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Analyzing spatial transcriptomics and neuroimaging data in neurodegenerative diseases

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Citation

Keo, D. (2020, December 3). *Analyzing spatial transcriptomics and neuroimaging data in neurodegenerative diseases*. Retrieved from <https://hdl.handle.net/1887/138480>

Version: Publisher's Version

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Title: Analyzing spatial transcriptomics and neuroimaging data in neurodegenerative diseases

Issue Date: 2020-12-03

CHAPTER 1

INTRODUCTION

1.1 MOLECULAR MECHANISMS OF NEURODEGENERATIVE DISEASES

1.1.1 NEURODEGENERATIVE DISEASES

The life expectancy of the global population is expected to keep increasing, especially in the western world where people live longer due to better health care and improved living conditions [1]. The downside is that increased age comes with age-related neurodegenerative diseases [2] that are characterized by the progressive loss of neurons in the central nervous system, eventually leading to deficits in brain functions affecting movement and cognition [3]. Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD) and affects 1% of the population at the age of 65 years [4]. Recently, it has been reported that PD is the fastest growing neurological disorder in the world and the number of cases is expected to keep increasing [5]. PD is characterized by the loss of dopaminergic neurons in the substantia nigra leading to motor dysfunction e.g., slowness, and rigidity. Currently available treatments help to control motor symptoms, but cannot slow down disease progression [6]. It is well-recognized that alterations within the basal ganglia neuronal circuit play a role in the etiology of PD, but the basal ganglia is also involved in the etiology of Huntington's disease (HD) [7,8]. Due to cell loss in the basal ganglia, both neurodegenerative diseases may be accompanied by neuropsychiatric symptoms including depression and schizophrenia, which drastically impacts the quality of life [9,10]. Computational tools enable the analysis of large biological datasets to better understand the molecular and clinical traits of neurodegenerative diseases. In this thesis, we mainly focused our research on PD, but we also studied HD and the risk to develop schizophrenia. Our research findings can aid to provide new insights into the etiology of PD and other neurodegenerative diseases with an outlook to improved treatment and preferably the early prevention of PD.

1.1.2 AGING VERSUS NEURODEGENERATION

Healthy aging and neurodegenerative diseases are generally associated with a decline in resistance to cellular stress that may lead to cell death affecting brain function [11]. Initially, PD patients show similar rates of dopaminergic cell loss as to healthy individuals, but as time progresses neurodegeneration is accelerated and the first signs of motor symptoms start to appear (Figure 1.1) [12]. The pre-motor stage is associated with mild motor symptoms, but non-motor features may also occur early in the course of the disease, e.g., symptoms of pain, depression, cognitive dysfunction, dementia, sleep disturbance, and constipation [13,14]. In the early stage of PD, symptoms are often confused with signs of aging and may therefore go unnoticed. As the disease progresses and symptoms start to impair daily activities, PD patients are diagnosed based on clinical assessment scores for motor and non-motor symptoms [15,16]. Generally, when a patient is first diagnosed, a substantial proportion of dopaminergic neurons in the substantia nigra has already been lost, and neurodegeneration has also spread to other regions of the central nervous system [6]. Findings over the past years have revealed that PD is a complex disease with some clinical challenges, for example the inability to make a definitive diagnosis at the early stages of PD and difficulties in managing the symptoms at later stages [17]. In general, the

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pathogenesis of PD is multifactorial and results from a combination of aging, and genetic and environmental factors [18].

