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# Fronto-striatal plasticity processes in humans: glutamatergic and genetic mechanisms

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## Table of Abbreviations

AAL.....	automated anatomical labeling
ANOVA.....	analysis of variance
BDNF.....	brain-derived neurotrophic factor
BOLD.....	blood oxygenation level-dependent
CNS.....	central nervous system
CSF.....	cerebrospinal fluid
DARTEL.....	diffeomorphic image registration algorithm
DLPFC.....	dorsolateral prefrontal cortex
DMN.....	default mode network
DMS.....	dorsomedial striatum
DRD1a.....	dopamine receptor D1a
DRD2.....	dopamine receptor D2
DLS.....	dorsolateral striatum
FEF.....	frontal eye field
fMRI.....	functional magnetic resonance imaging
FWE.....	family-wise error
FWHM.....	full width at half maximum
GABA.....	$\gamma$ -amino butyric acid
GLM.....	general linear model
GM.....	gray matter
Gpi.....	internal globus pallidus
LTP.....	long-term potentiation
M.....	mean
M1.....	primary motor corte
Met.....	methionine
MNI.....	Montral Neurological Institute
MRI.....	magnetic resonance imaging
MRS.....	magnetic resonance spectroscopy
MSL.....	motor skill learning
MSNs.....	medium-sized spiny neurons
NAA.....	N-acetylaspartate
NGF.....	nerve growth factor
NMDA.....	N-Methyl-D-Aspartate
PET.....	positron emission tomography
PMC.....	premotor cortex
PNS.....	peripheral nervous system
ROI.....	region of interest
S1.....	primary somatosensory cortex
SE.....	standard error
SMA.....	supplementary motor area
SNP.....	single-nucleotide polymorphism
SNr.....	substantia nigra pars reticulata
SPM.....	statistical parametric mapping
SRTT.....	serial reaction time task
STN.....	subthalamic nucleus
SVIPT.....	sequential visual isometric pinch task
TMS.....	transcranial magnetic stimulation
Trk.....	tyrosine kinase receptor
Val.....	valine
VBM.....	voxel-based morphometry
WM.....	white matter

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## 1. General Introduction

The human organism has the remarkable ability to evolve, to grow, to learn and to improve. It accomplishes this via adaptive neurobiological mechanisms commonly referred to as ‘neuroplasticity’ – ‘an intrinsic property of the nervous system retained throughout life that enables modification of function and structure in response to environmental demands via the strengthening, weakening, pruning, or adding of synaptic connections and by promoting neurogenesis’ (Pascual-Leone et al., 2011, p. 2). Due to the complex and highly interconnected nature of our brains, plasticity acts in cellular microcircuits as well as large-scale regional and interconnected networks. Traditionally, the principle of plasticity was assumed to act solely in critical periods of our postnatal development, but decades of research demonstrated that learning and plasticity processes can indeed take effect throughout the whole lifespan (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Consequently, it attracted great interest for the development of treatment options in pathological conditions like stroke or traumatic brain injury but also in the mitigation of symptoms in degenerative diseases like Parkinson’s disease or psychiatric disorders like schizophrenia, which is characterized by an aberration of learning and plasticity processes (Daskalakis, Christensen, Fitzgerald, & Chen, 2008; Hubener & Bonhoeffer, 2014; Kleim & Jones, 2008).

Especially the dynamic interplay between cortical and subcortical structures has been highly relevant for the study of plasticity and learning processes and the basal ganglia, specifically the striatum, have been identified as key structures within those circuits. Those so called fronto-striatal ‘loops’ are characterized by distinct anatomical structures, respective neurotransmitter systems and a specific set of motor, cognitive or affective behaviors. They are vital for the execution and learning of new behaviors and are organized in a closed loop, meaning projections from one area of the cortex innervate areas of the basal ganglia, which then project back to the same cortical area via the thalamus (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986; Chudasama & Robbins, 2006).

In human neuroscience, learning and (synaptic) plasticity processes are often investigated via transcranial magnetic stimulation (TMS) or transcranial direct-current stimulation (tDCS) (Krakauer & Mazzoni, 2011) and mapped to macroscopic functional, morphological or metabolite changes in the central nervous system (CNS). Due to the development of new high-resolution neuroimaging techniques, those processes are now a major subject of research. Methods such as functional magnetic resonance imaging (fMRI), which measures hemodynamic response activity (blood-oxygenation level dependent (BOLD)) (Logothetis, 2008; Poldrack, 2000), structural magnetic resonance imaging (sMRI) for anatomical acuity

and changes in gray (GM) or white matter (WM) organization (Caroni, Donato, & Muller, 2012; Draganski & Kherif, 2013) or magnetic resonance spectroscopy (MRS) for metabolite concentration (e.g. glutamate or N-acetylaspartate (NAA)) in certain brain regions (Ende, 2015; Schwerk, Alves, Pouwels, & van Amelsvoort, 2014) have been frequently applied and combined to shed light on this constantly evolving topic. On a molecular level, the discovery of the existence of plasticity factors such as certain neuroproteins and their genetic variation in humans helped to further understand dysfunctional plasticity processes and to bridge gaps in translational neuroscience (Martinez-Levy & Cruz-Fuentes, 2014; Park & Poo, 2013).

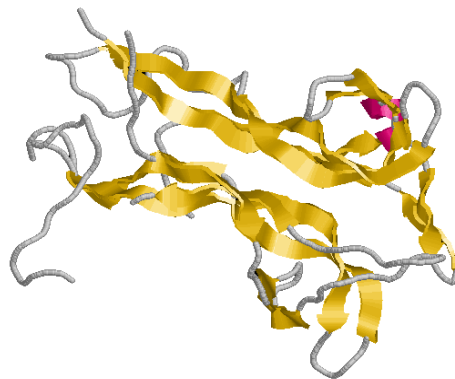
The objective of this thesis was to study human learning and plasticity processes in fronto-striatal circuits. A multilevel and multimodal neuroimaging approach was applied to draw inferences from a molecular level of genetic variation to underlying macroscopic brain correlates to human behavior. Data were collected within a large-scale project funded by the German federal ministry of education and research on 'Multimodal neuroimaging of frontal striatal plasticity in humans: biomarkers, genetic mechanisms, disease vulnerability and neurochemical modulation' (Dr. Dr. Heike Tost, BMBF 01GQ1102). Concept and respective hypotheses for this thesis (see 2.8) with its specific topic on genetic variation of multimodal motor plasticity within the striatum and connected cortical nodes were derived from the cross-sectional part and a healthy subject sample of this project, and were the author's personal contribution. This also included establishment of the experimental set-up and neuroimaging specifications, data piloting and measurement, data analysis and -interpretation as well as writing the manuscript (see 12 for significant contribution of others). Data from respective pilot studies were not included in this thesis.

Though derived from a healthy population, the established findings might prove fruitful for a better understanding of aberrant learning and plasticity processes in psychiatric populations such as schizophrenia (Daskalakis et al., 2008) and aid in the development of new treatment options.

## 2. Introduction

### 2.1. Neurotrophins

Neurotrophins are a small family of secreted proteins that are vital for various facets of mammalian central nervous system functioning. They are involved in the survival and differentiation of neurons, as well as synaptogenesis or activity-dependent forms of synaptic plasticity (for comprehensive reviews, see Huang & Reichardt, 2001; Lu, Pang, & Woo, 2005; Park & Poo, 2013; Poo, 2001). The research on neurotrophins dates back to the early 1950s when nerve growth factor (NGF) was first discovered in sympathetic and sensory neurons of the peripheral nervous system (PNS), promoting neuronal growth and survival during development (Cohen, Levi-Montalcini, & Hamburger, 1954; Levi-Montalcini, 1987) and has been further refined with the characterization of brain-derived neurotrophic factor (BDNF) in the pig brain supporting similar processes in sensory neurons as NGF (Barde, Edgar, & Thoenen, 1982). Four neurotrophic factors have been identified and characterized so far: NGF, BDNF, neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5) with BDNF being the one most widely expressed and investigated (Park & Poo, 2013) (see Figure 1).



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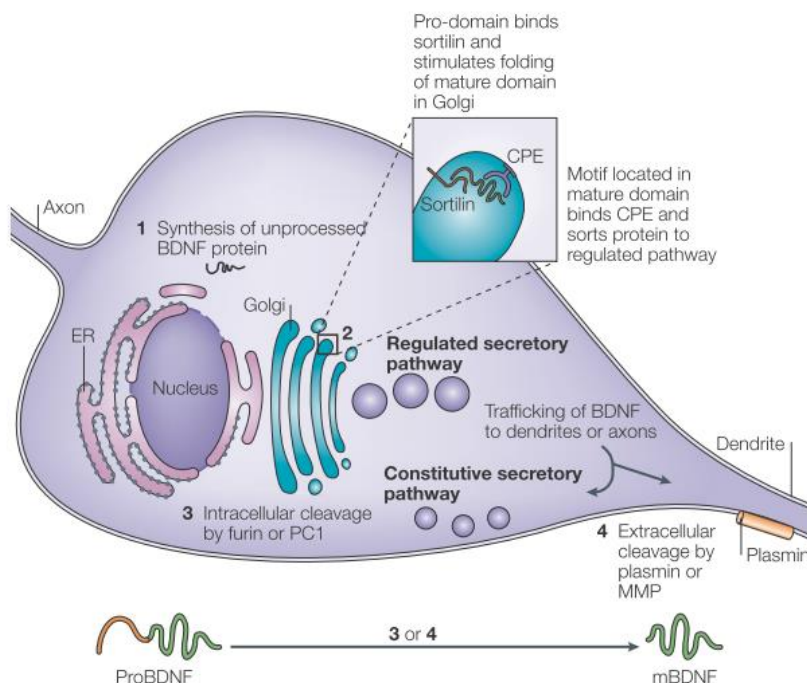
**Figure 1.** Structure of the brain-derived neurotrophic factor/neurotrophin 4 heterodimer. Figure was created with RasWin Molecular Graphics (RasMol, Version 2.7.5.2). Adapted from Robinson et al. (1999).

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All neurotrophins exert their effects by binding to two specific classes of transmembrane receptors. The p75 neurotrophin receptor (p75<sup>NTR</sup>) has equal affinity for all neurotrophins, while the tyrosine kinase receptor family (Trk) selectively binds neurotrophins. By this means, TrkA receptors are activated by NGF, TrkB receptors by BDNF as well as NT4/5 and TrkC receptors by NT3. BDNF and the other neurotrophins arise from precursor proneurotrophins synthesized in the endoplasmatic reticulum of neurons which are then folded and proteolytically cleaved to create mature proteins. The mature proteins are then

sorted into vesicles either to be secreted constitutively or regulated at the appropriate sites of release in axons or dendrites (see Figure 2) (reviewed e.g. in Huang & Reichardt, 2001; Lu et al., 2005).

For a long time precursor proteins were believed to be functionally inactive, but studies from the early 2000s demonstrated that they actually have a high affinity for the p75<sup>NTR</sup> receptor, while the mature variant preferentially binds to the Trk receptors, and by binding they can initiate apoptosis. Today, there exists convergent evidence that proneurotrophins are indeed secreted and may function as signaling molecules (R. Lee, Kermani, Teng, & Hempstead, 2001; Teng et al., 2005; J. Yang et al., 2014) and have been hypothesized to exert opposing effects to those of their mature variant in a 'yin and yang' dynamic (Lu et al., 2005).



**Figure 2.** The synthesis and sorting of BDNF. A schematic showing the synthesis and sorting of brain-derived neurotrophic factor (BDNF) in a typical neuron. First synthesized in the endoplasmic reticulum (ER) (1), proBDNF (precursor of BDNF) binds to intracellular sortilin in the Golgi to facilitate proper folding of the mature domain (2). A motif in the mature

domain of BDNF binds to carboxy-peptidase E (CPE), an interaction that sorts BDNF into large dense core vesicles, which are a component of the regulated secretory pathway. In the absence of this motif, BDNF is sorted into the constitutive pathway. After the binary decision of sorting, BDNF is transported to the appropriate site of release, either in dendrites or in axons. Because, in some cases, the pro-domain is not cleaved intracellularly by furin or protein convertases (such as protein convertase 1, PC1) (3), proBDNF can be released by neurons. Extracellular proteases, such as metalloproteinases and plasmin, can subsequently cleave the pro-region to yield mature BDNF (mBDNF) (4). MMP, matrix metalloproteinase. Reprinted with permission from Lu et al. (2005, p. 605).

## 2.2. Brain-derived neurotrophic factor (BDNF)

Numerous studies have shown that BDNF plays a pivotal role for synaptic plasticity as well as neuronal survival and growth in the central nervous system. The transcription and pre- and postsynaptic secretion of BDNF relies on neuronal activity, (for comprehensive reviews, see Gonzalez, Moya-Alvarado, Gonzalez-Billaut, & Bronfman, 2016; Lu, 2003; Park & Poo, 2013)

and the relevance of the BDNF-TrkB signaling pathway for long-term potentiation (LTP) and learning has been well established (Minichiello, 2009). Figurov and colleagues were one of the first to show that exogenous BDNF promoted induction of long-term potentiation in hippocampal slices by tetanic stimulation, while stimulation in the absence of BDNF resulted only in short-term potentiation (STP) (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996). Upon binding to the TrkB receptor, BDNF initiates three main signaling pathways leading to either synaptic plasticity and other plasticity behavior, neuronal growth and differentiation, or neuronal survival (reviewed in Minichiello, 2009). Therefore, BDNF holds an influential role in the differentiation of dendrites and axons as well as dendritic growth and morphogenesis in neuronal circuit development (Park & Poo, 2013).

BDNF is widely distributed in the entire central nervous system and acts in multiple neuronal pathways (Altar et al., 1997). Synaptic transmission seems to be fostered by BDNF through enhanced presynaptic neurotransmitter release (reviewed e.g. in Poo, 2001). Indeed, BDNF is mainly synthesized and released in glutamatergic neurons and interacts pre- and postsynaptically with TrkB receptors to trigger glutamate release and modify N-Methyl-D-Aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor structure and function (e.g. response potential) (reviewed e.g. in Carvalho, Caldeira, Santos, & Duarte, 2008; Park & Poo, 2013) (Caldeira et al., 2007; D'Amore, Tracy, & Parikh, 2013). Furthermore, long-term potentiation (LTP)—the crucial mechanism for neuronal reorganization, learning and memory—is dependent on NMDA-receptor mediated coactivation of neurons and can be modulated by BDNF expression (Sweatt, 1999).

### **2.3. *BDNF* val<sup>66</sup>met polymorphism**

In humans, there exists a functional genetic variant, the *BDNF* val<sup>66</sup>met polymorphism (rs6265), which is among the most widely investigated single-nucleotide polymorphisms (SNP) today. Since 2003, when it was first described as a functional variant (Egan et al., 2003), the respective number of publications has increased progressively but has also left us with an integrative gap between research fields, from molecular levels to human behavior, from rodent brain-slices to functioning human brains.

In the world population, the *BDNF* val<sup>66</sup>met polymorphism is observed in ~ 20% of the European population, in ~ 0.55% of Sub-Saharan Africans and ~ 44% of the Asian population (Petryshen et al., 2010).

The *BDNF*-gene itself is comprised of a main coding exon and nine differentially spliced promoters (Pruunsild, Kazantseva, Aid, Palm, & Timmusk, 2007). An alteration in the

composition of nucleotides, i.e. a switch of a guanine to adenine within the 5' pro-region causes a Valine (Val) to Methionine (Met) amino-acid substitution at residue 66 (val<sup>66</sup>met) of the BDNF-protein (Egan et al., 2003).

Known molecular consequence is the disrupted activity-dependent release of the mature protein by impaired intracellular trafficking and packaging of the precursor protein (Chen et al., 2004; Egan et al., 2003). This further results in aberrant NMDA-receptor-mediated glutamatergic transmission and plasticity in hippocampal, prefrontal or striatal structures (Jing, Lee, & Ninan, 2016; Ninan et al., 2010; Pattwell et al., 2012). Consequently, in humans, lower levels of glutamate as well as N-acetyl-aspartate (NAA)—a marker for synaptic density and neuronal integrity (Egan et al., 2003)—within the hippocampus have been observed via MR-spectroscopy (Gruber et al., 2012; Stern et al., 2008).

#### **2.4. *BDNF* val<sup>66</sup>met polymorphism in human neuroscience**

Due to the well described impact of BDNF on synaptic plasticity and neuronal morphology (see 2.2), the *BDNF* val<sup>66</sup>met polymorphism was one of the first functional variants to be investigated within the field of cognitive, affective and behavioral neuroscience, and its relevance for psychiatric disorders is well established.

Knowing about the influential role of BDNF in long-term potentiation (see 2.2), memory performance was among the first cognitive domains to be investigated, and episodic or declarative memory processes have consistently been shown to be impaired in Met allele carriers (Egan et al., 2003; Goldberg et al., 2008; Hariri et al., 2003). Furthermore, detrimental effects on hippocampus gray matter volume and function have been described as physiological substrates (Bueller et al., 2006; Frodl et al., 2007; Hariri et al., 2003; Pezawas et al., 2004). For other brain regions, impact on the cortical integrity and/or age related decline in Met-carriers have been reported in structures like the dorsolateral prefrontal cortex (DLPFC) (Kim et al., 2013; Pezawas et al., 2004), the temporal, occipital, cingulate and insular cortex (Ho et al., 2006; X. Yang et al., 2012), the amygdala (Sublette et al., 2008) as well as the thalamus and fusiform gyrus (Montag, Weber, Fliessbach, Elger, & Reuter, 2009), or the parahippocampal and left superior frontal gyri (Takahashi et al., 2008). Gray matter abnormalities in the striatum have not been reported so far.

