction or discomfort, the greater the strengthening or weakening of the bond.".

Importantly, Thorndike's theories and experiments showed that stimulus-reward contingencies are not restricted to body reflexes like saliva production (as earlier described by Pavlov in 1901), but rather that reinforcing stimuli (like food or electric shocks), can be used as psychological tool to be presented after or during adaptive or maladaptive actions, respectively, to increase or decrease the probability of the subject to engage in the behavior in the future. These ideas were groundbreaking in terms of the understanding of several types of learning, and gave rise to many modern scientific theories, nowadays also applied to human beings. For instance, therapeutic interventions (e.g. cognitive behavioral psychotherapy), work related motivation techniques, animal training or education all rely on the so called "operant conditioning" based on the "Law of Effect" by Thorndike.

Still, the neuroanatomical and neurofunctional properties of reinforcement learning were relatively unknown until the two scientists Olds and Milner discovered in 1954, that low voltage stimulation of a deep brain areas (approximately in septal and striatal regions) in rats facilitated learning responses during performance in simple tasks like maze running and problem solving (Olds and Milner, 1954). Many years later, in 1997, Schultz found that the firing of dopaminergic neurons in monkeys was directly associated with teaching signals and rewards, which resemble earlier described concepts of behavioral and computational learning theories (Schultz, 1997, 1998). Due to ethical reasons, in humans, direct electric recording of

single cells is difficult (especially in deep brain areas) and only possible in a few rare cases. However, modern imaging techniques like functional magnetic resonance tomography (fMRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) allows relatively safe investigation of neurochemical and functional activity in the brain. In accordance with earlier research on animals, research with fMRI and PET in humans recently demonstrated the important role of dopaminergic factors for reward learning in areas like the VTA (Dreher et al., 2008) and the striatum [in particular the ventral striatum (VS)] for reward learning in humans. Today the striatum is one of the main focusses in research related to reward-processing, movement, motivation and novelty-related decision making in humans (Rolls, 1994).

1.2 The Neurochemistry and Neuroanatomy of the Human Reward System—Present Knowledge

In the brain, dopamine is mainly generated in the substantia nigra, which provides direct input to the striatum via a connection referred to as the nigrostriatal pathway (Lindvall et al., 1983; Voorn et al., 1986). Further, the density of dopaminergic D_2 receptors is in general much higher in regions of the mesolimbic pathway compared to other brain regions (Meltzer and Stahl, 1976). Further, the amygdala, thalamus and hippocampus provide excitatory input to dopaminergic cells in the striatum via glutamatergic projections (Everitt et al., 1991; Haber et al., 1995; Grace, 2000; Ding et al., 2010). Via these projections, activity of neurons in the VS can be up-regulated. For instance, up-regulation may be regulated via complex feedback loops (involving both, inhibitory and excitatory connections) between the VS, the pallidum and the VTA (Grace et al., 2007). Via this loop, glutamatergic input from the hippocampus, and possibly from other areas, can drive dopaminergic activity in the mesolimbic pathway. Further, at the level of the striatum, glutamate can directly depolarize postsynaptic neurons through ionotropic receptors (NMDA receptor, AMPA receptor, kainate receptor)(Stahl, 2013).

Based on the strong striatal interactions between dopamine and glutamate, a central theory regarding a potential regulation of presynaptic dopamine function in the striatum has been formulated. Specifically, presynaptic dopamine may be driven by a balanced engagement of excitatory (“accelerator”) and inhibitory (“brake”) glutamatergic inputs (Carlsson et al., 1999). The PFC in particular has been proposed to inhibit striatal dopaminergic activity indirectly via GABAergic interneurons, ultimately influencing striatal dopamine activity (Carlsson et al., 1999; Usun et al., 2013). Further, glutamatergic input from hippocampus and

amygdala may rather represent direct excitatory glutamatergic input (Grace et al., 2007). Support for the model was observed in animal research, where it was shown that blockage of glutamate NMDA receptors in the PFC resulted in increased dopamine release specifically in the VS (Del Arco et al., 2008). Moreover, in our recent study, we observed a direct *in vivo* relationship demonstrating support for the model by Carlsson et al. the first time in human beings (Gleich et al., 2015). Interestingly, these two opposing effects of glutamate (brake vs accelerator) may also affect psychological and cognitive processes. For instance, it is conceivable that top down and bottom up processing in the brain may be associated with glutamate-dopamine interactions, as these processes represent similar functions (e.g. motivation vs inhibition) on a psychological level.

Thus, although dopamine has been the focus of neuroscientific research regarding reward in the last decades, it is now clear that many other neuronal and neurochemical mechanisms and interactions, as well as other brain areas are involved in reward learning. In particular, in addition to the role of the VS and VTA, more recently, the PFC and the anterior cingulate cortex (ACC) were indicated to be involved in regulation of neuronal activity in striatal regions by forming the main top-down executive on limbic, reward associated bottom-up processes (e.g., value coding, monitoring, gating, processing of emotion, inhibitory functions) (Ernst et al., 2006; Casey et al., 2008). Specifically inhibitory neurochemical and neurofunctional properties of the frontal cortex may be regulated by glutamate associated neurotransmission (Carlsson et al., 1999; Laruelle et al., 2003; Jocham et al., 2012; Duncan et al., 2013). Most recently, dopaminergic contributions to response inhibition were also identified in the human striatum (Ghahremani et al., 2012). Further, there is evidence from animal research that striatal dopamine-glutamate interactions change over the lifespan (Mora et al., 2008).

1.3 The Significance of Dopamine-Glutamate Interactions for Healthy Aging and Associated Mental Diseases

Adolescence is characterized by increased drug and alcohol use, careless behavior in traffic and hazardous sexual behavior (Casey et al., 2008; Steinberg, 2008). A popular neurodevelopmental theory aims to explain these elements of adolescent behavior (Galvan et al., 2007; Galvan, 2010; Somerville and Casey, 2010). The theory proposes that the frontal cortex develops slower in comparison to the limbic system (the VS in particular). As a result, the inhibitory part of the reward system (frontal regions) may be less active in comparison to

the limbic part, which may lead to more impulsive and risky behavior in adolescence due to less inhibitory control. These theories were further summarized together with other findings in the triadic model of motivated behavior (TMMB) by Ernst et al. (Ernst et al., 2006; Richards et al., 2013a). In support of this model, fronto-limbic connectivity shows strong changes during adolescence, mediated via glutamate guided pruning processes in the frontal cortex (Selemon, 2013). Additionally, animal research suggests that glutamate NMDA receptors show strong changes during adolescent development (Insel et al., 1990). Further, increased dopaminergic activity may be present in adolescence (Galvan, 2010; Wahlstrom et al., 2010). Thus, in addition to the structural imbalance in development of the PFC and limbic regions in adolescence, glutamate associated imbalance between frontal and limbic regions may also affect reward processing in adolescence (Sesack et al., 2003; Schwartz et al., 2012).

While developing into adulthood, risky and hedonic-oriented behavior in adolescents may normalize, whereas security-oriented actions become more common (Mohr et al., 2010a; Eppinger et al., 2011). Thus, also structural and neurochemical systems may develop towards more balanced fronto-limbic interactions. Later in life, (considering the age above 60 years old), there is evidence that fronto-limbic interactions may undergo similar (but reversed) changes compared to the transition from adolescence to adulthood. For instance, functional imaging studies reported decreased reward related striatal activity in older compared with younger participants during reward anticipation (Schott et al., 2007; Dreher et al., 2008). On a neurochemical level, there is evidence that glutamate in frontal and striatal areas (Schubert et al., 2004; Zahr et al., 2008; Hädel et al., 2013) as well as dopamine in limbic areas decrease during aging (Braskie et al., 2008; Kumakura et al., 2010). There are also indications that these changes in glutamatergic and dopaminergic neurotransmission may be associated with reduced performance in cognitive tasks associated with reward processing in older age (Zahr et al., 2008; Karlsson et al., 2011; Kalbitzer et al., 2012; Klostermann et al., 2012a).

Moreover, changes in dopamine and glutamate related factors throughout the lifespan may also contribute to the onset, preservation and reoccurrence of mental disease (Paus et al., 2008; de la Fuente-Sandoval et al., 2011; Howes et al., 2011; Bloemen et al., 2012). For instance, the “glutamate hypothesis of schizophrenia” is based on the assumption that glutamatergic changes are induced during adolescence, which later during the progress of the disease lead to dysregulation of striatal dopamine (Howes et al., 2011; Stahl, 2013). Thus, through investigation of dopamine, glutamate, behavior and the associated changes over the

lifespan, different neurochemical and functional states of the reward system can be explored via a quasi-experimental design.

