From the Institute for Systems Neuroscience
at Heinrich Heine University Düsseldorf

# Multi-modal Parcellation of the Human Striatum: Functions, Clinical Relevance and its Specific Connectivity

Dissertation

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# Zusammenfassung

Das menschliche Striatum ist Bestandteil der subkortikalen Kerne und spielt für die kognitiven und motorischen Funktionen eine wichtige Rolle. Eine Dysfunktion des Striatums ist z.B. bei Parkinson (PD) oder Schizophrenie (SCZ) typisch. Es ist bekannt, dass das menschliche Striatum aus mehreren funktionell und strukturell divergierenden Subregionen besteht. Bisher wurden die Modalitäten jedoch unabhängig voneinander analysiert. Das Ausmaß der multimodalen konvergenten Organisation des Striatums bleibt noch unklar. Das Striatum von Menschen und Makaken weist eine breite Homologie auf, da es mit verschiedenen psychologischen- und Verhaltensfunktionen zusammenhängt. Die Untersuchung der funktionellen und strukturellen Unterschiede zwischen den striatalen Subregionen von Menschen und Makaken kann dazu beitragen, die evolutionäre Divergenz besser zu verstehen und herauszufinden, warum der Mensch für bestimmte neuropsychiatrische Erkrankungen anfällig ist. Bisher bleibt der Unterschied in der funktionellen Organisation des Striatums beim artenübergreifenden Vergleich noch unklar. Ziel dieser Dissertation war es, 1) die multimodale Organisation des menschlichen Striatums zu untersuchen, indem die funktionelle Konnektivität im Ruhezustand (RSFC), die probabilistische Diffusionstraktographie (PDT) und die strukturelle Kovarianz (SC) miteinander verbunden und ihre strukturelle Atrophie in Bezug auf PD und SCZ untersucht werden. 2) Die striatalen Subregionen von Menschen und Makaken anhand ihrer homologen kortiko-striatalen Konnektivität zu vergleichen; und 3) eine standardisierte Toolbox *CBPtools* für die connectivity-based parcellation (CBP) Analyse einzuführen. In Studie 1 zeigten sich konvergente Cluster im dorsalen, dorsolateralen, rostralen, ventralen und kaudalen Striatum. Während sich bei PD und SCZ eine signifikante strukturelle Atrophie im rostralen und ventralen Striatum zeigte, war für PD eine Atrophie im dorsolateralen Striatum spezifisch. In Studie 2 wurde außerdem durch einen Vergleich zwischen verschiedenen Arten eine ungleiche kortiko-striatale RSFC innerhalb des dorsalen Caudats nachgewiesen. Darüber hinaus wurde eine abnormale RSFC nicht nur zwischen dorsalem Caudat, sondern auch zwischen rostralem Caudat, ventralem, zentralem und kaudalem Putamen sowie weit verbreiteten kortikalen Regionen bei PD- und SCZ-Patienten gefunden. Zusammenfassend deckte diese Dissertation eine modalübergreifende konvergente Organisation des menschlichen Striatums auf, mit der die strukturelle und funktionelle Variabilität bei Alterung und Krankheiten untersucht werden kann. Außerdem liefert sie Hinweise darauf, dass Anomalien im dorsalen Caudat mit Menschen-spezifischer Konnektivität zu neuropsychiatrischen Störungen beim Menschen beitragen könnten.

## Summary

The human striatum is a part of subcortical nuclei and plays an important role in both cognitive and motor functions. Its dysfunction has been implicated in the pathophysiology of various disorders, including Parkinson's disease (PD) and schizophrenia (SCZ). The human striatum is known to be composed of several functionally and structurally divergent subregions. However, previous studies independently investigated its functional and structural parcellations, the extent of multi-modal convergent organization of the striatum remains unclear. Also, human and macaque striatum have a wide homology because in both the striatum is related to several psychological and behavior functions. Investigating the functional and structural differences between human and macaque striatal subregions may help us to understand the evolutionary divergence and reveal why human is vulnerability to some neuropsychiatric diseases. So far, the difference in functional organization of the striatum with cross-species comparison is still unclear. In this dissertation, we aimed to 1) investigate the multi-modal organization of the human striatum by jointly analyzing the resting-state functional connectivity (RSFC), probabilistic diffusion tractography (PDT), and structural covariance (SC) and examine the structural atrophy of ensuing parcels in PD and SCZ; 2) compare human and macaque striatal subregions according to their homologous cortico-striatal connectivity; and 3) introduced a standardized toolbox '*CBPtools*' for connectivity-based parcellation (CBP) analysis. In study 1 we found convergent clusters in the dorsal, dorsolateral, rostral, ventral and caudal striatum and observed significant structural atrophy in the rostral and ventral striatum common to both PD and SCZ, and atrophy specifically attributable to PD in the dorsolateral striatum. In study 2, dissimilar cortico-striatal RSFC within the dorsal caudate was detected through cross-species comparison. In addition, abnormal RSFC was found not only between dorsal caudate, but also between rostral caudate, ventral, central and caudal putamen and widespread cortical regions for both PD and SCZ patients. In sum, this dissertation revealed a cross-modal convergent organization of the human striatum that can be used to investigate the structural and functional variability in aging and diseases; and provided a testable hypothesis that abnormalities in dorsal caudate with human-specific connectivity may contribute to human neuropsychiatric disorders.

