The Role of Human Dopamine Transporter in Cognition

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Anna-Maria Kasparbauer

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Zusammensetzung der Prüfungskommission:

Prof. Dr. Henning Gibbons (Vorsitzender)

Prof. Dr. Ulrich Ettinger (Betreuer und Gutachter)

Prof. Dr. Martin Reuter (Gutachter)

Prof. Dr. Bernd Weber (weiteres prüfungsberechtigtes Mitglied)

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1. Summary

The current thesis briefly introduces the dopamine system and specifically elucidates the role of the dopamine transporter within synaptic transmission. Knowledge from genetic, molecular, pharmacological and animal literature is summarized, in order to gain an understanding of the functional role of the dopamine transporter within cognitive and behavioural concepts. Converging literature emphasize the transporters crucial role on dopaminergic tone which is due to the impact on the allocation of extra- and intracellular dopamine.

The methodological part describes invasive and non-invasive neuroimaging modalities for the measurement of genetic and molecular influence of the human dopamine transporter. Additionally, analysis processes and gene expression that are applied in the experimental part are described in this section.

The experimental part presents theoretical background and outcome of three independent original studies that broadened knowledge of the influence of dopamine transporter on human cognition. The first study reveals a modulation of brain activation during inhibitory motor control as function of a genetic variant that potentially predicts striatal dopamine transporter density. In the absence of performance effects the dopamine transporter genotype shows a consistent effect on brain activation in contrast to another dopaminergic genotype of prefrontal function. The second study, investigated genetic and molecular predictors of a single dose of a dopamine transporter inhibitor, namely methylphenidate. The findings revealed an interaction between genotype and pharmacological intervention and implies genetic variability in the treatment outcome of catecholamine transporter inhibitors. The third study used the same compound in order to dissociate specific effects of striatal dopamine modulation from secondary dopamine stimulation with a cholinergic agent (nicotine) during an oculomotor task. In the absence of performance differences, an increase in the left frontal eye field was observed with a single dose methylphenidate. In contrast, nicotinic stimulation showed a reduction of brain activation.

The general discussion embeds the findings within the context of cognition and behaviour and suggests an explanation for the observed genetic and interaction effects in the context of synaptic dopamine transmission. Finally, overall limitations of the presented data is discussed.

2. Acknowledgements

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I dedicate this thesis to my family and friends who will surely never read it, but obstinately believe in me.

3. Table of Contents

"...what draws us into a story and keeps us there is the firing of our dopamine neurons, signaling that intriguing information is on the way."

Author: Lisa Cron,

Wired for Story: The Writer's Guide to Using Brain Science to Hook Readers from the Very First Sentence

4. Theoretical Framework

The theoretical background of this thesis introduces the neurotransmitter dopamine and specifically focus on the role of the dopamine transporter within dopaminergic functioning and its modulatory role in cognition. Successively, the theoretical framework is complemented by three empirical studies investigating dopaminergic transmission in human cognition.

4.1 Dopamine

Dopamine belongs to the small-molecule neurotransmitter category. Since its first detection (Dahlström and Fuxe, 1964) there has been a fast growing interest in its functional role. Although not immediately accepted by neuroanatomists, the initial major locations of dopaminergic neurons were attributed to the mesencephalon and the diencephalon. Early focus remained on the projection from the substantia nigra, pars compacta to the neostriatum and later to the projection between the ventral tegmental area and the olfactory tubercle and the ventral striatum (Moore and Bloom, 1978).

With the development of optical and ultrastructural immunocytochemistry an increasing understanding of the extent and organization of the dopamine neurons established in the late 1970s (Iversen *et al.*, 2010). Although, early work had identified a small, but concentrated projection of dopamine fibres in rodent prefrontal cortex, the discovery of dopamine fibres in the primate medial prefrontal cortex twenty years later (Lewis, 1992) formed the groundwork for the investigation of dopamine effects within cortical circuitry and its role in cognition. The rising interest in dopamine has been accelerated by its association with psychiatric disorders, such as schizophrenia (Howes and Kapur, 2009), addiction (Volkow, Wang, Telang, *et al.*, 2007), attention deficit hyperactivity disorder (ADHD) (Sikström and Söderlund, 2007), personality disorders (Mohr and Ettinger, 2014) and neurodegenerative disorders (Hirano, Shinotoh and Eidelberg, 2012).

Early interpretations named dopamine an ‘inhibitory’ transmitter (Connor, 1970; Mantz *et al.*, 1992; Thierry *et al.*, 1998), yet this description does not come close to the complexity of action triggered by dopamine. Neuromodulator is a far more appropriate portrayal of dopamine and gives justice to its highly complex pattern of action. A neuromodulatory role is assigned to transmitters that do not alter basal neuronal activity,

but promote or weaken evoked responses to other transmitters (Barchas *et al.*, 1978).

To fulfil this role, dopamine neurons possess distinct presynaptic mechanisms that allow 'tonic' and 'phasic' modes of firing and postsynaptic mechanisms regulating duration of receptor stimulation and direction of effect following D1 or D2 receptor activity (Grace and Bunney, 1984a, 1984b; Pucak and Grace, 1994). Tonic firing describes spontaneous single spike activity which has been associated with behavioural flexibility (Goto, Otani and Grace, 2007). Thus, the number of dopamine neurons influences the baseline tonic level (Grace, 1991; Floresco *et al.*, 2003). Burst firing or phasic activity triggers high amplitude intrasynaptic dopamine release and is subject to rapid dopamine transporter reuptake (Grace, 1991; Floresco *et al.*, 2003; Floresco, 2013; Gowrishankar, Hahn and Blakely, 2014).

Decline in motor function, cognitive flexibility, inhibition and working memory as function of age-related reduction of dopamine activity renders the significance of dopamine in motor control, cognitive control and executive function (Volkow, Gur, *et al.*, 1998).

The influence of dopamine on motor control, sensorimotor integration and motor learning suggests itself due to the predominant expression of dopamine in nuclei of the basal ganglia (Smith and Kieval, 2000). This structure is essentially involved in motor and oculomotor movement and connects with thalamic and prefrontal structures and provides the means to act as a selective gatekeeper for motor and cognitive programmes (Mink, 1996; Hayes *et al.*, 1998; van Schouwenburg, Aarts and Cools, 2010). Such selection processes include essential components of cognitive control, namely the suppression of inappropriate response, simultaneously with the selection of appropriate alternatives (Cools, 2008).

Several theories focus on the functional role of dopamine in learning and motivation based on the well-established observation of phasic release of dopamine to rewarding stimuli. Empirical work has strengthened the reward-prediction theory which postulates facilitation of learning by scaling dopamine release to the discrepancies between predicted and actual outcome (Cagniard *et al.*, 2006; Schultz, 2007). Accordingly, dopamine integrates motivational and learning processes to form an adaptive behavioural system (for detailed review of dopamine and learning and motivation, see R. A. Wise, 2004).

In short, the influence on motor control and motivation implicates that dopamine plays a key role in the adjustment of behavioural control mechanisms. This fine-tuning can be

distorted by drugs inducing dopamine release. Consequences can be euphoric feelings of well-being and heightened arousal and attention, but also self-destroying drug seeking or compulsive behaviour (Nutt *et al.*, 2015). Other examples of dysfunctional dopamine system and maladaptive behaviour is observed in obsessive compulsive disorder, schizophrenia, attention-deficit disorder or Parkinson's disease (Nieoullon, 2002; Koob and Volkow, 2016). Better understanding of these delicate tuning mechanisms on cognition applied by dopamine can help to interrupt or prevent the development of maladaptive behavioural strategies.

4.1.1 Dopamine Systems

The most prominent dopaminergic axonal projections are located in the mesencephalon forming several major dopaminergic pathways. Originally three different cell groups were classified based on their location: the ventral tegmental area (A10), substantia nigra pars compacta (A9) and the retrorubral area (A8) (Dahlström and Fuxe, 1964). These nuclei give rise to the mesolimbic, the mesocortical (A8 and A10) and the mesostriatal (nigrostriatal, A9) pathways (Figure 1). The mesolimbic pathway projects to the limbic striatum (nucleus accumbens) and the olfactory tubercle (Björklund and Lindvall, 2011) and is involved in motivation, emotion and reward (Wise and Bozarth, 1987; Nader, Bechara and van der Kooy, 1997). The mesocortical dopamine neurons project to the cingulate, entorhinal and medial prefrontal cortex and are involved in executive function, such as working memory and other higher cognitive processes (Le Moal and Simon, 1991). The mesostriatal pathway is topographically organized that medial cells of the substantia nigra pars compacta and the retrorubral area project ventrally to the nucleus accumbens and the ventral striatum, whereas more lateral located cells yield projections to the dorsal striatum forming the nigrostriatal pathway. The nigrostriatal pathway or nigrostriatal bundle, innervates areas that control motor behaviour in basal ganglia, such as caudate and putamen (Ungerstedt, 1971; Björklund and Lindvall, 2011). The tuberoinfundibular dopamine system projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion (Iversen *et al.*, 2010).

The successful treatment of striatal dopamine deficits in Parkinson's disease with dopaminergic agonists drove early research focus of dopamine towards motor control (Bernheimer and Hornykiewicz, 1965). The discovery of the mesocortical dopamine system by Thierry and colleagues (Thierry *et al.*, 1973; Berger *et al.*, 1974) in the mid-

1970s entailed a plethora of data on the functional role of dopamine in the prefrontal cortex and its role in cognition.

The anatomical layout permit dopamine a modulatory role on behaviour, specifically the adaptation of action and emotion (Nieoullon, 2002; Nieoullon and Coquerel, 2003). Additionally, dopamine is more abundant in frontal cortex than posterior parts of the brain (Nieoullon, 2002) which indicates functional correlates in higher-order cognition (Frith and Dolan, 1996; Miller and Wallis, 2010). Adaptive behaviour demands motivational and goal-directed processes which have been associated with limbic-striatal and fronto-striatal structures, respectively (Cools, 2008). Recent research has moved from the simple separation between nigral and ventral tegmental of dopamine projections to discrete forebrain targets to a more complex represenation of dopamine neuron subtypes expressed by variations in morphological features, co-transmitters and marker proteins (Björklund and Dunnett, 2007).

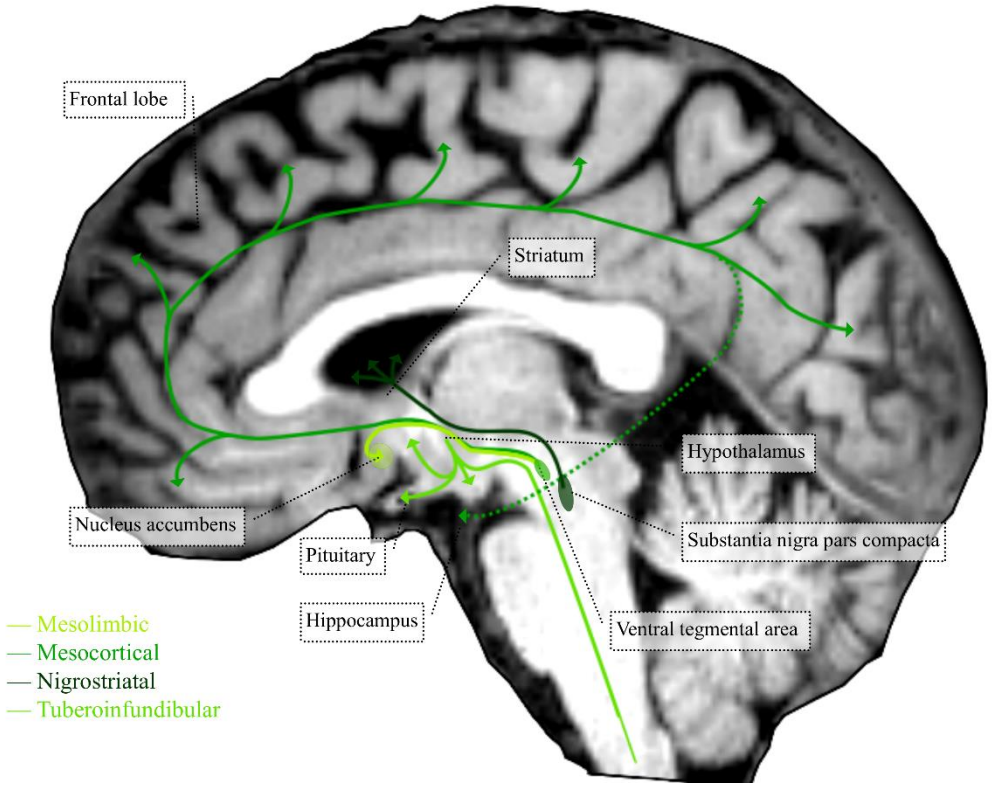


Figure 1. Dopamine Pathways.

4.1.2 Dopamine Life Cycle

The amino-acid tyrosine is the precursor for the synthesis of dopamine, as well as norepinephrine and epinephrine and contains the chemical structure catechol. The catalyst

for catecholamine synthesis is the enzyme tyrosine hydroxylase which turns the rate-limiting enzyme tyrosine to dopa. The enzyme dopa L-amino acid decarboxylase removes a carboxyl group yielding dopamine. The amount of dopa available determines the amount of dopamine synthesized (Figure 2A). Although dopamine qualifies as a neurotransmitter, further synthesis changes dopamine to norepinephrine also known as noradrenaline by dopamine beta-hydroxylase (in vesicles). Epinephrine is synthesized by phentolamine-N-methyltransferase acting on norepinephrine.

