



**Data Integration and trans-Omics
Analysis for Reconstructing relevant
Pathways and Networks underlying
Neurodegenerative Diseases**

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Abstract

Neurodegenerative diseases are characterized by the progressive decline of neuronal and glial structures and functions, affecting both the central and peripheral nervous system. This deterioration results in impaired cognitive and/or motor abilities. Despite their significant impact on patients' and caregivers' quality of life as well as on public health costs, and despite a great number of ongoing investigations, no effective treatment has been found, due to the complex nature of these disorders.

As complex diseases arise from a combination of genetic, environmental, and life-style factors, addressing them requires comprehensive identification and quantification of components encompassing gene, transcript and protein-level information to uncover the interconnected pathways, circuits, and networks involved. Advances in high-throughput technologies and bioinformatics, coupled with powerful computational and statistical modeling tools, enable the characterization of DNA sequences, transcripts, proteins, lipids, metabolites, and other biomolecules as entities on their specific omics-level, facilitating a broader understanding of disease mechanisms.

The objective of this thesis was to study neurodegenerative diseases using a multi-omics approach. To achieve this goal, four of the most prevalent neurodegenerative diseases were selected for analysis and comparison across four different omics levels. This approach aimed to uncover common mechanisms as well as distinct patterns among the diseases or omics levels, hopefully providing insights into the etiology and pathogenesis of these debilitating conditions. The diseases included the most prominent proteinopathies Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis, and Huntington's Disease. The omics levels examined were the Genome, the Transcriptome, the Proteome and DNA-Methylation (Epigenetics). Common features and mechanisms of neurodegeneration, such as protein misfolding and aggregation, chronic inflammation, mitochondrial dysfunctions, impaired Ca^{2+} homeostasis, a deregulated autophagy and apoptosis, and inadequate stress response could be confirmed for all four diseases. But also differences could be distinguished in a very promising field, the circadian rhythm, which we found to be disrupted in a disease-specific manner in all four diseases. These disruptions originate from a deregulated sleep pattern and a deregulated metabolism, which are both strongly prevalent in industrialized countries, leading to the very symptoms of neurodegeneration. In a case study focussing

on deregulated circadian rhythm genes our work shows how to proceed with the provided data. The results of this case study are pointing to the importance on restoring healthy sleep patterns in order to prevent or at least prolong early disease stages. Future work could be done in the same way for detecting disease-specific differences in the main metabolic pathways, the AMPK- and the mTOR pathways.

Zusammenfassung

Neurodegenerative Erkrankungen sind durch den fortschreitenden Abbau neuronaler und glialer Strukturen und Funktionen gekennzeichnet, der sowohl das zentrale als auch das periphere Nervensystem betrifft. Dies führt zu einer Beeinträchtigung kognitiver und/oder motorischer Fähigkeiten. Trotz ihres erheblichen Einflusses auf die Lebensqualität von Patienten und deren Angehörigen sowie auf die Kosten des Gesundheitswesens und trotz einer Vielzahl laufender Forschungsarbeiten wurden bisher keine wirksamen Behandlungen gefunden, was auf die komplexe Natur dieser Erkrankungen zurückzuführen ist. Da komplexe Erkrankungen durch eine Kombination genetischer, umweltbedingter und Lifestyle Faktoren entstehen, erfordert ihre Erforschung eine umfassende Identifizierung und Quantifizierung möglichst vieler beteiligter Komponenten, um die zugrunde liegenden miteinander verbundenen Signalwege, Kreisläufe und Netzwerke aufzudecken. Fortschritte in Hochdurchsatztechnologien und Bioinformatik, kombiniert mit leistungstarken rechnergestützten und statistischen Modellierungswerkzeugen, ermöglichen die Charakterisierung von DNA-Sequenzen, Transkripten, Proteinen, Lipiden, Metaboliten und anderen Biomolekülen auf ihren jeweiligen Omics-Ebenen und tragen zu einem umfassenderen Verständnis der Krankheitsmechanismen bei. Ziel der folgenden Arbeit war es, neurodegenerative Erkrankungen mit einem Multi-Omics-Ansatz zu untersuchen. Zu diesem Zweck wurden vier der häufigsten neurodegenerativen Erkrankungen für die Analyse und den Vergleich über vier verschiedene Omics-Ebenen hinweg ausgewählt. Mit diesem Ansatz sollten sowohl gemeinsame Mechanismen als auch spezifische Muster zwischen den Erkrankungen oder Omics-Ebenen aufgedeckt werden, um Erkenntnisse über deren Entstehung und Pathogenese zu gewinnen. Die untersuchten Krankheiten waren die Proteinopathien Alzheimer, Parkinson, Amyotrophe Lateralsklerose und Chorea Huntington. Die analysierten Omics-Ebenen waren das Genom, das Transkriptom, das Proteom und die DNA-Methylierung (Epigenetik). Die bekannten gemeinsamen Merkmale und Mechanismen der Neurodegeneration wie Proteinefehlfaltung und -aggregation, chronische Entzündungen, defekte Mitochondrien, gestörte Ca^{2+} -Homöostase, eine deregulierte Autophagy und Apoptose sowie unzureichende Reaktionen auf oxidativen Stress, konnten für alle vier Erkrankungen bestätigt werden. Gleichzeitig konnten jedoch auch Unterschiede in einem sehr vielversprechenden Gebiet, dem circadianen Rhythmus, festgestellt werden,

der bei allen vier Krankheiten auf krankheitsspezifische Weise gestört ist. Diese Störungen resultieren aus einem deregulierten Schlafmuster und einem dysfunktionalen Stoffwechsel, beides Probleme, die in industrialisierten Ländern stark verbreitet sind und die auch zu den typischen Symptomen der Neurodegeneration führen können. In einer Fallstudie, die sich auf deregulierte Gene des circadianen Rhythmus konzentrierte, zeigt unsere Arbeit, wie man mit den bereitgestellten Daten vorgehen kann. Die Ergebnisse dieser Fallstudie weisen darauf hin, wie wichtig es ist, gesunde Schlafmuster wiederherzustellen, um neurodegenerativen Erkrankungen vorzubeugen oder deren Beginn zumindest hinauszuzögern. Zukünftige Arbeiten könnten in ähnlicher Weise durchgeführt werden, um krankheitsspezifische Unterschiede in den zentralen Stoffwechselwegen, insbesondere den AMPK- und mTOR-Signalwegen, zu identifizieren.

List of Abbreviations

Aβ	amyloid β
AD	Alzheimer's Disease
ADAM10	ADAM Metallopeptidase Domain 10
AICD	APP Intracellular Domain
ALS	Amyotrophic Lateral Sclerosis
AMPK	AMP-activated Protein Kinase
ANG	Angiogenin
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
ATP	Adenosin Triphosphate
ATXN2	Ataxin 2
BACE1	β -Secretase or -site of APP cleaving enzyme
BBB	Blood Brain Barrier
BP	Biological Processes
C9orf72	Chromosome 9 open reading frame 72
ccg	Clock-controlled Genes
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain containing 10
CNS	Central Nervous System
CoA	Coenzyme A
CpG	Cytosine-Guanine

DCTN1	Dynactin 1
DEG	Differentially Expressed Genes
EOAD	Early Onset Alzheimer's Disease
eQTL	expression Quantitative Trait locus
ER	Endoplasmatic Reticulum
FAD	Familial Alzheimer's Disease
FAN1	FANCD2 And FANCI Associated Nuclease 1
FDA	U.S. Food and Drug Administration
FTD	Frontotemporal dementia
FUS	Fused in Sarcoma
GABA	γ -Aminobutyric acid
GO	Gene Ontology
GSH	Glutathione
GSK3β	Glycogen Synthase Kinase 3 β
GWAS	Genome-wide Association Studies
HD	Huntington's Disease
HMTM	Hydromethylthionine Mesylate
hnRNPA1	Heterogeneous nuclear ribonucleoproteins A1
HSP90	Heat Shock Protein 90
HTT	Huntingtin
HUGO	Human Genome Organisation
IgG1	Immunoglobulin G1
IL-1	Interleukin 1
KEGG	Kyoto Encyclopedia of Genes and Genomes
KIF5A	Kinesin heavy chain isoform 5A

LIST OF ABBREVIATIONS

LD	Linkage disequilibrium
LIG1	Ligase 1
lncRNA	long noncoding RNA
LOAD	Late-Onset Alzheimer's Disease
LPS	Lipopolysaccharide
LRRK2	Leucine-rich repeat kinase 2
MAO-B	Monoamine oxidase B
MATR3	Matrin 3
miRNA	micro RNA
MLH1	MutL Homolog 1
mQTL	methylation Quantitative Trait Locus
MS	Multiple Sclerosis
MSH3	MutS Homolog 3
mTOR	mechanistic Target of Rapamycin
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
ncRNA	noncoding RNA
NDD	Neurodegenerative Diseases
NF-κB	Nuclear Factor κ B
NFT	Neurofibrillary Tangles
NMDA	N-methyl-D-aspartate
NREM	Non-rapid Eye Movement
OPTN	Optineurin
PD	Parkinson's Disease
PFN1	Profilin 1
PINK1	PTEN-induced putative kinase 1

PMS1	PMS1 Homolog 2, Mismatch Repair System Component
PNS	Peripheral Nervous System
polyQ	Polyglutamine
PRKN	Parkin
PSD	Postsynaptic Density
PSEN	Presenilin
PUFA	Polyunsaturated Fatty Acid
RBD	Rapid Eye Movement Behavior Disorder
REM	Rapid Eye Movement
RNA-SEQ	RNA sequencing
ROS	Reactive Oxygen Species
SAD	Sporadic Alzheimer's Disease
SCFA	Short-chain Fatty Acid
SCN	Suprachiasmatic nucleus
siRNA	small interfering RNA
SNc	Substantia nigra pars compacta
SNCA	α -Synuclein
SNP	Single Nucleotide Polymorphism
snRNA	small nuclear RNA
SOD	Superoxide Dismutase
SQSTM1	Sequestosome 1
STX	Syntaxin
SUMO	Small Ubiquitin Like Modifier
TBK1	TANK binding kinase 1
TDP43	TAR DNA binding protein 43

LIST OF ABBREVIATIONS

TFBS	Transcription Factor Binding Sites
TNFα	Tumor Necrosis Factor α
TREM2	Triggering Receptor Expressed On Myeloid Cells 2
TUBA4A	Tubulin alpha 4A
UBQLN2	Ubiquilin 2
UNC5C	Unc-5 Netrin Receptor C
VCP	Valosin-containing Protein

All clock genes are described in more detail in Fig.11.1 in the Appendix and therefore are not included in the List of Abbreviations.

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Chapter 1

Neurodegenerative Diseases

All neurodegenerative diseases (NDDs) are characterized by a progressive decline of neuronal and glial structures and functions, affecting both central (CNS) and peripheral nervous system (PNS). This deterioration leads to impaired cognitive and/or motor functions. Cognitive functions affected include memory, attention, language, and executive function like planning, decision-making, and problem-solving.

Impaired motor functions manifest as difficulties in movement, coordination, and balance. Additionally, neurodegeneration can cause changes in mood and behavior, such as depression, anxiety, apathy, and aggression (Baquero & Martín, 2015; Galts et al., 2019). It can also affect the autonomic nervous system, responsible for regulating involuntary functions like heart rate, blood pressure, and digestion, resulting in issues like orthostatic hypotension, constipation, and urinary incontinence (Idiaquez & Roman, 2011).

Overall, neurodegeneration leads to progressive decline in multiple aspects of neurological function, significantly impacting an individual's quality of life and independence. While most NDDs primarily affect older individuals, typically manifesting after the age of 60, there are also inherited familial forms that can appear earlier in life. Unlike the natural aging process, the degradation of nerve cells in NDDs occurs at a faster rate and to a more significant extent (Bloomingdale et al., 2022; Farooqui & Farooqui, 2009).

1.1 Complexity of NDDs

Like all complex diseases, NDDs result from a multifaceted interaction of genetic, environmental, and lifestyle factors. Some of these possible

factors are depicted in Fig.1.1

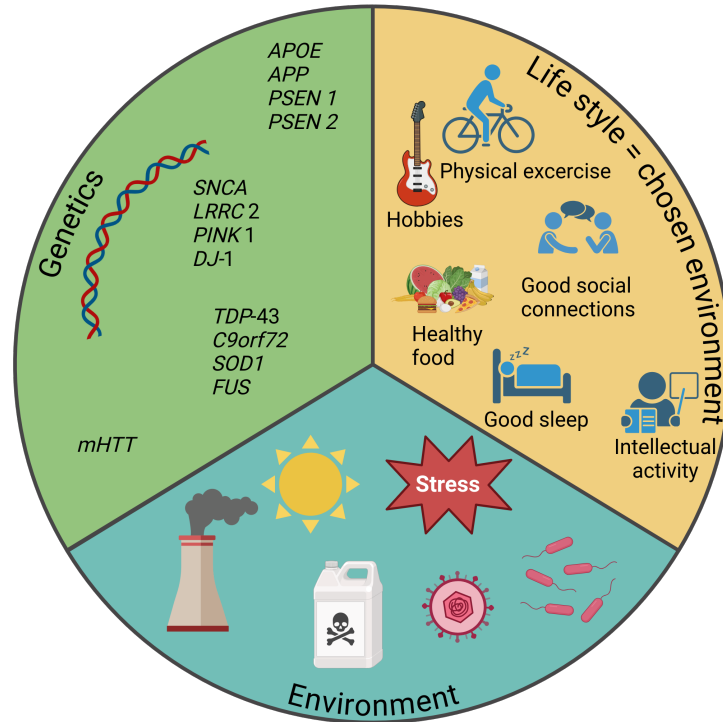


Figure 1.1: Possible Origins of NDDs

NDDs result from a complex interplay of genetic, environmental and lifestyle factors. The genetics sector shows genes, that predispose to AD, PD, ALS, and HD, which will be discussed in further detail in paragraphs 2.1.1, 2.2.1, 2.3.1, and 2.4.1. Environmental factors like air pollution, exposure to toxins or traumatic brain injuries but also chosen lifestyle factors can further induce neurodegenerative processes. (Adapted from Hecker et al., 2021)

The genetic sector in Fig. 1.1 shows genetic mutations that can disrupt the function of genes essential for neuronal or glial functioning, leading to the early onset of severe neurological disorders that are independent of lifestyle or environmental factors. For example, the mutant Huntingtin gene (*HTT*) in Huntington’s disease (HD) is the primary cause of the condition (MacDonald et al., 1993). Mutations in the *APP*, *PSEN1* and *PSEN2* genes can lead to the hereditary early onset form of Alzheimer’s disease (AD), whereas the $\epsilon 4$ allele of the apolipoprotein E (*APOE*) is a common risk factor for late onset AD (see also paragraph 2.1.1). *SNCA*, *LRRC2*, *PINK1* and *DJ 1* are known risk genes for Parkinson’s disease (PD) (see paragraph 2.2.1) and *TDP43*, *C9orf72*, *SOD1* and *FUS* are the five most common genetic causes for Amyotrophic lateral sclerosis (ALS) (see paragraph 2.3.1).

Despite the presence of known genetic mutations, most cases of the

disease do not follow a straightforward hereditary pattern. Instead, a combination of mostly unknown genetic variants serves as risk factors. When coupled with unfavorable environmental and lifestyle factors, these genetic predispositions may contribute to the onset of neurodegenerative disorders (NDDs) (Harari & Cruchaga, 2016; P. Li et al., 2019). Additionally, epigenetic alterations, such as changes in DNA methylation, histone modifications, or disruptions in epigenetic regulatory pathways and enzymes, appear to play a role in the development of many NDDs. Aging, which is the primary risk factor for NDDs, particularly leads to alterations in epigenetic regulation, further contributing to disease progression and susceptibility (Gangisetty, Cabrera, & Murugan, 2018; Lardenoije et al., 2015; Saul & Kosinsky, 2021).

Environmental factors as those depicted in Fig. 1.1, like air pollution and exposure to toxins like agricultural pesticides, and missing access to green spaces also have been found to negatively affect health and wellbeing (Kelly & Fussell, 2015; Manisalidis, Stavropoulou, Stavropoulos, & Bezirtzoglou, 2020). Exposure to toxic substances, including alcohol and lead, can lead to neurodegeneration, particularly with prolonged exposure (Brown, Lockwood, & Sonawane, 2005). These toxins may directly induce neuronal cell death or impair the function of neuronal or glial cells, contributing to neurodegenerative processes (De La Monte & Kril, 2014; Kamal et al., 2020).

Traumatic brain injuries or physical damage, such as tumors, ischemia, or strokes, exacerbated by accompanying inflammation, scar tissue formation, and tissue repair mechanisms often result in degeneration of neurons in the affected area (Brett, Gardner, Godbout, Dams-O'Connor, & Keene, 2022; Gupta & Sen, 2016).

Furthermore, viral or bacterial infections have been identified as widely underestimated risk factors for NDDs. Infections can trigger inflammatory responses and other pathological processes that contribute to the development and progression of NDDs (Lotz, Blackhurst, Reagin, & Funk, 2021; Zubair Alam et al., 2017).

Lifestyle choices made by an individual (see Fig. 1.1) can significantly impact health. A key example is chronic sleep deprivation, which is one of the leading risk factors for various diseases associated with modern civilization. The invention of electric lighting and the

regulation of nighttime temperatures through housing and heating systems have resulted in a noticeable shift in the sleep-wake cycle, going hand-in-hand with a loss of sleep quality (Blume, Garbazza, & Spitschan, 2019; Yetish et al., 2015). Stress aggravates the problem of sleep deprivation by deregulating levels of epinephrine and cortisol, which in turn negatively affects homeostasis of metabolism and sleep (O’Byrne, Yuen, & Butt, 2021).

Malnutrition, characterized by a diet high in fat and sugar, leads to dysregulation of the microbiome and metabolism. This can ultimately contribute to the development of chronic diseases, including obesity, heart disease, and type 2 diabetes (AlDabal & BaHammam, 2011; Hirotsu, Tufik, & Andersen, 2015; Rangaraj & Knutson, 2016), which are also known risk factors for NDDs, particularly for AD (Medina-Remón, Kirwan, Lamuela-Raventos, & Estruch, 2018; Procaccini et al., 2016; Razay, Vreugdenhil, & Wilcock, 2006).

Both obesity and aging tend to promote a sedentary lifestyle. Reduced physical activity is another well-known risk factor for nearly all diseases. Regular exercise and physical activity improve cardiovascular health, muscle strength and flexibility, immune response, and mental health (Booth, Roberts, & Laye, 2012; Matheson et al., 2011). Intellectual activities, such as learning new skills, reading, and maintaining social connections, enhance mental alertness and overall well-being (Y.-H. Chang, Wu, & Hsiung, 2021; M. Jordan, 2023; X. Wang, An, He, & Fang, 2021).

Integrating Genetic, Environmental, and Lifestyle Factors in Multi-Targeted Treatment Strategies for NDDs

Genetic predisposition and environmental factors such as air pollution, exposure to toxins, infectious diseases, or brain injuries from accidents are often beyond an individual’s control. However, lifestyle factors including diet, physical and mental activity, sleep quality, stress management, substance use, and social connections are, to some extent, controllable and can significantly influence overall well-being.

Given the complex nature of NDDs and the role of both genetic and environmental factors in disease progression, it is essential to adopt multi-targeted treatment strategies. According to Swerdlow, research is still too much dominated by disease pathways that were found due

to genetic analyses in early onset patients, especially in AD (Swerdlow & Khan, 2004). As these patients exhibit the same pathological hallmarks as late onset patients, research concentrates mainly on the amyloid cascade and Tau hypotheses (Ballatore, Lee, & Trojanowski, 2007; Haass et al., 1992; Hardy & Selkoe, 2002) and thus de-emphasizes the connection between aging, a deregulated metabolism and AD.

However, multi-targeted treatment strategies should combine pharmacological interventions with non-pharmacological approaches and lifestyle modifications. By integrating these approaches, it may be possible to slow the progression of neurological diseases in elderly individuals and mitigate the impact of NDDs on public health (M. Jordan, 2023).

1.2 Classification of NDDs

NDDs are characterized by progressive deterioration, both structurally and functionally, of neural tissue, irrespective of whether it stems primarily from neuronal or glial cell decay, and whether it predominantly affects the CNS or PNS (Armstrong, 2012; Kovacs, 2018). However, clinically the term NDDs is used more restrictively and typically comprises diseases characterized by progressive neurofunctional decline thought to be of neuronal origin within the CNS. AD, PD, ALS, and HD are the most prominent examples of this. Diseases of the PNS caused by neuronal degeneration are termed peripheral neuropathies or simply neuropathies.

Many diseases do not follow this relatively broad classification, because the intricate interplay of astroglia, the myelin-forming glia, and neurons, and their mutual dependencies to ensure optimal neural and neuronal function renders the distinction between neuronal- and glial-mediated neurodegeneration difficult. For example, Multiple Sclerosis (MS) and leukodystrophies do start in the CNS, but not primarily as a neuronal defect; instead, they begin with defects in myelin-forming glia due to degenerating myelin production or the destruction of myelin by toxins or immune attacks, ultimately leading to degeneration of axons and neurons (Faissner, Plemel, Gold, & Yong, 2019).

Also, physical damage resulting from injury, tumor, ischemia, or stroke, intensified by associated inflammation, scar tissue formation,

and tissue repair mechanisms often result in degeneration of neurons in the affected area (Gupta & Sen, 2016).

Consequently, depending on the level of understanding of the disease, NDDs can be categorized based on their primary clinical characteristics (such as dementia-type disorders, motor neuron diseases, parkinsonism-type diseases), brain regions and cell types involved, biochemical cause (like proteinopathies, demyelinating diseases), or environmental causes (like physical damage, toxins). This classification is not rigid as diseases can belong to multiple categories (Kovacs, 2018).

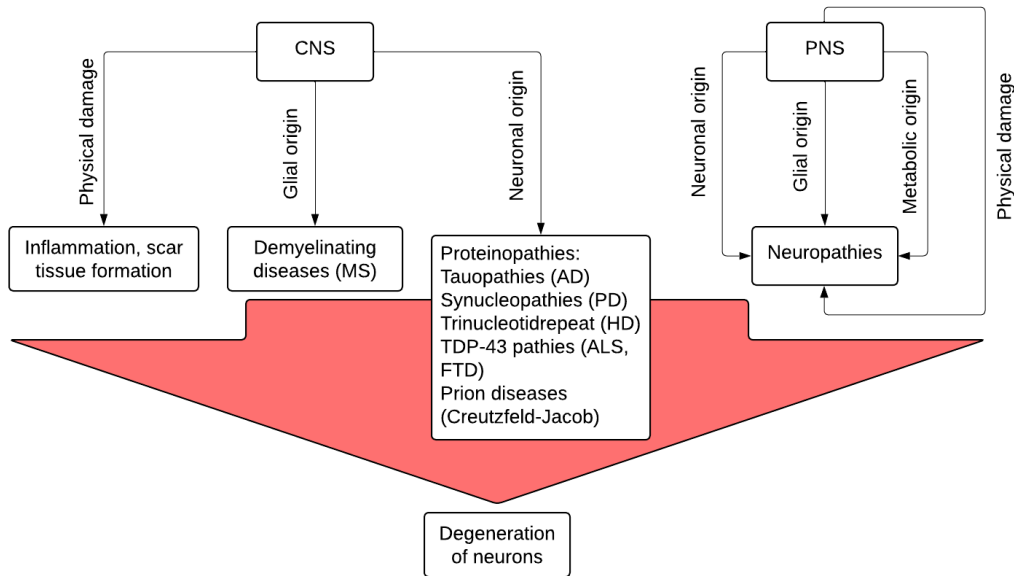


Figure 1.2: Categorization of neurodegeneration

Neurodegeneration can result from physical damage, glial or neuronal cell decay both in the CNS and PNS, which can lead to different types of NDDs.

1.3 Proteinopathies

Biochemically, many prominent NDDs originate from disorders of protein degrading processes, which lead to the aggregation of misfolded proteins in neurons and glia cells (Bertram & Tanzi, 2005; Bourdenx et al., 2017), and are thus classified as proteinopathies, see also Fig.1.2.

These proteinopathies can be further subcategorized based on their underlying biochemical mechanisms as e.g. tauopathies (resulting from hyperphosphorylation of tau), synucleopathies (caused by aggregation of synuclein), polyglutamine diseases (stemming from

trinucleotide repeat expansion), and prion diseases (arising from conformational changes followed by aggregation).

Protein aggregation can be triggered by protein variants that are more prone to aggregate formation, an excessive accumulation of protein due to deficiencies in ubiquitin-proteasome and autophagolysosome protein clearance mechanisms, or, like in the case of prion diseases, a transmissible form of misfolded protein capable of inducing misfolding in normal variants of the same protein. However, as recent research indicates that all protein aggregates might exhibit prion-like behavior (Ariazi et al., 2017; Pignataro & Middei, 2017; Prusiner, 2013), this last classification may be again too rigid.

The general consensus about the steps leading to proteinopathy-induced neurodegeneration is that an impaired protein homeostasis leads to misfolding and aggregation of predisposed proteins, which are neurotoxic in their oligomeric state. These oligomers also seem to spread trans-synaptically in a prion-like manner and beyond that even can cross seed other proteins like tau (Takalo, Salminen, Soininen, Hiltunen, & Haapasalo, 2013). To eliminate these toxic oligomers, an inflammation reaction is triggered, characterized by elevated levels of pro-inflammatory cytokines like tumor necrosis factor α (TNF α) and IL-6 (Sonninen, Goldsteins, Laham-Karam, Koistinaho, & Lehtonen, 2020). This leads to the activation of reactive astrocytes and microglia, which, in a self-perpetuating cycle, contribute to chronic neuroinflammation and consequently exacerbate neuronal damage.

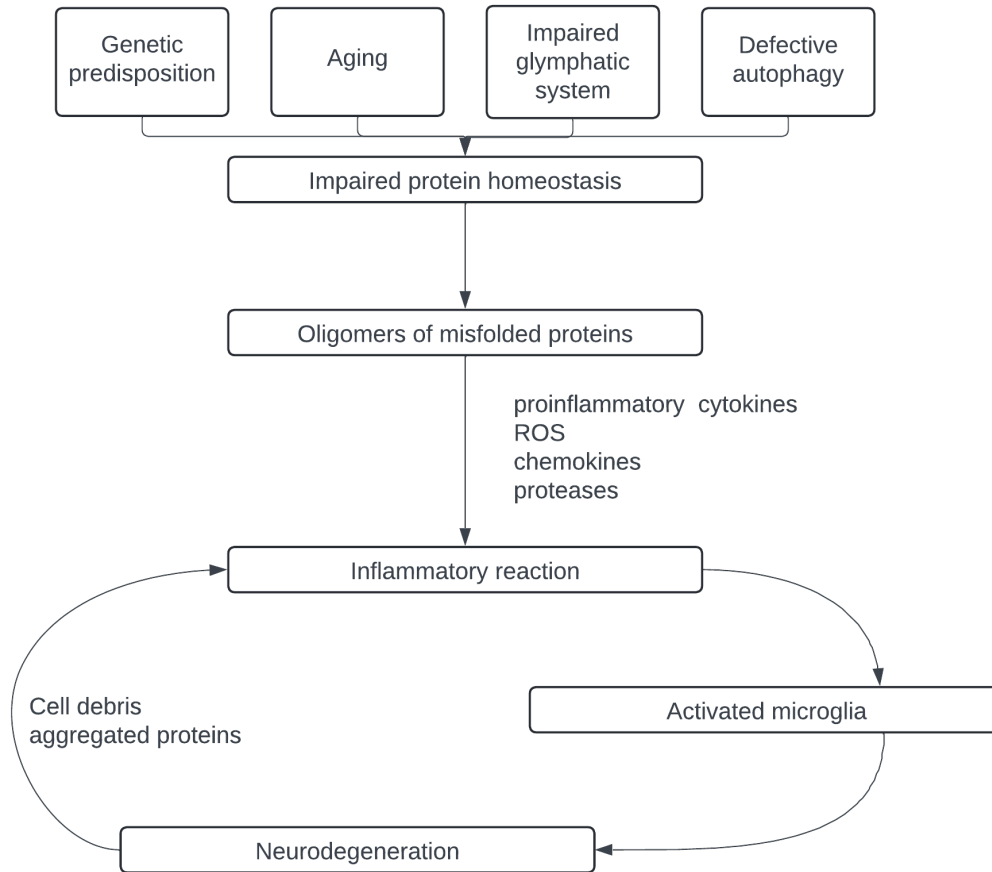


Figure 1.3: Proteinopathy-induced neurodegeneration

Impaired protein homeostasis can lead to misfolding and aggregation of predisposed proteins, which form neurotoxic oligomers. These oligomers can spread trans-synaptically in a prion-like manner and can even cross seed other proteins like tau. To eliminate these toxic oligomers, an inflammation reaction is triggered, characterized by elevated levels of pro-inflammatory cytokines like $\text{TNF}\alpha$ and IL-6. This leads to the activation of reactive astrocytes and microglia, which, in a self-perpetuating cycle, contribute to chronic neuroinflammation and consequently exacerbate neuronal damage.

Chapter 2

The four most prominent NDDs

In this study, we focused on the four most prominent proteinopathies of the CNS: AD, PD, HD, and ALS, due to their high prevalence and significant impact. The majority of these disorders are age-related NDDs, and their prevalence is expected to rise further as the global population ages. Despite sharing molecular and physiological similarities, these diseases also exhibit notable differences in the brain regions affected and their genetic and regulatory origins.

In the following chapter, a brief overview of these four diseases will be provided, along with a discussion of the genes involved in the rare hereditary cases. Understanding the dysfunctional genes' tasks can shed light on the impaired pathways contributing to each specific disease. It may be assumed that sporadic forms of these diseases suffer from the same disrupted signaling pathways, but not through the mutation of individual genes but possibly through the combination of numerous small single nucleotide polymorphisms (SNPs) and epigenetic modifications. Complex traits in the human body are typically not determined by a small number of master regulator genes but arise from the combination of small effects across a variety of in part compensatory genes (Schork, 1997). The resulting complexity challenges research into these multifaceted diseases.

2.1 Alzheimer's Disease (AD)

AD is the most common cause for dementia in the industrialized world, accounting for 60-70% of cases (Marcos-Rabal et al., 2021). Due to longer life expectancy this former rare disease has become a real challenge with the likelihood of developing AD increasing exponentially with age, approximately doubling every 5 years after the age of 65 (Minati, Edginton, Bruzzone, & Giaccone, 2009;

Zucchella et al., 2018). Nowadays more than 35 million people worldwide suffer from AD and according to current estimates the number of cases will almost triplicate by 2040. In the United States alone, 5 million or 1 in 9 people over the age of 65 are living with AD (Marcos-Rabal et al., 2021). In Germany around 1,5 million people are affected with 30.000 new cases every year (Hampel et al., 2011).

The rising prevalence of AD in conjunction with obesity in industrialized nations suggests a potential link between adiposity, obesity-related metabolic disorders such as insulin resistance and type 2 diabetes, and the development of AD (Alford, Patel, Perakakis, & Mantzoros, 2018; Pugazhenth, Qin, & Reddy, 2017). Elevated levels of glucose (hyperglycemia), lipids (hyperlipidemia), and insulin (hyperinsulinemia) have been identified as significant risk factors for the onset of type 2 diabetes, dementia, and accumulation of amyloid β ($A\beta$) (Anstey, Cherbuin, Budge, & Young, 2011).

Clinically, AD is characterized by progressive cognitive deterioration due to severe atrophy of the cerebral cortex and subcortical structures. At the neuropathological level AD is primarily characterized by the occurrence of extracellular plaques formed by deposition of $A\beta$ plaques and intraneuronal neurofibrillary tangles (NFTs) composed of the hyperphosphorylated Tau protein (Mudher & Lovestone, 2002). The extracellular aggregates consist of small β -amyloid peptides, which are cleaved from amyloid precursor protein (APP) and self-assemble into dense extracellular deposits, resulting in neuroinflammation and neurodegeneration.

2.1.1 Genetic origin of AD

The hereditary early onset (EOAD) or familial form (FAD) of AD was found to be associated with mutations in genes related to $A\beta$ synthesis (Mattson, 2004), namely APP with 52, presenilin1 (PSEN1) with 215, and PSEN2 with 31 known mutations, that are inherited in an autosomal-dominant fashion (Cruts, Theuns, & Van Broeckhoven, 2012). However, taken together mutations in these 3 genes only explain 5-10% of the EOAD patients (Cacace, Sleegers, & Van Broeckhoven, 2016).

The vast majority of patients develop AD sporadically after the age of 65. This form of AD is called late onset AD (LOAD) or sporadic AD (SAD) .

Genetic analysis of these LOAD patients further revealed several risk genes like apolipoprotein E (APOE), triggering Receptor Expressed On Myeloid Cells 2 (TREM2), and unc-5 Netrin Receptor C (UNC5C) (Colonna & Wang, 2016; Guerreiro, Brás, & Hardy, 2013; Wetzel-Smith et al., 2014), and more than 20 low-risk genetic loci (Kunkle et al., 2019; Lambert et al., 2013).

The most important genetic risk factor for LOAD is the $\epsilon 4$ allele of the *APOE* gene (Bu, 2009; Saunders et al., 1993). APOE is a lipid-binding protein involved in cholesterol metabolism and is immunohistochemically localized to senile plaques, vascular amyloid deposits, and NFTs in AD brains.

The *APOE* gene has three common alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, with respective frequencies of approximately 8.4%, 77.9%, and 13.7% in the population. The primary differences between these alleles lie in amino acid residues 112 and 158 of the APOE protein (C.-C. Liu, Kanekiyo, Xu, & Bu, 2013).

Population-based studies have revealed a significant association between the *APOE4* allele and increased risk of developing LOAD, with an $\epsilon 4$ allele frequency of approximately 40% in affected individuals (Poirier et al., 1993; Strittmatter et al., 1993). In contrast, the *APOE2* allele appears to confer a protective effect against the development of LOAD (C.-C. Liu et al., 2013). Thus, the *APOE4* genotype has been shown to influence both timing and extent of amyloid deposition in the brain (Tiraboschi et al., 2004).

Further research has elucidated multiple roles for APOE in AD pathogenesis, including its involvement in the clearance of $A\beta$ (Selkoe, 1991) (Hardy & Allsop, 1991), enhancement of $A\beta$ neurotoxicity, and promotion of $A\beta$ filament formation (J. Ma, Brewer Jr, & Potter, 1996). Additionally, the Reelin signaling pathway, which plays a critical role in synaptic plasticity and neuronal migration, has been shown to protect synapses against $A\beta$ toxicity through interactions with APOE receptors.

These findings collectively suggest that targeting APOE4 may represent a promising therapeutic strategy for AD (Hoe et al., 2009).

2.1.2 Main Hypotheses leading to AD

Numerous signaling cascades and pathways have been implicated in the pathogenesis of AD. The main existing hypotheses (and possible

medications) will be outlined in the following paragraph, including the amyloid and tau propagation hypotheses, which hold protein aggregation responsible as the origin of AD. The mitochondrial cascade and the neurovasculature hypotheses claim that neurodegenerative processes start even earlier due to reduced energy supply of the brain, whereas the cholinergic and synaptic hypotheses find the origin of degenerating neurons in the decreased production and transport of the neurotransmitter and subsequent decline of synapses.

Amyloid cascade hypothesis

The amyloid cascade hypothesis suggests that an early and crucial step in the development of AD is linked to the buildup of $A\beta$ (Hardy & Allsop, 1991; Selkoe, 1991). This accumulation is driven by faulty cleavage of APP, resulting in an increased quantity and altered quality of $A\beta$, as well as impaired clearance mechanisms. Initially, this leads to the formation of toxic soluble peptide oligomers, which later aggregate into insoluble and probably inert plaques. These plaques first appear in the entorhinal cortex and hippocampus before spreading to the entire cortex and even peripheral organs and tissues.

APP is a transmembrane glycoprotein with an extensive extracellular domain and a shorter intracellular domain. It exhibits characteristics of a cell surface receptor and is expressed in various tissues, with a particular abundance in synapses. APP likely plays a crucial role in several biological processes, including nervous system development (Sosa et al., 2017), neuromuscular junction formation (Stanga et al., 2016), synaptic plasticity (Klevanski et al., 2015; S. H. Lee et al., 2020), axonal growth (Robinson, 2013; Southam, Stennard, Pavez, & Small, 2019), antimicrobial activity (Moir, Lathe, & Tanzi, 2018), and iron export (Duce et al., 2010; Tsatsanis et al., 2020).

Under physiological conditions, 90% or more of APP is first cleaved by α -secretase ADAM Metallopeptidase Domain 10 (ADAM10), that cuts APP within the $A\beta$ domain, generating a membrane-anchored fragment (C83) and releasing soluble APP α . C83 is then cleaved by γ -secretase, releasing p3 fragment and the APP Intracellular Domain (AICD) (De Strooper & Annaert, 2010). Soluble APP- α molecules may have some beneficial roles, including coordination of cellular responses and other proliferative effects (Dar & Glazner, 2020), the functions of the other fragments is only vaguely known (Pardossi-

Piquard & Checler, 2012). AICD may function as a transcription factor but is quickly degraded (Cupers, Orlans, Craessaerts, Annaert, & De Strooper, 2001; Kametani & Haga, 2015; Kopan & Ilagan, 2004).

The remaining 10% of APP is cleaved by the β -secretase site of APP cleaving enzyme (BACE1) at the N-terminal end of the $A\beta$ domain (Cole & Vassar, 2008; Sinha et al., 1999), resulting in the release of soluble $APP\beta$ from a membrane-anchored fragment known as C99. This C99 fragment is further cleaved by γ -secretase which consists of subunits PSEN1 and 2, nicastrin (NCT), anterior pharynx-defective 1 (Aph-1), and presenilin enhancer 2 (Pen-2), to produce $A\beta$ in the intraluminal space and AICD in the cytosol. Accumulation of C99 could be shown to induce neurotoxicity and vesicular trafficking impairment (Roy, Zhang, Lee, & Trojanowski, 2005; Yoshikawa, Aizawa, & Hayashi, 1992), suggesting that APP C-terminal fragments (C83, C99, and AICD) may be toxic and require elimination (Robakis & Georgakopoulos, 2014). Cleavage of C99 by γ -secretase can occur at various positions, resulting in the production of $A\beta$ peptides of different lengths (mainly 38 to 42 aa), which are highly resistant to proteolytic degradation (De Strooper & Annaert, 2010).

In AD, there is an imbalance towards increased production of pathogenic $A\beta_{42}$, which is more hydrophobic and prone to aggregation than shorter forms. While $A\beta$ is a normal metabolic product of APP and not inherently toxic under physiological conditions (Bryan, Lee, Perry, Smith, & Casadesus, 2009), oligomeric forms have been shown to be neurotoxic. These oligomers impair synaptic function (William et al., 2012), reduce dendritic spines, inhibit long-term potentiation, promote long-term depression, and impair learning and memory (Shankar et al., 2008) by permeating cellular membranes and causing dysfunction and cell death (Y.-r. Huang & Liu, 2020).

Interestingly, the distribution of senile plaques can be extensive in the brains of elderly individuals without dementia (Chételat et al., 2013; Davis, Schmitt, Wekstein, & Markesbery, 1999), and some AD patients exhibit minimal amyloid deposits (Edison et al., 2007; Y. Li et al., 2008). This suggests that $A\beta$ deposition is an aging-related phenomenon rather than a direct cause of AD onset.

Misfolded $A\beta$ oligomers not only possess direct neurotoxic properties but also initiate neuroinflammatory processes (McGeer &

McGeer, 2001), primarily involving activation of innate immune cells in the CNS and activation of the complement cascade, cytokine and chemokine networks, acute phase reactants, and adhesion molecules. These alterations affect $A\beta$'s ability to bind to other proteins like APOE (discussed below) and influence $A\beta$ clearance.

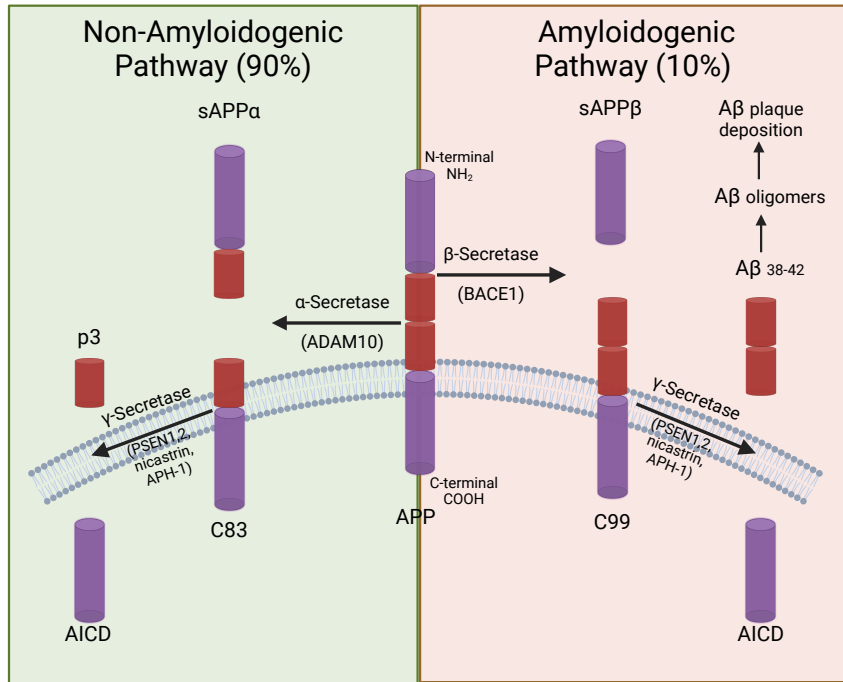


Figure 2.1: Amyloid formation in AD

The amyloid cascade model suggests that developing AD is linked to the accumulation of $A\beta$ driven by the faulty cleavage of the APP, resulting in increased levels of amyloid β ($A\beta$) in terms of both quantity and altered quality. Under physiological conditions, 90% or more of APP is first cleaved by α -secretase (ADAM 10), that cuts APP within the $A\beta$ domain, generating a membrane-anchored fragment (C83) and releasing soluble APP α . C83 is then cleaved by γ -secretase complex consisting of subunits presenilin, nicastrin, Aph-1, and Pen-2, releasing p3 fragment and AICD. The remaining 10% of APP is cleaved by β -secretase (BACE1) at the N-terminal end of the $A\beta$ domain, resulting in the release of sAPP β from a membrane-anchored fragment C99. This C99 fragment is further cleaved by γ -secretase to produce $A\beta$ in the intraluminal space and AICD in the cytosol. (Adapted from Hur et al., 2022)

A mutation in the APP gene adjacent to BACE1 cleavage site has been shown to result in a 40% reduction of $A\beta$ formation in vitro (Jonsson et al., 2012). Additionally, the *BACE1* gene is located on chromosome 21, which is triplicated in individuals with Down's syndrome. Almost all individuals with Down's syndrome develop AD in their later years (X. Sun, Tong, Qing, Chen, & Song, 2006). Thus, reducing BACE1 became a tempting target for drug development, but due to complexity reasons it failed.

Various approaches targeting $A\beta$, including anti-aggregation agents, $A\beta$ transport enhancers, $A\beta$ vaccines, and passive immunization therapies against $A\beta$, have progressed to clinical trials (Bazzari, Abdallah, & El-Abhar, 2019). Among these, only Aducanumab (marketed as Aduhelm©) received U.S. Food and Drug Administration approval (B. Dunn, Stein, & Cavazzoni, 2021). Aducanumab is a human immunoglobulin $\gamma 1$ (IgG 1) monoclonal antibody targeting $A\beta$. It was approved for use in AD patients with mild cognitive impairment or in the early stages of dementia (J. Cummings et al., 2021). Aducanumab is capable of crossing the blood-brain barrier and selectively binding to both aggregated soluble oligomers and insoluble fibril forms of $A\beta$ plaques in the brain (J. Cummings et al., 2021). However, while Aducanumab was effective in reducing plaque accumulation, its ability to significantly improve cognitive deficits remains inconclusive. Due to severe side effects, Biogen withdrew Aducanumab from the market.

Tau propagation theory

Tau is one of the microtubule-associated proteins that regulate the stability of tubulin assemblies. This function is particularly crucial for neurons, as microtubules act as transport pathways for cargo within dendrites and axons (Braak & Del Tredici, 2018; Frost, Jacks, & Diamond, 2009; Kadavath et al., 2015).

The binding of tau to microtubules is influenced by its phosphorylation state. In AD, tau is hyperphosphorylated, which leads to its transformation from soluble tau to an insoluble paired helical filament. This altered form of tau is unable to bind to microtubules effectively (Joo et al., 2015; Kametani & Hasegawa, 2018). The consequent disruption in axonal transport can lead to the degeneration and death of specific glutamatergic projection neurons that are extensively interconnected (Arnsten, Datta, Del Tredici, & Braak, 2021). Neuropathological evidence suggests that tau, rather than $A\beta$, may be the primary initiator of sporadic AD (Multhaup, Huber, Buée, & Galas, 2015).

Tau pathology emerges approximately a decade before the onset of $A\beta$ plaques and is associated with calcium dysregulation and the transneuronal propagation of tau seeds. Unlike $A\beta$ levels, which

appear to be independent of disease stage, tau pathology strongly correlates with the severity of cognitive and clinical symptoms as well as with Braak stages (Braak & Braak, 1991). Tau pathology initially manifests in the transentorhinal region (stages I and II), subsequently spreading to the limbic region (stages III and IV), and eventually affecting neocortical areas (stages V and VI).

According to the tau propagation hypothesis, aggregates of fibrillar and misfolded tau disseminate in a prion-like manner within cells, ultimately spreading to various brain regions in AD patients. This propagation process disrupts signal transmission both within and between neurons, contributing to the progression of the disease (Arriagada, Marzloff, & Hyman, 1992; Grundke-Iqbal et al., 1986). Pathological tau may also drive $A\beta$ cleavage by trapping APP-containing endosomes in dendrites, and $A\beta$ is known to increase abnormal tau phosphorylation, leading to a vicious cycle of tau and amyloid pathology (Arnsten et al., 2021). Emerging research also suggests a potential correlation between APP metabolites, such as AICD and $A\beta$, and tau within the nucleus (Multhaup et al., 2015).

It could be shown that stress-induced hypophosphorylation of tau in neuronal cell nuclei plays a crucial role in protecting DNA under oxidative and hyperthermic stress conditions (Sultan et al., 2011). Hypophosphorylated tau binds to the AT-rich minor groove of DNA, which is a common way for proteins to physically bend and thus shield DNA from damage induced by free hydroxyl radicals (Y. Wei et al., 2008). Various lengths of $A\beta$ peptides, including $A\beta_{38}$, $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{43}$, are then internalized by cells and directed to the nucleus. Specifically, the $A\beta_{42}$ peptide interacts with gene regulatory elements, inducing changes in gene transcription similar to AICD.

Therapeutic strategies targeting tau can be categorized into tau assembly inhibitors, tau kinase inhibitors, O-GlcNAcase inhibitors, microtubule stabilizers, and immunotherapy drugs (Golde, 2014). Only a limited number of agents have undergone proof-of-principle testing as tau kinase inhibitors, microtubule-stabilizing agents, and inhibitors of heat shock protein 90 (Hsp90), which stabilize glycogen synthase kinase 3 β (GSK3 β) (Boutajangout, Ingadottir, Davies, & Sigurdsson, 2011). Additionally, some inhibitors of tau aggregation, such as TRx0237 (TauRx Therapeutics), are undergoing clinical trials.

Hydromethylthionine mesylate (HMTM), a derivative of Methylene Blue used as an approved antimalarial drug, has shown promising results in phase III clinical trials. TauRx Therapeutics announced in July 2023 that they would seek the HMTM regulatory approval in the US, UK and other territories, as brain atrophy rates in AD patients declined after 9 months of treatment (G. K. Wilcock et al., 2018; Wischik et al., 2022). These promising results might be distorted, however, by the fact that HMTM colors urine and feces, and that it is therefore not possible for a blinded placebo-controlled trial to be run for this drug (Wischik et al., 2022).

Vaccines targeting hyperphosphorylated tau, such as ACI-35 (AC Immune/Janssen) and AADvac1 (Axon Neuroscience SE), are also under evaluation in clinical trials (Novak et al., 2018). ACI-35 has shown promising results, demonstrating sustained antibody responses to phosphorylated tau and paired helical filaments for over a year without safety concerns.

Despite these advancements, tau-directed therapies are likely to encounter challenges similar to those faced by $A\beta$ -targeted trials. The efficacy of tau-directed therapies will require further evaluation in future studies.

Mitochondrial cascade hypothesis

In 2004, Swerdlov and Khan proposed a hypothesis suggesting that the disbalance of protein homeostasis might not be the initial step in the development of AD, but rather a consequence of bioenergetic dysfunction resulting from declining mitochondrial function (Swerdlov & Khan, 2004).

According to this hypothesis, each individual begins with a genetically determined baseline level of mitochondrial quantity and function, which can change over time due to both inherited factors and environmental influences. The development and progression of AD are believed to depend on both the initial mitochondrial function and the rate at which mitochondrial function deteriorates.

Reduced quantity and impaired quality of mitochondria are significant characteristics of both aging and NDDs, leading to decreased energy supply in the brain (Mattson, Gleichmann, & Cheng, 2008). One crucial function of healthy mitochondria is the regulated production

of reactive oxygen species (ROS). At low levels, ROS can have beneficial effects on cell survival and serve as signaling molecules for adaptive responses. They function as antimicrobial agents and regulate various cellular processes, including Nuclear Factor κ B (NF- κ B) transcriptional activity and autophagy (J. D. Dunn, Alvarez, Zhang, & Soldati, 2015).

Thus, maintaining a balanced production of ROS by healthy mitochondria is essential for cellular homeostasis and overall health. Mitochondria are the primary sources of ROS production in cells. In intact cells, approximately 90% of ROS are generated by mitochondria (Balaban, Nemoto, & Finkel, 2005), with the remainder coming from sources such as the endoplasmic reticulum (ER), peroxisomes, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and monoamine oxidases (D. P. Jones, 2006). In AD, there is a significant increase in ROS production, leading to an imbalance between pro-oxidants and antioxidants. This oxidative stress disrupts cellular redox circuits and damages essential macromolecules, including nucleic acids, lipids, proteins, and carbohydrates (Di Meo, Reed, Venditti, & Victor, 2016).

