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Shihao Huang, Zhihao Song, Jiayue Pan, Yixiao Luo & Yun Chen

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The emerging role of Circular RNAs in Neuropsychiatric Disorders

Shihao Huang^{1,2#}, Zhihao Song^{3#}, Jiayue Pan⁴, Yixiao Luo^{5,6,7*}, Yun Chen^{1,4*}

¹ Wuhan Asia Heart Hospital affiliated to Wuhan University of Science and Technology;

² Department of Neurobiology, School of Basic Medical Sciences, National Institute on Drug Dependence, Peking University, Beijing, China;

³ Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, China;

⁴ School of Medicine, Wuhan University of Science and Technology, Wuhan, China, 430065;

⁵ Beijing Key Laboratory of Mental Disorders, National Clinical Research Center for Mental Disorders & National Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China;

⁶ Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China;

⁷ The First-Affiliated Hospital of Hunan Normal University, Hunan Province People's Hospital, Changsha, 410081, China.

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#These authors contributed equally

* Corresponding author:

Prof. Yixiao Luo

Beijing Key Laboratory of Mental Disorders, National Clinical Research Center for Mental Disorders & National Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China.

E-mail: luoyx@hunnu.edu.cn

Dr. Yun Chen

Wuhan Asia Heart Hospital affiliated to Wuhan University of Science and Technology.

E-mail: chenycuncy@wust.edu.cn

Abstract

Circular RNAs (circRNAs) are a unique class of endogenous, single-stranded non-coding RNAs characterized by a covalently closed circular structure. They exhibit tissue-specific expression patterns and have been implicated in the pathogenesis of a wide range of diseases. In the brain, circRNAs are abundantly expressed and evolutionarily conserved, where they play critical roles in neurodevelopment, neuronal differentiation, and synaptic plasticity. Recent studies have revealed that circRNAs are broadly expressed across eukaryotic species and display distinct expression profiles associated with various pathological conditions, particularly neuropsychiatric disorders. However, despite the identification of thousands of circRNAs through high-throughput sequencing technologies, only a small subset has been functionally characterized. In this review, we underscore the emerging significance of circRNAs in neurological and psychiatric disorders. Their exceptional stability and diverse modes of action suggest that circRNAs could serve as key nodes within future precision medicine frameworks. Nevertheless, progress toward clinical translation is currently limited by incomplete mechanistic understanding, small study cohorts, and persistent challenges in therapeutic development. To overcome these barriers, more systematic, large-scale, and mechanism-driven investigations, coupled with innovative strategies and technologies, will be required to fully realize the clinical potential of circRNAs.

Keywords: circular RNAs; brain development; neuron differentiation; synaptic plasticity; neuropsychiatric diseases

1. Introduction

The advent of the 21st century witnessed a paradigm shift in molecular biology, as evidenced by large-scale projects such as FANTOM3 [1], demonstrating extensive non-coding RNAs (ncRNAs) expression across murine tissues despite the absence of identifiable open reading frames (ORFs). These findings emphasized the functional importance of ncRNAs. Comprehensive transcriptomic studies have uncovered that nearly 90% of the human genome undergoes transcription, with merely 1-2% of these transcripts encoding proteins, while the majority are classified as ncRNAs [2]. A substantial proportion of ncRNAs are highly expressed in the mammalian brain, exhibiting precise spatiotemporal patterns, suggesting they have significant functional roles rather than being mere transcriptional byproducts [3].

As a distinct category within the ncRNA family, circular RNAs (circRNAs) distinguished by their unique circular structure formed through an atypical "back-splicing" event, where the 5' and 3' splice sites are covalently joined to create a closed-loop RNA [4-7]. CircRNAs exhibit considerable diversity in both their biogenesis and structural organization. This diversity gives rise to multiple subtypes, including single-exon circRNAs, multi-exon circRNAs, exon-intron circRNAs (EicRNAs), and intronic circRNAs (ciRNAs), each potentially exerting distinct functional roles [8-10]. First identified in viroids during the 1970s [11], these circular molecules were predominantly considered superfluous products resulting from aberrant splicing events in eukaryotic systems for many years [12]. However, the development of sophisticated sequencing platforms and innovative computational tools have propelled circRNAs to the forefront of RNAs research in the past decade [13-15]. In general, circRNAs contain binding sites for specific microRNAs (miRNAs) and function as miRNAs sponges, thereby reducing the bioavailability of these short non-coding RNAs [15,16]. Furthermore, the central nervous system exhibits particularly

high expression levels of circRNAs [14,17], where they can regulate neuronal development, synaptic plasticity, and neurogenesis, processes often disrupted in neuropsychiatric disorders.

Neuropsychiatric disorders, including depression, schizophrenia (SCZ), autism spectrum disorder (ASD), and neurodegenerative diseases such as Alzheimer's and Parkinson's, affect millions globally and present substantial challenges for diagnosis and treatment. These disorders are characterized by dysfunctions in brain regions and circuits that underlie emotional regulation, cognition, and behavior [18-22]. The complexity of neuropsychiatric conditions arises from the interplay of genetic, environmental, and neurobiological factors, with many disorders showing a clear hereditary component. Despite extensive research, the precise molecular mechanisms underlying these disorders remain largely unclear. Recent studies highlight the potential importance of non-coding RNAs, particularly circRNAs, in modulating disease-related pathways.

Current research has revealed the potential involvement of circRNAs in modulating essential neurobiological processes such as synaptic function, neuronal plasticity, and stress responses, which are disrupted in neuropsychiatric disorders [23] [24]. Altered circRNA expression has been observed in multiple conditions, such as depression [25], Alzheimer's disease (AD) [26], and Parkinson's disease (PD) [27], suggesting their potential involvement in disease pathogenesis. Moreover, their stability and tissue-specific expression profiles have made circRNAs attractive candidates as biomarkers for diagnosing and monitoring the progression of these conditions [28].

In this review, we first overview the relationship between circRNAs and brain development. Then, we summarize the latest research exploring the roles of circRNAs in neuropsychiatric disorders, and highlight the promising clinical potential of these molecules as disease-specific biomarkers for diagnosis and prognostic. Finally, we discuss unresolved issues regarding the role of circRNAs in neuropsychiatric disorders that require further investigation.

2. CircRNAs: Contributions to Brain Development and Plasticity

2.1 *CircRNAs and Brain Development*

CircRNAs, identified as dynamically expressed molecules in the mammalian brain, have profoundly reshaped our understanding of gene regulation during neurodevelopment. In 2015, the first study reported that circRNAs exhibit distinct spatiotemporal expression patterns in mammals, with unbiased analyses revealing their highly complex regulatory landscape [29]. Subsequent research has further uncovered their critical roles in brain development, particularly in neuronal differentiation, axon growth, and synapse formation[30-32].