For example, in response to behavioural stimuli, dopamine is released from vesicles into the synaptic cleft, extrasynaptic dopamine level rises to a plateau and interacts with postsynaptic receptors. Dopamine receptors are divided into D1-like (D1, D5) and D2-like (D2, D3, D4) subgroups (for a detailed review see: Beaulieu & Gainetdinov, 2011). The subdivision is based on G-protein coupling (Vallone, Picetti and Borrelli, 2000). After reaching the plateau, dopamine levels slowly return to baseline through different routes, namely diffusion, reuptake and degradation (Chen and Reith, 2000; Wayment, Schenk and Sorg, 2001; Cragg and Rice, 2004; Rodriguez *et al.*, 2013). Released dopamine is catabolised by catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO) or more effectively taken back into the axon terminal via Na^{+}-dependent cell membrane transporters and packed back into vesicles through vesicular monoamine transporters or metabolized via MAO (Figure 2B). The primary mechanism of dopamine clearance vary amongst brain areas. Inhibition of norepinephrine transporters and MAO in prefrontal cortex prolongs extracellular dopamine levels two- to four fold. In mice lacking the COMT mechanism, prolongation is doubled, whereas a lack of dopamine transporters did not influence prefrontal extracellular dopamine levels (Wayment, Schenk and Sorg, 2001; Käenmäki *et al.*, 2010). In contrast, dopamine transporters are responsible for 95% of dopamine uptake in the striatum and play a crucial role in the maintenance of presynaptic dopamine storage, whereas in the hippocampus the norepinephrine transporter is the primary route of dopamine uptake (Cass *et al.*, 1993; Gainetdinov *et al.*, 1998; Borgkvist *et al.*, 2011).

Reuptake differentiates catecholamines from neurotransmitters such as acetylcholine and makes the neurotransmitter system sensitive to prolongation of synapse action. To gain further understanding of the specificity of dopamine innervations and the effects on cognitive and behavioural function, these mechanisms are useful targets of specific dopaminergic modulation. For example, substances acting on transporters can influence brain function and offers therapeutic opportunities.

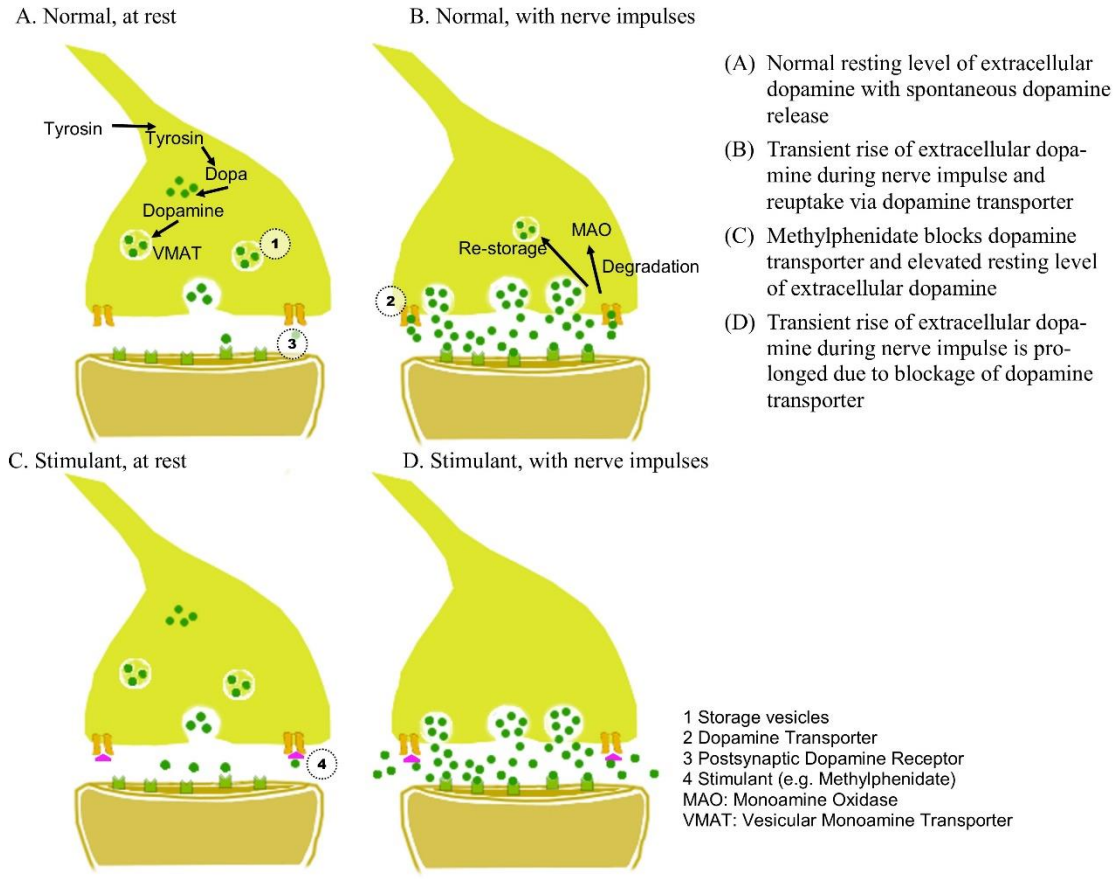


Figure 2. Dopamine Synthesis and Synaptic Transmission

4.2 Dopamine Transporter

The time course of dopamine transmission is tightly regulated by termination mechanisms. By challenging reuptake or degradation processes with a range of pharmacological tools it is possible to stimulate dopaminergic neurons (Wayment, Schenk and Sorg, 2001; Cragg and Rice, 2004; Käenmäki *et al.*, 2010). Majorly, in striatal

regions the dopamine transporter regulates transmission by recycling extracellular dopamine back into the pre-synapse. Therefore, this structure offers an opportunity to specifically target striatal dopamine effects and allows to further examine the reciprocal projections from striatum to the prefrontal cortex during cognition.

The following paragraphs only briefly describe dopamine transporter structure and function, a more detailed description would be beyond the scope of the current work (for detailed information see: Chen & Reith, 2000; Gowrishankar, Hahn, & Blakely, 2014).

4.2.1 Structure and Localization

The dopamine transporter is expressed exclusively in dopaminergic neurons within the central nervous system. Peripherally, the protein is found in stomach, pancreas and kidney. The highest expression is found in midbrain neurons originating in the substantia nigra and ventral tegmental area. Within the midbrain the expression is maximal at caudal, ventral and lateral groups of dopamine neurons and decreases medially in the ventral tegmental areas (González-Hernández *et al.*, 2004). Lower dopamine transporter amounts are found in cortex, amygdala and hypothalamus.

From a developmental perspective dopamine transporters appear at later stages, after embryonic midbrain neurons express tyrosine hydroxylase and synthesize dopamine. At this stage dopamine release is already established (Gainetdinov *et al.*, 1998).

At the cellular level the dopamine transporter is localized in the plasma membrane of neuronal perikary, dendrites, axons, synaptic terminals, and tubulovesicular intracellular structures (Nirenberg *et al.*, 1996, 1997; Ciliax *et al.*, 1999). The dopamine transporter belongs to the family of SLC6A Na+/Cl—dependent transporters which also encompass the serotonin and norepinephrine transporters (Giros *et al.*, 1992; Chen, Reith and Quick, 2004). In the midbrain it is the main regulator of dopamine signal termination (Gainetdinov *et al.*, 1998). The uptake of extraneuronal dopamine terminates dopamine action at pre- and post-synaptic sites, followed by re-entering of dopamine into synaptic vesicles through vesicular monoamine transporters (VMAT) and storage until its next release. Reuptake mechanisms are very effective and characteristic for the regulation of dopaminergic signalling and homeostasis (Chen and Reith, 2000; Cheng and Bahar, 2015).

As described above, the density of dopamine transporters varies among different dopamine cell groups which suggest that differential amount of dopamine transporters

indicates differences in dopamine signalling in given anatomical regions, e.g. classical synaptic signalling or more volume transmission type signalling (Gainetdinov *et al.*, 1998). Further, due to their high binding potential with diverse pharmacological agents, dopamine transporters are commonly used as specific markers for dopaminergic neurons (Gainetdinov *et al.*, 1998; Uhl, 2003). Thus, dopamine transporter availability or genetic markers of the dopamine transporter offer an opportunity to index dopamine neurons and dopamine activity (Costa *et al.*, 2011; Volkow *et al.*, 2015) which has resulted in considerable research interest in this transporter and its influence on cognition and behaviour.

4.2.2 Synaptic Adaption and Dopamine Transmission

Considerable evidence on the crucial role of the transporter in dopamine transmission and its molecular impact comes from studies with mice lacking dopamine transporters (Giros *et al.*, 1996). Giros et al (1996) developed a strain of mice without the dopamine transporter gene (DAT KO mice). Behavioural consequences include abnormal dietary habits (slow weight gain), high locomotor activity, difficulty in adapting to novel stimuli accompanied with inflexible behaviour and a tendency to react more aggressive in stressful situations (Gainetdinov, 1999; Spielewoy *et al.*, 2000; Sora *et al.*, 2001).
Further, the deletion of the dopamine transporter gene results in cellular adaptation to a hyperdopaminergic state, namely increased extracellular dopamine concentration, decreased neuronal dopamine receptors and decreased tyrosine hydroxylase phosphorylation (Giros *et al.*, 1996; Jaber *et al.*, 1996, 1997; Salvatore, Calipari and Jones, 2016). These alterations of dopaminergic pathways are already apparent in dopamine transporter deficient mice with 50% reduced dopamine transporter density.
Amplitude of phasic dopamine release reaches a mere 6.8% in DAT KO mice compared to normal animals and the enzyme tyrosine hydroxylase is decreased by 74-90% in terminal fields of striatum and nucleus accumbens. Intracellular dopamine levels are reduced by 95% despite an increase of dopamine synthesis. Specifically in dorsal striatum compared to mesolimbic areas, dopamine release and tissue content of dopamine in DAT KO mice is strongly dependent on dopamine synthesis, indicating the importance of dopamine transporter to replenish intracellular stores of dopamine and to sustain dopamine release (Giros *et al.*, 1996; Gainetdinov *et al.*, 1998; Jones *et al.*, 1998; Salvatore, Calipari and Jones, 2016). Furthermore, the clearance of extracellular

dopamine is prolonged by the factor 100 compared to wild type mice (Gainetdinov *et al.*, 1998). This hyperdopaminergic state during tonic signalling which is 5-times higher than in wild-type mice (Jones *et al.*, 1998), has been linked to the hyperactive symptoms in DAT KO mice and gave rise to the animal model for ADHD (Gainetdinov and Caron, 2001). Indeed, reduced striatal binding for a specific dopamine transporter radio tracer [^{123}I]FP-CIT was observed in patients with ADHD which strengthened the link between a hyperdopaminergic state with hyperactivity symptoms (Hesse *et al.*, 2009).

An artificial augmentation of dopamine transporters in another strain of mutant mice leads to a hypodopaminergic state, namely 40% reduction in the concentration of extracellular dopamine and cellular adaptation including a 50% increase of dopamine transporter activity and upregulation of postsynaptic dopamine receptors (Salahpour *et al.*, 2008; Ghisi *et al.*, 2009; Calipari and Jones, 2014). Behaviourally, these mutant animals display higher sensitivity to drug-induced reward and psychomotor properties to amphetamine, but no effects on basal locomotor properties, even after blockage of dopamine transporter with, e.g. methylphenidate (Salahpour *et al.*, 2008).

In normal animals, dopamine transporter activity indirectly modulates phasic signalling which is triggered by reward and sensory signals and plays a crucial role in learning mechanisms (Schultz, 2007). Dopamine release in DAT KO mice is not sufficient to evoke phasic extracellular increase over the basal dopamine level sustained by the altered tonic activity which offers an explanation for observed spatial cognitive deficits and difficulties in suppressing inappropriate responses and selection of salient stimuli (Benoit-Marand, Jaber and Gonon, 2000). Interestingly, a summary of study results on extracellular dopamine in gene-modified mice, shows that both reduced and increased expression of dopamine transporters lower the peak concentration of extracellular dopamine in response to pulse stimulation compared to wild-type controls (Figure 7A, Best, Nijhout, & Reed, 2009). This indicates that dopamine release is not strictly proportional to dopamine transporter density and further reveals regulatory mechanisms for transient dopamine release after consecutive bursts. Furthermore, Cragg and Rice (2004) argue that dopamine clearance, specifically during burst firing, depends more on diffusion rather than rapid uptake and the influence of dopamine transporter is seen in the extended lifetime and augmented net concentration of extrasynaptic dopamine. Nonetheless, there is converging evidence that the rate of dopamine uptake influences intracellular dopamine quantity available for stimulated release, thus the dopamine transporter is an important factor modulating dopaminergic tone (Ferris *et al.*, 2014).

Taken together, molecular differences in the expression of the dopamine transporter impact dopamine release and therefore dopaminergic transmission. Deficiency or the absence of the dopamine transporter translates to impaired selection of salient stimuli and impeded control over inappropriate responses (Benoit-Marand, Jaber and Gonon, 2000). This suggests dopamine transporter characteristics can be predictive of behavioural control (Meiergerd, Patterson and Schenk, 1993; Parsons, Schad and Justice, 1993; Cass and Gerhardt, 1994).

4.2.3 Genetics

The dopamine transporter gene exhibits a remarkable level of cellular specificity with the most robust expression in midbrain dopamine neurons (Bannon *et al.*, 2001). The gene in humans encoding the dopamine transporter is the *SLC6A3* gene located at chromosome 5p15.3 (Giros *et al.*, 1992; Vandenbergh *et al.*, 1992). Within the 3' untranslated (UTR) region of the dopamine transporter gene lies a variable number of tandem repeat (VNTR) of a forty base pair (bp) sequence which is one of the most studied genetic variants of the dopamine transporter and will be the focus of this section (Vandenbergh *et al.*, 1992; Swanson *et al.*, 2000; VanNess, Owens and Kilts, 2005; Volkow, Wang, Newcorn, *et al.*, 2007; Kieling *et al.*, 2010). The VNTR sequence ranges from three to 13 (Vandenbergh *et al.*, 1992; Kang, Palmatier and Kidd, 1999), with the nine-repeat (9R or 440 bp) and the ten-repeat (10R or 480bp) alleles being the most common variants (Vandenbergh *et al.*, 1992; Bannon, 2005).