The main site of mitochondrial ROS production is the electron transport chain during oxidative phosphorylation. In this process, molecular oxygen (O_2) is reduced to water (Thomas, Witting, & Drummond, 2008). However, electrons can leak from the transport chain and react with molecular oxygen, resulting in the formation of superoxide O_2^- at complexes I and III (Hirst, King, & Pryde, 2008; Nickel, Kohlhaas, & Maack, 2014). To maintain ROS levels within a balanced range, mammalian mitochondria are equipped with various antioxidant enzyme systems. These systems act promptly to modify mitochondrial ROS as soon as they are produced. The superoxide dismutase (SOD) family of enzymes catalyzes the conversion, or dismutation, of superoxide O_2^- into hydrogen peroxide (H_2O_2). While H_2O_2 is also toxic, it is further degraded by enzymes such as catalases, thioredoxins, and glutathione peroxidases (Mitozo et al., 2011).

Alterations in the expression and activity of SODs have been associated with aging and various diseases, including cancer, cardiovascular diseases, and NDDs. This highlights the critical role of mitochondrial ROS regulation in maintaining cellular homeostasis and the potential implications of ROS dysregulation in disease

pathogenesis (Finkel & Holbrook, 2000; Halliwell, 2022; Mitozo et al., 2011). Growing evidence suggests that production of ROS increases due to mitochondrial damage long before clinical manifestation of AD or $A\beta$ pathology (Uttara, Singh, Zamboni, & Mahajan, 2009). In cell culture studies, it has been demonstrated that mitochondrial function affects APP expression and processing, leading to increased $A\beta$ production (Gabuzda, Busciglio, Chen, Matsudaira, & Yankner, 1994; Gasparini et al., 1997). This suggests that impaired mitochondria may initiate the amyloid cascade observed in AD.

In healthy cells, damaged mitochondria are typically removed through a process called mitophagy, where autophagosomes selectively engulf and degrade dysfunctional mitochondria. This mechanism is crucial for maintaining cellular homeostasis, as impaired mitochondria can lead to energy depletion, oxidative stress, calcium overload, and activation of caspases, ultimately resulting in neuronal death observed in NDDs (Ashrafi & Schwarz, 2013). Therefore, in addition to excessive ROS production, impaired mitophagy plays a significant role in aging and neurodegeneration. Studies have shown that mitophagy stimulation can reverse memory impairment and diminish insoluble $A\beta$ and tau hyperphosphorylation (Fang et al., 2019). Thus, deficiencies in mitophagy may represent an early trigger in the etiology of AD and could potentially serve as a therapeutic target (Fang et al., 2019; Kerr et al., 2017).

Despite the promising potential of targeting mitochondrial health for AD treatment, clinical trials focusing on mitochondrial well-being were not successful neither led to a real marketable AD drug (Mi, Qi, Brinton, & Yin, 2021; J. Wang & Chen, 2016).

Neurovascular hypothesis

The neurovascular hypothesis addresses another reason for reduced energy supply of the brain during aging and AD stating that vascular dysregulation can significantly impact brain health by causing brain hypoperfusion, hypoxia, and neurovascular inflammation (Sparks et al., 1990).

A complex network of neurons, astrocytes, and vascular cells supports the integrity of brain structure and function as it ensures the delivery of essential substrates and facilitates the efficient drainage

of metabolic waste products across the bloodbrain barrier (BBB) (Zlokovic, 2008). Given the brain's high energy demand and limited energy storage capacity, maintaining a precise balance of microenvironmental conditions and metabolic processes is a challenging task.

Many factors can lead to changes in the neurovasculature, which in turn affect the occurrence and progression of AD. An impaired BBB allows potentially harmful molecules, such as toxins and immune cells, to enter the brain, which may contribute to neuroinflammation and neuronal damage (Zlokovic, 2008). A decreased cerebral blood flow results in reduced delivery of oxygen and glucose to the brain. This hypoperfusion impairs neuronal function and contributes to the formation of A β plaques and tau tangles (Jaeger et al., 2009).

Conditions such as hypertension, diabetes, and atherosclerosis are known to affect the vascular system. AD is sometimes referred to as "diabetes type 3" due to the significant involvement of impaired insulin signaling in its progression. In AD brains, insulin levels and insulin receptor expression are reduced (Correia et al., 2012), while plasma insulin and A β levels are increased, indicating impaired insulin clearance may elevate plasma A β levels.

Midlife obesity and adiposity are important risk factors for an earlier onset of dementia and A β accumulation (Anstey et al., 2011; Hassing et al., 2009), although hyperlipidemia and high levels of cholesterol could not directly be linked to AD (Proitsi et al., 2014). One possible explanation is that adipose tissue secretes inflammation factors, such as TNF- α , interleukin-1 (IL-1), and IL-6 (Christensen & Pike, 2015), which may induce insulin resistance, produce A β deposits, and stimulate excessive tau phosphorylation (Letra, Santana, & Seica, 2014).

Neuroimaging studies in AD patients show that neurovascular dysfunction is found even before the onset of neurodegenerative processes (Bookheimer et al., 2000; Knopman & Roberts, 2010; Ruitenberg et al., 2005). Targeting vascular health could be a potential strategy for preventing or slowing the progression of AD. Researchers are exploring various therapeutic approaches to improve vascular function. Angiotensin II receptor blockers, ACE inhibitors and statins have been shown to protect the BBB, calcium channel blockers like nimodipine enhance cerebral blood flow, and diabetes medications

like metformin might combat the impaired insulin signaling.

The cholinergic or synaptic hypothesis

The cholinergic hypothesis, proposed by Peter Davies and A.J.F. Maloney in 1976 (Davies & Maloney, 1976), suggests that a decreased production and transport of the neurotransmitter acetylcholine in the brains of individuals with AD is a primary cause of the disease (Hampel et al., 2018). Their study compared the activities of key enzymes involved in neurotransmitter synthesis across 20 regions of AD and control brains. They found reduced activity specifically in choline acetyltransferase, resulting in decreased acetylcholine levels at synapses in the amygdala, hippocampus, and cortex of AD brains (Fotiou, Kaltsatou, Tsiptsios, & Nakou, 2015; H Ferreira-Vieira, M Guimaraes, R Silva, & M Ribeiro, 2016).

Acetylcholine plays a vital role in both the peripheral and central nervous systems, serving all pre- and post-ganglionic parasympathetic nerve cells, as well as pre-ganglionic sympathetic nerve cells. A potential reason for reduced acetylcholine synthesis in AD brains may be a lack of adenosine triphosphate (ATP) due to mitochondrial dysfunction (also see Mitochondrial cascade hypothesis), as choline acetyltransferase requires choline, acetyl-CoA, and ATP for its activity.

To address this, medications have been developed to enhance and prolong the effect of acetylcholine in the synapse by inhibiting acetylcholinesterase, an enzyme that degrades approximately 25,000 molecules of acetylcholine per second (J. Liu, Chang, Song, Li, & Wu, 2019). Drugs like Donepezil inhibit acetylcholinesterase, while others like Rivastigmine and Galantamine also inhibit butyrylcholinesterase, a nonspecific cholinesterase. These drugs aim to maintain high concentrations of acetylcholine within synapses, thereby enhancing cholinergic signaling in the CNS, autonomic ganglia, and neuromuscular junctions.

Since the FDA approved Tacrine as the first AD treatment in 1995, acetylcholinesterase-inhibitors have been in use for over two decades. Tacrine, a reversible acetylcholinesterase-inhibitor, initially gained popularity but saw a decline in prescriptions due to its hepatotoxicity. As a result, its usage has largely been discontinued with the intro-

duction of second-generation acetylcholinesterase-inhibitors. These include Donepezil, Rivastigmine, and Galantamine, and are currently widely prescribed. They offer fewer side effects, higher central selectivity, and have shown to improve cognition in patients with mild to moderate AD. Notably, patients treated with Rivastigmine and Galantamine have exhibited better daily living abilities and overall functional outcomes compared to those treated with Donepezil (Bullock et al., 2005; G. Wilcock et al., 2003).

However, the efficacy of acetylcholinesterase-inhibitors in treating cognitive symptoms of dementia remains modest, as indicated by the latest meta-analysis (Knight, Khondoker, Magill, Stewart, & Landau, 2018). Furthermore, the effects of these drugs are not continuous (S. Schneider, 2000), suggesting that while they can provide some relief from cognitive symptoms, they may not offer a consistent or long-term solution for AD.

The dendritic hypothesis

One of the recognized issues in AD involves the decline of excitatory glutamatergic synapses (Cochran, Hall, & Roberson, 2014). Glutamate serves as the primary excitatory neurotransmitter in the nervous system, and glutamatergic synapses are rich in N-methyl-D-aspartate (NMDA) receptors. These receptors play a crucial role in regulating synaptic plasticity and facilitating learning and memory functions (Cotman, Monaghan, & Ganong, 1988; Hu, Liu, Chang, & Berg, 2002).

NMDA receptors are a type of ligand-gated, non-selective ionotropic glutamate receptors (iGluR). They are densely located in regions like the hippocampus and cerebral cortex, predominantly within the postsynaptic density (PSD) of excitatory synapses (Monaghan & Cotman, 1986). The PSD is a membrane-associated mega-organelle that is highly enriched with glutamate receptors, as well as their downstream signaling and scaffolding proteins. The activities and processes surrounding the NMDA receptor supercomplex within the PSD are essential for mediating dendritic abnormalities observed in AD.

A β has been identified as a factor that initiates these abnormalities by potentiating synaptic transmission (Puzzo et al., 2008). This heightened synaptic activity subsequently leads to increased calcium

influx (Q. Liu, Xie, Lukas, John, & Wu, 2013), which in turn activates multiple signaling pathways, which collaborate to disrupt the balance between excitation and inhibition, contributing to the pathological processes observed in AD (Maestú, de Haan, Busche, & DeFelipe, 2021; Varela, Etter, & Williams, 2019).

Targeting these harmful signaling cascades using NMDA receptor antagonists could be a potential therapeutic approach. However, because the physiological activity of NMDA receptors is crucial for normal neuronal function, completely blocking all NMDA receptor activity can lead to significant side effects such as hallucinations, agitation, and anesthesia. For an NMDA receptor antagonist to be clinically effective, it should selectively block excessive activation without interfering with the receptor's normal function (J. Liu et al., 2019).

Memantine, a noncompetitive antagonist of NMDA glutamate receptors, works by blocking current flow, especially calcium currents, through NMDA receptors, thereby reducing the excitotoxic effects of glutamate (J. W. Johnson & Kotermanski, 2006). It received marketing approval in Europe in 2002 and was approved by the US FDA in 2003. In addition to its direct effects on NMDA receptors, Memantine can also reduce the inhibition of α -secretase, shifting the balance to the non-amyloidogenic pathway and therefore potentially inhibiting the production of $A\beta$ (Lesné et al., 2005).

However, the French Pharmacoeconomic Committee downgraded its rating of the medical benefit provided by memantine in AD from "major" to "low" (François, Sicsic, Elbaz, & Pelletier Fleury, 2017), a conclusion supported by a recent meta-analysis (Knight et al., 2018). This suggests that while Memantine may offer some therapeutic benefits, its overall efficacy and clinical significance in treating AD remain subject to scrutiny and further research (Ebrahim & Oremus, 2018).

2.1.3 Treatment and Outlook

The complexity of AD arises from the intricate and interdependent nature of its various pathological pathways. While drug development efforts have targeted individual aspects of AD pathology, addressing multiple interconnected pathways simultaneously presents a significant challenge. Additionally, as it is still not entirely clear what

constitutes the cause versus the consequence of the disease this makes it even more difficult to determine the appropriate timing and focus for interventions to effectively address the complex downstream symptoms.

Furthermore, the ubiquitous nature of many of these processes in the body necessitates precise targeting to avoid off-target effects and potential toxicity. All known aspects of AD have been subject to pharmacological investigation, yet there is still no medication that can effectively alleviate let alone cure the condition.

Nanotechnology-assisted drug delivery strategies offer a promising approach to overcome some of these challenges. By encapsulating therapeutic agents within biocompatible and biodegradable nanoparticles, it is possible to enhance drug bioavailability, facilitate transport across the BBB, and achieve targeted delivery to specific cells or tissues within the brain. Additionally, nanotechnology can enable controlled release of drugs, allowing for precise modulation of therapeutic dosing (Sood, Jain, & Gowthamarajan, 2014; Z Ahmad et al., 2014).

2.2 Parkinson's Disease (PD)

PD is the second most common neurodegenerative disorder, it mainly affects people over 40 with a universal prevalence of 2% in men and 1.3% in women (Elbaz et al., 2002). It manifests through motoric defects, such as bradykinesia, tremor, stooped posture, and rigidity but can also be associated with non-motor symptoms like dementia that add to overall disability (Ascherio & Schwarzschild, 2016). Its hallmark is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) due to protein aggregates of α -synuclein (α -SYN).

PD lacks a definitive biomarker, making diagnosis primarily reliant on clinical history and examination. The progression and development of PD are typically categorized using the staging system proposed by Braak (Braak et al., 2003).

Similar to AD, a huge abundance of possible disease mechanisms have been postulated, including α -synuclein proteostasis, oxidative stress, defective mitochondrial function, calcium dyshomeostasis, deficient axonal transport and neuroinflammation (Poewe et al., 2017).

Also several environmental factors have been identified as potential risk factors for PD. Exposure to pesticides, herbicides, and heavy metals has been linked to an increased risk of developing PD, as suggested by various epidemiological studies (Ascherio & Schwarzschild, 2016; Ben-Shlomo et al., 2024).

Conversely, habits like smoking and caffeine consumption appear to be associated with a reduced risk of PD (Ben-Shlomo et al., 2024). Age remains the most significant risk factor for the development of PD (Pang et al., 2019).

Additionally, head injuries, disturbances in gut microbiota (gut dysbiosis), and certain infections are also recognized as risk factors for PD (Baizabal-Carvallo & Alonso-Juarez, 2020; Smeyne, Noyce, Byrne, Savica, & Marras, 2021; Taylor et al., 2016).

2.2.1 Genetic origin of PD

PD is primarily a sporadic condition, with 10 to 15% of cases attributed to genetic mutations. These mutations involve various genes, including α -Synuclein, also called Parkin 1 (SNCA/PARK1), Parkin (PRKN), PARK9, DJ1/PARK7, leucine-rich repeat kinase 2 (LRRK2), and PTEN-induced putative kinase 1 (PINK1), among others (Billingsley, Bandres-Ciga, Saez-Atienzar, & Singleton, 2018).

SNCA is an ubiquitously expressed gene localizing to presynaptic nerve terminals in the brain. Based on its structure, physical properties and interacting partners, several hypotheses for the normal function of SNCA have been proposed, including the regulation of dopamine release and transport, induction of fibrillization of microtubule-associated protein tau, and exertion of a neuroprotective phenotype in non-dopaminergic neurons (Siddiqui, Pervaiz, & Abbasi, 2016). This neuroprotective effect involves inhibiting the expression of p53 and the transactivation of proapoptotic genes, ultimately leading to decreased activation of caspase-3 (Hashimoto & Masliah, 1999). However, in high concentrations, the α -synuclein protein appears to be lethal to neurons due to missense mutations in SNCA which promote apoptosis by altering the expression of p53 (Da Costa, Paitel, Vincent, & Checler, 2002; Lücking & Brice, 2000).

LRRK2 and PARK9 localize to vesicles and membranes (lysosomes, endosomes, and mitochondria) and have been implicated in regulating synaptic vesicle trafficking and neurotransmitter release (Matta et al., 2012). LRRK2 additionally has a positive impact on autophagy, oxidative stress and inflammation (Herbst & Gutierrez, 2019; H. N. Nguyen et al., 2011; Plowey, Cherra III, Liu, & Chu, 2008).

PRKN, an ubiquitin E3 ligase, assists in the role of mitochondrial maintenance and can cause autophagy of non-functioning mitochondria.

Also PINK1, DJ1 (PARK7) and PARK9 are involved in mitochondrial homeostasis by acting as antioxidants during oxidative stress in the brain. Dopaminergic neurons are characterized by their high metabolic activities resulting in the increased production of harmful ROS, which subsequently induce mitochondrial damage (Haddad & Nakamura, 2015), eventually resulting in neuronal cell death (Blesa, Trigo-Damas, Quiroga-Varela, & Jackson-Lewis, 2015).

Both familial and sporadic PD are characterized by the selective loss of dopaminergic neurons in SNc. As mentioned above, this loss is primarily caused by the accumulation of misfolded and aggregated α -SYN fibrils within neurons, forming structures known as Lewy bodies (Goedert, Spillantini, Del Tredici, & Braak, 2013). The SNc is a critical region of the brain responsible for regulating movement and muscle contraction. Neurons in this area utilize the neurotransmitter dopamine to transmit signals. Dopamine is not only essential for motor function but also plays a pivotal role in the reward pathway, influencing positive emotions and facilitating learning processes (Glimcher, 2011).

The loss of dopamine-producing cells results in a deficiency of dopamine in the striatum. During the normal aging process there is a natural decline in dopamine-producing neurons in the midbrain. When this decline reaches a critical threshold, clinical symptoms of PD may manifest. Thus, the total number of dopaminergic neurons an individual possesses can influence their risk and the age of onset of PD (Von Linstow, DeLano-Taylor, Kordower, & Brundin, 2020). Treatments supplementing dopamine are primarily used for PD treatment.

However, other neurotransmitter systems are also dysfunctional in PD, including serotonin, acetylcholine, and norepinephrine systems (Factor, McDonald, & Goldstein, 2017; Maillet et al., 2016; Pasquini et al., 2018). This explains why some PD symptoms are refractory to dopamine-based medications.

2.2.2 Main Hypotheses leading to PD

Similar to AD, PD involves a diverse array of molecular processes, although it is initiated by distinct risk factors. These processes encompass various pathways and factors, including protein aggregation, oxidative stress, mitochondrial dysfunction, disrupted calcium homeostasis, impaired axonal transport, and neuroinflammation, many of which are also implicated in AD (Jellinger, 2014; Maiti, Manna, & Dunbar, 2017). The subsequent paragraph will discuss in more detail additional biochemical pathways specific to PD emergence.

α -Synuclein aggregation

The accumulation of abnormal α -synuclein aggregates is a leading theory to account for the loss of nigrostriatal neurons in PD. As mentioned above α -synuclein has neuroprotective properties and is involved in synaptic vesicle dynamics, intracellular transport, mitochondrial function, and brain lipid metabolism.

While α -synuclein is predominantly expressed in the CNS's presynaptic terminals, it can also be found in peripheral tissues and blood (Malek et al., 2014; Witt, 2013). Cells maintain a balance of intracellular α -synuclein through the ubiquitin-proteasome system, lysosomal autophagy, and extracellular proteases. Disruptions in these degradation pathways can result in the buildup of α -synuclein, where soluble monomers easily aggregate into oligomers, then protofibrils, and finally large, insoluble fibrils (Gerakis & Hetz, 2018).

Like the amyloid plaques in AD, misfolded α -synuclein can spread from cell to cell in a prion-like manner through interconnected circuits of the nervous system (Soto, 2012), inducing neuronal damage. The age-related weakening of the brain's proteolytic defenses is thought to contribute significantly to this accumulation (Stefanis, 2012).

Unlike amyloid plaques, which can also be found in non-demented

elderly individuals, Lewy bodies and Lewy neurites are characteristic pathological features of PD (Mikolaenko et al., 2005). Their presence in aging individuals is often interpreted as presymptomatic PD or dementia with Lewy bodies (Markesbery, Jicha, Liu, & Schmitt, 2009).

Gut dysbiosis

Not only is the gut microbiota considered as one of the important factors in regulating the gut-brain interactions (Ling, Xiao, & Chen, 2022; Y. Wang & Kasper, 2014), there also exists the hypothesis that the pathological process of PD originates in the gut from where it spreads to the brain through endocrine, immune, and direct neural mechanisms (Braak, De Vos, Bohl, & Del Tredici, 2006).

Individuals with PD often exhibit a reduced diversity of gut microbiota and changes in specific bacterial taxa compared to healthy individuals, which can lead to increased intestinal inflammation and permeability (leaky gut). These changes may contribute to the translocation of harmful microbial products and inflammatory molecules into the bloodstream, potentially triggering systemic inflammation and neuroinflammation. Gut microbiota also play a role in the metabolism of neurotransmitters, such as dopamine and serotonin, which are dysregulated in PD.

Injection of human α -synuclein fibrils into the gut tissue of healthy rodents was sufficient to induce aggregated α -synuclein pathology within the vagus nerve and brainstem (Holmqvist et al., 2014). Also, human α -synuclein overexpressing mice that received fecal microbiota transplantation from PD patients showed increased severity of manifestations compared to those receiving fecal microbiota from healthy individuals, suggesting a potential causal role of gut dysbiosis in the development of PD (Sampson et al., 2016).

Notable changes in gut microbial composition associated with PD include an increase in the relative abundances of *Verrucomicrobiaceae* and *Akkermansia* and a decrease in *Prevotellaceae* and *Prevotella* (Boertien, Pereira, Aho, & Scheperjans, 2019). PD-related gut dysbiosis, such as increased *Akkermansia* and decreased short-chain fatty acids (SCFAs)-producing bacteria, can increase intestinal permeability and inflammation, exposing the intestinal neural plexus to toxins like lipopolysaccharides (LPS) and pesticides, which may lead

to abnormal aggregation of α -synuclein fibrils and generation of Lewy bodies (Bullich, Keshavarzian, Garssen, Kraneveld, & Perez-Pardo, 2019; Hirayama & Ohno, 2021).

Studies have also demonstrated that oral administration of the enterobacterium *Proteus mirabilis*, which is markedly increased in PD mouse models, can provoke selective death of dopamine neurons and motor deficits in mice, accompanied by neuroinflammation and accumulation of α -synuclein aggregates in both the colon and brain (Choi et al., 2018). Furthermore, the gastric pathogen *Helicobacter pylori* has been associated with increased severity of motor dysfunction, decreased dopamine levels in the brain, and decreased levodopa absorption, as well as autoimmune and inflammatory reactions (Bhattarai, 2018).

Thus, while the precise cause-effect relationships between gut microbiota and PD are not fully understood, emerging evidence from PD animal model studies supports that dysbiotic gut microbiota can aggravate PD pathology, while re-establishment of the gut microbiota can potentially delay or even prevent the onset of PD (M. Zhu et al., 2022), suggesting the gut microbiota both a potential diagnostic tool and therapeutic target for PD.

Ferroptosis

Ferroptosis has been implicated in the loss of dopaminergic neurons in PD (Do Van et al., 2016). It is an iron-dependent form of programmed cell death characterized by oxidative stress, inflammation, and ultimately cellular death. This process is initiated by disruptions in iron metabolism and intense lipid peroxidation (Dixon et al., 2012).

Within the cytosol, Acyl-CoA synthetase converts coenzyme A (CoA) into free polyunsaturated fatty acids. These PUFA molecules can integrate into phospholipids, which are subsequently oxidized by lipoxygenases, leading to lipid peroxidation. The antioxidant glutathione (GSH) serves to counteract lipid peroxidation, thereby inhibiting ferroptosis (Friedmann Angeli et al., 2014; Skouta et al., 2014). *DJ-1*, a significant risk gene associated with familial PD, as mentioned above, indirectly suppresses ferroptosis by enhancing GSH production (Cao et al., 2020).

Both iron and α -synuclein are found in Lewy bodies in the midbrain of PD patients (Castellani, Siedlak, Perry, & Smith, 2000). As a metal-binding protein, α -synuclein is found to bind to these iron molecules, which at least partly explains the conformational changes leading to its aggregation (Golts et al., 2002).

Iron homeostasis within neural networks is maintained by microglia and astrocytes. Accumulated iron activates microglia, prompting the release of proinflammatory cytokines that contribute to neuroinflammation and apoptosis (Thomsen et al., 2015).

2.2.3 Treatment and Outlook

To assist in early and differential diagnosis, various imaging techniques such as dopamin transporter-single-photon emission computed tomography, structural magnetic resonance imaging, and magnetic resonance diffusion-weighted imaging, along with genetic testing, are commonly employed. Additionally, olfactory function testing using Sniffin Stick tests can be useful, as hyposmia or anosmia is present in approximately 90% of individuals with PD (Postuma et al., 2018).

Treatment primarily focuses on symptom management, utilizing dopamine-based therapies like Levodopa, catechol-O-methyl transferase inhibitors, anticholinergics, and monoamine oxidase B (MAO-B) inhibitors to enhance or prolong the effects of dopamine, thus alleviating initial motor symptoms (Schapira et al., 2006). Nonmotor symptoms, such as psychiatric symptoms and cognitive impairments, can be addressed with selective serotonin reuptake inhibitors and cholinesterase inhibitors, respectively (Mao, Qin, Zhang, & Ye, 2020). Also interventions aimed at modulating gut microbiota composition, such as probiotics, prebiotics, dietary changes, or fecal microbiota transplantation, are under consideration (Hirayama & Ohno, 2021).

Although several novel anti-Parkinsons therapeutic agents such as anti-apoptotic agents, MAO-Bs, microRNAs, and viral vector gene therapy have demonstrated promising results in preclinical studies using various animal models (Kabra, Sharma, Kabra, & Baghel, 2018; Mao et al., 2020), their efficacy in human intervention studies or clinical trials remains limited.

2.3 Amyotrophic Lateral Sclerosis (ALS)

ALS is the most heterogenous of the four NDDs. It is characterized by a rapid degeneration of both upper and lower motor neurons in various regions of the CNS, including the motor cortex, brain stem nuclei, and anterior horn cells of the spinal cord. This degeneration leads to progressive muscle weakness and atrophy (muscle wasting), resulting in functional impairments. Weakness typically begins in the muscles of the limbs (referred to as spinal onset), with distal muscles being affected more frequently than proximal muscles. However, in about one-third of cases, the brain stem is affected first (bulbar onset), leading to difficulties in activities such as chewing, speaking (dysarthria), and swallowing (dysphagia).

Ultimately, the progressive weakness and dysfunction of respiratory muscles lead to respiratory failure, which typically limits survival to 2-5 years after onset of the disease (Masrori & Van Damme, 2020). Additionally, approximately 10-15% of ALS patients also develop FTD, a condition characterized by changes in behavior, personality, and language abilities due to degeneration of the frontal and temporal lobes of the brain (Phukan, Pender, & Hardiman, 2007).

In Europe, the estimated incidence for ALS is 2-3 out of 100,000 persons per year, with a prevalence of 10-12 cases per 100,000 persons. Men have slightly higher risk of developing ALS, with a ratio of 1.2-1.5 to women. The age group with the highest risk is typically between 45 to 75 years (Logroscino et al., 2018). This data suggests that aging may not be the predominant risk factor for ALS, unlike in conditions such as AD or PD. However, ALS might be under-recognized in older individuals, as symptoms of weakness or wasting could be mistaken as normal signs of aging or overlooked in individuals with multiple medical conditions (Huisman et al., 2011). If the observed decline in ALS risk with age is indeed genuine, it indicates that the underlying mechanisms of neurodegeneration in ALS, particularly in older individuals, may differ from those in AD and PD (Al-Chalabi & Hardiman, 2013).

Favorable prognostic indicators for ALS include an onset before the age of 50 and initial symptoms in the lower limbs, along with a longer interval between the first symptom and diagnosis. Surprisingly, hyperlipidemia has also been associated with a better prognosis (Dupuis

et al., 2008). Conversely, poor prognostic indicators include an onset in the bulbar or respiratory regions after the age of 65, a shorter time from symptom onset to diagnosis, and a lipid profile indicating low cardiovascular risk (Goutman et al., 2022).

2.3.1 Genetic origin of ALS

In approximately 10% of ALS cases, there is a suggestive family history indicative of an autosomal dominant inheritance pattern, while the remaining 90% of cases appear to occur sporadically (Masrori & Van Damme, 2020).

The five most common genetic causes of ALS include hexanucleotide expansions in the chromosome 9 open reading frame 72 (C9orf72) (DeJesus-Hernandez et al., 2011; Renton et al., 2011), mutations in $\text{Cu}^{2+}/\text{Zn}^{2+}$ SOD1 (Rosen et al., 1993), TAR DNA binding protein 43 (TARDBP, leading to TDP43 protein) (Kabashi et al., 2008; Sreedharan et al., 2008), fused in sarcoma (FUS) (Kwiatkowski et al., 2009; Vance et al., 2009), and TANK binding kinase 1 (TBK1) (Cirulli et al., 2015; Freischmidt et al., 2015). These genetic variants account for approximately 70% of familial ALS cases and 10% of sporadic ALS cases, collectively explaining about 15% of all ALS cases.

Even if not the underlying cause of ALS, ubiquitinated inclusions of TDP43 are found in nearly all ALS cases (Keon et al., 2021; Neumann et al., 2006). Normally, TDP43 shuttles between the nucleus and cytoplasm, with its primary localization being nuclear. However, in ALS, TDP43 mislocalizes to the cytoplasm, where it becomes phosphorylated and forms insoluble aggregates within the cytoplasm of motor neurons. Depletion of nuclear TDP43 and the formation of cytoplasmic aggregates are considered hallmarks of ALS (Mackenzie, Rademakers, & Neumann, 2010).

Mutations in *SOD1* do not only cause damage by impairing the antioxidative function of the SOD1 enzyme itself. Instead, mutant SOD1 proteins gain toxic properties as they tend to misfold and aggregate, forming insoluble inclusions within motor neurons (Rosen et al., 1993).

Similarly, mutations in genes such as *FUS*, *OPTN*, and *UBQLN2* can also result in protein aggregation.

Even in cases of C9orf72 hexanucleotide repeat expansions, which is the most common genetic cause of ALS, the accumulation of translational products from intronic dipeptide repeats (GGGGCC) occurs, despite this repeat being located in a noncoding region of the gene (DeJesus-Hernandez et al., 2011; Gijssels et al., 2012; Renton et al., 2011). C9orf72 protein plays roles in nuclear and endosomal membrane trafficking as well as autophagy. The hexanucleotide repeat of C9orf72 is repeated up to approximately 30 times in healthy individuals. Expansions of this segment to hundreds or thousands of repeats cause familial ALS and FTD; in addition, these expansions sometimes cause sporadic ALS. The repeat sequence RNA escapes to the cytoplasm, where it generates five potentially toxic repeat dipeptides through a noncanonical translation process, that can be initiated by a non-AUG codon in a process called Repeat Associated Non-AUG translation, or RAN translation. Additionally, the transcripts of hexanucleotide repeats form RNA foci in the nucleus, sequestering nuclear proteins and rendering them unavailable to the cell (Green et al., 2017; Y.-B. Lee et al., 2017).

2.3.2 Main Hypotheses leading to ALS

In addition to the well-studied genes mentioned earlier, research has identified over 20 additional genes implicated in the development of both familial and sporadic ALS (Chia, Chiò, & Traynor, 2018). Many of these genes play crucial roles in the key neuronal pathways RNA metabolism, protein quality control and degradation, cytoskeletal and axonal transport, mitochondrial function, and regulation of inflammation, and will be discussed in the following paragraphs.

Disturbed RNA metabolism

A considerable number of RNA binding proteins are implicated in the pathogenesis of ALS. Proteins such as TDP43 and FUS but also angiogenin (ANG) and senataxin (STX) (Yamasaki, Ivanov, Hu, & Anderson, 2009), matrin3 (MATR3) (Coelho et al., 2015), heterogeneous nuclear ribonucleoproteins A1 (hnRNP A1) (Dreyfuss, Matunis, Pinol-Roma, & Burd, 1993) and A2B1 (hnRNPA2 B1) (Alarcón et al., 2015), as well as ataxin2 (ATXN2) (Ostrowski, Hall, & Mekhail, 2017) are primarily located in the nucleus and play crucial roles in transcription, splicing, noncoding RNA metabolism, and microRNA biogenesis (Buratti et al., 2010).

Most of these proteins contain low-complexity domains that allow them to bind not only to RNA but also to other proteins. Mutations associated with ALS have been found to increase the propensity of these proteins to bind, leading to self-assembly and the formation of aggregates (Kim et al., 2013). This auto-aggregation process is facilitated within stress granules, which are non-membrane-bound structures formed under cellular stress that contain RNA complexes stalled in translation (Bosco et al., 2010). The self-assembly of mutant RNA-binding proteins can give rise to toxic, self-propagating conformations that spread disease within and between cells, similar to the mechanisms observed in prion diseases.

Failure of proteasis, protein quality control, and degradation

Protein aggregates, or perhaps their oligomeric complex precursors, disrupt the usual balance of proteins within cells, causing cellular stress. Molecular chaperones may assist in reshaping misfolded proteins; however, if the cell becomes overwhelmed with misfolded proteins, they are tagged for breakdown through ubiquitination via the ubiquitin-proteasome system. Alternatively, protein aggregates may also undergo lysosomal degradation via the autophagy pathway after binding to sequestosome 1 (SQSTM1).

Mutations in TBK1, OPTN, SQSTM1, UBQLN2, C9orf72, and valosin-containing protein (VCP) disrupt protein degradation pathways, potentially contributing to the accumulation of TDP43 protein. UBQLN2 plays a crucial role in delivering ubiquitinated proteins to the proteasome, facilitating their degradation (Deng et al., 2011). SQSTM1, which encodes the protein p62, targets ubiquitinated proteins to the phagophore, a precursor of the autophagosome (Fecto et al., 2011). OPTN, acting as a receptor for autophagy, interacts with ubiquitinated cargo and the phagophore membrane (Maruyama et al., 2010). TBK1 phosphorylates OPTN, activating it to facilitate autophagic degradation (Freischmidt et al., 2015). Additionally, VCP (J. Johnson et al., 2010) and the C9orf72 protein (Webster et al., 2016) also participate in the interaction between ubiquitinated cargo and the phagophore membrane, contributing to the autophagic clearance of misfolded proteins.

Cytoskeletal and axonal transport

Mutations in tubulin alpha 4A (TUBA4A), profilin 1 (PFN1), kinesin heavy chain isoform 5A (KIF5A), and dynactin1 (DCTN1) disrupt cytoskeletal dynamics and axonal transport processes in neurons (De Vos & Hafezparast, 2017; Eykens & Robberecht, 2015). Specifically, mutations in PFN1 and TUBA4A have been shown to destabilize the tubulin network and lead to deficits in axonal transport.

The dynactin complex, which serves as an important activator of the dynein motor, plays a crucial role in stabilizing the binding of cargoes and modulating motor function. Mutations in the gene encoding the DCTN1 subunit of the dynactin complex have been associated with ALS or FTD (Bercier et al., 2019; Munch et al., 2004). Additionally, mutations in the C terminus of kinesin 1, encoded by KIF5A, may impair the anterograde transport of cargoes along microtubules (Brenner et al., 2018; Nicolas et al., 2018).

Mitochondrial function

Coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10) encodes a mitochondrial protein that is predominantly localized at the cristae junctions within the intermembrane space. Mutations in this gene have been implicated in FTD and ALS (Bannwarth et al., 2014). Both endogenous and overexpressed mutant CHCHD10 have been shown to alter the ultrastructure of mitochondrial cristae and induce fragmentation of the mitochondrial network. Furthermore, respiratory chain deficiency has been observed, indicating that CHCHD10 plays a critical role in maintaining ATP production and oxygen consumption (Bannwarth et al., 2014). Additionally, mitochondria from fibroblasts harboring CHCHD10 mutations exhibit poor genome repair following oxidative stress, further underscoring the importance of CHCHD10 in mitochondrial function and cellular homeostasis (Genin et al., 2016).

Regulation of inflammation

Research has associated ALS with dysregulated astrocytes that exhibit cytotoxic effects on neurons (see also paragraph 1.3). The CNS consists of neurons as well as non-neuronal cells, including glia, which reside in the parenchyma and are subdivided into microglia, astrocytes, oligodendrocytes and oligodendrocyte progenitors, and

pericytes, endothelial and ependymal cells, which reside in other cellular compartments.

Microglia execute crucial functions in the maintenance of CNS homeostasis by providing nurture and support to neurons and other cells via the secretion of soluble factors, synaptic refinement, clearance of dead cells or misfolded proteins, and protection from infectious agents (Colonna & Butovsky, 2017).

Astrocytes represent 20-40% of glial cells (Verkhratsky & Nedergaard, 2018; Von Bartheld, Bahney, & Herculano-Houzel, 2016) and have an important role in maintaining ion, neurotransmitter and energy homeostasis. They also contribute to synaptic pruning, and provide trophic support to neurons (Vainchtein & Molofsky, 2020). However, disruptions in CNS homeostasis can trigger astrocytes to become reactive, leading to substantial changes in their transcriptomic profile (Sofroniew & Vinters, 2010; Zamanian et al., 2012).

Myelin-producing oligodendrocytes, which represent approximately 50-75% of glial cells (Von Bartheld et al., 2016), play a crucial role in the CNS. In addition to their primary function in facilitating neuronal action potential propagation through myelination, oligodendrocytes also provide metabolic support to neurons (Philips & Rothstein, 2017). Working in coordination with astrocytes, oligodendrocytes contribute to the maintenance of axonal integrity, survival, and adaptation (Michalski & Kothary, 2015; Philips & Rothstein, 2017).

Furthermore, TBK1, in addition to its above-mentioned role in autophagy and mitophagy (Oakes, Davies, & Collins, 2017), can mediate the activation of NF- κ B in response to certain growth factors, which in turn leads to cytokine production. Additionally, TBK1 serves as an inducer of type-1 interferons, making it a critical kinase for the antiviral innate immune response.

2.3.3 Treatment and Outlook

Clinical management of ALS primarily focuses on symptom management, as there is currently no cure for the disease. Various symptoms of ALS, such as spasticity, sialorrhea (excessive drooling), and muscle cramps, can be addressed with different medications and interventions (Masrori & Van Damme, 2020; on Diagnosis et al., 2012).

Currently, the only drug approved by the European Medicines Agency for ALS treatment is riluzole, which acts as a glutamate antagonist and can extend mean patient survival by 36 months (Hinchcliffe & Smith, 2017). Given that the average survival time is 3 years, this might be considered a certain achievement. However, it may cause common side effects such as nausea, diarrhea, fatigue, dizziness, and liver problems.

Edaravone, a free radical scavenger, has been more recently approved for ALS treatment in the USA, Japan, and some other countries. It has shown a modest but significant effect on some ALS patients, particularly in the early stages of the disease (Petrov, Mansfield, Moussy, & Hermine, 2017). However, a phase III randomized double-blind study of intravenous edaravone raised some concerns due to its small study size, short duration, patient selection criteria, and lack of data on survival (Abe et al., 2017; Al-Chalabi et al., 2017).

2.4 Huntington's Disease (HD)

HD is characterized by the degeneration of the GABAergic medium-sized spiny neurons of the caudate nucleus of the striatum followed by later-stage degeneration of the cortex. This progressive neuronal loss leads to involuntary movements, cognitive decline, behavioral and psychiatric disturbances, and depression (Damiano, Galvan, Déglon, & Brouillet, 2010; McQuade et al., 2014; Roos, 2010).

HD is a global phenomenon with a prevalence of approximately 12 per 100,000 individuals in populations of European descent (Evans et al., 2013). The onset of motor symptoms can occur at any age, ranging from childhood to old age, with a mean age of onset around 45 years. Disease duration typically spans 10 to 15 years (Langbehn, Hayden, Paulsen, & of the Huntington Study Group, 2010; Ross et al., 2014).

Unlike other NDDs, HD is clearly genetic, following an autosomal-dominant inheritance pattern. This makes it an interesting model for studying neurodegenerative processes from their early stages and for closely monitoring the progression of symptoms over time, perhaps finding common mechanisms in development and manifestation of neurodegeneration.

It is caused by the expansion of a CAG repeat in exon 1 of the *HTT* gene, resulting in a polyglutamine (polyQ) expansion in the N-terminus of *HTT*. The expanded repeats lead to the abnormal aggregation of HTT into inclusion bodies within neurons. These aggregates are believed to be directly neurotoxic and also to impair axonal transport. Despite its genetic origin, the pathology of HD typically becomes apparent later in life, suggesting a cumulative neurotoxic effect (McQuade et al., 2014).

To date, nearly 50 diseases are known to be caused by the expansion of simple repeats, nine of which are polyglutamine diseases with HD being the most common of them (Khristich & Mirkin, 2020).

2.4.1 Main Hypotheses leading to the onset of HD

Age of onset is dependent on number of triplet expansions

In healthy individuals, the range of CAG repeat size is typically between 6 and 35, whereas in affected individuals it ranges from 40 to 121, with longer repeats generally associated with earlier onset of symptoms. People who have 36 to 39 CAG repeats show reduced penetrance, for thus far unknown reasons they may or may not develop symptoms of HD. The loss of CAA interruption discussed below might provide a possible explanation for this phenomenon (Black et al., 2020).

The number of inherited repeats is both meiotically and somatically unstable. It tends to expand in germ cells during differentiation, and because it is less stable during spermatogenesis than during oogenesis, the mutation inherited from the father often leads to a faster increase in the length of triplets and thus an earlier onset in the offspring compared to when inherited from the mother (Tabrizi, Flower, Ross, & Wild, 2020).

Moreover, during an individual's lifetime, there is a phenomenon of tissue-specific triplet expansion, particularly affecting the striatum and cortex of the brain. Post-mortem examinations have revealed repeats of over 1,000 CAG repeats in these brain regions, while other tissues such as blood or the cerebellum remain relatively stable (Kennedy et al., 2003; J.-M. Lee et al., 2012; Swami et al., 2009).

This phenomenon of somatic instability is attributed to faulty DNA mismatch repair due to DNA slippage. During DNA replication and transcription, regions of repetitive DNA sequences, in this case CAG repeats, can form short DNA hairpin/loop structures. Mismatch repair proteins recognize these mismatched DNA sequences, but instead of removing them, the loops become incorporated into the gene sequence during the repair reaction (G. Liu, Chen, Bissler, Sinden, & Leffak, 2010). Different genetic variants of proteins involved in DNA repair, particularly mismatch repair, are likely to influence the age at onset and rate of progression of HD. These proteins may serve as potential therapeutic targets to delay the onset of the disease (Tabrizi et al., 2020).

Indeed, large GWA studies such as those conducted by the Genetic Modifiers of Huntingtons Disease (GeM-HD) Consortium, identified several genes linked to replication and DNA repair. Examples include FAN1, a DNA endo- and exonuclease involved in interstrand crosslink repair and replication fork recovery, as well as MLH1, MSH3, PMS1, and PMS2, which together form the MutL mismatch repair endonuclease complexes. Additionally, LIG1, a ligase that seals DNA to complete replication and repair, was implicated (Hensman Moss et al., 2017; J. M. Lee et al., 2019, 2015).

Modulating DNA repair factors such as MSH3, FAN1, PMS2, and LIG1 holds therapeutic potential in HD and other repeat expansion diseases (Flower et al., 2019; Goold et al., 2019; J. M. Lee et al., 2019). Downregulating MSH3, MutL α , MutL γ , and LIG1, inhibiting their interactions, or upregulating FAN1 and PMS1 could potentially reduce somatic CAG expansion and improve the disease course of HD (McAllister et al., 2022). Notably, MSH3 and LIG1 are tolerant of loss-of-function mutations (Ochaba et al., 2016), making them attractive targets for knockdown strategies that could be protective against HD (J. M. Lee et al., 2019). In summary, the modulation of DNA repair pathways presents significant therapeutic promise for HD and other repeat expansion disorders (Tabrizi et al., 2020).

Age of onset is dependent on sequence variation of triplet expansion

Also variants of HTT itself were identified to influence the age of onset. HTT exhibits sequence variation within the CAG repeat,

where normally a CAACAG motif is present at the 3' end of the CAG tract, encoding two additional glutamines. Research has demonstrated that this CAA interruption delays the onset of the disease by 9.5 years, a phenomenon also observed in other triplet expansion diseases (Massey & Jones, 2018; Wright et al., 2019). It has also been shown that loss of the CAA interruption is present in 32% of symptomatic reduced penetrance range patients (36 to 39 CAGs). That means that the loss of the CAACAG motif not only causes significantly earlier disease onset, but also might be one cause for disease outbreak in reduced penetrance patients (Black et al., 2020)

Moreover, the loss of the CAA interruption has been associated with increased somatic expansion of the HTT CAG repeat in various tissues. Interestingly, uninterrupted CAG repeat length of mutant HTT was found to be a more accurate predictor of the age at HD onset than the number of glutamines in the protein. Therefore, strategies aimed at introducing interruptions into the CAG repeat of HTT hold promise as potential treatments for HD (Wright et al., 2019).

Normal HTT is a large, ubiquitously expressed transport protein that shuttles between the nucleus and cytoplasm via active transport (Xia, Lee, Taylor, Vandelft, & Truant, 2003; Zheng, Li, Holmes, Marasa, & Diamond, 2013). It plays crucial roles in CNS development, axonal transport, synaptic function, and cell survival (Saudou & Humbert, 2016). To fulfill its diverse functions, HTT undergoes various posttranslational modifications, including phosphorylation, SUMOylation (small ubiquitin-like modifier), ubiquitylation, acetylation, proteolytic cleavage, and palmitoylation (Ehrnhoefer, Sutton, & Hayden, 2011).

In mutant HTT the polyQ expansion induces a conformational change that hinders the proper placement of these post-translational modifications. Consequently, this alteration leads to changes in function and stability, as well as in cleavage patterns and subcellular distribution of the protein. The abnormal folding of mutant HTT also results in soluble monomers initially forming toxic oligomers, eventually forming fibrils and large inclusions in both the nucleus and cytoplasm (DiFiglia et al., 1997). These aggregates trigger an inflammatory immune response and exert significant stress on cellular ER and the proteasome, which are responsible for removing cellular debris.

Thus, both the loss of function in normal HTT protein and the toxic gain of function in mutant HTT contribute to the disruption of multiple intracellular pathways, ultimately leading to neurodegeneration (DiFiglia et al., 1997; S. C. Johnson, Rabinovitch, & Kaeberlein, 2013).

2.4.2 Treatment and Outlook

Currently, there is no cure for HD but there are medications available to help manage its symptoms and improve quality of life. Tetra-benazine is commonly used to treat chorea by reducing dopamine levels. Antipsychotics like haloperidol and risperidone address psychiatric symptoms, while antidepressants help with depression and anxiety. Anxiolytics may alleviate anxiety and agitation, and anticonvulsants control seizures if present. Dopamine-depleting agents like deutetrabenazine and valbenazine also reduce chorea.

As an autosomal dominant progressive neurodegenerative movement disorder with a single genetic target, HD could be an ideal model for gene therapy. Among the various potential approaches, the advancement of antisense oligonucleotides against parts of mutant HTT which are introduced into the nucleus by viral or non viral vectors is the most advanced. Other options within RNA modulation include microRNAs and regulators of RNA processing, while at the DNA level, zinc finger proteins offer promise.

Numerous products are currently undergoing clinical trials, varying in application method, systemic availability, and specific effects. An essential distinction lies in whether the therapy targets all forms of the huntingtin protein equally or focuses on particularly harmful variants like the Exon1 protein. Unfortunately, the outcomes of the recently concluded GENERATION HD1 study of Tominersen conducted by Hoffman-La Roche were somewhat disappointing, likely attributed to side effects causing cerebrospinal fluid circulation issues. Nonetheless, these results represent a step forward in the quest for an effective gene therapy for HD (Bräuer & Falkenburger, 2023; Byun, Lee, & Kim, 2022).

Chapter 3

Omics levels used in this study

Understanding the phenotype of a cell or an organism involves unraveling the intricate interactions among various molecular classes, regulated by interconnected networks. Research aims to decode these networks to comprehend the molecular intricacies within healthy cells and tissues, as well as deviations in disease states. Investigating NDDs presents additional challenges due to limited access to the brain, requiring post-mortem analyses when significant tissue damage has already occurred.

Nevertheless, genome-wide association studies (GWAS), transcriptomic and proteomic analyses, and to a certain extent, epigenomic studies have generated vast datasets from postmortem brains of patients and non-demented individuals affected by AD, PD, HD, and ALS. Each omics level provides unique yet complementary information, offering a comprehensive view of disease mechanisms.

Limitations in omics data analyses for NDD

Poor diagnostic accuracy for NDDs due to the absence of biomarkers significantly contributes to diluting the information content. Clear boundaries between diseases such as AD, FTD, mild cognitive impairment, Parkinson-like dementia, dementia with Lewy bodies, and other types of dementia are often lacking (Erkkinen, Kim, & Geschwind, 2018). Consequently, incorrect cases may be included in disease studies, or pre-NDD cases may be used as controls, particularly in the case of AD.

The use of unscreened controls, given the high prevalence of AD in the aging industrialized population, poses a significant risk of introducing substantial noise into the study (Escott-Price & Hardy,

2022). In more recent and larger studies, especially those concerning AD and PD, proxy cases are often integrated, further diluting the true disease association of identified genes or loci (Bellenguez et al., 2022; De Rojas et al., 2021; Jansen et al., 2019; Kunkle et al., 2019; Wightman et al., 2021). These proxy NDDs cases are not diagnosed by practitioners but by their caregivers and relatives (Escott-Price & Hardy, 2022).

Also, the appropriate use of age-matched controls is crucial in the context of NDDs (Satizabal et al., 2016). While age matching may have little impact on results for many rare diseases, it is of highest importance for NDDs, where age is the primary risk factor. In the case of AD, for example, the APOE gene is a significant risk factor and is also linked to conditions such as diabetes and longevity (Deelen et al., 2019; Schächter et al., 1994). Studies have shown that the APOE $\epsilon 4$ allele is negatively associated with longevity, while the $\epsilon 2$ variant is positively associated. By simply including age as a covariate in a study, a robust but biologically incorrect association between NDDs and age-associated variants can be created, similar to associations seen with sex- and height-associated variants (Day, Loh, Scott, Ong, & Perry, 2016). Therefore, the appropriate use of age-matched controls is essential in the study of NDDs (Leonenko et al., 2021).

3.1 Genomics level

On the genomics level disease-related genes or loci are found by sequencing and comparing the DNA of patients and controls. Complex diseases do not depend on single point mutations, but on a combination of thousands of very small gene modifications apart from epigenetic and environmental factors. However, sequencing whole genomes of thousands of patients is neither feasible nor necessary, as any two unrelated people share about 99.5% of their DNA sequence and their genomes differ only at specific nucleotide locations called SNPs. Nearby SNPs on a chromosome are correlated and form haplotypes, so the knowledge of one SNP per region allows the deduction of the sequence of the whole region (Salisbury et al., 2003; Visscher et al., 2017). More than 675 million distinct variants are known by now in the Single Nucleotide Polymorphism Database dbSNP.

GWAS, a technique to identify genetic variations associated with

risk of disease or a particular trait, rapidly scans whole genomes of many people for those SNPs, that occur more frequently in people with a particular disease than in people without the disease. Each study can investigate hundreds or thousands of SNPs at a time and is thus particularly useful in finding genetic variations that contribute to common, complex diseases, such as cancer, diabetes, and NDDs among others. Many important disease genes and pathways have been found by this technique (Grenn et al., 2020; Wightman et al., 2021).