Also, anxiety-related phenotypes of the *BDNF* val<sup>66</sup>met polymorphism have been of particular interest due to the well-known implications of synaptic plasticity in fear conditioning (VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014). Consequently, effects of this functional variant have been shown for conditioned fear responses and alterations in

fear extinction (Chhatwal, Stanek-Rattiner, Davis, & Ressler, 2006; Rattiner, Davis, French, & Ressler, 2004; Soliman et al., 2010).

In clinical populations, there exists evidence for the impact of the Met allele in anxiety (e.g. post-traumatic stress disorder), mood, eating and psychotic/schizophrenic disorders (Notaras, Hill, & van den Buuse, 2015a). Indeed, BDNF exerts influential effects in cholinergic, dopaminergic and 5-hydroxytryptamin (5-HT) containing neurons which are assumed to be involved in the underlying biological mechanisms of a broad range of psychiatric disorders (Notaras, Hill, & van den Buuse, 2015b; Poo, 2001).

Schizophrenia, specifically, is a severe psychiatric disease with cardinal symptoms of hallucinations and delusions and a complex etiology of polygenetic-environmental interactions (Notaras et al., 2015a). The neurodevelopmental hypothesis characterizes this disorder with abnormalities that arise during pre- and postnatal differentiation of the central nervous system (Marenco & Weinberger, 2000). Syndrome characteristics therefore also comprise dysfunctional learning and plasticity processes that might account for the accompanied cognitive deficits in executive functions, working memory or visuospatial-processing (Daskalakis et al., 2008; Ho et al., 2006; W. Lu et al., 2012; Rybakowski et al., 2006; Stephan, Baldeweg, & Friston, 2006). As a corollary, alterations in NMDA-receptor-mediated transmission or plasticity and consequently BDNF signaling (see 2.3) have also been debated as major pathophysiological mechanisms for schizophrenic and psychotic disorders (Marsman et al., 2013; Snyder & Gao, 2013; Weinberger, 1999).

## **2.5. Paradoxical findings and compensatory strategies**

To date, the majority of studies suggest beneficial effects of the Val allele for a broad range of neural functions, although even seemingly established findings such as the association of the Val allele with larger hippocampus volume or better memory performance have recently come under scrutiny (Hajek, Kopecek, & Hoschl, 2012; Mandelman & Grigorenko, 2012; Molendijk et al., 2012), and proven difficult to replicate (Harris et al., 2006; Karnik, Wang, Barch, Morris, & Csernansky, 2010; Strauss et al., 2004); also the findings in clinical populations have been rather inconsistent (Notaras et al., 2015a).

In addition, it appears that reports on the seemingly paradoxical effects of the *BDNF* val<sup>66</sup>met polymorphism are gaining momentum. In particular, beneficial effects of the Met allele on the onset age of Huntington's disease (Alberch et al., 2005), the state of brain tissue damage in multiple sclerosis (Zivadinov et al., 2007), the recovery of cognitive functions after traumatic brain injury (Krueger et al., 2011) or cognitive functioning in lupus erythematosus

(Oroszi et al., 2006) have been reported as well as protective effects against psychiatric disorders (Geller et al., 2004; Hall, Dhilla, Charalambous, Gogos, & Karayiorgou, 2003; Sen et al., 2003; Sklar et al., 2002). Also, intriguingly, reports on increased white matter integrity in Met-carriers emerged in recent years (Chiang et al., 2011; Tost et al., 2013).

Indeed, from an evolutionary standpoint, beneficial effects of the mutant variant are to be expected since it would not have been preserved otherwise. Some researchers therefore argued the idea of neurobehavioral compensatory strategies. Banner and colleagues for example provided evidence for the preference of Met-carriers to use and recruit striatum dependent response strategies and interpreted this as compensatory strategy for hippocampal deficits (Banner, Bhat, Etchamendy, Joobar, & Bohbot, 2011). Lang and colleagues reported higher BDNF serum concentrations in Met-carriers (Lang, Hellweg, Sander, & Gallinat, 2009) which they argued to be a compensatory strategy for deficient activity dependent protein signaling (Chen et al., 2004; Tramontina et al., 2007). Also, compensatory increases in striatal volume and enhanced motor recovery after stroke have been shown in a Met-Met mouse model of the variant (Qin et al., 2014).

Taken together, there exists a growing body of evidence that carrying a Met-allele of the *BDNF* val<sup>66</sup>met polymorphism might not automatically signify a neurobehavioral deficit or disadvantage.

## **2.6. *BDNF* val<sup>66</sup>met polymorphism and motor skill learning**

Apart from declarative memory (see 2.4), effects of the non-synonymous coding variant have also been investigated in implicit or procedural mnemonic processes like motor learning and its neuronal sources.

### **2.6.1. *Motor skill learning***

Motor skill learning (MSL) refers to 'the increasing spatial and temporal accuracy of movements with practice' (Willingham, 1998, p. 558). Typically, motor skills evolve slowly over various sessions of training until nearly asymptotic performance is reached. They are acquired via an initial, fast learning phase of e.g. a single training session and a later, slower phase over multiple units (Dayan & Cohen, 2011). Decreases of error rates and/or increases in movement speed are usually used as indicators for successful motor skill learning (Doyon & Benali, 2005). There are definition boundaries of MSL to simple i.e. noncomplex motor learning (Luft & Buitrago, 2005), to simple motor-adaptation, where no novel movement pattern is generated, and to declarative knowledge since it cannot be verbalized



(Diedrichsen & Kornysheva, 2015). Examples of motor skills in our daily lives are riding a bike, playing an instrument or driving.

On a behavioral level, research so far mostly focused on the characterization of distinct sub processes and –mechanisms of motor skill learning. Distinctions have been made between action selection and action execution (Diedrichsen & Kornysheva, 2015) as well as between the generation of novel patterns of muscular activity (synergies) and the sequencing of those synergies (Waters-Metenier, Husain, Wiestler, & Diedrichsen, 2014).

Also, various learning concepts have been debated as underlying principles in MSL. Learning refers to ‘an enduring change in the mechanisms of behavior involving specific stimuli and/or responses that results from prior experience with those or similar stimuli and responses’ (Domjan, 2003, p. 14). Error-based learning is evident when our sensorimotor system registers a deviation of the predicted from the actual outcome of an action. Reinforcement-learning acts on the same principle but uses internal or external signals of success and failure to adapt the respective motor behavior. And use-dependent learning relies on behavioral changes through pure repetition of the action without any internal or external outcome estimators (Wolpert, Diedrichsen, & Flanagan, 2011).

On a timescale different stages of motor skill learning have been identified as the skill becomes more and more refined. The initial stage seems to be mostly driven by learning goal-directed actions and action (A)-outcome (O) contingencies. Most striking characteristic of motor skills, nevertheless, is the immense automatization with which the skill, once learned, can be executed. At the latter stage hence, motor skills are often called habits and are not driven by the consequences, but by the antecedents of the action. By this means, they can be automatically triggered by certain stimuli according to the stimulus (S)-response (R) learning principle of Thorndike (Thorndike, 1898). Recent models of motor skill learning in rodents therefore propose a transgression from A-O to S-R learning (Yin & Knowlton, 2006).

To further understand this transgression, new neurobehavioral learning concepts might be taken into account. Motor chunking, for example, has again gained prominence and refers to the observation that during motor sequence learning, performance not only increases in speed and accuracy, but also organizes into idiosyncratic temporal groups or motor memory chunks (reviewed in Diedrichsen & Kornysheva, 2015). This allows the efficient execution of a series of action elements as one single motor program and therefore represents a crucial step towards the automatization of motor behavior (Halford, Wilson, & Phillips, 1998; Wymbs, Bassett, Mucha, Porter, & Grafton, 2012).

Until now, a broad range of experimental tasks have been used to study motor skill acquisition in humans. This includes sequential finger tapping tasks (e.g. Karni et al., 1995), visual tracking (e.g. Shmuelof, Krakauer, & Mazzoni, 2012), juggling (e.g. Draganski et al., 2004) or whole body balancing (e.g. Taubert et al., 2010). Reis and colleagues, for example, used a sequential visual isometric pinch task (SVIPT) where subjects learned to sequentially navigate a cursor on a computer screen via pinching a force-transducer between the thumb and index finger of their dominant hand. Motor skill learning was measured via increases on a speed-accuracy trade-off function over one single as well as multiple training sessions (Fritsch et al., 2010; Reis et al., 2009).

Due to the variety of tasks used to study motor skill learning and the decades of research on this subject, neuroimaging literature on the neural substrates of human motor skill learning is vast and heterogeneous. Seitz and colleagues were among the first to study the anatomical correlates of motor sequence learning in humans via positron emission tomography (PET), and demonstrated changes in cerebral blood flow along with performance increases for cortical (sensorimotor cortex, premotor areas, supplementary motor areas, parietal areas), cerebellar, (para)limbic and striatal structures (Seitz, Roland, Bohm, Greitz, & Stone-Elander, 1990). Since then, numerous neurofunctional models of human motor skill learning using PET or fMRI evolved. A prominent model by Doyon and Ungerleider, for example, proposed two distinct circuits, a cortico-striato-thalamic loop and a cortico-cerebello-thalamo-cortical loop that are supposed to interact in the consolidation phase but activate distinctly once the skill is learned; either the cortico-cerebellar system for motor adaptation or the cortico-striatal system for motor sequence learning (Doyon & Benali, 2005; Ungerleider, Doyon, & Karni, 2002). Hikosaka and colleagues proposed a similar dual circuit-model upon the distinction of striatal subregions (Hikosaka, Nakamura, Sakai, & Nakahara, 2002). From today's point of view, those models are unable to provide a fully explicative framework on the neural substrates and functional dynamics of human motor skill learning owing to the fact that motor skill learning might involve multiple parallel processes, as well as task dependent temporal progression and brain activation.

In functional MRI, increases in activation tend to be interpreted as additional involvement of cortical substrates with training, while activation decreases suggest that fewer resources are necessary for efficient task performance (Poldrack, 2000). Summing up prior evidence on functional brain dynamics in human motor skill learning reveals a heterogeneous picture where early or fast motor learning is reflected by a decrease in task relevant response in the DLPFC, primary motor cortex (M1) and presupplementary motor area (preSMA) (Floyer-Lea & Matthews, 2005; Sakai et al., 1999; Toni, Krams, Turner, & Passingham, 1998), and activity increases in the premotor cortex (PMC), SMA, parietal cortex, striatum and cerebellum

(Floyer-Lea & Matthews, 2005; Grafton, Hazeltine, & Ivry, 2002; Honda et al., 1998). Slow MSL over days and weeks on the other hand has been associated with increased activity in M1, primary somatosensory cortex (S1), SMA, PMC and the striatum (Floyer-Lea & Matthews, 2005; Karni et al., 1995; Lehericy et al., 2005; Penhune & Doyon, 2002; Shmuelof, Yang, Caffo, Mazzone, & Krakauer, 2014), and decreases in e.g. cerebellar (lobule VI), prefrontal, inferior temporal or hippocampal activity (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Lehericy et al., 2005). Also, varying signal changes over 4 weeks of training have been observed which showed increases in e.g. M1 and SMA activity for the first two weeks and decreases of the same structures for the last two weeks (Ma et al., 2010).

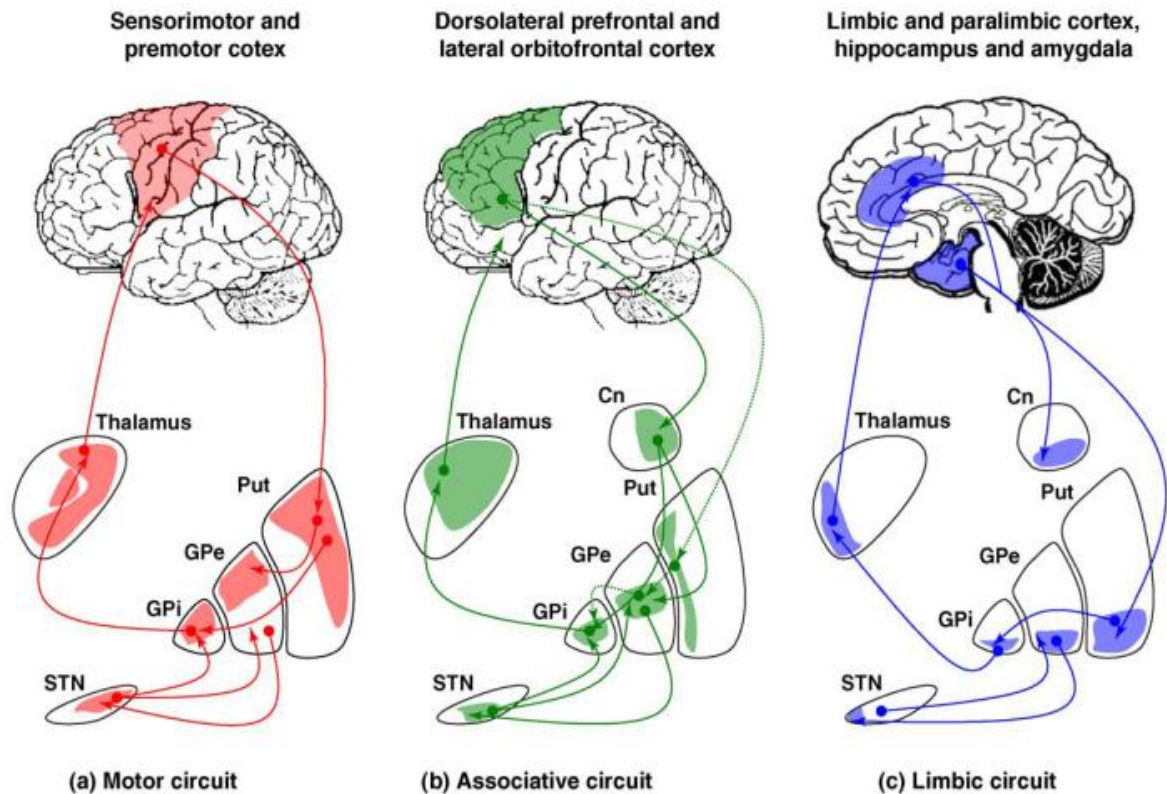
Taken together, motor skill learning may lead to functional region specific activity increases and decreases, depending on task demands and temporal progression. The interpretation and generalization of those fluctuations, nevertheless, remains elusive (Picard, Matsuzaka, & Strick, 2013; Poldrack, 2015). To address this issue, new analysis techniques gained momentum in recent years that used metrics like intrahemispheric coupling and effective connectivity (Friston, 2011; Ma et al., 2010; Sun, Miller, Rao, & D'Esposito, 2007), graph theory and dynamic brain networks (Bassett, Yang, Wymbs, & Grafton, 2015; Debas et al., 2014; Heitger et al., 2012) or motor sequence-specific multi-voxel pattern analysis (Wiestler & Diedrichsen, 2013). Nevertheless, conventional univariate fMRI-analyses can be useful on a confirmatory level to secure plausibility of the experimental set-up and analysis.

Morphological brain alterations related to motor skill learning have also been exceedingly investigated in the last two decades. Ground breaking studies on structural plasticity were able to demonstrate training-related longitudinal increases in gray matter volume and white matter integrity for example in V5 for juggling or fronto-parietal areas for whole body balancing (Draganski et al., 2004; Driemeyer, Boyke, Gaser, Buchel, & May, 2008; Kuhn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014; Lovden et al., 2012; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Takeuchi et al., 2010; Taubert et al., 2010; Wenger et al., 2012) as early as after 1-2h hours of intensive training (Hofstetter, Tavor, Tzur Moryosef, & Assaf, 2013; Sagi et al., 2012; Taubert, Mehnert, Pleger, & Villringer, 2016). Also, cross-sectional morphological group differences between experts of different domains, e.g. taxi drivers or musicians, and novices demonstrated differences in gray matter volume e.g. in the hippocampus, Heschl's gyrus or cerebellum (Bengtsson et al., 2005; Bermudez, Lerch, Evans, & Zatorre, 2009; Han et al., 2009; Maguire et al., 2000; Schneider et al., 2002). Gray matter structural integrity within the cerebellum has further been related to individual differences in motor sequence learning (Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012). Structural changes in gray or white matter related to motor skill learning in the striatum, however, have not been reported with confidence so far (Wenger et al., 2016).

In conclusion, human motor skill learning and its functional and structural substrates are among the most widely studied domains in human neuroscience and can look back on a rich and constantly evolving research history. So far, important insights into the underlying principles of procedural learning and plasticity have been gained. In regard to future research, there exists a broad range of well validated and experimentally controllable task designs.

### ***2.6.2. Cortico-striatal circuits and motor skill learning***

The brain circuitry involved in motor execution and motor (skill) learning has been well described in the literature as one of 3-4 fronto-striatal 'loops' that facilitate and regulate motor, cognitive and affective behavior in humans via interplay of positive and negative feedback processes between cortical and subcortical structures. First derived from anatomical labeling techniques in macaques (Alexander, Crutcher, & DeLong, 1990; Alexander et al., 1986), this multiple circuit model today has been widely accepted and validated among human neuroscientists (Di Martino et al., 2008; Draganski et al., 2008; Lehericy et al., 2004; Postuma & Dagher, 2006). Though slightly different model versions exist, in general the participating brain structures of the '*motor loop*' are the pre-, supplementary and primary motor cortices as well as the putamen, the globus pallidus and the thalamus; relevant brain structure of the '*cognitive/associative loop*' are the DLPFC, the caudate nucleus, the globus pallidus and the thalamus (Chudasama & Robbins, 2006) (see Figure 3). Note that different regions within the striatum/basal ganglia are appointed to a specific circuitry and cortical projection area. Therefore, the striatum has been divided into a ventral ('limbic') and a dorsal part with the latter being mostly relevant for motor learning. The dorsal striatum is further comprised of the caudate (part of the 'associative' striatum) which is equal to the dorsomedial striatum (DMS) in rodents and the putamen (part of the '(sensori) motor' striatum) which corresponds to the dorsolateral striatum (DSL) in rodents (Joel & Weiner, 2000; Parent & Hazrati, 1995; Selemon & Goldman-Rakic, 1985).