1.4 The Multimodal Imaging Approach

In recent years, the use of modern imaging methods like fMRI, PET or MRS imaging for neuroscientific research tremendously increased. However, most studies concentrated on one imaging method only. Although the interpretation of results is sometimes easier focusing on one imaging method only, due to the complexity of the human brain, it is also difficult to draw clear conclusions from isolated parameters. fMRI can only acquire an index of macroscopic activity of thousands of neurons indirectly (Logothetis, 2008), whereas single voxel MRS measures global neurotransmitter concentrations in isolated brain regions (Zhang and Shen, 2015). In contrast, PET can only acquire specific neurochemical mechanisms which are based on single receptors or enzymes (Herholz et al., 2013). Therefore, in the present projects, we decided to make use of a multimodal approach, to be able to investigate complex neuronal mechanisms more closely in interaction within the same participants. Still, we specifically chose to investigate reward and inhibition related processing, as neural associations of those functions were relatively restricted to striatal and frontal regions in recent research. Using this approach, we can reduce the complexity of multimodal imaging to few core areas so that all parameters can be acquired in the same region. Further, we can specifically investigate opposing neurochemical, neuronal and behavioral effects in combination (brake vs accelerator; frontal vs striatal activation; inhibition vs impulsivity, respectively) using parameters acquired from the different imaging modalities. Similar approaches, even though they are challenging, will be necessary in future neuroscientific research to be able to get a more complete view of the mechanisms of the human brain.

2. Aim of the Present Dissertation

The aim of the present dissertation was, to investigate theory and animal driven research regarding dopamine and glutamate associated parameters in the human brain over the lifespan. The results may lead to a better understanding of neurochemical and neurofunctional contributions to learning mechanisms during aging and may form a novel and basic scientific platform to investigate those factors in mental disease. The findings may further stimulate the development of dopaminergic and glutamatergic psychopharmacological agents (e.g. for

schizophrenia or addiction). Specific aims of the studies conducted are outlined in the following.

The general aim of Study 1 was to use fMRI to investigate basic developmental and age-related alterations in the reward network during reward anticipation. In adolescents, we expected increased neural activity in the VS during reward anticipation in comparison to young adults. In older adults, based on earlier research, we expected broader activation patterns in general, as well as increased neural activity (potentially compensatory) in the frontal cortex and decreased activity in the VS during reward anticipation.

In Study 2 we investigated the role of glutamate in VS activation during reward processing in young adults and adolescents from study 1. We expected an imbalance between glutamate in the frontal cortex and neural activation in the VS in adolescents compared to young adults.

Within the scope of Study 3 we investigated glutamate concentrations and dopamine synthesis capacity in the striatum and inhibition related activity in a single, continuous age group, covering a broad range of the lifespan (20-80 years). We expected inhibition-related behavior and neural activity to be related to dopamine synthesis capacity in the striatum. Further, based on former studies, we expected dopaminergic and glutamatergic parameters to be positively related. Additionally, we hypothesized that all parameters may be associated with age.

3. Methods

3.1 Study Design

Study 1: "*Reward Anticipation in the Adolescent and Aging Brain*"

102 mentally and physically healthy, right-handed human subjects in three age groups were included: 34 adolescents (13-16 years), 34 young adults (19-35 years), and 34 older adults (61-80 years). All participants underwent fMRI scanning and conducted a reward task to investigate reward associated brain function.

Study 2: "*Frontal Glutamate and Reward Processing in Adolescence and Adulthood*"

Due to the findings observed in study 1, we investigated the influence of frontal glutamate (ACC; acquired by MRS) on reward related processing (fMRI) in mentally and physically healthy 28 young adults and 33 adolescents from study 1.
Study 3: "*Glutamatergic Action on the Dopamine Driven Neural Signature of Response Inhibition*"

In study 3, we recruited 44 mentally and physically healthy human subjects between 20 and 80 years and applied 3 different imaging modalities (fMRI, MRS and FDOPA-PET) to quantify dopamine and glutamate associated indices, as well as functional brain activity during inhibition related neuronal processing.

3.2 Imaging Methods

3.2.1 Functional Magnetic Resonance Imaging

To investigate structural and functional properties of the brain, magnetic resonance imaging (MRI) can be used. MRI utilizes magnetic properties of hydrogen nuclei present in water molecules (and therefore in the whole body). In a resting state, hydrogen nuclei spin in a so called "resonance frequency". When the participant is placed in the MRI scanner, a strong magnetic field is applied to force hydrogen nuclei to spin synchronously (comparable to the alignment of a compass needle to the magnetic field of the earth). When the magnetic field is turned off, the nuclei fall back to their original equilibrium, and at the same time emit a radio signal which can be recorded by coils. Using information from the different amount of time different tissues take to fall back to their original equilibrium spin (called "relaxation time"), a 3 dimensional volume of the brain can be reconstructed (Huettel et al., 2009). *Functional* MRI generally utilizes similar physical properties of hydrogen molecules, but additionally makes use of principles of blood oxygenation. In particular, different magnetic properties of oxygenated and non-oxygenated blood result in different relaxation times, an effect termed "blood oxygen level dependent" (BOLD) signal. Thus, this signal allows an indirect measure of neuronal activity via oxygen consumption by neurons. fMRI is generally accepted as safe and non-harmful technique as long as magnetization related safety rules are strictly followed (e.g. no metal implants or metal containing tattoos)(Huettel et al., 2009).

3.2.1.1 Acquisition of fMRI/MRI data

Acquisition of (f)MRI data in study 1, 2 and 3 was conducted at the Berlin Center for Advanced Neuroimaging (BCAN) on the Campus Charité Mitte using a 3 T Siemens TIM Trio

Scanner (Erlangen, Germany), equipped with a 12 channel head coil. Functional imaging was conducted using axially aligned gradient echo planar imaging (EPI). Additionally, for anatomical reference, 3D anatomical images of the whole brain were obtained for each study. Visual stimulation was presented via a video projector on a mirror system on top of the head coil. All paradigms were programmed using Presentation software (Version 14.9, Neurobehavioral Systems, Albany, CA, USA).

3.2.1.2 Slot Machine Paradigm

In study 1 and 2, we used a "slot machine task". Such a task may elicit strong activation in striatal and frontal reward circuits as shown in earlier research (Dreher et al., 2008; Van Leijenhorst et al., 2010). Further, the slot machine task is ecologically valid and therefore accessible to all investigated age groups. During the task, three wheels showing two different types of fruits were displayed (see Figure 1). Two horizontal bars were used to indicate when participants were able to start and stop the slot machine by pressing a button on an fMRI compatible button box (blue = start, green = stop). Participants start the rotating of the slot machine with a button press; after the second button press, the three wheels successively stopped rotating (from left to right). The stop of the third wheel terminated the trial and a feedback about the current win and the total amount of reward was displayed above the slot machine. Subsequently, the next trial started (see Figure 1). Participants gained 10 cents per trial when all fruits in a row were of the same identity. The experiment consisted of 60 trials in total, with 20 predetermined wins (see study "included studies" 1 and 2 for details).