## List of abbreviations

| | |
|---|---|
| **ARI** | adjusted rand index |
| **BOLD** | blood oxygenation level dependent |
| **CBP** | connectivity-based parcellation |
| **CDC** | context-dependent clustering |
| **DMN** | default mode network |
| **FEF** | frontal eye fields |
| **GM** | gray matter |
| **HC** | healthy controls |
| **INDI** | International Neuroimaging Data-sharing Initiative |
| **IPC** | inferior parietal cortex |
| **M1** | primary motor cortex |
| **MACM** | meta-analytic connectivity modeling |
| **PCC** | posterior cingulate cortex |
| **PD** | Parkinson's disease |
| **PDT** | probabilistic diffusion tractography |
| **PRIME-DE** | PRIMatE Data Exchange |
| **ROI** | region of interest |
| **RSFC** | resting-state functional connectivity |
| **SC** | structural covariance |
| **SCZ** | schizophrenia |
| **SMA** | supplementary motor area |
| **VBM** | voxel-based morphometry |
| **WM** | white matter |
| **dMRI** | diffusion magnetic resonance imaging |
| **fMRI** | functional magnetic resonance imaging |
| **preSMA** | presupplementary motor area |
| **sMRI** | structural magnetic resonance imaging |

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# 1 Introduction

My dissertation will first focus on multi-modal parcellation of the human striatum based on three modalities: resting-state functional connectivity (RSFC), probabilistic diffusion tractography (PDT), and structural covariance (SC). To reveal both the functional and clinical relevance of these striatal clusters, we investigated their functional characterization, and probed whether structural alterations of these striatal clusters differ between Parkinson's disease (PD) and schizophrenia (SCZ). In this part, we provided a multi-modal parcellation scheme for the human striatum, which can be employed in investigating the functional and structural variation of striatal subregions for development, aging, and diseases. My dissertation will also compare functional parcellation of the human and macaque striatum, to reveal evolutionary divergence of the striatum and may improve our knowledge on why human vulnerability to PD and SCZ. In addition, to help researchers applying the connectivity-based parcellation (CBP) to investigate functional and structural organization of the brain regions, we developed an open source, Python-based software package, called '*CBPtools'*. In summary, my work uncovered a convergent multi-modal functional and structural organization of the human striatum across three different imaging modalities, investigated their functions and clinical relevance, and revealed a functional striatal cluster with evolutionary divergence between human and macaque.

## 1.1 The human striatum: structure, connectivity, function and clinical relevance

The human striatum is a brain subcortical structure located close to the lateral ventricle and is also the primary input structure of the basal ganglia. During the embryological development, the striatum originates from the ventral telencephalon and it gradually develops into two nuclei, the caudate and the putamen, incompletely separated by the internal capsule (Mai and Paxinos 2011; Alheid et al. 1990). Cytologically, the caudate and putamen are considered identical and include two types of cells: small achromatic neurons and large multipolar neurons (Namba 1957; Carpenter 1981). Anatomical and physiological findings from primates suggest that the striatum receives diverse afferent projection from cerebral cortex, which then through the thalamus are projected back to the cerebral cortex forming multiple partial parallel anatomical loops (Alexander et al. 1986; Alexander and Crutcher 1990). Particularly, the putamen mainly receives afferent projections from motor and somatosensory cortex, while the projections from frontal eye fields, dorsolateral prefrontal cortex and lateral orbitofrontal

cortex respectively terminate in the body parts of, dorsolateral, and ventromedial caudate. Moreover, the ventral striatum receives diverse afferent projection not only from anterior cingulate area, but also from the "limbic" structures. These multiple loops also provide an anatomical basis for the functional diversity of the striatum, indicating its topographical organization and functional heterogeneity. Generally, the striatum is well known for its prominent role in diverse cognitive functions and goal-directed behaviors, such as working memory, reward and reinforcement learning (Lewis et al. 2004; Pauli et al. 2016; Haber et al. 2006). Through receiving diverse afferent projection from cerebral cortex and forming multiple cortico-striatal circuits, the striatum mediates individual motivations and emotions that drive planning, cognition that generate appropriate strategy, and finally, the execution of the action (Haber 2003; Nakano et al. 2000).

Given its functional importance in cognitive, emotional, executive and motor functions, the human striatum has been implicated in the pathophysiology of several diseases. Among them, PD (Owen et al. 1992; Zhai et al. 2018) and SCZ (Li et al. 2020; Simpson et al. 2010) are two major, socio-economically relevant disorders that are clearly linked to the dysfunction of the striatum. Currently, the most common view is that the degeneration of dopaminergic nigrostriatal neurons significantly contribute to the pathology of PD (Dauer and Przedborski 2003). This degeneration may lead to abnormal depletion of striatal dopamine. Given dopamine as a crucial neurotransmitter with an important role in control of body movements, this decreased level of striatal dopamine and its receptors contributes to irregular movements, a significant clinical symptom in PD patients. In SCZ, both hyper and hypo dopamine activity are related to different symptoms (Brisch et al. 2014). In particular, the increase in subcortical release of dopamine includes the positive symptoms of schizophrenia, such as hallucinations and delusions. Moreover, recent findings suggest that the dopaminergic dysfunction (hyperactivity) within the nigrostriatal pathways significantly contribute to the pathology of SCZ (McCutcheon et al. 2019).

In sum, as an important component of the subcortical nuclei, the striatum receives diverse afferent projection from cerebral cortex and forms several cortico-striatal pathways that are related to cognitive functions and goal-directed behaviors. Dopaminergic dysfunction in the striatum significantly contribute to several movement and psychiatric disorders, including in Parkinson’s disease and schizophrenia.

## 1.2 Functional and structural parcellation of the human striatum

The striatum receives topographic projections from the cerebral cortex, which are further reflected in its structural and functional subdivisions, i.e., parcellations. In-vivo and non-invasive neuroimaging technique, such as resting-state functional magnetic resonance imaging (fMRI), diffusion MRI (dMRI) and structural MRI (sMRI), have been widely used to investigate the functional and structural parcellation of the striatum for decades. These neuroimaging techniques provide different connectivity measurement that captures modality-specific structural or functional neurobiological features of brain organization. Recently, exploiting the differentiated nature of connectivity patterns for individual brain regions, forming distinct connectivity fingerprints for each module, has prompted the rapidly developing family of CBP approaches in neuroimaging research (Eickhoff et al. 2015; Eickhoff et al. 2018). This section will introduce the CBP approach with its methodological details, and then review previous functional and structural parcellation of the human striatum.