Limitations of the technique

There are several limitations concerning GWAS (Tam et al., 2019; Visscher et al., 2017). Most importantly, the identified variants and genes may not necessarily be causal or biologically relevant to the associated disease (Boyle, Li, & Pritchard, 2017) but are likely to tag a functional region or variant in high linkage disequilibrium (LD). Variants in noncoding regions containing regulatory sequences may impact distant genes by altering three dimensional chromatin conformation (Ecker et al., 2012; Spielmann & Klopocki, 2013).

GWA loci typically have small effect sizes and explain only a modest proportion of trait heritability (Manolio et al., 2009). Currently, only variants occurring in 1% or more of a population are considered, but rare variants remain understudied due to methodological issues in identifying them and the cost of generating sufficiently powered whole exome/genome sequencing datasets (Auer & Lettre, 2015).

Another challenge is the balance between sample size and meaningfulness. Increasing the size of a GWA study can provide more information on genes and pathways involved, leading to more accurate disease prediction through polygenic risk score analysis. However, with an increasing size of GWAS, the number of associated trait loci identified inevitably increases, diluting the information content (Escott-Price & Hardy, 2022; Wightman et al., 2021).

One potential solution to this problem could involve the use of trans-ethnic studies or founder populations. These approaches have demonstrated that genetic population differences can lead to novel discoveries that might require a much larger sample size in a single population (D. Li et al., 2022; Reitz et al., 2013). Populations of

ethnic or religious groups with origins traceable to a limited number of ancestors, resulting in a more homogeneous genetic background, have been successfully utilized to identify robust and subsequently validated disease associations. Despite smaller sample sizes, more of these founder population studies should be conducted, as they may exhibit significantly higher frequencies for some variants that are rare in genetically more heterogeneous populations (D. Li et al., 2022; Reitz et al., 2013).

Moreover, epistasis or the fact, that the presence of one gene can alter the phenotypic expression of another gene, has to be taken into account in understanding the genetic basis of complex traits and diseases. It adds complexity to genetic analysis and requires careful consideration when studying the genetic architecture of traits or diseases (J. H. Moore & Williams, 2009).

Last but not least, the lack of study independence poses a great problem in understanding the genetic architecture of neurodegeneration. Nearly all earlier disease GWAS are now part of the current disease GWAS in a russian-doll-like nested way. For example, in AD the large Wightman et. al. 2021 study with over a million individuals, 90,338 (46,613 proxy) cases and 1,036,225 (318,246 proxy) controls included studies of Jansen et. al. (2019) and Kunkle et. al. (2019) which both also contained the study of Lambert et. al. (2013), but this was ultimately only included once in the Wightman study (Jansen et al., 2019; Kunkle et al., 2019; Lambert et al., 2013; Wightman et al., 2021). Still, when larger studies include all smaller ones, imperfections like deficient age-matching or incorrectly assigned cases amplify. Thus systematic errors get mixed up into the updated analyses, diluting the true NDD associations.

3.2 Transcriptomics level

Transcriptomics is the study of the transcriptome, which encompasses the complete set of transcripts present in a cell, along with their abundance, during a specific developmental stage or under certain physiological conditions. This includes various types of transcripts, such as messenger RNAs (mRNAs), as well as different categories of noncoding RNAs (ncRNAs). NcRNAs can be further classified into two main groups: housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs, such as transfer RNAs (tRNAs), ribosomal

RNAs (rRNAs), and small nuclear RNAs (snRNAs), are crucial for maintaining basic cellular functions (Dong & Chen, 2013). On the other hand, regulatory ncRNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and small interfering RNAs (siRNAs), participate in various physiological processes, such as genomic imprinting, immune response regulation, and developmental pathways (L. Chen, Guo, Li, & He, 2019).

Thus, transcriptomics not only encompasses everything related to RNAs, including their transcription, expression levels, functions, localization, transport, and degradation, it also involves studying the structures of transcripts and their parent genes, including start sites, 5' and 3' end sequences, splicing patterns, and posttranscriptional modifications (Lowe, Shirley, Bleackley, Dolan, & Shafee, 2017).

For the metastudy of this work, the focus lay on quantifying mRNA levels in post-mortem brain tissues. This choice was made to ensure comparability across different omics levels, with a common reference point being the protein names according to the Human Genome Organisation (HUGO) nomenclature.

Two main techniques are commonly used to deduce and quantify the transcriptome: microarrays and RNA sequencing (RNA-Seq). Microarrays involve quantifying a predefined set of sequences by hybridizing fluorescently labeled cDNA with custom-made or commercial high-density oligo microarrays. On the other hand, RNA-Seq utilizes high-throughput sequencing to capture all RNA sequences present in a sample (Z. Wang, Gerstein, & Snyder, 2009).

Hybridization-based approaches, such as microarrays, offer high throughput and cost-effectiveness. However, they come with several limitations. Firstly, they rely on existing knowledge about the genome sequence, which can restrict their applicability. Secondly, they often exhibit high background levels due to cross-hybridization, and their detection range is limited by both background noise and signal saturation (Okoniewski & Miller, 2006; Royce, Rozowsky, & Gerstein, 2007).

In contrast, RNA-Seq does not depend on pre-existing genomic sequences, allowing for the detection of transcripts that may not match known genomic regions. It provides precise information on transcription boundaries down to single-base resolution and can identify sequence variations, such as SNPs, within transcribed regions

(Cloonan et al., 2008; Morin et al., 2008). Moreover, RNA-Seq offers low background noise because DNA sequences can be accurately mapped to unique genomic regions. It also has no restriction concerning the upper limit of quantification, being a correct mirror of the existing expression level and enabling the detection of a broad range of transcript expression levels. In comparison, microarrays often lack sensitivity for genes expressed at low or high levels, resulting in a narrower dynamic range (Z. Wang et al., 2009).

Despite these differences, both RNA-Seq and microarray techniques yield comparable results for identifying differentially expressed genes in patients and healthy controls (Mantione et al., 2014). Therefore, studies using both methods were integrated into our analysis.

Limitations of the technique

Interpreting transcriptomics data faces challenges due to two main factors: the imperfect correlation between mRNA and protein levels, and the variability in mRNA composition across different cell types within an organ.

Despite the fact that proteins are synthesized from mRNA, the relationship between mRNA levels and protein abundances is only moderately correlated. This nontrivial mRNA protein relation is a general phenomenon ranging from yeast to human (Gygi, Rochon, Franza, & Aebersold, 1999). Several biological factors contribute to this nontrivial relationship. On the posttranscriptional and translational levels, various mechanisms enhance or repress the synthesis of proteins from mRNA molecules.

These mechanisms include RNA consensus sequences and secondary structures, which influence translational initiation frequency (Kozak, 1999)(Chursov, Kopetzky, Bocharov, Frishman, & Shneider, 2013). Additionally, RNA interference (Kurreck, 2009; Pillai, Bhattacharyya, & Filipowicz, 2007), and codon bias (Komar, 2016) play roles in modulating protein synthesis from mRNA. The individual half-life of proteins in cells is a major post-translational factor affecting the correlation between mRNA and protein levels. Active degradation processes, such as those mediated by the ubiquitin-proteasome system and autophagy, as well as protein secretion from the cell, distort the relation between the amount of mRNA and resulting protein. Protein

half-life is influenced by various factors, including intrinsic protein stability, post-translational modifications such as phosphorylation and ubiquitination, and protein localization. The lifespan of proteins can vary widely, ranging from just a few seconds to several days (Glickman & Ciechanover, 2002; McShane et al., 2016; Varshavsky, 1997).

Recent advancements in single-cell RNA-Seq (scRNA-Seq) have revealed that even within a single organ, cells form subpopulations with distinct protein profiles due to their diverse functions. Consequently, analyses at the bulk tissue level may obscure the complexity of disease-specific alterations occurring across different cell types (De Strooper & Karran, 2016). Nevertheless, due to the limited availability of single-cell data, our analyses primarily relied on bulk RNA sequencing data. But even bulk RNA-Seq data can become quite complex, especially when considering aspects such as differential exon usage or the distinction between various transcripts of the same protein-coding gene. In the genome browser Ensembl (Harrison et al., 2024), for instance, there are often dozens of transcripts assigned to a single protein, expanding the analysis to the sub-gene level. This diversity of transcripts provides valuable information about how genes are expressed and modified to produce different isoforms of a protein, going far beyond the simple view of "1 gene = 1 transcript = 1 protein." However, in the RNA-Seq analyses we used, this complexity was reduced to a simplified perspective, where only the frequency of gene expression is counted, without considering the various transcript variants that arise from alternative splicing or the use of different exons. This reduction of course leads to the loss of valuable information, which could be critical for understanding gene regulation or identifying biomarkers.

When studying transcriptomics, questions concerning spatial and temporal effects of transcripts arise. For instance, how does the concentration of specific transcripts in one cell type affect neighboring cells, and what is the dynamic interaction between all the processes that are triggered in relation to each other? The cutting-edge next step in this field would be spatio-temporal transcriptomics, but this technology is not yet fully available. It is extremely expensive and still lacks the necessary resolution. However, within the next 10-15 years, this might become feasible, offering a whole new level of quality in understanding the interactions between transcripts.

3.3 Proteomics level

Proteomics is the large-scale study of proteins, particularly of their interactions, function, composition, structure and their cellular activities (Chambers, Lawrie, Cash, & Murray, 2000; Deracinois, Flahaut, Duban-Deweer, & Karamanos, 2013), which makes it another important layer to gain a deeper understanding of organismal structure and function compared to genomics and transcriptomics.

The proteome, representing the complete set of proteins, varies across different conditions, cell types, and developmental stages, reflecting the diverse requirements and stresses experienced by cells or organisms. Post-translational modifications further diversify the proteome, with common modifications including phosphorylation, ubiquitinylation, methylation, acetylation, glycosylation, oxidation, and nitrosylation. Proteins may undergo multiple modifications, often in time-dependent combinations, adding to the complexity of protein structure and function (Van Riper, De Jong, Carlis, & Griffin, 2013).

Proteomics has three main fields: expression proteomics, functional proteomics, and structural proteomics. Expression proteomics investigates not only the identification and confirmation of the number of different protein types (proteome width), but also measures protein copies number in particular tissues (proteome depth) (Ponomarenko et al., 2016). Functional proteomics aims to identify protein interactions, which is valuable for understanding cell signaling cascades, identifying potential disease biomarkers, and developing therapeutic interventions (Ngounou Wetie et al., 2014), and structural proteomics determines the three-dimensional structure of both isolated and interacting proteins, e.g. within membranes or nuclear pores.

Two principles of analysing proteins can be distinguished: bottom-up and top-down workflows. In bottom-up (peptide-based) approach, proteins are digested by trypsin. The resulting peptides are then separated by liquid chromatography and identified by mass spectrometry. Another bottom-up approach is called shotgun proteomics. Here, the digestion of protein occurs without fractionation, and liquid chromatography is used afterwards to separate the peptides identified by mass spectrometry. Top-down proteomics analyzes whole proteins or polypeptides directly with mass spectrometry, often using electrospray ionization (ESI) and matrix-assisted laser

desorption/ionization (MALDI). Bottom-up has limited protein sequence coverage, missing many alternative splice variants and post-translational modifications. Top-down preserves all protein modifications but faces challenges with poor protein solubility (Al-Amrani, Al-Jabri, Al-Zaabi, Alshekaili, & Al-Khabori, 2021). Both methods require careful sample preparation and validation steps.

Purifying and analyzing proteins from complex biological mixtures such as cell lysates requires high-throughput techniques. The two primary methods allowing large-scale analyses are protein microarrays and mass spectrometry.

Microarrays use a chip which consists of a support surface such as a glass slide, microtitre plate, beads, or nitrocellulose membrane, with an array of capture proteins attached. Fluorescently labeled probe molecules are added to the array, and any interaction between the probe and the immobilized protein generates a fluorescent signal, which is detected by a laser scanner. Protein microarrays are fast, automated, cost-effective, and highly sensitive, requiring minimal amounts of samples and reagents (Aslam, Basit, Nisar, Khurshid, & Rasool, 2016).

Mass spectrometry, on the other hand, is excellent for identifying unknown components in a sample and quantifying low-abundance proteins and peptides. The principle of mass spectrometry involves ionizing protein molecules and measuring their mass-to-charge ratio. In the process, proteins are either analyzed intact in the top-down approach or digested into smaller peptides in the bottom-up approach. These ionized molecules are then passed through a mass analyzer, which separates them based on their mass-to-charge ratio. The resulting data generates a mass spectrum, which helps identify and characterize the proteins, including their sequence and structural features. It can detect single amino acid substitutions and post-translational modifications and quantify individual protein isoforms (Noor, Ahn, Baker, Ranganathan, & Mohamedali, 2021).

Limitations of the technique

Proteomics is an indispensable level of study, offering insights that cannot be extracted from the genomics or transcriptomics levels. However, due to its complexity and technical challenges, proteomics

also has limitations. As the proteome is highly diverse, with proteins varying widely in abundance, size, and solubility, it is challenging to detect all proteins in a sample, especially low-abundance or membrane-bound proteins. Proteins require careful preparation to avoid degradation and maintain solubility, especially for complex or difficult-to-digest proteins.

Protein microarrays provide qualitative data on protein presence, but they are less effective at quantifying protein abundance or dynamic changes, and at detecting low-abundance proteins or post-translational modifications. They rely on pre-selected capture probes and are therefore limited to known proteins and structurally similar ones. Challenges include the identification and isolation of antibodies or capture molecules for every protein in the human genome, as well as finding suitable surfaces and attachment methods to maintain protein structure and activity. Also, non-specific binding between probes and proteins can lead to false-positive signals, reducing the reliability of results or the array-bound proteins may lose their native structure or function during immobilization, affecting the accuracy of interactions and detection (Aslam et al., 2016).

Mass spectrometry, on the other hand, may not detect all metabolites, as some do not ionize with certain methods. Signals from high abundance proteins can drown out those from low abundance proteins, making potentially very important proteins difficult to analyze (Noor et al., 2021). It generates vast, complex datasets requiring advanced bioinformatics tools. Identification of proteins and peptides relies completely on the quality of data in databases and programs for alignment with known proteins, such as UniProt (Breuza et al., 2016) and PROSITE (Hulo et al., 2006). Only proteins listed in these databases can be identified by these algorithms (Aslam et al., 2016).

Overall, proteomics generates fewer and less reproducible data than transcriptomics, and is much more dependent on standardized protocols in sample preparation between different laboratories, making comparisons challenging. Despite these limitations, proteomics remains indispensable for understanding cellular processes and disease mechanisms.

3.4 Epigenomics level

Epigenomics explores heritable modifications that affect gene activity without altering the DNA sequence itself. These modifications include chemical changes to DNA bases and alterations to chromosomal structures. Key modifications involve DNA methylation of cytosine nucleotides, along with modifications like histone methylation, acetylation, and phosphorylation. These reversible changes can influence gene expression by affecting the binding of transcription factors to regulatory elements. Epigenetic modifications are responsive to various environmental factors like age, diet, stress, and disease (Al Aboud, Tupper, & Jialal, 2018).

Aging organisms often exhibit generalized histone loss, along with local and global chromatin remodeling (Dang et al., 2009). There is also an imbalance between activating and repressive histone modifications, leading to global transcriptional changes. Additionally, there are alterations in DNA methylation patterns, site-specific loss and gain in heterochromatin, and significant nuclear reorganization (Sen, Shah, Nativio, & Berger, 2016). Identifying these regulatory alterations in diseases is challenging, given the abundance of enzymes with redundant functions. Rather than being driven by a few genes, evidence suggests disease-related changes involve large-scale alterations in transcription patterns (Urduingio, Sanchez-Mut, & Esteller, 2009).

The regulation of gene expression during transcription and translation processes remains a vast area of study with many unknown mechanisms. However, certain key players such as DNA methylation, histone modifications, chromatin architecture, and ncRNAs can be investigated using versatile detection methods. Each modification requires specific tools for analysis. For instance, basic tools for studying DNA methylation include digestion assays and bisulfite sequencing of DNA, which have been widely used in research (Frommer et al., 1992; Hatada, Hayashizaki, Hirotsune, Komatsubara, & Mukai, 1991).

DNA methylation is the most intensively investigated epigenetic mechanism. Among the different DNA methylation modifications 5-methylcytosine is the most widely distributed methylation type in eukaryotes, and the most studied and understood DNA modification pattern overall (P. A. Jones & Takai, 2001). It involves the

addition of a methyl group directly to a cytosine nucleotide within a cytosine-guanine sequence (CpG), which are often clustered together to form a CpG island. CpG islands are common targets for epigenetic DNA methylation, notably the CpG islands within promoter regions. Approximately 70% of gene promoter regions contain CpG islands (Saxonov, Berg, & Brutlag, 2006), but their possible function or effect has yet to be explored. Methylated cytosines within a promoter region can recruit proteins that bind to transcription factor binding sites (TFBS), suppressing gene expression by inhibiting interaction between DNA and transcription factors. This methylation-induced interaction impediment results in the formation of heterochromatin, where nucleosomes tighten around the DNA, preventing transcriptional machinery from accessing it (L. D. Moore, Le, & Fan, 2013). Consequently, DNA methylation within promoter regions can lead to gene silencing. However, DNA methylation cannot be considered as a general regulatory mechanism of gene silencing (Medvedeva et al., 2014). Rather, it is one of numerous partly still unknown factors that influence DNA, nucleosome, and chromatin dynamics (S. Li, Peng, & Panchenko, 2022).

Cancers often show marked hypermethylation of tumor suppressor genes and hypomethylation of proto-oncogenes, both of which contribute to tumor carcinogenesis (McMahon, Karunasena, & Ahuja, 2017). Beyond cancer, DNA methylation is known to be involved in tissue-specific gene regulation, genomic imprinting, X chromosome inactivation, and aging. Over time, DNA methylation levels change in predictable ways at specific genomic locations, which can be used as markers of biological aging. One of the most well-known models, the Horvath's clock, estimates cellular age using DNA methylation at 353 specific CpG sites (Horvath, 2013). It can reveal if someone is aging faster or slower than their chronological age, with higher biological age linked to increased disease risk and lower biological age suggesting healthier aging. A more advanced model is the GrimAge clock (A. T. Lu et al., 2019), which is specifically designed to predict time-to-death and risk of age-related diseases, offering insights into an individual's overall longevity. By integrating additional biomarkers beyond DNA methylation, it provides a more comprehensive picture of biological aging compared to earlier models like Horvath's clock (A. T. Lu et al., 2019). In the context of our research on neurodegeneration, the interesting question immediately arises of whether altered methylation patterns are a cause or consequence of aging and disease.

Aging and diseases like neurodegenerative conditions can lead to DNA methylation changes, typically with global hypomethylation and localized hypermethylation (H. Lu, Liu, Deng, & Qing, 2013). These shifts may result from accumulated cellular and genomic damage. However, altered methylation could also drive aging and disease by deactivating genes crucial for repair and immune function. Genetic variants affecting methylation (mQTLs) may further elevate disease risk. To resolve this, more large-scale studies comparing methylation patterns in patients and healthy controls are needed.

Histone modifications play a crucial role in regulating gene expression by altering the structure and function of chromatin. Chromatin immunoprecipitation (ChIP) is a widely used technique to investigate local posttranslational modifications of histone tails and monitor changes in these modifications in response to various stimuli (Dahl & Collas, 2008; Gilmour & Lis, 1984).

Histone modifications encompass enzyme-catalyzed processes such as acetylation, methylation, phosphorylation, and ubiquitinylation. Each modification has specific effects on DNA-histone interactions within nucleosomes (Alaskhar Alhamwe et al., 2018). For instance, acetylation typically occurs at positively charged lysine residues on histone tails, leading to the weakening of DNA-histone interactions. This process results in chromatin opening, making it more accessible for transcriptional machinery and facilitating gene expression. Indeed, while histone acetylation has a relatively straightforward impact on gene expression, the effects of other histone modifications are complex and greatly influenced by the state of neighboring DNA molecules (Bannister & Kouzarides, 2011).

To understand chromatin architecture, researchers employ chromatin accessibility methods and chromatin conformation capture techniques. These approaches help identify active chromatin regions and determine physical associations between different genomic regions, such as promoters and enhancers. Through these studies, researchers gain insights into the spatial organization of chromatin and its role in regulating gene expression (L. Song & Crawford, 2010).

Limitations of the technique

Improvement in epigenomic profiling assays and increasing amounts of epigenetic data publicly available in epigenomic data portals allow

a deeper understanding of normal epigenomes and disease-related disturbances (Amin, Onuchic, & Milosavljevic, 2015). Integrating the epigenomics level into our study should lead to more insights about adaptational and disease processes, as protein composition and its changes are the most exact mirror of the functionality of a cell.

However, the associations observed between epigenetic variation and disease lack robust evidence of causality. In many cases epigenetic variation may be a consequence of disease rather than a cause. Also, the methods for comparative epigenomic analysis are still in their infancy and numerous challenges are faced when mining heterogeneous epigenomic datasets (Y. Li, 2021).

To gain a deeper understanding of how genetic variations influence gene expression across different tissues, cell types, and conditions, the international eQTL Consortium was formed in 2017. It works to identify expression quantitative trait loci (eQTLs) by collecting and analyzing large datasets that link genetic variation to gene expression levels. Its largest project, the Genotype-Tissue Expression Project (GTEx), has created a comprehensive resource linking genetic variation to gene expression across numerous tissues, which can be found in the open access Ensembl eQTL Database (Yates et al., 2020).

Methylation quantitative trait loci (mQTLs) represent a newer area of research that focuses on specific genomic regions where genetic variations are linked to changes in DNA methylation levels, typically at CpG sites. Like eQTLs, which link genetic variants to gene expression, mQTLs associate genetic variations with epigenetic changes, particularly DNA methylation. Often studied alongside eQTLs, mQTLs help provide a more comprehensive understanding of gene regulation. The field distinguishes between *cis*-mQTLs, which are located within 1 Mb of the methylation site they affect, and *trans*-mQTLs, which impact distant genomic regions. Despite the enormous complexity, this research is sure to reveal valuable insights over time.

However, the existing data contain only a small percentage of existing epigenetic regulations. Additionally, results obtained from different techniques stand equally together with no indication of hierarchy between the different regulation mechanisms. Due to this lack of comparability, we only integrated studies of methylation differences. Thus, the epigenomic data could only be regarded as an additional layer to

the genomic, transcriptomic and proteomic level in our metastudy.

3.5 Outline of the thesis

This thesis aimed to investigate four of the most prevalent NDDs using a trans-omics approach to uncover potentially shared, but also disease-specific mechanisms. Despite their distinct phenotypes, NDDs share similar disrupted molecular pathways such as protein aggregation in the brain, inflammation, dysregulated autophagy and apoptosis, and mitochondrial dysfunction. Identifying commonly dysregulated genes across these diseases could provide insights into their origins. Comparing these findings to HD, a clearly inherited condition, may help pinpoint shared dysregulated genes.

We gathered publicly available genomic, transcriptomic, and proteomic data from 177 studies involving over one million patients to reveal shared genetic patterns across AD, PD, HD, and ALS across the three omics layers. We could confirm significant relationships between the diseases on transcriptomic and proteomic levels by identifying pathways and GO terms strongly associated with neurodegeneration. This study was published in December 2020 and is provided in Chapter 4 (Section 4.1).

In a second study, we adopted a network-based approach to delineate specific processes in individual diseases and omics layers. Using data from 234 studies comparing patients with healthy controls, we integrated an additional layer, the methylomic data. To better differentiate processes linked to specific gene sets, we constructed protein-protein interaction networks for each omics layer of each NDD. Using the Louvain algorithm, we isolated communities of high modularity within these networks. Functional analyses of these communities revealed distinct processes associated with different gene sets. This study was published in June 2022 and is detailed in Chapter 4 (Section 4.2).

Chapter 4

Publications

4.1 Common Factors in Neurodegeneration: A Meta-Study Revealing Shared Patterns on a Multi-Omics Scale

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My contributions to this article are listed in the Appendix 11.3:
Contributions to individual publications

Article

Common Factors in Neurodegeneration: A Meta-Study Revealing Shared Patterns on a Multi-Omics Scale

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Abstract: Neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), and amyotrophic lateral sclerosis (ALS) are heterogeneous, progressive diseases with frequently overlapping symptoms characterized by a loss of neurons. Studies have suggested relations between neurodegenerative diseases for many years (e.g., regarding the aggregation of toxic proteins or triggering endogenous cell death pathways). We gathered publicly available genomic, transcriptomic, and proteomic data from 177 studies and more than one million patients to detect shared genetic patterns between the neurodegenerative diseases on three analyzed omics-layers. The results show a remarkably high number of shared differentially expressed genes between the transcriptomic and proteomic levels for all conditions, while showing a significant relation between genomic and proteomic data between AD and PD and AD and ALS. We identified a set of 139 genes being differentially expressed in several transcriptomic experiments of all four diseases. These 139 genes showed overrepresented gene ontology (GO) Terms involved in the development of neurodegeneration, such as response to heat and hypoxia, positive regulation of cytokines and angiogenesis, and RNA catabolic process. Furthermore, the four analyzed neurodegenerative diseases (NDDs) were clustered by their mean direction of regulation throughout all transcriptomic studies for this set of 139 genes, with the closest relation regarding this common gene set seen between AD and HD. GO-Term and pathway analysis of the proteomic overlap led to biological processes (BPs), related to protein folding and humoral immune response. Taken together, we could confirm the existence of many relations between Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis on transcriptomic and proteomic levels by analyzing the pathways and GO-Terms arising in these intersections. The significance of the connection and the striking relation of the results to processes leading to neurodegeneration between the transcriptomic and proteomic data for all four analyzed neurodegenerative diseases showed that exploring many studies simultaneously, including multiple omics-layers of different neurodegenerative diseases simultaneously, holds new relevant insights that do not emerge from analyzing these data separately. Furthermore, the results shed light on processes like the humoral immune response that have previously been described only for certain diseases. Our data therefore suggest human patients with neurodegenerative diseases should be addressed as complex biological systems by integrating multiple underlying data sources.

Keywords: multi-omics; Alzheimer’s disease; Parkinson’s disease; Huntington’s disease; amyotrophic lateral sclerosis; neurodegeneration

1. Introduction

Neurodegenerative diseases (NDDs), including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, are heterogeneous, progressive diseases characterized by a loss of neurons, an accumulation of aggregated and misfolded proteins [1–4], cognitive decline and locomotive dysfunction [5–7]. Despite decades of research and considerable progress in identifying risk genes, potent biomarkers, and environmental risk factors, this progression cannot be impeded. As details regarding the various (patho-)physiological processes associated with neurodegenerative diseases remain unclear, the diseases are still incurable. At the same time, it has become generally accepted that the underlying mechanisms are polyfactorial and depend on the complex interplay of multiple (partly unknown) genetic and non-genetic variables [8–14].

Influences on the development of NDDs can be classified into broader functional groups based on their primary site or mode of action into intracellular mechanisms, local tissue environment influences, and systemic influences [15]. These pathways and mechanisms are highly related and can have overlapping or interacting components that can collectively modulate neurodegenerative processes. We slightly adapted this categorization based on Ramanan [15], and depict the processes associated with each of the three categories in Figure 1. Candidate pathways influencing the balance of neuronal survival and degeneration within the cell are misguided apoptosis and autophagy [16,17], dysfunction in mitochondria [18–20], various forms of cell stress [15,21,22], defective cytoskeletal proteins and impaired protein expression regulation [23–26]. Within the local tissue environment, impaired cell adhesion pathways lead to limited neurotransmission and cell proliferation, a permeable blood–brain barrier (BBB), and dysfunctional extracellular matrices (ECMs) [27–29]. Excessive immune response and inflammation [30–33] and a dysregulated lipid and sugar metabolism lead to disturbances in the whole systemic environment [34–36].

Intracellular mechanisms	Local tissue environment	Systemic environment
• mitochondrial functions • cell cycle (mitosis, meiosis) • expression regulation (transcriptomic, (post)translational, epigenetic) • endocytosis (vesicles, lysosomes, secretion) • cytoskeleton (actin filaments, microtubuli, kinesin) • stress response (oxidative, heat, cold, DNA damage) • transport • homeostasis • autophagy (ubiquitin/proteasome) • Apoptosis	• cell adhesion (attachment, tight junctions, gap junctions, Blood-Brain-Barrier) • cell migration • cell differentiation • cell proliferation • extracellular matrix • organ development (brain, bone, muscle) • signal transduction (synapsis, ionchannels, membrane shuttle, receptor)	• immune system (inflammation, infection response, innate immune response) • metabolism (energy, maintenance) • endocrine factors • vascular factors • neurotrophic factors • aging

Figure 1. Classification of candidate pathways contributing to neurodegeneration into three groups according to their cellular mechanisms or their primary site of action. The categorization is based on Ramanan's pathways to neurodegeneration [15] and aims to help in classifying the current knowledge surrounding neurodegeneration.

By far the most prevalent of NDDs, Alzheimer's disease (AD) is an inexorably progressive brain disorder that affects higher cognitive functions [37–39]. The accumulation of abnormally folded

extracellular β -amyloid (senile plaques) and intracellular phosphorylated tau (neurofibrillary tangles) proteins are the distinctive pathological hallmarks of the disease that might trigger synaptopathies, glial inflammation and eventually neuronal death in the cerebral cortex, subcortical regions, temporal and parietal lobes and cingulate gyrus [40–42] and even effects the gut microbiome [43].

Parkinson's disease (PD) is the second most common neurodegenerative disorder, mainly affecting the motor system [44,45]. The aggregation of α -synuclein into Lewy bodies and Lewy neurites, primarily in the substantia nigra pars compacta, and the resulting loss of dopaminergic neurons leads to distinctive symptoms including resting tremors, bradykinesia, stooped posture and, in some cases, dementia [46–48].

Huntington's disease (HD) is a progressive neurodegenerative disease that can lead to chorea, cognitive decline, psychiatric disorders and depression [49,50]. It manifests pathologically with the significant loss of the striatum's GABAergic medium-sized spiny neurons [51,52] due to the intracellular accumulation of misfolded Huntingtin protein [53,54]. While both, familial and sporadic forms of AD and PD exist, HD is an autosomal dominant neurodegenerative disease caused by the expansion of a CAG repeat in the exon 1 of the huntingtin gene translating into a polyglutamine (polyQ) expansion in the N-terminus of the Huntingtin protein [54–56].

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting both the upper and lower motor neurons [57–59], and is characterized by progressive muscular paralysis reflecting the degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord [60–62]. Paralysis is progressive and leads to death due to respiratory failure within 2–5 years [57,58]. Most ALS cases are sporadic, but 5–10% of cases are familial with mutations of the *SOD1* and *TARDBP* (TDP-43) genes [59,63]. Cellular aggregates, including FUS, SOD1, TDP-43, OPTN, UBQLN2, and the translational product of intronic repeats in the gene *C9ORF72* are found both in the sporadic and the familial form [64].

The described overlap of phenotypic traits of the NDD suggests common pathogenic mechanisms underlying distinct NDDs. Compared to studying individual diseases separately, identifying and analyzing the common dysfunctional proteins and dysregulated diseases' pathways might elucidate fundamental insights into their pathogenic process [65]. It was previously shown that there is nearly no overlap between AD, PD, and ALS on genomic data and some shared pathways for AD, PD, ALS, and HD in transcriptomic data [66], but proteomic data and the latest entries in the databases have not been considered. Besides looking for overlapping genes between the different NDDs or omics layers, we also analyzed whether this number is sufficiently high to claim a significant relationship between NDDs or omics layers. An overview of the methodologic procedure is given in Figure 2. By investigating 177 studies in total, this meta-study was able to detect stable signals that arise mainly in late-stage NDDs across tissues, methods and omics layers, which could help unravel patterns across neurodegenerative diseases. Such findings could contribute to a better understanding of the underlying neurodegeneration process and might also have pharmacological relevance for various neurodegenerative diseases.

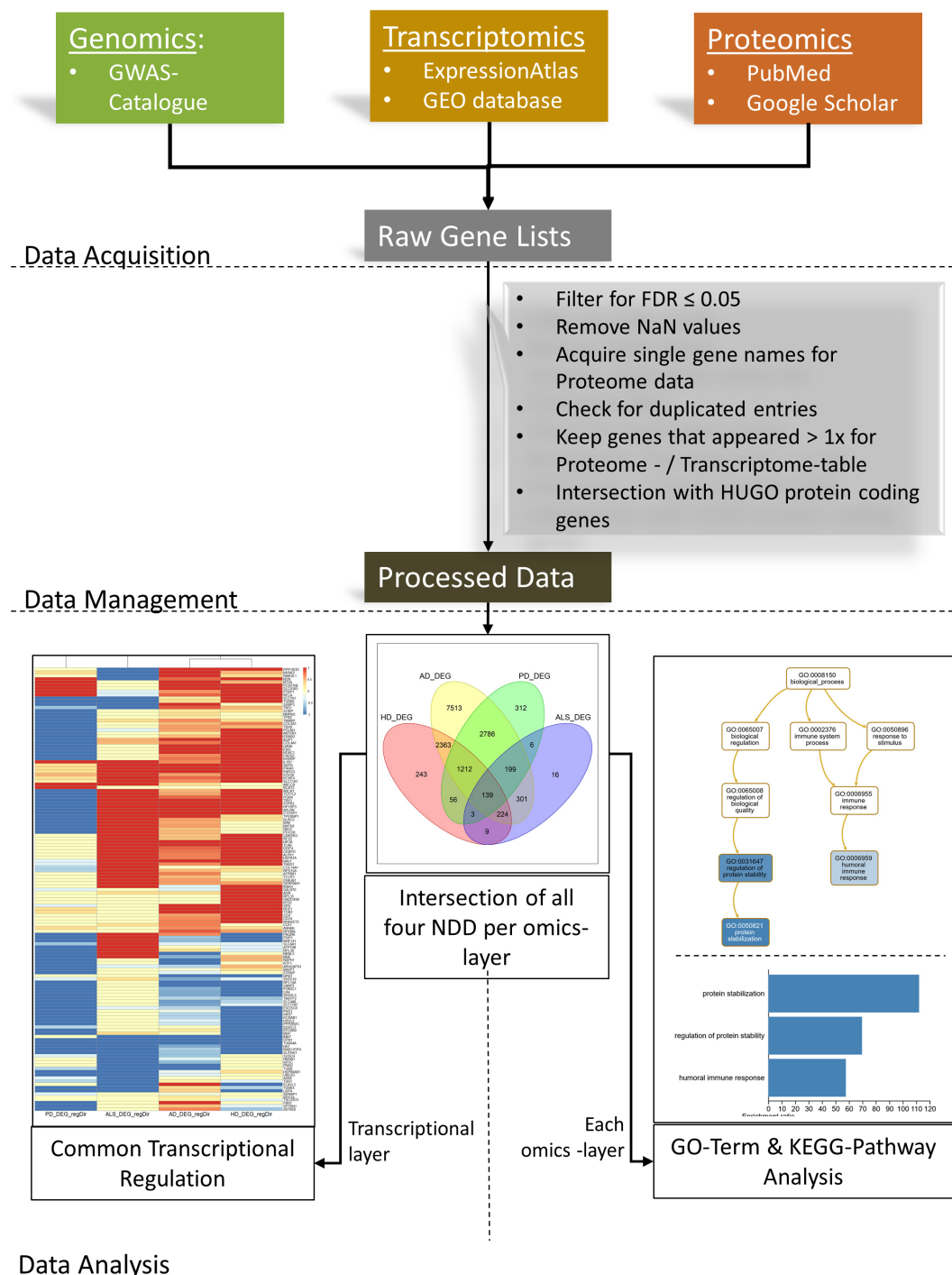


Figure 2. Workflow Overview: Data acquisition was performed using the genome-wide association studies (GWAS) Catalog for genomic data, the European Bioinformatics Institute (EMBL-EBI) Expression Atlas and the Gene Expression Omnibus database for transcriptomic data, and literature research in PubMed and Google Scholar for proteomic data. After filtering these raw data tables and applying some data transformation, the processed data were used for the data analysis. For every omics layer, the intersections of all four analyzed NDDs were visualized as Venn diagrams. Common transcriptional patterns were searched with a hierarchical clustering approach and visualized as a heatmap showing the mean transcriptional direction of regulation per gene, and a dendrogram showing the clustering results. Finally, each set of genes after the intersections was used for the Kyoto Encyclopedia for Genes and Genomes (KEGG) pathway and GO-Term analyses.

2. Materials and Methods

2.1. Data Acquisition/Literature Research

2.1.1. Genome

The genome-wide association studies (GWAS) Catalog data for Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) were downloaded on 28 April 2020. The GWAS Catalog contains single nucleotide polymorphism (SNP) data of GWAS studies for SNPs showing a statistical significance of SNP-trait p -value $< 1 \times 10^{-5}$ in the overall population. For every SNP, data such as p -value, upstream gene(s), mapped gene, reported gene(s) and many more are stored. We focused on the genes given as "Reported Gene(s)" in the four examined diseases' full data tables for our analysis. The experimental factor ontology (EFO) numbers for the exact search pattern were EFO_0000249 (Alzheimer's disease), EFO_0002508 (Parkinson's disease), Orphanet_399 (Huntington's disease), and EFO_0000253 (Amyotrophic lateral sclerosis). A table containing all studies' names and the number of investigated samples for each disease is appended in the Supplementary Table S1. In total, 116 studies with genomic data were used for the analyses [67–182], seven of which contained data of more than one of these NDDs.

2.1.2. Transcriptome

We browsed the Gene Expression Omnibus (GEO) [183] and the Expression Atlas [184] databases. The GEO is a public data repository in which microarray and RNA-seq datasets can be found. The keywords for the GEO database were <name of disease> AND ("microarray" OR "RNAseq") AND "human". The latest literature research was done in July 2020. The Expression Atlas is a service of the European Bioinformatics Institute (EMBL-EBI) and provides re-analyzed and manually curated data of more than 3000 experiments. It was used in release 35 (May 2020, <https://www.ebi.ac.uk/gxa/home>) and scanned for Alzheimer, Parkinson, Huntington and amyotrophic lateral sclerosis, using the filter "Homo sapiens" in the section Differential Experiments.

An overview of all of the studies used to gather the transcriptomic data is provided in Table 1. In the Supplementary materials (Table S2), a table is provided showing each study's information and a table of the proportion of all used tissues and severity states per disease (Supplementary File S4). Of the studies used, 55% utilized microarray experiments, 40% used RNA sequencing and 5% were based on single cell RNA sequencing experiments. In total, transcriptomic data of 39 studies was acquired [185–223].

Table 1. Overview of the number of cases and controls and the total number of studies per disease throughout all analyzed transcriptome studies. In total, data of 2181. Samples were gathered from 39 studies analyzing transcriptomic data. * One study conducted experiments for AD and HD. Thus, in total proteomic data of 22 studies was used.

Transcriptome	Case	Control	Sum of Samples	Studies
AD	187	194	381	11
PD	252	215	467	11
HD	73	99	173	10
ALS	470	691	1161	8
Σ	982	1199	2181	40 (39 *)

2.1.3. Proteome

We browsed publications from the last 10 years in PubMed and Google Scholar with the keywords: ("neurodegenerative diseases" OR "Alzheimer* disease" OR "Parkinson* disease" OR "Huntington* disease" OR "Amyotrophic Lateral Sclerosis") AND (proteomics OR "quantitative proteomics" OR "differentially expressed proteins" OR biomarkers) AND human NOT mice. An overview statistic

regarding the number of samples and studies for the proteomic data is given in Table 2. A table showing each study's information is provided in the Supplementary materials (Table S3), as well as a table of the proportion of all used tissues and severity states per disease (Supplementary File S4). In total, 22 studies were used for proteomic data acquisition [36,50,190,193,224–240].

Table 2. Overview of the number of cases, controls and the total number of studies per disease throughout all analyzed proteome studies. In total, data of 1969 samples were gathered from 22 studies analyzing proteomic data. * Two studies conducted experiments for AD and PD. Thus, in total proteomic data of 22 studies was used.

Proteome	Case	Control	Sum of samples	Studies
AD	853	444	1297	9
PD	146	167	313	7
HD	39	29	68	5
ALS	162	129	291	3
Σ	1200	769	1969	24 (22 *)

More than 90% of the non-control patients in the proteomic data and 84% in the transcriptomic data were classified with a moderate or severe disease state. Furthermore, 63% of the transcriptomic data experiments and 67% of the proteomic data experiments were conducted with brain material. The remaining experiments were conducted with blood, spinal cord, cerebral spinal fluid or induced pluripotent stem-cells. A detailed table can be found in the Supplementary materials (Table S3). Studies that turned out to show no single gene with a false discovery ratio < 0.05 were not considered for our statistics in Tables 1 and 2 and not counted as one of our 177 studies as none of their results contributed to our analyses.

2.2. Data Management

The raw genomic, transcriptomic and proteomic data tables from 177 different studies were transformed into standardized tables for each disease on every omics layer. Different conversions were applied within this data management process, such as converting fold change to $\log_2$ -fold change ($\log_2FC$), $\log_{10}$ - p -value to p -value, the removal of entries with a missing gene name or separating rows that contained several gene names (proteomic data). Differences in multiple testing corrections were accepted, such as differences in the exact calculation of the fold change ($\log_2FC$, G-fold change). Only those genes with a false discovery ratio (FDR) ≤ 0.05 were selected after applying those conversions where necessary. Further, all genes that appeared as differentially expressed in only one experiment on the transcriptomics or proteomics level were discarded, to further reduce the number of genes that appeared randomly. Finally, all remaining genes from the genomic, transcriptomic and proteomic data sources intersected with the latest list of protein-coding gene symbols (04.08.20) from the HUGO Gene Nomenclature Committee to exclude non-standard gene names.

2.3. Data Analysis

We analyzed the gathered data in three different ways (see also Figure 2).

2.3.1. Intersection

By intersecting the three analyzed omics layers per disease and the four diseases per omics layer, it is possible to test if the number of shared genes between some omics layers or diseases are significantly increased. We used a hypergeometric test to test the overlapping sets, with the total amount of 19,324 gene symbols of protein-coding genes (HUGO Gene Nomenclature Committee 04.08.20) [241] as the total population. Intersections were performed and visualized using the R (version 4.0.2) package *venn* (version 1.9) [242].

2.3.2. Common Regulation between NDDs on a Transcriptomic Level

It was tested for the intersection of all NDDs on the transcriptomic level, if the direction of regulation for different NDDs was equal. The mean direction of regulation was computed as follows. Equation (1): Calculation of mean regulation of direction

$$MeanRegDir(gene) = \frac{1}{n} \sum_{i=1}^n \left(sig(gene_{foldChange_i}) \right) \quad (1)$$

with

n = number of appearances for gene with $FDR \leq 0.05$

$$sig(x) = \begin{cases} 1, & \text{if } x > 0 \\ -1, & \text{if } x < 0 \end{cases}$$

In order to test for a correlation between the transcriptomic regulation of the four analyzed NDDs, a correlation test was performed using R's `cor.test()` function. Additionally, the information about the mean direction of regulation (see. Equation (1)) of these genes was used to cluster the four analyzed NDDs based on the 139 genes appearing in the intersection of all transcriptomic data. Hierarchical clustering and creating a heatmap showing the results were performed using the R package `pheatmap` (version 1.0.12) [243].

2.3.3. GO-Term- and Pathway Analyses

Independent of the test results, these sets of overlapping genes were also used for Kyoto Encyclopedia for Genes and Genomes (KEGG)-pathway analyses [244] and GO-Term [245] analyses. We used the R API `WebGestaltR` 0.4.4 of the online tool `WebGestalt` 2020 [246] to perform overrepresentation analyses (ORA) for all possible intersections per disease and per omics layer. For performing the ORA, the command `WebGestaltR` was used with the options:

- `enrichDatabase = c("pathway_KEGG", "geneontology_Biological_Process", "geneontology_Cellular_Component", "geneontology_Molecular_Function")`
- `interestGeneType = "genesymbol"`
- `referenceSet = "genome"`
- `topThr = 10000`
- `reportNum = 10000`

The organism was set to "hsapiens" by default.

As the number of significantly overrepresented biological processes was very high in the ORA of the transcriptomic overlap for AD, PD, ALS and HD, the affinity propagation of the R package `apcluster` [247] was used. This method is already built in the `WebGestalt` tool and utilizes the affinity propagation method [248] to reduce the set of all biological processes to highly representative ones.

3. Results

3.1. Intersection

To quantify if the number of overlapping genes between AD, PD, HD and ALS was high for one omics layer, a hypergeometric test was performed. The number of genes found in the GWAS Catalog was highest for AD, with 434 single nucleotide polymorphisms (SNPs). For PD, 218 SNPs were found; 68 were found for ALS and 34 SNPs for HD. The number of overlapping SNPs between each pair of diseases ranged from zero to eleven and was significantly high for the pairwise overlaps between AD and PD as well as AD and ALS in a hypergeometric test (see Figure 3). For the transcriptomic data, AD again showed the highest number of genes, with a total of 14,737 genes that were differentially expressed in at least two experiments. PD showed 4713 differentially expressed genes, ALS showed

897 and HD showed 4249. All pairwise comparisons of diseases on the transcriptomic level showed a highly significant enrichment in the number of overlapping genes. For AD, 1964 gene names could be related to differentially expressed proteins. We found 434 gene names for PD, 155 for ALS and 104 for HD. All pairwise overlaps between the four diseases were enriched for the proteome data with high significance.



Figure 3. Venn diagrams and hypergeometric test results for the overlap between significant single nucleotide polymorphism (SNP)-trait associations (genomic level) and significantly differentially expressed genes on the transcriptomic (middle) and proteomic (bottom) levels for AD, PD, HD and ALS. All tested intersections show highly significant enriched numbers of overlapping genes for the transcriptomic and proteomic data. The genomic data show significantly enriched numbers of overlapping genes for the AD-PD and AD-ALS intersections.

3.2. Common Regulation of NDDs on the Transcriptomic Level

The intersection of all four diseases' transcriptomic data contained 139 genes. The hierarchical clustering result of the four NDDs based on these genes can be found in Figure 4 and shows an inner cluster formed of HD and AD consecutively extended by ALS and then PD.

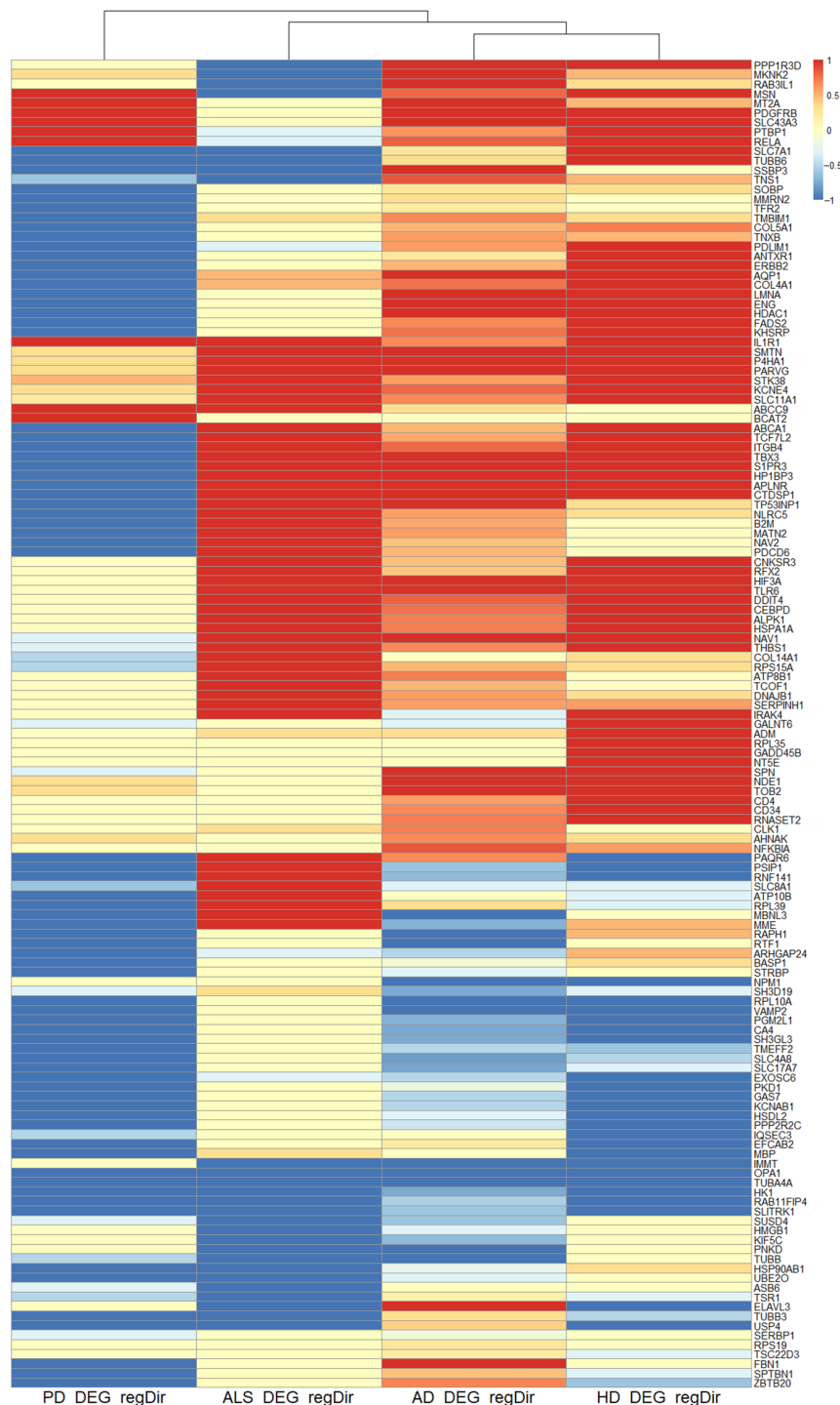


Figure 4. Heatmap with hierarchical clustering results of the mean regulation of all 139 genes that were maintained in all four NDD transcriptomic data. The clustering led to an inner cluster containing HD and AD transcriptomic data. This cluster was next clustered to the ALS transcriptomic data and finally these three NDD were clustered to PD. Colors represent the mean direction of regulation (see Equation (1)).

The results of the correlation analysis are shown in Table 3. The most significant relation in terms of the mean direction of regulation existed between AD and HD with a p -value $< 2.2 \times 10^{-16}$. The correlation value of 0.657 showed a strong relation. All other pairwise comparisons showed a significant relation with correlation values > 0.3 , except for the non-significant comparison between PD and ALS (correlation < 0.047).

Table 3. Results of the one stratum analysis of the linear regression model calculated with the cor.test function in R. The p -value and correlation values are given for all pairwise comparisons of the analyzed NDDs. The analyzed values are the mean direction of regulation of all transcriptomic data kept after intersecting the four NDDs. p -Values < 0.05 are shown in red.