CircRNAs are highly upregulated during both early and late stages of human pregnancy, participating in key neurodevelopmental pathways, including axonogenesis, neuron guidance, and synaptic organization [33]. For example, circSLC45A4, which is highly expressed in the frontal cortex of human embryos at 22 weeks of gestation, regulates neuronal differentiation, and its perturbation leads to spontaneous differentiation of SH-SY5Y neuroblastoma cells [34]. Comparative analysis across species further reveals that brain tissue exhibits significantly higher abundance and diversity of circRNAs compared to other organ systems [15,35]. In rodents, the expression of circRNAs in the brain increases progressively with age, with the lowest levels observed in young rats and a steady rise throughout development [35]. Specific circRNAs, such as those transcribed from Pvt1, Ano3, Sec14l5, and Rnf169 genes, show continuous upregulation from embryonic stages to adulthood, where their corresponding linear mRNA transcripts peak postnatally [36]. Similarly, transcriptomic profiling of the porcine cerebral cortex further demonstrates that circRNAs expression are developmentally regulated. Upregulated transcripts converge on stress adaptation, reproductive and immune regulation, and metabolic control,

whereas downregulated transcripts predominantly involve neuronal function, stress pathways, and signal transduction, highlighting the dynamic reprogramming of circRNAs networks during cortical maturation [37].

Taken together, these findings suggest that circRNAs exhibit evolutionarily conserved yet species-specific expression patterns, regulating key neurodevelopmental processes in stage-dependent manner. Their dynamic expression implies a fundamental role in orchestrating neuronal maturation, connectivity, and plasticity during brain development.

2.2 CircRNAs in Neuron Differentiation and Synaptic Plasticity

Beyond their roles in early neurodevelopment, circRNAs are key regulators of neuro differentiation and synaptic plasticity, both of which are critical for cognitive functions [14,17,32,38,39]. Their expression varies across distinct brain regions, including the prefrontal cortex, olfactory cortex, striatum, cerebellum, and hippocampus, with many exhibiting region-specific enrichment [14]. Notably, an analysis of 6231 brain-expressed circRNAs identified 4030 shared between the cortex and hippocampus, while others displayed region-specific expressed patterns, suggesting specialized functional roles [40].

Many circRNAs originate from genes that regulate neuronal differentiation and synaptic transmission [17,41]. Moreover, subcellular localization studies indicate that a significant proportion of this circRNAs are concentrated in synaptoneurosomes, where they may directly influence synaptic function [14,17]. At the molecular level, circRNAs modulate synaptic activity by regulating synaptic protein expression, long-term potentiation (LTP), and long-term depression (LTD) [42],[43]. They also participate in key signaling pathways, including NMDA receptor-mediated signaling, MAPK signaling, and GABA receptor function, which govern synaptic

plasticity and neurotransmission [44,45]. Importantly, synaptic activity itself regulates circRNA expression, suggesting a reciprocal relationship between circRNAs and synaptic modifications [17].

Together, these findings highlight circRNAs as integral components of neuron differentiation and synaptic remodeling. Their ability to fine-tune synaptic efficacy and plasticity suggests that they play crucial role in higher-order cognitive processes such as learning and memory.

2.3 Brain Development and Neural Plasticity Regulated by CircRNAs

CircRNAs influence brain development through diverse molecular mechanisms, including interactions with microRNAs (miRNAs), RNA-binding proteins (RBPs), and transcription factors, forming intricate regulatory networks that govern neuronal differentiation and plasticity [46-50]. Their ability to act as miRNA sponges, sequestering specific miRNAs to modulate gene expression, is a well-documented mechanism by which circRNAs shape neural development. For example, circZNF827 interacts with miRNAs involved in neuronal differentiation, thereby regulating the expression of genes essential for neurogenesis [51].

CircRNAs also regulate synaptic function by influencing the expression and localization of synaptic proteins. Studies have shown that certain circRNAs modulate PSD-95, synaptophysin, and AMPA receptor subunits, thereby affecting synaptic strength and plasticity [17,52,53]. Additionally, circRNAs participate in epigenetic regulation, influencing chromatin remodeling and transcriptional programs that govern neuronal differentiation and maturation [54,55].

To comprehensively examine the molecular mechanisms by which circRNAs influence neuronal differentiation and synaptic plasticity, we compiled key findings in Table 1. Additionally, we also examining how these molecules contribute to brain development through complex direct and indirect actions (**Figure 1**). Based on the available evidence, we conclude that circRNAs in

the brain not only contribute to neuronal differentiation and maturation but also exert broader regulatory influences on synaptic plasticity and neural circuit development. Their spatiotemporal expression patterns and ability to interact with diverse molecular partners highlight their fundamental role in shaping the structural and functional organization of the brain. Further research is essential to uncover the precise mechanisms through which circRNAs influence neurodevelopment and their potential roles in neuropsychiatric disorders.

3 CircRNAs: Implications in Neuropsychiatric Disorders

3.1 CircRNAs in neurological diseases

3.1.1 Alzheimer's Disease

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is pathologically characterized by the accumulation of neurotoxic amyloid β protein ($A\beta$), hyperphosphorylation of tau plaques, neuroinflammation, and extensive neuronal atrophy within the brain [56-58]. Emerging evidence from circular transcriptome studies has revealed significant alterations in circRNAs expression profiles in AD patients compared to healthy controls, as demonstrated through analyses of cerebrospinal fluid, peripheral blood, and brain region samples [59-63].

Recent investigations have identified 408 differentially expressed circRNAs in the prefrontal cortex of AD patients, with particular attention to two circular transcripts of GSK3 β that correlate with tau protein hyperphosphorylation [64]. Furthermore, Dube et al. identified 3,547 differentially expressed circRNAs, including 28 transcripts whose expression levels strongly correlated with dementia severity, neuropathological progression, and AD diagnosis [65]. These findings are corroborated by studies in AD animal models, where 253 aberrantly expressed circRNAs were identified in SAMP8 mice, a model for sporadic AD [66-71]. Bioinformatics analyses suggest these

circRNAs primarily modulate AD progression through A β clearance, myelin function regulation, and synaptic maintenance [71].

The functional implications of circRNAs in AD are extensive, encompassing RNA splicing, autophagosome assembly, cytokinesis, apoptotic processes, and various signaling pathways including adenylyl-activated protein kinases (AMPK) and p53 [68,70,72], which are intricately linked to AD pathology [73,74]. As illustrated in Figure 2 and Table 2, most AD-associated circRNAs function as miRNA sponges, influencing cell apoptosis, inflammatory responses, and oxidative stress, thereby contributing to cognitive impairment and memory loss. Notably, certain circRNAs may synergistically promote neurotoxic A β formation, creating a vicious cycle that exacerbates AD progression. The discovery of circular tau proteins, generated through rolling circle translation of circRNAs from the human tau gene, further underscores the complex role of circRNAs in AD pathology [75]. Collectively, these findings underscore the contribution of differential circRNAs expression to the pathological changes and progression of AD.