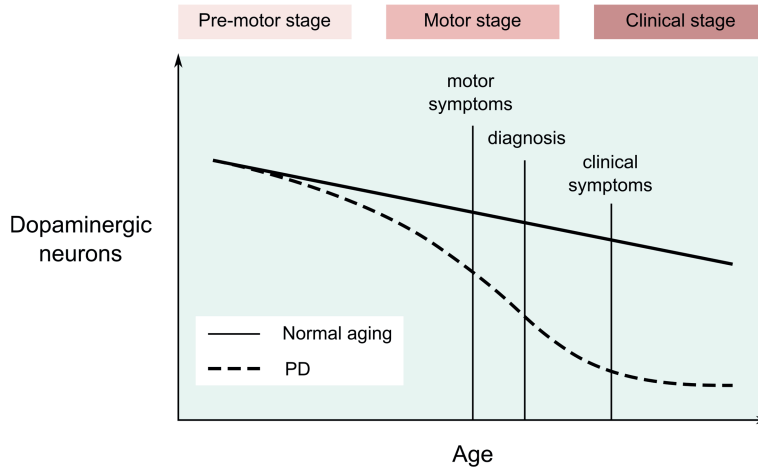


Figure 1.1 Schematic representation of the progression of the level of dopaminergic neurons during normal aging versus aging in Parkinson's disease (PD).

1.1.3 NEUROPATHOLOGY AND CAUSE OF PARKINSON'S DISEASE

PD diagnosis is essentially clinical but has to be confirmed upon post-mortem neuropathological examination by confirming the loss of dopaminergic neurons in the substantia nigra and the presence of protein inclusions called Lewy bodies (LBs) [19]. The Braak staging scheme has been proposed to assess the staging of the brain pathology in PD for neuropathological diagnosis [20]. According to Braak's theory, LBs first appear in the brainstem and then spread to selective brain regions during the course of the disease, manifesting in motor and non-motor symptoms (Figure 1.2). PD comprises a spectrum of disorders with different subtypes, for which most also share the LB pathology [21]. LBs are composed mainly of α -synuclein proteins encoded by the gene *SNCA* that plays a regulatory role in dopamine homeostasis [22]. There are also PD cases where LBs are not found in the brain. These patients were usually early-onset (before the age of 40 years), slow progressing, and neuronal loss was mostly restricted to the substantia nigra [23]. Aside from PD, there are a number of other atypical parkinsonian syndromes (e.g., dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration) that show abnormal protein depositions of α -synuclein or tau together with parkinsonism; a combination of PD-related symptoms, namely bradykinesia with rigidity, tremor, or postural instability [24]. Point mutations in the *SNCA* gene as well as duplication and triplication variants have been associated with familial PD, but how these genetic variants results in LB pathology remains unclear [25]. It has been suggested that the spreading of LB pathology seems to occur across anatomical brain networks and is mostly explained by α -synuclein expression [26]. Mutations in *SNCA* are involved in both familial and sporadic PD, but it is unclear whether *SNCA* has a causative role or it is just a bystander of disease

mechanisms [21]. Other genetic mutations in more than 20 genes have been identified in familial and population studies of PD patients, including rare monogenic causes [27–30], however only 10% of PD cases is ascribed to monogenic mutations [31]. The heritability of risk to develop PD is 60% which can be partly explained by pathogenic mutations and the major risk genes, but the remaining 40% is due to yet unidentified genes [32].

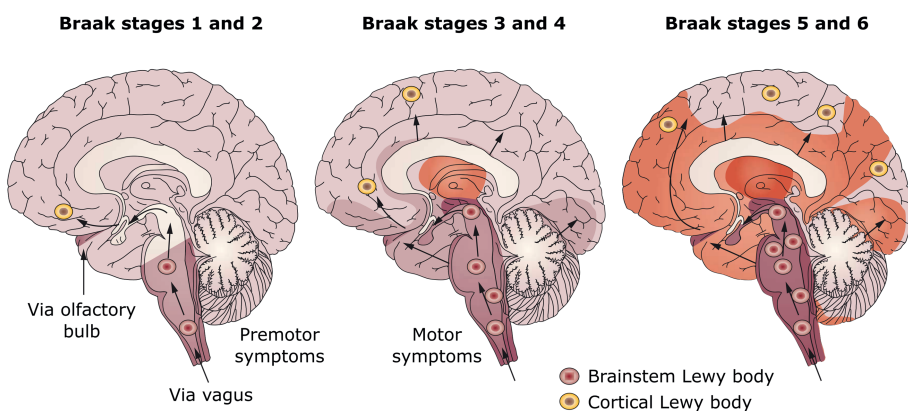


Figure 1.2 Braak staging scheme of Parkinson's disease. The six Braak stages describe the spread of Lewy bodies from the brainstem to limbic and cortical regions and are associated with the progression of clinical symptoms. Image adapted from Doty (2012) [33].