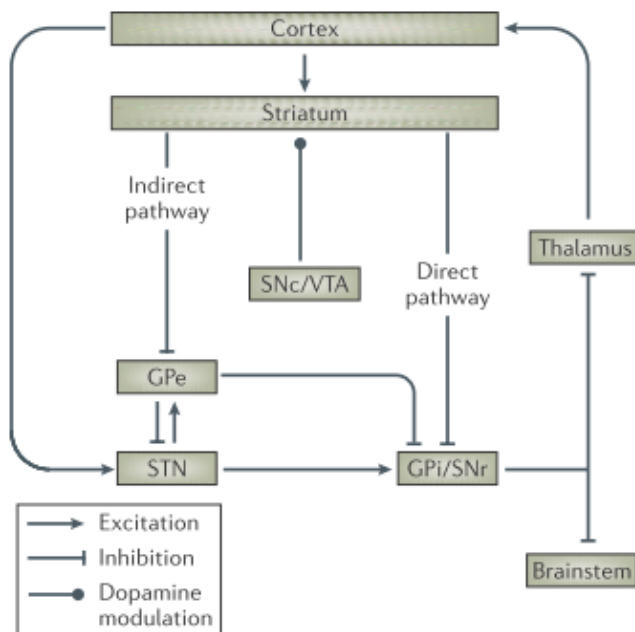


**Figure 3.** Schematic diagram illustrating the main cortico-basal ganglia-thalamocortical circuits within the human brain. This figure shows a pseudo-anatomical arrangement of the (a) motor, (b) associative and (c) limbic pathways (GPI = internal globus pallidus, STN = subthalamic nucleus, GPe = external globus pallidus, CN = caudate nucleus, Put = putamen). For explanations see text. Reprinted with permission from Krack, Hariz, Baunez, Guridi, and Obeso (2010, p. 475).

The striatum plays a central role for motor skill learning and activity-dependent plasticity (Bateup et al., 2010; Dang et al., 2006) and is generally believed to be the key structure for optimal action selection, learning and habit formation (for comprehensive reviews, see Ashby, Turner, & Horvitz, 2010; Penhune & Steele, 2012; Yin & Knowlton, 2006). It receives projections from almost all cortical areas and transmits the processed information to the respective output structures of the basal ganglia (reviewed e.g. in Baydyuk & Xu, 2014; Bolam, Hanley, Booth, & Bevan, 2000).

Approximately 95% of striatal neurons are medium-sized spiny neurons (MSNs) that use  $\gamma$ -amino butyric acid (GABA) as transmitter. Based on their projection sites and protein expression, those MSNs are divided into a direct and an indirect pathway of equally sized neuronal populations. The direct pathway is comprised of striatonigral MSNs that receive projections from excitatory glutamatergic neurons from sensorimotor cortex and thalamus and directly target the basal ganglia GABAergic output nuclei i.e. the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). From there, axons are sent to the motor

nuclei of the thalamus (ventral lateral nucleus pars oralis (VLo))). This results in disinhibition of excitatory thalamocortical projections and subsequent activation of the premotor cortex for action selection or movement facilitation. Neurons within the direct pathway express substance P and the dopamine receptor D1a (DRD1a).



**Figure 4.** A schematic of the main connections of the basal ganglia. Simplified illustration of basal ganglia anatomy based on a primate brain. The direct and indirect pathways from the striatum have net effects of disinhibition and inhibition on the cortex, respectively. STN, subthalamic nucleus; GPe, external globus pallidus; GPI, internal globus pallidus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; VTA, ventral tegmental area. Reprinted with permission from Yin and Knowlton (2006, p. 465).

The indirect pathway striatopallidal MSNs, on the other hand, form inhibitory connections with the GABAergic pallidal neurons, which target glutamatergic neurons in the subthalamic nucleus (STN). STN then projects to the output nuclei GPI and SNr where they build excitatory connections with the GABAergic inhibitory neurons. From there, axons are sent to the ventroposterior thalamic motor nuclei, and—equivalent to the direct pathway—the circuit is completed via glutamatergic projections to the cortical mantle. The outcome of the indirect pathway is assumed to result in an inhibition of thalamocortical projections which would subsequently reduce premotor drive and suppress movement behavior. Relevant

neuropeptides within the indirect pathway are enkephalin (Enk) and the dopamine receptor D2 (DRD2) (reviewed in Kawaguchi, 1997; Kreitzer & Malenka, 2008; Parent & Hazrati, 1995; Yin & Knowlton, 2006) (see Figure 4).

How is the process of motor skill learning and motor habit formation implemented within fronto-striatal circuits? Despite the traditional view of fully segregated loops, primate studies provided evidence for a functional and structural overlap as well as interactions between circuits (Haber, Fudge, & McFarland, 2000; Middleton & Strick, 2002). The dynamic transformation from goal-directed motor behavior to motor habits (see 2.6.1) seems to reflect a switch from the cognitive to the motor ‘loop’, specifically from DMS/associative striatum to DLS/sensorimotor striatum (Yin & Knowlton, 2006). Preliminary research further

points out selective involvement of glutamate for early DMS learning and dopamine for habit DLS learning (Packard & White, 1991; Yin, Knowlton, & Balleine, 2006). Evidence for this 'circuit-switch' hypothesis stems from animal studies that differentiated between short-term/fast/action-outcome (A-O) motor learning and long-term/habit/stimulus-response (S-R) learning. Selective lesion to the DLS, for example, disrupted habit formation in rodents (Yin & Knowlton, 2004; Yin, Ostlund, Knowlton, & Balleine, 2005), and inactivation of the associative striatum via injection with the GABA agonist muscimol disrupted the learning of new sequences in monkeys (Miyachi, Hikosaka, Miyashita, Karadi, & Rand, 1997). Also, firing patterns of active neurons during initial motor learning decreased in the DMS as learning increased, while a small population of neurons in the DLS increased their firing rates as motor training and habit formation continued over training sessions and days (Costa, Cohen, & Nicolelis, 2004; Tang, Pawlak, Prokopenko, & West, 2007; Yin et al., 2009).

In humans, striatal motor learning processes have been investigated via the application of neuroimaging techniques. In a meta-analysis of 70 motor learning fMRI experiments, Hardwick and colleagues concluded that the putamen (part of the striatum) was consistently activated in both serial reaction time tasks (SRTT), which demands the acquisition of novel motor sequences, as well as sensorimotor tasks, where subjects are trained in new kinematics and muscle synergies (Hardwick, Rottschy, Miall, & Eickhoff, 2013). Changes within the striatum with continued practice were shown by Lehericy and colleagues who trained their subjects daily on a motor sequence learning task for 4 weeks and conducted regular fMRI probes. They observed striking functional changes within the striatum between scanning sessions, meaning signal decreases in the rostradorsal associative striatum and signal increases in the caudoventral sensorimotor striatum (Lehericy et al., 2005). Other studies were able to replicate this pattern showing increased activation in the sensorimotor putamen and decreases in the associative striatum parallel to motor skill automatization (Floyer-Lea & Matthews, 2005; Puttemans, Wenderoth, & Swinnen, 2005; Remy, Wenderoth, Lipkens, & Swinnen, 2008; Seidler et al., 2005; Steele & Penhune, 2010).

Both human and rodent studies, furthermore, highlighted the role of the striatum for motor chunking and parsing of action sequences (see 2.6.1). Motor sequence learning in rodents revealed that as learning progressed, specific neuronal firing patterns became evident. Certain cells only fired at the beginning and at the end of one action chunk, but otherwise sustained their activity, while other sets of neurons started to oscillate in harmony with the single action elements of the sequence but were flanked in parallel by cell assemblies that inhibited their activity during the whole motor sequence. Therefore grouping of action sequences during motor skill learning seems to be reflected in distinct and specific activity of nigrostriatal cell recordings (Jin & Costa, 2010; Jin, Tecuapetla, & Costa, 2014). On a

macroscopic level in human neuroimaging, striatal activity has also been consistently related to motor learning as well as motor chunking (Orban et al., 2010; Wymbs et al., 2012).

Glutamate and NMDA-receptor function also seem to play a crucial role in motor skill execution and -learning. As described in detail previously, the striatum receives glutamatergic afferents from cortical regions and the thalamus. As a corollary, deficient glutamate signaling has been related to impairments in MSL. For instance, conditional NMDA-knockout models demonstrated reduced capabilities in action selection, goal-directed learning and adaptation to environmental changes within direct and indirect pathways of the striatum (Lambot et al., 2016). Also, administration of NMDA-antagonists into the dorsal striatum disrupted (early) motor skill acquisition (Lemay-Clermont, Robitaille, Auberson, Bureau, & Cyr, 2011; T. Nakamura et al., 2017).

Taken together, the striatum and its key afferent neurotransmitter glutamate play a highly relevant role in the acquisition and automatization of motor skills. Furthermore, one of the main functions of the striatum is believed to be motor chunking and parsing. Nevertheless, it has to be pointed out that motor chunks are not generally believed to be 'stored' in the striatum, but in line with recent research and systems neuroscience approaches, the involvement of cortical control and multiple neuronal circuits is highly relevant for motor skill learning and habit formation (Graybiel & Grafton, 2015).

### ***2.6.3. Previous findings***

Due to its prominent role for learning and plasticity processes, the impact of brain-derived neurotrophic factor and its respective genetic mutant variant in humans, the *BDNF* val<sup>66</sup>met polymorphism, has also been investigated within the field of motor skill learning. Indeed, BDNF is activity-dependently released in the striatum via anterograde transport from neuronal assemblies located in the cerebral cortex, the substantia nigra pars compacta, the amygdala and the thalamus (reviewed e.g. in Baydyuk & Xu, 2014) and the pivotal role of the striatum for motor learning has been described in detail in the previous section.

The existing literature on effects of this functional genetic variant in motor skill learning and motor plasticity in humans is scarce and heterogeneous. So far, carriers of the Met allele showed reduced motor-evoked potentials and motor map reorganization after transcranial magnetic stimulation (Antal et al., 2010; Cheeran et al., 2008; Kleim et al., 2006). Functional imaging studies further reported lower training-related reductions in activity of relevant motor structures like the pre- and primary motor cortex or supplementary motor area (McHughen et al., 2010).



On a behavioral level, deficits in Met-carriers were also demonstrated. Fritsch and colleagues, for example, trained their subjects on a sequential visual isometric pinch task for five days and measured the increase in motor skill over training days. At the end, carriers of the Met allele showed a significant reduction in skill acquisition compared to Val/Val-carriers (Fritsch et al., 2010). Further studies also reported shortcomings of long-term retention in a visuomotor adaptation task (Joundi et al., 2012) as well as higher error rates in short-term learning and poorer long-term retention in a driving-based motor learning task (McHughen et al., 2010).

However, inconsistent findings and replication failures have also been reported in this domain (Cirillo, Hughes, Ridding, Thomas, & Semmler, 2012; Freundlieb et al., 2012; M. Lee et al., 2013; Li Voti et al., 2011; McHughen & Cramer, 2013; Morin-Moncet, Beaumont, de Beaumont, Lepage, & Theoret, 2014; K. Nakamura et al., 2011; Witte et al., 2012). For example, Freundlieb and colleagues (2012) observed no differences between Val- and Met-carriers in a motor learning serial reaction time task or Li Voti et al. (2011) failed to demonstrate differences in TMS-induced plasticity and respective improvement in kinematics between genotype groups.

Also, paradoxical effects of the Met allele became evident. Indeed, it proved to be advantageous for response inhibition (Beste, Baune, Domschke, Falkenstein, & Konrad, 2010) and in functional MRI Met-carriers demonstrated compensatory activations in specific structures of the motor circuitry i.e. the supplementary motor area (SMA) and cingulate motor area during a simple motor execution task (Cardenas-Morales, Gron, Sim, Stingl, & Kammer, 2014).

Altogether, the portrayal of *BDNF* val<sup>66</sup>met polymorphism influences in motor skill learning remains fragmented. There exists convergent evidence of deficits in long-term motor learning, the role of this variant in short-term motor skill learning, nevertheless, remains largely unexplored or limited by inconsistent findings.

## **2.7. Multimodal magnetic resonance imaging**

Magnetic resonance imaging was first developed in the 1970s, when Lauterbur and colleagues demonstrated the applicability of a static magnetic field and transverse gradient magnetic fields to reconstruct images of H<sub>2</sub>O glass capillaries with respective changes in proton spin frequency signals (Lauterbur, 1989). Subsequently, from the 1980 onwards, MRI was introduced in clinical diagnostics to obtain structural images of specific organs within the human body. In the early 1990s then, the first functional magnetic resonance imaging

studies were conducted. Kwong and colleagues, for example, were among the first to demonstrate the noninvasive BOLD-effect in the human primary visual cortex during a sensory stimulation task (Kwong et al., 1992). This resulted in a new era of non-invasive exploration of the brain in structural and functional detail (Logothetis, 2008). Therefore, new high-resolution imaging techniques advanced progressively in the last decades and evolved into indispensable tools for clinical or scientific applications. Today, magnetic resonance imaging offers diverse modalities from structural MRI (sMRI) (gray or white matter structure) to functional MRI (BOLD-effect) to MR-spectroscopy (metabolite concentration) (Friston, 2009).

Consequently, multimodal integration approaches also advanced exceedingly in the last 10 years. In general, multimodal imaging refers to ‘the collective information offered in multiple imaging modalities’ (Liu et al., 2015, p. 171) and can either be acquired simultaneously or sequentially. So far, multimodal integration has mainly focused on combinations of structure—structure (e.g. sMRI—diffusion tensor imaging (DTI)), structure—function (e.g. sMRI—fMRI) or function—function (e.g. electroencephalography (EEG)—fMRI) (Liu et al., 2015). These approaches have been applied in the development of comprehensive biopsychopathological theories as well as more sensitive diagnostics and specific treatment options in neuropsychiatric disorders such as Alzheimer’s disease (Perrin, Fagan, & Holtzman, 2009) or schizophrenia (Cooper, Barker, Radua, Fusar-Poli, & Lawrie, 2014).

Prior studies on *BDNF* val<sup>66</sup>met polymorphism influences in motor learning, so far, have focused on one single imaging modality, in most cases fMRI or sMRI (see 2.6.3). The extended imaging genetics literature on respective genotype effects in diverse research fields, provides evidence for two modality integration; for instance fMRI and PET on hippocampus function during working memory (Wei et al., 2017) or sMRI and fMRI in resting state connectivity (Wang et al., 2014). To the author’s knowledge, to date, no study exists that has integrated sequential multimodal magnetic resonance imaging genetics effects of the *BDNF* val<sup>66</sup>met polymorphism in three imaging modalities.

## **2.8. Conclusion, open questions and hypotheses**

*BDNF* val<sup>66</sup>met polymorphism and striatal motor skill learning are among the most widely investigated topics in human neuroscience. Nevertheless, studies combining both research fields remain scarce. Indeed, most research so far has focused on the hippocampus as central substrate to investigate dysfunctional brain correlates in Met allele carriers, while the striatum as key structure for fronto-striatal plasticity as well as procedural learning and motor chunking remains largely unexplored. Changes in striatal gray matter volume or

glutamate concentration have not been reported so far and effects on learning related brain function remain fragmented. Therefore, this thesis intended to investigate via a multimodal neuroimaging approach if gray matter abnormalities, aberrant glutamate concentration and differential brain function between Met- and Val-carriers during a motor skill learning task could also be observed in the human motor striatum. Furthermore, deficits in long-term human motor learning have been proven but the effects on short term motor skill learning are rather inconclusive to date and its relationship to aberrant striatal mechanisms remains unexplored.

Therefore, the following hypotheses were drawn to be investigated in the subsequent sections:

1. Does short term motor skill learning, striatal structure via voxel-based morphometry (VBM), neurochemistry i.e. glutamate measured with MR spectroscopy (MRS) and cortico-striatal brain function indexed via functional magnetic resonance imaging (fMRI) in Met allele carriers of the human *BDNF* val<sup>66</sup>met polymorphism deviate from that of Val homozygotes?
2. Do possible behavioral differences in short term motor skill learning between genotype groups of the *BDNF* val<sup>66</sup>met polymorphism relate to striatal structure, neurochemistry or cortico-striatal brain function?
3. Do overall interindividual differences in short term motor skill learning relate to striatal structure, neurochemistry or cortico-striatal brain function?
4. Can paradoxical, beneficial or compensatory effects in Met allele carriers be observed in striatal structure, neurochemistry or cortico-striatal brain function?



### 3. Methods

#### 3.1. Subjects

135 healthy right-handed volunteers (mean age = 26.96 +/- 9.05 years, 80 females, mean education = 15.69 +/- 1.19 years) with parents and grandparents of European origin participated in the study. All participants were recruited from communities in and around the cities of Mannheim, Germany, and provided written informed consent for a protocol approved by the institutional review board of the Medical Faculty Mannheim. Exclusion criteria included contraindications for magnetic resonance imaging (MRI), the presence of a lifetime history of psychiatric, neurological or significant general medical illness, pregnancy, a history of head trauma, and current alcohol or drug abuse. None of the volunteers had a first degree relative with a psychiatric disorder or received psychotropic pharmacological treatment.