The functional effect has been investigated intensely yielding disparate findings. Some studies reported enhanced transcription of the reporter construct with nine-repeat sequence (Michelhaugh *et al.*, 2001), others reported this for the ten-repeat vector (Fuke *et al.*, 2001), whereas others found neither sequence affect the transcription rate (Greenwood and Kelsoe, 2003).

In vivo imaging has provided similar inconsistent results. Higher striatal dopamine transporter availability was observed for nine-repeat allele carriers (van Dyck *et al.*, 2005; van de Giessen *et al.*, 2009), but others found the opposite, namely reduced amount of dopamine transporters in nine-repeat carriers (Heinz *et al.*, 2000) compared with ten-repeat homozygotes and another group failed to detect any association between the VNTR and dopamine transporter density (Martinez *et al.*, 2001). Despite inconsistent findings, two independent meta-analyses concluded higher striatal dopamine transporter

availability in healthy human individuals for nine-repeat carriers with effect size of approximately g=.67 (Costa *et al.*, 2011; Faraone *et al.*, 2014).

Furthermore, the VNTR polymorphism has been linked to ADHD (Coghill and Banaschewski, 2009; Franke *et al.*, 2012). ADHD appears to have a strong heritable component (Gillis *et al.*, 1992) and therapeutic effects are achieved with dopamine transporter ligands (methylphenidate and amphetamine). Although it is difficult to establish a robust link due to experimentally confounding factors such as clinical heterogeneity, comorbidity, interfering symptoms, and long-term medication between genotype and neurotransmission in patient studies (Berto *et al.*, 2000; Koren, 2003), the ten-repeat allele has been coined a 'high-risk' allele for ADHD (Gizer, Ficks and Waldman, 2009). Further, there has been evidence that ten-repeat homozygous carriers show weaker treatment response (Winsberg and Comings, 1991; Kambeitz, Romanos and Ettinger, 2014) and impulsive behaviour in non-clinical samples (Mata *et al.*, 2012).

Meta-analyses have not confirmed a direct link between this polymorphism and behavioural measures of cognitive function in healthy subjects and patients with ADHD (Rommelse *et al.*, 2008; Ettinger, Merten and Kambeitz, 2016). On the other hand, neuroimaging studies support the influence of the VNTR and cognitive function, including working memory (Bertolino *et al.*, 2006; Caldú *et al.*, 2007; Stollstorff *et al.*, 2010; Brown *et al.*, 2011; Gordon *et al.*, 2012; Wittmann *et al.*, 2013), emotion processing (Taurisano *et al.*, 2013; Bergman *et al.*, 2014), reward sensitivity (Yacubian *et al.*, 2007; Dreher *et al.*, 2009; Franklin *et al.*, 2009; Hahn *et al.*, 2011) and inhibitory control, even in the absence of behavioural effects.

Despite disparate findings, there is valid evidence from animal, pharmacological and neuroimaging studies that indicate a functional role for the polymorphism in the regulation of the dopamine transporter (Rao, Sorkin and Zahniser, 2013; Rajala *et al.*, 2014) and the modulation of mental operations in various cognitive domains (Garcia-Garcia *et al.*, 2010; van Schouwenburg, Aarts and Cools, 2010; Cummins *et al.*, 2012; Sambataro *et al.*, 2015).

4.2.4 Ligands

Intense investigation of the dopamine transporter is due to the high potency for various pharmacological agents. The dopamine transporter is the target of drugs of abuse such as cocaine and many therapeutic agents used to treat depression and ADHD. The inhibition

of dopamine transporter correlates with drug reinforcement and suggests a role of the dopamine transporter in substance abuse and addiction (Ritz *et al.*, 1987). Ligands for the dopamine transporter include amphetamine and methamphetamine (substrates), and blockers like cocaine and methylphenidate (inhibitor). The continuous administration of substrates evokes a downregulation of transporter activity, followed by internalization of the transporter. For example amphetamine and related substrates increase extracellular dopamine by promoting reverse transport (Gainetdinov and Caron, 2003). In contrast, inhibitors, such as methylphenidate, indirectly impact the rate of dopamine release by blockage of dopamine transporters (Pucak and Grace, 1994; Leonard *et al.*, 2004) and hinder, therefore, the reuptake of extracellular dopamine, specifically during phasic transmission (Wall, Gu and Rudnick, 1995) (Figure 2C & D). One of the most common ligands is methylphenidate, a catecholamine transporter inhibitor that also blocks norepinephrine transporter (Hannestad *et al.*, 2010) and the first-choice treatment for ADHD with a large effect size (g=.8-1.0) (Banaschewski *et al.*, 2006; Faraone and Buitelaar, 2010).

The pharmacokinetics of methylphenidate are widely studied and resemble those of cocaine, amphetamine and methamphetamine (Kallman and Isaac, 1975; Ritz *et al.*, 1987; Patrick and Markowitz, 1997; Huss and Lehmkuhl, 2002).

Weight-adjust oral dosage of methylphenidate (0.3 to 0.6 mg/kg) is thought to block approximately 50% of dopamine transporters in healthy adults and therefore prolong stimulation of postsynaptic receptors due to increased intrasynaptical dopamine level (Volkow *et al.*, 1995, 2001; Volkow, Wang, *et al.*, 1998). A very common observation is a dosage-dependent effect on behaviour of dopaminergic agonists which also holds for methylphenidate. Low doses can reduce locomotor activity and distractibility, but at too high doses it causes an overwrought state of the central nervous system (Seeman and Madras, 2002).

Simulation of uptake inhibition in dopamine cell transmission shows that basal dopamine level increases linearly and additionally at a certain level of dopamine transporter blockage a decoupling of postsynaptic receptors from pauses of phasic firing patterns takes place, i.e. receptors become tonically active regardless of firing pattern (Dreyer and Hounsgaard, 2012). In other words, dopamine receptors are less sensitive to pauses in dopamine cell firing at a critical level of uptake inhibition. The differential consequences of this dose-dependent effect become clear in single cell-recordings of dopamine neurons in the ventral tegmental area which show opposing effects of dopamine transporter

blockage with methylphenidate on firing rates. Besides a dose-dependent linear increase of responsive neurons, results show that with lower dosage (0.6mg/kg) the majority of neurons decreased their firing rate, whereas at higher dosage (2.5 and 10.0mg/kg) mainly an increase of firing rate was observed (Jones and Dafny, 2015).

Thus, the qualitative effect of dopamine transporter inhibition depends strongly on the level of blockage and the basal dopamine activity (see 4.2.2). Volkow and colleagues (Volkow *et al.*, 2001) describe the relation between dopamine transporter blockage and dopamine release as follows: "for an equivalent level of dopamine transporter blockage, methylphenidate would be more potent in a subject whose baseline release of dopamine is high than in a subject whose baseline release is low" (p. 4). This suggests that methylphenidate is more effective in subjects with higher dopamine transporter density which can be explained by the generally higher dopamine release in these subjects and serves as an ideal compound to target specific dopaminergic function. This dovetails with current findings of the same research group which demonstrate a positive correlation of dopamine transporter density and dopamine release in a healthy control group (Volkow *et al.*, 2015).

A recent review of single dose studies in healthy adults underlines the importance of dosage and lists precognitive effects of methylphenidate for working memory, processing speed, verbal learning, memory, attention and inhibition (Linssen *et al.*, 2014; see 6.2.1).

4.3 Goal of Dissertation

The dopamine transporter modulates extracellular dopamine level and governs frequency and amplitude of firing patterns (Floresco *et al.*, 2003; Cagniard *et al.*, 2006). The current thesis employs knowledge from animal and pharmacological studies to gather information on the specificity of dopamine transporter effects on neural operations during cognitive function in healthy human subjects. In contrast to behavioural effects, neuroimaging data provide a more sensitive measure of genetic and pharmaceutical variation on cognition (Honey and Bullmore, 2004; Greene *et al.*, 2008). Thus, in a multimodal imaging approach, dopamine transporter specific effects on cognition were examined.

The experimental section consists of three empirical studies addressing the relationship of the dopamine transporter with cognition and brain function: (1) the association between

a dopamine transporter genotype and cognition, personality and brain function, (2) the role of the dopamine transporter genotype in predicting effects of the dopamine transporter-blocking compound methylphenidate, and (3) the effects of methylphenidate on brain function in comparison to another compound known to indirectly increase dopamine levels, viz. nicotine.

5. Methods

Neuroimaging methods allow the examination of neural activity as a function of different dopamine transporter markers in relation to cognition in healthy humans (Cropley *et al.*, 2006). The following section gives an overview of methods used in identifying genetic and molecular markers in the adjacent empirical work as well as detailed information on functional magnetic resonance imaging.

5.1 Functional Magnetic Resonance Imaging (fMRI)

5.1.1 Basic Physical Principles

Functional magnetic resonance imaging is a non-invasive method to measure brain activity. The signal represents the behaviour of hydrogen proton spin measured with magnetic resonance imaging (Logothetis *et al.*, 2001). The protons either align parallel or anti-parallel to an externally applied strong magnetic field B_0 (common field strength in human studies 1.5 to 3 Tesla). A majority of protons will align parallel, the lower energetic state. Although the surplus of parallel aligned protons is very small, this leads to a net magnetization oriented parallel to the magnetic field B_0 (net magnetization vector). This net magnetization vector is tipped out of its equilibrium position with a radio frequency pulse applied perpendicular to the B_0 and an amplitude B_1 matching the precession frequency of the protons. The precession frequency is given by Larmor-frequency (w), defined by the magnetic field strength B_0 and the gyromagnetic ratio (γ) which is a fixed parameter for each nucleus type:

$$w = B_0 * \gamma$$

The radio frequency pulse causes the protons to absorb energy and tilts the magnetization vector from the horizontal plane (dimension z) to the transversal plane (xy). Additionally, the precession of the spins are caused to rotate in phase. The frequency emitted by the transversely rotating magnetization vector can be measured with a receiver coil placed around the head. The transverse magnetization decays quickly, which is described as relaxation. The dipoles strive back to a lower energy state aligned with B_0 and release their energy (longitudinal relaxation or spin-lattice relaxation). This process is described

by a time-constant T_1 (time it takes for 63% recovery of magnetization along the z-axis). The time-constant T_2 describes the time it takes for 37% of the transversal magnetization (xy plane) to decay (spin-spin relaxation). The latter occurs, because protons influence each other and lose their in-phase rotation. Static field inhomogeneity leads to a faster transversal relaxation as predicted by T_2^*. In order to acquire images, this technique uses the relaxation processes, which are differentially fast depending on the tissue. Thus different tissues are visible as different contrast in images. For the spatial reconstruction field gradients are applied to B_0 which allows to specifically excite only small slice to tissue with a radio frequency pulse of a given frequency. The individual signals corresponding to the spatial positions along the axes, are then decoded using Fourier Transformation. The time between two radio frequency pulses is called repetition time (TR); the time between excitation and measurement is called echo time (TE). These parameters are chosen to determine the influence of the time-constants on the image contrast. All the presented studies used gradient-echo EPI sequences which are very fast and efficient in tracking hemodynamic response (Logothetis, 2008).

5.1.2 Haemodynamic Response in fMRI

In order to investigate cognitive processes and the influence of dopamine on brain function and cognition, a correlate of brain activity is necessary. Functional magnetic resonance imaging (fMRI) makes use of the blood-oxygen-level-dependent (BOLD) contrast. Oxygenated blood, oxyhaemoglobin (Hb), is diamagnetic and enhances the signal. In contrast deoxyhaemoglobin (dHB) is paramagnetic and produces field distortions with lower signal. Local increase in blood oxygenation is linked to neural activity and glucose metabolism. Vascular changes allow oxygen extraction from the blood and therefore an increase of regional blood flow, blood volume and blood velocity (for details see Ances et al., 2008). During neural activity more oxygen is need and extracted from the blood, this is accompanied by a local excess in blood oxygen and produces a better BOLD signal. This increased BOLD signal occurs with a latency of three to six seconds after the onset of neural activity, but varies depending on task and brain regions (for details see Heeger & Ress, 2002). FMRI excels due to its high spatial resolution, but has a rather poor temporal resolution compared to for example electroencephalography, due to the hemodynamic delay.

Characteristic for the BOLD signal in response to a stimulus is a specific temporal profile

which needs to be kept in mind during planning and analysing an fMRI study. The time lag between energy consumption and oxygen supply delays the actual BOLD response and is described as "initial dip". After four to six seconds the response reaches the peak and further 30 seconds are necessary for the signal to regain the baseline state. This is especially important to consider when timing experimental events and the repetition of events within one category of interest.

BOLD signal does not correlate perfectly with neurons' firing rate, but there seems to be a strong link with pre-synaptic activity and secondary with action potentials rather than output signals in a given brain region (Logothetis and Wandell, 2004; Logothetis, 2008). Though, it is important to note that the mechanisms are more complex and not only arise from increase in firing of task sensitive neurons, but also from an interplay between excitatory and inhibitory neuronal communication (Logothetis, 2008). Nevertheless, keeping in mind the natural restrictions, today BOLD fMRI is a powerful tool to bridge the gap between neuronal correlates and cognitive processes (for extensive reviews see: Cabeza & Nyberg, 2000; Niendam et al., 2012). This method allows the observation of differential activation and localization of cognition-relevant brain areas according to experimental, e.g. genetic or pharmaceutical, conditions.