### 1.2.1 CBP: history and applications

Regional specialization and functional integration are the two fundamental organizational principles of the human brain which are closely related to each other, as functionally specialized brain regions are likewise characterized by a distinct set of connectivity. Accordingly, CBP divides a predefined brain region (i.e., region of interest, ROI) into distinct subregion, i.e. a group of voxels, based on the connectivity profiles of individual voxels within that ROI [for review, see Eickhoff et al. (2015)]. Historically, CBP was first performed based on whole brain white matter (WM) structural (fiber) connectivity derived from dMRI (Behrens et al. 2003; Wiegell et al. 2003). This structural connectivity is usually examined by using probabilistic diffusion tractography (PDT). Following this success, similar approaches were applied to investigate the functional organization of a given ROI by estimating resting-state functional connectivity (RSFC) (Kim et al. 2010), or to investigate the correlation between functionally related subregions and their changed gray matter (GM) volume as estimated by structural covariance (SC) (Liu et al. 2015). Each of these modalities (PDT, RSFC and SC) represents a different aspect of brain connectivity: PDT estimates fiber pathways as a proxy for anatomical connectivity between brain regions by delineating the probability that tracts originating at a particular voxel reach any particular voxel in the brain (Jones 2008; Johansen-Berg and Rushworth 2009). The likelihood of passing through each voxel in the white matter then provides the connectivity profile of a particular ROI

voxel. RSFC delineates correlation of time series of blood oxygenation level dependent (BOLD) signal between distant brain regions in the absence of an externally purported task. This is possible because inter-neuronal communication is constantly occurring and is reflected by ongoing fluctuations of activity, which can be measured using fMRI. SC estimates group-level (across subjects) correlation between GM volume of each voxel in a given ROI and that of other voxels in the whole-brain.

In CBP studies, through the use of clustering algorithms, voxels within a given ROI are grouped into sub-groups or subregions based on the similarity of their connectivity pattern with the whole-brain. In previous applications, *k*-means clustering analysis was the probably most popular clustering approach and has been successfully used in many studies for performing CBP on different modalities and different brain regions (Plachti et al. 2019; Genon et al. 2018b; Ray et al. 2015; Reuter et al. 2020; Chase et al. 2020; Hartwigsen et al. 2019; Pauli et al. 2016; Jung et al. 2014; Crippa et al. 2011; Xu et al. 2020). It divides a given ROI into a preselected number (*k)* of non-overlapping clusters (Nanetti et al. 2009). In addition, there are many other clustering algorithms such as hierarchical and spectral clustering, but it is difficult to know beforehand which algorithm is optimal (Thirion et al. 2014).

### 1.2.2 Functional parcellation of the striatum

Several previous studies (Janssen et al. 2015; Jung et al. 2014; Choi et al. 2012; Jaspers et al. 2017) have investigated the functional organization of the striatum using CBP. Generally, these studies first estimated the RSFC between each striatal voxel and other voxels of the whole-brain (or specified cortical functional networks), and then gathered those striatal voxels showing similar connectivity pattern to generate a striatal subregion by using clustering algorithms. We summarize the results from several previous studies that estimated RSFC to parcel the striatum in the supplementary materials of Study 1 (Liu et al. 2020).

### 1.2.3 Structural parcellation of the striatum

According to cortico-striatal fiber connectivity, previous studies (Tziortzi et al. 2013; Draganski et al. 2008) have investigated structural parcellation of the striatum based on PDT. These studies estimated the probabilistic fiber connectivity between each striatal voxel and different cortical regions. The striatal voxel showing maximum probability of fiber connectivity to the same cortical regions were gathered into the same striatal subregion. We also summarize previous studies using the PDT to investigate the

structural parcellation of the striatum in the supplementary materials of Study 1 (Liu et al. 2020).

### 1.2.4 Multi-modal parcellation of the human striatum

Previous studies divided the striatum into subregions based on a single neuroimaging modality (RSFC or PDT). However, it's still unclear to what extent these subdivisions converge or diverge across different neuroimaging modalities. In Study 1, we investigated the multi-modal organization of the striatum by jointly clustering connectivity from three neuroimaging modalities: RSFC, PDT and SC. The aim of this multi-modal analysis was to provide a holistic "map" of the striatum reflecting fundamental biological heterogeneity and homogeneity in its subdivisions.

A primary challenge for obtaining multi-modal striatal parcellation is combining the subregions revealed by the connectivity pattern due to each modality. One possible way is to use a post-hoc combination from the uni-modal maps. Several previous studies have used this method to examine the multi-modal organization of brain regions, such as hippocampus (Plachti et al. 2019), insula (Kelly et al. 2012) and nucleus accumbens (Xia et al. 2017). However, a post-hoc combination does not explicitly model the dependencies among different modalities, which may induce a sub-optimal multi-modal parcellation (Gabasova et al. 2017). To address this issue, we employed the context-dependent clustering (CDC) algorithm (Gabasova et al. 2017) which is an integrative clustering approach that can model the heterogeneity across the contexts or modalities, i.e. RSFC, PDT and SC. Unlike other integrative clustering methods, CDC does not assume a shared cluster structure across all the contexts, making it a good choice for multi-modal CBP. More detailed information about the application of the CDC algorithm in multi-modal CBP can be found in the Materials and Methods [Multi-modal Connectivity-Based Parcellation (CBP)] of Study 1 (Liu et al. 2020). Through applying CDC algorithm, we identified functional and structural convergent subregions of the human striatum.

### 1.2.5 Investigating functional and clinical relevance of striatal subregions

We adopted the "behavioral domain" and "paradigm class" from BrainMap database (http://www.brainmap.org/index.html) (Eickhoff et al. 2011; Genon et al. 2018a) to investigate the relevant functions of these convergent striatal subregions. This database includes more than 17,047 manually-curated neuroimaging experiments. For each experiment, the coordinates of peak voxels of different active brain regions from specific psychological conditions has been recorded. The behavioral

domains contain the categories and subcategories of cognition, emotion, action, perception and interoception. The paradigm classes categorize which specific task is employed. The ‘‘forward inference’’ and ‘‘reverse inference’’ were used to characterize the functional profile of the striatal subregions (Liu et al. 2020).