1.1.4 GENETIC CAUSE OF HUNTINGTON'S DISEASE

HD may serve as a model to study neurodegenerative diseases as it is monogenic, dominantly inherited, and also a disorder of protein misfolding [34]. The striatum is most severely affected in HD, but other brain areas also show neuronal loss [35]. Interestingly, HD and PD are characterized by opposite movement disorders: slowness and rigidity are symptoms observed in PD, while excessive and uncontrolled movements are typical in HD [36]. The nigrostriatal circuit, connecting the striatum and substantia nigra, plays a role in the initiation or termination of voluntary movements and is impaired in disorders like PD and HD (Figure 1.3) [37]. The cause of HD is a CAG-trinucleotide repeat expansion in the *HTT* gene coding for polyglutamine (polyQ) amino acids in the huntingtin protein and leads to improper folding of mutant huntingtin proteins (Figure 1.4) [38]. The CAG-trinucleotide normally occurs with up to 35 repeats in tandem, while an increased number of repeats of 40 or more causes HD [39]. Interestingly, the size of the repeat expansion has a strong negative correlation with the age at onset of the disease [40] and the expanded CAG-repeat length in other genes also determines the age at onset of a wide spectrum of other neurodegenerative diseases including multiple spinocerebellar ataxias (SCAs), dentatorubralpallidoluysian atrophy (DRPLA), and spinobulbar muscular atrophy (SBMA) which are also characterized by progressive motor and cognitive deficits [41]. Furthermore, it has been shown that the age of onset in HD is also influenced by the CAG-repeat variations in other genes associated with polyQ diseases suggesting that there are interactions between polyQ genes [42]. Defects in DNA repair mechanisms are thought to underlie the age at onset of HD and SCAs

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[43]. In addition, movement disorders that appear in PD and HD, including parkinsonism and chorea, are also frequent in SCAs [44]. This suggests that PD and polyQ diseases share common disease mechanisms and that genetic factors can influence disease onset.

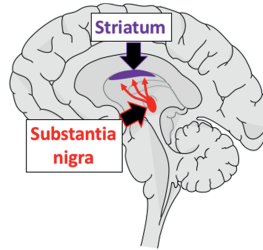


Figure 1.3 The nigrostriatal pathway is one of the four dopamine pathways and connects the striatum to the substantia nigra. Image credit: Pharmwiki [45].

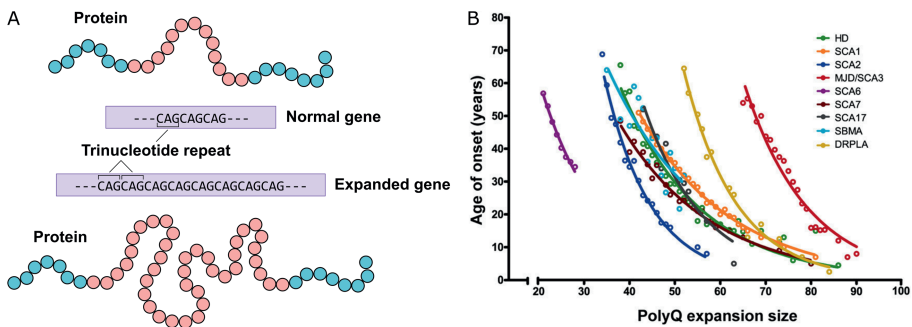


Figure 1.4 CAG-trinucleotide repeat expansions in polyglutamine (polyQ) diseases. (A) CAG-repeats are translated to polyglutamine amino acids, but an expansion in the number of repeats causes the misfolding of proteins. (B) Age at onset is strongly influenced by the CAG-repeat size in the causative gene of nine polyQ diseases. Circles depict the mean age at onset for a given expansion size based on multiple cohorts of patients. Image adapted from Kuiper et al. (2017) [46].