NDD	AD-PD	AD-ALS	AD-HD	PD-ALS	PD-HD	ALS-HD
p -value	0.0001185	0.000131	$< 2.2 \times 10^{-16}$	0.5887	2.422×10^{-6}	0.0002744
Correlation	0.320714	0.3187755	0.6566416	0.04625543	0.387635	0.3040112

3.3. GO-Term- and Pathway-Analyses

As the number of possible combinations of omics layers and diseases was very high, this study concentrated on describing the GO-Term and KEGG pathway analyses of the genes appearing in the intersection of all diseases per omics layer. GO-Terms and the contributing genes were analyzed in accordance with the conceptual model of candidate pathways contributing to neurodegeneration [15]. Results of the intersection of all four analyzed NDDs were also visualized as directed acyclic graphs that show the GO-Term hierarchy leading to the significant terms (Figure 5).

3.3.1. Transcriptomic Intersection of AD, PD, ALS and HD

The 28 overrepresented Biological Process (BP)-Terms for the intersection of all four diseases' transcriptomic data were reduced to the eight most representative ones using affinity propagation (Figure 5D). All results of the GO-Term and KEGG pathway analyses performed are also given in the Supplementary File S5. The resulting enriched sets can mainly be related to cellular response to heat and stress (in our case hypoxia), but also the NOD2 signaling pathway, the negative regulation of apoptosis, a positive regulation of angiogenesis and cytokines, RNA catabolic processes and extracellular matrix organization (Figure 6). All of the six detected Cellular Component (CC)-Terms are related to focal adhesion, plasma membrane, and endoplasmic reticulum (ER) lumen (Figure 5A). The seven overrepresented Molecular Function (MF)-Terms can be categorized into structural molecule activity (structural constituent of cytoskeleton, extracellular matrix structural constituent) and protein binding (platelet-derived growth factor binding, growth factor binding, integrin binding, cell adhesion molecule binding, NF- κ B binding), as shown in Figure 5B. The KEGG pathway analysis showed prostate cancer as the only significant result (FDR = 0.025).

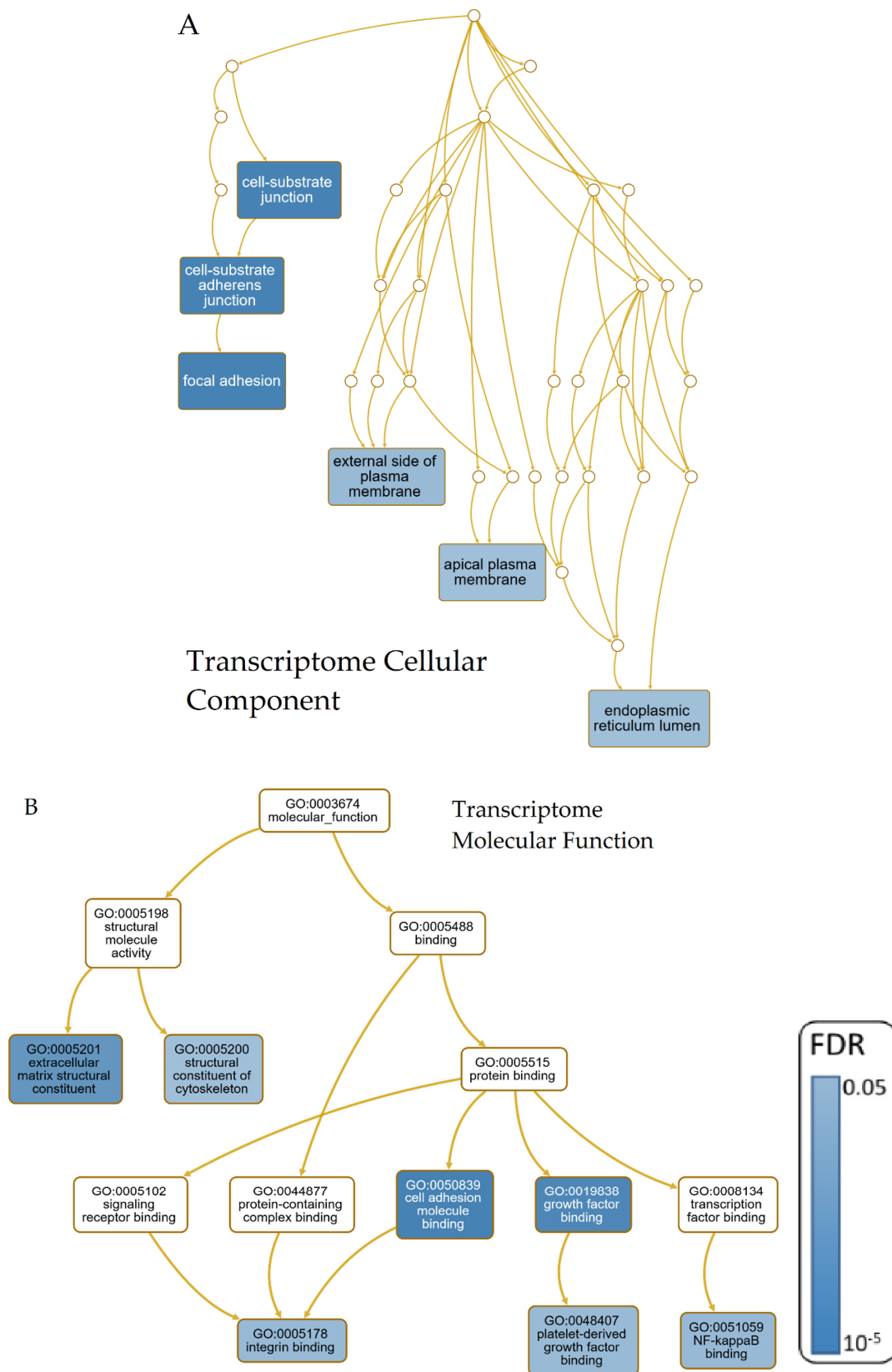


Figure 5. Cont.

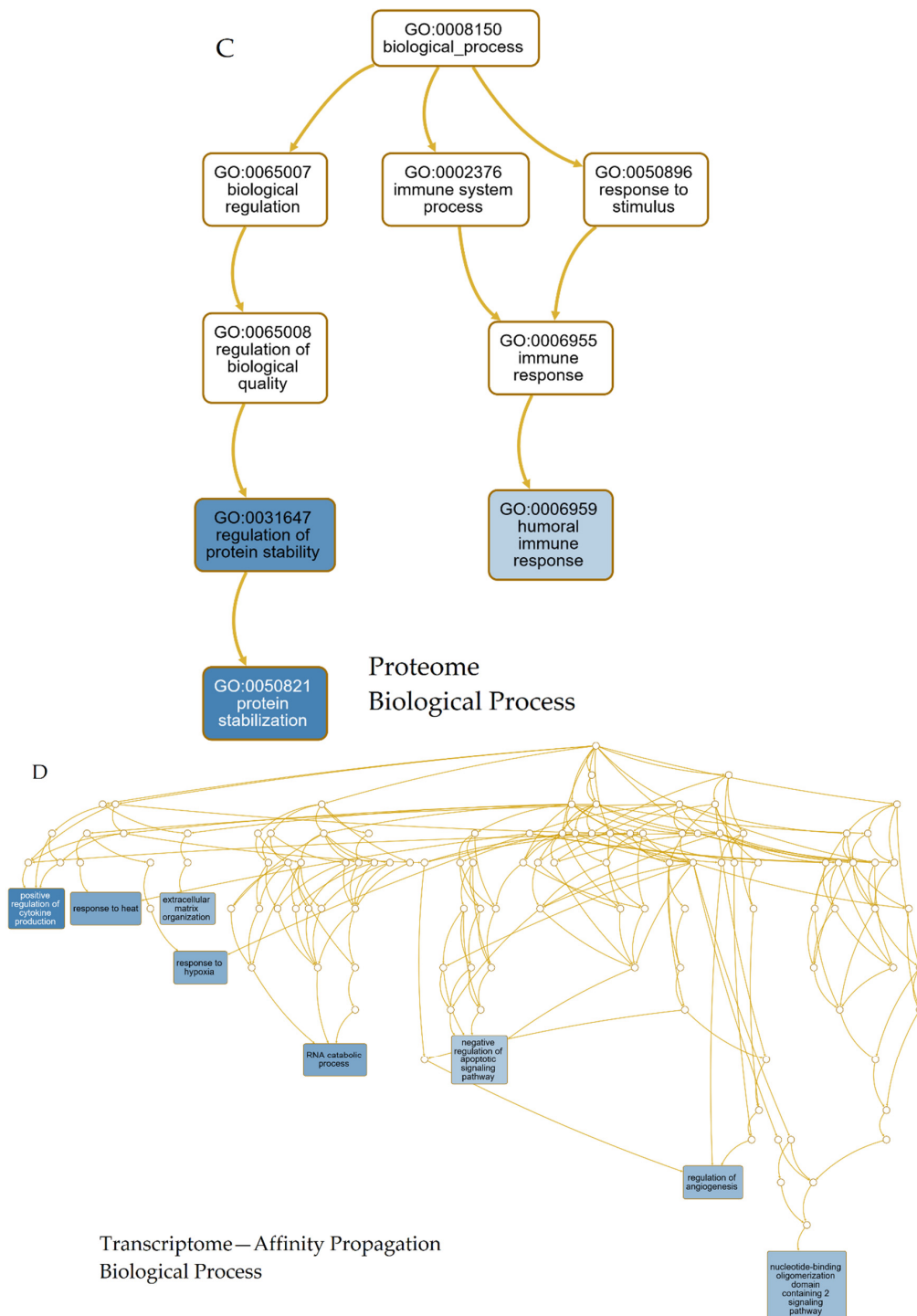


Figure 5. Directed acyclic graph showing the significant results (false discovery ratio (FDR) ≤ 0.05) of the GO-Term ORA of the Cellular Component and Molecular Function of the transcriptomic overlap of all four NDDs (A,B), the Biological Process terms of the proteomic data (C) and the Biological Process terms of the transcriptomic data after affinity propagation (D). Blue shading indicates the value of the FDR. For better readability, all GO-Terms leading to the significant ones were hidden in (A,D).

Enriched Set	Involved Genes			FDR	Enrichment	Category
nucleotide-binding oligomerization domain containing 2 signaling pathway	HSPA1A	NFKBIA	RELA	0.025	33.726	Intracellular mechanisms
Response to heat	CD34	DNAJB1	HSP90AB1	0.007	7.7644	
	HSPA1A	PDCD6	PSIP1			
	THBS1	TP53INP1				
Negative regulation of apoptotic signaling pathway	HDAC10	HSPA1A	LMNA	0.045	4.9735	
	OPA1	RELA	TCF7L2			
	THBS1	TMBIM1				
Response to hypoxia	ADM	AQP1	CD34	0.010	4.9138	
	DDIT4	HIF3A	HP1BP3			
	LMNA	OPA1	PDLIM1			
	SLC8A1					
RNA catabolic process	EXOSC6	HSPA1A	KHSRP	0.007	4.7474	
	NPM1	RNASET2	RPL10A			
	RPL35	RPL39	RPS15A			
	RPS19					
Regulation of angiogenesis	B2M	CD34	CD4	0.020	4.7670	
	HK1	HMGB1	HSPA1A			
	IL1R1	MBP	RELA			
	SLC11A1					
Extracellular matrix organization	ADM	APLN	AQP1	0.020	4.2766	
	CD34	ENG	ERBB2			
	HMGB1	MMRN2	PDCD6			
	THBS1					
positive regulation of cytokine production	ANTXR1	COL14A1	COL4A1	0.001	4.8411	
	COL5A1	ENG	FBN1			
	ITGB4	P4HA1	SERPINH1			
	THBS1					

Figure 6. Significant results (FDR < 0.05) of the biological process (BP) GO-Term analysis for the transcriptomic overlap in the four analyzed NDDs after performing affinity propagation. The names of the enriched sets are shown in the left column, followed by the contributing genes on their right. For each significant set, the FDR and enrichment is given. The enriched BP sets are categorized in the groups Intracellular Mechanisms, Local Tissue Environment and Systemic Environment based on Ramanan's conceptual model of candidate pathways contributing to neurodegeneration [15], which is also depicted in Figure 1.

3.3.2. Proteomic Intersection of AD, PD, ALS and HD

For the intersection of proteomic data for all four analyzed NDDs, three significantly overrepresented GO-Terms were found for BP (Figure 5C). Two of them are related to maintenance of protein stability and the third term to the immune system (humoral immune response). No significant results were discovered through MF, CC or the KEGG pathway analysis.

4. Discussion

4.1. Intersections

The number of shared genes with significant SNP-trait associations between the four NDDs on the genomic level was significantly enriched only for the AD-PD and AD-ALS comparisons. Interestingly, there was no single overlapping gene in the aforementioned study from 2018 on the association of genomic data between AD and PD and zero to two between AD and ALS, depending on the exact method [66]. For the proteomic and transcriptomic data, all numbers of pairwise overlapping genes

were significantly enriched. However, the total number of overlapping genes between all four NDDs on the proteomic layer was rather low, with four genes, and did not exist at all on the genomic level. On the other hand, the transcriptomic data showed an overlap of 139 genes and thus allowed for a more distinctive analysis of GO-Terms, pathways and the concordance of regulation between the four analyzed NDDs. Nevertheless, the significance of all pairwise comparisons on the transcriptomic and proteomic levels confirms that there is a significant relation between all four analyzed NDDs—at least on the transcriptomic and proteomic level. The following evaluation of the GO-Term and KEGG pathway analysis was intended to reveal the nature of this relationship.

4.2. GO-Term and Pathway Analyses

4.2.1. KEGG Pathway Analysis

As the result of the pathway analysis (prostate cancer) seemed unexpected as a common factor of neurodegeneration, we further researched the gene set leading to this KEGG pathway. Of the six genes in the prostate cancer pathway we found several genes that were both connected to cancer and neurodegeneration in general, including *NFKBIA*, *RELA* and *PDGFRB*. NF- κ B and RelA form a dimer with a transactivating domain that binds to specific DNA sequences as transcription factor controlling genes that are involved in immune and inflammatory responses and control of cell proliferation and apoptosis [249]. Misregulation of NF- κ B can lead to cancer [250], neurodegenerative [251], autoimmune and other inflammatory diseases [252].

Platelet-derived growth factor receptor β (PDGFRB) is a cell-surface receptor that plays an essential role in the regulation of cell proliferation, survival, differentiation, chemotaxis and migration, as well as in blood vessel development, where it can lead to uncontrolled blood vessel formation and cancer due to mutational activation or upregulation [253].

Consequently, at least half of the genes contributing to the prostate cancer gene set in our analysis are also associated with the formation of NDDs. Interestingly, a study in 2014 already described the existence of a significant overlap of genes described for either some types of cancer, such as prostate cancer, or NDDs such as AD and PD, based on their direction of regulation [254]. Nonetheless, the KEGG pathway analysis did not provide further insight into common factors of neurodegeneration.

The overrepresented GO-Terms for biological processes in the genes appearing in the intersection of all four NDDs on the transcriptomic level showed highly concordant results with a meta-study of AD, PD and ALS from 2019 [255] that analyzed the raw data of 259 individuals. That study found biological processes associated with heat shock proteins, cellular responses to heat, stress response and, additionally, GABA synthesis and protein folding, which were overrepresented in the four used datasets. They stated the importance of heat shock proteins (HSPs) as a general target of NDDs [256], and the importance of HSP-associated pathways in HD [257]. We, too, found cellular responses to heat and stress (in our case hypoxia), but also the NOD2 signaling pathway, the negative regulation of apoptosis, a positive regulation of angiogenesis and cytokines, RNA catabolic processes and extracellular matrix organization. However, no significant overrepresentation was found for GABA synthesis in our analysis of the intersection of the AD, PD, HD and ALS transcriptomic data. Protein stabilization as well as immune response was overrepresented in our comparison of the proteomic overlap of AD, PD, ALS and HD.

According to the literature, the GO-Term analysis revealed biological processes (reduced by affinity propagation) that are highly relevant to NDDs.

4.2.2. Response to Heat

The cell's response to heat is managed by heat shock proteins (HSPs), most of which are, despite of their names, expressed at average growth temperatures (37 °C). They belong to the cellular protein quality control and act as molecular chaperones to guide proteins from production to degradation. During aging, reduced amounts of HSPs and the increasing number of proteins requiring additional

chaperoning can lead to an overstrained quality control system and ultimately to protein aggregation initiation [256].

4.2.3. RNA Catabolic Process

Dysfunctional RNA catabolic processes have already been described for ALS and the nuclear RNA-binding protein TDP-43, which is integrally involved in RNA processing pathways, controlling the life cycle of RNAs from synthesis to degradation. In ALS, a cytoplasmic mislocalization and accumulation of TDP43 leads to TDP43 aggregates, misregulation of RNA processing and subsequent neuronal dysfunction [258,259]. Also, in AD aberrant phosphorylation, ubiquitination, cleavage and/or the nuclear depletion of TDP-43 in neurons and glial cells has been reported [260]. Our data suggest that the TDP-43 proteinopathy or another mechanism that leads to dysfunctional RNA catabolic processes plays a role in all four analyzed NDDs.

4.2.4. Positive Regulation of Cytokine Production and Angiogenesis

The positive regulation of cytokine production and the regulation of angiogenesis are tightly connected because angiogenesis, the formation of new blood vessels from preexisting vessels, is partly induced by cytokines, as described for AD [261]. Amyloid- β plaques and neurofibrillary tangles induce activated microglia and elevated levels of pro-inflammatory cytokines [262]. Some of these cytokines, such as tumor necrosis factor- α (TNF α), interleukin (IL)-1 β and transforming growth factor- β (TGF β) induce partly impaired angiogenesis, which builds up functional but also malfunctional vessels [263]. Due to decreased vascularity in the aging brain, hypoxia also stimulates the angiogenic process and endothelial activation. Activated endothelial cells elaborate several proteases, inflammatory factors and other products with biologic activity that may promote neuronal death [264,265]. Due to our findings, it can be assumed that protein aggregation in any of the four analyzed NDDs leads to neuroinflammation, which is accompanied by upregulated cytokines and impaired subsequent angiogenesis. As pro- and antiangiogenic factors regulate angiogenesis, both, cytokines and cytokine blockades could serve as potential pharmaceutical targets modulating angiogenesis in chronic inflammation [263,266].

4.2.5. Response to Hypoxia

Hypoxia is a well-described multifaceted cause of NDDs. As mentioned above, aging and brain injuries like small infarcts lead to lower oxygen levels in the brain. During hypoxic events, high levels of free oxygen and nitrogen radicals are produced through mitochondrial complex III, which cannot be compensated for due to lower levels of antioxidants in aging and diseased brains, thus leading to the oxidative damage of vital cellular components [267]. Also, the impaired cellular homeostasis of metals like Ca²⁺ can be triggered by hypoxic conditions, resulting in changes in excitation and the inhibition of neuronal and glial cells. Synaptic transmission in the central nervous system (CNS) is susceptible to hypoxia, as it requires 30–50% of cerebral oxygen. Already very early during age-related hypoxia, a decrease in synaptic efficacy occurs [268].

4.2.6. Extracellular Matrix Organization

Extracellular matrix (ECM) molecules in the central nervous system form highly organized structures around cell somata, axon initial segments, and synapses. They play prominent roles in early development by guiding cell migration, neurite outgrowth and synaptogenesis, and by regulating synaptic plasticity and stability, cognitive flexibility and axonal regeneration in adults. Upregulation of ECM molecules—in particular through reactive astrocytes, after brain injuries and during aging, neuroinflammation and neurodegeneration—results in the formation of a growth-impermissive environment and impaired synaptic plasticity. Thus, targeting the expression of specific ECM molecules, associated glycans and degrading enzymes may lead to the development of new therapeutic strategies promoting regeneration and synaptic plasticity [269].

4.2.7. Nucleotide-Binding Oligomerization Domain Containing 2 Signaling Pathway

The nucleotide-binding oligomerization domain containing 2 of the NOD2 signaling pathway is part of the immune response by recognizing bacteria with a muramyl dipeptide (MDP) moiety and thus activating the transcription factor NF- κ B, which regulates the transcription of a large number of genes, especially those involved in the immune and inflammatory response, control of apoptosis and cell proliferation. Misregulation of NF- κ B can lead to cancer, but also to NDDs and other inflammatory diseases. Studies have showed that the E3 ubiquitin ligase parkin targets NOD2 for ubiquitylation and subsequent degradation in order to regulate astrocyte endoplasmic reticulum stress and inflammation. Mutations in the Parkin gene, which are one reason for familial PD, lead to an overrepresentation of NOD2 [270]. Also, bacterial and viral infections are a known cause of AD. In our study, the NOD2 signaling pathway was significantly overrepresented for the intersection of all four NDDs' transcriptomic data, leading to the hypothesis that bacterial or viral immune response might be a crucial factor for PD, HD and ALS as well.

4.2.8. Negative Regulation of Apoptotic Signaling Pathway

Seven of the eight found BP after affinity propagation for all four NDDs' transcriptomic data, seemed concordant with the literature. Also, the CC, which are mainly about focal adhesion but also about the cell-substrate adherens junction, cell-substrate junction, external side of plasma membrane, endoplasmic reticulum lumen and apical plasma membrane, fit very well to the BP. The significantly overrepresented MF, which are extracellular matrix structural constituent, cell adhesion molecule binding, structural constituent of cytoskeleton, integrin binding, platelet-derived growth factor binding, growth factor binding and NF- κ B binding are in accordance to the BP. Only the negative regulation of the (extrinsic) apoptotic signaling pathway seems surprising, as enhanced intrinsic or extrinsic apoptosis is typical of NDDs, leading to the severe loss of neurons that characterizes these diseases. A lower rate of apoptosis is a typical hallmark of cancer where even damaged cells are not abolished. However, ORA is based on a set of genes not taking the direction of their regulation into account. This direction of regulation was to some extent heterogenous between the four analyzed NDDs (see Figure 4) and, for each of the four NDDs, some of the genes contributing to the gene set was downregulated for the negative regulation of apoptotic signaling pathways. Consequently, the direction of regulation stated in the BP terms is not directly linked to the true direction of regulation in the NDDs.

4.2.9. Protein Stabilization and Regulation of Protein Stability

Regulation of protein stability is the top-level term for the maintenance of unfolded protein, protein destabilization and protein stabilization. Unfolded proteins are a common characteristic of neurodegenerative diseases, as the accumulation of misfolded proteins causes stress response mechanisms in the endoplasmic reticulum (ER) [271]. Chronical ER stress caused by protein accumulation can lead to the initiation of apoptosis and, consequently, neurotoxicity [272]. Protein stabilization of TDP-43 has been described as one of the underlying factors of neuronal TDP-43-dependent toxicity in ALS and frontotemporal dementia [273]. It can be concluded that alterations in the general regulation of protein stability are described in both the general formation of neurodegeneration and the specific mechanisms for single NDDs, such as ALS. Additionally, the ER was also present as a cellular component that was significantly overrepresented in the transcriptomic gene set, which further enhances the idea of ER stress being involved as a common factor of neurodegeneration.

4.2.10. Humoral Immune Response

The central nervous system (CNS) has always been considered to be the sole domain of the innate immune response rendered by the microglia. However, immune cells are increasingly recognized as being able to access to the CNS in both health and disease [274]. Lymphocytes can enter the CNS through the blood–brain barrier (BBB), the blood-meningeal barrier and the blood-cerebrospinal fluid

(CSF) barrier [275,276]. Under healthy steady-state conditions, B cells are present in very low numbers in the CNS parenchyma and CSF [277], but in cases of CNS inflammation like multiple sclerosis, B cell numbers can increase by at least several orders of magnitude in the CNS parenchyma and perivascular spaces, and by severalfold in the CSF [278,279]. B cell-depleting therapy in patients with multiple sclerosis with rituximab and ocrelizumab has reduced inflammation significantly [274]. Understanding how the adaptive immune system participates in the pathogenesis of NDDs might deliver new possibilities for their treatment.

For PD, there is evidence that humoral immune response has been involved in course of the disease. Although B cells have not been detected in the brains of patients with PD [280], deposits of immunoglobulin G (IgG) have been found on the dopaminergic neurons in these patients, and Lewy bodies themselves are coated with IgG [281], which suggests that dopaminergic neurons might be targeted by these immunoglobulins.

In AD, the adaptive immune system could, apart from a possible involvement of plaque removal, be responsible for the immune response of infections with herpesviruses and other pathogens, which are acknowledged to be a possible source of AD. Our data suggest that the humoral immune response could be a target for further investigations in HD and ALS as well.

Interestingly, the GO-Term analysis showed an overall differing result between the proteomic and transcriptomic data. The BP terms for protein folding and the immune system are also highly consistent with the knowledge about the origin of neurodegeneration, as well as the findings that emerged from the transcriptomic analyses, but it is noteworthy that the analysis of the proteome contains characteristic findings that extend the transcriptomic insights.

4.2.11. Common Regulation on the Transcriptomic Level

The hierarchical clustering of these 139 genes formed an inner cluster consisting of AD and HD (Figure 4). The correlation analysis showed a highly significant relation between these 139 genes for AD and HD with a high correlation value (p -value $< 2.2 \times 10^{-16}$ correlation: 0.66). This result shows that the set representing the least common denominator of the four NDDs is regulated in a very similar manner in HD and AD. Although this does not necessarily say anything about the significance of these genes in the course of the development of individual diseases, the high degree of concordance between the biological processes we have just described (Figure 6) for the 139 genes appearing to be significantly differentially regulated in all four analyzed NDDs and the actual development of neurodegeneration is striking.

5. Conclusions

GWA studies significantly contributed to understanding NDDs over the last 15 years, with several-hundred disease-associated risk loci. However, no targeted therapies have emerged from these GWA studies for most NDDs [282]. As NDDs are causing profound transcriptomic changes in the aging brain, it is crucial to take transcriptomic data analysis into account when analyzing NDDs [283]. Further translation from transcriptomic changes to proteomic occurs only indirectly and shows only a limited correlation between mRNA and protein expression [284]. Consequently, even the combination of genetic and transcriptomic data is not adequate to give a complete picture of the changes taking place due to NDDs. Each additional level of information can contribute to a better understanding of the complex interrelationships of these interacting omics layers.

To address the challenges of such complicated diseases, the whole field of biomedicine is changing towards creating and facilitating a variety of databases and analysis pipelines for separate omics layers and multi-omics integration [285]. Many of these pipelines are mainly data-driven and enable clustering and supervised machine learning techniques to find essential patterns of features contributing to the identification of, for example, proteins that are associated with NDDs [286], or to reveal cross-talk patterns in multi-omics data [287].

According to the necessity of approaching complex diseases with the use of multiple omics-layers, data-driven methods and large amounts of data, we combined the data of three omics layers from databases and literature mining of more than 1 million subjects and 177 studies to show the shared genes between the four analyzed NDDs and extract the pathways and processes in which they are overrepresented.

To classify the gained information in this study, it is crucial to keep in mind that the transcriptomic and proteomic data were gathered from various tissues, partly different severities of diseases and using different methods. Ninety percent of the non-control patients in the proteomic data and 84% in the transcriptomic data were classified with a moderate or severe disease state. Of the experiments, 63% in the transcriptomic data and 67% in the proteomic data were conducted with brain material, while the remaining were conducted with blood, spinal cord, cerebral spinal fluid or induced pluripotent stem-cells. A detailed table can be found in the Supplementary materials (S4). Consequently, the signals in this meta-study represent stable signals found mainly across brain tissues emerging in the late stage of NDDs, rather than subtle effects that might only be present in just one specific brain region or in earlier disease states. In accordance with the law of large numbers, meta-studies like ours are particularly well-suited to finding the results that represent real effects in partly noisy data. Such real effects occur repeatedly and were therefore able to exceed our own defined threshold of occurrences in two different experiments, thus contributing to further analyses. Even in the ORA, subtle effects of noisy data (e.g., from early stage disease studies) that were still present would probably be canceled out by the number of other strong signals and the fact that the majority of the used data are based on late stage NDDs.

The highly significant overrepresentation of genes in the intersection of proteomic and transcriptomic data in all investigated NDDs shows the importance of simultaneously analyzing multiple omics layers. Additionally, this analysis showed the relevance of questioning old results using updated databases. While no single overlapping gene was found in 2018 between the genomic data of AD and ALS, and only two were found between AD and PD [66], the same analysis led to significant overlaps between AD and PD and AD and ALS. The common factor relating to neurodegeneration from a 2019 study [255] that used the data of 259 samples could partly be confirmed. We also found biological processes for response to heat and stress (hypoxia) as well as protein folding to be significantly overrepresented. However, we could not reproduce the finding of an overrepresentation of the GABA synthesis pathway or any related terms. Additionally, the NOD2 signaling pathway, the negative regulation of apoptosis, positive regulation of cytokines and angiogenesis, RNA catabolic processes, extracellular matrix organization and humoral immune response emerged from our analysis. All of these results emerging from the GO-Term analysis of the transcriptomic and proteomic data seem highly plausible as common factors of neurodegeneration, and shed light on processes like humoral immune response that have previously been described only for certain diseases.

Accordingly, this meta-study reveals highly significant processes common to all analyzed NDDs and might therefore contribute to the development of pharmaceutical measures against neurodegeneration in general. Regarding future research on this topic, it might be helpful to expand the repertoire of omics layers by epigenomics and concentrate further on the differences between these separate NDDs according to the regulation of these common genes. Additional analysis of the overlap between different omics layers at the level of individual diseases, as well as differences in the intersection of AD, PD and ALS in contrast with the autosomal dominant disorder HD could also provide new insight in light of knowledge of the processes common to all NDDs.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4409/9/12/2642/s1>, Table S1: Overview of studies used for gathering genomic data—GWAS Catalog study information, Table S2: Overview of studies used for gathering transcriptomic data—Transcriptome study information, Table S3: Overview of studies used for gathering proteomic data—Proteome study information, File S4: NDD_Disease State and Tissues, File S5: GO-Term and Pathway Analyses.

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and S.S.; writing—review and editing, S.G., N.R., S.K. and S.S.; visualization, N.R., S.K.; supervision, S.G.; funding acquisition, S.G. All authors have read and agreed to the published version of the manuscript.

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4.2 The Big Picture of Neurodegeneration: A Meta Study to Extract the Essential Evidence on Neurodegenerative Diseases in a Network-Based Approach

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The Big Picture of Neurodegeneration: A Meta Study to Extract the Essential Evidence on Neurodegenerative Diseases in a Network-Based Approach

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The common features of all neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease, are the accumulation of aggregated and misfolded proteins and the progressive loss of neurons, leading to cognitive decline and locomotive dysfunction. Still, they differ in their ultimate manifestation, the affected brain region, and the kind of proteinopathy. In the last decades, a vast number of processes have been described as associated with neurodegenerative diseases, making it increasingly harder to keep an overview of the big picture forming from all those data. In this meta-study, we analyzed genomic, transcriptomic, proteomic, and epigenomic data of the aforementioned diseases using the data of 234 studies in a network-based approach to study significant general coherences but also specific processes in individual diseases or omics levels. In the analysis part, we focus on only some of the emerging findings, but trust that the meta-study provided here will be a valuable resource for various other researchers focusing on specific processes or genes contributing to the development of neurodegeneration.

Keywords: neurodegenerative diseases, metastudy, multi-omic analyses, bioinformatics, hub genes and pathways

INTRODUCTION

The typical features of all neurodegenerative diseases (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease (HD), are the accumulation of aggregated and misfolded proteins and the progressive loss of neurons, leading to cognitive decline and locomotive dysfunction. Still, they differ in their ultimate manifestation (e.g., dementia, Parkinsonism, motor neuron impairment), the affected brain region [e.g., hippocampus (AD), Substantia nigra (PD), striatum (HD), upper and lower motor neurons (ALS)], and the kind of proteinopathy [amyloidosis, tauopathies (AD)], a-synucleinopathy (PD), CAG triplet elongation (HD) and TAR DNA-binding protein 43 (TDP-43) aggregates (ALS) (Roos, 2010; Zarei et al., 2015; Rosenberg et al., 2016; Armstrong and Okun, 2020; Pathak et al., 2021).

Adult neurons maintain energy-intensive functions, such as membrane excitability, neurotransmission, and plasticity. They cannot rejuvenate by dividing, so they are especially reliant on a high supply of energy, the maintenance of protein and organelle quality control, rapid delivery of molecules within and out of cells, and the trafficking of organelles and other factors over considerable distances within the cell (Franco-Iborra et al., 2018; Gan et al., 2018). There are myriads of biological processes involved in the well functioning of the brain, whose malfunction can lead to neurodegeneration. Hallmarks among others are an aberrant cell cycle regulation, mitochondrial dysfunction, ER stress, impaired protein folding and quality control, deregulated autophagy and apoptosis, oxidative stress and insufficient DNA damage repair, missing homeostasis, a malfunctioning extracellular matrix, excitotoxicity, aberrant axonal transport, and excessive neuroinflammation (Coppedè and Migliore, 2015; Lindberg et al., 2015; Nah et al., 2015; Briston and Hicks, 2018; Cabral-Miranda and Hetz, 2018; Sonbol, 2018; Guzman-Martinez et al., 2019; Armada-Moreira et al., 2020; Guo et al., 2020; Joseph et al., 2020; Iatrou et al., 2021). To disentangle the multitude of processes associated with neurodegenerative diseases, we collected data from four omics-layers in four neurodegenerative diseases from 234 studies. These data are analyzed in a network-based approach that provides structure regarding the most represented processes, hub genes, and differences in regulation between specific omics-layers and diseases by building communities within networks for each omics-layer in each condition.

To provide an overview of the central biological processes and the pathways involved, we have divided them into broader categories according to their primary location or mode of action, namely, intracellular mechanisms, local tissue environment influences, and systemic influences (Ramanan and Saykin, 2013). On the cellular level, a deregulated cell cycle and misguided autophagy and apoptosis lead to degenerated neurons. Within the local tissue environment, an intact extracellular matrix (ECM), an unimpaired cell development, signal transduction, and transport of vital molecules are of fundamental importance. Excessive immune response and a dysregulated metabolism lead to significant disturbances on the systemic level.

Within our analyses, we found thousands of biological processes (BP) as defined by the Gene Ontology and local network cluster terms given by the string DB database. To allow an understanding within this complexity, we assigned those multilayered and diverse terms to 6 hallmarks: “cell cycle,” “autophagy/apoptosis,” “ECM/development,” “signal transduction/transport,” “immune system,” and “metabolism” for each community in all created networks. This observation allows us to extract processes distributed across diseases and omics-layers, which are mainly present in specific omics-layers or conditions. We only address the most striking results but see this work as an opportunity for other researchers working primarily on the effect of particular processor genes on neurodegeneration to study the gene communities associated with those processes in more detail. For example, a specific gene cluster containing the gene or process of interest can be extracted from the **Supplementary Data** sources we provide

(see **Supplementary Table 1—Genes Per Community**) and inserted, e.g., in string DB (<https://string-db.org/>). The resulting network can be selectively examined, and all publications, processes, pathways, etc., that are significantly associated with the respective candidates or networks can be analyzed. Consequently, we hope the big picture of neurodegeneration we draw here in our results will serve as an inspiring and rich source of data, providing a range of new insights and analysis perspectives for the scientific community. In the following, we introduce the six hallmarks, providing a preview of our associated low-level terms by showing them in *italics*.

Hallmark 1: Cell Cycle

Neuronal cells similar to muscle cells usually remain in a quiescent cell cycle state once they are differentiated due to their specialized functions. But cell cycle regulatory proteins like cyclins, CDKs, caspases, and p53 continue to be required for axonal migration, maturation, and survival (López-Sánchez et al., 2017; Joseph et al., 2020). One or more of these cell cycle proteins and pathways might get activated in response to various epigenetic or pathologic stimuli. Aberrant cell cycle reentry of neurons with duplication of the genetic material but without subsequent cell division is a well-known phenomenon. However, it is still unknown whether this is deleterious or beneficial. In the early stages of brain development, specific populations of neurons undergo incomplete mitosis and stay in a tetraploid state for the rest of their adult life. Still, a *de novo* neuronal tetraploidization in the adult brain seems to be an early indicator for neurodegeneration, with cells showing elevated molecular stress response and apoptotic marker proteins due to this aberrant *regulation of cell cycle* (Frade and Ovejero-Benito, 2015; López-Sánchez et al., 2017; Joseph et al., 2020). The correct assembly, positioning, and working of the mitotic *spindle apparatus* are essential for the development and differentiation of cells. Spindle orientation defects leading to an imbalance between symmetric and asymmetric divisions have been discussed as being linked to NDD. An asymmetric cell division leads to two daughter cells with different cell fates. An important example is the division of a stem cell, leading to a differentiated brain cell and another stem cell. The preconditions for an asymmetric cell division are the polarization of the content of the mother cell and the alignment of the mitotic spindle along the axis of polarity. If this process is disturbed by an impaired spindle orientation, this will have severe consequences in the development of the brain (Noatynska et al., 2012). During mitosis, motor proteins, together with Huntingtin, localize along spindle microtubules to segregate the chromosomes (Godin and Humbert, 2011). Thus, mutant Huntingtin could lead to defective neurogenesis during embryonic development leading to Huntington's disease later in life (Godin and Humbert, 2011; Wiatr et al., 2018). Defective *DNA repair* mechanism, together with elevated oxidative stress, is a typical hallmark for aging cells (Joseph et al., 2020). As the brain is the largest consumer of oxygen, reactive oxygen species (ROS) are the main inducers of DNA damage in neurons (Nissanka and Moraes, 2018). The accumulation of unrepaired damaged DNA might contribute to a cell cycle reentry of the neuron to increase polyploidy, thus compensating for the loss of information on

some parts of the DNA. Also, general terms like *transcription* (mitochondrial) *translation*, *RNA modification*, *spliceosome*, and *chromatin* organization were defined as subprocesses integrated into the hallmark called the cell cycle.

Obviously, transcription, translation, and chromatin remodeling as major contributors to protein homeostasis have a considerable impact on all cellular functions, and genetically or epigenetically misregulated transcription factors can enhance or weaken all the processes that lead to or prevent neurodegeneration like neuroinflammation, oxidative stress, and protein homeostasis (Berson et al., 2018; Jin et al., 2019). Especially neurons face the problem that their locus of transcription is distant from the locus of translation as protein synthesis is decentralized to meet the rapidly changing metabolic needs of axons and dendrites. Nuclear mRNA is transported from the cell body to the periphery as RNA/protein granules linked to motor proteins of the cytoskeleton by adaptor complexes. Conditions, such as mislocalization of the mRNA, a defective cytoskeleton, and deleterious adaptor complexes, lead to synaptic dysfunction, loss of synapses, and, ultimately, to neuronal death (Liu et al., 2017).

Hallmark 2: Autophagy and Apoptosis

Accurate folding and control over levels of many proteins are tightly regulated in neuronal cells by a protein quality control network consisting of molecular chaperones and an intact degradation system of misfolded or discarded proteins, consisting of the ubiquitin-proteasome system and *autophagic processes*. *Chaperone-mediated processes* are involved in the promotion of *de novo* folding of nascent proteins or the refolding of misfolded polypeptide chains, thereby preventing their aggregation (Hartl et al., 2011; Chaplot et al., 2020).

Proteins that cannot be folded correctly or are no longer needed are tagged by the attachment of the small protein ubiquitin (*ubiquitinylation*) and degraded by a multi-subunit protein complex called the *proteasome* or by autophagy, which is a universal lysosome-dependent intracellular degradation process for not only protein aggregates but also cell organelles and cytoplasmic constituents to maintain cell homeostasis (Nah et al., 2015; Schmidt et al., 2021). Lysosome-dependent autophagy can either be carried out by lysosomes acting by themselves in a process called micro-autophagy, or in macro-autophagy where cell organelles with a lipid double layer derived from the ER called omegasomes fuse with lysosomes to form autophagosomes (Mizushima and Klionsky, 2007; Li et al., 2012; Nah et al., 2015). In neurons, these autophagosomes are generated constitutively in the cell periphery and mature on their way to the cell body (Xie and Klionsky, 2007). The proteins ensuring this axonal transport are Huntingtin and Huntingtin-associated protein 1. As huntingtin is predominantly cleared by autophagy, the deficiency of intact huntingtin in HD is a double stress factor leading to the accumulation of polyglutamine-expanded huntingtin polyQ-htt and other cytoplasmic constituents that need to be degraded (Wong and Holzbaaur, 2014). Besides deficiencies in the protein quality control network leading to the typical protein aggregations in NDD, there are many more factors that impair homeostasis of

the cell, causing stress to the cells. Heat, toxins, mechanical damage, infections, starvation, hypoxia, and oxidants all lead to cellular *stress responses* that aim to control the induced damage and, if possible, to confer resilience to the stressor. The integrated stress response (ISR) is an elaborate signaling cascade, where different stress signals activate different protein kinases that converge in phosphorylating the core of the ISR, the α -subunit of the translation initiation factor 2 (eIF2 α). This leads to a reduction of global protein synthesis in favor of ISR-specific mRNAs, such as the activating transcription factor ATF4. ATF4 is the main effector of the ISR. It forms homo- and heterodimers that bind to DNA targets to control the expression of genes involved in cellular adaptation, mainly chaperones that refold denaturated proteins or tag them for immediate degradation (Harding et al., 2003; Fulda et al., 2010; Pakos-Zebrucka et al., 2016). To terminate the integrated stress response, dephosphorylation of eIF2 α is required. However, dephosphorylation of eIF2 α can also facilitate the production of death-inducing proteins in cases where the cell is so severely damaged that normal functioning and homeostasis cannot be restored (Pakos-Zebrucka et al., 2016). Highly regulated cascades of events will then lead to the decomposition of the cell in a process called apoptosis (Danial and Korsmeyer, 2004; Elmore, 2007; Fulda et al., 2010). Apoptosis is a caspase-mediated programmed cell death that can be triggered either by stress signals from within the cell or by signals that are released by the surrounding cells and that bind to cell-surface death-receptors (Danial and Korsmeyer, 2004; Elmore, 2007). Both intrinsic and extrinsic pathways ultimately induce cell death by activating caspases, enzymes that carry out the degradation of the cell, leading to cell shrinkage, plasma membrane blebbing, chromosome condensation and degradation, mitochondrial death with release of cytochrome C, cellular fragmentation, and formation of membranous apoptotic bodies. At the same time, phosphatidylserine residues are exposed at the cell surface to attract macrophages that phagocytize the cell fragments. The extrinsic pathway is activated by extracellular ligands (e.g., CD95 ligand, tumor necrosis factor α) binding to cell-surface death receptors, which either leads to the formation of the so-called DISC (death-inducing signaling complex) or the activation of nuclear factor kappa B (*NF κ B*) (Wang and El-Deiry, 2003; Lavrik et al., 2005). Caspase 8, which serves as the initiator caspase, is activated within this complex. If the activating stimulus is sufficiently large, caspase 8 begins activating the effector Caspases 3, 6, and 7. They translocate to the mitochondria to trigger pore formation in the outer mitochondrial membrane (Fan et al., 2005), which ultimately leads to mitochondrial permeability and death. The release of cytochrome C promotes caspase-9 activation, which triggers a cascade of proteolytic events. The intrinsic signaling pathway is controlled by the Bcl2-family of proteins and is triggered by cell-internal factors, such as DNA damage, osmotic stress, or growth factor withdrawal. The triggering cell event activates the transcription factor p53, leading to the expression of proapoptotic Bad protein. The Bad protein, in turn, activates the multidomain proapoptotic Bax protein, which triggers permeabilization of the mitochondrial outer membrane. As a result, similar to the extrinsic pathway,

cytochrome C escapes from the intermembrane space of the mitochondria and induces a proteolytic cascade (McIlwain et al., 2013; Wang and Tjandra, 2013; Chen et al., 2018).

The *NFκB signaling pathway* is activated during apoptosis either to enforce the ongoing apoptotic processes or to navigate the cell back to the survival pathway by stimulating the expression of anti-apoptotic genes, especially *TRAF1* and *TRAF2*, and thus overruling the activities of the caspases (Sheikh and Huang, 2003). NFκB is a family of transcription factors with multiple physiological and pathological functions. The NFκB complex exists in an inactive state in the cytoplasm. It consists of different NFκB dimers and inhibitory κB proteins (IκB) that prevent NFκB to enter the nucleus and bind to the DNA (Israël, 2010). NFκB can be activated by highly variable stimuli, including growth factors, cytokines like tumor necrosis factor alpha and interleukin 1-β, bacterial and viral antigens like lipopolysaccharides or double-stranded RNA and physicochemical insults like ionizing radiation or free radicals. All these different stimuli activate different phosphorylation cascades that, in the end, lead to an interaction with the IκB kinase (IKK) complex, which then leads to the phosphorylation of IκB in the NFκB complex. Once phosphorylated, IκB gets ubiquitinated and degraded by the proteasome. The released NFκB can now enter the nucleus to activate target gene expression that regulates immune responses, cell growth, and proliferation but also apoptosis (Qin et al., 2007). The selectivity of the NF-κB response is based on several factors, including dimer composition, timing, organization of chromatin, and cell type (Natoli, 2009; Sen and Smale, 2010). Besides the *NFκB signaling pathway*, an important low-level term in autophagy and apoptosis, was the *mTOR signaling pathway*. As mentioned above, an impaired autophagy in NDD leads to the accumulation of toxic protein aggregates that promote cellular stress and death. The kinase mammalian target of rapamycin (*mTOR*) is a central regulator of metabolism as it senses cellular nutrient, oxygen, and energy levels (Perluigi et al., 2015). It is a potent repressor of autophagy and reacts to food abundance with cell growth and proliferation, whereas, in times of starvation, it is inhibited, thus allowing the cells to derive energy from autophagic and apoptotic processes (Heras-Sandoval et al., 2020).

Hallmark 3: Extracellular Matrix Organization and Development

The extracellular matrix (ECM) is a three-dimensional network that reaches all cells of the body to provide structural support, segregate tissues, and regulate intercellular communication by many different biochemical processes. It consists of minerals and macromolecules like *collagen*, *elastin*, *enzymes*, *glycoproteins*, and *hyaluronan*, which is most abundant in the brain (Bonnans et al., 2014). These compounds contribute to a varying degree of stiffness and elasticity of the ECM throughout the body from hard bone to soft brain tissues. The mechanical properties of the ECM environment can be sensed by the cells, which is the precondition for processes like *cell migration*, *proliferation*, *differentiation and growth*, *apoptosis*, and, on a higher level,

the development of tissues and organs (Bonneh-Barkay and Wiley, 2009; Sethi and Zaia, 2017; Maguire, 2018). These processes also require a direct connection between cells and ECM. The ECM communicates with the cells by connecting to the cytoskeleton through *cilia* and (*focal adhesion complexes*) (Geiger and Bershadsky, 2002). The cytoskeleton is a functionally versatile filamental structure that transports and *localizes* the contents of the cell, it organizes the process of cell division, namely, chromosome segregation and cytokinesis, it connects the cell physically and biochemically to the external environment through interacting with the ECM (*cell adhesion*, *focal adhesion*, *cell junction*), and it enables the cell to move and change shape (*cell migration*, *cell differentiation*, *growth*, and *localization*) (Wozniak et al., 2004; Fletcher and Mullins, 2010). These functions are mediated by three filament types: microtubules, actin microfilaments, and intermediate filaments, which, in neurons, are called neurofilaments (Herrmann et al., 2007; Hohmann and Dehghani, 2019). Microtubules are hollow tubes consisting of tubulin dimers, which are stabilized by tau proteins. They grow out from the centrosome to the plasma membrane by constantly adding and subtracting tubulin dimers at both ends of the filament (Mitchison and Kirschner, 1984). They are responsible for the intracellular transport together with the motor proteins kinesin and dynein that transport, e.g., vesicles, nutrients, and essential organelles, but also broken-down neurotransmitters and misfolded proteins by extending along the axon and functioning as the cytoskeletal navigation pathways in the transporting process (Guo et al., 2020). The hyperphosphorylation of tau proteins as seen in AD results in microtubule destabilization and cytoskeleton abnormalities (Mandelkow et al., 1995; Barbier et al., 2019). Actin β- and γ-monomers, together with formin homology proteins, form linear polymers called actin microfilaments, which can then be arranged as a network with the help of the proteins Arp2 and Arp3. The Arp2/3-complex forms dimers that resemble actin dimers, but are much more stable. They attach themselves in a 70° angle and serve as nucleation cores for actin filaments activated by the nucleation-promoting factor proteins of the WASP/WAVE-family (Kurisu and Takenawa, 2009). Both filaments and networks stabilize the plasma membrane of the cells and control the position of the nucleus and other cell organelles (Pfisterer et al., 2017). They maintain and adapt cell shape, thus allowing for cytokinesis, organization of *cell junctions*, and enhancement of *cell adhesion*. *Cell migration* is achieved by the polymerization of new actin filaments in the forward edge of a moving cell that pushes the cell membrane forward in protrusions called lamellipodia. These protrusions form mechanical links between the actin filaments and the ECM called *focal adhesions*. Once attached, the rear of the cell body contracts, squeezing its contents forward past the adhesion point. Once the adhesion point has moved to the rear of the cell, the cell disassembles it, allowing the rear of the cell to move forward (Ananthakrishnan and Ehrlicher, 2007). The actin filaments also provide the tracks for cellular transport, allowing actin-based motor proteins (myosins) to transport organelles over short distances.

The interactions of α-actin und myosin but also troponin and tropomyosin are most sophisticated in muscle cells. These

highly specialized cells work together to contract and release muscles, thus leading to movement of the whole organism and to the *cardiac muscle action potential* (Cooper, 2000). Intermediate filaments are the major cytoskeletal proteins, which, in contrast to microtubules and microfilaments, are more heterogeneous, have tensile strength, and do not participate in cell motility (Herrmann et al., 2009). The intermediate filaments primarily provide structural support for the cell, especially for the long neuronal cells where they regulate the diameter of the axon and, thereby, the nerve conduction speed (Helfand et al., 2003).

All cells have intermediate filaments, but the protein subunits of these structures vary. They can be classified into six different types: Types I and II are the *keratins*, which are expressed in epithelia. Type III contains the proteins vimentin, which frequently colocalizes with microtubules, desmin, peripherin, and glial fibrillary acidic protein (GFAP). Type IV consists of the neurofilament proteins L, M, H, and internexin. Type V consists of the nuclear lamins, and Type VI consists of the protein nestin (Muñoz-Lasso et al., 2020). During embryonic development of the brain microtubules, microfilaments and neurofilaments work together to guarantee proper growth and guidance of axons; during adult life, they maintain neuronal homeostasis and plasticity. Given these fundamental processes rely on an intact cytoskeleton organization, it is not surprising that cytoskeleton defects, including alterations in microtubule stability, in axonal transport as well as in actin dynamics, have been characterized in several NDDs.