The PD and SCZ show both common and differing pathological neurodegenerative features within the striatum (Seeman and Niznik 1990; Moustafa and Gluck 2011), however, little is known about whether structural alterations in these two diseases are specifically attributable to individual striatal modules and whether such alterations differ between PD and SCZ. To investigate this, we used voxel-based morphometry (VBM) to examine whether structural (GM volume) alterations in our convergent striatal subdivisions differ between PD and SCZ. In sum, Study 1 uncovered a multi-modal convergent organization of the striatum and examined both the functional and clinical relevance of those subdivisions.

### 1.3 Functional organization of the human and macaque striatum

In fact, classical model regarding to the functional and structural organization of the striatum mainly comes from anatomical and physiological findings in monkeys (Alexander and Crutcher 1990; Alexander et al. 1986). This prior knowledge from non-human primates and subsequent neuroimaging findings in humans, suggests that the human striatum is potentially divided into several structural and functional subregions based on multiple cortico-striatal circuits (Choi et al. 2012; Leh et al. 2007; Tziortzi et al. 2014). For example, the head circuits of the caudate is related to short-term valuation, while the tail circuits of the caudate is involved in long-term valuation (Hikosaka et al. 2014). Numerous studies in macaques revealed both the caudate and the putamen play an important role in reward guided behavior and learning (Apicella et al. 2011; Hassani et al. 2001; Watanabe et al. 2003; Histed et al. 2009; Hikosaka et al. 2014; Hikosaka et al. 1989) and the structure and function of this cortico-striatal reward circuitry is conserved across humans and non-human primates (Haber and Knutson 2010). Although animal models provide important perspective of neural functions and structures, the findings in region-specific divergences may reveal human-specific features potentially associated with human-specific neuropsychiatric diseases. A direct comparison of brain organization between human and non-human primate can elucidate differentiation of brain regions and shed light on the process of species evolution.

Recently, with the application of non-invasive neuroimaging technique in non-human primate researches, comparison of human and macaque striatum have largely focused on the cortico-striatal circuits by using PDT from dMRI (Choi et al. 2017; Neggers et al. 2015; Xia et al. 2019). For example, Neggers et al. (2015) applied a comparison of cortico-striatal between cortical motor areas and the striatum between human and macaque by applying PDT. Structural connectivity between primary motor cortex (M1) and posterior part of the caudate and putamen was found in macaque. The frontal eye fields (FEF) connected to the head of the caudate and anterior putamen was also found in macaque. For human, the FEF and M1 largely connected to posterior putamen but only a small part of the caudate. Xia et al. (2019) applied PDT to locate the ventral striatum of human and macaque according to the cortico-striatal fiber connectivity. Next, they investigated the differences in connectivity fingerprints of the striatum between human and macaque. These results suggested that structural connectivity of the ventral striatum between human and macaque was dissimilar.

Although previous findings have provided us rich information about cortico-striatal structural connectivity of the human and macaque, there is still unclear regarding to the whole-brain RSFC of the macaque striatum and its parcellation that differ from human. As mention in section *1.2.1 CBP: history and applications,* RSFC estimate correlation of time series from BOLD fMRI signal, which reflects the temporal dependency of neuronal activation patterns between different brain regions [for review, see Van Den Heuvel and Pol (2010)]. This measurement has been widely applied in human studies (Barnes et al. 2010; Jung et al. 2014; Janssen et al. 2015; Jaspers et al. 2017), to investigate intrinsic neuronal activation pattern of striatum and reveal functional organization of striatal subregion. But how similar or different functional parcellation between human and macaque striatum are still unclear. Such a cross-species analysis may reveal the similarities in functional organization of the human brain compared to our phylogenetically close relatives, and reveal if this organization is unique to humans.

A growing number of studies are using MRI to compare functional and structural organization of the brain between humans and macaques (Vanduffel et al. 2014; Mars et al. 2018; Xu et al. 2019). However, previous studies usually have a very small numbers of non-human primate subjects (less than 10). During the past 20 years, the technological and methodological advances accelerate the development of the non-human primate studies, but neuroimaging date collection was limited by necessary facilities and capabilities in different research institute. Fortunately, to addresses these challenges, the PRIMatE Data Exchange (PRIME-DE) recently aggregated independently acquired non-human primate MRI datasets

and openly shared them by the International Neuroimaging Data-sharing Initiative (INDI) (Milham et al. 2020; Milham et al. 2018). The PRIME-DE may promote the progress of the comparative MRI, and allows us to perform the large-sample and multi-modal comparative MRI analysis.

In Study 2, we first investigated functional parcellation of the human and macaque striatum based on RSFC modality to intuitively show different and similar striatal subregions between human and macaque.

### 1.4 Striatal subregions with human-specific connectivity and their clinical relevance

It remains an open question whether the striatal organization is unique to humans and if it is involved in complex neuropsychiatric disorders which are often specific to humans. Generally, animal models, especially rodent and macaque models (Castner et al. 2004; Cenci and Crossman 2018), provide feasible pathological research, medicine treatment and clinical experiments for these neuropsychiatric diseases (Choudhury and Daadi 2018; Qiu et al. 2019). However, such neuropsychiatric diseases primarily affect human and are influenced by various factors, for example, personality, family, and social environment. It is hard to include such complex characteristics and social community that specific to human into the animal models. Hence, it is necessary to examine whether these functional and structural abnormalities of the striatal subregions that is unique to human are related to neuropsychiatric diseases. Previous studies have shown functional and structural abnormalities of striatal subregions between patients (with PD and SCZ) and healthy controls (HC) (He et al. 2019; Xu et al. 2016a). However, whether these striatal subregions are related to human-specific cortico-striatal connectivity compared to macaque is still unclear. In Study 2, we future identified those striatal subregions whose cortico-striatal RSFC is human-specific compared to macaque, and then examined difference in RSFC and GM volume between patients (with PD and SCZ) and HC to reveal the clinical relevance for these striatal subregions.