1.2 SPATIAL TRANSCRIPTOMICS TO STUDY NEURODEGENERATIVE DISEASES

1.2.1 TRANSCRIPTOMICS OF PARKINSON'S DISEASE

Although several genetic and environmental factors have been associated with the development of PD, the underlying pathobiology remains poorly understood. Transcriptomics can yield new insights into the disease mechanism by measuring genome-wide expression profiles of samples derived from brain tissue. The whole human genome is estimated to have ~20,000 protein encoding genes for which the amount of RNA transcripts per gene can be measured with microarray chips or RNA-sequencing techniques. The goal of most transcriptomic studies in PD is to find genes that are differentially expressed between PD patients and age-matched controls and assess whether they are enriched for genes associated with known biological pathways. The majority of these studies analyzed samples from the substantia nigra; a structure of the basal ganglia that shows loss of

dopaminergic neurons in PD. Transcriptomic studies of PD have been limited by the small number of samples (less than 40 PD cases) due to difficulties in sample selection, namely the limited availability of well-characterized patients, and cases and controls that should be well matched based on age, ethnicity, and gender [47]. To overcome this limitation, animal models have been developed to mimic the clinical symptoms of PD, however it remains unclear to what extent the underlying gene expression patterns reflect those in human PD or how well these animal models mimic phenotypes observed in PD [48,49]. Gene expression profiles have also been retrieved from blood samples of patients, however these samples do not reflect the transcriptomic signatures of the brain [47,50–52]. Furthermore, researchers have used induced pluripotent stem cells (iPSC) from patients to generate specific neuronal cell-types, such as dopaminergic cells, but iPSC technology is still challenging and poorly understood by scientists [53,54]. Another limitation of transcriptomic studies of PD is that brain samples are derived from patients in the late stage of the disease and therefore they cannot investigate the early changes that lead to the development of PD [55]. Improving our understanding of PD in its prodromal phase during midlife is essential to enable early stage PD diagnosis [14]. Finally, transcriptomic data from PD brains that are currently available do not cover many brain regions, and there are only few PD studies that analyzed multiple brain regions from the same donors [56]. Taken together, more extensive brain-wide gene expression analyses can help to understand the spatial context of gene expression and their functions that may be dysregulated in neurodegenerative diseases.

1.2.2 TRANSCRIPTOME MAP OF THE HEALTHY BRAIN

Spatial transcriptomics is a method where gene expression is analyzed in a spatial context to understand how gene transcription activity is organized across a tissue or organ, such as the brain. Generally, it seems that gene expression varies more between brain regions than between individuals [57]. The Allen Human Brain Atlas (AHBA) is a high resolution gene expression atlas covering the whole brain [58]. It was established by collaborative efforts of multi-disciplinary scientists and made publicly available for neurobiological research. Almost 4,000 samples were collected from post-mortem brains of six healthy adult donors without a neurological or neuropsychiatric history (Figure 1.5). To map brain-wide transcriptomic profiles, brains were carefully dissected while keeping track of anatomical annotations and spatial coordinates based on magnetic resonance imaging (MRI) scans. This brain-wide gene expression dataset helps to unravel functions of different brain structures and their spatial organization. Since its publication the AHBA has been used extensively to yield new insights into diseases of the central nervous system such as migraine [59], schizophrenia [60,61], and AD [62–65]. By analyzing the transcriptome of brain regions that are vulnerable in disease, studies were able to establish the expression patterns of disease-implicated genes and provide new insights into disease mechanisms. In studies of neurodegenerative diseases, brain regions of interest were defined based on the vulnerability to neurodegeneration and/or protein aggregation from imaging studies or pathological findings. Altogether, the AHBA has offered new opportunities to link molecular function to brain organization and defects in neurological diseases and can also be of great value to unravel the molecular mechanisms underlying vulnerable brain regions in PD or HD.