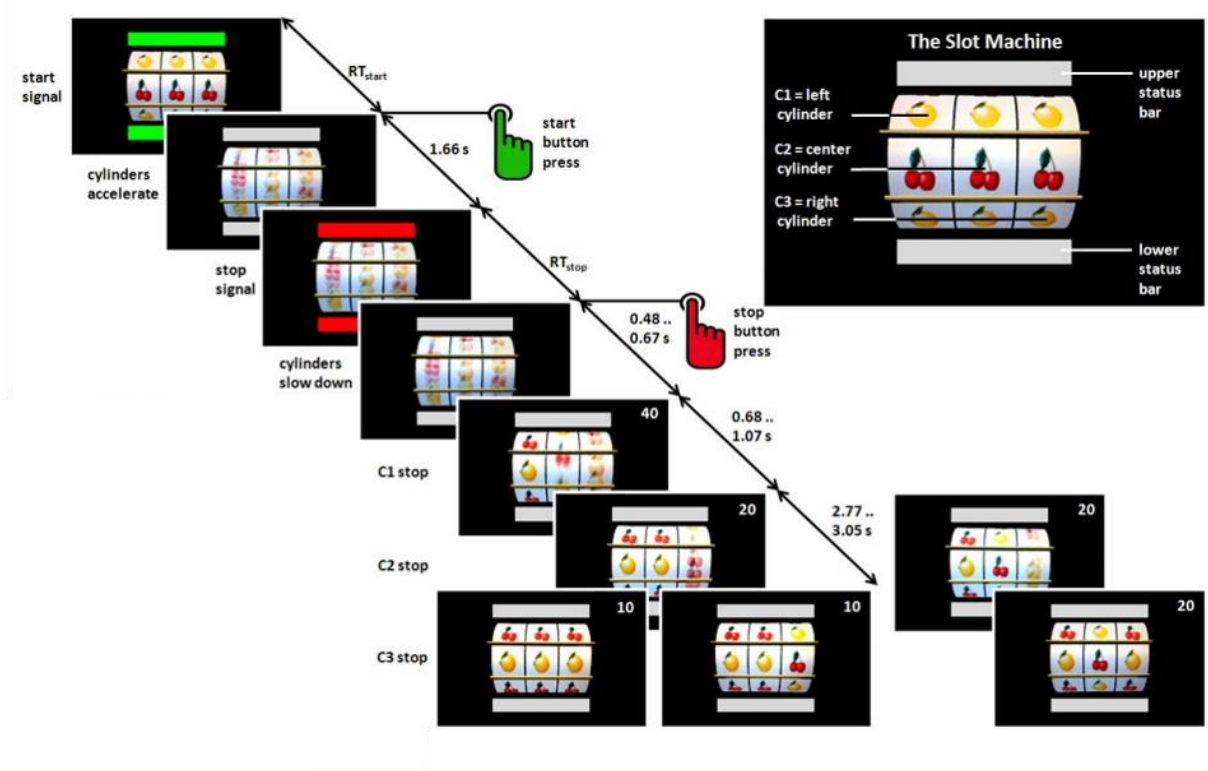

Figure 1: Structure of the Slot Machine Paradigm.

3.2.1.3 Stop-Signal Paradigm

In study 3, participants completed an adaptive stop signal paradigm (Logan and Cowan, 1984) during the fMRI scanning session. Participants were instructed to respond as fast as possible to a white arrow pointing either to right or left direction by pressing right or left button on a MRI compatible button box (see Figure 2). For stop trials (25% of trials), participants were instructed to inhibit their response when the white arrow changed color to red after a particular delay (stop signal delay, SSD). Logan and Cowan (Logan and Cowan, 1984) supposed that the go and the stop processes are two competing independent processes from which the so called "stop signal reaction time" (SSRT) can be estimated as index of inhibitory performance.

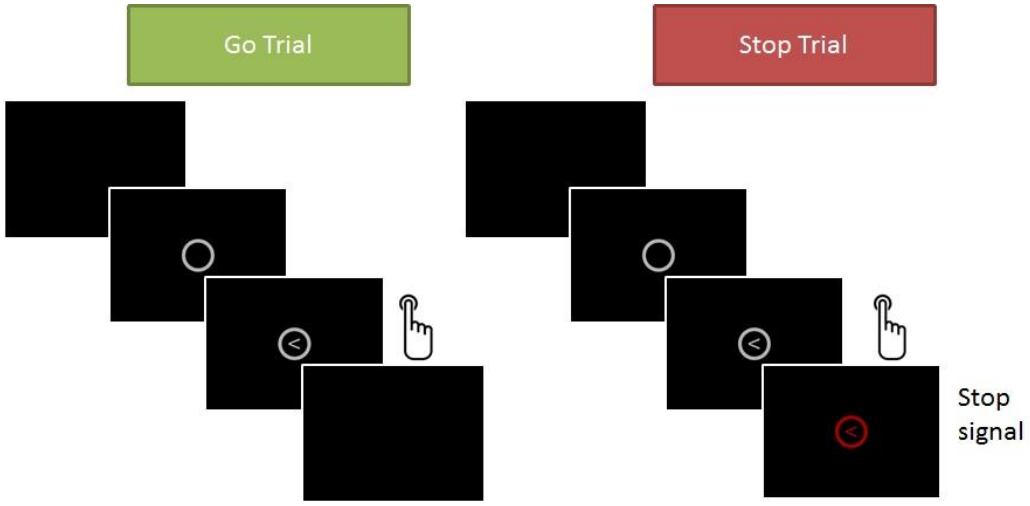

Figure 2: Structure of the Stop-Signal Paradigm

3.2.1.4 Statistical fMRI analyses

Functional imaging data was analyzed using Statistical Parametric Mapping software package (SPM8, Wellcome Department of Imaging Neuroscience). Functional data were corrected for slice timing and head motion and transformed into the stereotactic normalized standard space of the Montreal Neuroimaging Institute using the unified segmentation algorithm. Finally, functional data were resampled and spatially smoothed with a 3D Gaussian kernel. For statistical analysis, we conducted a classical event-related approach using a two-stage mixed-effects general linear model (GLM). On the single subject level, event-related separate regressors were included in all paradigms. Additionally, regressors of no interest were included. Finally, the six rigid body movement parameters were also included in the single subject GLM. Differential t-contrasts were calculated and taken to group level analysis. For extraction of parameters we used different approaches (see publication 1, 2 and 3 for details).

3.2.2 Magnetic Resonance Spectroscopy

Hydrogen-MRS (^{1}H -MRS) uses similar physical properties like (f)MRI and is a non-invasive technique to approximate relative concentrations of many brain metabolites. The basis of MRS metabolite quantification is, that the resonance frequency of a hydrogen atom depends not only on the magnetic field strength, but also on the chemical environment of the hydrogen atom, i.e. its position within the molecule. Interactions with neighboring atoms lead to a change in spin frequency (Stagg and Rothman, 2014). After recording, the ^{1}H-MRS signal is

transformed to a frequency spectrum where the positions of the signal peaks on the x-axis are expressed as "chemical shifts". Because these chemical shifts are unique to the molecule of interest, several compounds can be identified, and are commonly measured in units of parts per million (ppm). At 3 Tesla, the glutamate molecule has four major complexes of signals on the proton spectrum centred at 2.04, 2.11, 2.35, and 3.74ppm (Stagg and Rothman, 2014).

3.2.2.1 Acquisition of MRS data

Absolute glutamate concentrations in the ACC and the striatum were acquired with 3-Tesla ^{1}H-MRS using water suppressed and unsuppressed spectra, applying a specifically developed sequence to measure glutamate concentrations (Schubert et al., 2004).

3.2.2.2. MRS Voxel Localization

In study 2, a 20x30x25 mm voxel was placed in the ACC. The voxel was first aligned in parallel to the corpus callosum with the most ventral part of the voxel being immediately above the most dorsal part of the anterior corpus callosum. The anterior part of the voxel was then vertically lined up with the most anterior part of the genu. Finally, on a coronal plane, the voxel was placed to be as medial as possible (voxel position is shown in Figure 4).

For study 3, a 20x20x20 mm voxel was placed in the left striatum (see Figure 4). On a coronal plane, the voxel was first placed to contain the striatum in the center of the voxel. Further, the voxel was shifted dorsally and/or tilted counterclockwise on the coronal plane to include as much striatal and least insula gray matter (GM) structures and minimal cerebrospinal fluid (CSF) as possible. On the transversal and sagittal planes, the voxel was individually shifted and tilted to contain as much GM as possible.

3.2.2.3. Statistical MRS Analyses

MRS data in study 2 and 3 was analyzed using the "Linear Combination of Model spectra commercial spectral-fitting package" (LCmodel; Provencher, 1993; Göttingen, Germany), using water suppressed and unsuppressed spectra. Glutamate measured by MRS is considered to reflect the total content of glutamate in the region of interest (Rothman et al., 2011) independently of brain tissue compartments. Therefore, GM, white matter (WM) and CSF fractions within the MRS voxels were acquired using the unified segmentation approach (Ashburner and Friston, 2005) based on a high resolution T1 structural image. Subsequently,

absolute glutamate concentrations were adjusted for GM and WM (Glutamate adjusted = glutamate absolute*1/(GM+WM)).