### 1.5 *CBPtools:* a Python-based software package

Although CBP have been widely used to investigate the structural and functional organization of different brain regions based on their long-range connectivity, there is no standardized software for performing this method. Currently, CBP is accessible only in some research groups who develop their own tools in the world. This may lead to discrepant parcellation results between different laboratories adopting their own CBP software. Meanwhile, no standardized guidelines may induce different analysis steps when applied CBP in current studies, making difficult to compare these parcellation results and

interpretations. To address these issues, in Study 3, I participated in developing an open-source software package using Python (version 3.5+): *CBPtools* allowing researchers to perform an extensive CBP analysis for a given ROI. It also supports two modalities, RSFC based on fMRI data and PDT based on dMRI data as well as custom connectivity matrices. Researchers can set the analysis parameters according to the motivation of the study. Given more and more studies require efficient data analysis when employing a large number of subjects, *CBPtools* also supports parallel processing. For visualization, two kinds of output from *CBPtools* include textual matrices and graphical parcellation results.

In sum, in Study 3, we provide an overview of analysis steps in CBP, and develop a simple plug-and-play, open-source software package for researcher to perform CBP. For the application, we examined the functional and structural parcellation of three brain regions: presupplementary motor area and supplementary motor area (preSMA-SMA), amygdala and insula by using the *CBPtools*. We think this guidelines and tool can help researcher "Quick Start" in applying CBP. In addition, we hope this tool can contribute to promote reproducible and comparable parcellation results in CBP field.

## 1.6 Ethics protocols

*"The ethics protocols were approved by the Ethics Committee of Heinrich Heine University Düsseldorf (4039, 4096 and 2018-317-RetroDEuA). For PRIME-DE, all experimental procedures were approved by local ethics boards prior to any data collection. UK macaque datasets were obtained with Home Office approval and abide with the European Directive on the protection of animals used in research (2010/63/EU). For the NIN Primate Brain Bank/Utrecht University dataset, post-mortem specimens were loaned from the Netherlands Institute of Neuroscience Primate Brain Bank (PBB; http://www.primatebrainbank.org/). No individuals were sacrificed for PBB brain issue. Instead, brains were collected from individuals that died from natural causes or that had to be humanely euthanized for reasons unrelated to the tissue collection (Milham et al. 2018; Liu et al. 2020)."*

## 1.7 Aim of the studies

The aims of my project include; 1) joint multi-modal parcellation to identify functionally and structurally convergent striatal subregions (Study 1); 2) investigating the subregions for their functions, and structural alterations (GM volume) between patients (with PD and SCZ) and HC (Study 1); 3)

investigating functional parcellation of human and macaque striatum (Study 2); 4) comparing cortico-striatal RSFC of human and macaque striatal subregions to identify human-specific clusters, as well as examining difference in RSFC and GM volume of these striatal subregions between patients (with PD or SCZ) and HC (Study 2); 5) developing an open-source software package for CBP analysis (Study 3).

In sum, this project provided a holistic convergent view of human striatal functional and structural organization, compared human and macaque striatal subregions, and examined their cortico-striatal connectivity, revealed clinical relevance of the striatal subregions between patients (PD and SCZ) and HC. Also, with *CBPtools* we made CBP analysis easier which may promote further development of investigations of brain functional and structural organization.

**Three publications:**

1) Liu X, Eickhoff SB, Hoffstaedter F, Genon S, Caspers S, Reetz K, Dogan I, Eickhoff CR, Chen J, Caspers J, Reuter N, Mathys C, Aleman A, Jardri R, Riedl V, Sommer IE and Patil KR. Joint Multi-modal Parcellation of the Human Striatum: Functions and Clinical Relevance. *Neuroscience Bulletin*, 2020, 36(10): 1123-1136.

2) Liu X, Eickhoff SB, Caspers S, Wu J, Genon S, Hoffstaedter F, Mars RB, Sommer IE, Eickhoff CR, Chen J, Jardri R, Reetz K, Dogan I, Aleman A, Kogler L, Gruber O, Caspers J, Mathys C and Patil KR. Functional parcellation of human and macaque striatum reveals human-specific connectivity in the dorsal caudate. Accepted to publish in *NeuroImage*, 2021, 235: 118006.

3) Reuter N, Genon S, Masouleh SK, Hoffstaedter F, Liu X, Kalenscher T, Eickhoff SB and Patil KR. CBPtools: a Python package for regional connectivity-based parcellation. *Brain Structure and Function*, 2020, 225: 1261-1275.

## 5 Discussion

In Study 1 and Study 2 we applied unsupervised machine learning and statistical analysis techniques to multi-modal neuroimaging data to first investigate functional and structural organization of the human striatum, reveal functions and clinical relevance of the ensuing striatal subregions, and then to compare cortico-striatal RSFC between human and macaque striatal subregions. In Study 3, I took part in developing an open-source, python-based software *CBPtools* that can be used to investigate functional and structural parcellation of a given brain region. In detail, Study 1 uncovered a fundamental multi-modal organization of the human striatum, revealed these striatal subregions involving in emotion, cognition and execution functions, as well as their structural alterations between patients (with PD or SCZ) and HC. In Study 2, the focus was on comparing functional parcellation and cortico-striatal RSFC of striatal subregions between human and macaque, identifying the human-specific striatal clusters and examining abnormal RSFC and structural atrophy of these striatal clusters between patients (with PD or SCZ) and HC. In Study 3, we introduced the regular steps of CBP analysis and developed an open, Python-based software package: *CBPtools*, which can improve the application of CBP and better to understand functional and structural organization of our brain.