Hallmark 4: Signal Transduction and Transport

Neuronal signal transduction and transport of organelles and vital molecules along the axon maintain neuronal activity and health. In NDD, neuronal signaling is more and more impaired because of synaptic and cytoskeletal dysfunctions. The loss of synapses has detrimental consequences as they are critical to learning, memory, and behavior (Lepeta et al., 2016; Ardiles et al., 2017), and perturbations in axonal transport can lead to neuronal cell death (Perlson et al., 2010).

Cell communication in the brain is achieved by *neuronal signaling via synapses*. In this process, electrical activity is transferred from one neuron to another through neurotransmitters as chemical mediators. The most important neurotransmitters in the central nervous system are glutamate for the excitatory, and GABA and glycine for the inhibitory synapses, but also dopamine, serotonin, and acetylcholine (Fogarty et al., 2016). Action potentials that travel along axons induce an intracellular Ca^{2+} influx mediated by *voltage-gated calcium channels* at the presynaptic terminal. Increased Ca^{2+} levels are sensed by the synaptic vesicle protein synaptotagmin I, which induces the Soluble NSF Attachment Protein Receptor (SNARE) protein complex to mediate fusion of the neurotransmitter vesicles with the plasma membrane (*SNARE binding*), releasing them into the synaptic cleft (*neurotransmitter secretion*). The neurotransmitters then bind to and thus *activate receptors* of the postsynaptic cell, which can be either *ion channels* or G protein-coupled receptors. They transmit signals from the post-synaptic

membrane to the cell body by transducing the chemical signal into an electrical signal that depolarizes the postsynaptic cell and is transmitted downstream to the next neuron (Lepeta et al., 2016; Taoufik et al., 2018).

Rather than being just a gap, the synaptic cleft is full of trans-synaptic adhesion molecules that not only physically connect the pre- and post-synaptic compartment but also mediate recognition and signaling processes that are essential for the establishment, specification, and plasticity of synapses. Such synapse-organizing adhesion molecules include neuroligins and neuroligins, cadherins, integrins, receptor phosphotyrosine kinases, and phosphatases, such as ephrins and Rho GTPases (Missler et al., 2012; Jang et al., 2017). Deficiencies in the complex synaptic functioning are not only seen in neurodegenerative diseases but also in neuropsychiatric disorders, suggesting that the loss of synapses is not the endpoint incident of the disease but, rather, a triggering event (Taoufik et al., 2018).

Axonal transport, in general, is a process where the motor proteins kinesin and dynein loaded with diverse cargos navigate along the microtubules of the cytoskeleton. Anterograde axonal transport delivers proteins, lipids, mRNA, and mitochondria to the distal synapse, whereas retrograde transport clears misfolded or aggregated proteins and brings distal trophic signals to the soma (Millecamps and Julien, 2013; Sleight et al., 2019).

Transmembranal transport systems in neurons are the *anterograde ER to Golgi transport* with COP II-coated vesicles and the *retrograde trans-Golgi-Network* transport with COP I-coated vesicles (Martínez-Menárguez et al., 2019; Wang L. et al., 2020).

Neurotransmitters or other secretory molecules leave the ER packed in COPII-coated vesicles to be further processed in the Golgi apparatus before being secreted into the synaptic cleft. After an action potential, neurotransmitter and receptors are recycled by the cell. They are protected from lysosomal degradation by COPI-coated vesicles of the retrograde trafficking and redirected to the ER where they are recycled for the next release (Lu and Hong, 2014).

Deficiencies in axonal transport through defects in the cytoskeletal organization, the impairment of motor protein attachment to the microtubules or the destabilization of motor-cargo binding but also aberrant transmembranal anterograde and retrograde transport between ER and Golgi apparatus can induce synaptic failure and ultimately lead to neurodegeneration, as shown in AD, PD, ALS, and HD (Perlson et al., 2010; Guo et al., 2020).

Hallmark 5: Immune System

A fundamental feature in NDD is the dysregulation of the innate *immune response* in the central nervous system by chronic inflammation. The innate immune response of the brain represents not only the first line of defense against invading microorganisms (*defense response to other organisms*) but also responds to endogenous stress like dying or damaged cells after cellular stress. It consists primarily of microglial cells and astrocytes. Microglia are resident tissue macrophages and the principal mediators of *inflammation* (Frank-Cannon et al., 2009), whereas astrocytes mainly supply neurons with nutrients and energy and form the blood-brain barrier (Blackburn et al.,

2009). Both microglia and astrocytes express on their cell-surface pattern-recognition receptors that detect pathogen-associated molecular patterns like residues from bacteria, viruses, fungi but also danger-associated molecular patterns, which can be abnormal endogenous proteins, iron overload, antibodies, cytokines, and chemokines, including toll-like receptors (Akira et al., 2006; Medzhitov, 2007). Also, complement factors bind to these receptors, initiating the *complement and coagulation cascade*, which enhances the immune response of microglia and astrocytes.

Pathogen- and danger-associated molecular patterns induce neuroinflammation by activating the transcription factor NF κ B in microglial cells. NF κ B induces the synthesis of proinflammatory cytokines like Interleukin-1 β (IL-1 β), IL-6, IL-12, interferon gamma (IFN- γ), chemokines, including the C-C motif chemokine ligand 2 and tumor necrosis factor alpha (TNF- α), but also prostaglandins (Schaefer, 2014; Guzman-Martinez et al., 2019) to promote efficient clearance of cell debris and plaques. Also, these factors, being released into the cell environment, activate the astrocytes to both increase the permeability of the blood-brain barrier for easier recruitment of B- and T-adaptive immune cells (*leukocyte activation*) in the brain parenchyma and to release intracellular signals like neurotrophic and growth factors and cytokines, promoting neuronal survival, neurite growth, and neurogenesis (Jha et al., 2019). At the same time, microglial cells synthesize and release short-lived cytotoxic factors, such as superoxide radicals, nitric oxide, and reactive oxygen species that help remove pathological agents (Harry and Kraft, 2008; Jurga et al., 2020).

Although an acute insult may trigger oxidative and nitrosative stress and a slightly more permeable blood-brain barrier, this reaction is typically short-lived and unlikely to be detrimental to long-term neuronal survival (Kurutas, 2015). But disease-induced protein aggregations like oligomers of tau and A β , aging, and other risk factors can lead to chronic neuroinflammation with a long-standing and, often, self-perpetuating neuroinflammatory response that persists long after the initial injury or insult. Permanently activated microglia may not be able to remove amyloid-beta deposits, which, in turn, contributes to further plaque accumulation as opposed to clearance (Frank-Cannon et al., 2009). Also, the permanently increased oxidative and nitrosative stress leads to damaged neurons, synaptic dysfunction, loss of synapses, and neuronal death (Schain and Kreisl, 2017; Shabab and Zorofchian, 2017; Kinney et al., 2018), aggravated by the fact that astrocytes lose their neurotrophic function during the progressive loss of neurons. This process called astrogliosis affects considerably the neurons and their integrity (Sofroniew and Vinters, 2010; Sofroniew, 2015). Chronic inflammation can also trigger signaling pathways that activate brain tau hyperphosphorylation in residues that are not modified under normal physiological conditions, again leading to degenerated neurons and, finally, the now permeable blood-brain barrier allows much more pathogens to enter the brain than the innate immune response can cope with (Gendelman, 2002).

Hallmark 6: Metabolic Processes

We associated the highest number of low-level terms across all six hallmarks to the metabolism hallmark as its pathways and biological processes are involved in all basic physiological processes, and the homeostasis of the compounds and their interactions is vital for the well-functioning of the organism. As neurons but also astrocytes, oligodendrocytes, and microglia are highly dependent on a continuous energy supply. One of the most significant hallmarks for NDD is the dysfunction of mitochondria. Mitochondrial metabolism, comprising the oxidation of pyruvate and fatty acids, the citric acid cycle, the oxidative phosphorylation within the respiratory chain, and the formation of antioxidants, was assigned to the hallmark metabolism, which also contains metabolic processes in the cytoplasm like fat metabolism, protein, carbohydrate, and nucleic acid metabolism, but also homeostasis of the cell. Lipid molecules are key components of the brain's complex structure and function, with lipids comprising around 50% of the brain's dry weight (O'Brien et al., 1964). Many neurological diseases are caused by mutations in genes that are involved in lipid metabolism (Mesa-Herrera et al., 2019; Petit et al., 2020). As associated low-level terms, we included *lipid*-, *cholesterol*-, *sphingolipid* metabolism, *lipoproteins*, *carboxylic acid*, and *fatty acid oxidation*. Lipids function as key regulators of neurotransmission; cholesterol is a membrane stabilizer and organizer during synaptic vesicle exo- and endocytosis; sphingolipids and their metabolites are regulators of the fluidity of cell membranes and second messengers in signal transduction (Puchkov and Haucke, 2013; Barber and Raben, 2019). Being hydrophobic, lipids and cholesterol must be transported through the blood by *lipoproteins*. The term carboxylic acid was mostly connected to biological processes concerning the citric acid cycle and was thus assigned to mitochondrial metabolism, like fatty acids, which are degraded in the mitochondria in an energy-generating process called β -oxidation (Petit et al., 2020).

Main low-level terms of protein metabolism were branched amino acid degradation and *proteoglycans*. Valine, isoleucine, and leucine are essential branched-chain amino acids (BCAAs). Their catabolism starts in muscle mitochondria and yields NADH and FADH₂, which can be utilized for ATP generation. In the brain, BCAAs contribute to the synthesis of excitatory glutamate and inhibitory gamma-aminobutyric acid (GABA) and, at the same time, can reduce the production of serotonin and the catecholamines because they compete for transport across the blood-brain barrier with the aromatic amino acids tryptophan, tyrosine, and phenylalanine, which are the precursors of these neurotransmitters (Fernstrom, 2005). AD metabolomics studies demonstrate that altered *branched-chain amino acids* metabolism accompanies Alzheimer's disease development. Lower plasma valine levels are correlated with accelerated cognitive decline in AD and the severity of motor dysfunction in HD (Polis and Samson, 2020; Xu et al., 2020). No clear correlation between the levels of BCAA and ALS or PD could be found (Bjornevik et al., 2019; Xu et al., 2020).

Carbohydrates are the main source for energy production in the brain and are broken down by glycolysis, the tricarboxylic

acid cycle, and oxidative phosphorylation (Attwell and Laughlin, 2001). The main causes for defective glucose usage in NDD are deleterious mitochondria and a decreased secretion of insulin, coupled with resistance to its actions, problems that link NDD to type II diabetes (Ristow, 2004; Haan, 2006; Seneff et al., 2011; Schaeffer et al., 2021).

During nutritional uptake, the insulin pathway secures the release of the hormone insulin into the blood, which then binds to insulin receptors on the cell surface and thus regulates the uptake of glucose into the cells. But insulin also controls divergent signaling pathways like the Act-pathway or the MAP-kinase pathway, which are involved in cell growth and differentiation (Saltiel and Pessin, 2002). Studies with mouse models have shown that insulin is also involved in the excitability of (hippocampal) neurons (Dai et al., 2014). AD neurons show a reduced action potential due to soluble A β , an effect that is aggravated by missing insulin and that can be partially reversed by the anti-cancer agent bexarotene (Cramer et al., 2012; Dai et al., 2014).

Another important task of carbohydrates is the glycosylation of proteins and lipids in the ER. In the brain, glycosylated proteins participate in a myriad of processes, from electrical gradients to neurotransmission (Conroy et al., 2021), and glycolipids are crucial for the interaction of cells and for signal transduction (Reily et al., 2019). Thus, an intact *N*-glycosylation and *O*-glycosylation of lipids and proteins are important for the well functioning of the brain, and disrupted glycosylation can lead to NDD (Moll et al., 2020), e.g., *O*-GlcNAcylation of CNS proteins important for axonal and synaptic function is significantly reduced in AD, ALS, HD, and PD patients' tissue (Liu et al., 2004; Lüdemann et al., 2005; Kumar et al., 2014).

Nucleotides are not only the building blocks of DNA and RNA but also are involved in cellular metabolism, with, especially, ATP and NADH as energy carriers and cAMP, a second messenger molecule, as a translator of signals from outside to cellular processes. Thus, these molecules are involved in all basic physiological processes critical to the proper function of the organism (Huang et al., 2021). Nucleotides are either built *de novo* or, as this process takes much energy, recovered during the degradation of DNA and RNA in a nucleotide salvage pathway. A disbalance in the synthesis pathways again disturbs energy homeostasis and many cellular processes like proliferation, differentiation, migration, and apoptosis. The *respiratory chain complex* in the mitochondria not only efficiently produces energy but also reactive oxygen species that can harm the mitochondrial DNA. Antioxidants like glutathione protect mitochondria and cells against damage, but, if this *homeostasis* is disturbed, oxidative stress induces the destruction of mitochondria and apoptosis of neuronal and other brain cells (Kausar et al., 2018).

MATERIALS AND METHODS

To make all steps from data acquisition *via* data management to data analysis comprehensible, we will outline these steps following that order. The data analysis is composed of several steps, the analysis of the intersections of the individual omics-layers per NDD, the analysis of the conformity of the mean

regulatory direction across omics-layers per NDD, as well as the core of the data analysis: the generation and evaluation of the protein-protein interaction networks, and the generation and evaluation of the communities.

Data Acquisition

In this meta-study, we used datasets of four different omics-layers: Genomics (SNP data), Transcriptomics, Proteomics, and Methyloomics. In the following, we describe where these data were acquired from.

The SNP data are based on the genome-wide association studies (GWAS) Catalog (Buniello et al., 2019), which has been updated on November 18, 2021. The experimental factor ontology (EFO) numbers for the exact search pattern were EFO_0000249 (Alzheimer's disease), EFO_0002508 (Parkinson's disease), Orphanet_399 (Huntington's disease), and EFO_0000253 (Amyotrophic Lateral Sclerosis). For all NDD but HD, a child term was given, which was also included in the data acquisition step. In total, 153 studies with genomic data were used for the analyses (Maraganore et al., 2005; Fung et al., 2006; Coon et al., 2007; Reiman et al., 2007; Schymick et al., 2007; van Es et al., 2007; Van Es et al., 2008, 2009; Abraham et al., 2008; Bertram et al., 2008; Cronin et al., 2008, 2009; Li et al., 2008, 2021; Webster et al., 2008; Beecham et al., 2009, 2015; Carrasquillo et al., 2009; Harold et al., 2009; Lambert et al., 2009, 2013a,b; Landers et al., 2009; Latourelle et al., 2009; Pankratz et al., 2009, 2012; Satake et al., 2009; Simón-Sánchez et al., 2009; Edwards et al., 2010; Feulner et al., 2010; Hamza et al., 2010; Heinzen et al., 2010; Laaksovirta et al., 2010; Naj et al., 2010, 2011; Seshadri et al., 2010; Shatunov et al., 2010; Stein et al., 2010; Antúnez et al., 2011; Do et al., 2011; Furney et al., 2011; Hollingworth et al., 2011, 2012; Hu et al., 2011, 2016; Kim et al., 2011; Kramer et al., 2011; Liu et al., 2011, 2021; Logue et al., 2011; Nalls et al., 2011, 2014, 2019; Saad et al., 2011; Spencer et al., 2011; Wijsman et al., 2011; Chung et al., 2012, 2018; Cummings et al., 2012; Kamboh et al., 2012a,b; Kwee et al., 2012; Lill et al., 2012; Meda et al., 2012; Cruchaga et al., 2013; Davis et al., 2013; Deng et al., 2013; Jonsson et al., 2013; Langefeld, 2013; Martinelli-Boneschi et al., 2013; Miyashita et al., 2013; Reitz et al., 2013; Diekstra et al., 2014; Fogh et al., 2014, 2016; Goris et al., 2014; Hill-Burns et al., 2014, 2016; Kauwe et al., 2014; Nelson et al., 2014; Pérez-Palma et al., 2014; Ramanan et al., 2014; Ramirez et al., 2014; Sherva et al., 2014, 2020; Vacic et al., 2014; Xie et al., 2014; Hirano et al., 2015; McLaughlin et al., 2015; Tosto et al., 2015; Wang et al., 2015, 2021; Biernacka et al., 2016; Chen et al., 2016; Deming et al., 2016; Herold et al., 2016; Jun et al., 2016, 2017; Pickrell et al., 2016; Schott et al., 2016; Traylor et al., 2016; Van Rheenen et al., 2016; Watanabe et al., 2016; Benyamin et al., 2017; Chang et al., 2017; Foo et al., 2017, 2020; Lee et al., 2017; Mez et al., 2017; Moss et al., 2017; Siitonen et al., 2017; Sims et al., 2017; Chao et al., 2018; Gusareva et al., 2018; Marioni et al., 2018; Miron et al., 2018; Mukherjee et al., 2018; Nicolas et al., 2018; Pottier et al., 2018; Wallen et al., 2018; Yashin et al., 2018; Bandres-Ciga et al., 2019; Blauwendraat et al., 2019, 2020; Dekker et al., 2019; Jansen et al., 2019; Kunkle et al., 2019, 2021; Lo et al., 2019; Moreno-Grau et al., 2019; Nazarian et al., 2019a,b; Wei et al., 2019; Zhu et al., 2019; Cha et al., 2020; Hong et al., 2020;

Nakamura et al., 2020; Ryu et al., 2020; Alfradique-Dunham et al., 2021; Bone et al., 2021; DeMichele-Sweet et al., 2021; de Rojas et al., 2021; Kang et al., 2021; Loesch et al., 2021; Park et al., 2021; Reddy et al., 2021; Rodrigo and Nyholt, 2021; Sakaue et al., 2021; Schwartzentruber et al., 2021; Shigemizu et al., 2021; Smeland et al., 2021; Tan et al., 2021; Wightman et al., 2021).

For the transcriptomic and proteomic layer, we used the studies that we have identified previously (Ruffini et al., 2020), using the Gene Expression Omnibus (GEO) (Barrett et al., 2013), the Expression Atlas (Papatheodorou et al., 2018) databases, and doing literature research (Ruffini et al., 2020). For the transcriptomic data, the keywords used in the GEO database were <name of disease> AND (“microarray” OR “RNAseq”) AND “human,” The Expression Atlas was used in Release 35 (May 2020, <https://www.ebi.ac.uk/gxa/home>) and scanned for Alzheimer’s, Parkinson’s, Huntington, and Amyotrophic Lateral Sclerosis, using the filter “Homo sapiens” in the section “Differential Experiments.”

For the proteomic data, literature search was conducted in PubMed and Google Scholar, with the keywords: (“neurodegenerative diseases” OR “Alzheimer’s* disease” OR “Parkinson’s* disease” OR “Huntington* disease” OR “Amyotrophic Lateral Sclerosis”) AND (proteomics OR “quantitative proteomics” OR “differentially expressed proteins” OR biomarkers) AND human NOT mice for publications from 2010 to 2020.

Of the included experiments, 63% of the transcriptomic experiments were performed with brain material, while 67% of the proteomic experiments were conducted with brain material. Among the non-control patients, 84% were classified as having a moderate or severe condition in the transcriptome experiments and 90% in the proteome experiments. In total, transcriptomic data of 39 studies (Blalock et al., 2004, 2011; Zhang et al., 2005; Dunckley et al., 2006; Lesnick et al., 2007; Liang et al., 2007; Scherzer et al., 2007; Simunovic et al., 2009; Cox et al., 2010; Elstner et al., 2011; Dumitriu et al., 2012, 2016; Feyeux et al., 2012; Berchtold et al., 2013; Hokama et al., 2014; Riley et al., 2014; Calligaris et al., 2015; Dijkstra et al., 2015; Labadorf et al., 2015; Magistri et al., 2015; Prudencio et al., 2015; Raman et al., 2015; Ring et al., 2015; Kapeli et al., 2016; Lin et al., 2016; Scheckel et al., 2016; Lim et al., 2017a,b; Gagliardi et al., 2018; Mehta et al., 2018; Stopa et al., 2018; Mathys et al., 2019; Meyer et al., 2019; Otake et al., 2019; Swindell et al., 2019; Switońska et al., 2019; Al-Dalahmah et al., 2020; Dols-Icardo et al., 2020; Higginbotham et al., 2020) and proteomic data of 22 studies were acquired (Fang et al., 2009; van Dijk et al., 2012; Varghese et al., 2013; McQuade et al., 2014; Riley et al., 2014; Collins et al., 2015; Dumitriu et al., 2016; Hondius et al., 2016; Ratovitski et al., 2016; Lachén-Montes et al., 2017, 2019; Seyfried et al., 2017; Umoh et al., 2018; Zhang et al., 2018; Higginbotham et al., 2019, 2020; Iridoy et al., 2019; Bader et al., 2020; Johnson et al., 2020; Oeckl et al., 2020; Rotunno et al., 2020; Wingo et al., 2020) (see also **Table 1**). A table giving the number of samples per condition, the severity state of the included samples, and the used technology is given in **Supplementary Table 4**.

For the methylomic data, we used all data from the PDMethDB (Wang C. et al., 2020) (last accessed December 13,

TABLE 1 | A summary of the number of used studies per disease and omics-layer.

NDD	Genome	Transcriptome	Proteome	Methylome	Studies
AD	79	11	9	10	109
PD	46	11	7	7	71
HD	2	10	5	2	19
ALS	26	8	3	2	39
Σ	153	40 (39)	24 (22)	21 (20)	238 (234)

In total, data of four studies were used for more than one omics-layer, resulting in 234 different studies as a basis for this meta-studies data analysis. In brackets, the actual summed number of unique studies used is shown, as some studies contained information of two NDDs.

2021), the EWAS Atlas (Li M. et al., 2019) (accessed 01.02.21) for the four respective diseases, and other data we found through literature research using PubMed and Google Scholar. Queries for “epigenome-wide” OR “epigenome wide” OR “EWAS” OR “genome-wide” AND “methylation” OR “genome wide” AND “methylation,” as well as “metastudy” AND “neurodegenerative disease” AND “epigenetic,” were used to find studies published after 2010. Combined, the databases and literature research resulted in the inclusion of data of 20 studies (Bakulski et al., 2012; Kaut et al., 2012; Masliah et al., 2013; de Jager et al., 2014; Lunnon et al., 2014; Sanchez-Mut et al., 2016; Watson et al., 2016; Zhang et al., 2016; Young et al., 2017, 2019; Gasparoni et al., 2018; Smith et al., 2018, 2019; Zadel et al., 2018; Altuna et al., 2019; Li P. et al., 2019; Tarr et al., 2019; Go et al., 2020; Lu et al., 2020; Marshall et al., 2020), one of which contained data for both AD and PD. As the higher availability of methylome data for Alzheimer’s and Parkinson’s diseases made it possible, we chose to include exclusively brain tissue-derived data for those two diseases. However, as the data availability for HD and ALS were much poorer, only blood tissue data were included for those NDDs. In total, we gathered data from 234 different studies for the four respective diseases and omics-layers (see **Table 1**).

Data Management

The raw gene lists obtained from the transcriptomic, proteomic, and methylomic data were filtered for a false discovery ratio (FDR) ≤ 0.05 , the proteomic data were mapped to gene names, and all the obtained gene names (from genomic, transcriptomic, proteomic, and methylomic data) were then mapped to the list of current protein-coding gene symbols (22 March 2021) from the HUGO Gene Nomenclature Committee (Tweedie et al., 2021) by mapping all alias names to the original gene symbol. Those names that were not found as any gene symbol or alias were discarded. The following data management step consisted of removing those genes that appeared as significantly altered only once in our transcriptomic, proteomic, and methylomic data. However, since the database for our methylomic and proteomic data in ALS and for the proteomic data in HD was very sparse, we decided to retain all significant genes for these gene lists to interpret a potentially noisy signal instead of hardly any signal at all.

Mean Direction of Regulation

The transcriptomic, proteomic, and methylomic data also contained information about the regulation of these significant genes/proteins. This information was contained as G-fold change (FC), log2 FC or other in transcriptomic and proteomic experiments, and as beta values in some methylomic experiments. To make this information from the different data sources as comparable as possible, we derived the mean direction of regulation (MeanRegDir) for all significantly conspicuous genes in each of the three omics levels, which equals to 1 if a gene/protein was overexpressed/hypomethylated in the disease group in every instance in which it occurred. Conversely, MeanRegDir indicates a value of -1 if a gene in the disease group was downregulated/hypomethylated in all experiments in which it appeared as significantly striking. If the signal is ambiguous, MeanRegDir will give a value between -1 and 1 , as indicated in Equation (1).

Equation 1: Calculation of mean regulation of direction

$$\text{MeanRegDir}(\text{gene}) = \frac{1}{n} \sum_{i=1}^n \left(\text{sig} \left(\text{gene}_{i\text{foldChange}} \right) \right)$$

with

n = number of appearances for gene with $\text{FDR} \leq 0.05$

$$\text{sig}(x) = \begin{cases} 1, & \text{if } x > 0 \\ -1, & \text{if } x < 0 \end{cases}$$

$\text{gene}_{i\text{foldChange}}$ = fold change of gene_i

Method 1: Omics-Layer Intersections per Disease

By intersecting the four analyzed omics-layers per disease, we were able to test whether the number of shared genes between each pair of omics-layers per disease was significantly increased. We used a hypergeometric test for the overlapping sets, with the total amount of 19,207 gene symbols of protein-coding genes (HUGO Gene Nomenclature Committee, 22 March 2021) (Braschi et al., 2019) as the total population. To also have a measure for the effect size of the significantly high numbers of genes in the overlapping sets and thus being able to differentiate between the differently significantly found large gene sets, we calculated the effect size of the hypergeometric test results by setting the difference between observed and expected value in relation to the standard deviation of the hypergeometric distribution. This led to the following formula and the value eff_{size} that gives the number of standard deviations by which our expected value is beyond/below the expected value:

Equation 2: Effect size of the hypergeometric test results

$$\text{eff}_{\text{size}} = \frac{\text{overlap}_{\text{obs}} - \text{overlap}_{\text{exp}}}{\text{std}_{\text{hypergeom}}}$$

with:

$$\text{std}_{\text{hypergeom}} = \sqrt{n \cdot \frac{K}{N} \cdot \frac{N-K}{N} \cdot \frac{N-n}{N-1}}$$

with:

$\text{overlap}_{\text{obs}}$ = observed overlap between the two omics layers

$\text{overlap}_{\text{exp}}$ = expected overlap between the two omics layers

N = population size (whole gene background)

K = number of successes in the population

(number of genes in the first omics layer)

n = number of draws

(number of genes in the second omics layer)

k = number of observed successes

(number of overlapping genes)

Intersections were performed and visualized using the R (version 4.0.2) (Urbanek et al., 2014) package *venn* (version 1.10) (Dusa, 2016).

Method 2: Multi-Omics Conformity Stacked Bar Plots

In order to visualize those genes, which are appearing as altered/differentially expressed in multiple omics-layers, stacked bar plots showing conformity in genomics, transcriptomics, proteomics, and methylomics data (**Supplementary Presentation 2—StackedBarPlots**) were created using the python package *matplotlib* (Hunter, 2007). As the overlap between genomics and the other three omics-layers was rather low, stacked bar plots were also created for those genes appearing only in transcriptomic, proteomic, and methylomic levels. Plots were only created if there was any overlap. To gain insights into the direction of regulation (up- or downregulation) for the overlapping genes, the stacked bars are also color-coded. The color represents the ratio of studies in which a gene was significantly up- or downregulated (see Equation 1 Calculation of mean regulation of direction). This data representation shows information about the certainty of the direction of differential regulation as well as coherency between transcriptomic, proteomic, and methylomic over- or underrepresentation or hyper-/hypomethylation, respectively.

Correlation Test

The *pearson* function that is available in the *scipy.stats* module (Virtanen et al., 2020) was used to compute the correlation and its two-sided *p*-value for the relation between transcriptomic and proteomic direction of regulation. The correlation analysis showed if there was a significant correlation between the direction of regulation in the pairwise intersection between the transcriptomic, proteomic, and methylomic levels. The value of the pairwise correlation and information about the *p*-value of the correlation test was calculated for each pairwise intersection of the transcriptomic, proteomic, and methylomic data layers for each disease. The results are shown as a heatmap in **Figure 2**.

Method 3: Protein-Protein Interaction Networks

The significantly distinctive genes and proteins that emerged in our analysis represented a variety of processes connected to the

respected NDD. Consequently, the functional analysis of all genes that emerged for an individual omics-layer for a particular NDD would lead to results showing a combination of different related processes and would, therefore, lower the statistical power of the hypergeometric test and interpretability of the results.

To better separate the distinct processes related to our gene sets, we constructed protein-protein interaction (PPI) graphs for each omics-layer of each NDD and isolated communities of high modularity within that graph with the *louvain* algorithm (Blondel et al., 2008). These communities of high modularity were then used for the functional analyses and showed clearly distinct processes for our different gene sets.

Network Construction

PPI networks were constructed to visualize and utilize protein-protein interaction data for each omics layer per NDD, which were subsequently used to identify communities of high modularity and associated hub genes within each network. The networks were constructed using the Python module *louvain* (2.6.3) (Hagberg et al., 2008). The PPI data were based on the *louvain* dataset for human PPI enrichment (species = 9,606, accessed on October 18, 2021) and were filtered for those PPI with a combined score ≥ 400 (default value). The combined score in string DB consists of a combination of the individual scores (annotated pathways, gene neighborhood, ...), emerging from the underlying databases and is typically higher than the individual scores, as it expresses increased confidence if a connection between two genes is supported by different types of evidence (von Mering et al., 2005). This resulted in a graph that consisted of nodes representing the genes that are connected by weighted edges, representing the combined interaction score of the involved genes. These weights were later used in the hub gene identification to represent the importance of an edge or to calculate a distance between edges as $distance = 1/weight$, depending on each centrality algorithms input requirements.

Furthermore, the modularity of the networks was computed using the Python module *louvain*, with the *louvain.algorithms.community.quality.modularity* function with a resolution parameter set to 1. For this function, modularity is defined as described by Newman (2010) and shown below:

Equation 3: Modularity

$$Q = \frac{1}{2m} \sum_{ij} (A_{ij} - \gamma \frac{k_i k_j}{2m}) \delta(c_i, c_j)$$

with

m = number of edges

A = adjacency matrix of Graph G

k_i = degree of node u_i

γ = a resolution parameter (for this analysis, set to 1)

$\delta(c_i, c_j) = \begin{cases} 1, & \text{if } u_i \text{ and } u_j \text{ are in the same community} \\ 0, & \text{otherwise} \end{cases}$

Community Creation

The community search was carried out using the Python module *community* (1.0.0b1) with the *community.best_partition* function, which computes a partition of the graph, maximizing

the modularity using the *louvain* heuristics (Blondel et al., 2008). As the *louvain* algorithm's result varies with the order in which the input is given, we applied the *louvain* algorithm 100 times with permuted input of the whole network for each omics-layer in each disease and calculated the whole graph's modularity, picking the best result in terms of network modularity as our final community output.

Functional Analysis and Hallmark Definition

For each of the resulting communities, we performed the functional annotation using the stringDB API (stringDB Version 11.5) and further focused on all communities with at least one biological process with an $FDR \leq 0.05$, as we considered those communities as most helpful for creating a meaningful redefinition of the neurodegenerative hallmarks. We also visualized these communities of the networks in Arcplots and Matrixplots using the Python module *nxviz* (0.7.2).

Derived from the functional analysis results, we defined six hallmarks that resemble the most meaningful categorization of our results, given prior knowledge and the most recurring processes throughout our multi-omics analysis of the four NDDs. When interpreting the functional analysis results and defining not only the six hallmarks but also low-level terms for each hallmark, we especially focused on the GO terms, pathways, and stringDB local network clusters that were associated with our communities. The stringDB local network clusters are precomputed protein clusters from stringDB that are derived from hierarchical clustering of the whole stringDB PPI network and further reduced by excluding all child clusters that are too redundant and only vary from the parent cluster by less than five proteins. These clusters' names are then derived from the proteins' annotation given in databases from *Gene Ontology* (GO) (Carbon et al., 2021), *KEGG* (Kanehisa et al., 2021), *Reactome* (Fabregat et al., 2016), *UniProt* (Bateman et al., 2021), *Pfam* (Mistry et al., 2021), *SMART* (Letunic et al., 2021), and *InterPro* (Blum et al., 2021).

The actual analysis of the associations between our communities and the low-level terms was performed by comparing the found number of associations with the expected number of associations per NDD and omics-layer based on the overall distribution. Additionally, we performed an X²-Test across all NDDs and, also, across all omics-layers to see if there was a statistically significant difference between the expected and observed numbers of associations across the four NDDs or across the four omics-layers for all six defined hallmarks.

Hub Gene Identification

To find out if, for some of our extracted communities, there were key players clearly playing the most prominent role in their respective communities, we aimed to identify the hub genes in our communities, meaning the most central node in our community networks. In network theory, there are different concepts for determining the centrality of a node, meaning the node's dominance within the network. Three widely used centrality measures were originally described by Freeman in the late '70s, namely, degree centrality, betweenness centrality, and closeness centrality (Freeman, 1977, 1978; Freeman et al., 1979),

based on the number of direct links between a node and other nodes, the mediation role of a node in a network and on the sum of the shortest paths to all other nodes in the network, respectively. For closeness centrality, the Wasserman- and Faust-improved formula was used (Wasserman and Faust, 1994). These three centrality measures were computed with the Python module *networkx* and were based on the following formulas:

Equation 4: Degree centrality of node u_i

$$C_d(u_i) = \frac{1}{N} * \sum_{j=1}^N X_{ij}$$

with:

$$\begin{aligned} i &\neq j; \\ N &= \text{number of nodes in the graph}; \\ X_{ij} &= \begin{cases} 1, & \text{if } u_i \text{ and } u_j \text{ are connected by an edge} \\ 0, & \text{otherwise} \end{cases} \end{aligned}$$

Equation 5: Betweenness centrality of node u_i

$$\begin{aligned} C_b(u_i) &= \frac{n-1}{\sum_{j=1}^{n-1} d(u_i, u_j)} * \frac{n-1}{N-1} \\ C_b(u_i) &= \sum_{s,t \in V} \frac{\sigma(s, t|u_i)}{\sigma(s, t)} \end{aligned}$$

with:

$$\begin{aligned} s, t &\neq u_i; s \neq t; \\ V &= \text{set of all nodes in the graph}; \\ \sigma(s, t) &= \text{the number of shortest } s, t \text{ paths} \\ \sigma(s, t|u_i) &= \text{the number of shortest } s, t \text{ paths going through } u_i \end{aligned}$$

Equation 6: Closeness centrality of node u_i (Wasserman- and Faust-improved formula)

$$C_c(u_i) = \frac{n-1}{\sum_{j=1}^{n-1} d(u_i, u_j)} * \frac{n-1}{N-1}$$

with:

$$\begin{aligned} n &= \text{number of reachable nodes from } u_i; \\ N &= \text{number of nodes in the graph}; \\ d(u_i, u_j) &= \text{shortest path's distance between node } u_i \text{ and node } u_j \end{aligned}$$

In addition to these three centrality measures originally proposed by Freeman, we also computed the eigenvector centrality of each node (Newman, 2010; Bonacich, 2015), which gives a centrality score to each node that is proportional to the sum of the centrality scores of each node's neighbors.

Equation 7: Eigenvector centrality of node u_i

$C_e(u_i)$ is the i -th element of the vector x defined by:

$$Ax = \lambda x$$

with A = adjacency matrix of the graph with eigenvalue λ .

The current literature on finding hub genes in biological networks differs but often uses the node degree (Li et al., 2018;

Zhou et al., 2018) or weighted gene coexpression network analysis (Zhang and Horvath, 2005) as a basis for identification of hub genes. Here, we combined the four mentioned centrality measurements that give information for each node u_i about:

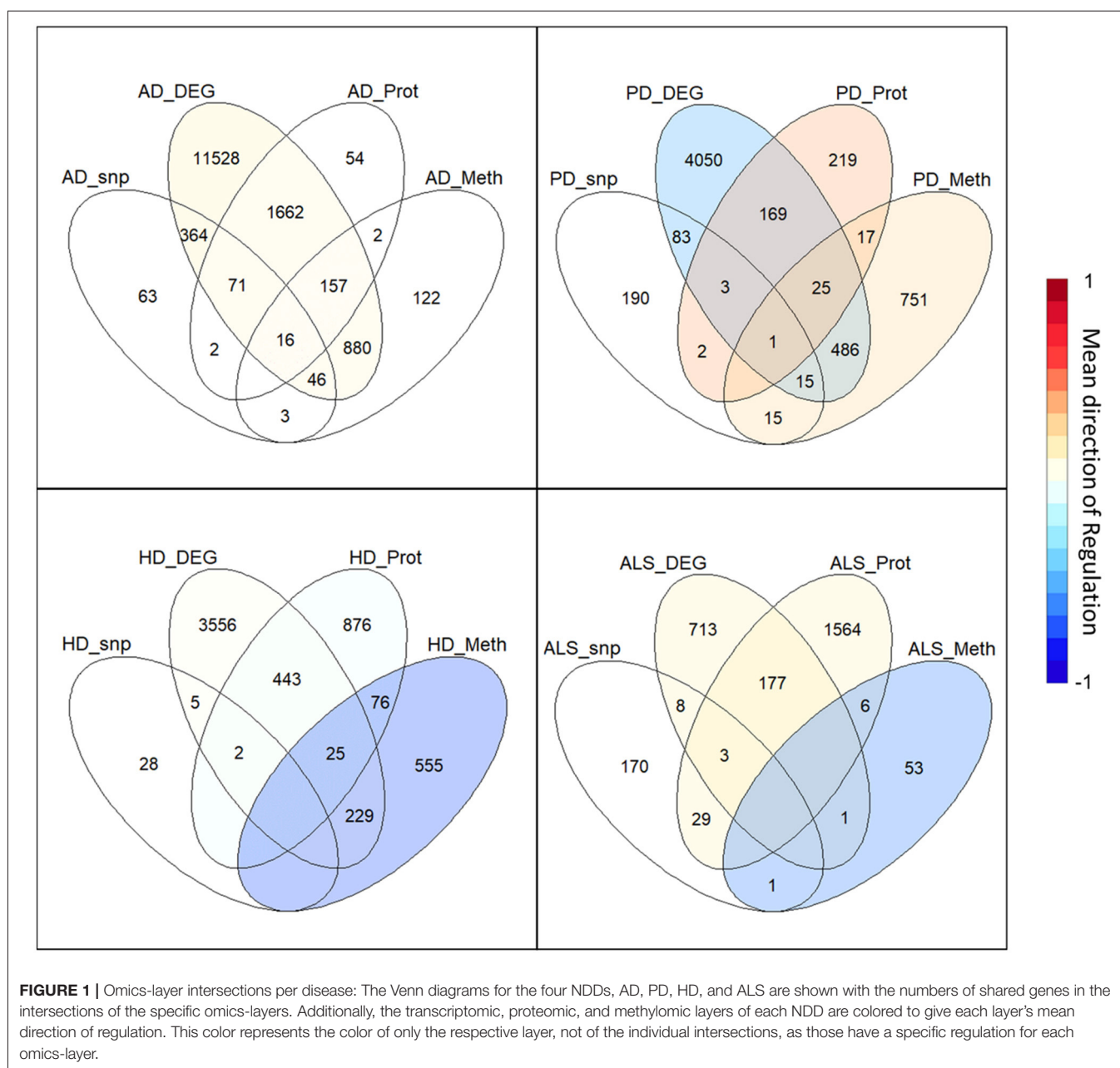
- The number of other nodes in the network connected to u_i
- The number of shortest paths between two other nodes in which u_i is involved
- The accumulated distance to all other nodes in the network from u_i
- The importance of nodes connected to u_i

We considered hub genes in our communities as those that are among the most important nodes in several of these centrality measures. Accordingly, we defined hub genes as being among the top three nodes in at least three of the four centrality measures mentioned. Genes that appeared among the three most central nodes in the network on all four calculated measures of centrality, or that were the single most central nodes according to at least three measures of centrality, were given special consideration for subsequent interpretation of hub genes in our community networks.

RESULTS

Omics-Layer Intersections per Disease

The intersection of the four analyzed omics-layers per disease showed significantly high numbers of shared genes between the transcriptomic and proteomic levels for all four analyzed NDDs (Figure 1, Table 2). All other pairwise intersections show a significantly high number of shared genes in two to three of the analyzed NDDs, while AD shows significantly high numbers of shared genes for all pairwise intersections of omics-layers. AD also showed the highest number of genes in total across all omics-layers with 14,970 genes. PD followed with 6,026, and then HD with 5,795 and ALS with 2,725 genes (Figure 1). The mean direction of regulation was close to 0 for all omics-layers in AD (0.13, -0.1, -0.06 for transcriptomic, proteomic, and methylomic data, respectively); in PD, the mean direction of regulation was -0.59 for the transcriptomic level, 0.42 for the proteomic level, and 0.33 for the methylomic level. For HD, the methylomic layer showed a mean direction of regulation of -0.8, while the other omics-layers were closer to 0 (0.04 transcriptomic, -0.18 proteomic). In ALS, the transcriptomic and proteomic layers showed a positive mean direction of regulation (0.12 and 0.16), while the methylomic layer showed a strong negative mean direction of regulation (-0.75). For the genomic level, there are no mean directions of regulation as these data show an association between the presence of specific SNPs and the respective NDDs. The calculated effect sizes for the hypergeometric test results show the highest values in the transcriptomic-proteomic intersection for all NDDs, with differences between expected and observed numbers of genes of more than 10 standard deviations (stds) except for PD (second highest value with 9.9 stds). In PD, the highest effect size was achieved in the transcriptomic-methylomic intersection with 13



stds difference. All other comparisons showed much weaker effect sizes, with values below 5 stds.

Multi-Omics Conformity

The correlation between the transcriptomic and proteomic mean direction of regulation of the genes in the transcriptomic and proteomic layers' intersection in AD, HD, and ALS was significantly high (all $p < 10^{-5}$) (see **Figure 2**). The correlation for this layer intersection in PD was not significantly high. However, the correlation was slightly positive, even though the mean direction of regulation for the whole transcriptomic PD data was highly negative (-0.59), while it was highly positive (0.42) for the whole proteomic PD data. All other correlations

of mean direction of regulation in the pairwise intersections between transcriptomic, proteomic, and methylomic layers per disease were neither significantly high nor low ($p \geq 0.05$).

Protein-Protein Interaction Networks

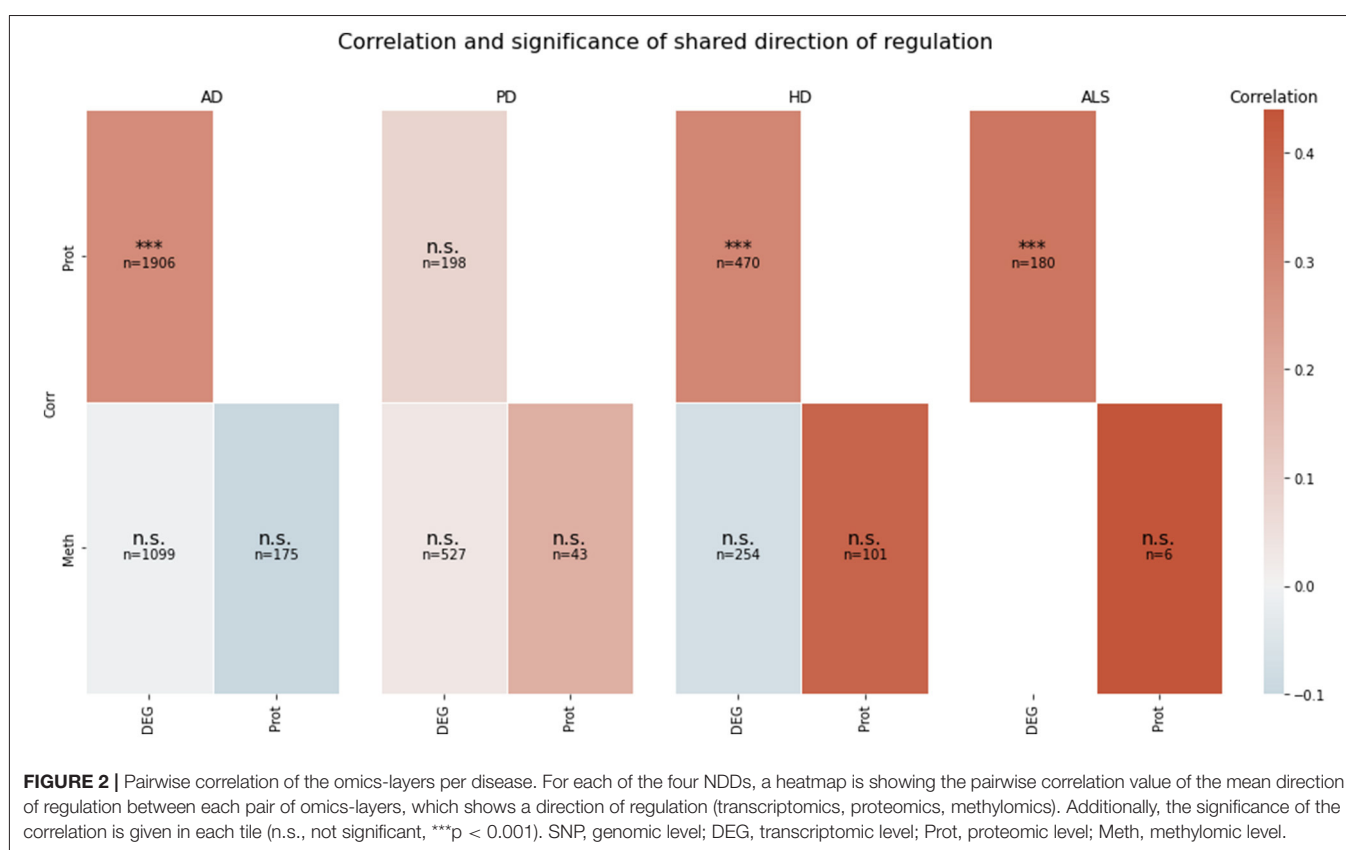
The network construction step led to a PPI network for each analyzed omics-layer in all four analyzed NDDs. However, the constructed communities of the networks based on the genomic layer in HD and ALS, as well as the methylomic layer in ALS, showed a little functional signal. Consequently, we focused on the remaining 13 PPI networks for the analysis.

These remaining networks varied between 7 (PD proteome) and 15 (PD methylome) communities with sufficient functional

TABLE 2 | Omics-layers intersections per disease: the number of resulting genes in each pairwise intersection of omics-layers per disease was tested for enrichment in a hypergeometric test.

NDD	DEG-Prot		DEG-SNP		DEG-Meth		Prot-SNP		Prot-Meth		Meth-SNP	
	<i>p</i>	Eff. size	<i>p</i>	Eff.size	<i>p</i>	Eff.size	<i>p</i>	Eff.size	<i>p</i>	Eff.size	<i>p</i>	Eff.size
AD	0	22.5	1.6E-12	6.4	0.00	11.1	1.3E-05	4.4	1.5E-06	4.8	1.4E-06	5.1
PD	0	9.9	8.2E-04	3.2	0.00	13.0	0.56	−0.4	6E-03	2.5	0.01	2.2
ALS	0	11.3	0.29	0.4	0.79	−1.1	2E-03	3.0	0.33	0.2	0.14	0.4
HD	0	10.3	0.53	−0.3	1.4E-06	4.8	0.49	−0.4	4.6E-06	4.7	0.81	−1.3

The results show that the number of significantly striking genes that emerged in transcriptomic and proteomic data was significantly high in all four analyzed diseases. The number of genes in the other pairwise intersections was only significantly high in two to three of the analyzed diseases. AD, the NDD with the largest database in our study, showed significantly high numbers of genes in all pairwise intersections. Additionally, the effect sizes of these hypergeometric test results are depicted as explained in Equation (2). Especially, the intersections between transcriptomic and proteomic layers show large effect sizes in all groups. Cells associated with significant overlaps are depicted in bold letters. SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level.



annotation (any biological process with $FDR \leq 0.05$) to be further considered in our analysis. The modularity of these 13 PPI networks varied after community creation between 0.484 (PD proteome) and 0.588 (ALS proteome), thus showing a small deviation in modularity values across the different NDDs and omics-layers. The modularity value is positive if the communities in the network show higher interconnectedness than randomly expected; negative values if there are less connections within the communities than randomly expected are strictly lower than 1 (Equation 3: Modularity). Thus, the 13 networks that we further consider show more connections within their communities than expected by chance (as all have positive modularity values).

Examples of those network plots for PD are given in **Figures 3–6**. The networks for AD, HD, and ALS can be found in the **Supplementary Presentation 1—Network Figures**.