It is well known that circRNAs exhibit high stability in exosomes and plasma [72], which endows them with significant potential as diagnostic biomarkers for diseases [76,77]. A recent study showed a substantial correlation between the expression of circRNAs and clinical and neuropathological severity of dementia [65]. Notably, changes in circRNAs expression occurred before the considerable symptoms of AD emergence and were significantly associated with autosomal dominant AD [65]. These results imply that circRNAs may be used not only as a diagnostic marker for AD but also as a predictor of AD risk.

Furthermore, circRNAs have been considered to be promising therapeutic targets in the context of AD. *Panax notoginseng* saponins, the main active ingredient of herbal medicine, have demonstrated efficacy in enhancing cognitive function, reducing A β deposition, and mitigating

oxidative stress in AD models [78][79]. AD model mice treated with total saponin from *Panax ginseng*, the treatment significantly altered the expression of some circRNAs in the hippocampus. Further exploration demonstrated that these circRNAs were involved in AD-related molecular pathways and biological processes, suggesting that PNS may relieve AD-related symptoms by regulating the expression of AD-related circRNAs [69]. Similarly, berberine is another herbal medicine that has been shown to effectively alleviate AD symptoms and play a key role in neuroprotection [80,81]. In human neuronal (HN) cells treated with A β 42, berberine was found to upregulate the expression of circHDAC9, thereby mitigating the neurotoxic effects of A β 42 [82]. This suggests that berberine exerts neuroprotective effects in AD patients through the circHDAC9 pathway. These findings indicate that strategies targeting circRNAs hold significant clinical potential in the treatment of AD and the alleviation of its associated symptoms.

In summary, circRNAs are fundamentally involved in the progression from normal cognitive function to AD pathogenesis, primarily through their distinct expression profiles. Their dual potential as both diagnostic biomarkers and therapeutic targets holds significant promise for the development of early intervention strategies and more effective clinical management of AD.

3.1.2 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons in the substantia nigra. Recent advancements in next-generation sequencing have revealed a significant number of differentially expressed circRNAs in the cortex, hippocampus, striatum, and cerebellum of PD mouse models [83]. Bioinformatic analyses indicate that these circRNAs are intricately involved in critical neuronal processes, including the cGMP-PKG signaling pathway, glutamatergic synaptic transmission, axonal guidance, and neurogenesis-associated

cellular morphogenesis, thereby playing a pivotal role in PD pathogenesis [84-86].

A hallmark of PD pathology is the abnormal accumulation of alpha-synuclein (α -Syn) [87]. Among the circRNAs implicated in PD, CDR1as has emerged as a key regulator by functioning as a molecular sponge for miR-7, effectively sequestering and negatively regulating its expression [15,88]. The miR-7, in turn, inhibits α -Syn mRNA translation by targeting its 3'-UTR, thereby reducing α -Syn protein levels and protecting neurons from oxidative damage [89]. Additionally, miR-7 promotes the clearance of α -Syn aggregates through autophagy induction [90] and exerts neuroprotective effects via the NF- κ B pathway [91]. Notably, the therapeutic drug pramipexole has been shown to modulate this pathway by reducing miR-7 expression, leading to decreased α -Syn levels, further underscoring the clinical relevance of this regulatory axis.

Another critical circRNA, circDLGAP4, is significantly downregulated in PD models. Functional studies demonstrate that circDLGAP4 regulates miR-134-5p and CREB expression, thereby maintaining cell viability, reducing apoptosis, mitigating mitochondrial damage, and enhancing autophagy [92]. Furthermore, circDLGAP4 recruits EIF4A3 to upregulate HMGA2, increasing its mRNA stability, which contributes to neuroprotection in PD through the attenuation of inflammation and oxidative stress [93]. As summarized in Table 3, PD-associated circRNAs predominantly function as miRNA sponges, influencing dopaminergic neuron survival by modulating apoptosis, inflammation, and α -Syn expression. The expression levels of these circRNAs are closely correlated with the severity of clinical manifestations in PD, and their restoration has been shown to attenuate neurodegeneration, highlighting their potential as neuroprotective agents and therapeutic targets.

3.1.3 Other neurological diseases

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the selective degeneration of motor neurons in the brainstem and spinal cord. Numerous studies have identified a significant number of differentially expressed circRNAs in the tissues and sera of ALS patients [94-97]. Among these, circSETD3 and circSUSD1 exhibit negative correlations with disease onset, while circTNRC6B and circFAM120A levels are positively associated with functional impairment [96]. Notably, circTNRC6B levels also correlate negatively with disease duration and survival time, and both circSUSD1 and circTNRC6B demonstrate high specificity and sensitivity as potential diagnostic biomarkers [96]. Furthermore, Mutations in the FUS gene, a known risk factor for ALS, have been shown to disrupt circRNA biogenesis, suggesting that FUS-regulated circRNAs may contribute to ALS pathogenesis [98-100]. However, direct evidence linking circRNAs to ALS progression remains limited, warranting further investigation.

Huntington's Disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by CAG trinucleotide repeat expansions in exon 1 of the HTT gene [101]. The HTT CAG mutation has been shown to impair circRNA biogenesis, with circRNA expression decreasing monotonically as CAG repeat lengths increase [102]. Interestingly, circHTT, derived from exons 2-6 of the HTT gene, is upregulated in the posterior cerebral cortex of HD patients, and its expression positively correlates with CAG repeat numbers [103,104]. Increased circHTT levels contribute to HD pathogenesis by reducing cell proliferation, decreasing nuclear HTT localization, and altering nuclear and cellular morphology [103,104]. These findings suggest that an imbalance between linear mRNAs and circRNAs may disrupt neural adaptation, driving HD progression.

Multiple System Atrophy

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease with limited circRNA research to date. A single study has identified and validated five circRNAs—originating from IQCK, MAP4K3, EFCAB11, DTNA, and MCTP1—in the frontal cortex of MSA patients [105]. These findings provide a foundation for further exploration of circRNA roles in MSA pathology.

In summary, circRNAs play diverse and critical roles in the pathogenesis of various neurological diseases, including PD, ALS, HD, and MSA. Their involvement in key molecular pathways, coupled with their potential as diagnostic biomarkers and therapeutic targets, underscores the need for continued research into their functional mechanisms and clinical applications.

3.2 CircRNAs in psychiatric disorders

3.2.1 Depressive disorder

Depressive disorder, a prevalent emotional disorder, is characterized by persistent feelings of sadness, despair, and anhedonia. Recent advances have highlighted the potential of circRNAs as biomarkers due to their high stability, evolutionary conservation, and cell- or tissue-specific expression patterns [106,107]. Studies have identified numerous differentially expressed circRNAs in the blood of individuals with depressive disorder, some of which exhibit diagnostic and prognostic potential [25,108-111].

For instance, elevated levels of circHIPK2 in the blood of patients with major depressive disorder (MDD) correlate positively with anxiety and depression symptoms, and its dynamic changes predict antidepressant treatment efficacy [112]. This positions circHIPK2 as a promising diagnostic and prognostic biomarker. Additionally, circHIPK2 has emerged as a potential therapeutic target, with evidence suggesting that gut microbiota-mediated regulation of its expression influences astrocyte function, thereby contributing to depression pathogenesis [113].