3.2.3 Positron Emission Tomography

PET imaging has many clinical and research related applications. Still, it is considered as invasive technique, as it requires radioactive substances, so called "radiotracers", to be injected in the blood stream of the participants prior to investigation. A radiotracer consists of biologically active molecules of interest which are paired with a chemically incorporated radioactive "tracer atom". This radiotracer often mimics the function of a certain aspect of neurotransmitters or receptors in body tissue. After injection (usually in an arm vein), the radiotracer is distributed in the body or brain and emits a (positively charged) positron. This positron travels away from its molecule of origin (the radiotracer) and annihilates with a (negatively charged) free electron from the environment. During annihilation, gamma radiation is emitted in 180° of the origin of annihilation. These beams can then be recorded by so called "coincidence detectors" of the PET scanner. Eventually, the collected data can be reconstructed in a 3 dimensional volume and represents an estimate of the distribution of the radiotracer (Herholz et al., 2013).

In the present study, we decided to use F-18 labeled fluorodihydroxyphenylalanine ([^{18}F]DOPA) as radiotracer. [^{18}F]DOPA has similar properties in comparison to endogenous L-3,4-dihydroxy-phenylalanine (L-DOPA), which is decarboxylated by aromatic L-aminoacid-decarboxylase in synaptic vesicles to form dopamine. Thus, analogous to L-DOPA, after injection, [^{18}F]DOPA gets transported into dopaminergic neurons via the blood-brain barrier, where it is eventually metabolized into fluorodopamine and stored in presynaptic vesicles (Gjedde et al., 1991; Hiroaki Hoshi, 1993). After [^{18}F]DOPA it is taken up by neurons, dopamine synthesis capacity can be estimated by PET imaging. We specifically selected [^{18}F]DOPA PET due to its important role in aging and mental disease (Kumakura et al., 2010; Howes et al., 2011).

3.2.3.1 Acquisition of PET Data

PET data was acquired at the department of nuclear medicine at the Rudolf Virchow Hospital in Berlin, using a PET/CT scanner (Philips Gemini TF16) in 3-D mode. After a low dose transmission CT-scan, a dynamic 'list-mode' emission recording lasting 60 minutes started simultaneously with intravenous bolus administration of 120-200 MBq [^{18}F]DOPA.

3.2.3.2 Statistical Analysis of PET Data

For statistical analysis, dopamine synthesis capacity was quantified as [^{18}F]DOPA K_i (min^{-1}) voxel-by-voxel using Gjedde-Patlak linear graphical analysis (Patlak and Blasberg, 1985). Radioactivity time curves in a standard cerebellum mask as defined in the WFU Pick Atlas excluding vermis (Tzourio-Mazoyer et al., 2002) were used as input function. The linear fit was restricted to the time interval 20-60 min post injection. We extracted parameter estimates in a cluster in the left caudate nucleus that was revealed by fMRI analysis.

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4. Results

4.1 Study 1: *Reward Anticipation in the Adolescent and Aging Brain*

The fMRI analysis demonstrated a strong activation of the a priori hypothesized reward network in all groups in general. Globally, the three groups showed activation differences in subcortical (bilateral VS and thalamus), prefrontal (bilateral DLPFC, bilateral, precentral gyrus, ACC, and SMA), anterior insular and parietal areas (bilateral IPL and superior parietal lobule (SPL)). More specific, adolescents activated core reward regions (VS and ventromedial PFC (VMPFC) more strongly than younger adults. Furthermore, older adults showed a stronger recruitment of fronto-parietal regions compared to both younger groups (DLPFC, IPL, and SPL). Detailed results are presented in Figure 3.

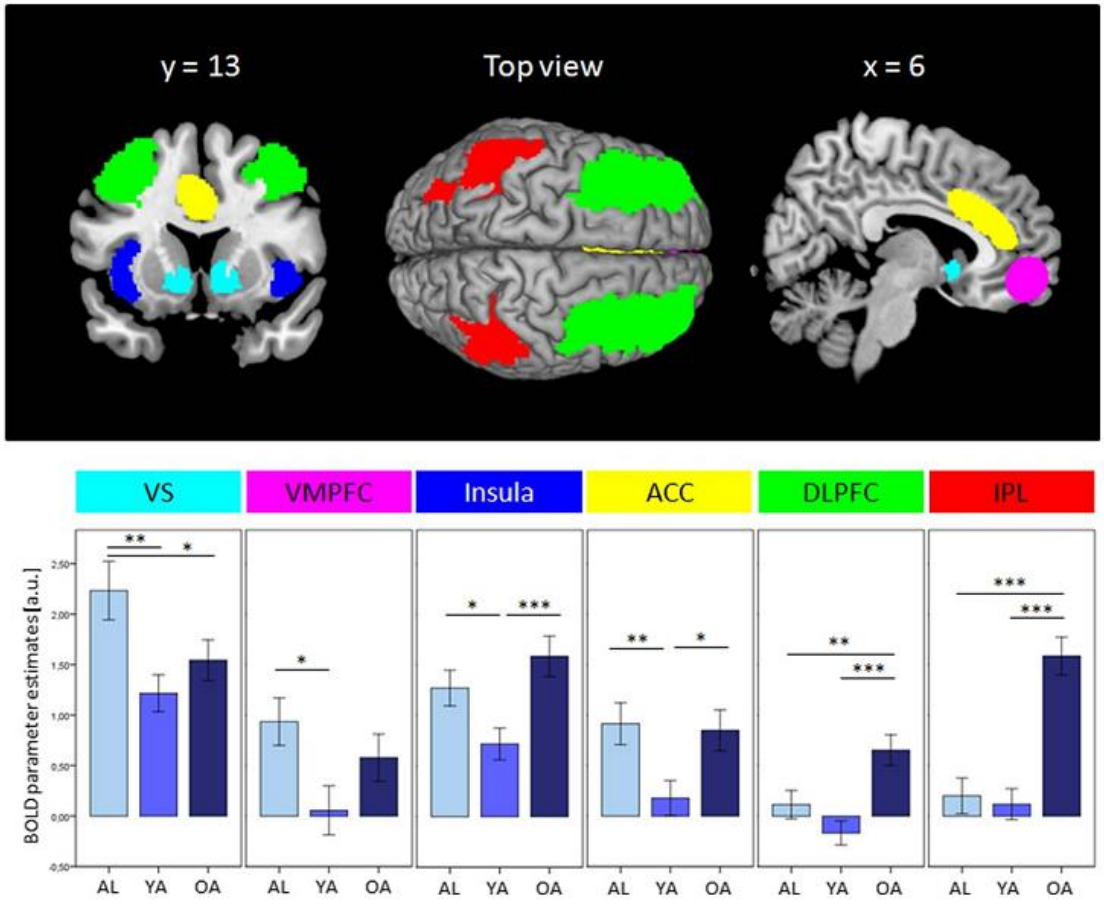

Figure 3: Regions of Interest and Differences in Reward Processing between Young Adolescents, Young Adults and Older Adults during Performance with the Slot Machine Task

Upper row: Anatomical presentation of ROIs. Bottom row: Bar graphs for each ROI and group (x-axis). Y -axis represents the mean BOLD parameter estimates of each ROI during reward processing in arbitrary units. Error bars represent standard error of means. ROI region of interest, VS ventral striatum, VMPFC ventromedial prefrontal cortex, ACC anterior cingulate cortex, DLPFC dorsolateral prefrontal cortex, IPL inferior parietal lobule, AL adolescents, YA younger adults, OA older adults, a.u. arbitrary units.

4.2 Study 2: *Frontal Glutamate and Reward Processing in Adolescence and Adulthood*

After extraction of fMRI data from the ventral striatum ROI, a binary logistic regression indicated that the interaction between glutamate and BOLD signal in the VS during reward processing significantly predicted whether subjects were in the adolescent or the young adult group (see Table 1). In post-hoc tests, a significant negative correlation between the glutamate concentration in the ACC and striatal BOLD signal was present in adolescents, but not in the adult group (see Figure 4). The two correlations differed significantly from each other (Fisher's $Z = -2.32$, $p<0.05$).