Hallmark Definition

The hallmarks of neurodegenerative diseases that we defined based on the functional analyses of the communities are a deregulated **Cell Cycle**, defects in **autophagy and apoptosis** on the cellular level, a defective **Extracellular Matrix Organization** and misguided cell and organ **development**, the impaired **Signal Transduction/Transport** of vital molecules within and between cells within the local tissue environment, an excessive **Immune**

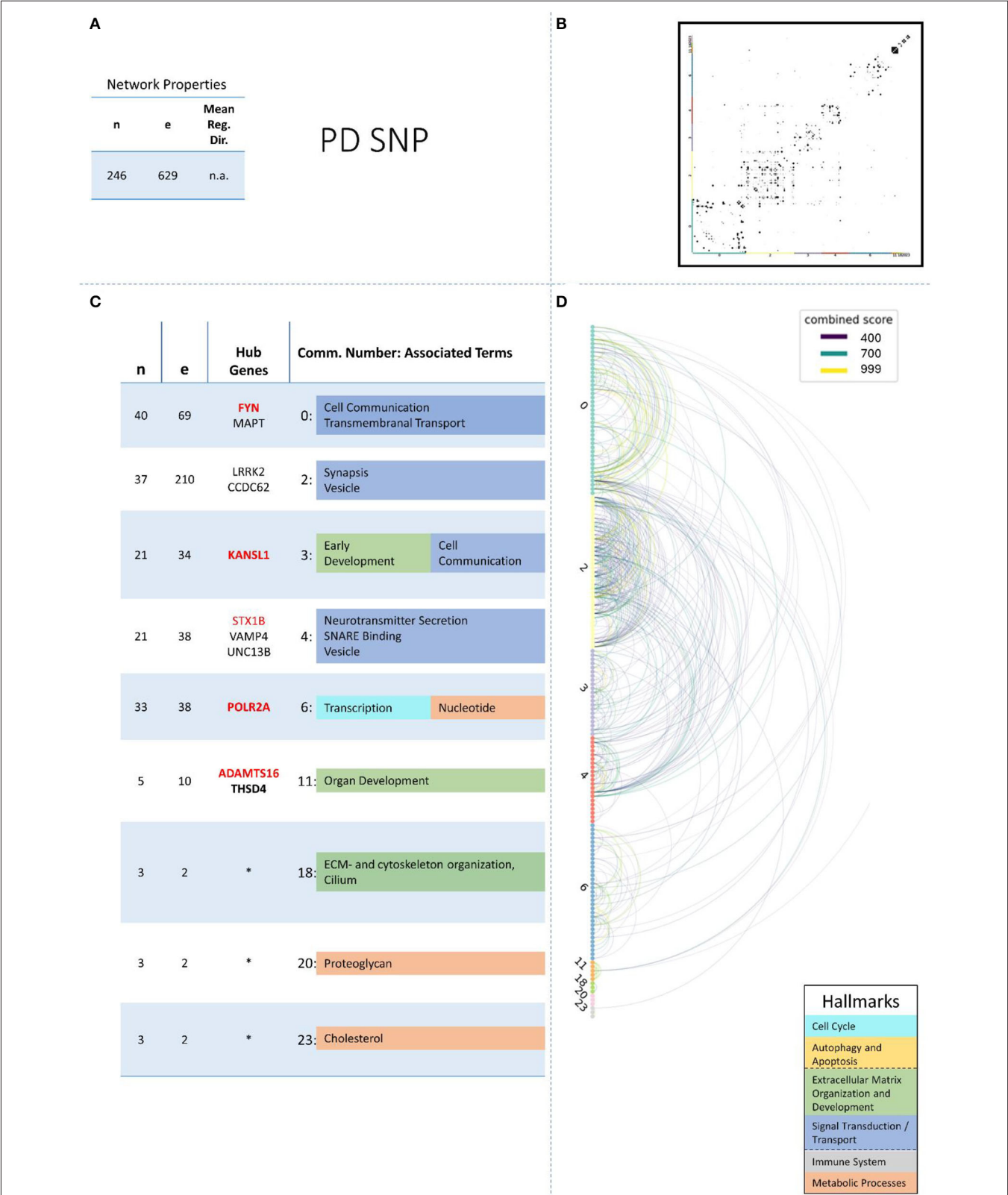


FIGURE 3 | connections with a combined score ≥ 400 between each two genes are also given in a matrix plot **(B)** and an Arcplot **(D)** that are ordered by community. The latter shows the confidence of the connection between two genes additionally by the color of the arc. The general properties of each individual community, as well as their hub genes and the categorization of their functional annotation, are given in the table in Subfigure **(C)**. The connected processes are colored by the associated hallmarks that are also displayed in the bottom right corner.

System response, and defective **Metabolic Processes** in the whole systemic environment.

The results of the χ^2 -test showed that there is a significant difference between the expected and observed values for the four omics-layers across all six hallmarks ($p < 0.05$), but not for the four NDDs across all six hallmarks (see **Supplementary Table 3—Low-Level Term Associations**).

The most striking results we found when analyzing the accumulated numbers of associations between our communities and low-level terms across the four NDDs and also across the four omics-layers were the low number of associations found in PD for the Immune System hallmark and the low number of associations in the methylomic layer in the Metabolic Processes hallmark while having a high number of associations in the proteomic layer.

A more detailed description of the results is presented in the following:

Cell Cycle

In the category of Cell Cycle 56 communities could be assigned to the low-level terms *Regulation of Cell Cycle*, *Spindle Apparatus*, *DNA repair*, *Transcription*, *RNA Modification*, *Spliceosome*, *Translation*, *Mitochondrial Translation*, and *Chromatin*.

AD showed the most low-level terms (21), followed by PD, HD, and ALS (15, 13, 7), while the transcriptomic and methylomic layers showed a higher number of low-level terms (21, 20) than the proteomic and genomic layers (11 and 4) (see **Table 3**). In general, for the hallmark Cell Cycle, the numbers of associations between communities and low-level terms neither strongly differed across NDDs nor across omics-layers from the expected values, given the overall distribution of associations across all hallmarks, NDDs, and omics-layers.

Autophagy and Apoptosis

Of all NDDs and omics-layers, 46 communities were involved in autophagy and apoptosis specified by low-level terms like *Chaperone-Mediated Process*, *Proteolysis*, *Ubiquitinylation*, *Proteasome*, *Stress Response*, *Apoptotic Process*, and the *mTOR* and *NfκB Signaling Pathways*.

Again, AD showed the most associations (16), followed by PD, HD, and ALS (13, 9, and 8), as shown in **Table 4**. The expected number for ALS is 5, in contrast to the observed 8 associations, but, overall, the deviations between observation and expectation for the NDDs in this hallmark were quite low.

The distribution of associations across the four omics-layers shows that the transcriptomic data had the most associations (20), followed by the proteomic, methylomic, and genomic layers (14, 9, and 3). Here, the discrepancy between observation and expectation is larger, with the methylomic data showing only 9 associations, whereas 14 are expected, and the transcriptomic and

proteomic layers showing 4 and 3 more associations, respectively, than expected.

Extracellular Matrix Organization and Development

In total, 80 associations were found between communities and the low-level terms for *Extracellular Matrix (ECM)* and *Cytoskeleton Organization*, with the different fibril components *Actin* -, *Collagen* -, and *Keratin Cytoskeleton*, *Cilium* as the bridge between ECM and cytoskeleton, *Cell Adhesion*, *Focal Adhesion*, *Cell Junction*, *Cell Migration* along microtubules, *Cell Differentiation and Growth* (e.g., neuron, axon, dendrite, organelle), *Localization* of cells or proteins, *Organ Development* (brain, muscle, heart, bone, blood vessels), and *Early Development* (embryogenesis and cell fate commitment).

The distribution of the number of associated low-level terms across the four NDDs is according to the expectation that can be derived from the summed number of associations across all low-level terms, with AD showing the highest number of associations (33), followed by PD (26), HD (14), and ALS (7), as given in **Table 5**, with having the highest deviation between observation and expectation for HD.

However, the distribution of associations across the different omics-layers for the hallmark ECM Organization and Development deviates from the expectation for the proteomic and methylomic layers. The highest number of associations can be observed on the methylomic layer, closely followed by the transcriptomic (31, 27) and then by the proteomic and genomic layers (13, 9). Here, the methylomic layer shows a nearly 25% higher number of associations than expected, while the number for the proteomic layer is nearly 30% lower than expected.

Signal Transduction/Transport

This hallmark consisted of the low-level terms *Cell Communication*, *Neuronal Signaling*, *Synapsis*, *Ion- and Voltage-Gated Channel*, *Neurotransmitter Secretion*, *SNARE Binding*, *Receptor Activity and Recycling*, *Axonal Transport*, *Vesicle (exo- and endocytosis, clathrin coat, extracellular exosome)*, *Transmembrane Transport (small molecules, e.g., AA)*, *Trans-Golgi-Network (retrograde)*, *ER to Golgi transport (anterograde)*, and *(Cardiac) Muscle Action Potential*.

The hallmark Signal Transduction/Transport united the most associations between communities and low-level terms (88), having the most associations in AD (34), followed by PD (31), HD (17), and ALS (6). Compared to the number of expected associations, ALS showed a reduction of 4 associations (−40%) and PD, an increase of 5 associations (approximately + 20%) compared to the expectation.

Observing the results per omics-layer, it becomes apparent that not the transcriptomic but the methylomic layer showed the most associations for this hallmark (31). The number of associations in the transcriptomic layer is lower than the

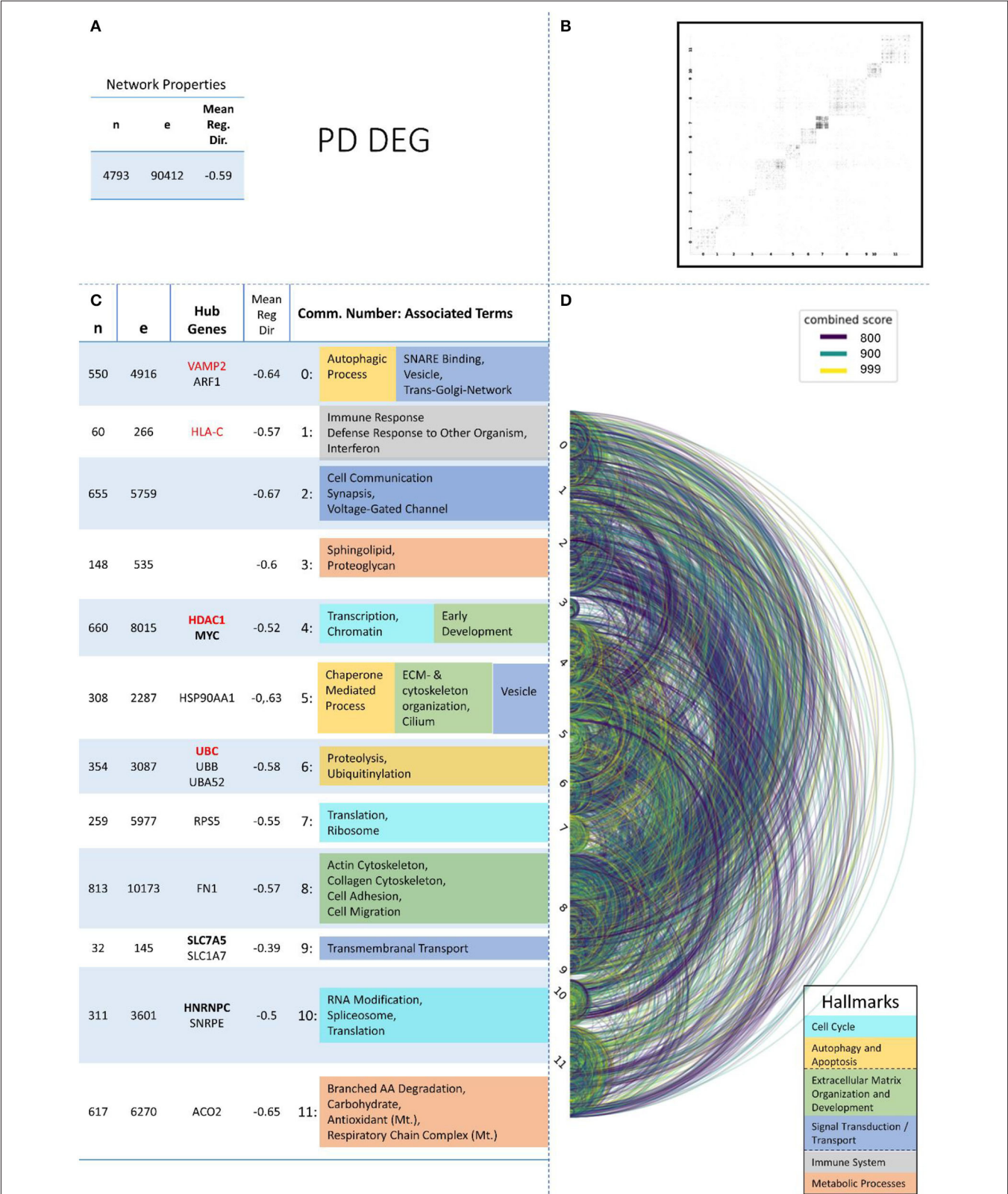


FIGURE 4 | connections with a combined score ≥ 800 between each two genes are also given in a matrix plot **(B)** and an Arcplot **(D)** that are ordered by community. The latter shows the confidence of the connection between two genes additionally by the color of the arc. The general properties of each individual community, as well as their hub genes and the categorization of their functional annotation, are given in the table in Subfigure **(C)**. The connected processes are colored by the associated hallmarks that are also displayed in the bottom right corner.

methylomic layer's associations (24), followed by the proteomic (18) and genomic layers (15), as given in **Table 6**. While the transcriptomic layer shows surprisingly little associations (–22%), the genomic layer, on opposite, shows a surprisingly high number of associations (+50%), in contrast to the expectation.

A closer look at all low-level terms in relation to the individual NDD's omics-layers (see **Supplementary Table 3—Low-Level Term Associations**) also shows that two out of the three associations for *Axonal Transport* are found in the methylomic PD network, and two out of the four *Receptor Activity* associations are found in the AD genomic network.

Looking at the aggregated data per layer in each omics-layer also shows a high number of genomic PD associations (8 out of 88 for Signal Transduction/Transport), far exceeding the overall 4% proportion of low-level terms associated with the PD genomic layer.

At the same time, the proportion of transcriptomic ALS communities associated with the low-level terms of these hallmarks (2 of 88) is only half the proportion that might be expected based on the overall distribution of low-level terms associated with the transcriptomic ALS layer (>5%).

Immune System

Only 28 associations between communities and the low-level terms related to Immune System were found, making it the hallmark with the lowest number of associations. Low-level terms, which were referred to by these communities, were *Immune Response*, *Defense Response to Other Organisms*, *Cytokine*, *Interferon*, *Complement and Coagulation Cascade*, *Inflammation*, and *Leukocyte Activation*.

The highest number of associations was found in AD (13), followed by HD (7), ALS (5), and PD (3), making this the only hallmark in which PD showed the lowest number of associations (see **Table 7**). This number of associations found across all omics-layers in PD is more than 60% lower than expected.

The findings in the aggregation per omics-layers seem less surprising, with the transcriptomic layer showing the most associations (12), followed by the methylomic (7), proteomic (5), and genomic layers (4).

Metabolic Processes

The hallmark Metabolic Processes consisted of the low-level terms *Lipid*, *Cholesterol*, *Sphingolipid*, *Fatty acid oxidation [mitochondrial (Mt.)]*, *Carboxylic Acid (Mt.)*, *Lipoprotein*, *Protein*, *Carbohydrate*, and *Nucleotide*, most of which referred to the respective metabolic processes and of terms like *Glycosylation*, *NADH (Mt.) Homeostasis*, *Respiratory Chain Complex (Mt.)*, and *Antioxidant (Mt.)*, which were tagged with the “Mt.” term if they represent processes that occur in the mitochondrion rather than in the cytoplasm.

Looking at the accumulated associations between communities and low-level terms across the four different NDDs (see **Table 8**), the most associations can be found across the communities of AD (26), followed by PD (20), HD (14), and ALS (7). This distribution across NDDs perfectly matches the expected distribution of associations.

However, the distribution across the four omics-layers is more conspicuous, as Metabolic Processes are the only hallmark having the majority of the associations in the proteomic layer (25). This is closely followed by the transcriptomic (24) and then the methylomic and genomic layers (13 and 5). Following the overall distribution of associations across the omics-layers, only 16, instead of 25, associations were expected across the proteomic layers (+56%) of all NDDs, but 20, instead of 13, associations were expected for the methylomic layers of all NDDs (–35%).

The individual omics-layers per NDD showed that, especially, the proteomic layer of PD and AD had enriched numbers of associations for this hallmark, both with having more than 33% of their community associations to the low-level term in Metabolic Processes, while, overall, only ~18% were expected.

DISCUSSION

Omics-Layer Intersections per Disease

The intersection of genes found in genomic, transcriptomic, proteomic, and methylomic data per disease showed that, while the number of shared genes between the transcriptomic and proteomic level was significantly high in all four investigated NDDs, the significance of the intersections was more heterogeneous in the other comparisons.

Only AD showed a significant number of shared genes in all pairwise intersections of the four analyzed omics-layers. The fact that ALS methylomic and HD genomic data consisted of only two studies and thus had a very small database (61 and 35 genes) may have contributed to the non-significance of pairwise comparisons that considered the methylomic level for ALS and the genomic layer for HD. However, even though the database was much broader for HD methylomic data (885 genes), these genes also stem from only two studies, but showed significant overlaps in all pairwise intersections, except for the one with genomic data. Summarizing, especially those pairwise comparisons with a low number of expected overlapping genes, seemed to not show a significantly large pairwise overlap. All pairwise intersections that are based on two large groups of genes and, therefore, showed an expected number of shared genes ≥ 10 also showed a significantly high number of overlapping genes in these hypergeometric tests (**Supplementary Table 2—Hypergeom Test Per Disease**).

The fact that the effect size was highest for the transcriptomic-proteomic intersection in AD, ALS, and HD and, also, very high

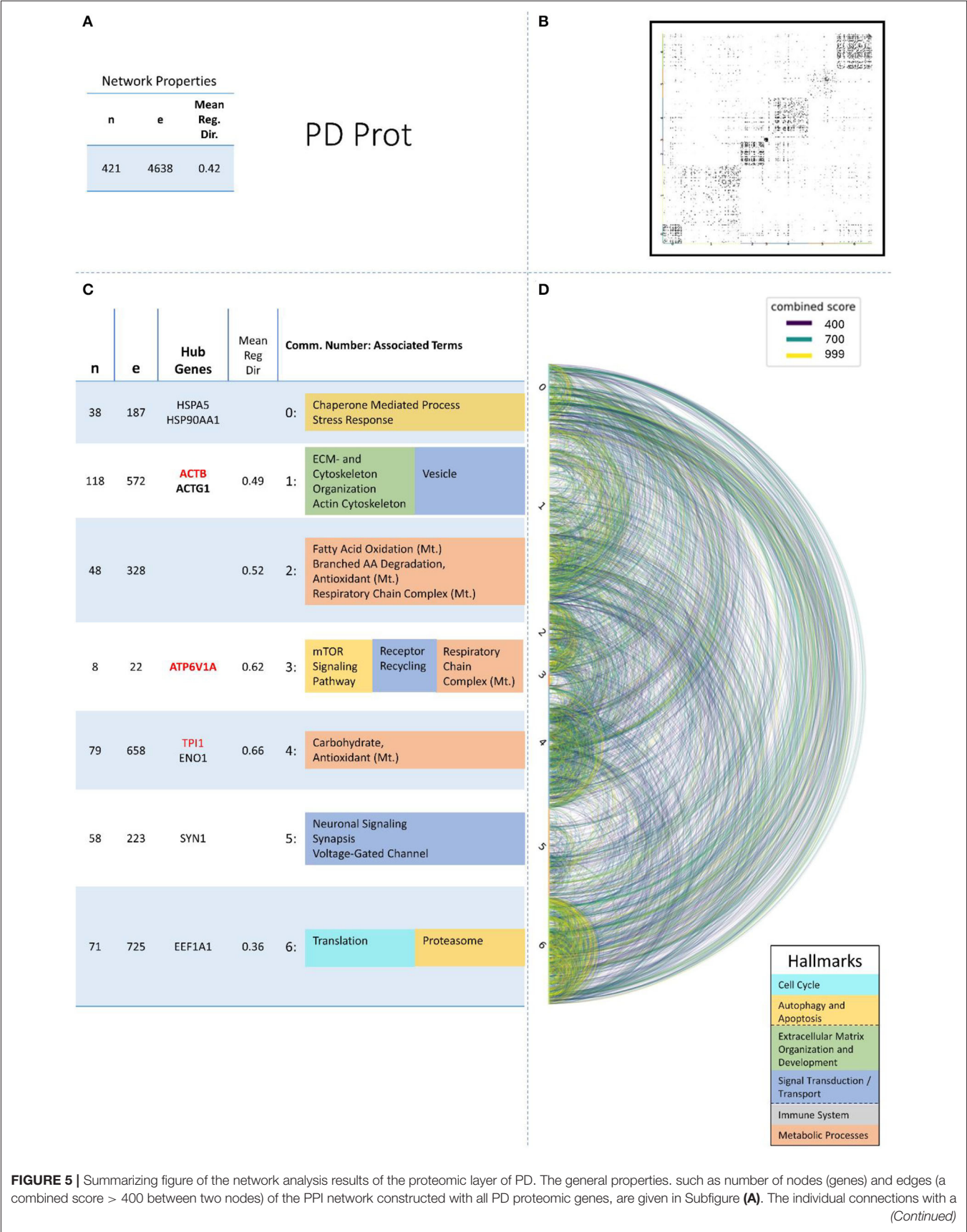


FIGURE 5 | combined score ≥ 400 between each two genes are also given in a matrix plot **(B)** and an Arcplot **(D)** that are ordered by community. The latter shows the confidence of the connection between two genes additionally by the color of the arc. The general properties of each individual community, as well as their hub genes and the categorization of their functional annotation, are given in the table in Subfigure **(C)**. The connected processes are colored by the associated hallmarks that are also displayed in the bottom right corner.

in PD (9.9) seems as if these layers shared the most striking relation in terms of overlapping genes. However, in PD, the effect size is even higher between the transcriptomic and methylomic layers. PD is also the only disease in which not proteomic and transcriptomic layers showed the largest database in terms of including the most genes but the transcriptomic and methylomic data did. Thus, in all NDDs, especially those intersections, showed the largest effect sizes that were based on the omics-layers, with the most genes per NDD. The statement that the transcriptomic and proteomic layers of our data showed high significantly enriched numbers of genes in their overlap in all analyzed NDDs holds true; however, it is, to this point, unclear if the high effect sizes in contrast to the other intersections are due to biological facts or to the broader database for these omics-layers in our data.

A more surprising point is the fact that the mean direction of regulation was vastly unequal to zero for both, the transcriptomic and the proteomic data in PD. This was also the case for the methylomic layer of HD and ALS, but, given that the transcriptomic and proteomic layers of PD are based on much more studies (11 and 7, while 2 studies for HD and ALS methylome), this high absolute mean direction of regulation, in combination with the dichotomy of these values, constitutes an interesting finding. The finding of a mainly (70%) negative direction of regulation for PD transcriptomic differentially expressed genes was already described in a meta-study, focusing only on microarray data (Kelly et al., 2019). However, the reason for this phenomenon remains unclear.

Multi-Omics Conformity

The finding of significant overlaps between the transcriptomic and proteomic data for only three out of four NDDs seems to be surprising and to hint at an extraordinary phenomenon in the posttranscriptional or translational processes in PD. However, given that the mean direction of regulation for the PD transcriptomic data was highly negative (-0.59), while the PD proteomic data were, overall, highly positive (0.42), it is striking that the genes in the intersection of these two omics-layers are still positively correlated, even though not significantly. Thus, this result might show a signal for some altered posttranscriptional behavior in PD in contrast to the other NDDs, but this could also be an artifact of the striking negative mean direction of regulation in the transcriptomic and the similarly strong positive mean direction of regulation in the proteomic data that were discussed earlier.

However, even the highly significant correlations between the transcriptomic and proteomic data in AD, HD, and ALS reached values of $r = 0.283$ (AD) to $r = 0.344$ (ALS), which might seem surprisingly small, following James Watson's simplified version of the central dogma of molecular biology (Watson et al., 1988).

Even though proteins are produced from mRNA, the correlation between mRNA levels and protein abundances is moderate. This non-trivial mRNA–protein relation is a general phenomenon, ranging from yeast to humans (De Sousa Abreu et al., 2009), and can have biological or, simply, technical reasons. Biological reasons can be found both on the posttranscriptional and on the translational levels, where many different mechanisms enhance or repress the synthesis of proteins from a certain copy number of mRNA molecules (Crick, 1958; Varshavsky, 1997; Fire et al., 1998; Kozak, 1999; Glickman and Ciechanover, 2002; Pillai et al., 2007; Kurreck, 2009; Maier et al., 2009; Chursov et al., 2013; Komar, 2016; Liu et al., 2016; McShane et al., 2016; Lau et al., 2018).

Protein-Protein Interaction Networks The Hub Gene HDAC1

On the transcriptomic level of all 4 diseases communities were found, that showed Histone Deacetylase 1 (*HDAC1*) as one of their hub genes. *HDAC1* deacetylates lysine residues on the N-terminal part of the core histones H2A, H2B, H3, and H4, thereby contributing to epigenetic silencing of active chromatin (Carroll et al., 2018). *HDAC1* plays an important role in transcriptional regulation, cell cycle progression, and developmental events. This was also reflected in the low-level terms of the associated communities of all four diseases: In AD and PD, they referred to transcription, chromatin, and early development, together with the hubgenes *TP53*, *EP300*, and *MYC*, respectively. In ALS, the low-level terms referred to regulation of cell cycle, transcription, and chromatin, together with the hub gene *CCND1*. HD showed low-level terms about cell differentiation, cell and early development, together with the hubgenes *MYC* and *TP53*.

All the hubgenes that were related to *HDAC1* are involved in similar processes like regulation of cell cycle, cell growth and migration, and development by influencing the chromatin formation (*EP300*), binding to DNA as transcription factors (*TP53*, *MYC*) or regulating other proteins (*CCND1*). Beyond the aforementioned similarities, researchers can, maybe, find differences in how the diseases developed by comparing the functions of the hub genes and their StringDB protein networks per disease.

The Hub Genes BIN1, ABCA7, and PICALM

BIN1, *ABCA7*, and *PICALM* were found to be among the three most central nodes in, at least, three of our four centrality measures and were, therefore, defined as hub genes in our analysis for the AD genomic community that was associated with the two processes, proteolysis and ECM/cytoskeleton. Approximately, 38 genes were involved in this network, showing 284 interactions giving an average node degree (N_d) of 14.9.

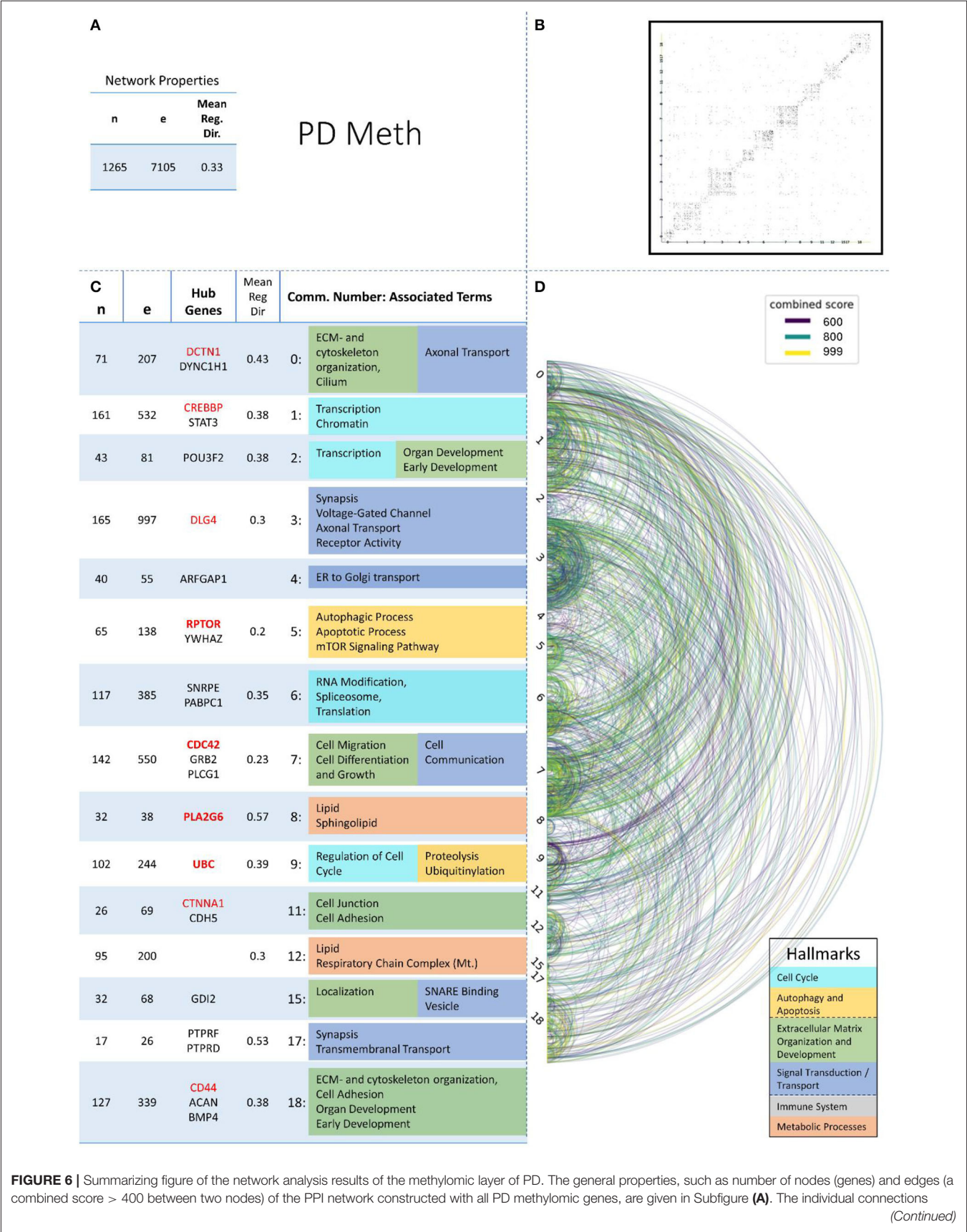


FIGURE 6 | with a combined score ≥ 600 between each two genes are also given in a matrix plot **(B)** and an Arcplot **(D)** that are ordered by community. The latter shows the confidence of the connection between two genes additionally by the color of the arc. The general properties of each individual community, as well as their hub genes and the categorization of their functional annotation, are given in the table in Subfigure **(C)**. The connected processes are colored by the associated hallmarks that are also displayed in the bottom right corner.

TABLE 3 | Accumulated number of low-level terms per NDD and per omics-layer for the hallmark Cell Cycle.

		Per disease				Total	Per omics-layer			
		AD	PD	ALS	HD		SNP	DEG	Prot	Meth
Low-level term										
Cell cycle	Regulation of cell cycle	2	1	1	1	5	0	2	0	3
	Spindle apparatus	1	0	0	0	1	0	1	0	0
	DNA repair	3	0	0	1	4	1	1	0	2
	Transcription	2	4	1	1	8	1	3	0	4
	RNA modification (degradation, processing, transport)	4	2	1	3	10	1	3	3	3
	Spliceosome	2	2	1	2	7	0	2	3	2
	Translation	3	4	2	3	12	0	5	4	3
	Mitochondrial translation	2	0	0	1	3	0	1	1	1
	Chromatin (organization, binding, modification)	2	2	1	1	6	1	3	0	2
Total		21	15	7	13	56	4	21	11	20
Expected		22	17	6	11	56	6	20	13	17

The column for the total number of low-level terms found refers to both the sum across all four NDDs and the sum across all four omics-layers. This table is intended to provide summary information about the accumulated data—the number of individual low-level terms per omics-layer for each disease can be found in the **Supplementary Table 3**. SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level.

TABLE 4 | Accumulated number of low-level terms per NDD and per omics-layer for the hallmark autophagy and apoptosis.

		Per disease				Total	Per omics-layer			
		AD	PD	ALS	HD		SNP	DEG	Prot	Meth
Autophagy and apoptosis	Low-level term									
	Autophagic process	2	2	2	1	7	1	4	1	1
	Chaperone mediated process	2	2	1	2	7	0	4	3	0
	Proteolysis	2	2	1	0	5	1	2	1	1
	Ubiquitinylation	1	2	1	2	6	0	3	1	2
	Proteasome	2	1	1	2	6	0	1	4	1
	Stress response	2	1	0	0	3	1	1	1	0
	Apoptotic process	1	1	1	2	5	0	3	0	2
	mTOR signaling pathway	3	2	1	0	6	0	1	3	2
NfκB signaling pathway	1	0	0	0	1	0	1	0	0	
Total		16	13	8	9	46	3	20	14	9
Expected		18	14	5	9	46	5	16	11	14

The column for the total number of low-level terms found refers to both the sum across all four NDDs and the sum across all four omics-layers. This table is intended to provide summary information about the accumulated data—the number of individual low-level terms per omics-layer for each disease can be found in the **Supplementary Table 3**. SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level.

Mutations in these three genes are well-known risk factors in AD, and all the three of them are tightly connected to amyloid β metabolism.

BIN1 or Bridging Integrator-1 is a key player in the control of plasma membrane shaping. The depletion of BIN1 increases cellular β -site APP-cleaving enzyme 1 (BACE1) levels through impaired endosomal trafficking and reduced lysosomal degradation, resulting in an increased A β production.

ABCA7 is a member of the superfamily of ATP-binding cassette (ABC) transporters, which transport various molecules

across extra- and intra-cellular membranes. As with BIN1, ABCA7 could be shown to be involved in the generation and processing of amyloid β peptides (Sato et al., 2015), but also in the lipid metabolism and in phagocytosis and immune response (Dib et al., 2021).

PICALM, the phosphatidylinositol-binding clathrin assembly protein, also affects AD risk primarily by modulating production, transportation, and clearance of β -amyloid (A β) peptide, but other A β -independent pathways are discussed, including tauopathy (Dean and Shaw, 2010), synaptic dysfunction (Jahn

TABLE 5 | Accumulated number of low-level terms per NDD and per omics-layer for the hallmark Extracellular Matrix Organization and Development.

		Per disease				Per omics-layer				
		AD	PD	ALS	HD	Total	SNP	DEG	Prot	Meth
Extracellular matrix organization and development	ECM- and cytoskeleton organization	6	5	2	2	15	3	2	4	6
	Actin cytoskeleton	2	2	2	2	8	0	4	4	0
	Collagen cytoskeleton	2	1	1	1	5	0	4	0	1
	Keratin cytoskeleton	0	0	0	1	1	0	0	1	0
	Cilium	2	3	0	0	5	1	2	0	2
	Cell adhesion	4	3	0	2	9	1	3	2	3
	Focal adhesion	2	0	0	0	2	0	1	0	1
	Cell junction	0	1	0	0	1	0	0	0	1
	Cell migration (along microtubules)	1	2	0	1	4	0	1	0	3
	Cell differentiation and growth (e.g., neuron, axon, dendrite, organelle)	6	1	1	3	11	1	4	1	5
	Localization (cellular, of protein...)	1	1	0	1	3	0	1	0	2
	Organ development (brain, muscle, heart, bone, blood vessels)	4	3	1	0	8	2	2	1	3
	Early development (embryogenesis and cell fate commitment)	3	4	0	1	8	1	3	0	4
Total		33	26	7	14	80	9	27	13	31
Expected		31	24	9	16	80	9	28	19	24

The column for the total number of low-level terms found refers to both the sum across all four NDDs and the sum across all four omics-layers. This table is intended to provide summary information about the accumulated data—the number of individual low-level terms per omics-layer for each disease can be found in the **Supplementary Table 3**. ECM, Extracellular Matrix; SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level.

and Scheller, 2006), disorganized lipid metabolism (Eisenstein, 2011), immune disorder (Carter, 2010), and disrupted iron homeostasis (Xu et al., 2014).

These genes, together with the other 35 genes found to interact closely with the two low-level terms proteolysis and ECM/cytoskeleton, can now be studied in more detail by specialists in the field with respect to the relationship between the known functions of the genes and the processes in which they are involved. This combination of all three genes was only found in AD, and any of these three was found as a hub gene only in the AD genomic network.

However, *BIN1* was also present in the transcriptomic [community 0 (C0)], proteomic (C1), and methylomic (C7) levels of PD, representing mainly ECM and Development and Signal Transduction/Transport processes but also one for Autophagy and Apoptosis. *PICALM* was also part of C0 in the PD transcriptomic network. In HD, the proteomic network showed both, *BIN1* and *PICALM* in C0, which represent Signal Transduction/Transport processes like SNARE Binding and Vesicle. In ALS, none of these genes were involved in any considered community.

The Hub Gene APOE

APOE, the well-known risk gene for late onset AD, was found on the genomic level in AD in a community associated with

the low-level terms cholesterol and lipoprotein, but also on the transcriptomic level of ALS associated with the low-level terms complement/coagulation cascade and immune response.

The complement cascade stimulates phagocytes to clear microbes and damaged cell materials, it promotes inflammation, and attacks the pathogen's cell membrane. It, thus, combines innate and adaptive immune responses and additionally integrates the coagulation system into the defense response against other organisms (Kenawy et al., 2015). In addition, some of the early components of this cascade play a beneficial role in synapse elimination during the development of the nervous system, although excessive complement-mediated synaptic pruning in the adult or injured brain may be detrimental in multiple neurodegenerative disorders (Schartz and Tenner, 2020). A correlation between ALS and the complement system has been frequently described (Carpanini et al., 2019; Kjældgaard et al., 2021), but a connection to *APOE* still remains elusive.

Here, our study may provide a good starting point for exploring the community to which *APOE* belongs and the genes to which it is linked in this network. The fact that *APOE* is among the top three nodes according to all four measures of centrality implies that it plays an important role in this network, as it is among the three most interconnected genes, has direct links to other very important genes in the network, and plays an important role in mediating between pairwise-linked genes

TABLE 6 | Accumulated number of low-level terms per NDD and per omics-layer for the hallmark Signal Transduction/Transport.

Low-level term		Per disease				Total	Per omics-layer			
		AD	PD	ALS	HD		SNP	DEG	Prot	Meth
Signal transduction/ transport	Cell communication	4	4	2	3	13	3	3	2	5
	Neuronal signaling	1	1	0	0	2	0	1	1	0
	Synapsis	6	5	0	2	13	3	3	3	4
	Ion channel	1	0	0	2	3	0	1	0	2
	Voltage-gated channel	4	2	0	1	7	1	2	0	4
	Neurotransmitter secretion	2	1	0	2	5	1	2	2	0
	SNARE binding	2	3	1	1	7	1	2	3	1
	Receptor activity	3	1	0	0	4	2	0	0	2
	Receptor recycling	1	1	0	0	2	0	0	2	0
	Axonal Transport	0	2	0	1	3	0	0	0	3
	Vesicle (exo- endocytosis, clathrin coat, extracellular exosome)	5	6	2	2	15	2	4	5	4
	Transmembranal transport (small molecules, e.g., AA)	2	3	0	1	6	1	3	0	2
	Trans-Golgi-network (retrograde)	1	1	1	1	4	0	2	0	2
	ER to Golgi transport (anterograde)	1	1	0	0	2	0	1	0	1
	(Cardiac) muscle action potential	1	0	0	1	2	1	0	0	1
Total		34	31	6	17	88	15	24	18	31
Expected		34	26	10	18	88	10	31	21	27

The column for the total number of low-level terms found refers to both the sum across all four NDDs and the sum across all four omics-layers. This table is intended to provide summary information about the accumulated data—the number of individual low-level terms per omics-layer for each disease can be found in the **Supplementary Table 3**. SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level; AA, amino acids.

TABLE 7 | Accumulated number of low-level terms per NDD and per omics-layer for the hallmark Immune System.

Low-level term		Per disease				Total	Per omics-layer			
		AD	PD	ALS	HD		SNP	DEG	Prot	Meth
Immune system	Immune response	1	1	1	1	4	0	2	0	2
	Defense response to other organisms	2	1	1	1	5	1	3	0	1
	Cytokine	2	0	0	1	3	1	0	0	2
	Interferon	2	1	1	2	6	1	3	0	2
	Complement and coagulation cascade	2	0	2	2	6	0	3	3	0
	Inflammation	2	0	0	0	2	0	1	1	0
	Leukocyte activation	2	0	0	0	2	1	0	1	0
	Total	13	3	5	7	28	4	12	5	7
Expected		11	8	3	6	28	3	10	7	9

The column for the total number of low-level terms found refers to both the sum across all four NDDs and the sum across all four omics-layers. This table is intended to provide summary information about the accumulated data—the number of individual low-level terms per omics-layer for each disease can be found in the **Supplementary Table 3**. SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level.

in the network, while it is also among the three nodes that have the shortest paths to all other nodes in the network. Although APOE has not been previously reported to be associated with the complement and coagulation cascades, it is strongly associated with a subnetwork of genes that are significantly overrepresented in this very process. About one third of the directly linked 19 genes are directly involved in the complement cascade (C1QB,

C1QC, C3, C4A, C4B, CFH); another third is involved in cholesterol synthesis and transport (ABCA1, ABCB1, HMGCR, LDLR, MSR1, NPC2); A2M disrupts inflammatory cascades but also is involved in the lipoprotein metabolism; BACE2, CTSB, and PSEN are involved in the proteolytic processing of the amyloid precursor protein; CP is a metalloprotein that binds most of the copper in plasma and is involved in the peroxidation

TABLE 8 | Accumulated number of low-level terms per NDD and per omics-layer for the hallmark Metabolic Processes.

		Per disease				Per omics-layer				
		AD	PD	ALS	HD	Total	SNP	DEG	Prot	Meth
Metabolic processes	Lipid	2	2	0	1	5	0	2	0	3
	Cholesterol	2	1	0	1	4	2	1	0	1
	Sphingolipid	1	2	0	0	3	0	2	0	1
	Fatty acid oxidation (Mt.)	2	1	0	3	6	0	1	3	2
	Carboxylic acid (Mt.)	1	0	1	1	3	0	1	1	1
	Lipoprotein	2	0	1	1	4	1	0	3	0
	Protein	0	0	1	0	1	0	1	0	0
	Branched AA degradation	2	2	0	1	5	0	3	2	0
	Proteoglycan	1	2	0	0	3	1	2	0	0
	Carbohydrate	3	2	1	2	8	0	2	4	2
	Glycosylation	1	0	0	0	1	0	1	0	0
	Nucleotide	3	1	0	0	4	1	1	1	1
	NADH (Mt.)	1	0	0	0	1	0	0	1	0
	Homeostasis	1	0	0	1	2	0	1	1	0
	Antioxidant (Mt.)	2	3	1	0	6	0	2	4	0
	Respiratory chain complex (Mt.)	2	4	2	3	11	0	4	5	2
	Total	26	20	7	14	67	5	24	25	13
	Expected	26	20	7	14	67	7	23	16	20

The column for the total number of low-level terms found refers to both the sum across all four NDDs and the sum across all four omics-layers. This table is intended to provide summary information about the accumulated data—the number of individual low-level terms per omics-layer for each disease can be found in the **Supplementary Table 3**. Mt, mitochondrial; SNP, genomic level; DEG, transcriptomic level; Prot, proteomic level; Meth, methylomic level; AA, amino acids.

of Fe (II) transferrin to Fe (III) transferrin. PCYOX1 cleaves the thioether bond of prenyl-L-cysteines, and PSRC1 may participate in p53-mediated growth suppression.

Discussion of Methodological Approach

We attempted to limit the data included in this study to those derived from brain tissue whenever possible. For this reason, and because of the generally greater availability of data, we analyzed data in this study mainly from patients in the late stages of their respective NDD. This results in better comparability and less noise within the data but should be considered in the analysis and conclusions drawn from these studies, as effects occurring mainly in early stages of disease progression may not be apparent in this analysis.

It should also be noted that we included only data of studies that were published and, furthermore, available in PubMed, Google Scholar, the GWAS Catalog (Buniello et al., 2019), the GEO database (Barrett et al., 2013), the Expression Atlas (Papatheodorou et al., 2018), PDMethDB (Wang C. et al., 2020) or the EWAS Atlas (Li M. et al., 2019). Therefore, as pointed out in Pan et al. (2005), this introduces some language bias, as our methodology did not include searching for results published in other than the English language in, e.g., local journals, which was shown to influence the strength of *p*-values between, e.g., Chinese and non-Chinese studies (Pan et al., 2005; Tang, 2005). Also, we did not consider unpublished as well as insignificant data. However, as our approach was mainly aimed for giving a comprehensive and broad overview and, therefore, mainly focused on those genes that were found as significant in, at least,

two experiments, regardless of the exact strength of the actual *p*-value, we consider this problem of publication bias as a minor one for our approach as the number of overexaggerated and false-positive disease associations should be strongly reduced by this methodology.

For some approaches used in this study, it was necessary to choose between different possible approaches, e.g., for the hallmarks to be used or the definition of hub genes. In addition, the network creation of the louvain algorithm is non-deterministic and, therefore, subject to a random influence in the creation of the networks. To minimize this random influence, we applied the louvain algorithm with the input shuffled 100 times anew for each of the analyzed networks, and then chose the iteration that produced the highest modularity. With this approach, we found that the modularity between the different iterations did not change much; however, taking the best of 100 runs makes the results of the louvain community creation more reliable.

The definition of hallmarks and hub genes involves some flexibility, so we have attempted to define hallmarks in light of previous definitions of hallmarks for neurodegeneration (e.g., Ramanan and Saykin, 2013) and of our actual observed subprocesses in the functional analyses. As there are myriads of centrality measurements for nodes in a network, we took centrality measurements into account that were connected to the number of direct links between a node and other nodes, the mediation role of a node in a network, and to the sum of the shortest paths to all other nodes in the network, respectively (Freeman, 1977, 1978; Freeman et al., 1979). In addition,

we chose to include the eigenvector centrality of each node (Newman, 2010; Bonacich, 2015), which gives a centrality score to each node that is proportional to the sum of the centrality scores of each node's neighbors to cover some varieties of ways for defining centrality of a node in a network.

CONCLUSION

The results of this study present a comprehensive picture drawn from the results of the analysis of 234 studies across four neurodegenerative disorders and four omics layers. Roughly summarizing, the 69 low-level terms we chose to categorize into 6 hallmarks show a significantly different distribution across the different omics layers, but not across the four diseases, which might be due to the inclusion of mainly late-stage disease data for broadening the database. The number of genes in the intersection of two diseases and the correlation of their regulatory direction was mainly distinctive between the transcriptomic and proteomic levels.

However, the possibilities for further analysis arising from this study are, at least, as important as the results just mentioned. For example, the communities found, and the processes associated with them can be compared with regard to the direction of regulation of the communities, the presence and absence of processes at certain levels/diseases, or, also, with regard to the hub genes found, as we have already exemplified with three examples in the discussion. Consequently, we not only provide an overview—the big picture of neurodegeneration—but also many new starting points for further research going deeper into individual communities or even genes within these communities. We achieve this by providing comprehensive illustrations as well as all relevant tables for exploring specific communities and their associated genes. Ultimately, identifying the hub genes and the other genes involved in the different clusters may make it easier to develop therapeutics by both getting a better idea of which

protein can be targeted in a chosen process but, at the same time, whether too many other important processes could be disturbed by the potential inhibition or amplification.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

NR and SK wrote the manuscript, designed the research question, performed the analysis, wrote code, interpreted the data, and visualized the results. SS and RH contributed to writing, interpreting the data, and editing the manuscript. SG conceptualized the research, contributed to writing and interpretation, edited the manuscript, supervised the study, and acquired the funding. All authors have read and agreed to the published version of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnagi.2022.866886/full#supplementary-material>

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Chapter 5

Proceedings of this work

Hundreds of NDDs exist, and with few exceptions, their underlying causes remain unknown (Przedborski, Vila, & Jackson-Lewis, 2003). Even when the origin can be pinpointed, as in the case of HD, the exact cellular mechanisms triggering neurodegeneration are still largely speculative.

NDDs impose a substantial socioeconomic burden, affecting health-care systems, economies, families, and caregivers. Early detection, medication, or proactive prevention measures are crucial to mitigate this burden and improve the quality of life for individuals afflicted with these debilitating conditions. However, as demonstrated in previous sections, the origins and progression of NDDs remain elusive despite ongoing research, as they result from a complex interplay of genetic, environmental, and lifestyle factors (Marras, Canning, & Goldman, 2019).

Even patients with similar disease progression are challenging to compare due to varying life circumstances. A major challenge further complicating research efforts is that these diseases manifest in the intricately structured and difficult-to-access brain. Due to the BBB, direct medication is almost impossible, limiting research to proxy tissues such as blood or cerebrospinal fluid and post-mortem brain tissues.

The aim of this thesis was to identify commonalities but also differences in the development of the four most prominent NDDs, AD, PD, HD, and ALS in a multi-omics approach by analyzing publicly available datasets.

5.1 Choice of NDDs

In our study, we focused on AD, PD, HD, and ALS. These diseases were selected because they represent prominent proteinopathies of the CNS with many shared features, despite their distinct phenotypes, as illustrated in previous sections.

HD, being a clearly monogenic disease, was included to shed light on pathways that might also be implicated in the origins of the other three conditions.

Except for monogenic NDDs like HD, the diagnosis of NDDs is generally challenging due to the absence of specific disease markers. This results in data that may be ambiguous and difficult to interpret.

For this reason, two other prominent diseases Frontotemporal Dementia (FTD) and Multiple Sclerosis (MS) were not included in our study. FTD can easily be mistaken for other forms of dementia especially AD, normal aging or even psychiatric disorders (Cycyk & Wright, 2008; D. Ma, Lu, Popuri, Wang, & Beg, 2020; H. D. Nguyen, Clément, Planche, Mansencal, & Coupé, 2023), while the diagnosis of MS is only based on the principle of exclusion (Calabrese et al., 2019; Solomon et al., 2023).

Another factor influencing our choice was the availability of data. Especially AD and PD, given their high prevalence and impact, are among the most extensively studied NDDs and provide a wealth of data to analyze.

5.2 Choice of approach

The complexity of NDDs demands thorough investigations from all possible angles. Hundreds of genes, transcripts, and proteins have been implicated in the characteristic features of NDDs, the most prominent of which include inflammation, impaired protein folding and degradation, defective mitochondria, deregulated apoptosis, and inadequate stress response, as emphasized in previous sections.

These clinical features are interconnected and form complex molecular networks, the exploration of which is only feasible in a computational approach. Publicly available databases offer extensive collections

and quantifications of the accumulated knowledge about genes and proteins involved in NDDs.

To gain a deeper understanding of NDDs and their interconnected pathways, circuits, and networks, our initial approach was to detect shared patterns between the four selected NDDs at the genomics, transcriptomics, and proteomics levels.

In a second step, differences in disease origin and progression were investigated to find specific processes in individual diseases.

While achieving true data integration to correlate different types of data and understand their interactions in influencing biological processes or disease states remains a challenge due to the lack of adequate tools (La Cognata, Morello, & Cavallaro, 2021), our data provide hints of potential connections and new patterns.

This will be illustrated with the case study of sleep and disrupted circadian rhythms in chapter 7, where we found disease-specific disruptions in all four diseases. These disruptions can originate from deregulated sleep patterns and metabolism, both of which are highly prevalent in industrialized countries and contribute to the symptoms of neurodegeneration.

In a case study our work shows how to proceed with the provided data. The results of this case study are pointing to the importance on restoring healthy sleep patterns in order to prevent or at least prolong early disease stages.

5.3 Choice of Omics-levels

In the field of omics, various layers or types of data can be analyzed to gain insights into biological systems. For our work we chose to explore the genomics, transcriptomics, proteomics and methylomics level, as shown in detail in the introduction.

The genomics level represents the entire genome, including its DNA sequence and its variations such as SNPs (see paragraphs 3.1 and 3.1.1). Transcriptomics focuses on RNA transcripts produced in a cell or tissue, including mRNA, ncRNA, and alternative splicing events (see paragraphs 3.2 and 3.2.1). As we only included genes that could

be mapped to the HUGO nomenclature, we excluded all ncRNAs and focused solely on the differentially expressed mRNA.