Other circRNAs, including circZNF141, circRNA_103636, circFKBP8, circMBNL1, and circDYM, also show altered expression in MDD patients, offering novel diagnostic and therapeutic insights [109,110,114,115]. Notably, circDYM has been extensively studied for its role in depressive-like behaviors. Zhang et al. demonstrated that circDYM alleviates depressive-like behaviors by targeting miR-9 to regulate microglia activity [116], while Li et al. found that it mitigates hippocampal neuron injury via miR-497a-5p [117]. Clinically, circDYM levels are significantly reduced in MDD patients and correlate with depressive symptom severity [115]. Importantly, repetitive transcranial magnetic stimulation increases circDYM levels, and artificial vesicle-mediated delivery of circDYM can cross the blood-brain barrier to exert therapeutic effects [118]. These findings underscore the clinical potential

of circDYM in MDD treatment.

As summarized in Table 4 and illustrated in Figure 3, circRNAs contribute to depression through three primary mechanisms: (1) activating microglia to enhance inflammation and promote apoptosis, (2) impairing astrocyte structure and function, and (3) promoting neuronal apoptosis and impairing synaptic plasticity. Collectively, these studies highlight the pivotal regulatory role of circRNAs in depressive disorder pathology.

3.2.2 Schizophrenia

Research on circRNAs in SCZ remains limited, with only a few studies exploring their potential roles. Merely two teams have reported that circRNAs are differentially expressed in the brains of SCZ patients [119,120]. Mahmoudi et al. identified 1,142 differentially expressed circRNAs in the dorsolateral prefrontal cortex of SCZ patients, 30% of which originate from genes previously associated with SCZ [119]. Additionally, Zimmerman and colleagues found that the circHomer1a expression was significantly reduced in the prefrontal cortex of SCZ patients, which impaired cognitive flexibility and contributed to the development of SCZ by altering the expression of genes associated with synaptic plasticity and neurological diseases [120]. Furthermore, some research identified a significant amount of differentially expressed circRNAs in the peripheral blood of SCZ individuals [121-126]. Importantly, Yao et al. verified that the aberrant expression of circPLEKHA2 in the blood of SCZ patients could function as a novel potential diagnostic and therapeutic biomarker for SCZ [122].

The diagnosis of SCZ currently relies mainly on symptomatic changes and the clinical experience of psychiatrists. However, these subjective measures may lead to misdiagnosis or failure to diagnose. Therefore, it is necessary to explore objective indicators to improve the early diagnosis and prognosis of SCZ. CircRNAs are relatively stable and easy to detect in peripheral blood and exhibit high spatial,

temporal, and tissue specificity [41,127], implying their possibility to serve as biomarkers for SCZ diagnosis and treatment.

Current research on the role of circRNAs in SCZ remains in its nascent stage, with several critical challenges impeding progress. A primary limitation is the scarcity of well-characterized SCZ patient samples, which significantly constrains the validation of circRNAs as reliable diagnostic biomarkers or therapeutic targets. To establish the clinical relevance of circRNAs in SCZ, rigorous clinical studies with larger cohorts and comprehensive experimental validation are imperative. Additionally, the current SCZ animal models exhibit substantial limitations in recapitulating the complex pathophysiology of the disorder, thereby restricting investigations into the potential mechanistic roles of circRNAs in SCZ pathogenesis. Consequently, there is an urgent need for more sophisticated research approaches to elucidate the precise molecular functions and regulatory mechanisms of circRNAs in the etiology and progression of SCZ.

3.2.3 Bipolar disorder

Bipolar Disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of mania (or hypomania) and depression, representing extreme mood dysregulation. Emerging evidence has implicated circRNAs in the pathophysiology of BD. Notably, circCCNT2, a circRNA derived from the cell cycle-related gene CCNT2, exhibits significantly elevated levels in both the anterior cingulate cortex and peripheral blood lymphocytes of BD patients [128]. Intriguingly, lithium, a first-line mood stabilizer for BD, has been shown to reverse the aberrant expression of circCCNT2 in lymphocytes, suggesting its potential role as a therapeutic biomarker or modulator in BD treatment [128]. Another critical circRNA, circHomer1a, demonstrates significant downregulation in the prefrontal cortex and induced pluripotent stem cell-derived neurons of BD

patients. Its expression levels are inversely correlated with the duration of BD, implying a potential role in disease progression [120]. Furthermore, dysregulation of circRNAs derived from the NEBL and EPHA3 genes has been observed in the brains of BD patients [129]. Given EPHA3's established roles in memory function [130] and anxiety regulation [131], both core clinical features of BD—these findings suggest a plausible link between circRNA dysregulation and BD symptomatology.

Recent investigations have extended these findings to peripheral biomarkers, revealing widespread alterations in circRNA expression profiles in BD patients' blood. A comprehensive study identified 94 significantly dysregulated circRNAs in the peripheral blood of BD patients, potentially forming an endogenous regulatory network involving circRNA-miRNA-mRNA interactions that may contribute to BD pathogenesis [132]. Supporting these observations, Mahmoudi et al. reported 34 circRNAs with significant expression changes in BD patients' peripheral blood [121]. Owing to their tissue-specific expression patterns and remarkable stability in peripheral circulation, these circRNAs have emerged as promising candidates for diagnostic biomarkers in BD [129]. However, further validation through large-scale, longitudinal studies is required to establish their clinical utility and elucidate their precise roles in BD pathophysiology.

3.2.4 Autism spectrum disorders

Autism spectrum disorders are highly heritable neurodevelopmental conditions characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior, with emerging evidence implicating dysregulated circRNAs in their complex etiology. Recent investigations utilizing diverse ASD animal models have revealed substantial alterations in circRNA expression profiles, providing novel insights into the molecular underpinnings of ASD [133-136]. In the valproic acid-induced ASD mouse model, Wang et al. identified 1,059 differentially expressed circRNAs potentially

associated with critical ASD-related pathways, including the TGF- β , NOTCH, MAPK, and long-term depression (LTD) signaling pathways [135]. The BTBR T+tf/J (BTBR) mouse model, considered a robust representation of ASD pathophysiology, not only recapitulates core behavioral phenotypes (e.g., impaired social interaction, reduced ultrasonic vocalizations, and repetitive grooming behaviors) but also mirrors neurodevelopmental abnormalities and immunobiochemical alterations observed in human ASD [137-139]. Notably, in this model, researchers detected 29 upregulated and 12 downregulated circRNAs in the hippocampus, with circCdh9—derived from the ASD-associated Cdh9 gene—showing dysregulation across multiple ASD-relevant brain regions, including the prefrontal cortex and amygdala [136]. Among these, circCdh9 derived from the Cdh9 gene that is a key pathogenic gene of ASD. It was shown that circCdh9 was not only dysregulated in the hippocampus of ASD mice but also other ASD-associated brain regions, including the prefrontal cortex and the amygdala [136]. These findings collectively underscore the pivotal role of circRNAs in ASD pathology, with their dysregulation likely reflecting the disorder's multifactorial etiology.