Table 1: Binary Logistic Regression Predicting Group Membership (Adolescents vs Adults)

	b Coefficient	SE	Wald	d.f.	p	Odds Ratio
VS-BOLD	-.03	.37	.01	1	.94	.97
Amygd BOLD	.01	.35	.00	1	.99	1.01
Glu	.44	.35	1.64	1	.2	1.56
Glu*VS BOLD	1.17	.51	5.32	1	**.02***	3.22
Glu*Amygd BOLD	-.24	.42	.32	1	.57	.79
VS-BOLD*Amygd BOLD	.16	.29	.29	1	.59	1.17
Constant	-.09	.31	.08	1	.78	.92

SE: Standard Error; d.f.: Degrees of Freedom; VS: Bilateral Ventral Striatum; Amygd: Bilateral Amygdala; Glu: Glutamate concentration in anterior cingulate cortex; BOLD: Blood Oxygen Level Dependent Signal; BOLD contrast reflects win against loss conditions *: Significant results

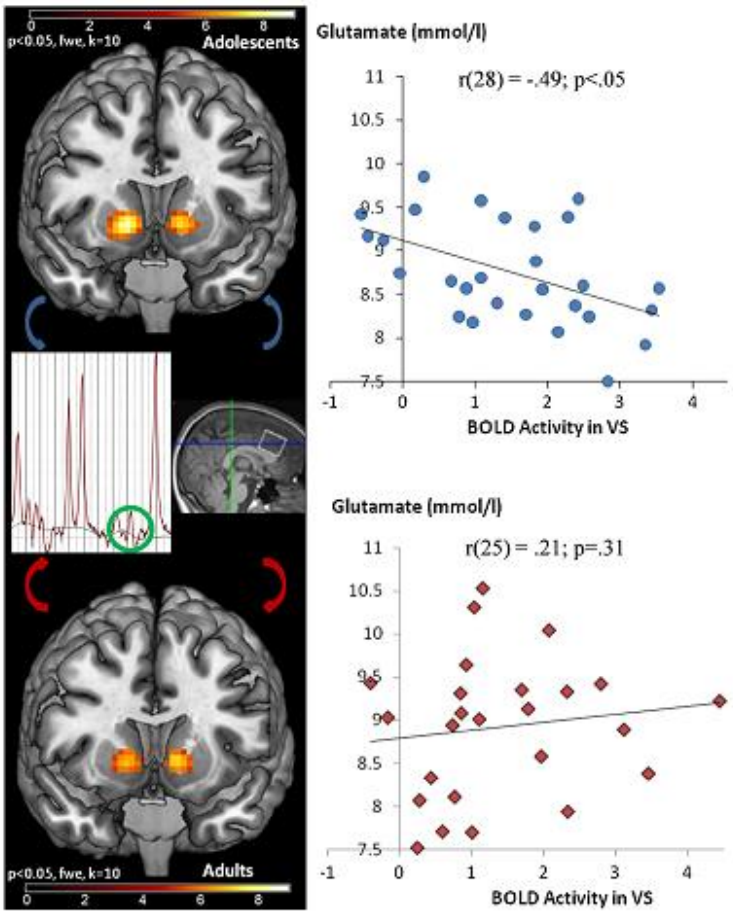

Figure 4: Relationship of Glutamate Concentrations in the ACC and BOLD Response during Reward Processing in Adolescents and Young Adults

VS BOLD signal and ACC glutamate concentration relationship within the groups (adolescents vs. adults). FWE family wise error, k minimal cluster size, win against loss contrast is displayed for the fMRI results. The green circle marks the glutamate peak in the spectrum

4.3 Study 3: *Glutamatergic Action on the Dopamine Driven Neural Signature of Response Inhibition*

A positive association between striatal inhibition-related BOLD activity and presynaptic-related dopamine properties was observed. Further, the results showed that striatal glutamate concentration mediates the relationship of presynaptic striatal dopamine and the striatal inhibition-related BOLD activity (see Figure 5). When controlling for glutamate concentration, this relationship did not remain significant, indicating that glutamate plays a regulatory key role within the striatum (see Figure 5). Furthermore, behavioral inhibition performance was inversely related to striatal inhibition-related BOLD activity (r(38)=–0.352; p=0.03). No effects of aging on any of the investigated variables were observed.

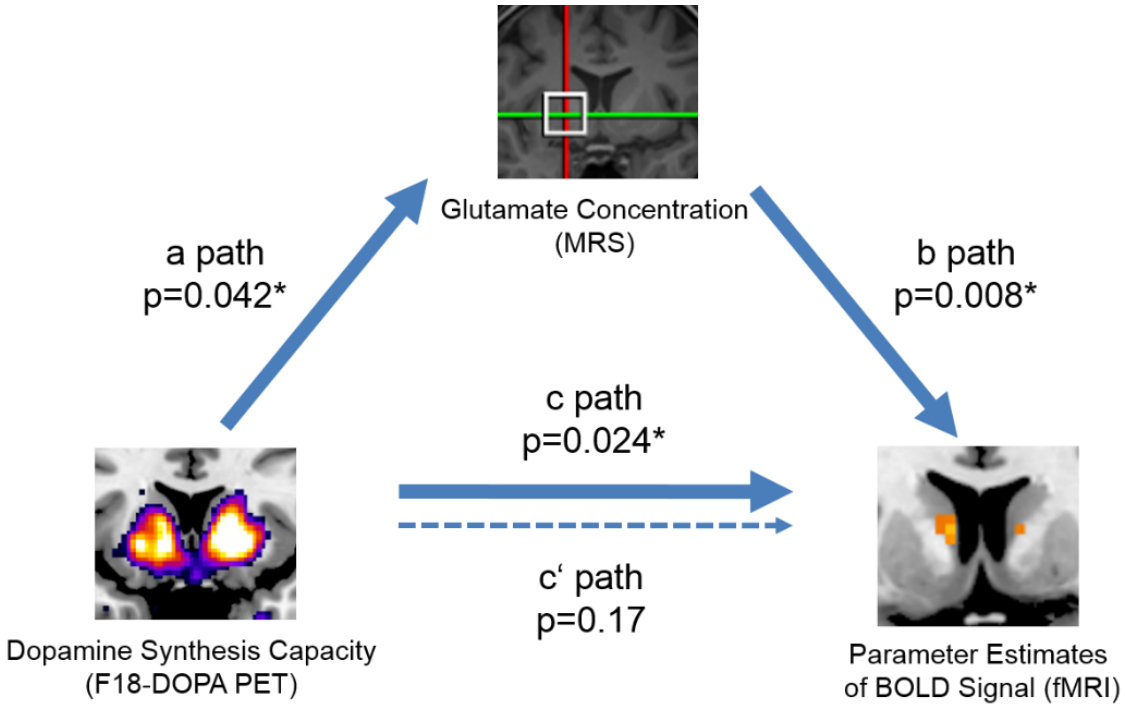

Figure 5: Mediation Model of Striatal Dopamine, Striatal Glutamate and Striatal fMRI Activation during Performance with the Stop Signal Task

Pathmodel of multimodal imaging measurements revealed that the influence of dopamine synthesis capacity on BOLD parameter estimates (c path, solid arrow) was mediated by glutamate concentration within the striatum. When excluding mediator influence, relationship did not remain significant (c‘ path, dashed arrow). Furthermore, mediator glutamate concentration was positively associated with dopamine sysnthesis capacity (a path) and BOLD parameter estimates (b path). MRS = Magnetic resonance spectroscopy; PET = Positron emission tomography; BOLD = Blood-oxygen-level dependent; fMRI = functional magnetic resonance imaging.

5. Discussion

5.1 Processing of Reward over the Lifespan

In the present dissertation, it was shown that neural processing of reward changed over the lifespan from adolescence to older adulthood areas in core reward areas (VS/VMPFC) and frontal/parietal areas (DLPFC, IPL). Additionally, lifespan-related changes may be associated with changes in dopaminergic and glutamatergic systems in reward-related areas. I will discuss those findings in the following sections.

5.1.2 Neurofunctional Reward Related Changes from Adolescence into Young Adulthood

During adolescence, rewarding stimuli are highly salient and may lead to impulsive and risk-taking behavior (Casey et al., 2008; Galvan, 2010). In study 1, this increase in salience may be reflected in stronger recruitment of reward core areas (like the VS and VMPFC) in adolescents compared to young adults and older adults. Further, in accordance with neurodevelopmental theories, a maturation imbalance between the early matured striatum and a protracted development of the prefrontal cortex were hypothesized to be on the basis of this finding (Galvan et al., 2007; Galvan, 2010; Somerville and Casey, 2010). In contrast, some studies showed a hyporesponsive striatal response to reward cues in adolescents (Bjork et al., 2004, 2010). However, these studies included a wider age range (12-17) compared to other studies [(Galvan et al., 2006, 2007) 13-17 years; (Van Leijenhorst et al., 2010): 14-15 years)]. Interestingly, striatal-prefrontal maturation imbalance may be strongest during mid-adolescence between 13 and 16 years (Steinberg, 2008), which resembles the age range in the present study. However, different task designs might also have had an influence on the results. For instance, the studies by Bjork et al. used monetary incentive delay tasks with abstract cues, developed for adults (Knutson et al., 2001), whereas other studies used cartoons (Galvan et al., 2006, 2007) or a slot machine task (Van Leijenhorst et al., 2010). The latter stimuli may probably be more appealing for adolescents than abstract cues (Richards et al., 2013b). The hyperactivation of the core areas of reward processing (VS and VMPFC) in adolescents may also be associated with higher levels of dopamine in reward related areas during adolescence (Galvan, 2010; Wahlstrom et al., 2010). However, direct acquisition of dopaminergic indices (e.g. via PET imaging) are impossible in adolescents due to ethical reasons.