The proteomics level aims to characterize the entire complement of proteins present in a cell, tissue, or organism. This includes protein abundance, modifications (such as phosphorylation or glycosylation), and interactions (see paragraphs 3.3 and 3.3.1). Again, our study concentrated on the different amounts of protein in patients' tissue compared to controls, excluding modified proteins. The epigenomics level studies chemical modifications to DNA and histone proteins that regulate gene expression without altering the underlying DNA sequence. This includes DNA methylation, histone modifications, regulatory ncRNAs, and chromatin remodeling (see paragraphs 3.4 and 3.4.1). Due to sparse data availability and for reasons of comparability, we decided only to include methylomics data.

Integrating data from these omics levels holds promise for elucidating disease pathways, but challenges remain in integrating and interpreting diverse datasets. Current limitations include insufficient data and inadequate computational tools for meaningful integration of omics data. Standardized bioinformatic approaches and improved statistical methods are needed to extract biological insights effectively (La Cognata et al., 2021).

Moreover, comprehensive datasets covering all disease stages, not just advanced stages, are essential for thorough understanding and interpretation of omics data in NDDs.

While the chosen levels already give a good overview over involved disease pathways, in future it would be interesting to exploit the metabolomics levels to get insights into cellular processes and metabolic pathways.

Especially, focusing on the lipidomics and glycomics level could shed light on lipid and carbohydrate pathways implicated in complex diseases. Lipidomics characterizes the lipid composition, abundance, and distribution present in biological samples (Gross, 2017), whereas glycomics studies the structure, composition, and function of complex carbohydrates (R. D. Cummings & Pierce, 2014). As complex diseases are all connected to a derailed metabolism, especially lipid and carbohydrate pathways, these levels could lead to

greater insights into disease origin, progression and maybe prevention.

For example lipidomic analyses performed on AD tissues have highlighted inflammatory processes with increased levels of phospholipase A2 and lipid peroxidation products (Moses et al., n.d.). The identification of lipids derived from docosahexaenoic acid (DHA), such as neuroprotectin D1, which exhibit potent anti-inflammatory, anti-apoptotic, and neuroprotective properties (Hong, Gronert, Devchand, Moussignac, & Serhan, 2003), further emphasizes the potential significance of lipids in neurodegenerative conditions.

Furthermore, disruptions in the brain microenvironment, including dysregulation of proteins involved in glycolysis, mitochondrial energy metabolism, and lipid metabolism, have been identified (Butterfield, Boyd-Kimball, & Castegna, 2003). These findings, coupled with the recognition of the APOE allele ($\epsilon 4$) as a risk factor for LOAD, which is known to be associated with abnormal sterol, sphingolipid and sulfatide metabolism in brain (Bandaru et al., 2009), underline the importance of investigating lipid and carbohydrate disturbances in the progression of AD.

Ultimately, the availability of data and the ability to map all selected omics layers to the same vocabulary (gene and protein names) were the reasons for selecting the four omics layers for the analyses. Despite data limitations, investigating these levels could yield valuable insights, especially in confirming findings related to deregulated major pathways like the AMP-activated protein kinase (AMPK) or the mechanistic target of rapamycin (mTOR) pathway or the closely related circadian rhythm.

5.3.1 Discussion of GWAS data

Intersecting the genes associated with all four NDDs on the genomics level surprisingly revealed no shared risk genes. Even after excluding the only true monogenetic disease, HD, no shared genes could be detected among AD, PD, and ALS.

This lack of overlap may be partly attributed to the varying amount of data, as there is significantly more available data for AD and PD compared to the rarer ALS. Furthermore, the GWAS catalog, the resource genomic data was extracted from, lists SNP-disease

associations conservatively, showing only those with a p-value $\leq 5.0 \times 10^{-8}$. However, these findings also align with existing literature (Maselli et al., 2023; Wainberg, Andrews, & Tripathy, 2023; Wightman et al., 2021). Unlike what is observed in other diseases such as neuropsychiatric (X. Zhu, Need, Petrovski, & Goldstein, 2014) or autoimmune disorders (Richard-Miceli & Criswell, 2012), there is minimal overlap in genetic susceptibility loci among NDDs.

Even when risk genes are shared across different diseases, it cannot be automatically assumed that they affect the same pathological pathways or have the same disease-promoting effects. Variations within a single gene, such as different haplotypes, can have opposing effects on disease susceptibility.

For instance, APOE in AD is disease-promoting only in its $\epsilon 4$ variant, while the $\epsilon 2$ variant appears to be protective. Interestingly, one of the 12 shared risk genes for AD and PD is APOE. However, in PD, the APOE $\epsilon 2$ allele, rather than the APOE $\epsilon 4$ allele, was found to be positively associated with the disease (X. Huang, Chen, & Poole, 2004).

Pleiotropic genes, which influence two or more seemingly unrelated phenotypes, further complicate the determination of gene function. For example, the hexanucleotide repeat expansion in the C9orf72 gene, associated with ALS, also plays a significant role in FTD. Although these diseases co-occur in some families, suggesting shared pathophysiology, they exhibit distinct characteristics (phenotypes) and developmental patterns (De Jager, Yang, & Bennett, 2018).

These complexities highlight the intricate nature of the emergence of NDDs. While they may share similar features in later stages, their genetic origins appear to vary. With the recent launch of data from GTEx and the eQTL consortium (see paragraph 3.4), future research could explore how SNPs in different NDDs influence gene expression via eQTLs. This may reveal whether different SNPs ultimately disrupt the same biological pathways, despite originating from distinct genes. The findings are likely to be highly tissue- or cell type-specific.

5.3.2 Discussion of transcriptomics data

Transcriptomic data is generally more abundant than e.g. proteomics and methylomics, due to well-established and cost effective techniques like RNA-seq or microarrays. On the one hand, this makes the data easier to compare, especially as they are typically globally assessed. On the other hand, the overrepresentation analyses of an abundance of data, especially in case of very well-studied diseases, are typically returning a vast number of results that are hard to reduce to relevant terms. It is not trivial to interpret them in a meaningful yet unbiased manner. The affinity propagation or set cover methods offered by WebGestalt (Liao, Wang, Jaehnig, Shi, & Zhang, 2019) are objective ways of reducing these sets of results, yet it is not guaranteed that all relevant terms are still included. By reducing data in the mathematical most meaningful way it is possible to lose some terms that might have hinted to some biologically important processes. However, doing this subjectively with a desired outcome in mind is obviously also inappropriate.

Therefore, for paper two, after an initial screening of all results and the literature we defined a number of hallmarks to classify a vast number of terms found throughout the analysis and assigned them then in a second iteration to these terms throughout all diseases and omics layers to have a quantifiable measure that is still informed by the current literature and findings on the topic of NDDs (see also paragraph 6.1). In general, overrepresentation analyses are highly depended on the quality and comprehensiveness of the underlying databases such as Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa, Furumichi, Tanabe, Sato, & Morishima, 2017) or StringDB (Szklarczyk et al., 2023) and these databases are to date still very broad. They do not differentiate between different cell types nor do they quantify the effects that single players in a pathway have on each other.

A more biological problem of transcriptomic data is, that they are usually taken from bulk tissue. Cell type specific effects are masked or even cancelled out by this approach. Only the mean effect across the whole assessed tissue can be investigated, but single cell type effects could easily be overlooked.

5.3.3 Discussion of proteomics data

On the proteomics level, only four genes intersected. Overall, not many proteins were found. This may be attributed to several technical challenges associated with proteomics, which can impact the reliability and reproducibility of results.

Firstly, the proteome is highly complex, with a vast number of proteins exhibiting diverse structures, functions, and expression levels. Proteomics techniques rely mostly on mass spectrometry, and identifying peptides with high accuracy and sensitivity remains challenging, particularly for low-abundance proteins and peptides with overlapping mass spectra (Aslam et al., 2016). High-abundance proteins can mask the detection of low-abundance proteins, making it difficult to identify and quantify all proteins present in a sample.

Additionally, proteins undergo various post-translational modifications, such as phosphorylation, glycosylation, and acetylation, which can significantly impact their structure, function, and interactions. Detecting and characterizing these post-translational modifications adds complexity to proteomics analysis (Van Riper et al., 2013).

Lastly, variability in experimental conditions and data analysis strategies can affect the reliability and reproducibility of results. Variations in sample preparation, instrument settings, and data processing pipelines can introduce inconsistencies and biases, making it challenging to compare results across studies or laboratories.

5.3.4 Discussion of epigenetics data

In Paper 2, we integrated an extra layer of analysis to enable the comparison of epigenetic regulatory directions. This was undertaken to explore instances where a gene of interest exhibited differential expression at either the transcriptomics or proteomics level.

However, at least in the context of our analysis on disruptions of the circadian clock, the gene lists were too sparse to provide meaningful insights. Hardly any gene was found on 2, let alone 3, levels and therefore could not be examined in terms of their regulatory direction or other contexts.

As pointed out in the introduction, regulation of gene expression

during transcription and translation processes is still a vast field of investigation with many unknown processes, so for comparability reasons, we concentrated only on DNA methylation detection methods which naturally limited the amount of data obtained. Also, global methylomic assessments have only gained significant momentum in the past 5 to 10 years as can be seen in Fig. 5.1

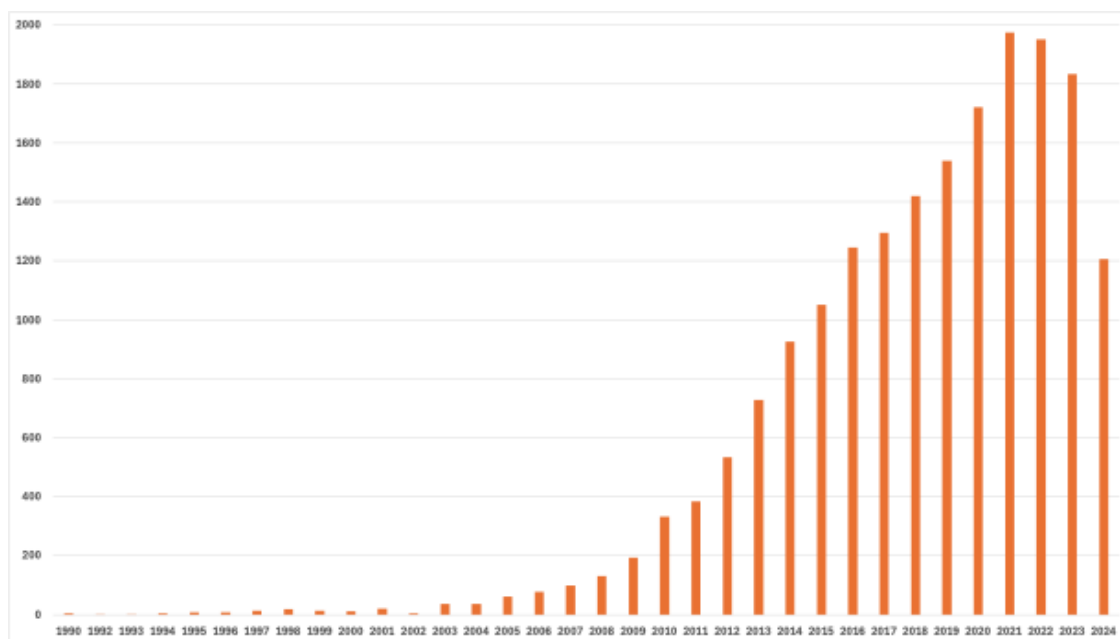


Figure 5.1: Studies published in PubMed concerning NDDs and epigenetics from 1990 to Aug 2024

Global methylomic assessments have only gained significant momentum in the past 5 to 10 years

Chapter 6

Defining hallmarks of neurodegeneration

Complex diseases like cancer, cardiovascular, autoimmune and neurodegenerative diseases, diabetes, and depression are daunting in the breadth and scope of their diversity, spanning origin, pathology, and response to therapy. Given the overwhelming multiplicity of disease-inducing conditions and pathways, defining hallmarks as a conceptual scaffold can help to distill this complexity into an increasingly logical science, where significant disease-promoting pathways can be distinguished and investigated in more detail.

The complexity of NDDs is evident in the diverse genotypes and phenotypes observed in patients. While the gradual loss of neurons due to plaque formation and associated inflammatory processes is a common feature across all NDDs, the pathways leading to this outcome appear to be numerous.

Disruptions in regulation at both the DNA and protein levels result from altered cell-cell communication and intracellular signal transduction, leading to changes in signaling pathways associated with apoptosis, mitophagy, necroptosis, and autophagy (Bloomingdale et al., 2022).

These disruptions contribute to the accumulation of misfolded proteins that cannot be efficiently cleared by the glymphatic system, which is already compromised in its function due to age and disease (Bloomingdale et al., 2022). In response to the presence of protein aggregates, microglia and astrocytes, the innate immune cells of the brain, mount a chronic inflammatory response, which is likely responsible for the destruction of neighboring neurons (Korolev, 2014; Scheltens et al., 2016). Concurrently, mitochondrial dysfunction and

loss result in increased radical formation and reduced energy supply within the brain (Swerdlow & Khan, 2004).

In addition to genetic mutations and variants, other factors such as bacterial or viral infections (Lotz et al., 2021; Zubair Alam et al., 2017) as well as imbalances in the interplay between microbiome and brain, are also being considered as potential triggers for disease onset (AlDabal & BaHammam, 2011; Rangaraj & Knutson, 2016).

Hence, on the molecular level, a multitude of biological processes contribute to neurodegeneration. As pointed out in the introduction, these include aberrant cell cycle regulation and DNA repair mechanisms, genetic mutations, and epigenetic modifications. Additionally, impaired protein folding and quality control, deregulated autophagy and apoptosis, oxidative and ER stress, mitochondrial loss, compromised energy metabolism and homeostasis, impaired cytoskeleton and axonal transport, excitotoxicity, neuroinflammation, glial dysfunction, and dysfunction of the BBB all play crucial roles in the pathogenesis of NDDs (Bloomingdale et al., 2022; Gan, Cookson, Petrucelli, & La Spada, 2018; Wilson et al., 2023).

To gain a better understanding of the central biological processes and pathways involved in neurodegeneration, various comprehensive classifications have been developed. With each of these classifications, researchers emphasize different factors based on literature knowledge or their own laboratory research.

For instance, Gan et al. focuses on defective protein quality control, impaired autophagy-lysosomal pathways, protein seeding and propagation, stress granule biology, protein aggregation, compromised mitochondrial homeostasis, synaptic toxicity leading to network dysfunction, and an excessive innate immune response. Bloomingdale et al. narrows down his hallmarks to disrupted proteostasis, oxidative and ER stress, metabolic dysfunction, and an altered neuroimmune system (Bloomingdale et al., 2022). Meanwhile, Wilson et al. identifies pathological protein aggregation, aberrant protein homeostasis, synaptic and neuronal network dysfunction, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death as the primary hallmarks of neurodegeneration (Wilson et al., 2023).

Interestingly, the hallmarks of aging as defined by López-Otín, Blasco, Partridge, Serrano, and Kroemer address very similar processes. The main categories include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation and dysbiosis. Given that neurodegeneration is often viewed as accelerated aging by many researchers, these aging hallmarks also need to be considered when defining appropriate hallmarks for NDDs (López-Otín et al., 2023).

6.1 Defining hallmarks of neurodegeneration within this work

Following our GO-term, KEGG, and StringDB local network cluster analyses across the four diseases and omics levels, we aimed to align our findings with the BP, KEGG pathways, and StringDB terms we identified by developing our own data-driven classification system.

We defined six hallmarks according to their primary location or mode of action based on the classification of Ramanan and Saykin, 2013 (Ramanan & Saykin, 2013) and subsequently categorized the BP, KEGG pathways, and StringDB terms according to these hallmarks.

In Paper 2, we encountered a significantly greater number of pathways compared to Paper 1, largely due to extensive gene lists associated with a single omics layer in one disease. As a result, we had to expand the subcategories of our hallmarks. We refined these low-level terms to 69 significant terms that best represented the hundreds of enriched biological processes extracted from our data.

The six hallmarks are an aberrant **cell cycle** including impaired DNA repair, modified transcription and translation processes and altered chromatin organisation, as well as deregulated **autophagic and apoptotic processes**, all functioning as **intracellular mechanisms**, defects in the **extracellular matrix and in developmental processes** as well as an aberrant **signal transduction and transport** as **intercellular mechanisms in the local tissue environment**, and an impaired **immune system** and **metabolism** in the **systemic environment**, signaling within the whole body.

These hallmarks are described more thoroughly by the 69 low-level terms, that were represented most often in our analyses as shown in Fig.6.1. Taken together hallmarks and low-level terms give an adequate picture of neurodegeneration.

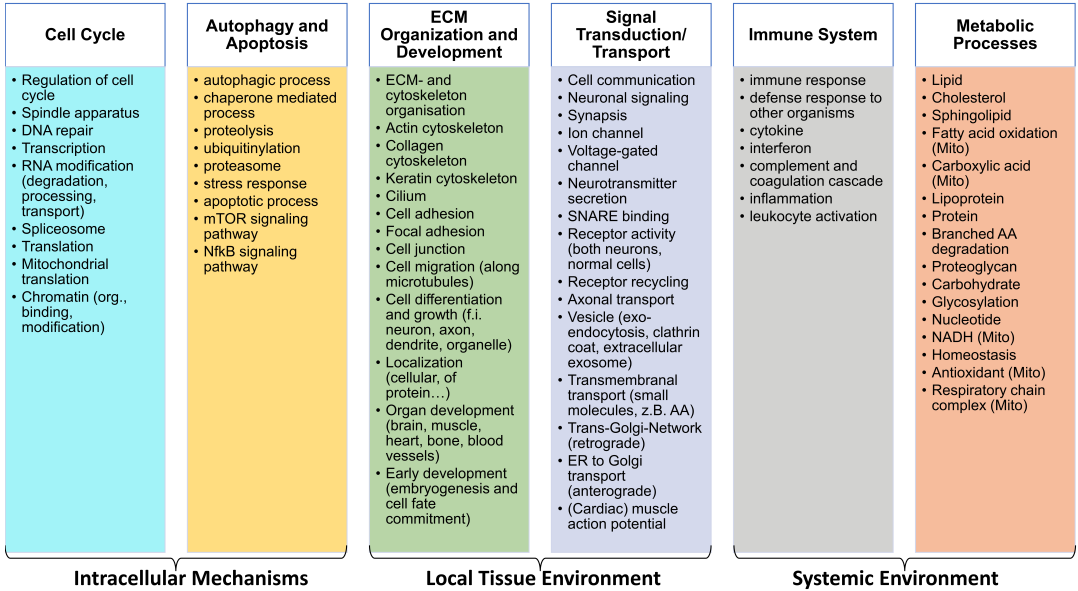


Figure 6.1: Hallmarks and low-level terms defining neurodegeneration Six hallmarks categorized according to their primary location or mode of action with their 69 subcategories found in GO term analyses, KEGG pathways, and StringDB terms. The color scheme is used for the network figures in paper 2. (Adapted from Ramanan 2013)

Segmenting biological processes into a series of categories undoubtedly enhances clarity and logical organization. However, it also inevitably introduces ambiguities and even distortions, given that any biological system is far too intricate to be simplified into a handful of manageable causal relationships.

Generally, it proves challenging to designate hallmarks, as an excessive number of selected hallmarks may become overly detailed and voluminous, making interpretation difficult and resulting in too many fragmented processes, which in reality are interconnected and mutually dependent. Conversely, selecting too few hallmarks risks oversimplification and generalization of the pathways involved.

Certain categories might appear arbitrary; for instance, signal transduction and transport are included in the category of local tissue environment, yet they could also be classified as cellular or systemic processes. However, given that many related biological processes indicated shorter distances between brain cells, signal transduction and

transport were categorized accordingly.

6.2 Categorizing the data according to the hallmarks

After having investigated for similarities between the four NDDs to find common pathways that lead to neurodegeneration, the next step to get a closer understanding of the underlying mechanisms was the search for peculiarities and characteristics of the distinct diseases. Different pathways leading to similar results, namely neurodegeneration, might allow deeper insights about cross connections of NDDs and shed light on their origin and development.

In contrast to Paper 1, where the list of overlapping genes was manageable, this time we found ourselves dealing with an abundance of data, as the gene lists were not filtered for genes appearing in the intersection of the four NDDs but investigate on a single disease level.

Large-scale gene lists may offer new insights but also possess their own intrinsic problems, because they lead to long lists of highly general biological processes. Even after employing the affinity propagation function of WebGestalt, it was often impossible to derive any clear low-level term.

To address this problem, in paper 2 we employed the Louvain community detection algorithm (Blondel, Guillaume, Lambiotte, & Lefebvre, 2008) on PPI networks constructed by StringDB using our gene lists. This led to the identification of functionally associated communities, for which hubgenes and the most frequently represented low-level terms could further be assigned. Through this approach, we were able to identify more meaningful, and sometimes even very specific pathways, providing insights into important processes in neurodegeneration amidst a still large number of very general terms.

Terms like Caspase recruitment domains (CARDs), which are related to inflammation and apoptosis, or the Serine C-palmitoyltransferase complex, which is an enzyme involved in the sphingolipid metabolism lead to a deeper understanding of neurodegenerative processes.

Since there is currently no tool available to automatically classify hundreds of pathways, this step required manual intervention, which implies that the classification of related processes and the definition of

hallmarks depend on the scientists expertise and on prior knowledge from the literature.

While this approach undoubtedly introduces biases and limitations due to current knowledge constraints, it also enables a broad, data-driven analysis using large-scale omics data by involving the manual step of assigning communities to associated biological subprocesses. Until more viable tools become available to automatically annotate the plethora of functional associations to well-defined subprocesses and hallmarks, the manual approach remains the only viable option for handling these extensive datasets (La Cognata et al., 2021).

6.2.1 Problems from the bioinformatics point of view

Still, identifying singular pathways that could distinguish one disease from another remained challenging. Size and diversity of gene lists influence the specificity of enriched GO terms, often leading to the identification of broad and general BP rather than specific and detailed functional annotations due to the statistical nature of enrichment analysis. When analyzing a large set of genes, the enrichment analysis calculates the overrepresentation of GO terms within that set compared to a background or reference set of genes.

If the gene list is extensive, it likely contains a diverse range of genes involved in various biological processes. As a result, the enrichment analysis may identify GO terms associated with broad biological functions that are relevant to many genes in the list. These terms are often generic and encompass fundamental biological processes such as "cellular process," "metabolic process," or "biological regulation."

Furthermore, when dealing with large gene lists, many genes may be associated with multiple GO terms, leading to redundancy and overlap among the enriched terms. As a result, the analysis may prioritize general terms that encompass a wide range of gene functions to avoid redundancy - a problem mainly found in hierarchically organized databases such as Reactome and the Gene Ontology (Vivar, Pemu, McPherson, & Ghosh, 2013).

6.2.2 Problems from the biological point of view

From the biological point of view, this difficulty of identifying singular discriminative pathways between the NDDs stems primarily

from the involvement of nearly all processes of body function in neurodegeneration.

After textmining of $> 200,000$ publications, Morgan et al. found that 91% of all KEGG pathways could be linked to AD, highlighting the complexity and the almost global functional reach of the disease (Morgan et al., 2022). As research on a disease intensifies and the number of patients studied increases, more dysregulated genes are discovered, leading to highly diverse and less meaningful gene lists for each disease. This is particularly true for AD, the most commonly studied NDD, where our gene list on the transcriptomics level included almost 15,000 genes.

Secondly, to mitigate the effects of mutations, the body has numerous highly protective redundant gene products that perform similar roles within a pathway. These redundant proteins can compensate for mutated or misregulated proteins. Therefore, each patient may possess a unique set of involved genes that ultimately contribute to the same disease outcome. Increasing the number of patients consequently leads to lists of significant genes that may exhibit minimal overlap (Jin et al., 2014).

Thirdly, only a small fraction of these redundant genes, but also of involved ncRNAs and many other factors are fully understood in terms of their function and interactions. Therefore, they are either not yet listed in databases or are only documented for a subset of the pathways in which they are actually involved and so the real connections to pathways are further diluted. Presumably, numerous pathways beyond those currently identified are significant for the development of neurodegeneration.

Yet another reason for the challenge in identifying singularly disease-defining pathways might stem from the fact that our gene lists are primarily derived from late-stage patients. These patients had already succumbed to their disease, and their brains were similarly deteriorated across all four diseases. The differentially expressed genes identified at this stage likely do not provide a comprehensive picture of the disease course. Instead, they may predominantly reflect later-stage impairments leading to excessive apoptosis.

Last but not least, due to the absence of definitive markers, diagnosis

is not always straightforward for NDDs. Consequently, gene lists may not strictly comprise disease-inducing genes but may include numerous false positives. Therefore, it cannot be ruled out that individuals selected as healthy controls may, in reality, be early-stage diseased patients.

Despite their often very general BP, significant differences still exist between NDDs and other conditions such as cancer or diabetes. This suggests that the processes we found by our analyses were meaningful enough to effectively characterize neurodegeneration. However, to pinpoint differences that truly distinguish NDDs, deeper exploration into singular processes and genes is necessary.

Chapter 7

Case study: Circadian clock

Given that our work was intended for researchers in specialized fields, the following paragraph will show an example of how to proceed with the data we provide.

A known dataset from a research lab can be expanded with our much more comprehensive data lists to include new proteins which the Louvain Algorithm had identified as belonging to a category. The function of these new proteins can then be verified in the laboratory. In this way, already known molecular pathways can be systematically expanded, and importantly, connections between different pathways can be more easily identified. In the analysis of complex diseases, where practically all molecular pathways are affected or involved in some way (Morgan et al., 2022), our approach can make a significant contribution to untangling this overwhelming complexity.

The circadian clock and its effects leading to neurodegeneration provide a good example of this and will be discussed in the following. Chronic diseases arise from the accumulative consequence of our lifestyles, of our genetic material and of aging in general (Atallah et al., 2018). Diseases such as cardiovascular diseases, type 2 diabetes, cancer or NDDs are the global leading cause of mortality. Lifestyle interventions are most effective in reducing metabolic risk factors, disease progression or even side effects of a disease and they also contribute to decelerate the aging process (Turner, Lira, & Brum, 2017). Unhealthy lifestyle augments inflammation and oxidative stress, which in turn lead to genome instability which is often associated with aging or the above-mentioned diseases.

Modifiable health behaviors frequently advocated include sleeping at least 7 h per night (Watson et al., 1768), consuming 5 or more

servings per day of fruits and vegetables (Lee-Kwan, 2017), limiting time in sedentary behaviors, obtaining at least 150 min per week of moderate-to-vigorous physical activity (Garber et al., 2011), and not smoking (R. C.-C. Chang, Ho, Wong, Gentleman, & Ng, 2014). But even when reduced to only three factors, sleep is among them, next to nutrition and physical exercise (Burke & Dunne, 2022).

Examining our data closer with respect to these lifestyle factors, a deregulated circadian clock and an impaired AMPK pathway, also called the anti-aging pathway (Ruderman, Carling, Prentki, & Caccicedo, 2013) could be distinguished with varying regulation patterns within the four diseases. Circadian rhythm dysregulation has been increasingly recognized for leading to negative health outcomes, such as increased risk of premature aging, metabolic syndrome, depression, cancer, and cardiovascular and neurological dysfunction (Hood & Amir, 2017) as shown in Figure 7.1.

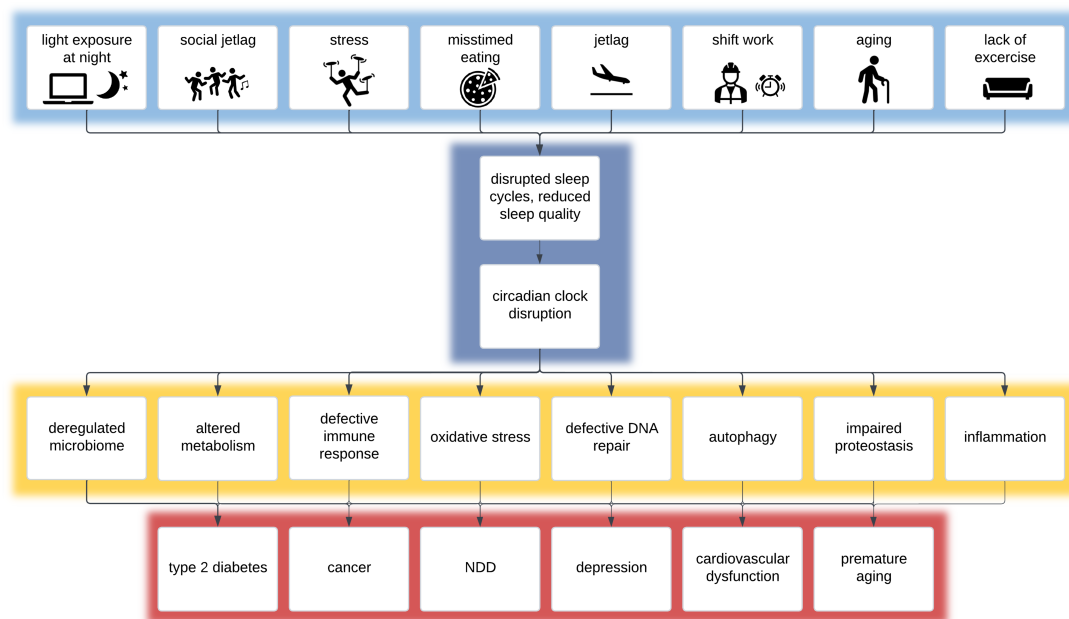


Figure 7.1: Reasons and effects of circadian clock disruption

Chronic disruption of the circadian clock due to consistently poor sleep quality can significantly affect vital physiological processes, potentially leading to chronic diseases.

There are 4 stages of sleep that can be distinguished during one sleep cycle: 3 phases of non-rapid eye movement (NREM) sleep that progress from stage 1 (falling asleep) to stage 3 (deep sleep) and one phase of rapid eye movement (REM) sleep. The higher the stage of NREM sleep, the harder it is to wake a person up.

Then, the brain cycles back through the NREM sleep stages. It takes 60 to 90 minutes to cycle through all stages of NREM sleep. Under normal conditions this sleep cycle is repeated four to five times a night. Early in the night, NREM sleep is usually deeper and longer; later in the night, a higher proportion of each cycle is made up of REM sleep (Iber, 2007)(Morris, Aeschbach, & Scheer, 2012).

Body temperature, breathing, heartrate, and muscle and brain activity decrease gradually after falling asleep and during light and deep sleep phases. At the same time, brain activity slows, but there are short bursts of activity that actually help resist being woken up by external stimuli. Stage 2 sleep can last for 10 to 25 minutes during the first sleep cycle, and each N2 stage can become longer during the night. Collectively, a person typically spends about half their sleep time in N2 sleep.

During deep sleep muscle tone, pulse, and breathing rate decrease as the body relaxes even further. Brain activity has an identifiable pattern of delta waves. This stage is critical to restorative sleep, allowing for bodily recovery and growth. It may also bolster the immune system. Even though brain activity is reduced, there is evidence that deep sleep contributes to memory building and boost of creativity.

During REM phase, brain activity is high due to vivid dreaming, as are processes like memory building, learning and creativity, whereas muscle activity reaches its lowest point due to temporary muscle paralysis (Carskadon & Dement, 2005).

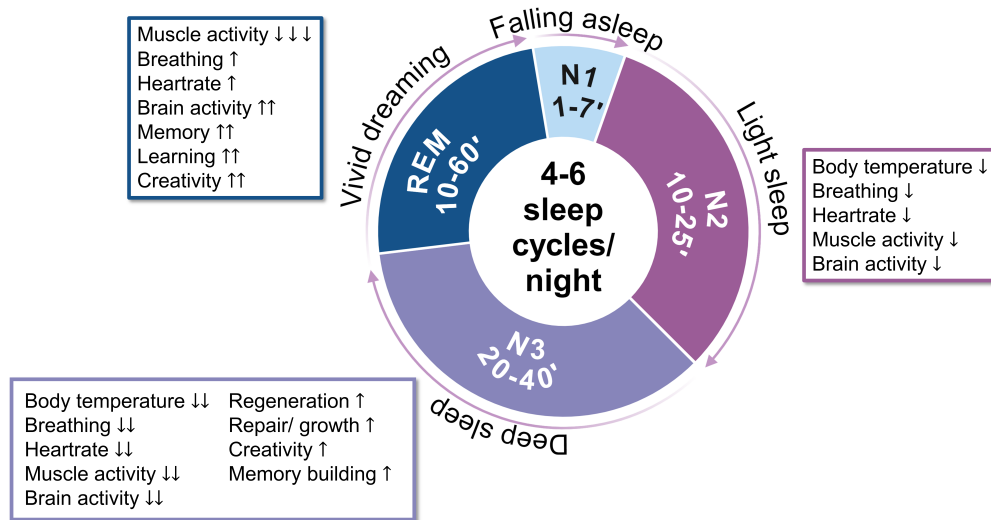


Figure 7.2: The four stages of a sleep cycle and its effects on body and brain functions. Sleeping consists of 4 to 6 sleep cycles per night, which can be divided into three NREM and one REM phase while restoring body and brain functions. (Adapted from Patel, 2024)

7.1 Significance of the circadian clock

The circadian clock is an internal time-keeping system, that synchronizes our body functions with solar time (Edery, 2000). It regulates various physiological processes through the generation of approximately 24 hour circadian rhythms in gene expression, which are translated into rhythms of physiological functions including metabolism, sleep, body temperature, heart rate, blood pressure, hormone and neurotransmitter secretion, and immune and renal function (Hastings, Maywood, & Reddy, 2008).

The two major components are the central clock, residing in the suprachiasmatic nucleus (SCN) of the brain, and the peripheral clocks that are present in nearly every tissue and organ system.

Both the central and peripheral clocks can be reset by environmental cues, also known as Zeitgebers. The predominant Zeitgeber for the central clock is light, which is sensed by the retina and signals directly to the SCN. The central clock aligns the peripheral clocks with the external light/dark cycle through neuronal and hormonal signals (Ko & Takahashi, 2006). Additional Zeitgebers that synchronize the peripheral clocks are feeding-fasting rhythms, physical activity and body temperature (Morris et al., 2012).

At the molecular level the circadian clock regulates gene expression to create a peak of protein expression within every 24 hours, determining when a particular physiological process is most active in accordance with the solar day.

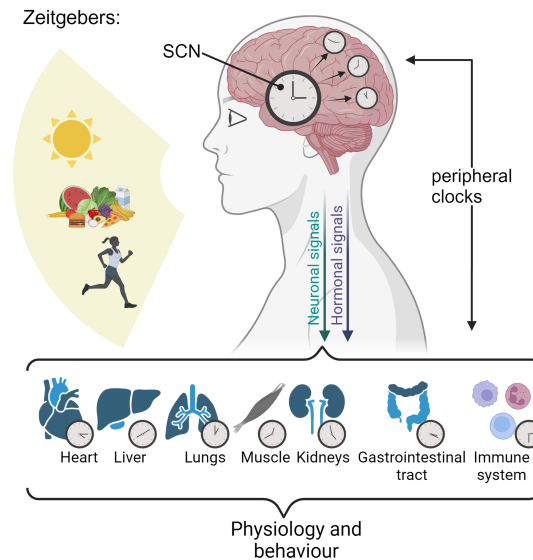


Figure 7.3: Central and peripheral clocks regulating physiology and behaviour
The central clock in the SCN is predominantly controlled by light and aligns with the peripheral clocks in the body and other brain regions through neuronal and hormonal signals. Additional Zeitgebers that synchronize the peripheral clocks are feeding-fasting rhythms, physical activity and body temperature. (Adapted from Hickie et al., 2013)

7.2 Mode of action

Mammalian clocks primarily rely on alterations in the expression of specific genes and proteins, forming a cell-autonomous transcriptional-translation autoregulatory feedback loop. This loop is synchronized to a circa 24-hour rhythm in gene expression, essential for the behavioral and physiological rhythmicity of the organism (Leng, Musiek, Hu, Cappuccio, & Yaffe, 2019).

The core clock genes include the transcription factors Circadian Locomotor Output Cycles Kaput (*CLOCK*) or Neuronal PAS Domain Protein 2 (*NPAS2*; paralog of *CLOCK*) and Brain and Muscle ARNT-Like 1 protein (*BMAL1*), which encode activators, and *PER1*, *PER2*, and *PER3*, *CRY1* and *CRY2*, which encode repressors within the three main feedback loops (Meng et al., 2008).

Light activates the core feedback loop, during which *CLOCK* or

NPAS2 and BMAL1 or BMAL2 activate the *Per1*, *Per2*, *Cry1*, and *Cry2* genes by binding to the E boxes of their promoters. As Eboxes are among the most common promoter elements in the genome, the clock can transcriptionally control a large array of genes.

During daytime, the proteins Period (PER1, PER2) and Cryptochrome (CRY1, CRY2) accumulate and begin to dimerize and translocate to the nucleus, where during night time they repress transcription of clock-controlled genes (ccg) and their own genes by destabilizing the CLOCK|NPAS2:BMAL1|BMAL2 heterodimer.

At the same time, the accumulation of PER and CRY is down-regulated by several cytoplasmic and nuclear proteins, including Beta-Transducin Repeat Containing E3 Ubiquitin Protein Ligase (BTRC) and Casein Kinase 1 (*CSNK1*=CK1) for PER, and F-Box Proteins 3 and 21 (FBXL3, 21) for CRY. The binding of these proteins directs PER and CRY to proteasomal degradation (Lamia et al., 2009). Consequently, CLOCK:BMAL1 is able to once again facilitate *CRY* and *PER* transcription. The CLOCK:BMAL1/PER:CRY interaction is further influenced by additional feedback loops.

In a second feedback loop, CLOCK and BMAL1 also regulate the expression of the *Nr1d1/2* genes, which encode the nuclear receptors REV-ERB α and β , respectively. These nuclear receptors compete with the retinoic acid-related orphan receptors, ROR α , ROR β , and ROR γ , for binding to *BMAL1* and *NFIL3* gene promoters, thereby providing both positive (ROR) and negative (REV-ERB) regulation of BMAL1 transcription.

In a third feedback loop, NFIL3 together with D-box binding protein (DBP), as well as CLOCK and BMAL1, regulate a rhythm in the REV-ERB α/β nuclear receptors (Ko & Takahashi, 2006).

These three interlocked transcriptional feedback loops regulate the majority of cycling genes, leading to rhythms in various different physiological systems, from sleep to metabolism and aging (Rijo-Ferreira & Takahashi, 2019).

Core clock genes are far too important to be without proxies, therefore many paralogs exist that can substitute their function. For example BMAL2 forms dimers with CLOCK or NPAS2, substituting BMAL1.

Fine adjustment of the circadian clock is done by a still unknown number of transcription factors and histone modifiers, amongst which are E1A Binding Protein P300 (EP300), Sirtuin1 (Sirt1), Basic Helix-Loop-Helix Family Member E40, 41 (BHLHE40,41), and the Circadian Associated Repressor Of Transcription (CIART). All clock genes are described in more detail in Fig.11.1 in the Appendix and therefore are not found in the List of Abbreviations.

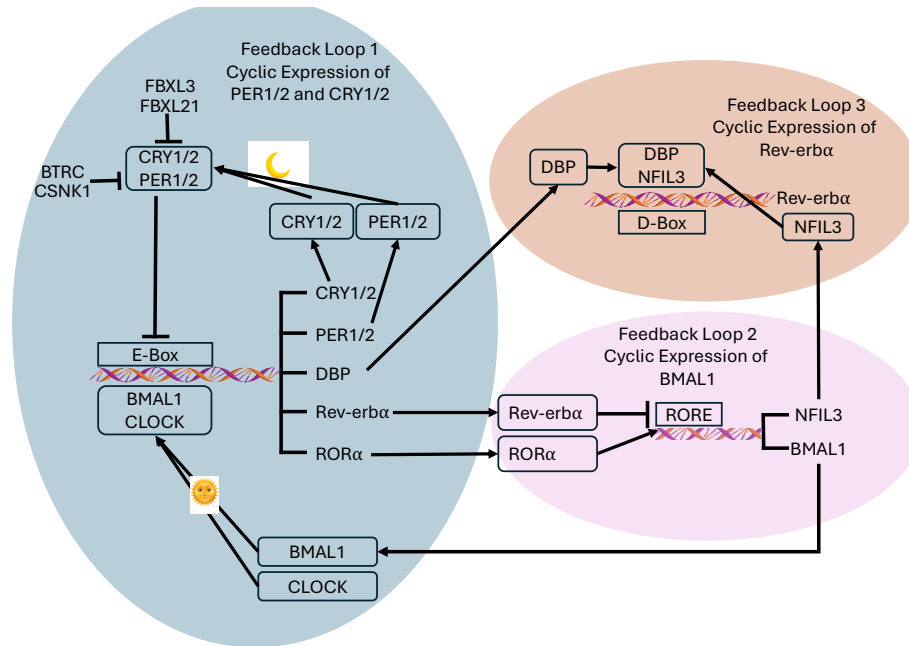


Figure 7.4: Mechanism of circadian clock

The circadian clock consists of three interlocked transcriptional feedback loops. The core feedback loop is activated by light, during which CLOCK and BMAL1 dimerize and activate the *Per1*, *Per2*, *Cry1*, and *Cry2* genes. During daytime, the proteins Period (PER1, PER2) and Cryptochrome (CRY1, CRY2) accumulate and begin to dimerize and translocate to the nucleus, where during night time they repress transcription of several clock-controlled genes (ccg)(not shown) and their own transcription by destabilizing the CLOCK:BMAL1 complex. With no new PER1/2 and CRY1/2 being generated and the existing PER1/2:CRY1/2 dimer being degraded during night, CLOCK and BMAL1 again dimerize. In a second feedback loop, CLOCK and BMAL1 indirectly also regulate the expression of the *Nr1d1/2* genes, which encode the nuclear receptors REV-ERB α and β , respectively. These nuclear receptors compete with the retinoic acid-related orphan receptors, ROR α , ROR β , and ROR γ , for binding to *BMAL1* and *NFIL3* gene promoters, thereby fine adjusting the regulation of BMAL1 transcription. In a third feedback loop, NFIL3 together with D-box binding protein (DBP), as well as CLOCK and BMAL1, regulate a rhythm in the REV-ERB α/β nuclear receptors. These three interlocked transcriptional feedback loops regulate the majority of cycling genes, leading to rhythms in various different physiological systems, from sleep to metabolism and aging.

7.3 Circadian clock disruptions in neurodegeneration

While it is recognized that circadian dysfunction in older adults can be partly attributed to degeneration of the SCN, the link between circadian rhythms and neurodegeneration is far from being understood (Leng et al., 2019).

Any disturbance in the delicate balance of circadian rhythms and the sleep/wake cycle can have adverse consequences for human health (Bass & Takahashi, 2010; Elizabeth & Weaver, 2011; Musiek & Holtzman, 2016). In a bidirectional mode the ongoing disease pathology can impact circadian rhythms, and the disrupted circadian rhythms may accelerate disease pathology by impairing peripheral circadian processes such as glucose and lipid metabolism (Bass & Takahashi, 2010), immune system function (Curtis et al., 2015; Gibbs et al., 2012; Keller et al., 2009), hormone secretion (Meléndez-Fernández, Liu, & Nelson, 2023), gut microbiome oscillations (Mukherji, Kobiita, Ye, & Chambon, 2013), and protein homeostasis (Musiek et al., 2013), which are the typical hallmarks for neurodegeneration (see chapter 6).

Disorders of sleep and of circadian rhythms occur very early in the course of several NDDs and are symptomatic hallmarks of AD, PD and HD (Hatfield, Herbert, Van Someren, Hodges, & Hastings, 2004; Videnovic, Lazar, Barker, & Overeem, 2014). Sleep disturbances may precede the onset of more typical symptoms by decades (Lim, Kowgier, Yu, Buchman, & Bennett, 2013; Schenck, Boeve, & Mahowald, 2013). The most striking example is rapid eye movement behavior disorder (RBD), a condition in which the above mentioned normal muscle paralysis is lost during REM sleep (Fig.7.2). More than 80% of all RBD patients will eventually develop PD or another synucleinopathy (Schenck et al., 2013).

Sleep loss likely contributes to the synaptic dysfunction and memory impairment of many NDDs because as shown in Fig.7.2, slow wave sleep plays a critical role in memory consolidation in the hippocampus (Norimoto et al., 2018; Rasch & Born, 2013). Increasing evidence shows that abnormal sleep also drives neurodegenerative pathology directly by inducing neuroinflammation (Manchanda, Singh, Kaur, & Kaur, 2018) and aberrant protein homeostasis (Naidoo, Giang, Galante, & Pack, 2005) and which are at least partly due to dis-

turbance of the glymphatic system during sleep loss (Rasmussen, Mestre, & Nedergaard, 2018).

The glymphatic system, comprised of glial-lined perivascular channels, facilitates the drainage of cerebrospinal fluid through aquaporin 4 channels into the brain's interstitial tissue, removing waste solutes. Its heightened activity during slow wave sleep (Fultz et al., 2019; Xie et al., 2013) underscores the vital role sleep plays in clearing neurotoxic proteins, such as $A\beta$ and tau (Iliff et al., 2014, 2012).

Conversely, sleep deprivation accelerates the accumulation of these harmful proteins (Holth et al., 2019), suggesting a potential vicious cycle wherein impaired sleep or neurodegeneration initiates a cascade of pathology. Evidence supporting this includes the observation that sleep disturbances precede neurodegenerative symptoms (Malhotra, 2018), epidemiological studies linking chronic sleep deprivation to increased dementia risk (L. Shi et al., 2018), and research on airline staff indicating a causal link between chronic sleep disruption and neurodegeneration (Cho, Ennaceur, Cole, & Suh, 2000).

Understanding the relationship between sleep and neurodegeneration is critical for public health due to the widespread prevalence of chronic sleep deficiency (Y. Liu, 2016). Investigating the different patterns of sleep pathologies might offer valuable insights into diverse patterns and mechanisms of neurodegeneration and their relation to a deregulated circadian clock.

For example, insomnia and a disrupted sleep cycle are prevalent across various neurodegenerative conditions, but the sundowning syndrome, meaning that the behavioral symptoms worsen during late afternoon, is especially seen in AD (Volicer, Harper, Manning, Goldstein, & Satlin, 2001), while PD is associated with RBD and excessive daytime sleepiness (Loddo et al., 2017). HD shows various patterns of sleep disorders, e.g. delayed sleep phase and increased REM latency (Aziz, Anguelova, Marinus, Lammers, & Roos, 2010), circadian changes of melatonin synthesis (Aziz et al., 2009), difficulties in falling asleep, frequent nocturnal awakenings, and resulting excessive daytime sleepiness (Herzog-Krzywoszanska & Krzywoszanski, 2019). Although sleep disturbances are also common in ALS, they are rather the consequence of disease than its cause as they stem primarily from physical symptoms, such as muscle cramps, pain, reduced mobility,

spasticity, mucus retention, and restless legs syndrome. In addition, depression and anxiety may lead to significant insomnia (Boentert, 2019).

In light of experimental data, circadian rhythm disruption that lowers duration and quality of sleep, poses as a self-perpetuating vicious cycle in a bi-directional pathophysiological relationship with the neurodegenerative process. Continuous disease progression can affect circadian rhythms, and the resulting disruption in these rhythms may, in turn, accelerate the progression of disease pathology (Colwell, 2021).

It would be highly valuable to analyze sleep patterns in depth for different diseases to potentially find tailored solutions for each. However, measuring sleep without disturbing it through probe-taking or extensive patient wiring is extremely difficult, especially for patients in advanced stages of disease.

One possibility of exploring the origin of deregulated circadian rhythms could be considering closely the molecular differences between the diseases. Our data reveal distinct patterns of deregulated circadian clock genes and proteins, predominantly identified at the transcriptomics and methylomics levels. Interestingly, with the exception of REV-ERB β in PD, these disruptions are not evident at the genomics level. This may suggest that disruptions of the circadian clock are more often acquired during an individual's lifetime rather than inherited.

All prominent clock genes play roles in transcriptional regulation, either by directly binding to promoters as transcription factors or by modulating histones (Rijo-Ferreira & Takahashi, 2019). Notably, the majority of deregulated core clock genes identified for each disease were clustered within a single community alongside other DNA regulators.

This indicates that the Louvain algorithm effectively grouped interconnected data. Further investigation of the genes within these affected communities could lead to valuable research insights into additional genes that influence the circadian clock. We considered especially the genes which constitute the KEGG pathway Circadian Rhythm hsa4710. They represent the proteins of the three main loops but they

also refer to metabolism in taking AMPK into account and the proteins of the SCF complex (SKP1, CUL1, and RBX1) which catalyzes the ubiquitination of proteins destined for 26S proteasomal degradation.

7.3.1 Circadian clock disruption in AD

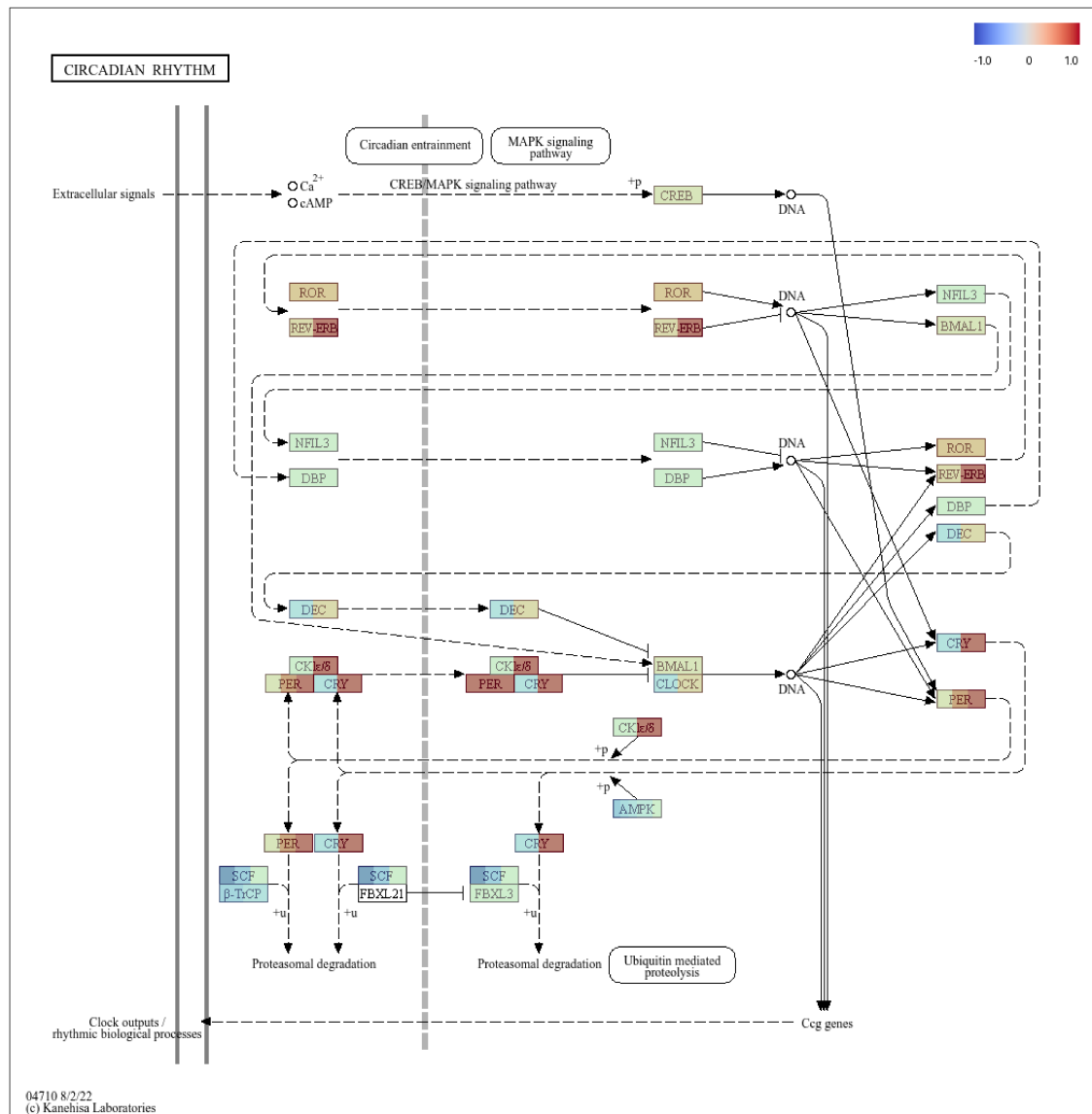


Figure 7.5: KEGG Circadian rhythm genes dysregulated in AD on the transcriptomic level

The color scheme of the figure is based on the mean direction of regulation across all assessed studies with the color blue for down- and red for upregulation. -1 means all studies that found the respective gene significantly differentially expressed showed it as downregulated. 0 means, it was on par between up- and downregulation, so e.g. 3 studies found it up- and 3 studies found it downregulated. Accordingly, +1 means that all studies found it upregulated.