#### 3.2. DNA-extraction and genotyping

Genomic DNA was extracted from whole blood according to standard procedures. The val<sup>66</sup>met single-nucleotide polymorphism (rs6265) in the 5' proregion of the *BDNF*-Gene was determined using a TaqMan 5' nuclease assay (Life Technologies, USA). Accuracy was assessed by duplicating 15 % of the original sample.

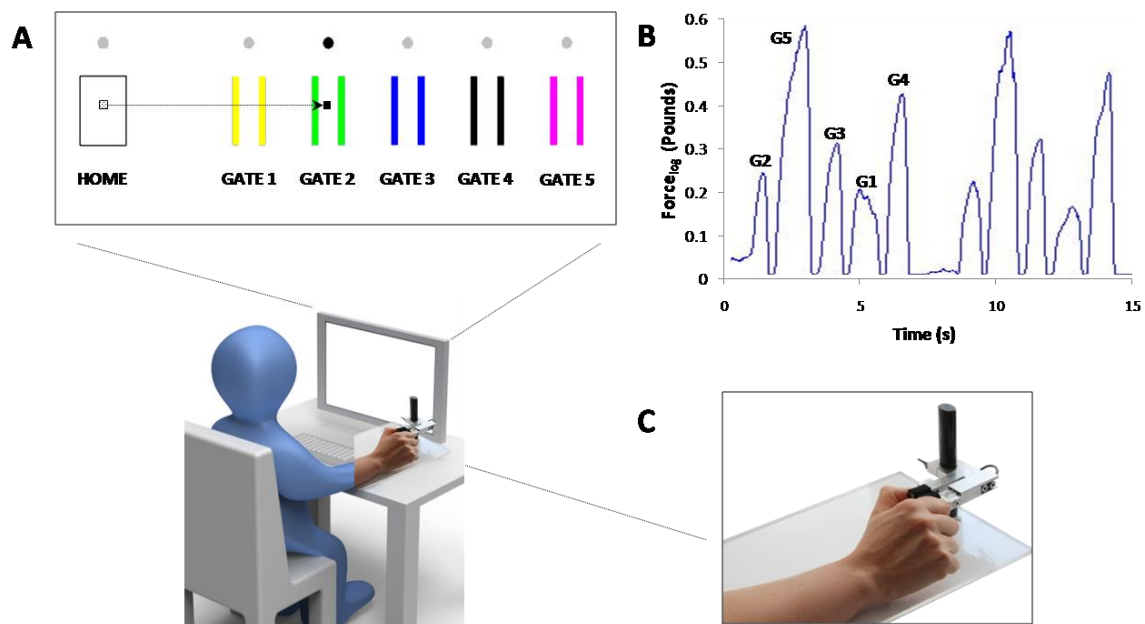
The observed genotype distribution (Val/Val = 81, Val/Met = 52, Met/Met = 2) did not differ significantly from Hardy-Weinberg equilibrium ( $P = 0.08$ ). Deviation from Hardy-Weinberg-Equilibrium was tested using an exact test (<https://ihg.gsf.de/cgi-bin/hw/hwa1.pl>). Due to the low frequency of the *BDNF* Met-allele (0.18) and thus the resulting small number of Met/Met homozygotes, we refrained from independent statistical analysis of this genotype group, but—analogue to previous studies with this variant (Pezawas et al., 2004)—Val/Met and Met/Met individuals were merged in one group for all analyses (Huang & Reichardt, 2001; Lu et al., 2005).

#### 3.3. Procedure

All subjects received one training session on an established sequential visual isometric pinch task (Reis et al., 2009) in the laboratory and shortly after the training (mean delay 32.5 +/- 7.05 min) they were transferred to the magnetic resonance (MR) scanner where they performed an experimentally balanced version of the task and structural MR imaging as well as MR spectroscopy was performed.

### 3.4. Sequential visual isometric pinch task (SVIPT)

Subjects were seated 80 cm in front of a 24-inch monitor while holding a force transducer between the thumb and index finger of their right hand. Application of pinch force to the transducer moved a screen cursor from a home position horizontally to the right towards 5 target gates ( $G_1$ - $G_5$ ), while relaxation resulted in a leftward movement of the cursor back towards the home position. Subjects were instructed to modulate their pinch force so that the cursor navigates as quickly and accurately as possible along the following sequence: home- $G_2$ -home- $G_5$ -home- $G_3$ -home- $G_1$ -home- $G_4$ . To increase SVIPT difficulty, the pinch force was transduced logarithmically into cursor movement. To limit visual search processes, a dot-shaped cue was presented above upcoming correct gates in the sequence. At the beginning, participants underwent approximately 5 trials for familiarization with the set up and five training blocks of 35 trials of the sequence described above (see Figure 5).



**Figure 5.** Set-up of the sequential visual isometric pinch task (SVIPT). **(A)** Motor skill training in the laboratory (see text for details), manikin (©Petr Ciz – Fotolia.com). **(B)** Two exemplary trials of pinch force training data and sequence (home- $G_2$ -home- $G_5$ -home- $G_3$ -home- $G_1$ -home- $G_4$ ). Peaks indicate positions where cursor entered gates, bases indicate cursor at home position ( $G_1$  = gate 1,  $G_2$  = gate 2, etc.). **(C)** Pinch force device. Force was transduced via pinching two metal plates between the thumb and index finger of the dominant hand and transformed logarithmically into cursor movement on the computer screen (see text for details).

For functional MRI, subjects performed an adapted version of the SVIPT consisting of four balanced pseudorandomized conditions with 20 ‘mini-epochs’ (or performance trials) each: trained sequence (‘trained’, defined above), untrained sequences (‘novel’, e.g., Home- $G_3$ -

Home-G<sub>5</sub>-Home-G<sub>1</sub>-Home-G<sub>2</sub>-Home-G<sub>4</sub>), no sequence ('no sequence', Home-G<sub>3</sub>-Home-G<sub>3</sub>-Home-G<sub>3</sub>-Home-G<sub>3</sub>-Home-G<sub>3</sub>) and visual fixation of gates ('look').

Both paradigms were written in C++. In order to control for rapid changing gradient fields in the MRI scanner, the force-signal was sampled at 500 Hz and low pass-filtered at 10 Hz, while for the laboratory version a sampling rate of 200 Hz and a 20 Hz low pass filter was applied.

### 3.5. Behavioral data analysis

Data were analyzed using MATLAB R2011b (MathWorks, Natick, MA). Individual performance for each training block was quantified according to the methods described by Reis and colleagues (2009). Specifically, we assessed trial-wise movement times (from movement onset to stopping at G<sub>4</sub>) and error rates (number of missed gates) to calculate individual skill measures reflecting shifts in the speed-accuracy tradeoff function (SAF) with the following formula:

$$\alpha = \ln \left( \frac{1 - \text{error rate}}{\text{error rate}(\ln(\text{duration})^{5.424})} \right)$$

As discussed in more detail in Reis et al. (2009), this method avoids false interpretations of variations in position along an unchanged SAF as skill increases. Analogue to this study, motor skill learning was defined as differential measure between the skill measure of the first training block and the skill measure of the block with the maximum skill performance.

Statistical analysis was performed with IBM SPSS20 Statistics Software (Chicago, IL, USA) and all effects were tested for significance on a 5% alpha error level. The significance of motor skill learning was tested using a paired *T*-test of the first training block and the block with the maximum skill performance. To assess differences in motor skill learning between genotype groups, a univariate general linear model (GLM) was calculated with *BDNF* genotype group as factor, skill learning as dependent variable and age, sex, education years and baseline performance (skill measure block 1) as covariates to control for possible confounds known to affect learning processes (Luft & Buitrago, 2005).

Subject demographics and baseline variables (see 4.1) were tested for significant differences between genotype groups using a one-way analysis of variance (ANOVA) for continuously

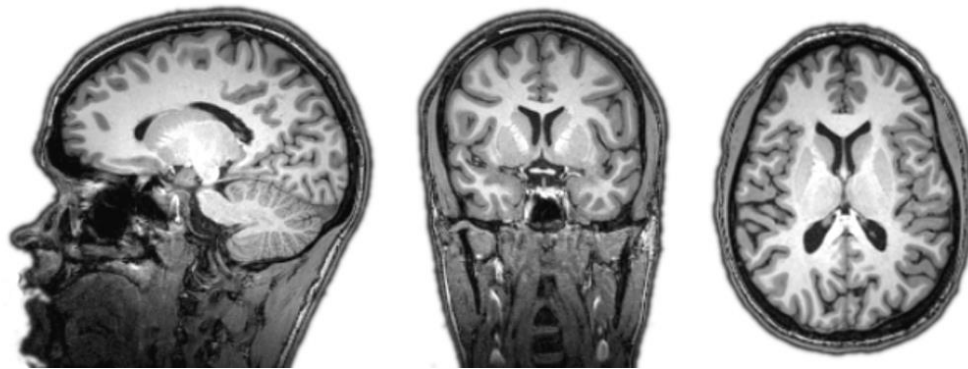
scaled variables or a Chi<sup>2</sup>-Test for categorically scaled variables (sex, playing musical instrument) as implemented in SPSS.

### 3.6. MR acquisition, processing and analysis

All MRI data were acquired on a 3T MRI scanner (Siemens Trio, Erlangen, Germany) with a 32-channel multi-array head-coil.

#### 3.6.1. Structural magnetic resonance imaging (sMRI)

Anatomical T1-weighted images were obtained using a magnetization-prepared rapid-acquired gradient echoes sequence (MPRAGE) with generalized auto-calibrating partially parallel acquisition (GRAPPA) (iPAT = 2) and the following specifications: TR = 2530 ms, TE = 3.8 ms, TI = 1100 ms, flip angle = 7, 1 mm isotropic voxels (see Figure 6).



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**Figure 6.** Structural T1-weighted exemplary image of one subject. Sagittal view (left), coronar view (middle), axial view (right).

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Automated image processing was performed using mainly default parameters of the voxel-based morphometry (VBM) toolbox (Ashburner & Friston, 2000) (VBM8, <http://dbm.neuro.uni.jena.de/vbm8>) implemented in the statistical parametric mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). Briefly, image processing included tissue classification into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and three other non-cerebral tissue classes, normalization to Montreal Neurological Institute (MNI) space with a diffeomorphic image registration algorithm (DARTEL), correction for image intensity non-uniformity, a thorough cleaning up of gray matter partitions, the application of a hidden Markov random field (HMRF) model and spatial adaptive non-local means denoising. The resulting tissue segments were multiplied by the Jacobian determinants of the deformation field to transform the GM density values into volume equivalents and modulated by nonlinear deformations to correct for total brain size. The resulting gray



matter images were smoothed with an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel and submitted to group-level voxel-wise statistical analysis. Statistical analysis was carried out using the 'ANOVA' option and post-hoc *T*-contrasts as implemented in SPM8. *BDNF* genotype (1. Group = Val/Val, 2. Group = Val/Met and Met/Met) was used as grouping factor and age, sex, education years and baseline performance as covariates to control for demographic characteristics known to affect brain structure and genetic variation (Li et al., 2014; Notaras et al., 2015a). For analysis of the interaction effect, we included group-wise behavioral differences in motor skill learning (see 3.5) between genotype groups from the training session as additional variate of interest. Since motor skill learning and performance is a highly lateralized process (Mattay et al., 1998; Solodkin, Hlustik, Noll, & Small, 2001) and only right-handed participants were included in the study we restrained our analyses to a region of interest in the left motor striatum using the motor-striatum mask as described in 3.6.3. Results were displayed at a threshold of  $P < 0.05$  ( $k = 10$ , uncorrected) and family-wise error (FWE)-corrected for multiple comparisons within our region of interest (ROI).

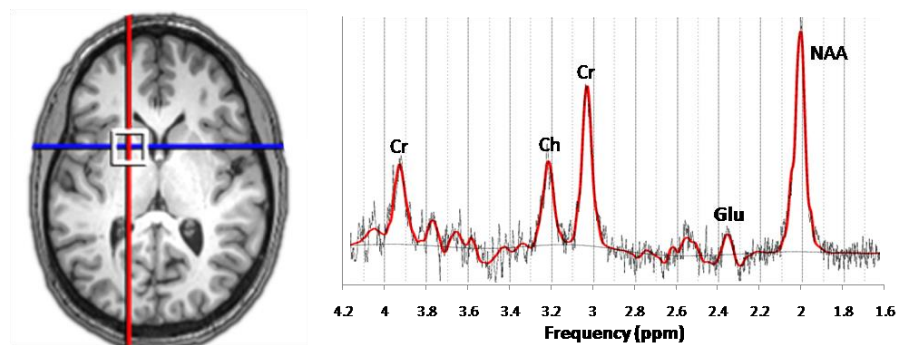
### **3.6.2. Magnetic resonance spectroscopy (MRS)**

Based on the obtained T1-weighted images (see 3.6.1), an 18 mm isotropic single voxel was positioned in the contralateral striatum of the executing right hand. Voxel location covered parts of the caudate head as well as anterior and middle portions of the putamen and globus pallidus. Special care was taken in preventing overlap with the lateral ventricles (see Figure 7). One water suppressed 1 H MR-spectrum was acquired with a point resolved spectroscopy sequence (PRESS) and the following specifications: TE = 80, TR = 3000 ms, NEX = 96 (Schubert, Gallinat, Seifert, & Rinneberg, 2004). In addition, fully relaxed unsuppressed water spectra were acquired with TR = 10 s and six different TEs (varying between 30 and 1500 ms) for eddy current correction and for extrapolating the absolute water signal at TE = 0. About 10 minutes of interactive shimming preceded the MRS measurement.

For MRS Data processing, spectral fitting was performed with LCModel (Provencher, 1993) and GAMMA-simulated basis-sets (Soher, Dale, & Merkle, 2007). Absolute quantification was accomplished for the metabolites glutamate, glutamate + glutamine (Glx), myo-Inositol (ml), N-acetylaspartate (NAA) + N-acetylaspartyl-glutamate (NAAG) (tNAA), phospho-creatine + creatine (tChr) and phosphocholine + glycerol-phosphocholine (Ch) with individual metabolite T2 relaxation time correction, correction for cerebrospinal fluid (CSF) through tissue segmentation of a 3D high resolution image data set (Weber-Fahr et al., 2002) and water scaling with the extrapolated absolute water signal at TE = 0. Data quality was assured

by excluding subjects with standard deviations greater than 20 (Cramér-Rao lower bounds < 20%) from further analysis.

Final sample size for MRS-statistical analysis therefore included 110 subjects (mean age = 25.08 +/- 7.22 years, 67 females, 40 Met allele carriers, mean education = 15.77 +/- 0.97 years). Glutamate concentration was entered into a SPSS general linear model as dependent variable, with BDNF genotype as group factor, motor skill learning as variable of interest and the covariates age, sex, education years, baseline performance and percentage of gray matter volume (GM / GM + WM) within the MRS PRESS-box. For the exploratory multivariate analysis of additional metabolites, the same model was used, with the other previously described metabolites (ml, tNAA, tChr, Ch) as dependent variables and further univariate effects were Bonferroni-corrected for multiple comparisons on a  $P < 0.009$  ( $0.5 / 4$ ) alpha error level.



**Figure 7.** MRS set-up. Axial view of the MRS-voxel PRESS-box in the striatum (right). Exemplary metabolite spectrum after fitting with LCModel (for details see text); Cr = creatin, Ch = cholin, Glu = glutamate, NAA = N-acetylaspartate, ppm = parts per million (left).

### 3.6.3. Functional magnetic resonance imaging (fMRI)

For fMRI, an echo-planar imaging (EPI) sequence with the following specifications was used: TR = 1790 ms, TE = 28 ms, flip angle = 76, 34 slices (1 mm gap), 3 mm isotropic voxel, matrix size: 64 × 64, field of view: 192 × 192, GRAPPA reconstruction (iPAT = 2).

Data preprocessing and analysis followed routines as implemented in the statistical parametric mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) executed in MATLAB 2011R (MathWorks, Natick, MA). All images were realigned to the first image of the scan run, slice time corrected, then normalized to standard stereotactic space (as defined by the Montreal Neurological Institute (MNI)) prior to smoothing with an 8 mm FWHM (full width

at half maximum) Gaussian filter. For each subject, random-effects statistical models of all task conditions were fitted to the processed images by convolving a box-car reference vector with the canonical hemodynamic response function as implemented in SPM8. At the model estimation stage, the data were high-pass filtered with a cutoff of 128 seconds to remove low-frequency drifts, and an autoregressive model of the first order was applied to account for serial correlations. Task-correlated motion effects were minimized by including the estimated movement parameters in the statistical model.

Contrast images between conditions of interest were calculated for each subject and then submitted to second-level general linear model (GLM) group-analysis as implemented in SPM8 using either the 'regression' option for plausibility and confirmation analysis or the 'ANOVA' option to test for differences between genotype groups and interaction effects. Subsequent *T*-contrasts were calculated to specify directionality of the effects.

For whole brain plausibility and confirmation analysis, contrasts between all motor conditions ('trained', 'novel' and 'no sequence') and the look condition were calculated ('move' > 'look'). For motor skill training-related functional changes, the contrasts 'novel sequence' > 'trained sequence' and 'trained sequence' > 'novel sequence' were calculated. Possible confounding factors known to influence motor training-related brain activity (Albouy et al., 2012; Orban et al., 2010) were controlled for by including age, sex, years of education and behavioral performance (skill measure) during scanning as covariates in the statistical regression model. Significance was measured at  $P < 0.05$  whole-brain corrected for family-wise error (FWE) with an extended threshold of  $k = 10$ .