Taken together, our results support the hypothesis of a hyperresponsive striatum to reward cues during adolescence in the age range between 13 and 16 years, specifically during performance of tasks which are appealing to adolescents (e.g. the slot machine task).

5.1.3 Neurofunctional Findings in Older Adults

We observed increased DLPFC and IPL activity in older adults compared to adolescents and younger adults during reward processing. Interestingly, DLPFC and IPL are involved in executive functions (Nee et al., 2013) and attentional control processes (e.g. inhibitory control) (Corbetta and Shulman, 2002). Further, DLPFC and IPL activity was associated with integration of reward-related information and learning of conditioned relationships between cue and consequence (Fletcher et al., 2001; Mohr et al., 2010b; Liu et al., 2011). In a recent review (Grady, 2012), the DLPFC and IPL were also discussed with regard to aging. This review showed that working memory (WMM) tasks demand strong executive functions and attentional processes and neurally lead to a recruitment the IPL and DLPFC (amongst others) (Owen et al., 2005; Nee et al., 2013). Further, WMM studies predominantly reported hyperactivation in the DLPFC and IPL in older adults compared to younger adults during low WMM loads, which was interpreted to reflect compensatory mechanisms. Transferred to the current study, we assume that gain anticipation leads to an increased attentional focus to the third still rotating wheel of the slot machine, which may require relatively low cognitive demand. Additionally, earlier studies indicated a role of dopamine and glutamate related change in striatal and frontal areas for cognitive aging which might be associated with this finding (Chang et al., 2009; Klostermann et al., 2012b; Zahr et al., 2013). However, in the present study, we did not specifically investigate the interaction between WMM related activity and reward processing, therefore more research is needed.

We did not observe a difference between younger and older adults during reward anticipation in the striatum, which coincides with findings by Samanez-Larkin et al. (Samanez-Larkin et al., 2007) and Rademacher et al. (Rademacher et al., 2013) but not with findings from Schott (Schott et al., 2007) and Dreher (Dreher et al., 2008). Further, in more complex reward-based tasks requiring strategic decision making for optimizing reward, older adults showed behavioral impairments and alterations in neural activity (Marschner et al., 2005; Mell et al., 2009; Mohr et al., 2010b; Eppinger et al., 2011). An impairment in gating function of the striatal signal to the prefrontal cortex may lead to the findings observed in more complex tasks. These changes might also be related to age-related neurochemical changes (dopaminergic or glutamatergic decline). We further investigated this hypothesis in study 3.

Taken together, present results suggest that reward associated processing may change from young adulthood to older adulthood, which is reflected in increased and broader activation in frontal areas but relatively preserved activation in striatal areas in the investigated age group.

5.1.4 Glutamate and Reward Related Processing during Adolescence

In study 2, we investigated the relationship between striatal-limbic BOLD activity and glutamate concentrations in the ACC during the processing of reward in adolescents and young adults. The results showed that glutamate is differently (namely negatively) related to neuronal activity during reward processing in adolescence compared to young adulthood.

Our interpretations of these findings are based on the earlier induced TMMB, which describes motivated behavior as the result from the balanced engagement of three different behavioral/neural systems: A reward driven approach system, reflected in striatal neuronal/dopaminergic signaling (Meyer-Lindenberg et al., 2002; Baas et al., 2004); second, the avoidance system, reflected in neuronal activity in the amygdala and other limbic areas, associated with serotonergic signaling; and the regulatory system formed by various frontal structures (Ernst et al., 2006). With regard to regulatory control in the frontal structures (in adolescence), recent research and theories suggest a central role of glutamate (Carlsson et al., 1999; Surmeier et al., 2007; Duncan et al., 2013; Selemon, 2013). It has further been shown that reward-related information is processed via a neuronal circuitry involving large glutamatergic projections from the ACC (among other areas) interacting with dopaminergic projections from the midbrain onto the VS (Richards et al., 2013b). The VS may integrate information projected via these pathways and returns this information to the frontal cortex via the ventral pallidum and midbrain areas (Richards et al., 2013b). Further, synaptic plasticity (regulated by glutamatergic factors) seems to be involved in the developmental refinement of the proper excitatory/inhibitory balance within the prefrontal cortex during adolescence (Selemon, 2013).

Taken together, we believe that the observed results in adolescents and young adults may represent developmentally different stages. We believe that in adults the homeostasis between glutamate in the ACC and BOLD-related dopamine activity in the striatum is more established. Subsequently, in young adults, changes in either glutamate concentration or dopaminergic activity in the VS may not influence dopamine and glutamate related striatal functional properties as strong as in adolescents.

5.2 Inhibitory Function Related Findings- Trimodal Results

In study 1, no differences in reward processing were observed in core reward areas like the VS between young and older adults. However, direct dopaminergic influence on response inhibition was indicated in striatal areas in recent research (Ghahremani et al., 2012) and striatal dopamine was shown to decline with increasing age (Braskie et al., 2008; Kumakura et al., 2010). Additionally, it was proposed that gating function of the striatal signal to the prefrontal cortex may be related to postsynaptic dopamine function in more complex tasks (Ghahremani et al., 2012). These changes might also be related to age-related neurochemical changes (Braskie et al., 2008; Zahr et al., 2008; Karlsson et al., 2011).

Therefore, we investigated inhibitory processing in the striatum in the age range between 20 and 80 years. Striatal neural activity in reinforcement areas was associated with dopaminergic and glutamatergic neurotransmission. However, in contrast to reward processing, functional and neurochemical aspects of response inhibition in the striatum seem to be less affected by aging. In the following, I will discuss the results in more detail.

A recent study by Ghahremani et al. (Ghahremani et al., 2012) highlighted a positive relationship between inhibition-related BOLD activity and dopamine D2/D3 receptor availability in the caudate nucleus. Dopamine synthesis capacity, which was measured in the current study, is associated with endogenous presynaptic dopaminergic neurotransmission, reflecting a background level of dopamine receptor stimulation (Ito et al., 2011; Schlagenhauf et al., 2012). Thus, with the present study using F18 DOPA PET we demonstrate that not only post- but also presynaptic dopaminergic status seems to be associated with functional properties of response inhibition. Furthermore, we showed that better individual inhibition performance was accompanied by stronger inhibition-related BOLD activity in the caudate nucleus. These findings are also in line with previous research (Vink et al., 2005; Ghahremani et al., 2012). Additionally, the striatal glutamate concentration was positively associated with striatal inhibition-related BOLD activity. Although studies quantifying glutamate concentrations in vivo in the striatum are very scarce, a recent MRS study reported a positive relationship of striatal glutamate concentration with performance in tests of executive functions (Zahr et al., 2008). This observation may argue for the role of glutamate within the fronto-striatal network, with relevance for executive functions and motor commands (Zahr et al., 2008; Chambers et al., 2009), which are negatively affected in older age. However, to our knowledge, this is the first study showing a relationship of striatal glutamate concentration to a neuronal correlate of response inhibition. Still, in contrast to functional and dopaminergic indices from earlier study

(Ghahremani et al., 2012), in the present study, we were unable to demonstrate a significant relationship between presynaptic dopamine function and behavioral inhibition performance. Thus, it may be that postsynaptic rather than presynaptic dopaminergic neurotransmission is directly related to response inhibition behavior.

We further did not observe aging effects regarding the response inhibition. Future research should investigate pre- and postsynaptic contributions to response inhibition more systematically. Still, in the present study we were able to add evidence regarding presynaptic dopaminergic neurotransmission and glutamate concentrations to the complex neurochemical interactions of response inhibition in the caudate nucleus.