Clinical studies have further corroborated the significance of circRNAs in ASD, revealing widespread and non-random expression patterns in key brain regions of ASD patients, including the prefrontal cortex, temporal cortex, and cerebellum [140-142]. Chen et al. identified 60 abnormally expressed circRNAs in postmortem ASD brains, with comprehensive multi-omics analyses revealing 8,170 ASD-related circRNA-miRNA-mRNA interaction axes [143]. These interactions involve critical ASD risk genes and encode proteins associated with inhibitory postsynaptic density, highlighting the potential regulatory roles of circRNAs in synaptic function. For instance, circARID1A has been shown to modulate ASD-associated risk genes (e.g., NLGN1, STAG1, HSD11B1, VIP, and UBA6) through its interaction with miR-204-3p [143]. These findings suggest that circRNA dysregulation in ASD may arise from complex interactions with genetic risk factors, collectively contributing to the disorder's

pathogenesis. The emerging evidence positions circRNAs as potential regulatory hubs and predictive biomarkers in ASD progression.

4. Conclusion and Future direction

In this review, we generalize the recent research on circRNAs and highlight their clinical meaning in the prediction, diagnosis, and therapy of neuropsychiatric diseases. Over the last few decades, there has been considerable progress in understanding the efficacies of circRNAs in ameliorating disease-associated symptoms of AD, PD, and stress-induced depression: (1) circRNAs could inhibit the accumulation of A β , promote A β clearance, and alleviate A β -induced apoptosis and inflammation; (2) circRNAs inhibit apoptosis, inflammation and α -syn expression to maintain dopaminergic neuronal function; (3) circRNAs could restore stress-induced microglial, astrocyte, and neuron dysfunction. However, there are relatively few studies on the function of circRNAs in BD, SCZ, and other neuropsychiatric diseases.

To effectively advance circRNAs toward clinical applications, several key challenges must be addressed. The precise molecular mechanisms underlying circRNAs function, as well as their roles in neuropsychiatric and neurodegenerative disorders, are still poorly characterized. Given the vast diversity of circRNAs, even within a single disease context there may be thousands of distinct species, and it remains unclear which act as principal drivers and which function synergistically—questions that require comprehensive and systematic investigation. Furthermore, many existing studies are limited by small sample sizes, constraining both generalizability and statistical robustness [144-146]. Consequently, advancing circRNAs toward clinical application will require rigorous validation through large-scale, high-quality, and mechanistically driven studies that extend beyond correlative expression analyses.

Moreover, the heterogeneity of patient populations, coupled with the cell-type specificity of circRNA expression, necessitates standardized protocols for clinical sample collection [147-149]. Advanced detection technologies are critical for the accurate quantification of these molecules. Integrating high-throughput RNA sequencing with sensitive methods, such as HIT-scISOseq, enables precise single-cell circRNA profiling [150]. Second, while circRNAs show promise as therapeutic targets, achieving precise and safe targeting remains a significant challenge. Gene-editing technologies, such as CRISPR/Cas13, and RNA interference (RNAi) techniques must be optimized to specifically target circRNAs while minimizing off-target effects [151-155]. Third, the development of effective delivery methods for circRNA-targeting tools is crucial for their therapeutic potential. RNA delivery carriers, such as nanoparticles and exosomes, can mitigate immune response-related side effects, although challenges persist in their production and efficient delivery [156-158]. Lastly, leveraging bioinformatics tools and artificial intelligence (e.g., MSTCRB and CRIECNN models) can facilitate more efficient and accurate analysis of circRNA-regulated brain functional networks, improving our understanding of their roles in neurodevelopment and disease[159-161].

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Authors' Contributions

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Data Availability

All data generated or analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Declaration of interests

All authors declare no competing interests.

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Not applicable.

Reference

1. Carninci, P.; Kasukawa, T.; Katayama, S.; Gough, J.; Frith, M.C.; Maeda, N.; et al. The transcriptional landscape of the mammalian genome. *Science* **2005**, *309*, 1559-1563, doi:10.1126/science.1112014.
2. Consortium, E.P. The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science* **2004**, *306*, 636-640, doi:10.1126/science.1105136.
3. Mercer, T.R.; Dinger, M.E.; Sunkin, S.M.; Mehler, M.F.; Mattick, J.S. Specific expression of long noncoding RNAs in the mouse brain. *Proc Natl Acad Sci U S A* **2008**, *105*, 716-721, doi:10.1073/pnas.0706729105.
4. Vicens, Q.; Westhof, E. Biogenesis of Circular RNAs. *Cell* **2014**, *159*, 13-14, doi:10.1016/j.cell.2014.09.005.
5. Guo, J.U.; Agarwal, V.; Guo, H.; Bartel, D.P. Expanded identification and characterization of mammalian circular RNAs. *Genome Biol* **2014**, *15*, 409, doi:10.1186/s13059-014-0409-z.
6. Jeck, W.R.; Sorrentino, J.A.; Wang, K.; Slevin, M.K.; Burd, C.E.; Liu, J.; et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. *Rna* **2013**, *19*, 141-157, doi:10.1261/rna.035667.112.
7. Jeck, W.R.; Sharpless, N.E. Detecting and characterizing circular RNAs. *Nat Biotechnol* **2014**, *32*, 453-461, doi:10.1038/nbt.2890.
8. Barrett, S.P.; Wang, P.L.; Salzman, J. Circular RNA biogenesis can proceed through an exon-containing lariat precursor. *Elife* **2015**, *4*, e07540, doi:10.7554/eLife.07540.
9. Conn, S.J.; Pillman, K.A.; Toubia, J.; Conn, V.M.; Salmanidis, M.; Phillips, C.A.; et al. The RNA binding protein quaking regulates formation of circRNAs. *Cell* **2015**, *160*, 1125-1134, doi:10.1016/j.cell.2015.02.014.
10. Li, Z.; Huang, C.; Bao, C.; Chen, L.; Lin, M.; Wang, X.; et al. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol* **2015**, *22*, 256-264, doi:10.1038/nsmb.2959.
11. Sanger, H.L.; Klotz, G.; Riesner, D.; Gross, H.J.; Kleinschmidt, A.K. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. *Proc Natl Acad Sci U S A* **1976**, *73*, 3852-3856, doi:10.1073/pnas.73.11.3852.
12. Kristensen, L.S.; Jakobsen, T.; Hager, H.; Kjems, J. The emerging roles of circRNAs in cancer and oncology. *Nat Rev Clin Oncol* **2022**, *19*, 188-206, doi:10.1038/s41571-021-00585-y.
13. Gao, Y.; Wang, J.; Zhao, F. CIRI: an efficient and unbiased algorithm for de novo circular RNA identification. *Genome Biol* **2015**, *16*, 4, doi:10.1186/s13059-014-0571-3.
14. Rybak-Wolf, A.; Stottmeister, C.; Glažar, P.; Jens, M.; Pino, N.; Giusti, S.; et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. *Mol Cell* **2015**, *58*, 870-885, doi:10.1016/j.molcel.2015.03.027.
15. Memczak, S.; Jens, M.; Elefsinioti, A.; Torti, F.; Krueger, J.; Rybak, A.; et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* **2013**, *495*, 333-338, doi:10.1038/nature11928.
16. Hansen, T.B.; Jensen, T.I.; Clausen, B.H.; Bramsen, J.B.; Finsen, B.; Damgaard, C.K.; et al. Natural RNA circles function as efficient microRNA sponges. *Nature* **2013**, *495*, 384-388, doi:10.1038/nature11993.
17. You, X.; Vlatkovic, I.; Babic, A.; Will, T.; Epstein, I.; Tushev, G.; et al. Neural circular RNAs are derived from synaptic genes and regulated by development and plasticity. *Nat Neurosci* **2015**, *18*, 603-610, doi:10.1038/nn.3975.
18. Tian, X.; Russo, S.J.; Li, L. Behavioral Animal Models and Neural-Circuit Framework of Depressive Disorder. *Neurosci Bull* **2025**, *41*, 272-288, doi:10.1007/s12264-024-01270-7.