Region of interest (ROI) specific analyses were carried out using masks derived from an independent sample of 25 subjects (mean age = 23.56 +/- 3.64, 15 females, 11 Met allele carriers, mean education = 15.6 +/- 0.79 years) following the same procedure as our study sample described above. One 'motor network' mask was created using the statistical *T*-map of the 'move' > 'look' contrast thresholded at  $P_{FWE} < 0.05$  and one contralateral 'motor striatum' mask was obtained using the statistical *T*-map of the same contrast restricted by anatomical bounds (left putamen mask from the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002)) and thresholded at  $P_{FWE} < 0.05$ . The latter mask was used for hypotheses driven effects on the striatum in structural and functional analyses, while the former mask was used as search region for exploratory effects of *BDNF* val<sup>66</sup>met genotype and motor skill learning on cortico-striatal motor network function. *P*-values were family-wise error (FWE) corrected for multiple comparisons within the respective region of interest.

To identify possible effects of *BDNF* val<sup>66</sup>met polymorphism, motor skill learning and/or their interaction on the motor striatum, we restricted our analysis to the contrasts 'move' > 'look'

and 'trained' > 'look' as dependent variables and estimated parameters within our region of interest using the second-level SPM8 'ANOVA'-option which included genotype (1. Group = Val/Val, 2. Group = Val/Met and Met/Met), motor skill learning and their interaction as well as the covariates described above (age, sex, education years, behavioral performance during scanning).

### **3.7. Replication sample**

Since effects of *BDNF* val<sup>66</sup>met polymorphism on striatal gray matter volume have not been reported so far, we intended to validate our results in an independent sample derived from a German multi-center imaging genetics consortium ("Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia", MoodS). Here we analyzed data from 286 healthy right-handed volunteers (mean age = 33.39 +/- 9.8 years, 154 females, mean education = 15.4 +/- 2.4 years) who were recruited from communities in and around Mannheim (n = 83), Berlin (n = 75) and Bonn (n = 128) using the same exclusion criteria as described above for our study sample.

Data acquisition, processing and analysis procedures were equivalent to those of our study sample with the exception of MR sequence specifications. T1-weighted images (MPRAGE) were acquired using a 12-channel multi-array head-coil with the following parameters: TR = 1570 ms, TE = 2.75 ms, TI = 800 ms, flip angle = 15°, 1 mm isotropic voxels. DNA extraction was performed using the same procedure as described in 3.2.. Genotype distribution (Val/Val = 185, Val/Met = 92 and Met/Met = 9) did not differ from Hardy-Weinberg equilibrium ( $P = 0.80$ ). Since our data contained samples from three different centers, we included an additional 'site' covariate in our statistical model.

## 4. Results

### 4.1. Sample demographics

Subject demographics, baseline performance as well as relevant variables known to influence motor skill learning did not differ significantly between genotype groups in any of the samples ( $P > 0.11$ ) (see Table 1 and Table 2).

Table 1. Subject demographics and baseline variables of study sample

	<i>sMRI/fMRI (n=135)</i>			<i>MRS (n=110)</i>		
	<i>Val/Val</i>	<i>Met</i>	<i>P</i>	<i>Val/Val</i>	<i>Met</i>	<i>P</i>
N	81	54		70	40	
Age (years)	26.2 ± 7.6	28.1 ± 10.8	0.24	24.9 ± 6.6	25.4 ± 8.3	0.75
Sex (N females)	50	30	0.48	45	22	0.34
Education (years)	15.6 ± 1.2	15.8 ± 1.2	0.46	15.7 ± 0.9	15.8 ± 1.1	0.55
Handedness (EHI)	96.2 ± 12.1	97.3 ± 10.7	0.56	97.0 ± 7.77	96.4 ± 12.3	0.75
Playing musical instrument (%)	65.4	64.8	0.94	62.9	67.5	0.63
Pre-training tiredness of right hand	9.7 ± 15.2	8.76 ± 13.3	0.71	9.8 ± 15.9	7.7 ± 11.5	0.46
Baseline performance (skill measure block 1)	-3.2 ± 0.55	-3.1 ± 0.52	0.44	-3.2 ± 0.57	-3.1 ± 0.53	0.51
Whole brain gray matter volume (mm <sup>3</sup> )	703.5 ± 66	699.8 ± 65	0.75	706.1 ± 67	711.1 ± 8.3	0.71

**Note:** Values are mean ± standard deviation. Handedness was derived from Edinburgh Handedness Questionnaire (EHI, Oldfield, 1971), scores from -100 to -40 indicate lefthanders, from -40 to 40 ambidextrous subjects and from 40 to 100 right-handers. Pre-training tiredness of the right hand was measured via a visual analogue-scale with values ranging from 0 ('not at all') to 100 ('maximal').

Table 2. Subject demographics of replication sample

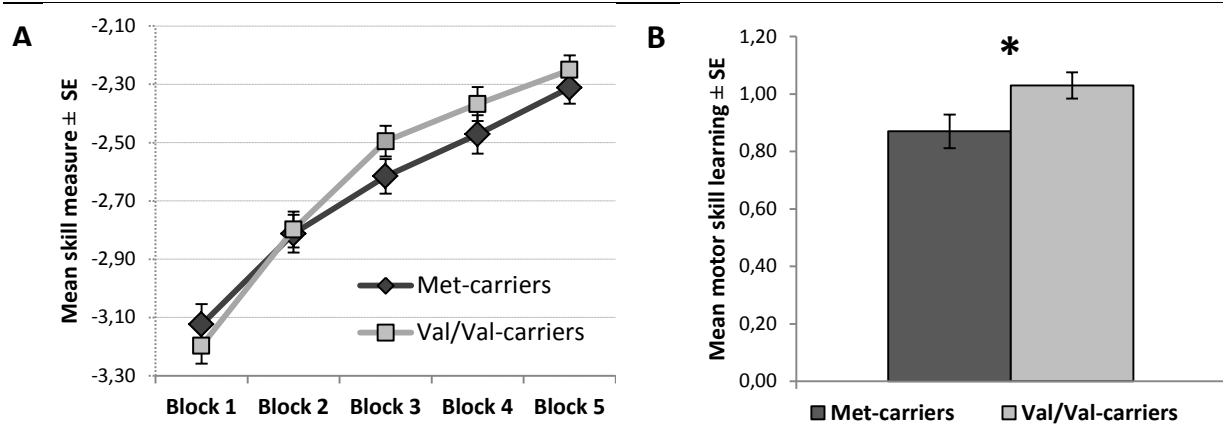
	<i>sMRI (n=286)</i>		
	<i>Val/Val</i>	<i>Met</i>	<i>P</i>
N	185	101	
Age (years)	32.71 ± 9.5	34.6 ± 10.4	0.11
Sex (N females)	98	56	0.69
Education (years)	15.4 ± 2.4	15.6 ± 2.4	0.51

**Note:** Values are mean ± standard deviation.

### 4.3. *BDNF* genotype and motor skill learning

Comparison between the skill measure of the first ( $M = -3.17$ ,  $SE = 0.06$ ) and the maximum performance block ( $M = -2.20$ ,  $SE = 0.04$ ) revealed a highly significant difference ( $T_{(134)} = -22.64$ ,  $P < 0.001$ ); mean number of the maximum performance block was 4.46 ( $SE = 0.07$ ).

Furthermore, we detected a significant main effect of genotype on motor skill learning ( $F_{(5,129)} = 4.01$ ,  $P = 0.047$ ) with decreased motor skill learning in Met allele carriers ( $M = 0.87$ ,  $SE = 0.06$ ) compared to Val homozygotes ( $M = 1.03$ ,  $SE = 0.05$ ) (see Figure 8).

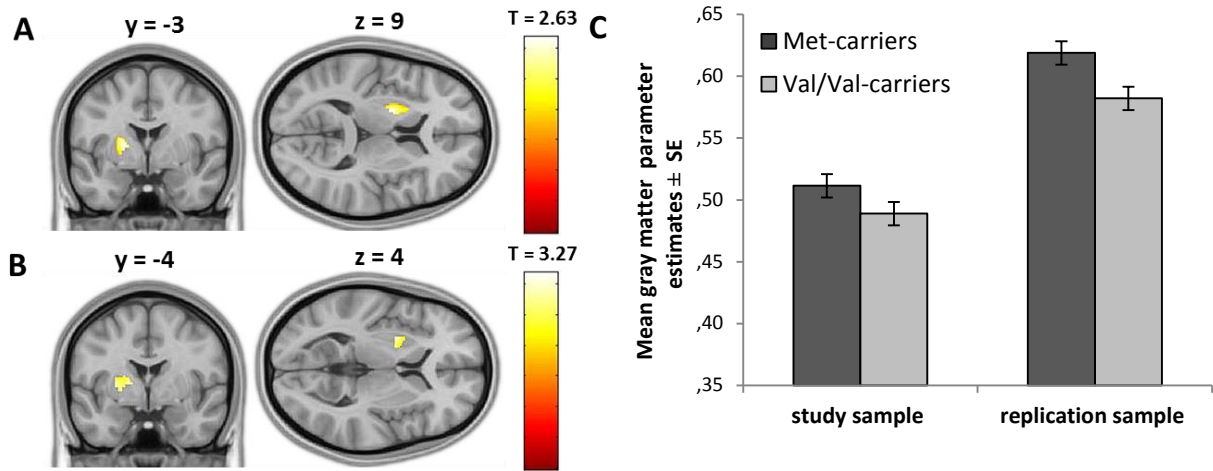


**Figure 8.** *BDNF* genotype and motor skill learning. **(A)** Mean increase in skill measure ( $SE =$  standard error) of the whole training period (block 1 to block 5) for each genotype group. **(B)** Differences in motor skill learning between genotype groups. \* $P < 0.05$ .

### 4.2. *BDNF* genotype, striatal gray matter volume and motor skill learning

SPM analysis revealed a trend towards a significant main effect of genotype on gray matter volume in the striatum, interestingly indicating greater gray matter volume for Met allele carriers ( $M = 0.51$ ,  $SE = 0.08$ ) than for Val homozygotes ( $M = 0.49$ ,  $SE = 0.08$ ; Peak-voxel MNI  $[-20, -3, 9]$ ,  $T_{(126)} = 2.63$ ,  $P_{(FWE)} = 0.073$ , ROI-corrected). Analysis of the replication sample (see 3.7) revealed a significant main effect of *BDNF* genotype on striatal gray matter volume, also showing greater values for Met-carriers ( $M = 0.62$ ,  $SE = 0.09$ ) than for Val/Val-carriers ( $M = 0.58$ ,  $SE = 0.05$ ; Peak voxel MNI  $[-14, 9, -11]$ ,  $T_{(279)} = 3.27$ ,  $P_{(FWE)} = 0.039$ , ROI-corrected), thereby confirming this result (see Figure 9).

Further analysis of our study sample failed to detect any significant voxels or clusters within our search volume for the interaction effect of genotype x motor skill learning or the main effect of motor skill learning ( $T_{(126)} < 1.66$ ,  $P > 0.05$ , ROI-corrected).



**Figure 9.** Main effect of *BDNF* genotype on gray matter volume in the contralateral striatum. **(A)** Motor skill learning study sample ( $n = 135$ ) and **(B)** replication sample ( $n = 286$ ), coronar section (left) and axial section (right). Effects are masked and  $P$ -values FWE ROI-corrected within a functional mask of the left motor striatum (for further details see 3.6.3). Coordinates are indicated in MNI-space. Colorbar indicates  $T$ -values ranging from 0 to 2.63 respective 3.27. **(C)** Mean gray matter parameter estimates (SE = standars error) of exported peak voxels for each sample and genotype group.

#### 4.3. *BDNF* genotype, striatal glutamate concentration and motor skill learning

Analysis of *BDNF* genotype and motor skill learning effects on glutamate concentration in the striatum revealed no significant main effect of genotype ( $F_{(8,101)} = 0.088$ ,  $P = 0.767$ ), motor skill learning ( $F_{(8,101)} = 0.391$ ,  $P = 0.533$ ) nor a significant interaction effect ( $F_{(8,101)} = 0.003$ ,  $P = 0.955$ ).

Exploratory multivariate analysis with the other four measured metabolites (myo-Inositol (mi), N-acetylaspartate + N-acetylaspartyl-glutamate (tNAA), phosphocreatine + creatine (tChr) and phosphocholine + glycerol-phosphocholine (Ch) (see 3.6.2)) as dependent variables also did not reveal any significant multivariate effect of genotype ( $F_{(8,101)} = 0.360$ ,  $P = 0.901$ ), motor skill learning ( $F_{(8,101)} = 0.757$ ,  $P = 0.606$ ) or their interaction ( $F_{(8,101)} = 0.491$ ,  $P = 0.814$ ). Univariate tests further showed no significant effect after adjusting for multiple testing by means of Bonferroni correction ( $P > 0.042$  for tCr).

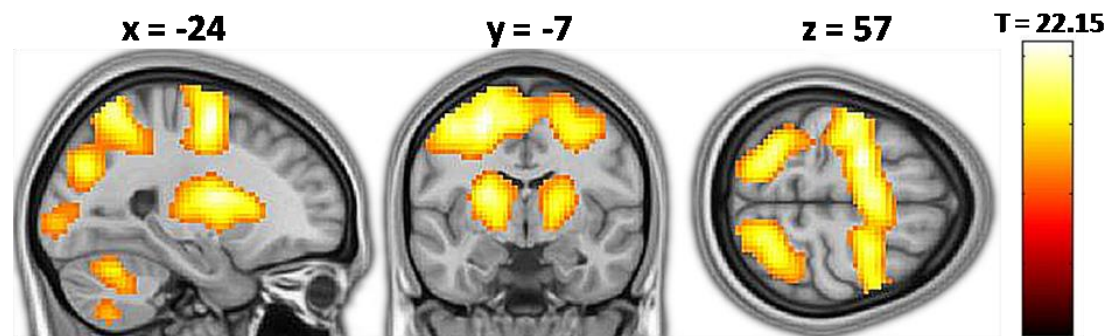
#### 4.4. *BDNF* genotype, cortico-striatal brain function and motor skill learning

##### 4.4.1. Plausibility and confirmation analysis

Plausibility analysis of contrasting all motor conditions with the look condition ('move' > 'look') revealed a broad functional motor network including amongst other regions the left primary motor cortex (M1), bilateral premotor cortex (PMC), supplementary motor

area (SMA), thalamus, putamen, insula, middle temporal gyrus (tertiary visual cortex (V5)), superior and inferior parietal cortex, middle occipital gyrus, cerebellum and right dorsolateral prefrontal cortex (DLPFC) (see Figure 10).

Due to significant functional overlap between brain regions, anatomical sub clusters were not detected by the SPM algorithm. Region specific peak voxels are indicated in Table 3.



**Figure 10.** Contrast ‘move’ > ‘look’. Sagittal section (left), coronar section (middle), axial section (right), coordinates are indicated in MNI-space.  $P < 0.05$ , whole brain FWE-corrected; covariates: age, sex, education years and behavioral performance during scanning. Color bar indicates  $T$ -values ranging from 0 to 22.15. Degrees of freedom (df) = 130.

**Table 3. Regional brain activations in the task-specific ‘motor-network’**

Hemisphere	Anatomical location AAL/conventional term	Cluster size	T-value	MNI coordinates		
				x	y	z
<b>‘Move’ &gt; ‘Look’</b>						
<b>Cluster 1</b>		<b>22720</b>				
Left	Superior frontal gyrus/dPMC		22.15	-24	-7	57
Left	Middle occipital gyrus/V5		21.32	-45	-73	3
Left	Precentral gyrus/M1		21.30	-42	-13	54
Right	Cerebellum (lobule VI)		20.74	12	-70	-21
	Cerebellar vermis (lobule VI)		20.69	6	-70	-18
	Cerebellar vermis (lobule VIIIa)		20.51	6	-73	-39
Left	Putamen		20.17	-24	-1	15
Left	Superior parietal lobule		20.07	-21	-61	63
Right	Middle temporal gyrus/V5		19.81	48	-64	3
Left	Supplementary motor area		19.56	-3	-1	57
Right	Middle temporal gyrus		19.31	45	-70	0
Left	Superior frontal gyrus/dPMC		19.26	-12	-4	60
Left	Cerebellum (lobule VI)		19.21	-9	-73	-21
Left	Thalamus		19.07	-15	-13	12
Left	Superior parietal lobule		18.89	-27	-55	57
Left	Precentral gyrus/vPMC		18.65	-51	2	42
Right	Inferior parietal cortex		18.22	30	-52	54

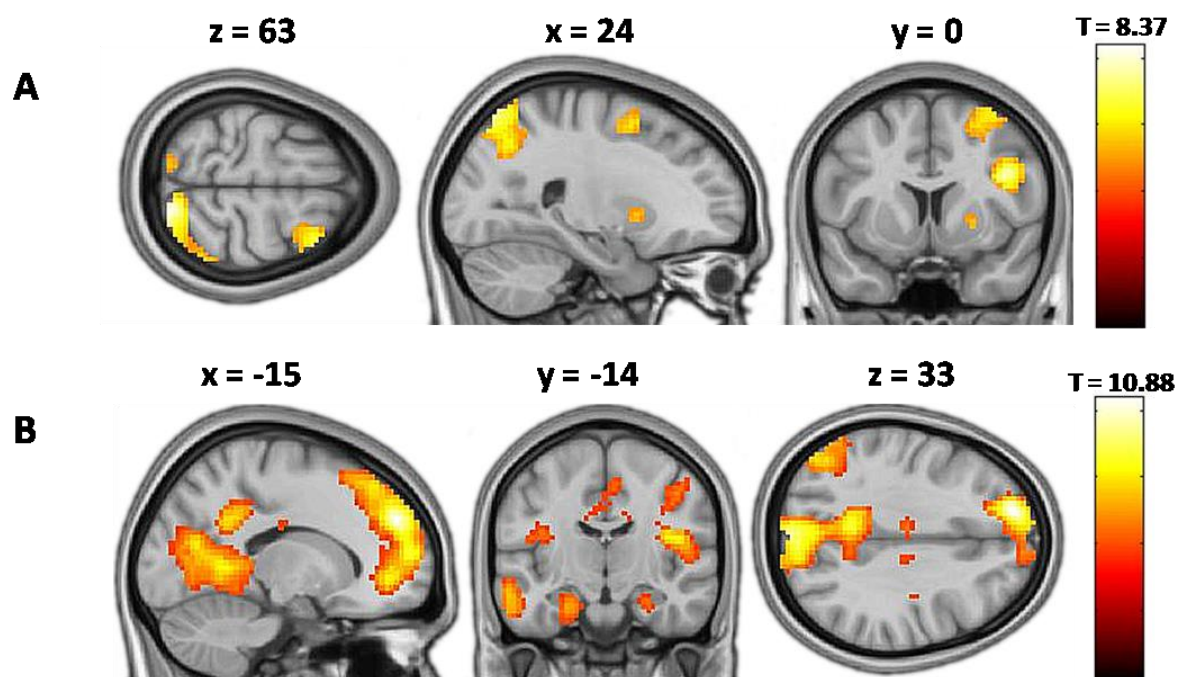


## Results

Right	Middle frontal gyrus/PMC	18.14	30	-4	54
Right	Putamen	17.73	27	2	12
Right	Superior parietal cortex	17.70	21	-61	57
Left	Insula	17.45	-27	11	9
Left	Superior occipital gyrus	17.22	-24	-79	30
Right	Middle occipital gyrus	17.10	30	-79	30
Right	Thalamus	16.61	18	-7	9
<b>Cluster 2</b>		<b>63</b>			
Right	Middle frontal gyrus/DLPFC	6.08	42	38	24

**Note:** Anatomical location was derived using the SPM8 anatomy toolbox (version 1.8.) (Eickhoff et al., 2005). dPMC = dorsal premotor cortex, vPMC = ventral premotor cortex, V5 = tertiary visual cortex, M1 = primary motor cortex. Conventional terms are used as indicated in the motor skill learning literature for better identification and recognition purpose. For additional specifications see 3.6.3.  $P < 0.05$ , FWE-corrected,  $T_{(130)} > 4.70$ .