### 5.1 Topographical organization of the human striatum

In Study 1, single-modal (RSFC, PDT and SC) and multi-modal parcellations results showed that the human striatum was divided into different subregions along the ventro-dorsal and rostro-caudal axes. At our final model ($n$ = 7), we obtained the ventral striatal cluster that was in line with most previous findings in functional and structural parcellations of the striatum. We also found the rostral striatum including the anterior caudate and putamen was similar to previous functional parcellation of the striatum based on RSFC (Jung et al. 2014; Choi et al. 2012; Jaspers et al. 2017). In addition, previous structural parcellation of the striatum by using PDT found the dorsal striatum was split into three striatal subregions along the anterior-posterior axis (Tziortzi et al. 2013). However, in our study, we only found a complete dorsal striatal cluster across different modalities. This result may reflect functional and structural homogeneity of the dorsal striatum. In sum, our results showed a stable functionally and structurally convergent organization of the striatum along the ventro-dorsal and rostro-caudal axes.

## 5.2 Convergent and divergent fundamental organization of the striatum

In Study 1, we found not only convergence, but also divergence striatal subregions among three modalities at different levels of subdivision ($n$ = 3-9). Generally, more divergent multi-modal clusters were found at lower levels ($n$ = 3-6). When the solution levels increased ($n$ = 7-9), more convergent striatal clusters across three modalities were observed. In detail, convergent striatal clusters including dorsal, dorsolateral, rostral, ventral, central and caudal (dorsal and ventral part) clusters for both left and right striatum were detected in multi-modal CBP analysis. Jarbo and Verstynen (2015) found functionally and structurally convergent organization of the rostral and dorsal striatum, because these two striatal subregions have similar convergent connectivity from orbitofrontal, lateral prefrontal, and posterior parietal cortices. In our study, using multi-modal CBP analysis, we reinforce these findings while further suggesting that the ventral, central and caudal clusters also exhibit a convergent functional and structural organization. Interestingly, we found more convergent striatal clusters with high level of subdivisions ($n$=7-9). At the coarser level, i.e. with few clusters, functional and structural parcellation may reflect different biological aspects of the striatum, in turn leading to divergent striatal subregions in multi-modal clustering. In addition, complex cortico-striatal projections form diverse integrative functional and structural circuits, which may induce more multi-modal convergent clusters at high level of subdivisions. Hence, more convergent functional and structural organization of the striatal subregions can be detected only at higher number of clusters in multi-modal CBP.

## 5.3 Functional characterization of striatal clusters

We applied the ‘‘behavioral domain’’ and ‘‘paradigm class’’ in the BrainMap meta-data (http://www.brainmap.org/) to examine the functions of each striatal subregions in Study 1. Most previous functional or structural parcellation of the striatum show that a symmetric subdivision in the striatum (Tziortzi et al. 2013; Pauli et al. 2016; Jung et al. 2014; Janssen et al. 2015), we hence created the symmetrical convergent striatal subregions in our study. The functions of each symmetrical convergent striatal subregion involve emotion, cognition and execution. In detail, the dorsolateral striatum (ventral caudate and dorsal putamen) was associated with several cognitive functions. The rostral and ventral striatal clusters were involved in commonly engaged behavioral functions, such as cognition and emotion. The caudal striatum (dorsal and caudal parts) was related to action execution functions. Our findings were consistent with previous studies (Cardinal et al. 2002; Pessoa 2009), which

indicated that the ventral striatum is involved in motivation and emotion, and play an important role in initiating behaviors. The caudate has been suggested to be involved in relevant cognitive functions, such as working memory and procedural learning (Grahn et al. 2008; Robinson et al. 2012), while the putamen is related to motor control and action execution (Marchand et al. 2008; Marchand et al. 2013). The striatum receives diverse projects from cerebral cortex and form multiple functional and structural circuits, which is related to goal-directed behaviors (Grace et al. 2007; Haber 2003). Such complex behaviors may require motivation at the beginning, and then a series of mental processes to select different strategies, and finally leading to action execution. Each striatal subregion may involve different functions, but they cooperate to process goal-directed behaviors.

### 5.4 Disease-related structural differences in striatal clusters

In Study 1, we found significantly lower GM volume of the entire striatum in patients (with PD and SCZ) than HC. Previous studies have found striatal morphological differences in patients (with PD and SCZ) compared to HC (Jia et al. 2015; Xu et al. 2016b; Fornito et al. 2009; Torres et al. 2016). In our study, significantly lower GM volume of rostral and ventral striatum were found in both PD and SCZ patients, however, significant structural atrophy in dorsolateral striatum was specifically attributable to PD patients. This may due to difference in pathology of PD and SCZ that induce divergent morphological changes in some striatal subregions for PD and SCZ patients. That is, the degeneration of dopaminergic nigrostriatal neurons that may result in abnormal depletion of striatal dopamine (Dauer and Przedborski 2003) in PD, while increased striatal dopamine activity may thought to be a fundamental mechanism for SCZ. In addition, most antipsychotic treatments target the dopaminergic receptors in the striatum and influence striatal metabolism in SCZ (Holcomb et al. 1996). These treatments may as well indirectly induce alteration in striatal morphometry.

### 5.5 Functional parcellation of the human and macaque striatum

In Study 2, we first investigated functional parcellation of human and macaque striatum by using RSFC. We found the human and macaque striatum were divided into caudate and putamen at the 2-cluster solution. Our parcellation results suggest a distinction of RSFC between the caudate and putamen for both human and macaque. As the caudate and the putamen in both human and macaque show anatomical division by the internal capsule, it is reasonable to find the caudate and putamen division based on their

distinct RSFC.

Increasing 'divergent' striatal clusters between human and macaque in visually can be found from a low to high level of subdivision. For example, at 6-cluster solution, the human anterior caudate that was not split, while the macaque anterior caudate was further divided into a dorsolateral and ventromedial cluster. This suggests a more homogenous RSFC within the human anterior caudate than within macaque anterior caudate. For dorsolateral and ventromedial cluster of the macaque anterior caudate, a previous non-human primate study has shown that the dorsolateral part structurally connects with the dorsolateral prefrontal cortex, while the ventromedial part connects with the lateral orbital frontal cortex (Alexander and Crutcher 1990). Our results are in line with and extend these previous findings, suggesting a convergent functional and structural connectivity of the anterior caudate in macaque.