19. Shi, J.; Yang, H.; Guo, H.; Liu, S.; Fan, F.; Fan, H.; et al. Resting-state functional connectivity of neural circuits associated with primary and secondary rewards linked to positive and negative symptoms of first-episode schizophrenia. *Asian J Psychiatr* **2025**, *110*, 104477, doi:10.1016/j.ajp.2025.104477.
20. Mooney, C.; Parlante, A.; Canarutto, G.; Grigoli, A.; Scattoni, M.L.; Ricceri, L.; et al. Deregulated mRNA and microRNA Expression Patterns in the Prefrontal Cortex of the BTBR Mouse Model of Autism. *Mol Neurobiol* **2025**, *62*, 10614-10634, doi:10.1007/s12035-025-04900-x.
21. Kim, E.J.; Park, S.; Schuessler, B.P.; Boo, H.; Cho, J.; Kim, J.J. Disruption of hippocampal-prefrontal neural dynamics and risky decision-making in a mouse model of Alzheimer's disease. *Cell Rep* **2025**, *44*, 116081, doi:10.1016/j.celrep.2025.116081.
22. Chen, L.; Sun, L.; Sun, J.; Wang, J.; Zhang, D.; Xia, M.; et al. Brain-clinical signatures of basal ganglia-related dysfunctional reorganisation in Parkinson's disease. *EBioMedicine* **2025**, *120*, 105917, doi:10.1016/j.ebiom.2025.105917.
23. Xie, X.; Li, K.; Liang, X.; Tian, L.; Lin, B.; Yan, J.; et al. Identification and characterization of circular RNA in the model of autism spectrum disorder from PM(2.5) exposure. *Front Genet* **2023**, *14*, 970465, doi:10.3389/fgene.2023.970465.
24. Tan, G.; Wang, L.; Liu, Y.; Zhang, H.; Feng, W.; Liu, Z. The alterations of circular RNA expression in plasma exosomes from patients with schizophrenia. *J Cell Physiol* **2021**, *236*, 458-467, doi:10.1002/jcp.29873.
25. Jiang, G.; Ma, Y.; An, T.; Pan, Y.; Mo, F.; Zhao, D.; et al. Relationships of circular RNA with diabetes and depression. *Sci Rep* **2017**, *7*, 7285, doi:10.1038/s41598-017-07931-0.
26. Song, C.; Zhang, Y.; Huang, W.; Shi, J.; Huang, Q.; Jiang, M.; et al. Circular RNA Cwc27 contributes to Alzheimer's disease pathogenesis by repressing Pur-alpha activity. *Cell death and differentiation* **2022**, *29*, 393-406, doi:10.1038/s41418-021-00865-1.
27. Duan, Y.; Wang, Y.; Liu, Y.; Jin, Z.; Liu, C.; Yu, X.; et al. Circular RNAs in Parkinson's Disease: Reliable Biological Markers and Targets for Rehabilitation. *Mol Neurobiol* **2023**, *60*, 3261-3276, doi:10.1007/s12035-023-03268-0.
28. Shi, Y.; Song, R.; Wang, Z.; Zhang, H.; Zhu, J.; Yue, Y.; et al. Potential clinical value of circular RNAs as peripheral biomarkers for the diagnosis and treatment of major depressive disorder. *EBioMedicine* **2021**, *66*, 103337, doi:10.1016/j.ebiom.2021.103337.
29. Venø, M.T.; Hansen, T.B.; Venø, S.T.; Clausen, B.H.; Grebing, M.; Finsen, B.; et al. Spatio-temporal regulation of circular RNA expression during porcine embryonic brain development. *Genome Biol* **2015**, *16*, 245, doi:10.1186/s13059-015-0801-3.
30. Kelly, D.; Bicker, S.; Winterer, J.; Nanda, P.; Germain, P.L.; Dieterich, C.; et al. A functional screen uncovers circular RNAs regulating excitatory synaptogenesis in hippocampal neurons. *Nat Commun* **2025**, *16*, 3040, doi:10.1038/s41467-025-58070-4.
31. Zhou, M.; Li, S.; Huang, C. Physiological and pathological functions of circular RNAs in the nervous system. *Neural Regen Res* **2024**, *19*, 342-349, doi:10.4103/1673-5374.379017.
32. Rybiczka-Tešulov, M.; Garritsen, O.; Venø, M.T.; Wieg, L.; Dijk, R.V.; Rahimi, K.; et al. Circular RNAs regulate neuron size and migration of midbrain dopamine neurons during development. *Nat Commun* **2024**, *15*, 6773, doi:10.1038/s41467-024-51041-1.
33. Chen, B.J.; Huang, S.; Janitz, M. Changes in circular RNA expression patterns during human foetal brain development. *Genomics* **2019**, *111*, 753-758, doi:10.18632/aging.101437

10.1016/j.ygeno.2018.04.015.