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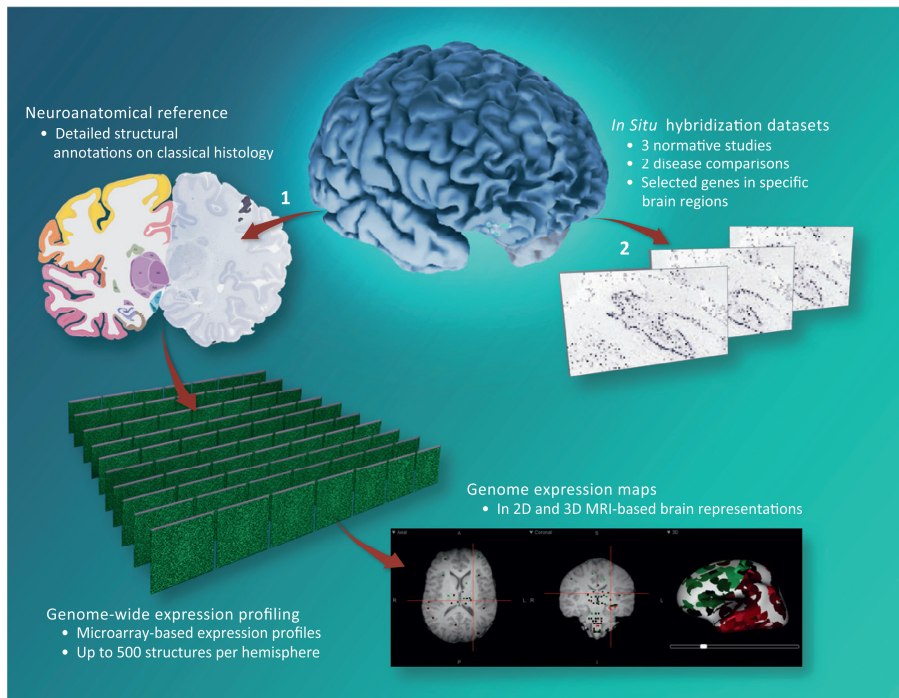


Figure 1.5 Allen Human Brain Atlas. Gene expression map of the healthy human brain. Image credit: Shen et al. (2012) [66].

1.3 COMPUTATIONAL APPROACHES IN INTEGRATING GENOMICS WITH NEUROIMAGING

1.3.1 PHENOTYPIC INFORMATION FROM NEUROIMAGING

Neuroimaging is a method to study functional neuroanatomy, brain-behavior relationships and the pathophysiology of brain disorders [67], and thus provides useful phenotypic features of the brain. It allows detecting differences in imaging features between a group of patients and controls in vivo to assess, for example, the loss of gray matter in PD brains. Differences between disease cases and controls are statistically assessed to highlight brain areas with significant structural or functional changes associated with the disease. The two main imaging techniques are structural MRI, that measures morphological properties of the brain (e.g., cortical thickness and volume), and functional MRI (fMRI), that measures blood oxygen flow to identify functionally connected brain regions based on their activity during task-based performance or in resting state. In PD imaging studies, the region of interest often includes anatomical structures of the basal ganglia, nigrostriatal projections, the cortex and other regions involved in the motor circuit [68,69]. Some MRI studies did not focus only on specific anatomical structures, but analyzed the entire brain to unbiasedly identify new brain regions vulnerable to atrophy in PD [70]. Structural covariance is an MRI method to identify anatomical networks of the brain based on gray matter variation across a population of individuals [71]. The co-varying regions in structural covariance networks

(SCNs) are thought to arise from functionally connected brain regions. Both functional and structural networks define a set of connected brain regions that can be compared between PD and controls to find associations with gray matter loss that is indicative of atrophy within such networks. Interestingly, several PD imaging studies highlighted relationships between structural or functional MRI changes in PD and the severity of clinical symptoms [72–78]. In addition, neuroimaging genetics studies analyzed MRI differences between groups of patients with different mutations associated with subtypes of PD [79–81] or AD [82]. It would be interesting to combine spatial transcriptomics with neuroimaging of PD brains to reveal deeper insights into the molecular mechanisms; however transcriptomic studies of PD have been limited to few selected brain regions.