5.1.3 Pharmacological fMRI

Pharmacological fMRI is defined as a measure of "the direct modulation of regional brain activity by drugs that act within the central nervous system (CNS) or the indirect modulation of regional brain activity through pharmacologically modified afferent input." (Wise and Tracey, 2006). This technique offers the opportunity to investigate drug action on brain systems, but also to develop measures of local drug effects (Stein, 2001). In the current work pharmacological fMRI is used as a neuroscientific tool to probe healthy brain function and to understand the contribution of neurotransmitter systems during cognition (Wise and Tracey, 2006). It is important to note that BOLD does not directly reflect molecular drug action, but given an appropriate design and experimental control, inferences can be drawn about substance effects on receptor systems and its behavioural correlates. The pharmacological modulation of task-induced BOLD is the approach most commonly used in human studies (Honey and Bullmore, 2004; Wise and Tracey, 2006). Substances can change task-induced activity either by changing neurovascular coupling or by modifying stimulus-induced neuronal activity without changes in neurovascular

coupling (Iannetti and Wise, 2007). Methylphenidate, for example, does not alter neural-hemodynamic coupling (Rao *et al.*, 2000; Mehta and Daly, 2011), therefore observed changes in brain activity or information processing are related to dopaminergic neuronal activity and not to changes in vasculature.

Another caveat is the interpretation of stimulant-induced BOLD increases or decreases. As for example, dopaminergic induced reduction of BOLD in anesthetized monkeys has been accompanied by increased energy metabolism, indicating that observed BOLD activation does not directly reflect neural response (Zaldivar *et al.*, 2014). Additionally direct injection of dopamine in visual cortex did not alter activation in this local area, but suggests that dopaminergic neuromodulation are effects demanding neuronal long-range interactions in dopaminergic circuits. Consequently, the site of action for dopaminergic compounds is not necessary the site of BOLD activation and modulation takes place through downstream receptor modulation.

5.1.4 Preprocessing and Analysis of fMRI Data

Detailed description of fMRI analysis can be found in several textbooks (Penny *et al.*, 2011; Poldrack, Mumford and Nichols, 2011; Huettel, Song and McCarthy, 2014), here the classical processing steps for acquired images are only explained in brief.

Imaging data is preprocessed before statistical analyses are applied with the main goal to reduce unsystematic noise components. Traditionally a series of *t* images is recorded with each image consisting of *v* voxels (cuboid pixel). The first step in data pre-processing is the *realignment* of images of the series to one reference image (first or mean image). With rigid body transformation and the six motion directions (translation and rotation movement in three spatial dimensions) the motion parameters are calculated (dimensions: x, y, z in mm; rotation: pitch, roll, and yaw in degrees). Obtained parameters describe small movements and can be used in a later step to reduce motion related noise in the model (Brett, Johnsrude and Owen, 2002). To improve normalization to a standard template, it is recommended to *co-register* functional images to an anatomical, higher resolution image of the same scanning session. Depending on the sequence of slice acquisition and the design, it is necessary to perform a *slice-time correction* and compensate for sampling of slices at different time-points. The next step transforms individual brain images in a common space. During *spatial normalisation* individual brain structures are warped until they correspond to structures of a standard brain. The

classical template was provided by Talairach and Tournoux (Talairach and Tournoux, 1988), but more recent studies use a template created by the Montreal Neurological Institute (MNI). The final step to decrease measurement noise includes *spatial smoothing* with a Gaussian kernel. This allows reduction of sensitivity for false positive results (Aguirre, 2006).

In order to identify voxel's time-series in which the signal is significantly higher than the noise, a *General Linear Model* (GLM) is applied to the preprocessed images (K. J. Friston *et al.*, 1995; Karl J Friston *et al.*, 1995). For this experimental conditions are contrasted to a baseline condition. These experimental conditions can be blocked or occur as single events and subsequently serve as regressors in the model. For each voxel's time-series (univariate analysis) the parameter estimate (β-value) describes the fit to the model. In brief, this model is expressed as:

$$y(t) = \beta * x(t) + c + e(t)$$

The observed data corresponds to *y(t)*, the experimental matrix with a vector of ones and zeros (presenting absence or presence of experimental stimulation) is described by *x(t)*, *c* is a constant (e.g., baseline intensity) and *e(t)* represents the error. Additionally, the time-series is convolved with the *haemodynamic response function* (HRF: temporal profile of the BOLD response see 3.1.2) to improve the fit of the model. At group-level, parameter estimates from individual subject GLMs are fed into a second-level GLM. This results in statistical parametric maps (SPM), displaying the improbability of their estimation (t-values). From these second-level SPM one can identify voxels that are significantly activated during corresponding experimental condition. As last step, the multiple comparison problem deriving from the mass univariate approach has to be taken care of. This is done by adjusting the statistical thresholds as expressed by the p-value. In order to localize activated voxels within brain structures several anatomical atlases can be used (Brett, Johnsrude and Owen, 2002).

5.2 Single Photon Emission Computed Tomography (SPECT)

To investigate the role of dopamine transporter in human it is also possible to measure density via single photon emission tomography (SPECT). This technique combines nuclear medicine imaging technique and computer tomography. In contrast to fMRI, this is an invasive method and requires a chemical to enter the tissue and bind to the molecular

target. These ligands consist of either small molecules, peptides, proteins or antibodies and second of a label that can be identified by an imaging modality. For SPECT these ligands are called radiotracers or radiopharmaceuticals. Various pharmaceuticals are eligible as radiotracers for dopamine transporter. The most common radiopharmaceuticals are ^{123}I-FP-CIT and 99mcTC-TRODAT-1 (Park, 2012; Shen, Liao and Tseng, 2012). Radiation detectors receive emitted gamma photons from the distributed radio-active pharmaceuticals similar to conventional nuclear medicine. However in contrast to conventional nuclear medicine methods, image reconstruction methods can generate a cross section image of the distributed radiopharmaceutical and create a more detailed representation of tissue properties (ALehyani, 2009).

In the present work SPECT scans were obtained after injection of ^{123}I-FP-CIT (DaTSCAN; GE Healthcare, Amersham,UK) using a Prism 3000 triple-headed gamma camera (Philips, formerly by Picker, Cleveland, OH, USA) equipped with high-resolution fan beam collimators (see also Costa et al., 2013). Analysis was performed by Prof La Fougère. Briefly, images were reconstructed by filtered back-projection and corrected for attenuation (Chang, 1978). Using a modified version of the Brain Analysis Software (BRASS, version 3.5; Hermes Medical Solutions) and standardized 3-D volumes of interest (VOIs), data were semi-quantitatively evaluated. This includes a multistep registration of individual images to an ^{18}F-DMFP template for healthy controls (Mathias Schreckenberger, University of Mainz) and adjustment of VOIs by automatic registrations with six degrees of freedom. For each participant whole striatum, caudate and putamen were identified. An additional VOI was defined in the occipital cortex of the template image in order to calculate the specific binding with the following formula: (striatum-occipital cortex)/occipital cortex. Specific binding was therefore corrected for unspecific uptake in the occipital cortex.

5.3 Candidate Gene Approach

Human cognition and brain function is significantly heritable (Friedman *et al.*, 2008; Greene *et al.*, 2008; Frank and Fossella, 2011). Additionally, performance increase or decrease after administration of dopamine-releasing stimulant is baseline dependent (Mehta and Riedel, 2006) which suggests genetic predisposition in dopaminergic functioning that not only influences drug response, but is also evident in variability of

cognition and behaviour. To investigate genetic influence it is either possible to use candidate gene designs, or genome wide designs (Frank and Fossella, 2011; Montag and Reuter, 2014). While it is important to identify common genetic variants that underlie common psychiatric disorders with genome wide association studies (GWASs), it seems that reported associations are composed of small effects of many common variants (Purcell *et al.*, 2009). In contrast, the candidate gene approach aims to investigate the influence of a specific gene on specific cognitive processes, or the contribution of the genes biochemical functionality on human mental operation (Frank and Fossella, 2011). Preferably, the genetic variant is associated with biochemical functionality as for example gene expression or protein synthesis. Critically, the associations are informed by previous literature on pharmacological or animal models linking the genetic polymorphism to protein function, synaptic characteristics or other molecular mechanisms and cognitive processes. For example, genetic variation in D2 receptor affinity determines direction of response to D2 agonist stimulation and is also predictive of learning and performance (for details see review by Frank & Fossella, 2011).

The gene variants in the empirical studies of this thesis were determined in the laboratory of Prof Dan Rujescu at the University of Munich. DNA was extracted from 3ml saliva using QIAamp DNA Blood Midi Kit (Qiagen, Germany).

5.3.1 *SLC6A3* 3´- UTR VNTR

As mentioned in 4.2.3 a widely studied genetic variant of the dopamine transporter is the *SLC6A3* 3'-UTR VNTR polymorphism. The functional role of the VNTR has been investigated extensively in animal and human models and confirms an association between dopamine transporter availability and genetic variation (Costa *et al.*, 2011; Faraone *et al.*, 2014). Most common genetic variants are carriers with at least 9 repeat allele or two copies of the 10R allele. Subsequently, the genotype groups of 10 repeat homozygotes and 9 repeat heterozygotes became the primarily studied genetic variations. Less frequent variants such as the 9 repeat homozygotes are usually combined within the group of 9 repeat alleles or excluded (Ettinger, Merten and Kambeitz, 2016).

For the *SLC6A3* VNTR, the following primers were used: forward, 5´-TGT GGT GTA GGG AAC GGC CTG AG-3´, reverse: 5´-CTT CCT GGA GGT CAC GGC TCA AGG-3´ (Vandenbergh *et al.*, 1992). A PCR reaction containing 50ng DNA, 10pmol of each primer, 5U Taq polymerase (Fermentas, Vilnius, Lithuania), and 100mM dNTP Mix

(Fermentas) was carried out with buffer supplied by the manufacturer in a final volume of 20 ml. Amplification was carried out in a Thermocycler (Eppendorf, Hamburg, Germany) using the following conditions: initial denaturation at 95 1C for 5 min, 35 cycles of denaturation at 95 1C for 30 s, annealing at 61 1C for 30 s, and elongation at 72 1C for 90 sec following a final elongation at 72 1C for 3 min. PCR products were separated on 2% agarose gel by electrophoresis and visualized by ethidium bromide staining and UV fluorescence.

5.3.2 *COMT* val^{158}met

In prefrontal cortex dopamine transporter is scarce (Ciliax *et al.*, 1999), therefore other mechanisms influence dopaminergic signalling. A gene encoding the dopamine degrading enzyme catechol-*O*-methyltransferase (COMT) has been associated with prefrontal dopamine function (Winterer *et al.*, 2006). A single nucleotide polymorphism (SNP) in this gene (reference sequence identification code rs4680) results in a valine-to-methionine substitution at codon 158 (val^{158}met) of the membrane-bound isoform of the protein. This allelic variation (also known as the val^{158}met polymorphism) is functional, as the met^{158} allele has about one third to one fourth of the activity of the val^{158} allele, resulting in less efficient catecholamine catabolism. Less COMT activity (met allele) implies more dopamine in the synapse and therefore more action at postsynaptic receptors, whereas greater COMT activity (val allele) implies less intrasynaptic dopamine. (Lotta *et al.*, 1995; Lachman *et al.*, 1996; Weinshilboum, Otterness and Szumlanski, 1999). In the prefrontal cortex dopamine metabolism depends more readily on enzymatic degradation by COMT than on transport and reuptake by the dopamine transporter (Slifstein et al., 2008). In contrast, in striatum, COMT is scarce, and dopamine transporter predominantly terminate dopaminergic signalling (Gainetdinov & Caron, 2003; see also 4.1.3.2). Hence, using both, *SLC6A3* VNTR and *COMT* as genetic predictors of dopaminergic transmission, allows dissociation of striatal and prefrontal influence on cognitive processes.

COMT rs4680 was genotyped using the MassARRAY platform (Sequenom, San Diego, CA) according to manufacturer's protocol. Briefly, PCR (ACG TTG GAT GTT TTC CAG GTC TGA CAA CGG and ACG TTG GAT GAC CCA GCG GAT GGT GGA TTT) and extension primers (ATGCACACCTTGTCCTTCA) were designed using the Assay Designer 4.0. 12,5ng of genomic DNA were used for Multiplex PCR reactions

with a mastermix containing 500µM dNTPs (ABgene, Hamburg, Germany), 100nM PCR primers, 1,625mM MgCl2 and 0,5U HotStar Taq polymerase (Qiagen, Hilden, Germany). Following SAP (shrimp alkaline phosphatase) treatment the iPLEX reaction cocktail containing extension primers (7-14µM), 1x iPLEX termination mix and 1x iPLEX enzyme was added to the PCR-products. After desalting the extension products with SpectroCLEAN resin, samples were spotted on SpecroCHIPs GenII and analysed with the MassARRAY MALDI-TOF mass spectrometer. Allele specific extension products and resulting genotypes were identified by Typer 3.4.

6. Experimental Section

The following section presents an overview of three neuroimaging studies investigating the effects of dopamine on impulsivity, motor, and oculomotor control. The theoretical background of animal and patient literature has shown that dopaminergic activation is crucial in behavioural control (Cools, 2008). Failure in behavioural control leads to impulsive reactions mediated by impaired action restraint, action cancellation and failure of inhibitory processes (Bari and Robbins, 2013). The neural mechanisms of inhibitory control have been described in a number of previous functional neuroimaging studies (Aron, 2007; Simmonds, Pekar and Mostofsky, 2008; Bari and Robbins, 2013; Criaud and Boulinguez, 2013), making them ideally suited as well-characterised behavioural probes for the study of pharmacological and gene effects at the level of brain function. Therefore, the first two studies apply inhibitory and cognitive control paradigms, as wells as impulsivity measures in the investigation of genetic and molecular influence of the dopamine transporter on performance and neural activation. The third study operates on a pharmacological dissociation between dopamine transporter inhibitor and a cholinergic agonist, in an effort to disentangle dopamine transporter specific effects from another compound which excels dopaminergic enhancement second to stimulation of the cholinergic transmitter system.