In sum, we found different functional parcellations between human and macaque striatum using RSFC, especially concerning its anterior part. The human and macaque striatum connect to brain regions that may exhibit disproportionate volumetric differences during primate evolution, such as human prefrontal cortex (Carlén 2017; Smaers et al. 2017), hippocampus and amygdala (Barger et al. 2014). This may lead to differences in RSFC of several striatal subregions and reflect in differential functional parcellations of the striatum between human and macaque.

## 5.6 Cross-species comparison based on homologous cortico-striatal RSFC

In study 2, we further compared human and macaque striatal parcellations based on their homologous cortico-striatal RSFC, this may directly reflect the extent of similarity and differences in striatal subregions between the two species. We found that the anterior caudate and the whole putamen showed similar cortico-striatal RSFC between human and macaque. Although the congruent relationship between RSFC and microstructural connectivity is still poorly understood (Moerel et al. 2014; van den Heuvel et al. 2015), our results may supplement previous studies showing similarities in the cellular and molecular composition and functions of these striatal subregions across species (Betarbet et al. 1997; Haber and Knutson 2010; Hardman et al. 2002; Lohrenz et al. 2016). For instance, the caudal putamen in humans is likely to be more associated with motor functions. Similar cortico-striatal RSFC of this region in humans and macaques may reflect a homologous mechanism and ability in primary action execution. This result was consistent with previous findings similar cortico-striatal motor circuits

relating to the caudal/lateral putamen across human, macaque and mouse (Balsters et al. 2020).

However, difference in the cortico-striatal RSFC of the dorsal caudate was observed in the two species. A previous study has found that the caudate integrates visual information and reward context during the decision-making (Doi et al. 2020). Specifically, functional connectivity between dorsal caudate and dlPFC was found in previous studies (Robinson et al. 2012; Choi et al. 2012), which is related to motivation generating, such as the expected reward for behaviors and the prediction of contingency in behavioral outcome (Haber and Knutson 2010; Balleine et al. 2007; Mucci et al. 2015). During anticipation of reward, the dorsal caudate shows activation in humans, which has been observed in real-life motivation (Mucci et al. 2015). According to the expected reward, it may mediate which action is selected and associate the actions with outcomes in the goal-directed behaviors. Several previous findings have showed that the cortico-striatal circuits in both human and non-human primates play an important role in reward and decision-making (Balleine et al. 2007; Burton et al. 2015; Hiebert et al. 2017; Hollerman et al. 1998). But different functions between subregions of the caudate, and in humans, the participation of the dorsal caudate in the goal-directed behaviors whether is influenced by complex social interactions which lead to altered functional and structural connectivity of the dorsal caudate between human and non-human primate is still unclear. Compared to non-human primate, humans encounter diverse rewards, more complex decision-making during the real social life (Santos and Rosati 2015). This may have induced altered neural activity of the dorsal caudate and exhibit difference in cortico-striatal RSFC of the dorsal caudate between human and macaque.

On one hand, similar cortico-striatal RSFC of the striatal subregions, including the anterior caudate and the whole putamen, between humans and macaques probably reflected their functional homology cross-species. On the other hand, we found the dorsal caudate showed difference in the cortico-striatal RSFC between human and macaque may due to evolution. More complex social life in humans than macaque, may affect the neural activity of the dorsal caudate during the evolution. We speculate that the dorsal caudate may become more strongly connected with the frontal regions, for increasing its involvement in social interactive functions.

## 5.7 Clinically relevant cortico-striatal RSFC alteration in striatal clusters

In Study 2, we investigated differences in cortico-striatal RSFC of striatal subregions between patients (with PD and SCZ) and HC.

Through postmortem tissue, previous studies have found both caudate and putamen to exhibit abnormal density of dendritic spines, which reflect the dysfunction of cortico-striatal connections in PD patients (Stephens et al. 2005). In-vivo neuroimaging studies further showed altered cortico-striatal RSFC in PD patients compared to HC (Hou et al. 2016; Luo et al. 2014; Helmich et al. 2010). We found significantly lower cortico-striatal RSFC between caudal putamen and inferior parietal cortex (IPC) in PD patients compared to HC in line with previous findings (Helmich et al. 2010). The degeneration of dopaminergic nigrostriatal neurons generally induces abnormal depletion of striatal dopamine. Especially, for PD, this abnormality in posterior striatum is expressed more heavily, which may induce dysfunction of motor control in PD patients. The caudal putamen is related to motor functions within the cortico-striatal circuitry. For IPC, Samuel et al. (1997) fond its hyperactivity was observed in PD patients during simple finger movement. This reflects PD patients may highly recruit this region when performed simple motor tasks. Decrease in cortico-striatal RSFC between caudal putamen and IPC may suggest dysfunction of motor network for PD patients, which commonly supports previous findings (Wu et al. 2009; Michely et al. 2015; Barbagallo et al. 2017). In addition, we found PD patients to show significantly increased RSFC between dorsal caudate (i.e., the human-specific cluster) and the IPC. This may due to the compensatory mechanism, because dopamine depletion in the caudate is relatively slight than that in putamen for PD patients. Hence, increase in RSFC between dorsal caudate and IPC may compensate for the severe dopamine depletion in the caudal putamen that have induced decreased RSFC with IPC.