1.3.2 NEUROIMAGING AND TRANSCRIPTOMICS TO STUDY NEURODEGENERATIVE DISEASES

Analyzing the transcriptional activity of structural or functional brain networks could reveal new insights into the molecular organization of the brain. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) allow whole brain imaging of molecular changes in patients *in vivo*, but are limited to the analysis of a single receptor, transporter, or enzyme [83]. The AHBA provides a whole-genome expression map of the healthy brain that can be combined with neuroimaging data to correlate transcriptomic signatures with phenotypic features of the brain. Each sample in the AHBA is annotated with spatial MNI coordinates that can be used to map the gene expression samples to brain regions defined by MRI, for example to determine which samples fall within or outside a region of interest. In recent years, studies have used varying approaches to combine neuroimaging data with the AHBA, but the processing of gene expression data has been highly variable [84]. In general, the AHBA is used to examine gene expression profiles across brain regions or networks that were identified in neuroimaging studies to find correlations with imaging features, such as network function or gray matter loss. In studies of neurological disorders, genes may behave differently across disease-related regions compared to control regions that are considered unaffected. The control region can be the whole brain, or a region known to not be involved in the disease. The differential activity of these genes that are correlated with imaging features inform about the cellular mechanisms that may be involved in disease. Gene co-expression analysis is a powerful robust method to understand transcriptomic organization [85]. Co-expression of samples across genes has revealed a network of samples that mimicked a network detected with fMRI [86]. Alternatively, the correlation between genes across a set of samples measures whether two genes behave similarly. This information can be used to create a network of putative gene interactions. Commonly, gene co-expression patterns have been analyzed in samples from specific tissues across individuals, but can also be examined spatially across samples from different brain regions. Analyzing spatial gene co-expression patterns in selected brain regions informs about the spatial organization of molecular pathways and on how gene interactions are regulated differently in different brain regions. Based on their co-expression similarity, genes may be clustered into groups referred to as co-expression modules. Whole brain analysis of both imaging features and gene expression patterns allows finding correlations between two data modalities [87–89]. Previous studies that combined neuroimaging data with spatial transcriptomics have shown that there are

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multiple ways to analyze gene expression patterns in brain regions defined by imaging technologies (Figure 1.6). In other words, analyzing the healthy transcriptome of brain regions associated with neurodegenerative diseases have shown to improve our understanding of genes and their role in disease pathology.

1.3.3 FUNCTIONAL INTERPRETATION OF FINDINGS

Genes resulting from computational analyses need to be investigated for the presence of interesting genes for which a functional role has been earlier described. Functional enrichment analysis assesses whether there is an overrepresentation of groups of genes associated with specific functions, pathways, diseases, or cell-types. There exists multiple curated databases with gene annotations that can be used for gene set enrichment analysis (the Gene Ontology resource [90,91], Reactome pathway database [92], KEGG [93], DisGENet [94], etc.) to aid in the functional interpretation of transcriptomic findings. Gene markers that are known to be uniquely expressed in specific cell-types can be used to identify the presence of cell-types. Immunohistochemical staining of cell-type markers is extensively used to reveal the presence and abundance of specific cell-types in brain slices, such as staining for *TH* (tyrosine hydroxylase) to reveal the loss of dopaminergic cells in PD [95]. In neurodegenerative diseases like PD and HD there is remarkable loss of neuronal cells compared to healthy individuals [96]. Interestingly, cell-types associated with immune responses (e.g., astrocytes, microglia) are more abundant in the neurodegenerative brain. Therefore, studies that perform transcriptomic analysis of bulk tissue samples between patients and controls have to be aware of the different cell populations within samples. Also, when comparing tissues from different brain regions, an overrepresentation of cell-type markers may reflect the anatomical organization of brain regions, for example gene markers for neuronal cells are highly expressed in the synapse-dense cortex. The cell-type composition has, with no doubt, an influence on the measured gene expression profile, but normally the true cell-type compositions of bulk tissue samples are unknown. Several methods have been proposed that use cell-type markers to estimate cell-type composition and correct differential expression analysis results based on these estimations [97–100].