34. Suenkel, C.; Cavalli, D.; Massalini, S.; Calegari, F.; Rajewsky, N. A Highly Conserved Circular RNA Is Required to Keep Neural Cells in a Progenitor State in the Mammalian Brain. *Cell Rep* **2020**, *30*, 2170-2179.e2175, doi:10.1016/j.celrep.2020.01.083.
35. Mahmoudi, E.; Cairns, M.J. Circular RNAs are temporospatially regulated throughout development and ageing in the rat. *Sci Rep* **2019**, *9*, 2564, doi:10.1038/s41598-019-38860-9.
36. Mfossa, A.C.M.; Thekkekkara Puthenparampil, H.; Inalegwu, A.; Coolkens, A.; Baatout, S.; Benotmane, M.A.; et al. Exposure to Ionizing Radiation Triggers Prolonged Changes in Circular RNA Abundance in the Embryonic Mouse Brain and Primary Neurons. *Cells* **2019**, *8*, doi:10.3390/cells8080778.
37. Chen, J.; Zou, Q.; Lv, D.; Raza, M.A.; Wang, X.; Li, P.; et al. Comprehensive transcriptional profiling of porcine brain aging. *Gene* **2019**, *693*, 1-9, doi:10.1016/j.gene.2019.01.019.
38. Cerda-Jara, C.A.; Kim, S.J.; Thomas, G.; Farsi, Z.; Zolotarov, G.; Dube, G.; et al. miR-7 controls glutamatergic transmission and neuronal connectivity in a Cdr1as-dependent manner. *EMBO Rep* **2024**, *25*, 3008-3039, doi:10.1038/s44319-024-00168-9.
39. Westholm, J.O.; Miura, P.; Olson, S.; Shenker, S.; Joseph, B.; Sanfilippo, P.; et al. Genome-wide analysis of drosophila circular RNAs reveals their structural and sequence properties and age-dependent neural accumulation. *Cell Rep* **2014**, *9*, 1966-1980, doi:10.1016/j.celrep.2014.10.062.
40. Gruner, H.; Cortés-López, M.; Cooper, D.A.; Bauer, M.; Miura, P. CircRNA accumulation in the aging mouse brain. *Sci Rep* **2016**, *6*, 38907, doi:10.1038/srep38907.
41. Xia, S.; Feng, J.; Lei, L.; Hu, J.; Xia, L.; Wang, J.; et al. Comprehensive characterization of tissue-specific circular RNAs in the human and mouse genomes. *Brief Bioinform* **2017**, *18*, 984-992, doi:10.1093/bib/bbw081.
42. Marfil-Marin, E.; Santamaría-Olmedo, M.; PerezGrovas-Saltijeral, A.; Valdes-Flores, M.; Ochoa-Morales, A.; Jara-Prado, A.; et al. circRNA Regulates Dopaminergic Synapse, MAPK, and Long-term Depression Pathways in Huntington Disease. *Mol Neurobiol* **2021**, *58*, 6222-6231, doi:10.1007/s12035-021-02536-1.
43. Liu, Y.; Chen, Z.; Lin, W.; Zhou, Y.; Liu, Z.; Zhao, R.; et al. Role of hippocampal circKcnk9 in visceral hypersensitivity and anxiety comorbidity of irritable bowel syndrome. *Front Cell Neurosci* **2022**, *16*, 1010107, doi:10.3389/fncel.2022.1010107.
44. Wang, X.; Xie, J.; Tan, L.; Lu, Y.; Shen, N.; Li, J.; et al. N6-methyladenosine-modified circRIMS2 mediates synaptic and memory impairments by activating GluN2B ubiquitination in Alzheimer's disease. *Transl Neurodegener* **2023**, *12*, 53, doi:10.1186/s40035-023-00386-6.
45. Xu, K.; Zhang, Y.; Xiong, W.; Zhang, Z.; Wang, Z.; Lv, L.; et al. CircGRIA1 shows an age-related increase in male macaque brain and regulates synaptic plasticity and synaptogenesis. *Nat Commun* **2020**, *11*, 3594, doi:10.1038/s41467-020-17435-7.
46. Piwecka, M.; Glazar, P.; Hernandez-Miranda, L.R.; Memczak, S.; Wolf, S.A.; Rybak-Wolf, A.; et al. Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. *Science* **2017**, *357*, doi:10.1126/science.aam8526.
47. Wang, G.; Han, B.; Shen, L.; Wu, S.; Yang, L.; Liao, J.; et al. Corrigendum to 'Silencing of circular RNA HIPK2 in neural stem cells enhances functional recovery following ischaemic stroke' [EBioMedicine 52 (2020) 102660]. *EBioMedicine* **2020**, *55*, 102751, doi:10.1016/j.ebiom.2020.102751.

48. Qi, Y.; Ma, N.; Chen, X.; Wang, Y.; Zhang, W.; Wan, J. CircRtn4 Acts as the Sponge of miR-24-3p to Promote Neurite Growth by Regulating CHD5. *Front Mol Neurosci* **2021**, *14*, 660429, doi:10.3389/fnmol.2021.660429.
49. Cao, S.M.; Wu, H.; Yuan, G.H.; Pan, Y.H.; Zhang, J.; Liu, Y.X.; et al. Altered nucleocytoplasmic export of adenosine-rich circRNAs by PABPC1 contributes to neuronal function. *Molecular cell* **2024**, *84*, 2304-2319 e2308, doi:10.1016/j.molcel.2024.05.011.
50. Li, W.; Shan, B.; Cheng, X.; He, H.; Qin, J.; Zhao, H.; et al. circRNA Acbd6 promotes neural stem cell differentiation into cholinergic neurons via the miR-320-5p-Osbpl2 axis. *J Biol Chem* **2022**, *298*, 101828, doi:10.1016/j.jbc.2022.101828.
51. Hollensen, A.K.; Thomsen, H.S.; Lloret-Llinares, M.; Kamstrup, A.B.; Jensen, J.M.; Luckmann, M.; et al. circZNF827 nucleates a transcription inhibitory complex to balance neuronal differentiation. *eLife* **2020**, *9*, doi:10.7554/eLife.58478.
52. Volk, N.; Pape, J.C.; Engel, M.; Zannas, A.S.; Cattane, N.; Cattaneo, A.; et al. Amygdalar MicroRNA-15a Is Essential for Coping with Chronic Stress. *Cell Rep* **2016**, *17*, 1882-1891, doi:10.1016/j.celrep.2016.10.038.
53. Pyakurel, A.; Savoia, C.; Hess, D.; Scorrano, L. Extracellular regulated kinase phosphorylates mitofusin 1 to control mitochondrial morphology and apoptosis. *Mol Cell* **2015**, *58*, 244-254, doi:10.1016/j.molcel.2015.02.021.
54. Li, H.; Wang, X.; Wen, C.; Huo, Z.; Wang, W.; Zhan, Q.; et al. Long noncoding RNA NORAD, a novel competing endogenous RNA, enhances the hypoxia-induced epithelial-mesenchymal transition to promote metastasis in pancreatic cancer. *Mol Cancer* **2017**, *16*, 169, doi:10.1186/s12943-017-0738-0.
55. van Sluis, M.; McStay, B. Nucleolar DNA Double-Strand Break Responses Underpinning rDNA Genomic Stability. *Trends Genet* **2019**, *35*, 743-753, doi:10.1016/j.tig.2019.07.001.
56. Canter, R.G.; Penney, J.; Tsai, L.H. The road to restoring neural circuits for the treatment of Alzheimer's disease. *Nature* **2016**, *539*, 187-196, doi:10.1038/nature20412.
57. Dourlen, P.; Kilinc, D.; Malmanche, N.; Chapuis, J.; Lambert, J.C. The new genetic landscape of Alzheimer's disease: from amyloid cascade to genetically driven synaptic failure hypothesis? *Acta Neuropathol* **2019**, *138*, 221-236, doi:10.1007/s00401-019-02004-0.
58. Scheltens, P.; Blennow, K.; Breteler, M.M.; de Strooper, B.; Frisoni, G.B.; Salloway, S.; et al. Alzheimer's disease. *Lancet* **2016**, *388*, 505-517, doi:10.1016/s0140-6736(15)01124-1.
59. Li, Y.; Lv, Z.; Zhang, J.; Ma, Q.; Li, Q.; Song, L.; et al. Profiling of differentially expressed circular RNAs in peripheral blood mononuclear cells from Alzheimer's disease patients. *Metab Brain Dis* **2020**, *35*, 201-213, doi:10.1007/s11011-019-00497-y.
60. Li, Y.; Fan, H.; Sun, J.; Ni, M.; Zhang, L.; Chen, C.; et al. Circular RNA expression profile of Alzheimer's disease and its clinical significance as biomarkers for the disease risk and progression. *Int J Biochem Cell Biol* **2020**, *123*, 105747, doi:10.1016/j.biocel.2020.105747.
61. Cervera-Carles, L.; Dols-Icardo, O.; Molina-Porcel, L.; Alcolea, D.; Cervantes-Gonzalez, A.; Muñoz-Llahuna, L.; et al. Assessing circular RNAs in Alzheimer's disease and frontotemporal lobar degeneration. *Neurobiol Aging* **2020**, *92*, 7-11, doi:10.1016/j.neurobiolaging.2020.03.017.
62. Sekar, S.; Cuyugan, L.; Adkins, J.; Geiger, P.; Liang, W.S. Circular RNA expression and regulatory network prediction in posterior cingulate astrocytes in elderly subjects. *BMC Genomics* **2018**, *19*, 340, doi:10.1186/s12864-018-4670-5.