In AD nearly all core clock genes are affected on the transcriptomics level (29/30), 22 of which belong to community AD_DEG6 (1620

diff. expr. genes in total). AMPK and CK1 δ are also found to be deregulated on the protein level whereas DEC1, BMAL1, CK2 ϵ , CUL1 and RORA are also found on the methylomic level (see Fig.11.2.

Low level terms assigned to this community were transcription and chromatin and the hubgenes are E1A-associated protein p300 (EP300), Histone deacetylase 1 (HDAC1) and Tumor Protein P53 (TP53), which are all three transcription factors involved in regulating the circadian clock, apart from being involved in other mostly unknown regulation processes. (Low level terms and Hubgenes can be found in the Network Figures in the Supplement of Publication 2)

EP300 and HDAC1 are both involved in histone (de-)acetylation, and TP53 is a transcription factor regulating hundreds of genes related to cell growth, acting as a tumor suppressor.

EP300 belongs to the central clock genes and functions as histone acetyltransferase for all four core histones in the nucleosome and thus regulates transcription via chromatin remodeling. It also participates in CLOCK or NPAS2-regulated rhythmic gene transcription and correlates with increase in PER1/2 mRNA and histone H3 acetylation on the PER1/2 promoter (Curtis et al., 2004).

HDAC1 belongs to a group of histone deacetylases closely related to sirtuins, which are class III histone deacetylases. They remove acetyl groups from lysine residues in histones and non-histone proteins, causing transcriptional repression (Hassig et al., 1998). HDACs are usually components of multiprotein complexes. HDAC1 together with Circadian Associated Repressor Of Transcription (CIART) represses the circadian transcriptional activator CLOCK-BMAL1 (Breuza et al., 2016), thus acting independently of the circadian transcriptional repressors CRY1, CRY2 and BHLHE41.

TP53 is a transcription factor whose protein levels and post-translational modification state alters in response to cellular stress like hypoxia, nutrient deprivation, DNA and spindle damage (Pitolli et al., 2019). In unstressed cells, p53 level is low (Aubrey, Kelly, Janic, Herold, & Strasser, 2018) but in response to cellular stress, rising levels of p53 cause a temporary arrest of cell cycle progression, enabling the cell to correct damaged DNA, and preventing the replication of damaged DNA. If DNA repair is successful, the cell

cycle resumes, but if DNA damage is irreparable, p53 eliminates the cell by inducing programmed cell death (J. Chen, 2016). Intriguingly, TP53 also has regulatory functions regarding the circadian clock by repressing CLOCK-BMAL1-mediated transcriptional activation of PER2 (Miki, Matsumoto, Zhao, & Lee, 2013).

In addition to Tau and A β -induced neuronal decline, as well as inflammation caused by reactive astrocytes and microglia, disruption of sleep and circadian rhythms is one of the earliest and most common indicators of AD (Schmitt, Grimm, & Eckert, 2017).

Studies on the Siberian hamster indicate that a dysregulated output from the SCN prevents robust entrainment of the peripheral clocks and leads to a marked disruption of cognition, whereas surprisingly, complete ablation of the SCN completely rescued memory processing. These data suggest that only while the SCN circuitry is genetically and neurologically intact, it can cause arrhythmia by suppressing the amplitude of clock gene oscillations within the SCN to zero, which leads to a dysregulation of acetylcholin and consequent inhibitory effects on memory processing in aging as well as preclinical AD (Ruby, 2021).

Restoring the functioning of the SCN in elderly people therefore seems highly interesting for early intervention of NDDs.

Also, disruption of circadian timing in AD is now thought of as a self-reinforcing feedback loop, where disruption of timing accelerates AD pathogenesis via amyloid deposition, oxidative stress and apoptosis that in turn lead to a further disruption of the circadian timing system (Chauhan, Chen, Kent, & Crowther, 2017; Musiek & Holtzman, 2016).

Altered methylation patterns of the BMAL1 promoter were found during early stages of AD and increased methylation correlated with tau pathology, cognitive disability and overnight wakefulness (Cronin et al., 2017; Hulme et al., 2020).

Moreover, AD-related processes like A β accumulation can directly influence cellular clock function by facilitating BMAL1 degradation in neuronal cells (H. Song et al., 2015). It could be shown that low levels of BAML1 in neurons cause an overexpression of BMAL1 and CLOCK in neuron-protecting astrocytes, which leads to their impaired function and even degradation in many ways (Lananna et al., 2018).

First, suppression of glial fibrillary acidic protein (GFAP) filaments, which constitute the cytoskeleton of astrocytes, raised levels of Il6 and Il33 inducing inflammation in cortical astrocytes (McKee, Lananna, & Musiek, 2020), and activation of caspase-3-dependent apoptosis promote instability and death of astrocytes (Yoo et al., 2020). As astrocytes are vitally important for neuron protection and nourishing their decrease in number will lead to neuronal undersupply and death (Lananna et al., 2018; H. Song et al., 2015).

Raised levels of BMAL1 and CLOCK in astrocytes also lead to suppression of hexokinase1 (HK1) and lactate dehydrogenase A (LDHA) proteins, which in turn leads to the transition from aerobic to anaerobic glycolysis. This results in lower energy levels in the brain. Altered glucose metabolism has been implicated in the pathogenesis of AD which is also sometimes called diabetes type III and the impaired circadian clock might be an interesting cause for this (Yoo et al., 2020).

Another interesting finding is that good-quality sleep attenuated the risk for developing AD in Apo ϵ 4 carriers (Lim, Yu, et al., 2013), showing that a balanced circadian rhythm could provide greater resilience to AD pathogenesis.

In line with the literature, our data suggest that disruption of the circadian clock is particularly dilapidated in AD, with far-reaching consequences for disease progression. Further investigations into the function of neighboring genes in the AD_DEG6 community may help shed light on the functioning and disruption of the clock.

Currently, several chronotherapeutic approaches aim to enhance cognition and slow down disease progression. These include early morning light therapy to resynchronize melatonin output and gamma frequency light treatment to facilitate effective connectivity between cortical and limbic brain regions. Such connectivity is correlated with attention, learning, and memory retrieval (Herrmann & Demiralp, 2005), processes influenced by the circadian timing system (Munn, Tyree, McNaughton, & Bilkey, 2015).

7.3.2 Circadian clock disruption in PD

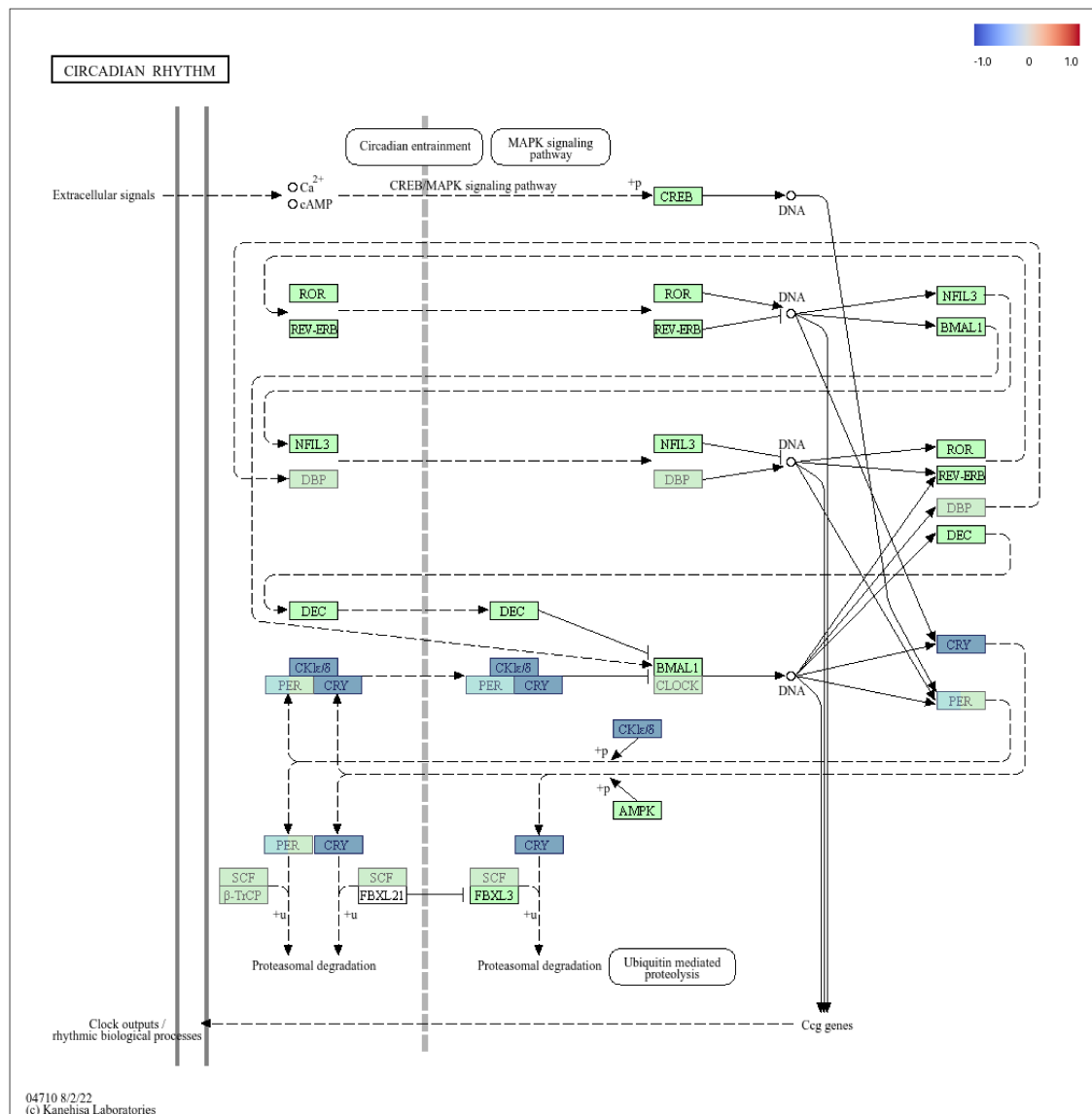


Figure 7.6: KEGG Circadian rhythm genes dysregulated on the transcriptomic level in PD (Explanation of color scheme see Fig. 7.5)

In PD one third of the core clock genes (10/30) were found to be deregulated on the transcriptomic level. Mutated *Rev-erb β* (NR1D2) was found as the only circadian protein of our study on the genomics level in community PD_SNP6 (transcription, metabolic processes: nucleotide). The AMPK subunit PRKAB1, DEC1 (BHLHE40), CK2 ϵ and RORB were found to be deregulated on the epigenetic level (see Fig. 11.2).

Seven out of ten differentially expressed genes were found in community PD_DEG4 (transcription, chromatin; early development) with the hubgenes HDAC1 (see paragraph 7.3.1) and MYC, a growth-

related transcription factor that promotes cell cycle progression, apoptosis, cellular transformation and angiogenesis, thus being a typical proto-oncogene. MYC is known to interfere with the circadian clock from cancer studies (Burchett, Knudsenclark, & Altman, 2021), but its involvement in neurodegeneration has yet to be shown. According to our data, transcription of MYC is upregulated in AD and HD but downregulated in PD. (Low level terms and Hubgenes can be found in the Network Figures in the Supplement of Publication 2)

As can be seen in Fig. 7.6 almost all differentially expressed genes are downregulated in PD, which poses the interesting question whether downregulation of circadian clock genes indicates an underlying cause of the disease, or whether this represents a downstream consequence of the underlying aetiology. Recent studies have shown that PD patients have lower expression levels of five clock genes (*BMAL1*, *CLOCK*, *CRY1*, *PER1* and *PER2*) and melatonin (Leng et al., 2019; T. Li et al., 2021).

Compared to healthy individuals, nighttime *BMAL1* expression levels of leukocytes have been observed to be significantly lower in PD-patient cohorts (Breen et al., 2014; Cai, Liu, Sothern, Xu, & Chan, 2010; Ding et al., 2011), although statements differed as to whether only drug-naïve (Cai et al., 2010) or also medicated patients were affected (Breen et al., 2014; Ding et al., 2011). One possible explanation for altered *Bmal1* expression in PD is that as dopamine is capable of regulating *BMAL1/CLOCK* heterodimer activity (Yujnovsky, Hirayama, Doi, Borrelli, & Sassone-Corsi, 2006), reduced dopamine levels, the characteristic feature of PD, will directly affect this central component of the molecular clock.

On the other hand, the rate-limiting enzyme of dopamine biosynthesis, the nigral tyrosine hydroxylase (TH), is controlled by *CLOCK* which is involved in the regulatory mechanism of dopamine synthesis and transport, as it can regulate the activity of TH, dopamine transporters, and their receptors at the transcriptional level by binding to the E-box element in the promoter region of dopamine synthesis-related genes (McClung et al., 2005). Therefore, dopamine deficiency may be cause or effect of alterations in the molecular clock in the brain and periphery.

Recent studies have indicated that BMAL1 may be relevant to NLRP3 inflammasome signaling (J. Huang & Li, 2024). The inflammasome is a multiprotein complex essential to the innate immune system. It mainly exists within the microglial cytoplasm in the CNS. When microglia are stimulated by pathogens or damage, the NLRP3 inflammasome is activated and promotes inflammation in the brain and pyroptosis of dopaminergic neurons (Haque et al., 2020). BMAL1 inhibits inflammasome activity by regulating NF- κ B and CLOCK (Spengler et al., 2012).

NF- κ B, a protein complex that controls the transcription of DNA, cytokine production, and cell survival, is necessary for the initiation of NLRP3 inflammasome signaling (Curtis et al., 2015). When NF- κ B is downregulated by BMAL1, assembly of the inflammasome cannot take place. On the other hand, CLOCK can directly activate NF- κ B signaling. BMAL1 counteracts this interaction between CLOCK and NF- κ B by recruiting CLOCK to form a heterodimer and thereby decrease free CLOCK (Spengler et al., 2012). Thus again BMAL1 deficiency can lead to overactivation of the NLRP3 inflammasome in the brain (Smith et al., 2021).

Increased expression of PER2 and REV-ERB α during the early morning has also been observed in PD patients (Breen et al., 2014). In a separate stabilizing loop, the REV-ERB α and retinoic orphan receptor genes fine-tune the oscillations generated by the main loop. Unlike other PER proteins, PER2 can directly interact with REV-ERB α to regulate BMAL1 expression (Schmutz, Ripperger, Baeriswyl-Aebischer, & Albrecht, 2010).

In our data BMAL1 appeared to be unaffected, maybe because of diverse tissues and different medication status and disease stage used in our meta study, but BMAL2, which may act as a paralog for BMAL1 (S. Shi et al., 2010), Clock, TH, NF- κ B, and Per2 and 3 were found to be deregulated by several of our studies.

Sleep deregulation is a major issue in PD as pointed out in paragraph 7.3. In the largest survey of nonmotor symptoms of PD, 64% of patients reported sleep problems, representing the second most common nonmotor complaint after psychiatric problems like anxiety or depression (Barone et al., 2009). Such problems are typically attributed to motor impairment, nocturia, sleep-disordered breathing, neuropsychi-

atric symptoms, and medications (Chaudhuri & Schapira, 2009) but our data (see Fig.7.6) suggest that sleep deregulation is an intrinsic feature of the disease itself. Our data also suggest, that circadian clock deregulation in PD is different from that of AD, as nearly all affected genes were downregulated.

7.3.3 Circadian clock disruption in HD

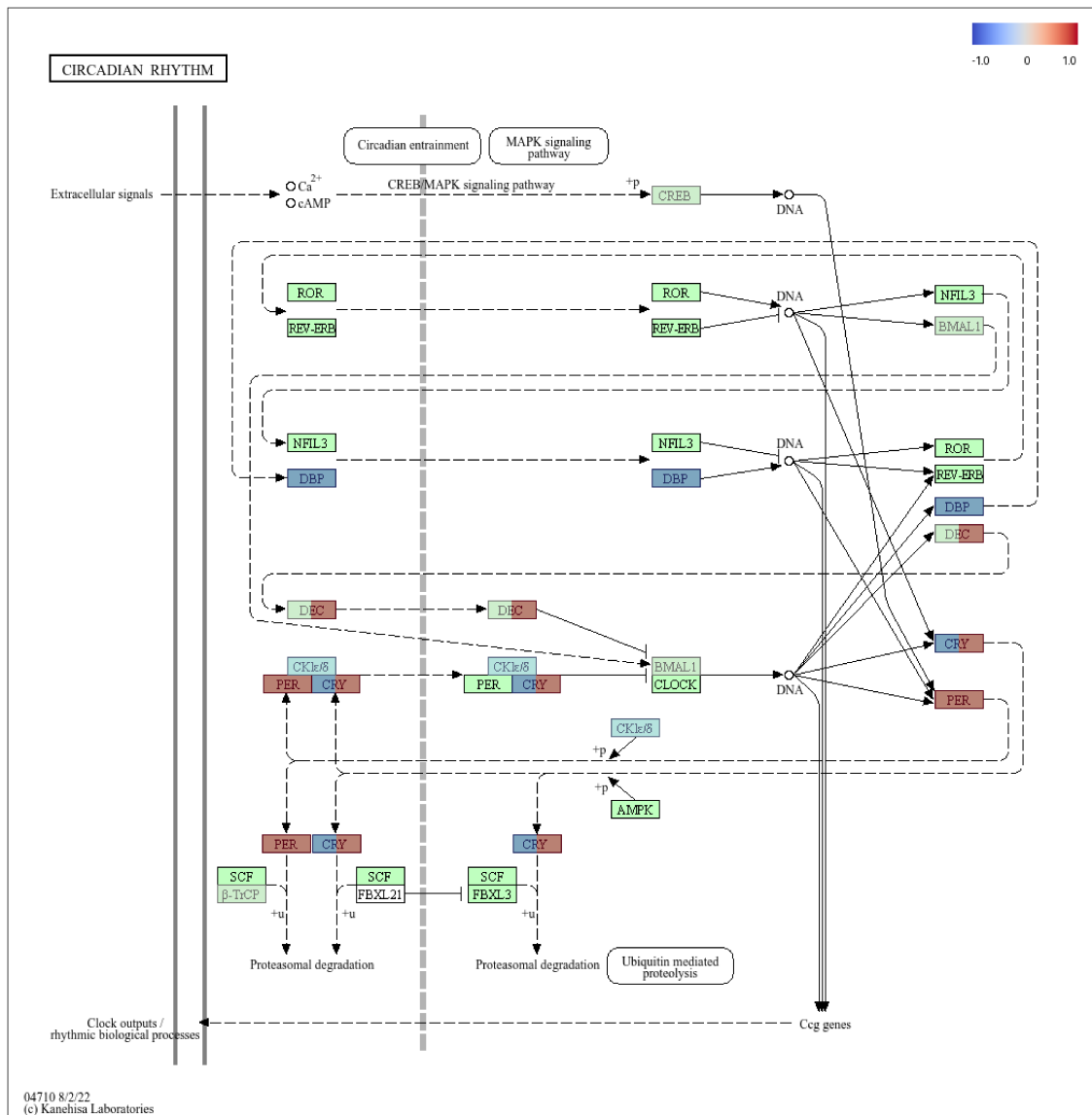


Figure 7.7: KEGG Circadian rhythm genes dysregulated on the transcriptomic level in HD (Explanation of color scheme see Fig. 7.5)

In HD one third (11/30) of the core circadian clock genes can be found to be differentially expressed on the transcriptomics level (see Fig.11.2, ten of them being found in one single community, HD_DEG10 (cell differentiation and growth, early development) with TP53, MYC and HDAC1 as hubgenes, two of which (TP53 and HDAC1) also were the hubgenes in the most prominent AD community, whereas

HDAC1 and MYC were hubgenes of the corresponding PD community.

As mentioned above, HDAC1 is involved in histone acetylation and TP53 is a transcription factor regulating hundreds of genes related to cell growth, DNA repair and apoptosis. MYC is a growth-related transcription factor that promotes cell cycle progression, apoptosis, cellular transformation and angiogenesis, thus like TP53 being a typical proto-oncogene.

Community HD_DEG10 consists of 716 genes, many of which are also related to genes of community 9 (ubiquitinylation, immune system: interferon) (Low level terms and Hubgenes can be found in the Network Figures in the Supplement of Publication 2).

Our findings imply that especially the core feedback loop is impaired with BMAL1, PER1, CRY1 and CRY2 being dysregulated. The pattern appears similar to AD and so are the symptoms of disturbed nocturnal sleep with reduced sleep efficiency, increased time awake after sleep onset, delayed REM sleep onset, and an increased proportion of time spent in the lightest stage of sleep versus a reduction of time spent in slow wave sleep and REM sleep (Voysey, Fazal, Lazar, & Barker, 2021).

Mutant HTT leads to transcriptional dysregulation as one of the earliest pathological alterations in HD (Sugars & Rubinsztein, 2003). As circadian rhythm is regulated by transcriptional feedback loops, it is possible that transcriptional defects of the circadian clock originate from random disruptions of transcription induced by mutant HTT. But importantly, nearly all genes of the second and third loop are still intact, at least according to our study.

This suggests that the observed circadian clock defects are gene specific and not a consequence of generic transcriptional dysregulation. Circadian dysfunction in HD might rather be driven by altered hormone levels, i.e. of melatonin and cortisol or circadian behaviour rhythms, and not because of the direct influence of mutant huntingtin protein on intrinsic clock gene function at a cellular level. This could be confirmed in a transgenic sheep model of HD, in which circadian behaviour abnormalities were reduced when animals were housed with controls providing normal circadian cueing (Jennifer Morton et al., 2014).

To interrupt the feedforward cycle between sleep and neurodegeneration, in which deranged sleep exacerbates symptoms of neurodegeneration, it might therefore be beneficial to ensure healthy sleep rhythms in early life of HD patients. So far there have not been any studies of clock genes in HD patients (Voysey et al., 2021), so our study could be a good starting point in this direction, suggesting interesting genes that could be investigated further.

7.3.4 Circadian clock disruption in ALS

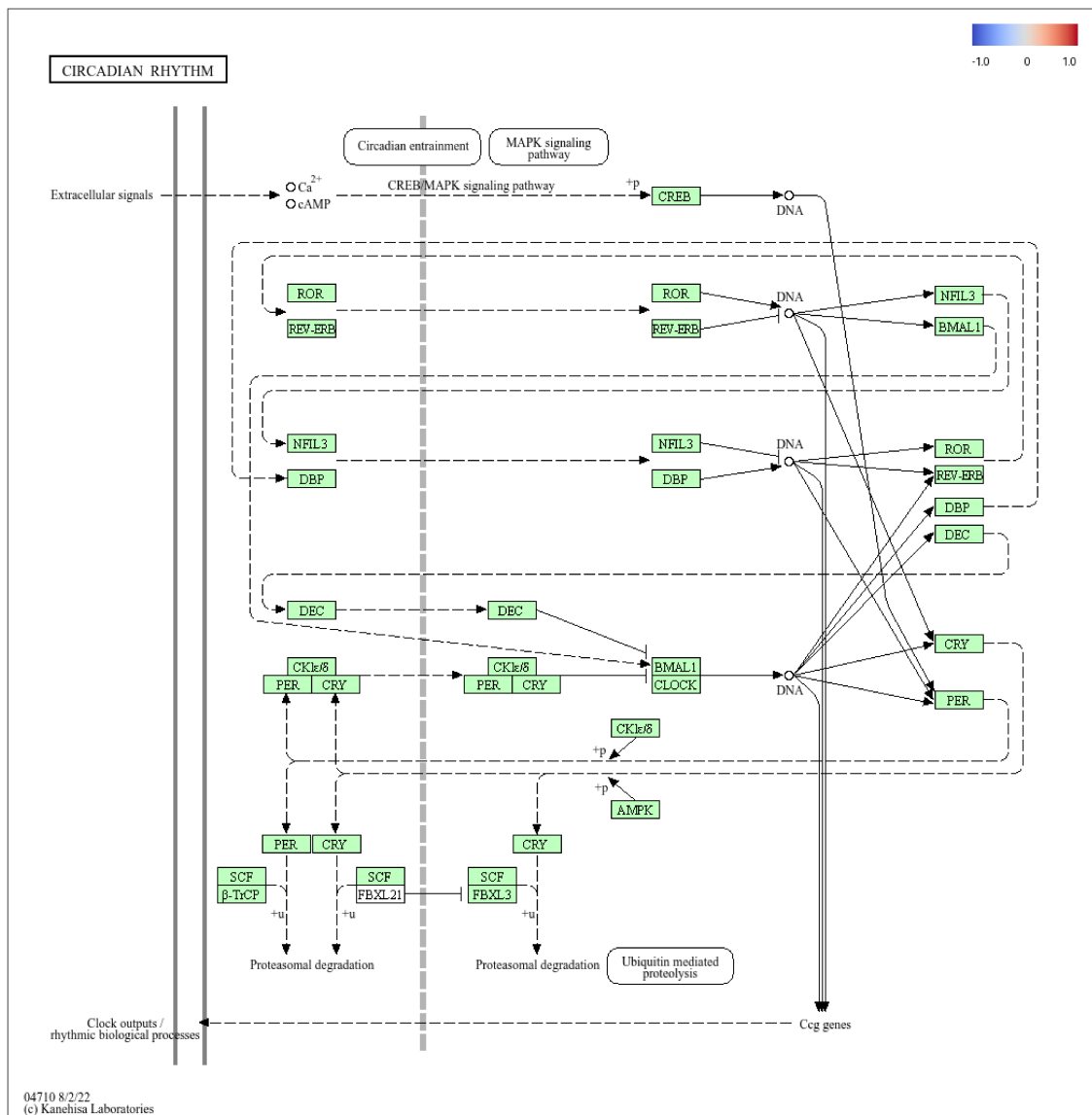


Figure 7.8: KEGG Circadian rhythm genes disregulated on the transcriptomic level in ALS (Explanation of color scheme see Fig. 7.5)

In ALS, differentially expressed main clock genes were only identified on the proteomics level (5/30). Neither the genomics, transcriptomics,

nor epigenetic levels contained another core clock gene. (see Fig.11.2)

This is noteworthy because many more patients were tested at the transcriptomics level compared to the proteomics level (470 patients in 8 transcriptomics studies vs. 162 patients in 3 proteomics studies). However, two transcriptomics studies involving a total of 408 patients used blood samples, which likely do not adequately reflect brain processes. To determine whether the circadian clock is indeed less affected in ALS, targeted post-mortem brain studies would be necessary.

CSNK1D and *CSNK1E* were identified in community 1 with the low-level term translation, AMPK subunits PRKAA1, PRKAB2 and PRKAG1 in community 3 (Autophagic Process and mTOR Signaling Pathway with the hubgene RPTOR) and CUL1 and SKP1, both parts of the proteolytic SCF can be found in community 8 (Proteolysis, Ubiquitinylation, Proteasome with the hubgenes RPS27A and UBA52). (Low level terms and Hubgenes can be found in the Network Figures in the Supplement of Publication 2).

The gene product of *CSNK1*, Casein kinase I (CK1), is a serine-threonine protein kinase that preferentially targets acidic proteins like caseins as substrates. It plays a role in numerous cellular processes, including DNA repair, cell division, nuclear localization, circadian clock regulation, and membrane transport. Additionally, CK1 is involved in developmental processes such as the Wnt signaling pathway and apoptosis. Seven monomeric isoforms of CK1 have been identified, namely alpha, beta, gamma1, gamma2, gamma3, delta, and epsilon, all of which appear to be involved in similar cellular processes (HATHAWAY & TRAUGH, 1982).

Interestingly, in vitro phosphorylation studies revealed that several sites within tau and TDP-43 are phosphorylated by CK1 δ (Kametani et al., 2009; G. Li, Yin, & Kuret, 2004). This phosphorylation seems to be responsible for spreading of TDP-43 in a prion-like manner from cell to cell because phosphorylated TDP-43 migrates from the nucleus into the cytoplasm (Posa et al., 2019) and co-localizes with tunneling nanotubes (TNTs) or TNT-like structures.

TNTs are significantly increased in sporadic ALS cells compared to healthy control cells maybe due to cellular stress (Y. Wang, Cui, Sun, & Zhang, 2011). They are built of actin in its polymeric

form F-actin, which interestingly also appears to be deregulated in community 5 (actin cytoskeleton/ cell communication). F-actin structures act as intercellular bridges that mediate the transfer of various cellular cargos and may well be involved in the transport of TDP-43 to other cells (Cordero Cervantes & Zurzolo, 2021; Cuevas et al., 2024). Cuevas et al. could show that CK1 inhibitors not only restore the functional homeostasis of TDP-43 pathology in a patient-derived cellular model of lymphoblasts but also prevent disease transmission among different cell types. CK1 inhibitors could therefore be an interesting therapeutic agent, not only for ALS but for all proteinopathies.

FUS, one of the most important risk genes in ALS (see paragraph 2.3.1) has been shown in mice to establish a novel feedback mechanism to regulate circadian gene expression. The core circadian protein REV-ERB α , binds to the Fus promoter and controls its expression. Concurrently, FUS is part of the same complex as PER/CRY and suppresses the expression of core circadian genes containing the E box motif, such as Per2 (Jiang et al., 2018).

Sleep disorders other than sleep-related breathing disorders due to progressive respiratory and upper airway muscle weakness have been less studied in ALS (Gnoni et al., 2023). However, accumulating evidence suggests that hypothalamic dysfunction and related SCN impairment may play a significant role in sleep disturbances in ALS patients (J. Liu et al., 2016).

Our data showed no irregularities in circadian genes at the transcriptomics level, but this could be attributed to the use of primarily blood samples for the transcriptomics data, as discussed earlier.

Overall, our data suggest differences in the impact on the circadian clock among the four NDDs, which is also consistent with the existing literature.

Chapter 8

Benefits and limitations of our research

Our research offers a valuable approach to studying the circadian clock or any other specialized field of interest. Our community-based analysis provides insights into new patterns of gene functions that may not be discernable when investigating individual genes alone. For example, well-known genes regulating the circadian clock are clustered closely within communities AD_DEG6, PD_DEG10, and HD_DEG4, respectively, due to their frequent mention together in research literature and databases.

However, these communities also encompass hundreds of other genes (1620 in AD, 662 in PD, 716 in HD), some of which are scattered around the known clock genes. The Louvain algorithm has grouped these additional genes, including transcription factors and epigenetic modifiers, closely with the clock genes. This suggests that they may functionally belong to each other, even though they have not been previously identified together experimentally. Therefore, these newly identified genes, now placed in a new context, could be intriguing subjects for further investigation to better understand the workings of the circadian clock.

Our findings regarding the circadian clock come with limitations due to their reliance on existing data. Each of the four diseases affects a different part of the brain, leading to different regions being examined post-mortem. In AD, the entorhinal cortex, hippocampus, and frontal cortex; in PD, the substantia nigra in the striatum; in HD, the putamen in the striatum; and in ALS, the motor cortex and the spinal cord are the most studied brain regions. To make things even more complicated, some studies could only use blood or cerebrospinal fluid as they were conducted during the lifetime of patients. As each part

of the brain and every organ has its own circadian clock, these data sets are therefore not directly comparable.

Chapter 9

Future work

The circadian clock and the sleep-wake cycle are multilayered, interconnected systems that affect brain function and neurodegeneration by multiple mechanisms. Despite great progress in understanding the basic mechanisms governing the circadian clock, our knowledge of how these systems are affected in the brain during aging and neurodegeneration is still rather superficial.

For future research, it would be particularly interesting to focus on single organs like the SCN or liver and obtain single-cell, post-mortem data specifically about the respective circadian clock in isolation. Comparing the data of all four diseases for a singular organ might lead to insights that clearly allow distinguishing these diseases.

It would also be interesting to compare early and late stage single-cell tissue per disease to investigate how differences in the clock evolve. Improved understanding of the role of involved and dysregulated proteins could lead to the development of pharmacological agents that, at a minimum, counter the decline of the sleep/wake cycle, but maybe even could delay the onset of symptoms by improving circadian regulation of proteostasis or reducing inflammation.

A more detailed understanding of the mechanism by which specific NDDs and pathogenic proteins influence the circadian and sleep systems, could also be gained by investigating the connection between central and peripheral circadian clocks and its effects on metabolic pathways and vice versa. As lifestyle in the industrialized world is not only characterized by too little sleep due to electrical light and stress but also by constant food abundance, leading to a dysbalance of the two most influential metabolic pathways, the catabolic AMPK- and the anabolic mTOR pathway, consequences of modern lifestyle are

not only a deranged circadian clock but also a deranged metabolism, which manifests in mounting cases of obesity, insulin resistance, diabetes and even neurodegeneration and cancer.

As elaborated in paragraphs 7 and 7.1 the circadian clock plays a key role in many physiological processes including cellular metabolism, inflammation, cell cycle, and redox homeostasis, very similar to the consequences of a deregulated metabolism. Revealing the complex reciprocal relationship between circadian clock and metabolic pathways, in which perturbations in one system affect the other one, could help to find new targets for early medication in order not to let this vicious circle arise in the first place.

Chapter 10

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Chapter 11

Appendix

11.1 List of circadian genes and their function

	Gene names	Paralogs	Function in circadian clock	Other known functions
AMPK	Adenosinmono-phosphat kinase 7 catalytic subunits PRKAA1,2 PRKAB1,2 PRKAG1,2,3		Connects circadian rhythm and metabolic processes by phosphorylating and thereby destabilizing CRY1	Energy sensor protein kinase. In response to reduction of intracellular ATP levels, AMPK activates energy-producing and inhibits energy-consuming processes
BHLHE40 =DEC1	Basic Helix-Loop-Helix Family Member E40	BHLHE41 = DEC2	Transcriptional repressor of BMAL1 and clock-controlled genes	Regulates peroxisome and mitochondrion biogenesis and functions, plays an important role in the skeletal muscle oxidative metabolism of unsaturated fatty acid and glucose (Chang et al., 2019), can be activated by hypoxia, immune factors, growth factors, and oxidative stress (Liu et al., 2023)
BMAL1	Brain and muscle ARNT-like protein 1	BMAL2	Together with CLOCK, BMAL1 forms the core positive feedback loop of the circadian clock during daytime. BMAL1/CLOCK activates transcription of its own repressors <i>Period</i> and <i>Cryptochrome</i>	Involved in gluconeogenesis, lipogenesis (Sancar et Brunner, 2014), regulation of interferon-stimulated genes, important factor in viral infection (Ehlers et al., 2018)
BTRC	Beta-Transducin Repeat Containing E3 Ubiquitin Protein Ligase		Substrate recognition component of a SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins.	Tumor-suppression gene, downregulated BTRC can significantly promote the invasion, migration, and mesenchymal transition of glioma cell lines (Zhou et al., 2021).
CIART	Circadian Associated Repressor Of Transcription		Represses the transcriptional activator activity of BMAL1/CLOCK independent from CRY1,2 and BHLHE41, by competing for the E-box elements of circadian gene promoters (Courtin et al., 2023)	Interacts with the glucocorticoid receptor (NR3C1) and contributes to the repressive function in the glucocorticoid response (By similarity). Key factor for SARS-CoV-2 infection (Tang et al., 2023)
CLOCK	Circadian locomoter output cycles protein kaput	NPAS2	Together with BMAL1, CLOCK forms the core positive feedback loop of the circadian clock during daytime. BMAL1/CLOCK activates transcription of its own repressors PER and CRY	Mutations have been linked to metabolic syndrome, infertility, mood disorders (Liu et al .,2022). CLOCK/BMAL1 activate transcription of <i>NAMPT</i> , leading to NAD, which is a cofactor for SIRT1 (Nakahata et al., 2009)
CREB1	Cyclic AMP-responsive element-binding protein 1			Induces transcription of genes in response to hormonal stimulation of the cAMP pathway
CRY1	Cryptochrome-1	CRY2	Together with PER1/2/3 forms core negative feedback loop of the circadian clock, regulates CLOCK/BMAL1 and second feedback loop	Involved in lipid and glucose metabolism by modulating the canonical Wnt/ β -catenin signaling pathway (Sun et al., 2018; Kalsbeek

			NR1D1/2/RORA/B/G, which activate and repress BMAL1 transcription. With CRY2, is dispensable for circadian rhythm generation but necessary for rhythm synchrony	et al., 2014), limits exercise capacity in skeletal muscles (Jordan et al., 2017)
CSNK1D=CK1δ	Casein kinase I isoform δ	CSNK1E=CK1ε	Determines the circadian period length, through the regulation of the speed and rhythmicity of PER1 and PER2 phosphorylation, controls PER1 and PER2 nuclear transport and degradation (Shirogane et al., 2005)	Participates in Wnt signaling and is part of β-catenin destruction complex (Liu et al., 2002). Positive regulator of mTORC1 and mTORC2 signaling in response to nutrients (GAO et al., 2011; Szwed et al., 2021), segregates chromosomes during mitosis (Brockman et al., 1992), regulates epithelial cell migration (Kuga et al., 2013), and inhibits NLRP3 inflammasome assembly (Li et al., 2020)
CUL1	Cullin-1		Cullin forms the major structural scaffold of the SCF complex and links the SKP1 domain to the RBX1 domain	
DBP	D-Box Binding PAR BZIP Transcription Factor		Resets circadian clock and plays key roles in the circadian inputs and outputs (Yoshitane et al., 2019)	Involved in detoxification and drug metabolism (Gachon et al., 2006)
EP300	E1A Binding Protein P300		Participates in CLOCK or NPAS2-regulated rhythmic gene transcription and correlates with increase in PER1/2 mRNA and histone H3 acetylation on the PER1/2 promoter (Curtis et al., 2004)	Histone acetyltransferase for all four core histones in the nucleosome, regulating transcription via chromatin remodeling
FBXL3	F-box/LRR-repeat protein 3		Substrate-recognition component of the SCF(FBXL3) E3 ubiquitin ligase complex involved in circadian rhythm function. Plays a key role in the maintenance of both the speed and the robustness of the circadian clock oscillation and mediates ubiquitination and subsequent degradation of CRY1 and CRY2 (Scott et al., 2016)	
FBXW11	F-box/WD repeat-containing protein 11		FBXW11 controls clock-dependent transcription via degradation of phosphorylated PER1 and phosphorylated PER2 and plays a key role in NF-kappa-B activation (Shirogane et al., 2005)	
NFIL3	Nuclear Factor, Interleukin 3 Regulated		Represses PER1 and PER2 expression	As a transcriptional regulator represses transcription of many cellular and viral genes

NR1D1=REV-ERBa	Nuclear receptor subfamily 1 group D member 1	NR1D2=REV-ERBβ	Forms a critical negative limb of the circadian clock by directly repressing the expression of core clock components BMAL1, CLOCK and CRY1	Transcriptional repressor coactivated by heme-binding. Regulates lipid and bile acid metabolism, adipogenesis, gluconeogenesis (Duez et al., 2008) and the macrophage inflammatory response (Pourcet et al., 2018)
PER1	Period circadian regulator 1	PER2 PER3	Together with CRY1/2 forms core negative feedback loop of the circadian clock, regulates CLOCK/BMAL1 and second feedback loop NR1D1/2/RORA/B/G, which activate and repress BMAL1 transcription, respectively	Modulates neuroinflammation by regulating the release of inflammatory mediators, such as CCL2 and IL6. In spinal astrocytes, represses the activation of NFκB (Sugimoto et al., 2014). Involved in regulation of renal sodium reabsorption (Stow et al., 2012). Modulates hair follicle cycling (Al-Nuaimi et al., 2014)
RBX1	Ring-Box1, E3 ubiquitin-protein ligase		Assists the transferral of ubiquitin from E3 to a lysine residue on the target protein (Wei et Sun, 2010)	
RORA	Nuclear receptor ROR-α	RORB RORC	Influences the period length and stability of the clock and regulates circadian expression of CLOCK, BMAL1, NPAS2 and CRY1. Competes with NR1D1 for binding to promoters of BMAL1, CRY1 and NR1D1 itself, resulting in NR1D1-mediated repression or RORA-mediated activation of clock genes expression	Key regulator of embryonic development, cellular differentiation, immunity, as well as lipid, steroid, xenobiotics, bone and glucose metabolism (Cook et al., 2015)
SCF=FBXL21	SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase complex consists of: BTRC, CUL1, FBXL3, FBXW11, RBX1, SKP1		multi-protein E3 ubiquitin ligase complex that catalyzes the ubiquitination of proteins involved in circadian rhythmicity	involved in cell cycle progression, signal transduction and transcription
SKP1	S-phase kinase-associated protein 1		SKP1 is an adaptor protein that is essential for the recognition and binding of F-box proteins	
SIRT1	Sirtuin 1		Acetylates histones in a rhythmical manner, thus contributing to circadian chromatin remodeling. Regulates the circadian expression of several core clock genes, including BMAL1, RORC, PER2 and CRY1 (Asher et al., 2008)	Together with ATP-dependent AMPK, NAD-dependent SIRT1 is involved in almost every cell function such as cell cycle, response to DNA damage, metabolism, apoptosis, and autophagy (Rahman et Rezuanul, 2011)

Figure 11.1: Circadian and metabolic or other functions of circadian genes from KEGG Pathway hs04710 (Proteins forming complexes are marked by the same color code)

11.2 Communities of circadian genes designated by Louvain Algorithm

KEGG hs04710	AD	PD	HD	ALS
AMPK=PRKAA1	DEG_12, Prot_6	/	/	Prot_3
AMPK=PRKAA2	DEG_12	/	/	/
AMPK=PRKAB1	DEG_12, Prot_6	Meth_5	/	/
AMPK=PRKAB2	DEG_12, Prot_6	/	/	Prot_3
AMPK=PRKAG1	DEG_12	/	/	Prot_3
AMPK=PRKAG2	DEG_12	/	/	/
AMPK=PRKAG3	/	/	/	/
BHLHE40=DEC1	DEG_6, Meth_4	Meth1	DEG_10	/
BHLHE41=DEC2	DEG_6	/	DEG_10	/
BMAL1	DEG_6, Meth_4	/	DEG_10	/
BMAL2	DEG_6	DEG_4	/	/
BTRC (SCF)	DEG_6	DEG_6	DEG_10	/
CIART	DEG_6	/	/	/
CLOCK	DEG_6	DEG_4	/	/
NPAS2	DEG_6	DEG_4	/	/
CREB1	DEG_6	/	DEG_10	/
CRY1	DEG_6	/	DEG_10	/
CRY2	DEG_6	DEG_4	DEG_10	/
CSNK1D=CK1 δ	DEG_11, Prot_6	DEG_7	DEG_12	Prot_1
CSNK2E=CK2 ϵ	DEG_11, Meth_4	Meth_5	/	Prot_1
CUL1 (SCF)	DEG_8, Meth_8	/	/	Prot_8
DBP	DEG_6	DEG_4	DEG_10	/
EP300	DEG_6	/	/	/
FBXL3 (SCF)	DEG_8	/	/	/
FBXW11 (SCF)	DEG_8	/	/	/
NFIL3	DEG_6	/	/	/
NR1D1=REV-ERBa	DEG_6	/	/	/
NR1D2=REV-ERB β	DEG_6	SNP6	/	/
PER1	DEG_6	/	DEG_10	/
PER2	DEG_6	DEG_4	/	/
PER3	DEG_6	DEG_4	/	/
RORA	DEG_6, Meth_4	/	/	/
RORB	DEG_6	Meth_1	/	/
RORC	/	/	/	/
SKP1 (SCF)	DEG_8	DEG_6	/	Prot_8
SIRT1	DEG_6	/	DEG_10	/

Figure 11.2: Communities of circadian genes designated by Louvain Algorithm for all four diseases. (Communities of all differentially expressed genes and proteins from which this list was extracted can be found in Table 1 in the supplement of Publication 2)

List of Figures

1.1	Possible Origins of NDDs NDDs result from a complex interplay of genetic, environmental and lifestyle factors. The genetics sector shows genes, that predispose to AD, PD, ALS, and HD, which will be discussed in further detail in paragraphs 2.1.1, 2.2.1, 2.3.1, and 2.4.1. Environmental factors like air pollution, exposure to toxins or traumatic brain injuries but also chosen lifestyle factors can further induce neurodegenerative processes. (Adapted from Hecker et al., 2021)	2
1.2	Categorization of neurodegeneration Neurodegeneration can result from physical damage, glial or neuronal cell decay both in the CNS and PNS, which can lead to different types of NDDs.	6
1.3	Proteinopathy-induced neurodegeneration Impaired protein homeostasis can lead to misfolding and aggregation of predisposed proteins, which form neurotoxic oligomers. These oligomers can spread transsynaptically in a prion-like manner and can even cross seed other proteins like tau. To eliminate these toxic oligomers, an inflammation reaction is triggered, characterized by elevated levels of pro-inflammatory cytokines like $\text{TNF}\alpha$ and IL-6. This leads to the activation of reactive astrocytes and microglia, which, in a self-perpetuating cycle, contribute to chronic neuroinflammation and consequently exacerbate neuronal damage.	8

2.1 Amyloid formation in AD The amyloid cascade model suggests that developing AD is linked to the accumulation of A β driven by the faulty cleavage of the APP, resulting in increased levels of amyloid β (A β) in terms of both quantity and altered quality. Under physiological conditions, 90% or more of APP is first cleaved by α -secretase (ADAM 10), that cuts APP within the A β domain, generating a membrane-anchored fragment (C83) and releasing soluble APP α . C83 is then cleaved by γ -secretase complex consisting of subunits presenilin, nicastrin, Aph-1, and Pen-2, releasing p3 fragment and AICD. The remaining 10% of APP is cleaved by β -secretase (BACE1) at the N-terminal end of the A β domain, resulting in the release of sAPP β from a membrane-anchored fragment C99. This C99 fragment is further cleaved by γ -secretase to produce A β in the intraluminal space and AICD in the cytosol. (Adapted from Hur et al., 2022) 14

5.1 Studies published in PubMed concerning NDDs and epigenetics from 1990 to Aug 2024 Global methylomic assessments have only gained significant momentum in the past 5 to 10 years 141

6.1 Hallmarks and low-level terms defining neurodegeneration Six hallmarks categorized according to their primary location or mode of action with their 69 subcategories found in GO term analyses, KEGG pathways, and StringDB terms. The color scheme is used for the network figures in paper 2. (Adapted from Ramanan 2013) 146

7.1 Reasons and effects of circadian clock disruption Chronic disruption of the circadian clock due to consistently poor sleep quality can significantly affect vital physiological processes, potentially leading to chronic diseases. 152

7.2 The four stages of a sleep cycle and its effects on body and brain functions Sleeping consists of 4 to 6 sleep cycles per night, which can be divided into three NREM and one REM phase while restoring body and brain functions. (Adapted from Patel, 2024) 154

- 7.3 Central and peripheral clocks regulating physiology and behaviour The central clock in the SCN is predominantly controlled by light and aligns with the peripheral clocks in the body and other brain regions through neuronal and hormonal signals. Additional Zeitgebers that synchronize the peripheral clocks are feeding-fasting rhythms, physical activity and body temperature. (Adapted from Hickie et al., 2013) 155
- 7.4 Mechanism of circadian clock The circadian clock consists of three interlocked transcriptional feedback loops. The core feedback loop is activated by light, during which CLOCK and BMAL1 dimerize and activate the *Per1*, *Per2*, *Cry1*, and *Cry2* genes. During daytime, the proteins Period (PER1, PER2) and Cryptochrome (CRY1, CRY2) accumulate and begin to dimerize and translocate to the nucleus, where during night time they repress transcription of several clock-controlled genes (ccg)(not shown) and their own transcription by destabilizing the CLOCK:BMAL1 complex. With no new PER1/2 and CRY1/2 being generated and the existing PER1/2:CRY1/2 dimer being degraded during night, CLOCK and BMAL1 again dimerize. In a second feedback loop, CLOCK and BMAL1 indirectly also regulate the expression of the *Nr1d1/2* genes, which encode the nuclear receptors REV-ERB α and β , respectively. These nuclear receptors compete with the retinoic acid-related orphan receptors, ROR α , ROR β , and ROR γ , for binding to *BMAL1* and *NFIL3* gene promoters, thereby fine adjusting the regulation of BMAL1 transcription. In a third feedback loop, NFIL3 together with D-box binding protein (DBP), as well as CLOCK and BMAL1, regulate a rhythm in the REV-ERB α/β nuclear receptors. These three interlocked transcriptional feedback loops regulate the majority of cycling genes, leading to rhythms in various different physiological systems, from sleep to metabolism and aging. . 157

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Fig. 1.1, 2.1, 7.1 to 7.3 were created by BioRender.com

Fig. 1.2 and 1.3 were created by Lucidchart.com

Fig. 7.5 to 7.8 were created by BioComet, a Community Explorer for Multi-omics Data by Nicolas Ruffini

11.3 Electronic supplement