While there are many genetic risk factors associated with PD, their functional role in the development of PD remains unclear. Several studies that combined neuroimaging data with the AHBA focused on the brain-wide expression of genetic risk factors and revealed regional gene activity that was correlated with imaging features in PD [101,102]. The expression pattern of genetic risk factors can aid to better understand how genetic mutations lead to molecular deficits in affected brain regions [103]. While genetic risk factors provide a direct link to the disease, whole transcriptomic analysis reveals more interesting genes that can explain the molecular mechanisms underlying neurodegenerative diseases. Previous studies have shown the various possibilities to analyze neuroimaging data with brain-wide transcriptomic data, and provide examples of how to use similar computational tools to unravel molecular mechanisms underlying brain regions and networks that are vulnerable to PD and HD.

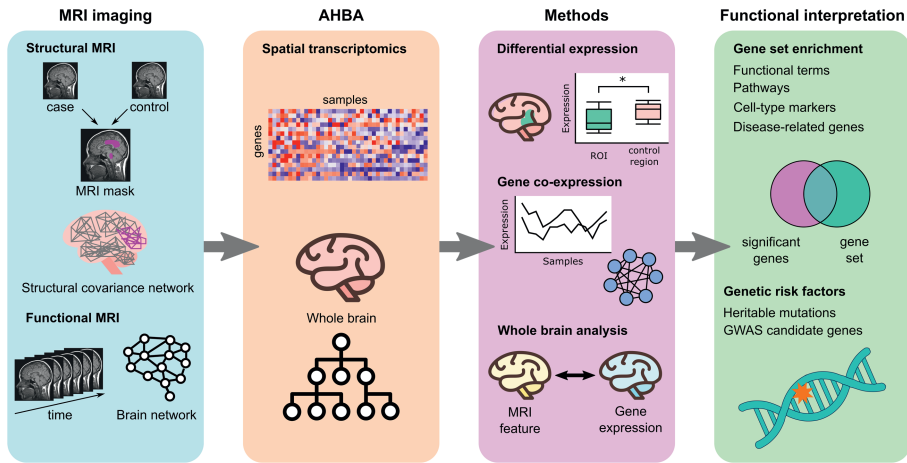


Figure 1.6 An overview of computational approaches to combine neuroimaging data with spatial transcriptomics from the AHBA to study neurodegenerative diseases. Neuroimaging provides phenotypic information and can be used to create structural or functional networks and find changes between disease cases and controls. Combining neuroimaging data with spatial transcriptomics enables the analysis of gene expression in brain regions that are vulnerable in disease. Brain samples from the AHBA were collected according to a hierarchical ontology. The whole brain is on top of the hierarchy and splits into more detailed brain structures. Common methods to analyze neuroimaging with spatial transcriptomics are differential gene expression in regions of interest (MRI mask), gene co-expression across selected samples, and whole brain analysis of both data modalities using an integrated approach. For functional interpretation, findings are assessed for the overrepresentation of known gene sets and/or genetic risk factors associated with the disease.