6.1 Summary Publication I

Kasparbauer, A.-M., Merten, N., Aichert, D. S., Wöstmann, N., Meindl, T., Rujescu, D., & Ettinger, U. (2015). Association of *COMT* and *SLC6A3* polymorphisms with impulsivity, response inhibition and brain function. Cortex, 71, 219–231. http://doi.org/10.1016/j.cortex.2015.07.002 (see Appendix A).

Inhibitory control describes the ability to suppress inappropriate actions. Commonly used paradigms in research are response inhibition tasks in which participants supress motor action in the presence of a stop stimuli (Aron, 2009; Bari and Robbins, 2013). Stop-signal, go/no-go, Stroop or anti-saccade tasks demand suppression of a habituated response and require to behave flexibly by updating or overwriting planned motor responses. Active inhibition of a response has been linked to the prefrontal cortex, particular the right

inferior frontal cortex (Aron, Robbins and Poldrack, 2014). Additionally, subcortical structures such as the putamen and caudate have been associated with inhibitory control mechanisms (Frank, Loughry and O'Reilly, 2001; Frank and O'Reilly, 2006; Cools, 2008; Aarts *et al.*, 2010; Zandbelt and Vink, 2010; Costa *et al.*, 2011; Costa, la Fougère, *et al.*, 2013). Furthermore, there is evidence from neuropharmacological and neuroimaging studies implicating dopaminergic fronto-striatal networks in prepotent response inhibition, particularly as measured by go/no-go, stop-signal and antisaccade tasks (Aron, Dowson, Sahakian, & Robbins, 2003; Criaud & Boulinguez, 2013; Hutton & Ettinger, 2006; Munoz & Everling, 2004; Nandam et al., 2011; Nandam, Hester, & Bellgrove, 2014; Simmonds, Pekar, & Mostofsky, 2008). Behavioural genetic studies (Anokhin, Heath, & Myers, 2004; Macare, Meindl, Nenadic, Rujescu, & Ettinger, 2014) as well as research on patients with ADHD, obsessive-compulsive disorder, drug addiction, schizophrenia and their unaffected relatives suggests that a genetic predisposition underlies deficits in response inhibition (Aron & Poldrack, 2005; Chamberlain et al., 2007; Ersche et al., 2012; Raemaekers, Ramsey, Vink, van den Heuvel, & Kahn, 2006). Particularly a subdivision of the striatum, the sensorimotor striatum an area essential to motor planning and activity (Lappin *et al.*, 2009), demonstrates a high heritability factor (Stokes *et al.*, 2013)

Consequently, genetic predisposition of frontal and striatal dopamine flux are potential predictors of inhibitory control performance and can further understanding of mechanisms contributing to impaired inhibition in patient population.

6.1.1 *SLC6A3* 3'-UTR VNTR Polymorphism Cognition and Brain Function

A genetic polymorphism of the dopamine transporter is a VNTR of the *SLC6A3* gene located in the 3' -UTR of the gene (4.2.3). The polymorphism has been scrutinized as potential predictor for attention, working memory, executive functions and long-term memory (Ettinger, Merten and Kambeitz, 2016).

There is evidence of associations between the *SLC6A3* 3'-UTR VNTR polymorphism and hemodynamic response during various cognitive tasks in healthy humans. During working memory, carriers of two copies of the 10 repeat allele (10/10) show higher connectivity in the salience network and regions of the default mode network (Gordon *et al.*, 2012) which was associated with higher subjective ratings of impulsivity. During

episodic memory formation 10/10 carriers showed lower right midbrain activation accompanied with lower learning rates and blunted response to error signals in ventral striatum (Schott *et al.*, 2006). Further, regions with lower 10/10 BOLD activation included anterior cingulate, caudate, insula and cerebellum.

Blunted striatal activity in 10/10 carriers to reward stimuli has been also observed by two other independent studies (Yacubian *et al.*, 2007; Dreher *et al.*, 2009). Others (Hahn *et al.*, 2011) have found a positive correlation between reward sensitivity and reward-related activity in 10/10 carriers but not in 9R carriers. Franklin et al. (Franklin *et al.*, 2009) found a positive correlation between ventral striatal activity and craving of smoking in 10/10 smokers, but not in 9R smokers. In a different study, 10/10 carriers showed increased striatal activations for motivation compared to neutral cues, this was also observed during reward-predicting items (Wittmann *et al.*, 2013). Genotype effects were also observed during verbal fluency which were expressed in increased activation for 10/10 carriers in left anterior insula and right caudate nucleus (Prata *et al.*, 2009; Pauli *et al.*, 2013).

Despite overwhelming evidence of impaired inhibitory control, specifically response inhibition in patients with ADHD (Aron and Poldrack, 2005) and the improvement of symptoms after administration of a dopamine transporter inhibitor (Pasini *et al.*, 2013), there is little investigation on the specificity of the dopamine transporter's functional role in healthy human subjects during inhibition.

Behavioural studies suggest homozygosity for the 10R allele to be linked to worse response inhibition (Cornish *et al.*, 2005) and increased impulsive behaviour (Gizer, Ficks and Waldman, 2009; Mata *et al.*, 2012). However, others found an opposing pattern with 9R homozygotes performing worse in a Stroop task compared to 10/10 and 9/10 carriers (Schneider *et al.*, 2014).

A meta-analysis searching for an association between the dopamine transporter genotype *SLC6A3* 3'-UTR VNTR and different cognitive functions in healthy samples has failed to find significant results (Ettinger, Merten and Kambeitz, 2016). In contrast, neuroimaging studies report significant effects on hemodynamic response in absence of performance effects (Bertolino *et al.*, 2009; Congdon *et al.*, 2009; Colzato *et al.*, 2010). Additionally, genetic imaging studies of adolescents during response inhibition revealed increased activation in frontal, medial and parietal regions in 10R carriers compared to non-10R carriers (Braet *et al.*, 2011); the opposite was observed in adult ADHD patients (Dresler *et al.*, 2010).

6.1.2 *COMT* val^{158}met Polymorphism and Cognition and Brain Function

The dopamine transporter is scarce in the cortex and therefore other mechanisms influence dopamine levels. For example COMT plays a particular role in dopamine flux in the prefrontal cortex and its mRNA expression is significantly higher in prefrontal structures compared to striatum (Matsumoto *et al.*, 2003; Chen *et al.*, 2004).

Several studies have reported a *COMT* val^{158}met (5.3.2) impact on executive function, working memory (Egan *et al.*, 2001; Bishop *et al.*, 2008) and attentional control (Blasi *et al.*, 2005; Winterer *et al.*, 2006). Generally, *COMT* impacts performance and processing of stable and flexible cognitive demands. Studies have revealed an advantage of the met allele across different tasks requiring both, maintenance and continuous updating of information, such as spatial working memory and cognitive control (Goldberg *et al.*, 2003; Diamond *et al.*, 2004; Tan *et al.*, 2007). For example in the Wisconsin Card Sorting Test, a task demanding intact prefrontal functioning, met allele carriers make fewer errors than val carriers (Egan *et al.*, 2001). While the difference in prefrontal activity between met and val carriers seems relatively robust, an overall effect of *COMT* polymorphism is not clear and effects strongly depend on particular task demands (Meyer-Lindenberg *et al.*, 2005; Tunbridge, Harrison and Weinberger, 2006; Barnett, Scoriels and Munafò, 2008; Dickinson and Elvevåg, 2009).

Evidence relating *COMT* to response inhibition and its neural correlates is inconsistent. Whilst there is evidence of the val allele being associated with better inhibition in the antisaccade task (Haraldsson *et al.*, 2010), the met allele has been associated with better performance in the Stroop task (Schneider *et al.*, 2014). Other studies have failed to observe significant associations with go/no-go and stop-signal task performance (Husain and Mehta, 2011; Stokes *et al.*, 2011; Plewnia *et al.*, 2013; Gurvich and Rossell, 2014).

With regard to brain function, val carriers showed reduced prefrontal hemodynamic response in the prefrontal cortex compared to non-val carriers during antisaccades in an fMRI study (Ettinger et al., 2008). Similarly, Congdon and colleagues (2009) observed reduced BOLD activation in the right inferior frontal cortex in carriers of the val allele during successful inhibition in the stop-signal task. The opposite pattern was observed in the posterior cingulate cortex during a go/no-go task (Stokes et al., 2011).

6.1.3 Rational of the Study

In brief, studies with negative findings at the level of inhibitory performance found associations between neural activation during inhibition and the *COMT* or *SLC6A3* polymorphisms (Ettinger *et al.*, 2008; Congdon *et al.*, 2009; Stokes *et al.*, 2011), suggesting that the investigation of brain function may be a more powerful method for the detection of gene effects than the study of behavioural measures alone (Meyer-Lindenberg and Weinberger, 2006; Greene *et al.*, 2008).

Neuroimaging studies combining the missense *COMT* val^{158}met and the *SLC6A3* 3'-UTR VNTR polymorphism have found cumulative and functionally distinct effects. For example Schott et al. (2006) found an impact of *COMT* in right prefrontal cortex and occipital regions but not in the midbrain during episodic memory formation (Schott *et al.*, 2006). Whereas during working memory and motivational tasks a gene-gene interaction becomes apparent. During working memory, a cumulative effect expressed by blunted response in 10/10 and met/met carriers in prefrontal cortex was observed by two independent research groups (Bertolino *et al.*, 2006; Caldú *et al.*, 2007). Similarly, during reward sensitivity, 10/10 and met/met carriers showed reduced responsiveness in caudate and ventral striatum as well as lateral prefrontal cortex compared to 9R and met/met carriers (Yacubian *et al.*, 2007; Dreher *et al.*, 2009).

Congdon and colleagues (Congdon *et al.*, 2009) were the first to examine the neurophysiological influence of *COMT* and *SLC6A3* 3'-UTR VNTR polymorphism during response inhibition. Their sample consisted of 43 healthy participants; however, investigation of gene-gene interaction was not possible. The results showed an influence of the *SLC6A3* 3'-UTR VNTR in subthalamic nuclei and supplementary motor cortex activation. This effect was mediated by a blunted response in 10/10 carriers during successful stop trials. Whereas an influence of *COMT* was found in right inferior frontal cortex with greater activation of groups with met alleles as compared to val/val carriers during successful go and successful stop trials. In contrast, Cummins and colleagues (Cummins *et al.*, 2012) did not find a modulation of brain activation with the dopamine transporter polymorphism during a similar stop-signal paradigm.

In sum, it seems that both the 10/10 and the val allele are genetic variants associated with lower neural response during response inhibition, strengthening the concept that reduced dopaminergic signalling during inhibitory processing may play a role in impaired response inhibition.

Previous genetic investigations on motor control are limited due to small sample sizes

(behavioural studies: N=130 to N=405; fMRI studies: N=36 to N=51) and their focus on a single motor inhibition task. Most studies selected only one response inhibition task, thereby failing to allow the assessment of the specificity of any observed associations within the domain of inhibitory function. Moreover, the only response inhibition studies combining the two polymorphisms (Congdon *et al.*, 2009; Colzato *et al.*, 2010; Stokes *et al.*, 2011; Gurvich and Rossell, 2014; Schneider *et al.*, 2014) did not investigate or report statistical interactions of the two polymorphisms with regards to inhibition performance, leaving open whether such gene-gene interaction effects may exist.

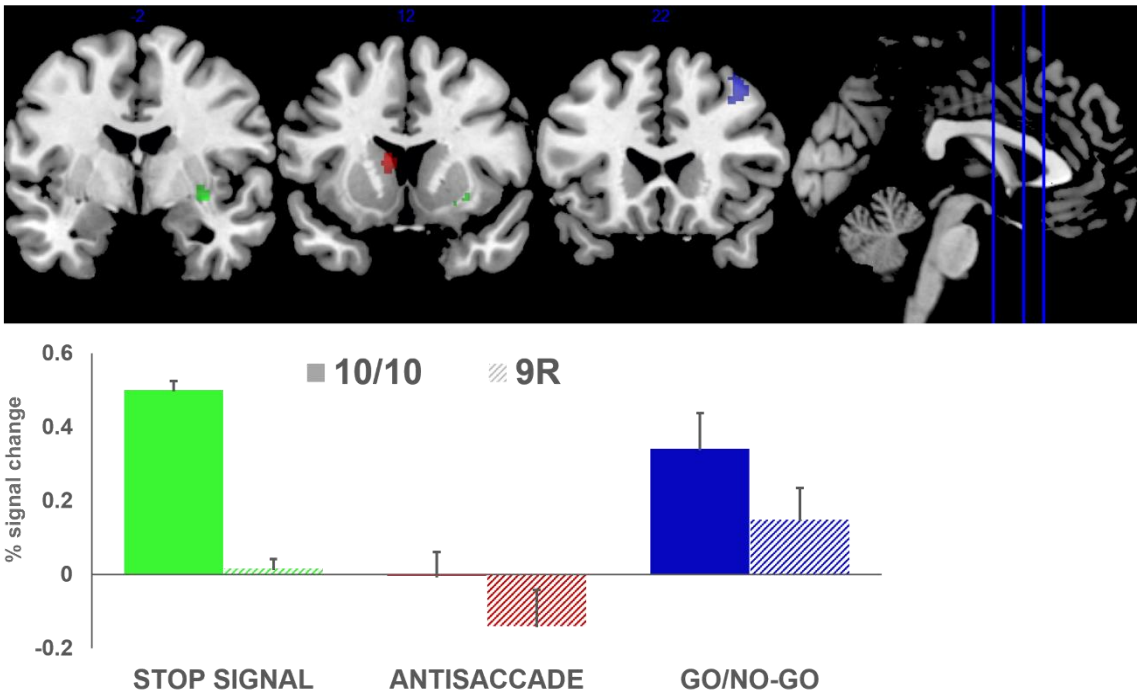
Therefore, the first study examines the influence of genetic markers of striatal and prefrontal dopamine turnover on a set of inhibitory and cognitive control tasks. In a large sample of 515 healthy adults performance measures of a response inhibition battery (see Appendix I Methods) was associated with genetic variations of *SLC6A3* 3'-UTR VNTR and *COMT* rs4680. Additionally, a well powered subsample (N=144) was studied while performing the go/no-go, stop-signal and antisaccade tasks in fMRI. Moreover, given the conceptual (Congdon, Lesch and Canli, 2008) and empirical (Aichert *et al.*, 2012) link between (poor) response inhibition and (high) impulsivity, a psychometric measure of impulsivity, the Barratt Impulsiveness Scale was included in the analysis (BIS; Patton, Stanford, & Barratt, 1995). Data were examined for main effects of *SLC6A3* and *COMT* polymorphism as well as their interactions in order to provide a thorough assessment of the role of these dopamine genes in fronto-striatal inhibitory control mechanisms.