Confirmation analysis of training-related brain activation (contrast 'novel' > 'trained') revealed, amongst others, attention-related and prefrontal activations with greater involvement of the right hemisphere including the middle occipital gyrus, superior and inferior parietal cortex, superior and inferior frontal gyrus and the putamen.



**Figure 11.** Regional brain activations related to motor skill learning. **(A)** Contrast 'novel' > 'trained' ( $P < 0.05$ , whole brain FWE-corrected). Axial section (left), sagittal section (middle), coronar section (right), coordinates are indicated in MNI-space. Color bar indicates  $T$ -values ranging from 0 to 8.37. Degrees of freedom (df) = 130. **(B)** Contrast 'trained' > 'novel' ( $P < 0.05$ , whole brain FWE-corrected). Sagittal section (left), coronar section (middle), axial section (right), coordinates are indicated in MNI-space. Color bar indicates  $T$ -values ranging from 0 to 10.88. Degrees of freedom (df) = 130.

The opposite contrast 'trained' > 'novel' on the other hand showed a prominent default mode network including, amongst others, the superior frontal and -medial gyrus, cuneus,

posterior cingulate cortex as well as activations in the ipsilateral motor cortex and memory related regions (middle temporal gyrus and (para)hippocampus). Specific brain regions and peak voxels for both contrasts are indicated in Figure 11 and Table 4.

**Table 4. Regional brain activations related to motor skill learning**

<i>Hemisphere</i>	<i>Anatomical location AAL/conventional term</i>	<i>Cluster size</i>	<i>T-value</i>	<i>MNI coordinates</i>		
				<i>x</i>	<i>y</i>	<i>z</i>
<b>'Novel' &gt; 'Trained'</b>						
<b>Cluster 1</b>		<b>880</b>				
Right	Middle occipital gyrus		8.37	33	-70	30
Right	Superior parietal lobule		7.96	15	-70	63
Right	Superior parietal lobule		7.14	30	-70	48
Right	Supramarginal gyrus		6.65	42	-37	45
Right	Inferior parietal lobule		6.44	36	-46	45
Right	Inferior parietal lobule		6.29	33	-52	48
Right	Superior parietal lobule		5.56	45	-49	60
Right	Superior parietal lobule		5.47	42	-56	68
<b>Cluster 2 – 8</b>						
Right	Inferior frontal gyrus/FEF	201	6.08	42	38	24
Right	Superior frontal gyrus/PMC	159	6.22	27	2	54
Right	Inferior temporal gyrus	88	6.55	54	-55	-12
Left	Superior parietal lobule	46	5.50	-15	-70	54
Left	Inferior parietal lobule	16	5.24	-36	-43	42
Left	Middle occipital gyrus	15	5.78	-27	-73	30
Right	Putamen	13	5.39	24	8	0
<b>'Trained &gt; Novel'</b>						
<b>Cluster 1</b>		<b>3876</b>				
	Cuneus		9.90	3	-85	27
	Cuneus		9.68	-6	-91	21
	Cuneus		9.65	0	-88	30
	Cuneus		9.46	-6	-85	27
Left	Posterior cingulate cortex		8.62	-6	-52	33
Right	Lingual gyrus		8.62	-6	-52	33
Left	Lingual gyrus		8.40	-9	-73	-3
Left	Lingual gyrus		8.21	-12	-58	3
Left	Calcarine gyrus		7.83	-6	-61	9
Left	Calcarine gyrus		7.64	-15	-70	15
Right	Precentral gyrus/M1		7.58	24	-28	63
<b>Cluster 2</b>		<b>2135</b>				
Left	Superior frontal gyrus		10.88	-15	50	33
Left	Middle orbital gyrus		10.19	-9	47	-9
Left	Superior medial gyrus		9.47	-9	56	15
Left	Superior medial gyrus		9.33	-9	56	9
Left	Supplementary motor area		8.19	-9	23	57
Left	Superior frontal gyrus		8.08	-12	38	51
Left	Superior frontal gyrus		7.11	-21	29	48
Right	Middle orbital gyrus		6.39	9	38	-9
Left	Olfactory cortex		5.50	-6	20	-9
<b>Cluster 3</b>		<b>393</b>				

## Results

Right	Rolandic operculum		8.59	45	-16	18
Right	Superior temporal gyrus		6.40	63	-25	6
<b>Cluster 4</b>		<b>330</b>				
Left	Angular gyrus		8.24	-48	-64	27
Left	Angular gyrus		7.81	-51	-58	27
<b>Cluster 5</b>		<b>285</b>				
Left	Middle temporal gyrus		8.40	-60	-19	-15
Left	Inferior temporal gyrus		6.81	-54	-4	-36
<b>Cluster 6</b>		<b>150</b>				
Left	Rolandic operculum		6.49	-39	-22	21
Left	Supramarginal gyrus		6.04	-54	-25	15
Left	Superior temporal gyrus		5.85	-51	-22	12
Left	Heschl's gyrus		4.81	-39	-28	9
<b>Cluster 7</b>		<b>147</b>				
Left	Inferior frontal gyrus		6.68	-33	29	-18
Left	Inferior frontal gyrus		6.26	-51	29	3
<b>Cluster 8</b>		<b>92</b>				
Right	Cerebellum		7.46	27	-88	-33
<b>Cluster 9</b>		<b>86</b>				
Left	Postcentral gyrus		5.78	-18	-37	69
Left	Postcentral gyrus		5.50	-15	-34	72
Left	Postcentral gyrus		5.45	-18	-31	69
<b>Cluster 10-14</b>						
Left	Parahippocampal gyrus	85	6.99	-24	-16	-24
Right	Superior temporal gyrus	31	5.72	60	-4	-12
Right	Hippocampus	30	5.54	27	-13	-21
Right	Anterior cingulate cortex	16	5.57	15	38	6

**Note:** Anatomical location was derived using the SPM8 anatomy toolbox (version 1.8.) (Eickhoff et al., 2005). FEF = frontal eye field, PMC = premotor cortex, M1 = primary motor cortex. Conventional terms are used as indicated in the motor skill learning literature for better identification and recognition purpose. For additional specifications see 3.6.3.  $P < 0.05$ , FWE-corrected,  $T_{(130)} > 4.76$

Confirmation analysis of behavioral parameters during fMRI acquisition revealed a significantly better performance in the 'trained' ( $M = -2.98$ ,  $SE = 0.036$ ) than in the 'novel' condition ( $M = -3.67$ ,  $SE = 0.040$ ;  $T_{(134)} = 25.50$ ,  $P < 0.001$ ).

### 4.4.2. BDNF genotype, cortico-striatal function and motor skill learning

SPM analysis showed no significant main effect of genotype, motor skill learning and/or their interaction within our search region of the motor striatum ( $T_{(127)} < 2.23$ ,  $P > 0.134$ , FWE ROI-corrected).

Further exploratory analysis on activity of the whole motor-network (contrast 'move' > 'look') yielded no significant main effect of genotype, motor skill learning and/or the interaction genotype x motor skill learning within our search region of the motor network ( $T_{(127)} < 3.37$ ,  $P > 0.313$ , FWE ROI-corrected).

For additional investigation of genotype impact and/or motor skill learning on specific training-related brain activation within the motor network, the 'train' > 'look' contrast was analyzed which yielded a broad fronto-striatal motor network as well as specific training-related modulations (see 8). This subsequent analysis demonstrated no effect of genotype in the striatum ( $T_{(127)} < 1.66$ ,  $P = 1$ , FWE ROI-corrected) or the whole motor network ( $T_{(127)} < 3.76$ ,  $P > 0.113$ , FWE ROI-corrected), but a trend of motor skill learning in the motor striatum ( $T_{(127)} = 2.60$ ,  $P = 0.065$ , FWE ROI-corrected), i.e. subjects with lower motor skill learning tended to have higher striatal activation during motor execution of the trained sequence. No further significant effects or trends within other nodes of the motor network were observed for the main effect of motor skill learning or the respective interaction with genotype ( $T_{(127)} < 3.41$ ,  $P > 0.288$ , FWE ROI-corrected).

## 5. Discussion

This study examined potential effects of the *BDNF* val<sup>66</sup>met genotype on short-term motor skill learning, striatal gray matter volume, striatal glutamate concentration and cortico-striatal brain function in healthy humans using multimodal neuroimaging methods and a well-established sequential visual isometric pinch task (Fritsch et al., 2010; Schambra et al., 2011; Zimerman et al., 2013).

*BDNF* val<sup>66</sup>met polymorphism causes aberrant activity-dependent intracellular trafficking, packaging and secretion of the BDNF neurotrophin (Chen et al., 2004; Egan et al., 2003; Ozan et al., 2010) with serious implications for learning and plasticity processes like impairments in episodic memory and hippocampal structural integrity (Hariri et al., 2003; Pezawas et al., 2004). Based on the prior literature, effects were expected in the motor striatum of the dominant hemisphere since motor functioning is strongly lateralized, short-term motor skill learning is highly dependent on striatal function (Hardwick et al., 2013), is altered in *BDNF* Met allele carriers (Fritsch et al., 2010) and this genotype group has been shown to rely more strongly on striatal behavioral strategies (Banner et al., 2011). Furthermore, special focus lay on paradoxical effects or compensatory strategies in Met allele carrier, since respective reports gained momentum in recent years (see 2.5). A multimodal analysis approach on striatal gray matter structure, glutamate concentration and brain function was chosen to yield a more comprehensive and integrative view on the respective physiological brain processes (Liu et al., 2015). Apart from genotype group, interindividual differences in short-term motor skill leaning were also included as independent variable in our statistical models to test for interaction effects with the *BDNF* val<sup>66</sup>met polymorphism, as well as explorative main effects. Since the striatum is only one node within a widely disturbed fronto-striatal network (Alexander et al., 1986), functional exploratory MRI analysis further included investigation of genotype effects in a larger cortico-striatal motor-network.

### 5.1. Effects of *BDNF* val<sup>66</sup>met polymorphism on motor skill learning and striatal gray matter volume

The first objective was to identify possible behavioral impairments in short term motor skill learning. Consistent with the prior literature, a significant reduction in motor skill learning in Met allele carriers was detected (Fritsch et al., 2010; McHughen et al., 2010), i.e. subjects of this variant showed a similar baseline performance in block 1 as homozygous Val allele carriers, but failed to improve their performance as effectively. This is in line with our molecular understanding of the polymorphism affecting short-term plasticity processes in

humans (Cheeran et al., 2008; Egan et al., 2003; Kleim et al., 2006) and adds new convergent evidence to the existing literature.

In a next step, the underlying macroscopic neuronal mechanisms behind those impairments i.e. possible alterations in striatal gray matter structure were specified. While the precise neurobiological underpinnings of VBM effects remain to be clarified, synaptogenesis and changes in neuronal morphology are believed to play a key role (Zatorre, Fields, & Johansen-Berg, 2012), and at least one rodent study provides direct evidence for a relationship between training-induced changes in MRI-based shape estimates and neuronal plasticity processes in the striatum (Lerch et al., 2011). In humans, gray matter increases in specific brain regions like the hippocampus, the heschl's gyrus or V5 have been related to experience-dependent adaptations like spatial navigation (Maguire et al., 2000), musical practice (Schneider et al., 2002) or mastery of juggling (Draganski et al., 2004).

This study detected paradoxically higher striatal gray matter volumes in carriers of the *BDNF* Met allele. While the causal interpretation of the data is limited by the cross-sectional design, this finding may point towards a pre-existing difference in the user-dependent plasticity of the striatum in this genotype group. Importantly, we were able to confirm the significant trend of a genotype main effect on striatal GM volume in a large independent sample, which strengthens the confidence in the study outcome. Nonetheless, since impairments in neural plasticity processes such as synapse formation may, in total, plausibly contribute to decreases in gray matter volume at the system level, the result of our study appears implausible at first. However, in prior observations, gray matter deficits in this variant were mainly observed in the hippocampus (e.g. Pezawas et al., 2004) and other paradoxical and beneficial effects have previously been described such as increased white matter integrity (Chiang et al., 2011; Tost et al., 2013) or protective effects against psychiatric disorders (e.g. Geller et al., 2004). While the hippocampus is mainly involved in the consolidation of declarative memory (Alvarez & Squire, 1994; Frankland & Bontempi, 2005; Nadel & Moscovitch, 1997), the striatum is a key structure for procedural learning and memory processes (e.g. Yin & Knowlton, 2006). Therefore, the increased gray matter volumes seen in Met allele carriers may relate to a compensatory mechanism influencing the hippocampus plasticity-impaired individuals towards a preferred use of striatal circuits.

Nevertheless, it should be noted that *BDNF* or *TrkB* knock-out rodent models did demonstrate a marked decrease of spine complexity and density in the striatum, while the growth of the hippocampus seemed largely unaffected by lack of BDNF during postnatal development (Baquet, Gorski, & Jones, 2004; Baydyuk et al., 2011; Rauskolb et al., 2010). However, a direct translation of this principle from rodents to humans might not be

adequate, especially since *BDNF* knock-out means total deletion of BDNF while the *BDNF* val<sup>66</sup>met polymorphism distinctly alters BDNF secretion. Also, translation from rodents to human principles is rather challenging. Recent research even proposed that substantial adult striatal neurogenesis might only be evident in humans and possibly non-human primates while absent in rodents (Bergmann et al., 2012; Ernst et al., 2014; Ernst & Frisen, 2015). Given that rodents are the animals commonly used to study molecular striatal neuroplasticity, this opens a new challenge and calls for cautious interpretations when integrating respective results from both research fields.

Interestingly, the main effect of motor skill learning and the interaction between motor skill learning and striatal gray matter volume failed to show significant results. Given the interpretation of a compensatory mechanism, one would assume that higher striatal gray matter volumes would relate to better motor skill learning in Met-carriers while this relationship might not be evident in Val/Val-carriers. Nevertheless, the gene-behavior interaction might lack the statistical power required to reveal a significant effect (Aschard, 2016). Also, direct relations between striatal gray matter structure and (motor) learning have not been reported so far in any human population. Even in Huntington's disease, which is characterized particularly by striatal atrophy, extrapyramidal motor symptoms occur as late as several years after the first observed reductions in striatal volume (Aylward et al., 2012). Therefore, one has to assume that this relationship might not be as linear and straight-forward as it seems and that striatal morphology might not be the best short-term or cross-sectional predictor for individual differences in motor skill learning, as intuitive as this might be by its anatomical location and circuit properties (Kreitzer & Malenka, 2008). Indeed, despite the growing number of studies on learning and plasticity-related morphological changes in humans, cross-sectional correlations between motor learning and gray matter volume in humans so far have only been reported for the lobules HIV and IV of the cerebellum (Steele et al., 2012), and longitudinal studies of structural changes with any kind of motor learning reported increases in gray matter volume in V5 for juggling (Draganski et al., 2004) or in frontal and parietal areas for whole body balancing (Taubert et al., 2010). One study detected gray matter increases in the striatum with left-hand writing practice, but refrained from a confident interpretation since those results proved non-significant in comparison to the control group (Wenger et al., 2016).

Critically, the exact interpretation of the genotype effect on striatal gray matter volume remains elusive. Does the increased volume in Met-carriers only stem from overuse of striatal as compared to hippocampal circuits? Why then do we still observe deficits in motor skill learning in Met allele carriers? And does 'more' striatal gray matter volume necessarily

confer a benefit or could it not also be a sign of an implicit deficit that—even if not directly— influences motor skill learning?