5.3 Indications of Glutamate-Dopamine Interactions and Reward Processing over the Lifespan for Mental Diseases

Interestingly, during adolescence, dopaminergic and glutamatergic factors undergo strong changes in reward circuits (Insel et al., 1990; Somerville and Casey, 2010). Further, research on young subjects at high risk for psychosis and schizophrenia patients showed abnormalities in glutamatergic and dopaminergic factors (Stone et al., 2010; Bloemen et al., 2011; Howes et al., 2011; Marsman et al., 2013; Schwerk et al., 2014) as well as indications of abnormal reward processing prior to the onset of psychosis (Juckel et al., 2012). Further, the onset of schizophrenia related symptomatology starts early in adolescence (Paus et al., 2008) and is highly associated with changes in dopaminergic and glutamatergic factors (Stone et al., 2010, 2010; Howes et al., 2012; Poels et al., 2014) as well as to abnormal reward processing (Esslinger et al., 2012; Grimm et al., 2014). After full-blown onset of psychosis, increased striatal dopamine synthesis capacity and abnormal reward processing is typical for schizophrenia (McGowan et al., 2004; Kumakura et al., 2007; Howes et al., 2012; Fusar-Poli and Meyer-Lindenberg, 2013). It has been proposed that a hypofunction of prefrontal NMDA receptors, which is also related to age associated processes during adolescence (Insel et al., 1990) may lead to the observed elevation of striatal presynpatic dopamine function in patients (Marsman et al., 2013; Poels et al., 2014; Schwerk et al., 2014). Additionally, striatal and prefrontal glutamate may contribute to increased dopamine activity observed in schizophrenia (Gleich et al., 2015).

Further, the presented findings can be considered relevant for other mental diseases. For instance, in addiction, blunted pre- and postsynaptic striatal dopamine function is a well-known finding (e.g. Volkow et al., 1996; Heinz et al., 2004; Martinez et al., 2005); Abnormal glutamate concentrations in various frontal lobe structures like the ACC were also reported (Mon et al.,

2012). Glutamate concentrations in the ACC were also observed to vary as a function of abstinence (Mon et al., 2012; Abé et al., 2013). Further, dopamine and glutamate related abnormalities may be related to the onset of addiction in adolescence (Nixon and McClain, 2010; Cohen-Gilbert et al., 2014; Setiawan et al., 2014). While animal models of addiction disorders have intensively investigated the interaction of glutamate and dopamine for reward learning (Adrover et al., 2014; Nimitvilai et al., 2014), human investigations are still largely lacking. Thus, the present findings provide a starting point for studying glutamate-dopamine interactions in humans across glutamate and dopamine associated mental diseases.

6. Conclusion

The present findings contribute to the understanding of lifespan-related changes in reward associated processing as well as to response inhibition and may further advance the understanding of healthy aging in terms of neurochemical and functional interactions. Moreover, the present work demonstrates the importance of taking lifespan-related alterations in dopaminergic, glutamatergic and functional parameters into account when conducting research in human beings of different ages. Additionally, those lifespan-related changes may be basic to the understanding of the onset of many glutamate and dopamine associated mental diseases and may also lead to better understanding and improvement of the effectiveness of psychopharmacological medication and therapy for mental disease throughout the life. Finally, the present studies emphasize the importance of multimodal imaging to investigate the interaction of major neurotransmitters with neurofunctional and behavioral parameters.

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8. Anteilserklärung

8.1 Eidesstattliche Versicherung

„Ich, Tobias Gleich, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „The Significance of Dopamine and Glutamate for Neuronal Reward Processing over the Lifespan“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.**icmje**.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

8.2 Anteilserklärung an den erfolgten Publikationen

Tobias Gleich hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Lorenz, Robert*, **Gleich, Tobias***, Beck, Anne, Pöhland, Lydia, Raufelder, Diana, Sommer, Werner, Rapp, Michael, Kühn, Simone, Gallinat, Jürgen. Reward anticipation in the adolescent and aging brain. Human Brain Mapping, 2014.

40%:

- Rekrutierung von gesunden Probanden
- klinische Untersuchungen von gesunden Probanden
- Begleitung und Betreuung der Probanden bei Neuropsychologischen Testungen und fMRT-Messungen
- Durchführung der MRT Messungen
- Dateneingabe mit SPSS
- Analyse der fMRT und Verhaltensdaten mittels SPM8/SPSS
- Schreiben des Manuskripts und substantielle Mitwirkung an der Anfertigung der Publikation in der vorliegenden Form
- Korrektur und Überarbeitung des Manuskripts

Publikation 2: Gleich, Tobias*, Lorenz, Robert*, Pöhland, Lydia, Raufelder, Diana., Deserno, Lorenz, Beck, Anne, Heinz, Andreas, Kühn, Simone, Gallinat, Jürgen. Frontal glutamate and reward processing in adolescence and adulthood. Brain Structure and Function, 2014.

70%:

- Rekrutierung von gesunden Probanden
- klinische Untersuchungen von gesunden Probanden
- Begleitung und Betreuung der Probanden bei Neuropsychologischen Testungen, fMRT-Messungen und MRS Messungen
- Durchführung der MRT und MRS Messungen
- Dateneingabe mit SPSS
- Vollständige Datenanalyse mittels SPM8, SPSS und LCmodel
- Schreiben des Manuskripts und substantielle Mitwirkung an der Anfertigung der Publikation in der vorliegenden Form
- Submission des Manuskripts
- Anfertigung der Publikation inklusive der Abbildungen in der vorliegenden Form (Review)

Publikation 3: Lorenz, Robert*, **Gleich, Tobias*,** Buchert, Ralph., Kühn, Simone, Gallinat, Jürgen. The role of dopamine and glutamate in functional and behavioral aspects of response inhibition in human striatum. Human Brain Mapping, 2015.

40%:

- Rekrutierung der gesunden Probanden
- klinische Untersuchungen der gesunden Probanden
- Begleitung und Betreuung der Probanden bei den fMRT, MRS- und PET Messungen
- Durchführung der fMRT, MRS und PET Messung
- Verfassen, Korrektur und Überarbeitung des Manuskripts
- Schreiben des Manuskripts und substantielle Mitwirkung an der Anfertigung der Publikation in der vorliegenden Form

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

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9. Ausgewählte Publikationen

Gleich, T., Lorenz, R. C., Pöhland, L., Raufelder, D., Deserno, L., Beck, A., … Gallinat, J. (2015). Frontal glutamate and reward processing in adolescence and adulthood. Brain Structure & Function, 220(6), 3087–3099. http://doi.org/10.1007/s00429-014-0844-3

Lorenz, R. C., Gleich, T., Beck, A., Pöhland, L., Raufelder, D., Sommer, W., … Gallinat, J. (2014). Reward anticipation in the adolescent and aging brain. Human Brain Mapping, 35(10), 5153–5165. http://doi.org/10.1002/hbm.22540

Lorenz, R. C., Gleich, T., Buchert, R., Schlagenhauf, F., Kühn, S., & Gallinat, J. (2015). Interactions between glutamate, dopamine, and the neuronal signature of response inhibition in the human striatum. Human Brain Mapping, 36(10), 4031–4040. http://doi.org/10.1002/hbm.22895

10. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

11. Publikationsliste

Erstautorenschaften/Geteilte Erstautorenschaften

Robert C. Lorenz*, **Tobias Gleich***, Ralph Buchert, Florian Schlagenhauf, Simone Kühn, Jürgen Gallinat: *Interactions between glutamate, dopamine, and the neuronal signature of response inhibition in the human striatum*. Human Brain Mapping 07/2015; DOI:10.1002/hbm.22895. **Impact Factor: 6.92**

Tobias Gleich*, Lorenz Deserno*, Robert C. Lorenz, Rebecca Boehme, Anne Pankow, Ralph Buchert, Simone Kühn, Andreas Heinz, Florian Schlagenhauf, Jürgen Gallinat: *Prefrontal and Striatal Glutamate Differently Relate to Striatal Dopamine: Potential Regulatory Mechanisms of Striatal Presynaptic Dopamine Function?*. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 07/2015; 35(26):9615-9621. DOI:10.1523/JNEUROSCI.0329-15.2015. **Impact Factor: 6.75**

Robert C. Lorenz*, **Tobias Gleich***, Simone Kühn, Lydia Pöhland, Patricia Pelz, Torsten Wüstenberg, Diana Raufelder, Andreas Heinz, Anne Beck: *Subjective Illusion of Control Modulates Striatal Reward Anticipation in Adolescence.*. NeuroImage 05/2015; 117. DOI:10.1016/j.neuroimage.2015.05.024. **Impact Factor: 6.36**