6.1.4 Summary of Key Findings

There were no significant associations between *COMT* or *SLC6A3* genotype and inhibitory performance or impulsivity. These negative findings are in agreement with other studies that failed to identify a significant influence of the polymorphisms on inhibitory control performance (Krämer *et al.*, 2007; Barnett, Scoriels and Munafò, 2008; Congdon *et al.*, 2009; Haraldsson *et al.*, 2009; Stokes *et al.*, 2011; Gurvich and Rossell, 2014). The three tasks share the recruitment of superior, middle and inferior frontal as well as striatal areas (Bari and Robbins, 2013; Criaud and Boulinguez, 2013; Jamadar, Fielding and Egan, 2013). Therefore, and given that the primary sites of expression of *COMT* and the *SLC6A3* 3'-UTR VNTR polymorphism are in the prefrontal cortex and striatum, respectively (Ciliax *et al.*, 1999; Matsumoto *et al.*, 2003), both whole-brain BOLD analyses and anatomically focussed analyses of superior, inferior and middle

frontal gyrus, and caudate and putamen was performed.

No association of *COMT* with BOLD was found. However, there were consistent main effects of *SLC6A3* genotype in all inhibitory contrasts: Homozygosity of the 10R allele was associated with greater fronto-striatal BOLD response than genotypes with at least one 9R allele (Figure 3). Previous evidence from meta-analyses implies lower striatal dopamine transporter expression in 10R homozygotes (Costa et al., 2011; Faraone et al., 2014). Section 4.2.2 describes a heightened and prolonged extracellular dopamine level in animals without or reduced dopamine transporter as well as decreased dopamine release. Taken this together, the effects of *SLC6A3* on BOLD can be explained by heightened and prolonged synaptic dopamine levels in 10/10 carriers, since extracellular dopamine level correlates positively with BOLD signal (Knutson and Gibbs, 2007; Schott *et al.*, 2008; Fazio *et al.*, 2011; see 7.2).



Legend. Main effect of *SLC6A3* VNTR polymorphism for stop-signal in right putamen (x = -2), antisaccade in left caudate (x = 12) and go/no-go task in right middle frontal gyrus (x = 22). MNI Coordinates. Left is left. Error bars depict standard error of mean.

Figure 3. Key findings Study 1

6.1.5 Summary Publication II

Kasparbauer, A.-M., Rujescu, D., Riedel, M., Pogarell, O., Costa, A., Meindl, T., la Fougère, C., Ettinger, U. (2015). Methylphenidate Effects on Brain Activity as a Function of *SLC6A3* Genotype and Striatal Dopamine Transporter Availability. *Neuropsychopharmacology*, *40*(3), 736–745. http://doi.org/10.1038/npp.2014.240 (see Appendix B)

A common observation within pharmacological research is the inter-individual difference in drug effect and outcome (Shastry, 2006), which also holds for dopaminergic compounds like methylphenidate. Therefore, the following publication investigated individual differences in response to methylphenidate.

6.1.6 Methylphenidate and Cognition and Brain Function

Methylphenidate offers the opportunity to challenge specifically the striatal dopamine system due to its binding preferences for dopamine transporter (see 4.2.4). Resting-state neuroimaging studies in healthy subjects revealed reduced functional connectivity between nucleus accumbens and basal ganglia and medial prefrontal cortex, as well as temporal cortex after a single dose of methylphenidate (Ramaekers *et al.*, 2013). Sripada and colleagues (2013) found decreased coupling between visual and somatomotor networks (Sripada *et al.*, 2013). Additionally, Farr et al. (2014) has described reductions in connectivity to the prefrontal cortex and suggest alterations of connectivity caused by methylphenidate driving catecholaminergic signalling beyond the normally balanced level of functioning and dampening prefrontal activity (Farr, Zhang, *et al.*, 2014). The same study has also reported enhanced connectivity to motor cortex and memory circuits. Similarly, Mueller and colleagues (2014) have found increased methylphenidate-induced connectivity in fronto-parietal networks with sensory-motor and visual cortex, but decreased connectivity in cortico-striato-thalamo-cortical structures (Mueller *et al.*, 2014). Taken together, these findings indicate that the impact of methylphenidate is beyond its molecular action site and provides evidence of intrinsic connectivity changes to structures important for cognitive functioning.

One of the earliest studies investigating single dose effects of methylphenidate and executive function has found increased attentional recruitment with methylphenidate only

under challenging task demands as measured with electroencephalography (Coons *et al.*, 1981). In another study, using a four-choice reaction time task, single dose of methylphenidate increased lateral premotor and medial posterior cortical activation measured with fMRI independent of task difficulty (Müller *et al.*, 2005). However plasma-concentration was positively correlated with strength of activation in motor and premotor cortex, temporoparietal cortex and caudate in the difficult version of the task. Similarly, increased recruitment of premotor, cingulate and parietal regions has been observed in an object-learning task with increased cognitive load (Bullmore *et al.*, 2003). In another learning paradigm methylphenidate reduced hemodynamic response in ventral striatum (Dodds *et al.*, 2008). Linssen et al. (2013) has found speeded response times and improved delayed memory consolidation, but no impact on neurophysiological markers of mental processing (Linssen *et al.*, 2012, 2013). Others showed an enhancement of attentional networks during learning and working memory (Anderer *et al.*, 2002; Tomasi *et al.*, 2011).

Marquand and colleagues (2011) have described the effects of methylphenidate during working memory as simulating reward during the encoding process (Marquand *et al.*, 2011). An indication for the selectivity of methylphenidate for task-relevant stimuli. During the 2-back (respond to the stimuli that was seen two trials prior) condition of the n-back working memory task methylphenidate improved error rate, which was accompanied by a reduction in lateral prefrontal activation. In contrast, in boys with ADHD methylphenidate upregulated inferior frontal cortex and normalized behavioural performance during the 2-back condition (Cubillo *et al.*, 2012). Improved accuracy in a conflict-monitoring task was observed by Ivanov and colleagues with methylphenidate (2014). Additionally, under the influence of the compound subjects exhibited lower task-related activity, specifically in reward-related structures irrespective of task difficulty (Ivanov *et al.*, 2014). The authors interpreted reduced activation and performance improvement in terms of enhanced efficiency of information processing in both reward and attentional systems. Similarly, during decision-making methylphenidate dampened activation in parietal association cortex and posterior cingulate cortex in comparison to placebo. Increased hemodynamic response was observed in bilateral parahippocampal and cerebellar activity (Schlösser *et al.*, 2009).

Several studies investigated methylphenidate-induced changes during inhibitory control paradigms. Studies using electroencephalography (EEG) did not find any performance effects in a go/no-go paradigm, but an increase of an early event related potential

associated with stimuli evaluation during go but not no-go trials (Anderer *et al.*, 2002; Hoegl *et al.*, 2011). Hester and colleagues (2012) have found improved capability to consciously detect performance errors after methylphenidate administration which was linked to reinforced activation difference in dorsal anterior cingulate cortex and inferior parietal lobe (Hester *et al.*, 2012). Pauls et al (2012) used a stop-signal paradigm and found reduced activation in right inferior frontal gyrus and insula during stop-trials (irrespective of motor inhibition) and continuous trials (infrequent go-signals) (Pauls *et al.*, 2012). Another study compared methylphenidate-induced changes to brain activity in a stop-signal task, but has found only increased putamen activation during failed inhibition trials in the go/no-go task (Costa, Riedel, *et al.*, 2013). In contrast, another research group revealed increased caudate, motor and inferior parietal cortex activation during successful stop trials (Farr, Hu, *et al.*, 2014). Further, Nandam and colleagues (Nandam, Hester and Bellgrove, 2014) showed a reduction of caudate activation under methylphenidate and increased activation in cingulate cortex. On another cognitive control task, the Stroop task, methylphenidate improved error rates and post-error slowing and reduced dorsal anterior cingulate activation during errors and increased activation in prefrontal cortex (Moeller *et al.*, 2012). A recent meta-analysis confirmed a positive effect of methylphenidate on response inhibition and response time variability in young ADHD patients (Coghill *et al.*, 2014).

In sum, administration of methylphenidate demonstrates positive effect on several domains of cognition and behavioural control specifically for ADHD patients (Coghill *et al.*, 2014). In contrast, in healthy subjects there is mixed evidence in regards to methylphenidate-induced enhancement of inhibitory control performance (Turner *et al.*, 2003; Nandam *et al.*, 2011; Allman *et al.*, 2012; Pauls *et al.*, 2012; Farr, Hu, *et al.*, 2014; Manza *et al.*, 2016). A possible predictor for the efficacy of methylphenidate comprises dopamine transporter disposition.

6.1.7 Dopamine Transporter Density

In addition to genetic predictors, dopamine transporter availability may provide another potential baseline predictor of methylphenidate response. Using positron emission tomography (PET), Tomasi and colleagues (2009) found a negative correlation between striatal dopamine transporter density and deactivation in precuneus and a positive correlation with deactivation in the ventral anterior cingulate (BA 24/32) during visual

attention paradigm (Tomasi *et al.*, 2009). Additionally, SPECT-quantified striatal dopamine transporter availability has previously been associated with treatment outcome in ADHD (la Fougère *et al.*, 2006). In healthy, increased striatal binding of a dopamine transporter radiotracer was associated with decreased BOLD activation in the supplementary motor area during performance of a motor task (Fazio *et al.*, 2011). However, no studies investigated dopamine transporter availability as predictor of methylphenidate effects on neural or cognitive measures. Recent meta-analyses attribute higher striatal dopamine transporter availability to *SLC6A3* 3'-UTR VNTR 9R carriers (Costa *et al.*, 2011; Faraone *et al.*, 2014), calling for a combination of these two potential predictors.

6.1.8 Rational of the Study

Summing up, the effects of methylphenidate on cognition are mixed and even within the same cognitive domain inconsistent. The second publication, examines potential molecular and genetic predictors of the dopamine transporter that could explain inter-individual variability of methylphenidate-induced changes. Thus, *SLC6A3* 3'-UTR VNTR (see 4.2.3) and dopamine transporter density in striatal structures serve as potential predictors of hemodynamic response and performance in an inhibitory control task. Only few pharmacogenetic studies are available on the *SLC6A3* genotype-dependent cognitive or neural response to methylphenidate. Loo and colleagues (Loo et al, 2003) found the VNTR to predict methylphenidate effects on behavioural performance and the electroencephalographic response in children with ADHD. Further evidence of the influence of the VNTR on methylphenidate effects comes from a transcranial magnetic stimulation study of cortical inhibitory activity in ADHD (Gilbert et al, 2006). However, so far there are no investigations of *SLC6A3* and methylphenidate-induced changes in BOLD in healthy subjects.

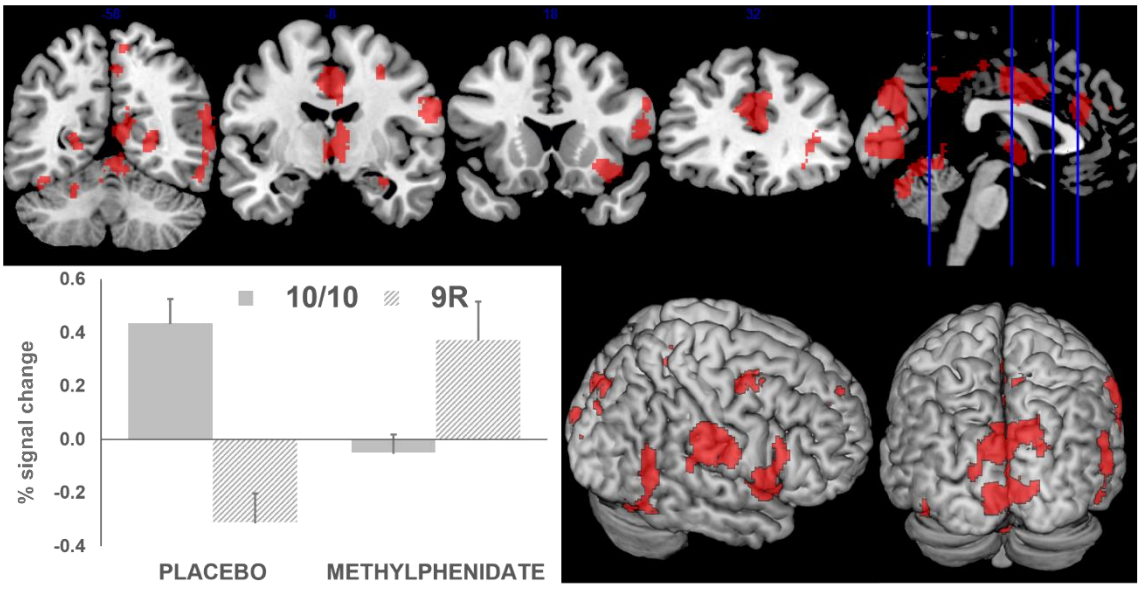
To identify genetic and molecular predictors of methylphenidate-induced changes in brain activity during response inhibition and pharmacologically, healthy male participants were challenged with a single dose methylphenidate during a response inhibition task. Briefly, BOLD response of fifty healthy males during a go/no-go task under the influence of 40mg methylphenidate and placebo was reassessed with genotype group as between subject factor. Additionally in a subset of thirty-five participants, baseline striatal dopamine transporter availability was ascertained with ^{123}I-FP-CIT SPECT and

correlated with amount of methylphenidate-induced change in hemodynamic response and behaviour.