Last but not least, we also need to scrutinize our methodological approach. Goto and colleagues (2013), for example, provided evidence that basal ganglia gray matter probabilities in VBM analysis might be an index of greater iron densities within the respective tissues rather than of increased volume of neuronal populations and might further lead to regional missegmentations of the VBM algorithm. Therefore, in our analyses, greater gray matter volumes in Met-carriers might also indicate increased striatal iron levels in the respective genotype group.

Taken together, this study suggests that the volumetric finding of increased gray matter volume in the striatum of Met allele carriers reflects a compensatory mechanism for respective hippocampal deficits, although methodological confounds cannot fully be out ruled. Another challenge for this hypothesis is that, despite the observed deficits in short-term motor skill learning in Met allele carriers, no evidence for a direct relationship between striatal volume and motor skill learning in either of the two genotype groups was provided. This is puzzling, but fits with the existing literature and further points out that direct inferences from regional brain morphology to human behavior cannot be drawn conclusively and that future research is needed to identify moderating and mediating factors.

## **5.2. Effects of *BDNF* val<sup>66</sup>met polymorphism and motor skill learning on striatal glutamate concentration**

Subsequent MR-spectroscopy analysis sought to unravel possible effects of *BDNF* val<sup>66</sup>met polymorphism on striatal neurochemistry characteristics, specifically glutamate concentration, with a special appeal to further understand the implausible positive genotype effect on striatal gray matter volume previously observed.

Glutamate is the major excitatory neurotransmitter in the human brain and the striatum receives glutamatergic afferents from the sensori-motor cortex and the thalamus (reviewed in Yin & Knowlton, 2006). Further, glutamate and BDNF interact synergistically to regulate neuroplasticity (Mattson, 2008). In humans, lower glutamate and N-acetylaspartate (NAA) levels for Met allele carriers in the hippocampus have been detected via MR spectroscopy (Gruber et al., 2012; Stern et al., 2008). Therefore, results were expected to yield either lower glutamate concentration in the striatum or respective paradoxical effects, i.e. higher glutamate concentration, since increased glutamatergic transmission in the dorsolateral striatum has recently been reported in a *BDNF* Met/Met rodent model (Jing et al., 2016).



Interestingly, no significant difference between genotype groups neither for glutamate nor for any other of the measured metabolites was observed. This was striking at first sight, especially given the results on gray matter volume. Nevertheless, the presumably problematic inference from striatal rodent to human models has been discussed in the previous section, and differences in striatal gray matter volume between genotype groups were controlled for in the respective analysis. Furthermore, *BDNF* val<sup>66</sup>met polymorphism only affects activity dependent signaling of BDNF and glutamate (Carvalho et al., 2008; Egan et al., 2003), while MRS measures glutamate concentration at rest (Rothman, Behar, Hyder, & Shulman, 2003). Also, effects of the *BDNF* val<sup>66</sup>met polymorphism on MRS markers seem to be regionally specific, as Gruber and colleagues concluded, who did not observe differences in glutamate MRS concentration in the posterior frontomedial cortex but selectively in the hippocampus (Gruber et al., 2012). Clinical research on disorders like attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) or schizophrenia for which aberrant glutamate signaling e.g. in the striatum is assumed to be a pathophysiological mechanism further demonstrated inconsistent MRS findings with either increased, decreased or non-altered striatal glutamate levels (reviewed in Naaijen, Lythgoe, Amiri, Buitelaar, & Glennon, 2015; Treen et al., 2016).

Exploratory statistical analysis on the relationship between motor skill learning and glutamate concentration in the striatum also revealed no significant effect, even though this relationship has been shown in at least one study with neuropsychological measures of motor performance in the grooved pegboard test (Zahr et al., 2013). Nevertheless, motor skill learning as operationalized in this study differs from the behavioral markers obtained in the grooved pegboard test, which measures fine-motor performance (speed, accuracy and eye-hand coordination) and not learning, or at least cannot separated those two measures from each other (Rourke, Yanni, MacDonald, & Young, 1973).

Overall, also in this subsection, the methodological MRS-approach has to be scrutinized. In humans, MRS is the best MR in vivo marker today to measure biochemical concentrations in the human body and brain and it is indispensable in clinical applications e.g. in oncology to assess tumor properties (Spratlin, Serkova, & Eckhardt, 2009). Nevertheless, in the human brain, spatial resolution of this measure is very low which opens a special challenge when drawing molecular inferences (Sanches, Crippa, Hallak, Araujo, & Zuardi, 2004). Glutamate MRS-measures can either be obtained from presynaptic, postsynaptic or, to a majority, from non-neuronal glial compartments where glutamate is transformed into glutamine for neuronal reuptake and re-synthesis (glutamate-glutamine cycle). Magnetic resonance spectroscopy quantifies glutamate concentration over all three compartments and further, reliability of separating glutamate from glutamate+glutamine at 3 Tesla magnetic field

strength has been under debate (reviewed e.g. in Ende, 2015; Naaijen et al., 2015). Therefore uncertainties are raised to the exact interpretation of the measure.

Also, localization of the respective region of interest lacks sufficient accuracy and is susceptible to operator characteristics. Therefore overall reliability or stability of the measure might be reduced (Marshall, Wardlaw, Cannon, Slattery, & Sellar, 1996). Furthermore, with ongoing age, the quality of basal ganglia spectra is usually impaired by iron and copper depositions which cause inhomogenities within the magnetic field and increase signal variance (Schwerk et al., 2014).

Taken together, the non-significant results of *BDNF* val<sup>66</sup>met genotype or motor skill learning on striatal glutamate concentration are puzzling but also consistent with the prior literature. Possible methodological confounds that might have obscured the respective effects cannot completely be out ruled, nevertheless, the tentative conclusion is drawn that *BDNF* Met-carriers might indeed not demonstrate altered resting state glutamate or other metabolite concentrations in the human striatum.

### **5.3. Effects of *BDNF* val<sup>66</sup>met polymorphism and motor skill learning on cortico-striatal function**

The following fMRI analysis investigated, whether effects of *BDNF* val<sup>66</sup>met polymorphism would also be evident in a functional probe of the motor skill learning task (SVIPT) in the striatum and/or exploratively in the whole fronto-striatal motor circuitry. Results of the plausibility and confirmation analyses are discussed prior to specific effects of genotype and interindividual differences in motor skill learning.

#### **5.3.1. Plausibility analysis**

As explained in detail in section 2.6.1, fMRI motor skill learning and –performance tasks so far, demonstrated consistent activation patterns with considerable overlap to structures of the fronto-striatal motor circuit (see 2.6.2).

As expected, plausibility analysis of contrasting all motor conditions with the look condition revealed a broad functional motor network with all relevant nodes of the ‘motor loop’ (pre-, supplementary and primary motor-cortices, putamen, globus pallidus and thalamus) (Chudasama & Robbins, 2006) as well as occipital, parietal, insular and cerebellar areas. This is in line with cumulating evidence of functional correlates of motor skill performance and learning (Hardwick et al., 2013). Since aim of this analysis was to demonstrate solid task

effects and to validate the dependent variable, a detailed discussion on the distinctive nodes and their respective function within this network is not given at this point. The interested reader is referred to some excellent meta-analyses and reviews (Dayan & Cohen, 2011; Hardwick et al., 2013; Penhune & Steele, 2012).

### ***5.3.2. Confirmation analysis of motor skill learning related functional effects***

Existent functional MRI studies on motor skill learning were commonly designed as longitudinal or online learning paradigms and revealed fluctuations between and within specific nodes of the motor network as training progressed over time points. Cross-sectional studies nevertheless also contributed decisively but revealed a heterogeneous activation pattern due to the broad range of control conditions and tasks used over studies (see 2.6.1). fMRI analysis strategy of this study followed established guidelines i.e. compared the experimental condition with a suitable control condition. By this means, whole brain activation for each subject from the control condition ('novel sequence') was subtracted from the experimental condition ('trained sequence'). Given that this was the first study to implement the visual-sequential isometric pinch-force task (SVIPT) (Reis et al., 2009) in the MR environment (see 10) and to demonstrate related brain activations, we did not know a priori what functional patterns to expect from the 'trained sequence' vs. 'novel sequence' contrast analysis.

Analysis of the training-related functional probe revealed for the 'novel' > 'trained' contrast greater activations in a right lateralized fronto-parietal network including the superior and inferior parietal lobule, the supramarginal gyrus, superior and inferior frontal gyri (frontal eye field (FEF)), the middle occipital cortex as well as the putamen. Even in comparatively early studies with split brain and neglect patients, specific involvement of the right hemisphere in visuo-spatial attention has been shown consistently (Franco & Sperry, 1977; Mesulam, 1981; Sperry, 1961). Performance of novel sequences in this SVIPT version should necessitate high visuo-spatial attention resources, since to accomplish this task, subjects need to visually follow and direct their gaze to the unpredictable appearance of the black dot over the gates and further monitor their respective motor output. Prior imaging research demonstrated that focusing attention on an object produced sustained activation in a specific dorsal attention system (DAN) including fronto-parietal regions, frontal eye-fields and visual regions in the occipital lobe. Upon occurrence of an unexpected but important event—e.g. the appearance of a black dot over the gate—there was additional involvement of a ventral attention system (VAN) including structures like the supramarginal gyrus and middle prefrontal cortex (Corbetta, Kincade, & Shulman, 2002; Corbetta, Patel, & Shulman,

2008). Indeed, the contrast 'novel sequence' > 'trained sequence' shows considerable participation of dorsal- and ventral visuo-spatial attention systems.

Furthermore, the observed activation pattern demonstrates substantial overlap with proposed fronto-parietal adaptive task control networks, including structures like the lateral prefrontal cortex, the posterior parietal cortex, the anterior insula or the medial prefrontal cortex. This network plays a pivotal role in the implementation and execution of novel tasks and is characterized by an extreme flexibility in balancing and adapting between routine and non-routine conditions (Cole et al., 2013; Dosenbach et al., 2007; Fair et al., 2007). Task control therefore should be indispensable for novel SVIPT performance, since this requires adapting constantly to unknown motor sequences.

Special interest lay in the activation cluster within the putamen (part of the striatum) due to its role in learning and plasticity and as key node within the fronto-striatal motor circuitry (see 2.8). Prior studies using motor learning paradigms revealed consistent involvement of this structure in novel as compared to trained or no-sequence conditions (Boecker et al., 1998; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997; Jueptner, Stephan, et al., 1997; Muller, Kleinmans, Pierce, Kemmotsu, & Courchesne, 2002). But note that the activation hotspot in this study was located in the anterior associative putamen, which might indicate involvement of the cognitive fronto-striatal 'loop' (see 2.6.2). Further, the anterior striatum has been implicated in processing salient (i.e. unexpected and eliciting an attentional-behavioral switch) and behaviorally relevant stimuli (Zink, Pagnoni, Martin, Dhamala, & Berns, 2003), and has been proposed to be a relevant structure within a whole network of salience processing (Raichle, 2011; Seeley et al., 2007). Performing novel as compared to known motor sequences should enhance salience of the respective stimulus material due to the unpredictable appearance of the black dot.

Taken together, the activation pattern of the 'novel sequence' greater 'trained sequence' contrast is consistent with the prior literature and recent functional models of human visuo-spatial attention, task control and salience processing.

The opposite contrast ('trained' > 'novel') revealed activations in a left lateralized network including the cuneus, posterior cingulate gyrus, lingual gyrus, superior frontal, medial and orbitofrontal gyrus, angular gyrus, superior temporal and heschl's gyrus, cerebellum, inferior frontal gyrus, postcentral gyrus, the hippocampus and parahippocampus as well as the right precentral gyrus (M1). This pattern shows considerable overlap with the so called default mode network (DMN), a brain system which is active 'when individuals are not focused on the external environment' (Buckner, Andrews-Hanna, & Schacter, 2008, p.1). Core regions of the DMN are the ventro-medial prefrontal cortex (VMPC), dorso-medial prefrontal cortex

(DMPC), posterior cingulate cortex and medial precuneus, inferior parietal lobe, lateral temporal cortex as well as the (para)hippocampus (H. Lu et al., 2012; Raichle, 2015). Furthermore, the DMN tends to be activated left lateralized (Agcaoglu, Miller, Mayer, Hugdahl, & Calhoun, 2015). The DMN has been associated with emotional processing, self-referential mental activity and the recollection of prior experiences but its purpose as either an independent cognitive function of spontaneous activity in comparison to the mere purpose of balancing task-dependent activity is still under debate (Raichle, 2015). So interestingly, DMN activation in the trained as compared to the novel sequence condition could simply reflect a better motor skill, but might also indicate that additional resources are liberated for processes like self-referential thinking or mind wandering. Relevance of the DMN in motor learning studies has consistently been demonstrated (e.g. via model free approaches) and activity of the DMN has been related to behavioral improvements in motor sequence learning (Debas et al., 2014; Kucyi, Hove, Esterman, Hutchison, & Valera, 2017; Tamas Kincses et al., 2008).

Concerning the hippocampus activation, there exists evidence for its involvement as relevant explicit learning structure especially in early acquisition phases and interactions with the striatum (implicit learning) for long-term motor memory consolidation were shown consistently (Albouy, King, Maquet, & Doyon, 2013; Albouy et al., 2008; Gheysen et al., 2017; Schendan, Searl, Melrose, & Stern, 2003).

Also, greater activation in the ipsilateral (right) primary motor-cortex (M1) of the executing hand (right) was observed. The dynamic interplay between both hemispheres for motor execution has exceedingly been investigated previously. Both TMS (Ferber et al., 1992; Koch et al., 2006; Wassermann, Fuhr, Cohen, & Hallett, 1991) and fMRI research (Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008; Newton, Sunderland, & Gowland, 2005; Nirakko et al., 2001) revealed an inhibitory influence of the contralateral motor cortex on the ipsilateral motor cortex during uni-manual motor execution. This mechanism is supposed to prevent interference from the other hemisphere and can be seen as advantageous for accurate movement of one hand without interference from the opposite hand (Newton et al., 2005) which might be especially relevant when acquiring new motor skills or motor sequences. Though a direct relationship of this interhemispheric inhibition mechanism to motor skill learning remains to be established, under the given assumptions, execution of a trained motor sequence seems to elicit less interhemispheric inhibition than execution of novel sequences.

Taken together, fMRI-contrasts of the plausibility and confirmation analysis revealed activation patterns consistent with the previous literature on functional correlates of motor

learning, visuo-spatial attention, task control and salience processing as well as self-referential thinking or mind-wandering, memory and interhemispheric inhibition.

### ***5.3.3. Effects of BDNF val<sup>66</sup>met polymorphism and motor skill learning***

Following the successful validation of our functional MRI probes, effects of *BDNF* val<sup>66</sup>met polymorphism on motor striatal or motor network activity yielded only non-significant results. This was especially puzzling, given the observed genotype effect on striatal gray matter structure (see 5.1).

Nevertheless, though there exists a certain structure-function relationship in human neuroimaging, it has predominantly been investigated in clinical populations like psychosis patients (Schultz et al., 2012), does seem to be region specific (reviewed e.g. in Sui, Huster, Yu, Segall, & Calhoun, 2014), and to the author's knowledge has not been demonstrated for the motor striatum in any population so far. For instance, Salgado-Pineda et al. (2004) demonstrated reduced fMRI activation during a continuous performance paradigm in frontal, cingulate, parietal, temporal and subcortical structures like the thalamus and reductions in gray matter volume via VBM analysis in some but not all of those regions. Also, Michael et al. (2011) provided evidence that this relationship is differential in clinical populations as compared to healthy controls (i.e. during a working memory task they observed negative correlations in the anterior cingulate cortex, temporal and cerebellar regions and respective positive correlations in healthy control subjects), while, for instance, during resting state structure-function associations within the default mode network were positive in both patient and healthy control groups (Lui et al., 2009). Though differential activation in the hippocampus between Val and Met allele carriers has been demonstrated (e.g. Hariri et al., 2003), the same authors failed to provide evidence of the same effect for a network of fronto-temporo-parietal regions though reductions in respective gray matter volume have been reported by other authors (e.g. Pezawas et al., 2004).

Taken together, inferences from brain structure to brain function have not been proven straightforward as they seem to depend on the respective population and brain region. In our case, results of the functional magnetic resonance imaging data did not provide new evidence to help interpret the structural finding. If a compensatory strategy in terms of preferential recruitment of a striatal circuitry is the underlying mechanism, one might have expected higher activation within this region as well. Nevertheless, lower fMRI activations tend to be interpreted as efficiency marker (Poldrack, 2000) and we do not know from the study data if greater striatal volume in Met-carriers is actually an efficiency or a deficiency marker.

Prior studies that investigated influences of *BDNF* polymorphism on functional correlates of motor performance and motor (skill) learning demonstrated alterations between genotype groups for cortical regions like the primary motor cortex, premotor cortex or supplementary motor area (Cardenas-Morales et al., 2014; McHughen et al., 2010), effects in the striatum were not observed. The same studies further reported inconsistent findings i.e. either greater or less activation within nodes of the motor circuitry for Met-carriers. Based on this state of scientific knowledge, genotype effects in the striatum were not to be expected, but effects in the cortical motor circuitry (i.e. M1, PMC, SMA), that were nevertheless also not observed. However, it is important to note that both studies comprised methodological weaknesses like—in contrast to this study—the renouncement of multiple comparison correction and very small sample sizes and therefore the validity of their results might be limited.

Interestingly though, a significant trend of motor skill learning on training related striatal activation was observed in an additional analysis of the functional neuroimaging data. This effect revealed that subjects who improved less during motor skill training tended to have higher striatal activation during performance of the trained sequence. Note, that behavioral motor performance during the fMRI experiment was controlled for in the analysis to eliminate respective confounds. This finding is in line with our previous understanding of higher fMRI activation being an indicator for less efficiency (Poldrack, 2000) and the specific role of the striatum for motor chunking and parsing in advanced learning stages (Graybiel & Grafton, 2015).