1.4 CONTRIBUTION OF THESIS

This thesis describes our research on exploring the relationship between the gene expression profile of different brain regions and age-related neurodegenerative disorders. We mainly focused our research on PD, but also used similar computational tools to understand molecular mechanism underlying HD and polyQ genes, as well as schizophrenia. Our main hypothesis is that certain genes are important to maintain normal molecular functions in the healthy state, while dysfunctioning of these genes may underlie the vulnerability to neurodegeneration in specific brain regions. We sought to answer multiple research questions to detect such genes and consequently improve our understanding of PD, and other neurodegenerative diseases:

- Which genes are differentially expressed in brain regions associated with disease?
- Which biological functions or pathways are associated with these genes?
- How is the spatial expression of genetic risk factors involved in disease?
- Which molecular interactions are associated with specific brain regions?

We used and developed various bioinformatics tools to combine neuroimaging data with spatial transcriptomic data to reveal genes of interest and its associated functions that may

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be involved in the pathology of neurodegenerative diseases. In each chapter, we exploited the AHBA to understand gene expression patterns across the healthy brain as a guide to better understand the molecular mechanisms underlying neurodegenerative diseases. With this approach, we rely on previous studies that have shown that spatial gene expression patterns can reveal new insights into the functional organization of the brain, and how dysfunctional regulation may lead to the development of neurodegenerative diseases.

In Chapter 2, we used spatial transcriptomics to study molecular functions of structural brain networks that may explain patterns of neurodegeneration in PD. Comparative analysis between the transcriptomics signatures of multiple SCNs obtained from MRI revealed the presence of cholinergic genes that may be associated with patterns of atrophy in PD.

In Chapter 3, we proposed that polyQ genes likely interact because CAG-repeat lengths within these genes strongly influences the age at onset of HD. We revealed co-expression between *HTT* and polyQ genes *ATN1* and *ATXN2* in anatomical structures involved in HD and a region associated with neurodegeneration in HD based on MRI images of patients. The co-expression patterns suggest potential interactions between the three polyQ genes in brain regions that are vulnerable in HD and the shared co-expressed genes among the three polyQ genes suggests the involvement of DNA repair pathways.

In Chapter 4, we used similar computational tools to investigate the molecular mechanisms underlying a stress network defined by task-based fMRI in individuals at risk of schizophrenia. Genes differentially expressed within the network showed associations with stress-related psychiatric disorders, neuronal cell populations, and neurotransmitter receptors. Many of the differentially expressed genes have been described to interact with the HPA-axis, a neuro-endocrine system that controls hormonal stress.

In Chapter 5, we propose that brain-wide gene expression patterns can predict cortical atrophy in PD brains and possibly the relationship between cortical atrophy and the severity of clinical symptoms. In this study, we used a multimodal approach to understand the behavior of groups of genes instead of individual genes and their correlation with patterns of neurodegeneration. Regional cortical thickness changes in PD were correlated with pathways associated with the maintenance of cellular health. Without any assumptions on the involvement of genes and vulnerable brain regions in PD, our findings highlight the activity of biological pathways across the cortex that are correlated with cellular maintenance mechanisms that previously have been associated with PD.

In Chapter 6, we used the Braak staging scheme for PD to define a set of brain regions that are known to be progressively affected during the different clinical stages of PD. The gradual spreading of Lewy bodies might be explained by the underlying molecular mechanisms of the involved brain regions. We revealed genes, including *SNCA* and other genetic risk factors, for which their healthy expression pattern correlated with the Braak stages of brain regions. These correlation patterns were not preserved in Braak stage-

involved regions of PD patients. Additionally, we highlighted two co-expression modules involved in dopamine biosynthesis and blood-oxygen control whose expression signature was shown to be correlated with Braak stages. Understanding the transcriptomic differences between brain regions with different vulnerabilities to PD provided new insights into the progression of PD.

Each chapter helps to understand the spatial organization of gene transcription activity and how dysregulation of molecular processes may lead to symptoms apparent in neurodegenerative diseases. Finally, we discuss the contribution of our work to HD and PD research and our perspective on future research to improve our understanding of neurodegenerative diseases.

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CHAPTER 1