The dysfunction of the striatum is considered as a fundamental element relating to different hypotheses of the etiology of SCZ (Howes and Kapur 2009; Fatemi and Folsom 2009). Similar to the pathophysiology of PD, dopamine dysregulation in the striatum also have been found in SCZ. In the current study, significant differences in cortico-striatal RSFC of all striatal clusters were found between SCZ patients and HC. Specifically, compared with HC, we found significantly stronger RSFC between dorsal caudate (i.e., the human-specific cluster) and widespread cortices, such as temporal, visual areas, secondary auditory cortex and primary somatosensory cortex. Previous studies (Kirino et al. 2019; Salvador et al. 2010) have reported increased RSFC between striatum and widespread cortices, such as

prefrontal, temporal and cingulate cortex, in SCZ patients. Such increased cortico-striatal RSFC may reflect disruption of segregation between subcortical and cortical functional networks in SCZ patients (Kirino et al. 2019). In addition, significantly increased RSFC between striatal clusters (dorsal caudate, ventral and central putamen) and posterior cingulate cortex (PCC) was found in SCZ patients compared to HC. The PCC is a critical region in the default mode network (DMN). Previous study has found hyperconnectivity between caudate and medial orbital prefrontal cortex (another region relating to the DMN) in SCZ patients (Salvador et al. 2010). Our results were in line with this previous finding and suggested that more widespread striatal regions were involved in disruption of DMN-striatum connectivity.

### 5.8 Performing CBP analysis with *CBPtools*

In study 3, we implemented a standardized pipeline *CBPtools* with regularly used steps of CBP analysis, and then applied the *CBPtools* to parcel the right presupplementary motor area and supplementary motor area (preSMA-SMA), amygdala and insula. The whole procedure in *CBPtools* is customizable. Through a configuration file that allows researchers to perform different processing for a given ROI. The parameters in *CBPtools* can be changed, which make reproduction and comparison of any parcellation work relatively easy. Researcher can quickly checked the parcellations results and generated the validity metrics by using the output from *CBPtools*. Also, researcher can applied these parcellation results for post hoc analysis, such as multi-modal integration of different cluster solutions. In addition, we provided the guidance for the user to select optimal parcellation results across all *k* cluster solutions. In the future, the *CBPtools* will support another two neuroimaging modalities, meta-analytic connectivity modeling (MACM) and SC, also adding an additional option that joint multi-modal CBP analysis. We hope this open *CBPtools* can improve the development of investigating functional and structural organization of the brain region in neuroscience field.

For the application of the *CBPtools*, we selected most popular and widely used functional (RSFC) and structural connectivity (PDT) modalities, as well as the *k*-mean clustering approach to examine the functional and structural parcellation of right preSMA-SMA, amygdala and insula.

Dividing the preSMA-SMA has been popularly used to verify CBP methods (Johansen-Berg et al. 2004; Klein et al. 2007; Kim et al. 2010; Zhang et al. 2015), given it provides a gold standard and furthermore

reflects the ability of the CBP procedure through comparing with the histological parcellations. The preSMA connects with the motor regions while the SMA connects with prefrontal regions, these changes in connecting with different cortical regions can be used to detect where the borders of these two regions are (Johansen-Berg et al. 2004). We found functional parcellation by using RSFC and structural parcellation by using PDT are both highly matched the histological parcellations of preSMA-SMA [adjusted rand index (ARI) of 0.71 for RSFC, and 0.76 for PDT]. These results suggested that we can assess histological reproducibility of the preSMA-SMA by using our *CBPtools*.

Compared with simple parcellation of the preSMA-SMA, previous studies found different optimal cluster solutions for the parcellation of the insula: from 2-cluster solution (Cauda et al. 2011), 3-cluster solution (Deen et al. 2011), 4-cluster solutions (Kurth et al. 2010) to various solutions (Kelly et al. 2012). These differences may due to relatively small sample size, difficulties for inter-subject alignment, variability in methods were used between different research groups (Reuter et al. 2020). In our study, we found 2-cluster solution that dividing the insula into anterior and posterior subdivisions, is stable for both functional and structural parcellation. Whether this solution is neurobiologically optimal should be investigated in the future.

We also found 2-cluster solution is optimal for the functional and structural parcellation of the amygdala. The amygdala was divided into dorso-ventral subdivision by using RSFC. This result was in line with previous findings of (Mishra et al. 2014) showing similar subdivision along the dorso-ventral axis. Different from functional parcellation, the amygdala was split into medial and lateral subdivisions by using PDT. In previous studies, Solano-Castiella et al. (2010) and Fan et al. (2016) also divided the amygdala along the medio-lateral axis at 2-cluster solution. Although existing divergence between functional and structural parcellation of the amygdala, whether special convergent subregion of amygdala can be detected by using multi-modal analysis should be examined in the future.

## 5.9 Conclusions

This dissertation first revealed a convergent functional and structural organization of the human striatum by using a multi-modal CBP approach. The dorsolateral striatum was associated with cognition, the rostral and ventral striatum were related to emotion and cognition separately, while the caudal striatum (dorsal and ventral parts) was involved in action execution functions. Common structural atrophy (GM

volume) in the rostral and ventral striatum were found for PD and SCZ, but the structural atrophy in the dorsolateral striatum was specifically attributable to PD. Next, based on functional CBP, we revealed that the human striatum constitutes dorsal, dorsomedial, and rostral caudate and ventral, central, and caudal putamen, while the macaque striatum was split into dorsal, and rostral caudate and rostral, and caudal putamen. We found dissimilar cortico-striatal RSFC of the dorsal caudate between humans and macaques, which suggesting its connectivity to be human-specific. Also, abnormal RSFC of this striatal cluster with widespread cortical regions was found in both PD and SCZ, but GM difference in this striatal cluster was observed only in PD. These results revealed shared and human-specific RSFC of striatal clusters reinforcing the complex functional organization the striatum. In addition, we developed an open source, Python-based software package (i.e., *CBPtools*) may help researchers to investigate functional and structural organization of the brain regions. In sum, this dissertation mainly revealed the multi-modal convergent organization of the human striatum, these striatal clusters can be applied in investigating both structural and functional variability for aging and diseases. Meanwhile, we investigated functional parcellation of the striatum with cross-species comparison and suggested abnormalities in dorsal caudate may be associated with human neuropsychiatric disorders.

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