To sum up, no evidence was provided for an effect of *BDNF* val<sup>66</sup>met polymorphism on striatal and/or motor network activity. This is consistent with the prior literature and emphasizes the challenge of structure-function associations in the human brain.

#### **5.4. General limitations**

To the author's knowledge, this is the first study to investigate effects of the *BDNF* val<sup>66</sup>met polymorphism on motor skill learning within cortico-striatal circuits via a multimodal neuroimaging approach. Despite the conceptual uniqueness of this research, there are also some limitations to consider. While specific limitations of certain sub-analyses have already been addressed in the respective previous subsections of this discussion, there are also some general points that need to be emphasized in the following.

Due to the small sample size and incidence of the recessive variant in European populations, Met/Met-carriers and Val/Met-carriers were classified as one group of Met-carriers. Given that there is clear evidence for a gene-dosage effect of the *BDNF* val<sup>66</sup>met polymorphism in

the animal literature (Chen et al., 2006), this might have masked the hypothesized effects on striatal glutamate concentration and function.

Another important point to consider is that of statistical power. Meta-analyses of the well described variant effect on hippocampus volume revealed only very small effect sizes (e.g.  $d = 0.13$  or  $SDM = 0.41$ ) and indicated necessary samples sizes greater than  $n = 1900$  (Hajek et al., 2012; Molendijk et al., 2012). Although the existing literature did not tell us what to expect as a priori effect size for striatal gray matter volume, one might tentatively assume an adequate effect size equivalent to that of the hippocampus. Despite that, studies of the respective polymorphism effects in the motor learning domain provided only very small sample sizes especially in Met-carrier groups (e.g.  $n = 17$  or  $n = 7$ ) (Fritsch et al., 2010; McHughen et al., 2010) and one might therefore tentatively call the validity of their results into question.

Furthermore, research in recent years has increasingly pointed out the importance of identifying moderating and mediating factors in imaging genetics research (e.g. Notaras et al., 2015a) and have refrained from studying single-nucleotide polymorphisms in certain domains. For example, the influence of demographic factors like sex or ethnicity has been demonstrated and proven to be indispensable for the interpretation of SNP effects (Smolders, Rijpkema, Franke, & Fernandez, 2012; X. Yang et al., 2012), as well as gene x gene interactions with other single-nucleotide polymorphism like the catechol-*O*-methyltransferase (*COMT*) val<sup>158</sup>met, the dopamine d2 receptor (*DRD2*) G > T variant or 3 polymorphisms of the neurotrophic receptor tyrosine kinase 2 gene (*NTRK2*) (Lin et al., 2013; Noohi et al., 2016; Witte et al., 2012). Also, recently, new genes and respective loci were identified to influence striatal volume like an intronic locus of the *DCC* gene that encodes a netrine receptor important for axon guidance and migration (Hibar et al., 2015). This necessitates multi-gene profiling in the research on striatal volume and motor skill learning.

## 5.5. Conclusion

Taken together, this study provides evidence for structural alterations within the motor striatum as well as deficits in short-term motor skill learning in Met allele carriers of the *BDNF* val<sup>66</sup>met polymorphism. This is in line with our understanding of the molecular mechanisms of this genetic variant and the interpretation as a compensatory striatal strategy. Biochemical (glutamate) or functional differences in the cortico-striatal motor network between genotype groups were not observed though, findings that were discussed in reference to the prior literature and methodological limitation of the respective imaging modalities.



Further, this study was the first to implement the behaviorally well validated SVIPT in the MR environment. Plausible activation patterns during motor skill execution were observed as well as strong training related task effects that were interpreted under the assumption of recent network models of visuo-spatial attention and task control or default mode activity and interhemispheric inhibition.

Exploratory analyses for effects of interindividual differences in motor skill learning on striatal gray matter structure and neurochemistry yielded no significant effects, results that were also discussed as consistent with the prior literature. However, a trend on motor-training related brain activity within the motor striatum was observed in the fMRI analysis, which fosters our understanding of the striatum's significant role for motor chunking and parsing of action sequences.

Despite some methodological considerations, this study—to the author's knowledge—is the first to study effects of *BDNF* val<sup>66</sup>met polymorphism in motor skill learning with at least a mildly adequate sample size and a multimodal neuroimaging approach. Though modality convergent evidence for a compensatory striatal mechanism in carriers of the Met allele was not provided, the results shed light on the distinctive qualities of the employed neuroimaging methods and their use in imaging genetics research of fronto-striatal learning and plasticity processes. At this stage of empirical evidence, gray matter volume seems to be a more adequate endophenotype than brain function or metabolite concentration. Only tentative speculations can be drawn at this stage to explain this pattern, but it is undeniable that BDNF exerts direct effects on neuronal morphology and structural integrity (see 2.3), while influence on hemodynamic BOLD-response is, if at all, indirect and possibly weak. The problematic interpretation of the MRS glutamate measure has been discussed in the respective section (see 5.2).

To sum up, human neuroscience constantly evolves. Nevertheless, the next step for future research should be to replicate and validate the results of this study. Further, novel analysis approaches are needed to develop a more comprehensive system of multimodal genotype effects in cortico-striatal (motor skill) learning and plasticity. As mentioned in previous sections, multi-gene profiling might be an important next step as well as more refined multimodal analysis strategies.



## 6. General Discussion and Outlook

This thesis investigated plasticity processes in human fronto-striatal circuits. Plasticity is the inherent feature of our nervous system to adapt to constantly changing intrinsic and extrinsic demands and is the fundamental basis for our ability to learn. Nevertheless, new skills also need to stabilize properly into respective memories as not to be constantly overwritten. This is the so called stability-plasticity dilemma (Ajemian, D'Ausilio, Moorman, & Bizzi, 2013) of skill learning and specific behavioral implications of this dilemma are still under debate.

Skill learning in the striatum enables the formation of stable motor memories. Those so-called 'habits' (Ashby et al., 2010) can be modulated by reward expectation contingencies, especially in the acquisition phase, but once the skill is learned properly, can be executed in an automatic stimulus-response driven action pattern (see 2.6.1). Plasticity is therefore a crucial factor in the acquisition but not necessarily in the execution phase of motor skills. Reduced motor skill learning or plasticity in Met allele carriers could therefore also signify greater stability of the respective motor execution. Due to our complex motor skill learning parameter, an aggregated proxy for speed plus accuracy (see 3.5), individual trial by trial fluctuations could not be investigated. However, prior research points out that Met allele carriers can actually overcome their deficits in motor plasticity (as indexed via TMS) through daily motor training on 5 consecutive days (McHughen, Pearson-Fuhrhop, Ngo, & Cramer, 2011). Therefore, stabilizing behavioral performance might have considerable beneficial implications for carriers of the Met allele. The striatum has been identified as key structure for motor stability and, as described in detail previously (see 2.6.1), 'motor chunking'—a concatenation of action sequences to be expressed habitually—has been assigned as main function of the striatum (Graybiel & Grafton, 2015). Those motor chunks can be framed through neuronal bracketing i.e. firing at start and endpoints of the action sequence within the striatum and have been interpreted as efficiency markers in terms of reduced cost of neuronal resources (Jin et al., 2014). Therefore, they provide excellent stability properties which might explain why Met allele carriers presumably prefer striatal learning strategies.

Nevertheless, it has to be pointed out that—when investigating behavioral processes like motor skill learning—the striatum is only one node within a widely distributed brain network and that brain networks can exhibit various properties that are qualitatively distinct from that of their individual nodes (Sporns, 2014). This needs to be considered when studying striatal mechanisms, and though this study tried to apply a network approach in the fMRI analysis, this might have only been the tip of the iceberg for further analyses. All in all, 'any procedure, genetic or otherwise, affects circuits not just the striatum' (Graybiel & Grafton,

2015, p. 5). Therefore, new network analysis strategies are needed in human neuroimaging, and this is especially true for learning and plasticity as those processes imply that the whole brain undergoes constant changes. Those approaches have just begun to expand, but have already guided us to a better understanding of the mechanisms of our brain. For example, Bassett et al. (2015) provided evidence that during a period of 6 weeks of motor sequence training, increases in task performance as an indicator for learning was related to the disengagement of fronto-parietal and cingulo-opercular top-down cognitive control hubs. Therefore, investigation of learning-related temporal fluctuations i.e. region specific engagement and disengagement within whole brain networks and respective sub circuits seems to be an essential next research step in further exploring fronto-striatal learning and plasticity processes in the human brain.

As mentioned in the previous section, human neuroscience evolves constantly. While we already gained valuable insights into the systems function of our brains and its aberrations in pathological conditions and neuropsychiatric disorders like schizophrenia, the transition of this knowledge into clinical application (e.g. improvement of existing treatment options or development of new treatment strategies) remains an ambitious endeavor. As the *BDNF* val<sup>66</sup>met polymorphism is a potential risk variant for psychosis (Notaras et al., 2015a), the present research—though derived from a healthy subject sample—might contribute to the development of striatum specific, implicit training strategies in schizophrenia. Schizophrenic patients have been identified with a broad range of cognitive dysfunctions (see 2.4). While those seem to be characterized primarily by deficits in explicit learning (e.g. declarative memory (Aleman, Hijman, de Haan, & Kahn, 1999)), the acquisition of procedural knowledge seems not principally to be impaired (Adini, Bonneh, Komm, Deutsch, & Israeli, 2015; Perry, Light, Davis, & Braff, 2000; Siegert, Weatherall, & Bell, 2008). Meta-analyses on cognitive training in schizophrenia demonstrated that patients can actually benefit from respective training strategies with medium effect sizes for immediate performance enhancements in diverse cognitive domains like processing speed or verbal working memory and small to medium effect sizes for remediation of global and social functioning (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Findings from this study might indicate that striatal learning strategies i.e. chunking and automatization could be an important mediating factor to explain those beneficial effects. This further emphasizes the relevance of neurocognitive therapies in addition to the preexisting treatment options for schizophrenic disorders.

In conclusion, findings of this study might enrich the debate on the plasticity-stability dilemma of skill learning and could further lead to implications for novel multimodal

neuroimaging networks analysis strategies as well as neurocognitive treatment options for schizophrenia.

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## 7. Summary

This thesis investigated fronto-striatal plasticity processes in the human brain via a multilevel (genes, brain, behavior) and multimodal neuroimaging (functional- and structural magnetic resonance imaging, magnetic resonance spectroscopy) approach. Neuroplasticity—an intrinsic property of our nervous system—can act in fronto-striatal circuits, specifically in the ‘motor-loop’. Within this circuitry, the striatum, as key structure, and glutamate, as important neurotransmitter, enable the acquisition and automatization of motor skills (e.g. playing an instrument). On a molecular level, brain-derived neurotrophic factor, a neurotrophin, is known to influence cellular plasticity processes, and a single-nucleotide polymorphism of the brain-derived neurotrophic factor gene (*BDNF* val<sup>66</sup>met), has been related to impairments in hippocampal learning and plasticity in humans. However, research and respective findings on the influences of this genetic variant in motor skill learning within the fronto-striatal motor-circuitry remain fragmented.

135 healthy right-handed subjects (mean age = 26.96 +/- 9.05 years, 80 females, 54 Met allele carriers) participated in this study. They received training on a sequential visual isometric pinch task in the laboratory and motor skill learning was measured via increases on a speed-accuracy trade-off function (skill measure). Subsequently, magnetic resonance imaging was performed. For functional magnetic resonance imaging, an adapted version of the pinch-force task was used, consisting of the trained, a novel and two control conditions. Furthermore, structural magnetic resonance imaging and magnetic resonance (glutamate) spectroscopy was conducted. Genomic DNA was extracted from whole blood according to standard procedures. Data were analyzed using classical toolboxes for brain imaging data (SPM8, VBM8), for spectroscopy data (LCModel) as well as Matlab-routines and statistics programs for behavioral data and further analysis. To validate the structural neuroimaging results, data of an independent replication sample of 286 healthy right-handed subjects (mean age = 33.39 +/- 9.8 years; 154 females, 101 Met allele carriers) were analyzed.

The behavioral results indicated that skill measure constantly increased across the training period. Further analysis also revealed a significant difference in motor skill learning among carriers of the *BDNF* val<sup>66</sup>met polymorphism (i.e., impairment in motor skill learning in Met allele carriers). On a structural level, the same individuals also tended to have significantly greater gray matter volume in the striatum, a finding that was replicated in the validation sample. Neurochemically, Met allele carriers did not have altered resting state striatal glutamate concentration or deviations from Val allele carriers in any other of the measured metabolites. Functional neuroimaging data demonstrated strong task-effects within a cortico-striatal motor network and plausible training-related brain activations. However, no

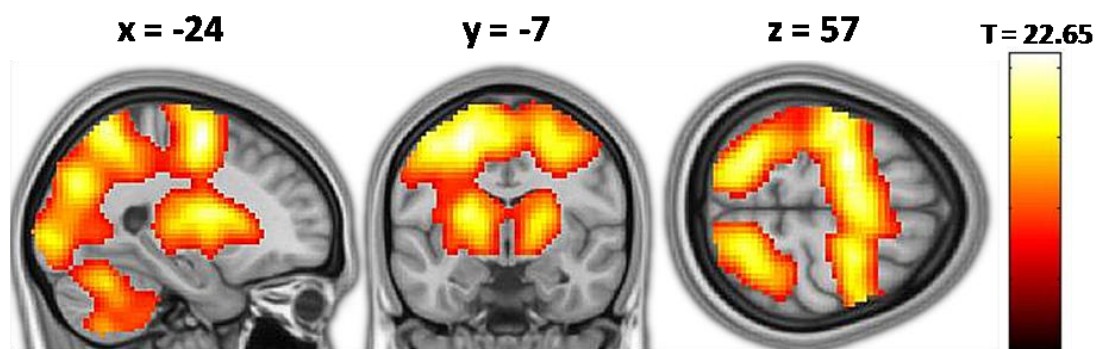
functional alterations in (training-related) activity within the fronto-striatal motor network for carriers of the Met variant were observed.

The behavioral findings of this study complement previous findings on deficits of Met allele carriers of the *BDNF* val<sup>66</sup>met polymorphism in long term motor skill learning and reinforce our understanding of the molecular basis of this functional variant. The observed structural effects were interpreted as a compensatory mechanism for hippocampal deficits and are discussed in light of the limitations of the present study. The non-significant genotype results on glutamate concentration and (training-related) brain function are also consistent with the prior literature. Furthermore, this pattern of results points to the distinct qualities of the three neuroimaging methods used in this study and highlights the uniqueness of this multilevel and multimodal neuroimaging approach to study fronto-striatal learning and plasticity processes in humans. The scientific and possible clinical implications of these findings were discussed.



## 8. Addendum

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**Figure 12.** Contrast 'trained' > 'look'. Sagittal section (left), coronar section (middle), axial section (right), coordinates are indicated in MNI-space.  $P < 0.05$ , whole brain FWE-corrected; covariates: age, sex, education years and behavioral performance during scanning. Color bar indicates  $T$ -values ranging from 0 to 22.65. Degrees of freedom (df) = 130.

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## 10. Own Publications

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- Baumeister, S., Hohmann, S., Wolf, I., Plichta, M. M., Rechtsteiner, S., **Zangl, M.**, . . . Brandeis, D. (2014). Sequential inhibitory control processes assessed through simultaneous EEG-fMRI. *Neuroimage*, *94*, 349-359. doi: 10.1016/j.neuroimage.2014.01.023
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- Bilek, E., Schafer, A., Ochs, E., Esslinger, C., **Zangl, M.**, Plichta, M. M., . . . Tost, H. (2013). Application of high-frequency repetitive transcranial magnetic stimulation to the DLPFC alters human prefrontal-hippocampal functional interaction. *J Neurosci*, *33*(16), 7050-7056. doi: 10.1523/JNEUROSCI.3081-12.2013
- Zangl, M.**, Geiger, L., Schäfer, A., Ruf, M., Reis, J., Meyer-Lindenberg, A., Tost, H. (2013). Alterations in brain function and connectivity linked to complex motor skill learning. *Annual meeting of the organization of human brain mapping (HBM)*. Poster presentation.
- Zangl, M.**, Geiger, L., Schäfer, A., Ruf, M., Reis, J., Meyer-Lindenberg, A., Tost, H. (2013). Training-related changes in brain function and interregional connectivity linked to complex motor skill acquisition. *Psychologie und Gehirn*. Poster presentation.
- Tost, H., **Zangl, M.**, Zang, Z.. Multimodal neuroimaging of fronto-striatal plasticity markers—Multimodal integration. *Annual meeting der BMBF-geförderten selbstständigen Forschungsgruppen in den Neurowissenschaften*. Talk.
- Tost, H., **Zangl, M.**, Meyer-Lindenberg A. (2013). Rethinking translation in schizophrenia: the Contribution of neuroimaging. In McArthur, R. A. (Ed.), *Translational Neuroimaging: Tools for CNS Drug Discovery, Development and Treatment*. London, Waltham, San Diego: Elsevier.
- Zangl, M.**, Schäfer, A., Geiger, L., Ella, A., Ruf, M., Fritsch, B., Reis, J., Meyer-Lindenberg, A., Tost, H. (2012). Adaptation and implementation of a plasticity-related complex motor skill acquisition task in the MRI-environment. *Annual meeting of the society of neuroscience (SFN)*. Poster presentation.
- Tost, H., **Zangl, M.**. Multimodal neuroimaging of fronto-striatal plasticity in humans (2012). *Annual meeting der BMBF-geförderten selbstständigen Forschungsgruppen in den Neurowissenschaften*. Talk.



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