6.1.9 Summary of Key Findings

No associations in behavioural task performance between genotype groups or striatal binding was detected. However, an interaction between the genetic variants of the *SLC6A3* 3'-UTR VNTR polymorphism and drug condition was found. During successful inhibition of a motor response, methylphenidate induced an increase of BOLD signal for carriers of 9R-allele and a decrease in 10/10 homozygotes in brain areas associated with motor inhibition (Figure 4). Interaction clusters fall within the typical task network (Criaud and Boulinguez, 2013) and areas modulated by methylphenidate during inhibition (Pauls *et al.*, 2012; Nandam, Hester and Bellgrove, 2014), including anterior cingulate and right lateralized prefronto-parieto-temporal structures.

Furthermore, striatal dopamine transporter availability was nominally greater in 9R carriers compared to 10/10 homozygotes (d=.40), in line with meta-analyses (Costa *et al.*, 2011; Faraone *et al.*, 2014), but did not predict BOLD or behavioural changes following



Legend. Interaction between drug and *SLC6A3* VNTR polymorphism during successful inhibition in no-go trials compared to successful oddball trials (infrequent go trials). Bar chart depicts mean signal change across all interaction clusters. Left is left. Error bars depict standard error of mean.

Figure 4. Key findings Study 2

methylphenidate administration.

These results show the effect of acute methylphenidate administration on brain activation is dependent on dopamine transporter genotype. During successful inhibition 9R carriers responded with an increase of brain activation whereas a reduction was observed in 10/10 carriers. The pattern in the placebo condition is qualitative similar to the previous study in which 10/10 carriers exert higher BOLD during inhibitory processes (see 7.2). SPECT data qualitatively confirms increased dopamine transporter density in 9R carriers, therefore an explanation for increased BOLD activity after the administration of a dopaminergic agonist might be increased dopamine release in this genotype group similar to a rewarding stimulation (Dreher *et al.*, 2009).

6.2 Summary Publication III

Kasparbauer, A.-M., Meyhöfer, I., Steffens, M., Weber, B., Aydin, M., Kumari, V., Hurlemann, R., Ettinger, U. (2016). Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. *NeuroImage, 141,* 52–59. http://doi.org/10.1016/j.neuroimage.2016.07.012 (see Appendix C)

6.2.1 Effects of Methylphenidate and Nicotine on Cognition

Although, there was no pro-cognitive effect of methylphenidate in study 2, there are several reports of improved cognitive performance during spatial working memory, sustained attention and in more complex tasks including planning and attentional-set shifting (Mehta and Riedel, 2006; Linssen *et al.*, 2014). Reports on methylphenidate-induced pro-cognitive effects on attention-based tasks (Bagot and Kaminer, 2014) has led to its popularity among students as cognitive enhancer (Outram, 2010). Although there may be ethical concerns surrounding the issue of cognitive enhancement (Hyman, 2011), it is of considerable scientific interest to further investigate the potential of biotechnological interventions to enhance human cognition. One of the aims of such investigations is to increase knowledge on the specific and shared neuronal underpinnings of enhancing compounds.

Similar to methylphenidate, nicotine is also known to have beneficial effects on attention and memory (Warburton, 1992). Previous literature confirms overlapping effects of these compounds on different attentional tasks in humans (Koelega, 1993), but also differential effects on attention measures in rodents (Bizarro *et al.*, 2004). So far, there has been no direct comparison of these two stimulating agents in healthy humans. Recent ethical debates on pharmaceutical cognitive enhancement in healthy (Fond *et al.*, 2015; Maier *et al.*, 2015; Whetstine, 2015; Marraccini *et al.*, 2016) and the high variability in treatment effectiveness of dopamine targeting compounds in patients (Kelton *et al.*, 2000; Cools, 2006; Kieling *et al.*, 2010; Martinez *et al.*, 2011; Jasinska *et al.*, 2014) demand a clearer picture of the stimulating effects of these two compounds on cognition and brain function.

6.2.2 Nicotine and Cognition and Brain Function

Nicotine is the pharmacological component to addictive tobacco smoking behaviour (Stolerman, Mirza and Shoaib, 1995; Di Chiara, 2000; Balfour, 2002a, 2002b; Mathieu-Kia *et al.*, 2002) and its psychopharmacological effects are diverse in healthy and patient population (Kelton *et al.*, 2000; De Biasi and Dani, 2011; Hahn, 2015). Nicotine binds to nicotinic acetylcholine receptors (nAChR) across the cortex and potentiates the cortical and subcortical release of acetylcholine, dopamine, noradrenaline and other transmitter types (Role and Berg, 1996; MacDermott, Role and Siegelbaum, 1999; López *et al.*, 2001; Wonnacott *et al.*, 2006; Wallace and Porter, 2011). Nicotine modulates dopaminergic neurotransmission by enhancing dopamine release in the mesocorticolimbic and nigrostriatal systems (Clarke and Pert, 1985; Changeux *et al.*, 1998; Laviolette and van der Kooy, 2004). The compound is subject to intensive research not only due to its addictive potential, but also because of its pro-cognitive effects. A plethora of studies exists, which investigate enhancement effects of nicotine on motor control, sensory processing, alertness, attention and memory (Heishma, Taylor and Henningfield, 1994; Heishman, Kleykamp and Singleton, 2010).

There is consistent evidence of nicotinic enhancement of attention in human literature (Stolerman, Mirza and Shoaib, 1995; Newhouse, Potter and Singh, 2004; Heishman, Kleykamp and Singleton, 2010), which is thought to enable performance improvement in higher cognitive operations. Attentional enhancement of nicotine is mediated by two mechanisms: the stimulation of α4β2* nicotinic acetylcholine receptors on glutamatergic neurons and the increase in tonic levels of acetylcholine (Demeter and Sarter, 2013). This linkage is strongly supported by the observed attentional impairments in clinical population with nAChR hypofunction (Nordberg *et al.*, 1995; Stolerman, Mirza and Shoaib, 1995; Perry *et al.*, 2000; Singh, Potter and Newhouse, 2004; Adams and Stevens, 2007; Petrovsky *et al.*, 2010; Kendziorra *et al.*, 2011).

Moreover, via nAChR subtypes (Wonnacott *et al.*, 2006), nicotine induces dopamine release in the nucleus accumbens (Pontieri *et al.*, 1996; Di Chiara *et al.*, 2004), a structure enriched with dopamine transporter (Ciliax *et al.*, 1999). At neurophysiological level, acute nicotine demonstrates higher potency for mesolimbic dopamine neurons and effects are more observable in dopamine neurons in the ventral tegmental area rather than substantia nigra (Kalivas, 1993).

Nonetheless, nicotinic receptors are also located on nigrostriatal pathway (Clarke and Pert, 1985) and an increase in ventral striatal dopamine level after acute administration

was found with PET (Brody *et al.*, 2004); others have found no association of nicotine with overall striatal dopamine availability (Montgomery *et al.*, 2007). Few studies propose that nicotine induces increased dopamine transporter function (Hart and Ksir, 1996).

At cognitive level, acutely administered nicotine reduces attentional dysfunction in patients with neurodegenerative diseases (Levin and Rezvani, 2002; Singh, Potter and Newhouse, 2004), schizophrenia (Petrovsky *et al.*, 2010) and ADHD (Levin *et al.*, 1996); in healthy individuals the enhancing effects on cognitive performance are less pronounced, but confirm positive effects on alertness, attention motor control and memory observed (Sacco, Bannon and George, 2004; Heishman, Kleykamp and Singleton, 2010).

Effects of nicotine on BOLD response are heterogeneous. Whilst some studies report increased activation in task-relevant networks along with attentional enhancement (Lawrence, Ross and Stein, 2002), others find decreased activation and performance improvement (Thiel, Zilles and Fink, 2005; Giessing *et al.*, 2006; Hahn *et al.*, 2007; Warbrick *et al.*, 2011). Nicotine-induced reduction of task relevant activation has been associated with early attentional functions independent of task conditions (Hahn *et al.*, 2009).

Routes of administration include subcutaneous injection (Ettinger *et al.*, 2009), nasal spray (Warbrick *et al.*, 2011), oral gums (Giessing *et al.*, 2006) and transdermal patches (Petrovsky *et al.*, 2013).

6.2.3 Smooth Pursuit Eye Movements

For the investigation of performance-enhancing effects, it may be advantageous to use simple tasks of sensory or motor functions. It can be difficult to separate stimulant-induced enhancement of sensory or motor functions in attention, learning and memory. Oculomotor tasks offer the opportunity to measure pharmacological effects on cognitive and motor functions (Reilly *et al.*, 2008). The kinematics and dynamics of the eyeball are straightforward (Robinson, 1964, 1965) and different movement types are generated by separate neural systems (Berman *et al.*, 1999).

For example, the smooth pursuit eye movement (SPEM) task requires a mechanism to track a moving object in extra-personal space without head movement and draws upon attention, motion processing and temporo-spatial prediction (Barnes, 2008). The neural

correlates of the required sensorimotor feedback system are well established and include motion processing regions, such as area V5, and attention and prediction-related regions in frontal and parietal cortices, namely frontal, parietal and supplementary eye fields and subcortical structures such as thalamus and putamen (Thier and Ilg, 2005; Lencer and Trillenberg, 2008; Meyhöfer *et al.*, 2015).

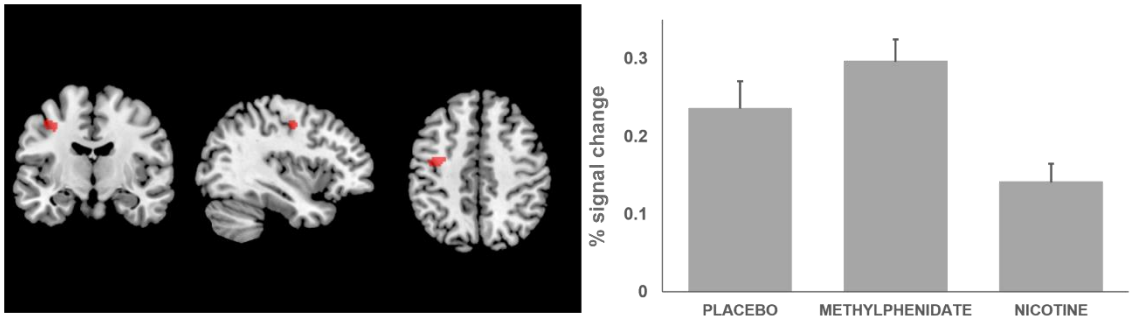
The pursuit system is a negative feedback control system, where the afferent pathways detect stimuli motion and the efferent pathways stimulate the eyeball in an effort to match eye and target motion (Lisberger, Morris and Tychsen, 1987). Performance can be measured globally as deviation between target and eye position by calculating the root mean square error (RMSE) of eye position. However, specific measures such as steady state velocity gain, eye velocity and saccadic frequency are also used to assess pursuit performance (Nagel *et al.*, 2006; O'Driscoll and Callahan, 2008; Levy *et al.*, 2010; Meyhöfer *et al.*, 2015; Steffens *et al.*, 2016).

Several studies have found beneficial effects of nicotine on smooth pursuit performance in smokers (Klein and Andresen, 1991; Domino, Ni and Zhang, 1997; Olincy *et al.*, 1998; Dépatie *et al.*, 2002), but not in non-smokers (Avila *et al.*, 2003; Schmechtig *et al.*, 2013). This suggests that previous findings of nicotinic enhancement may have been confounded by the operation of withdrawal effects. It should also be noted that some studies found adverse effects of nicotine on smooth pursuit performance (Sibony, Evinger and Manning, 1988; Thaker *et al.*, 1991).

6.2.4 Rational of the Study

Both nicotine and methylphenidate have been shown to enhance overlapping measures of attentional performance (Levin *et al.*, 2001; Bizarro *et al.*, 2004) and smooth pursuit (Sherr *et al.*, 2002; Allman *et al.*, 2012). For better understanding of the common and distinct mechanisms of action, the third study assessed the effects of single doses of nicotine and methylphenidate on smooth pursuit eye movements.

Eighty-two healthy male non-smokers performed a smooth pursuit eye movement task while recording eye movement and hemodynamic response via 3T scanner. A between-subjects, double-blind design was applied. Each subjects was randomly assigned to one of three groups: placebo (placebo patch and capsule), nicotine (7mg nicotine patch and placebo capsule), or methylphenidate (placebo patch and 40mg methylphenidate capsule). The task comprised of blocks of sinusoidal target movement with either high (0.4 Hz) or low (0.2 Hz) frequency and blocks of no target movement (fixation).



Legend. Main effect of drug in left frontal eye field (MNI Coordintates: x = -38, y = -10, z = 46. Left is left. Error bars depict standard error of mean.