Robert C. Lorenz*, **Tobias Gleich***, Jürgen Gallinat, Simone Kühn: *Video game training and the reward system*. Frontiers in Human Neuroscience 02/2015; 9:40. DOI:10.3389/fnhum.2015.00040. **Impact Factor: 2.9**

Robert C. Lorenz*, **Tobias Gleich***, Anne Beck, Lydia Pöhland, Diana Raufelder, Werner Sommer, Michael A. Rapp, Simone Kühn, Jürgen Gallinat: *Reward Anticipation in the Adolescent and Aging Brain*. Human Brain Mapping 10/2014; 35(10). DOI:10.1002/hbm.22540. **Impact Factor: 6.92**

Tobias Gleich*, Robert C. Lorenz*, Lydia Pöhland, Diana Raufelder, Lorenz Deserno, Anne Beck, Andreas Heinz, Simone Kühn, Jürgen Gallinat: *Frontal glutamate and reward processing in adolescence and adulthood*. Brain Structure and Function 07/2014; DOI:10.1007/s00429-014-0844-3. **Impact Factor: 4.57**

Tobias Gleich*, Jan .B. Deijen, Madeleine.L. Drent: *The Involvement of the Hypothalamic-pituitary-gonadal, Hypothalamic-pituitary-adrenal and Somatotrophic Axes in the Development and Treatment of Schizophrenia.* International Neuropsychiatric Disease Journal 13/2013. **Impact Factor: Noch nicht verfügbar**

Koautorenschaften

Anne Pankow, Teresa Katthagen, Sarah Diner, Lorenz Deserno, Rebecca Boehme, Norbert Kathmann, **Tobias Gleich**, Michael Gaebler, Henrik Walter, Andreas Heinz, Florian Schlagenhauf: *Aberrant Salience Is Related to Dysfunctional Self-Referential Processing in Psychosis*. Schizophrenia Bulletin 07/2015; DOI:10.1093/schbul/sbv098. **Impact Factor: 8.61**

Rebecca Boehme, Lorenz Deserno, **Tobias Gleich**, Teresa Katthagen, Anne Pankow, Joachim Behr, Ralph Buchert, Jonathan P. Roiser, Andreas Heinz, Florian Schlagenhauf: *Aberrant Salience Is Related to Reduced Reinforcement Learning Signals and Elevated Dopamine Synthesis Capacity in Healthy Adults*. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience 07/2015; 35(28):10103-10111. DOI:10.1523/JNEUROSCI.0805-15.2015. **Impact Factor: 6.75**

Simone Kühn, **Tobias Gleich**, Robert C. Lorenz, Ulman Lindenberger, Jürgen Gallinat: *Playing Super Mario induces structural brain plasticity: Gray matter changes resulting from training with a commercial video game.* Molecular Psychiatry 10/2013; Advance online publication. DOI:10.1038/mp.2013.120. **Impact Factor: 15.15**

Oswald J. N. Bloemen, Mariken B. de Koning, **Tobias Gleich**, Julia Meijer, Lieuwe de Haan, Don H Linszen, Jan Booij, Thérèse A. M. J. van Amelsvoort: *Striatal dopamine D2/3 receptor binding following dopamine depletion in subjects at Ultra High Risk for psychosis*. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology 05/2012; 23(2). DOI:10.1016/j.euroneuro.2012.04.015. **Impact Factor: 5.4**

Oswald J. N. Bloemen, **Tobias Gleich**, Mariken B. de Koning, Fabiana da Silva Alvis, Lieuwe de Haan, Don H. Linszen, Jan Booij, Thérèse A. M. J. van Amelsvoort: *Hippocampal Glutamate Levels and Striatal Dopamine D-2/3 Receptor Occupancy in Subjects at Ultra High Risk of Psychosis*. Biological psychiatry 07/2011; 70(1):e1-2; author reply e3. DOI:10.1016/j.biopsych.2010.11.030. **Impact Factor: 9.47**

Vorträge

- Kongress der Deutschen Gesellschaft für Biologische Psychiatrie in Aachen, Universitätsklinikum Aachen, 2014.Titel*: Die Bedeutung der fronto-limbischen Dopamin-Glutamat Interaktion für psychiatrische Störungen.*

- Donders Discussions Conference. Donders Institute for Brain, Cognition and Behaviour, 2014. Titel: *The relevance of fronto-limbic Glutamate-Dopamine interactions in healthy individuals across the lifespan and psychiatric diseases.*

- Mentale Gesundheit in Deutschland und Russland. Initiative für Klinik und Forschung. St. Petersburg, 2014.Titel: *Neuronale Korrelate von Videospielen: Therapieoption oder Abhängigkeitserkrankung?*

- Mentale Gesundheit in Deutschland und Russland. Initiative für Klinik und Forschung. Berlin, 2013.*Titel: Die Neurobiologie des Belohnungssystems.*

Poster Präsentationen

Juni 2015: Tobias Gleich, Lorenz Deserno, Robert Lorenz, Ralph Buchert, Anne Pankow, Rebecca Böhme, Simone Kühn, Andreas Heinz, Florian Schlagenhauf, Jürgen Gallinat:
„Dopamine-Glutamate Interactions in Fronto-Striatal Circuits in the Healthy Brain“
Annual Meeting of the Organization for Human Brain Mapping. Honolulu, USA.

Mai 2014: Tobias Gleich, Lorenz Deserno, Robert Lorenz, Ralph Buchert, Anne Pankow, Rebecca Böhme, Andreas Heinz, Florian Schlagenhauf, Jürgen Gallinat:
“The Relationship of Frontal Glutamate Concentrations and Ventral Striatal Dopamine Synthesis Capacity“
Annual Scientific Convention of the Society of Biological Psychiatry. New York, USA.

November 2013: Tobias Gleich, Rebecca Böhme, Lorenz Deserno, Anne Pankow, Jürgen Gallinat, Andreas Heinz, Florian Schlagenhauf:
„Glutamate concentrations and performance during operant conditioning in schizophrenia“
Konferenz der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde. Berlin, Deutschland.

September 2013: Tobias Gleich, Rebecca Böhme, Lorenz Deserno, Anne Pankow, Jürgen Gallinat, Andreas Heinz, Florian Schlagenhauf:
“Glutamate concentrations and performance during operant conditioning in schizophrenia”
European Conference on Schizophrenia Research, Berlin, Deutschland.

Juni 2013: Tobias Gleich, Robert C. Lorenz, Sa Luo, Julia Frenzel, Torsten Wüstenberg, Simone Kühn, Andreas Heinz, Jürgen Gallinat:
„Striatal BOLD activity and the association with frontal glutamate concentrations in aging”.
Annual Meeting of the Organization for Human Brain Mapping. Seattle, USA.

November 2012: Tobias Gleich, Robert Lorenz, Sa Luo, Julia Frenzel, Torsten Wüstenberg, Simone Kühn, Andreas Heinz , Jürgen Gallinat:

„Striatal BOLD activity and the association with frontal glutamate concentrations in aging"
Konferenz der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde. Berlin, Deutschland.

September 2012: ´ Tobias Gleich, Robert Lorenz, Simone Kühn, Michael Rapp, Andreas Heinz, Jürgen Gallinat:
"Glutamate concentration in the anterior cingulate cortex and sensation seeking over the lifespan"
Charité Conference on Psychiatric Research: Emotional Neuroscience.

Juni 2012: Tobias Gleich, Robert Lorenz, Simone Kühn, Michael Rapp, Andreas Heinz, Jürgen Gallinat:
"Glutamate concentration in the anterior cingulate cortex and sensation seeking over the lifespan"
Annual Meeting of the Organization for Human Brain Mapping. Peking, China.

November 2011: Tobias Gleich, Jan Berend Deijen, Madeleine.L. Drent:
„The role of hormones in the development and treatment of schizophrenia"
Konferenz der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde. Berlin, Deutschland.

September 2011: Tobias Gleich, Sabrina Golde, Robert C. Lorenz,
Simone Kühn, Michael Rapp, Andreas Heinz, Jürgen Gallinat:
"The role of hormones in the development and treatment of schizophrenia"
Charité Conference on Psychiatric Research: Emotional Neuroscience.

Danksagung

Ich möchte an erster Stelle ganz herzlich meinem Doktorvater Prof. Dr. med. Jürgen Gallinat für seine zuverlässige, kompetente, motivierende und freundliche Betreuung und Förderung während der Promotion danken. Außerdem danke ich Herrn Prof. Dr. med. Dr. phil. Heinz für die Unterstützung und Aufnahme in den wissenschaftlichen Bereich der Charité.

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