Figure 5. Key findings Study 3

6.2.5 Summary of Key Findings

On the behavioural level, no significant group difference was observed on any key behavioural measure of smooth pursuit, namely maintenance gain, saccadic frequency or mean RMSE. On the neural level, there was a main effect of drug group in the left frontal eye field (FEF). Increased activation was observed in the methylphenidate group compared to nicotine, with an intermediate response in the placebo group (Figure 5). The FEFs are a key region in the control of eye movements. During pursuit the FEFs are thought to regulate pursuit maintenances and also initiation and prediction of target movement (Lencer and Trillenberg, 2008). The FEFs receive subcortical input from superior colliculus and substantia nigra (Lynch, Hoover and Strick, 1994). Cholinergic stimulation of superior colliculus leads to improved initiation of eye movements (Aizawa *et al.*, 1999), whereas electrical stimulation of substantia nigra operates bidirectionally and either suppresses or enhances pursuit movement (Basso, Pokorny and Liu, 2005). Presumably methylphenidate exerts its effects via the nigrostriatal system originating

from the substantia nigra (John and Jones, 2007). The importance of an intact nigrostriatal system during pursuit performance has been demonstrated in Parkinson patients (White *et al.*, 1983). Thus, increased activity in the methylphenidate group reflects the enhancement of task relevant networks and confirms its role in the selection of salient stimuli (Benoit-Marand, Jaber and Gonon, 2000; Volkow *et al.*, 2004, 2005) as opposed to a compound with similar prodopaminergic effects independent of dopamine transporter blockage (see 7.3).

7. General Discussion

The dopamine transporter contributes crucially to dopaminergic transmission by affecting basal dopamine levels, postsynaptic receptor density and dopamine synthesis (4.2.2). The current work provides a linkage between genetic predisposition of the human dopamine transporter with neural correlates of inhibitory control and with response to pharmaceutical blockage of the dopamine transporter. The third study revealed dissimilar effects on task network between dopamine transporter blockage and nicotinic stimulation during a oculomotor task.

7.1 Cognition and Behaviour

The assessed dopamine transporter genotype (*SLC6A3* 3'-UTR) modulates activity in frontal and subcortical structures during inhibition of motor responses, which was seen by a consistent effect on hemodynamic response of the polymorphism on tasks of motor and oculomotor inhibition (Figure 3). Subjects homozygous for the 10 allele had significantly higher BOLD activity in comparison to 9R heterozygotes. These findings are consistent with previous evidence (Braet *et al.*, 2011). For example, a qualitatively similar pattern was found during reward anticipation and memory in the striatum and hippocampus, respectively (Wittmann *et al.*, 2013). Considering previous studies reporting worse response inhibition (Braet *et al.*, 2011; Cornish *et al.*, 2011) and increased impulsive behaviour (Gizer and Waldman, 2012; Mata *et al.*, 2012), the present findings are indicative of less efficient cognitive control mechanisms in 10R homozygotes. Furthermore, the second study qualitatively replicates the genotype difference in activation and reveals variability of BOLD response to a dopaminergic agonist as function of the dopamine transporter genotype. Genotype modulated task relevant brain activation in response to a dopamine reuptake inhibitor (Figure 4). For a subsample, dopamine transporter density was also available, however no influence of striatal dopamine transporter density on BOLD signal was found.

While the 10/10 carriers showed a reduction in BOLD signal, the 9R carriers who are thought to have higher dopamine transporter density (Costa *et al.*, 2011; Faraone *et al.*, 2014), demonstrated an increase of activation after pharmacological challenge. The observation of increased drug sensitivity in 9R carriers is in in line with rodent studies

demonstrating increased sensitivity to drug-induced effects for animals with an overexpression of dopamine transporters and with studies on reward-sensitivity (Salahpour *et al.*, 2008; Dreher *et al.*, 2009; Forbes *et al.*, 2009; Franklin *et al.*, 2009). Inhibitory motor control networks are an integrative part of cognitive control function (Aron, 2007). The unquestionable role of dopamine in motivation in addition to the present influence on cognitive control mechanisms underlines the regulatory role of the dopamine transporter in goal-directed behaviour. This is further supported by findings that indicate dopamine transporter genotype effects on social behaviour (Enter, Colzato and Roelofs, 2012). In sum, despite the negative findings of an association of the polymorphism and performance in various cognitive domains (Ettinger, Merten and Kambeitz, 2016), the present results indicate an essential role of the transporter in the adaptive regulation of cognition and behaviour.

7.2 Modulation of BOLD by *SLC6A3* 3'-UTR VNTR

An important question is how the dopamine transporter genotype influences neural activity measured with BOLD. Multi-modal neuroimaging research has shown positive associations between BOLD signal and dopamine release as well as extracellular dopamine (Chen *et al.*, 1997; Knutson and Gibbs, 2007; Schott *et al.*, 2008) and established a link between phasic firing of dopaminergic neurons with increased BOLD signal (Lohani *et al.*, 2016). Furthermore, increased BOLD activation in the absence of performance differences can be indicative of less efficient processing, i.e. for example more effort which requires the recruitment of extra neural resources (Ritsner, 2009; Poldrack, 2015).

Rodent studies with DAT KO or deficient mice suggest increased extracellular dopamine levels (hyperdopaminergic) with lower dopamine transporter availability and in DAT-tg mice reduced extracellular dopamine levels (hypodopaminergic) with higher dopamine transporter density along with higher dopamine release (see 4.2.2). If this concept is applied to the genotype groups, increased BOLD in the 10/10 carriers who are thought to have higher dopamine transporter availability (Costa *et al.*, 2011; Faraone *et al.*, 2014) could reflect higher potency of phasic transmission along with increased extracellular dopamine levels. The enhancement of extracellular dopamine level via blockage of dopamine transporter with methylphenidate and the consequential reduction of BOLD is

possibly caused by autoreceptor regulation (Lacey, Mercuri and North, 1987), or the transition from phasic to tonic firing as suggested by the model of Dreher and Hounsgaard (2012). Increased dopamine levels in the striatum in DAT-knockout mice has been associated with hyperactivity symptoms (4.2.2), in this context the heightened activation of 10/10 carriers could be interpreted as heightened effort to suppress an unwanted response and the generally enhanced dopamine level might be indicative of an increased potency to act on impulse. For example, decreased striatal dopamine transporter density and increased dopamine has been demonstrated in patients with restless legs syndrome (Earley *et al.*, 2011, 2013). However, this simplifies the processes of goal-directed action and a thorough explanation requires the dissection of inhibition and motor action networks. Nonetheless, the findings are in line with the genotype group's association of impaired response inhibition in ADHD (Cornish *et al.*, 2005), as well as impulsive behaviour in healthy (Mata *et al.*, 2012).

7.3 Methylphenidate and Nicotine

During an oculomotor task, the blockage of dopamine transporter with the compound methylphenidate resulted in an increase of frontal eye field activity in contrast to nicotine. The frontal eye fields are associated with spatial attention (Corbetta *et al.*, 1998) and voluntary eye movement control (Pierrot-Deseilligny, Milea and Müri, 2004).

Methylphenidate-induced increase in dopamine is more effective when given concomitantly with a salient stimuli (Volkow *et al.*, 2005). Thus, the methylphenidate-induced enhancement of task-relevant areas goes in line with the compounds effects on stimuli saliency (Volkow *et al.*, 2005; Linssen *et al.*, 2012; Farr, Hu, *et al.*, 2014). A moving stimulus is by itself a very salient visual input, when contrasted to a stationary target, as was done in study 3. Therefore, the observed differences in drug effects on frontal eye field may derive from dissimilar effects on baseline condition. If nicotine generally enhances neural processing regardless of stimuli saliency, one would expect smaller signal change compared to placebo. This is supported by the observation that nicotine enhances extra-striate cortex a region that closely interacts with frontal eye fields (Silvanto, Lavie and Walsh, 2006) in the absence of visual stimulation (Tanabe *et al.*, 2011). Consequently, nicotine reduction of BOLD could reflect lower signal-to-noise ratio for task relevant activation. In contrast, methylphenidate-induced increase of BOLD

during task and lower impact on baseline condition implies increased signal-to-noise-ratio. While such argumentation needs further proof, including assessment of baseline effects in a within subjects design, it agrees with the observed intermediate BOLD response to placebo.

Another possible explanation includes efficiency effects of nicotine and are described in more detail in 11.3 Appendix C (Publication **III)**(0).

The effects in studies with methylphenidate are very heterogeneous as well as effects of nicotine on dopaminergic function. An emerging pattern caused by variations in dopamine release is an inverted-u shaped dose-response profile of post-synaptic dopamine effects (Seaman, Yang, 2004). It appears that the dopamine systems are "tuned" so that low or high levels of dopamine activity impair performance in motor, behavioural or cognitive domains, which would be in line with switching from phasic to tonic activity as discussed in 4.2.2 (Robbins and Arnsten, 2009).

Additionally, inter-individual difference in response to nicotine and methylphenidate might mask other effects. Future studies on prodopaminergic enhancement of cognition would benefit from the inclusion of genetic and molecular markers as well as dose variation.

7.4 Methodological Considerations

Several limitations to the current studies have to be addressed. Pharmacological studies were only conducted on male subjects to reduce influence of hormonal fluctuations. This selection strategy maximizes sample homogeneity in terms of genetics and avoids influences of hormonal fluctuations in females but comes at the cost of reduced generalizability. The generalizability of the findings is limited to healthy, Caucasian males. Inclusion of female subjects would give a more realistic picture of psychopharmacological effects on dopaminergic transmission in normal healthy population. Additionally, an increase of sample size, specifically for each individual sample size of genotype groups would allow furthering dissecting the mechanisms leading to a different BOLD signal in the current studies and allow for greater sensitivity for small magnitude effects.

Only most frequent allelic variants were investigated, yet thorough investigation with candidate gene approach would benefit from inclusion of other variants and evenly

distributed heterozygotic 9R groups. A further limitation is the focus on a single 3'-UTR VNTR, which is only one of several polymorphisms thought to regulate striatal dopamine. Cummins and colleagues (Cummins *et al.*, 2012) completed the largest study yet to test linkage of catecholamine gene and response inhibition phenotype. Robust associations were found in the *SLC6A3* gene, the markers included the rs46000 and the rs37020 variants. Further, neuroimaging revealed an additive association between variants in the rs37020 allelic variants and task-related brain activation during stop-signal performance in prefrontal and striatal areas.

Further considerations include the affinity of methylphenidate to noradrenergic transporter (Hannestad *et al.*, 2010; Dela Peña, Gevorkiana and Shi, 2015) and the compounds potency to enhance dopamine transport into membrane-associated vesicles (Volz *et al.*, 2007). Further studies, are needed to clarify impact of noradrenergic transporter blockage.

Further issues arise from limitations in imaging techniques. SPECT method is limited by the semi-quantitative assessment of dopamine transporter, which however is inherent to most receptor and transporter SPECT and PET studies.

Future combined PET-fMRI investigations with dopamine transporter displacement measured after drug administration or with dopamine imaging as marker of dopamine release might elucidate further dependencies between molecular and genetic factors influencing the dopamine system during cognitive performance.

7.5 Concluding remarks

The current thesis links genetic and molecular characteristics of the dopamine transporter to neural activity and confirms functionality of the transporter as well as its potential use as non-invasive measure of dopaminergic activity in healthy subjects. Albeit a limitation, the homogeneous sample group of healthy male non-smokers and the well-powered samples in each study are also strength of the current work and an opportunity to gain knowledge on pharmaceutical and genetic effects in the absence of confounding factors, e.g. pathology, pharmacological treatment. The results highlight the power of candidate gene approach and allow assumptions on dopamine transporter effects on dopamine flux and the associated cognitive processes. Findings complement the understanding of regulatory impact on cognition and goal-directed behaviour as function of dopamine

transporter and present genetic markers as predictor of treatment response variability.

In sum, the quality of the current neuroscientific work lies in the combination of knowledge from animal research and the application of multimodal imaging, including genetic and pharmacological fMRI and its findings help to shape a more precise functional role of the dopamine transporter in cognition.

8. References

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9. List of Figures

10. List of Abbreviations

ADHD	attention deficit hyperactivity disorder
BOLD	blood oxygen level dependent
CNS	central nervous system
dHb	deoxyhaemoglobin
Bp	base pair
COMT	catechol-*O*-methyl transferase
DAT KO	dopamine transporter knockout mice
DAT-tg	dopamine transporter transgenic
DNA	deoxyribonucleic acid
EEG	electroencephalography
fMRI	functional magnet resonance imaging
Hb	oxyhaemoglobin
MAO	monoamine oxidase
PCR	polymerase chain reaction
PET	photon emission tomography
RMSE	root-mean-square error
SNP	single nucleotide polymorphism
SPECT	single photon emission computer tomography
TE	echo time
TR	repetition time
UTR	untranslated region
VMAT	vesicular monoamine transporters
VNTR	variable number of tandem repeats

11. Appendices: Publications

The present thesis is based on three original publications. To avoid violations of copyright, the articles were removed from the appendix section. The articles can be found online using the following references or in hardcopies of the present thesis at the *Universitäts- und Landesbibliothek Bonn*.

11.1 Appendix A (Publication I)

Published in

Kasparbauer, A.-M., Merten, N., Aichert, D. S., Wöstmann, N., Meindl, T., Rujescu, D., & Ettinger, U. (2015). Association of COMT and SLC6A3 polymorphisms with impulsivity, response inhibition and brain function. Cortex, 71, 219–231. http://doi.org/10.1016/j.cortex.2015.07.002

11.2 Appendix B (Publication II)

Published in

Kasparbauer, A.-M., Rujescu, D., Riedel, M., Pogarell, O., Costa, A., Meindl, T., la Fougère, C., Ettinger, U. (2015). Methylphenidate Effects on Brain Activity as a Function of SLC6A3 Genotype and Striatal Dopamine Transporter Availability. Neuropsychopharmacology, 40(3), 736–745. http://doi.org/10.1038/npp.2014.240

11.3 Appendix C (Publication III)

Published in

Kasparbauer, A.-M., Meyhöfer, I., Steffens, M., Weber, B., Aydin, M., Kumari, V., Hurlemann, R., Ettinger, U. (2016). Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. NeuroImage, 141, 52–59. http://doi.org/10.1016/j.neuroimage.2016.07.012