63. Puri, S.; Hu, J.; Sun, Z.; Lin, M.; Stein, T.D.; Farrer, L.A.; et al. Identification of circRNAs linked to Alzheimer's disease and related dementias. *Alzheimer's & dementia : the journal of the Alzheimer's Association* **2023**, *19*, 3389-3405, doi:10.1002/alz.12960.
64. Smukowski, S.N.; Danyko, C.; Somberg, J.; Kaufman, E.J.; Course, M.M.; Postupna, N.; et al. mRNA and circRNA mislocalization to synapses are key features of Alzheimer's disease. *PLoS genetics* **2024**, *20*, e1011359, doi:10.1371/journal.pgen.1011359.
65. Dube, U.; Del-Aguila, J.L.; Li, Z.; Budde, J.P.; Jiang, S.; Hsu, S.; et al. An atlas of cortical circular RNA expression in Alzheimer disease brains demonstrates clinical and pathological associations. *Nature neuroscience* **2019**, *22*, 1903-1912, doi:10.1038/s41593-019-0501-5.
66. Ma, N.; Pan, J.; Ye, X.; Yu, B.; Zhang, W.; Wan, J. Whole-Transcriptome Analysis of APP/PS1 Mouse Brain and Identification of circRNA-miRNA-mRNA Networks to Investigate AD Pathogenesis. *Mol Ther Nucleic Acids* **2019**, *18*, 1049-1062, doi:10.1016/j.omtn.2019.10.030.
67. Lee, W.J.; Moon, J.; Jeon, D.; Shin, Y.W.; Yoo, J.S.; Park, D.K.; et al. Possible epigenetic regulatory effect of dysregulated circular RNAs in Alzheimer's disease model. *Sci Rep* **2019**, *9*, 11956, doi:10.1038/s41598-019-48471-z.
68. Wang, Z.; Xu, P.; Chen, B.; Zhang, Z.; Zhang, C.; Zhan, Q.; et al. Identifying circRNA-associated-ceRNA networks in the hippocampus of A β 1-42-induced Alzheimer's disease-like rats using microarray analysis. *Aging (Albany NY)* **2018**, *10*, 775-788, doi:10.18632/aging.101427.
69. Huang, J.L.; Xu, Z.H.; Yang, S.M.; Yu, C.; Zhang, F.; Qin, M.C.; et al. Identification of Differentially Expressed Profiles of Alzheimer's Disease Associated Circular RNAs in a Panax Notoginseng Saponins-Treated Alzheimer's Disease Mouse Model. *Comput Struct Biotechnol J* **2018**, *16*, 523-531, doi:10.1016/j.csbj.2018.10.010.
70. Huang, J.L.; Qin, M.C.; Zhou, Y.; Xu, Z.H.; Yang, S.M.; Zhang, F.; et al. Comprehensive analysis of differentially expressed profiles of Alzheimer's disease associated circular RNAs in an Alzheimer's disease mouse model. *Aging (Albany NY)* **2018**, *10*, 253-265, doi:10.18632/aging.101387.
71. Zhang, S.; Zhu, D.; Li, H.; Li, H.; Feng, C.; Zhang, W. Characterization of circRNA-Associated-ceRNA Networks in a Senescence-Accelerated Mouse Prone 8 Brain. *Mol Ther* **2017**, *25*, 2053-2061, doi:10.1016/j.ymthe.2017.06.009.
72. Chen, L.L. The biogenesis and emerging roles of circular RNAs. *Nat Rev Mol Cell Biol* **2016**, *17*, 205-211, doi:10.1038/nrm.2015.32.
73. Cai, Z.; Yan, L.J.; Li, K.; Quazi, S.H.; Zhao, B. Roles of AMP-activated protein kinase in Alzheimer's disease. *Neuromolecular Med* **2012**, *14*, 1-14, doi:10.1007/s12017-012-8173-2.
74. Merlo, P.; Frost, B.; Peng, S.; Yang, Y.J.; Park, P.J.; Feany, M. p53 prevents neurodegeneration by regulating synaptic genes. *Proc Natl Acad Sci U S A* **2014**, *111*, 18055-18060, doi:10.1073/pnas.1419083111.
75. Welden, J.R.; Margvelani, G.; Maquera, K.A.A.; Gudlavalleti, B.; Sardón, S.C.M.; Campos, A.R.; et al. RNA editing of microtubule-associated protein tau circular RNAs promotes their translation and tau tangle formation. *Nucleic acids research* **2022**, *50*, 12979-12996, doi:10.1093/nar/gkac1129.
76. Meng, S.; Zhou, H.; Feng, Z.; Xu, Z.; Tang, Y.; Li, P.; et al. CircRNA: functions and properties of a novel potential biomarker for cancer. *Mol Cancer* **2017**, *16*, 94, doi:10.1186/s12943-017-0663-2.
77. Zhang, H.D.; Jiang, L.H.; Sun, D.W.; Hou, J.C.; Ji, Z.L. CircRNA: a novel type of biomarker for cancer. *Breast Cancer* **2018**, *25*, 1-7, doi:10.1007/s12282-017-0793-9.

78. Huang, J.; Wu, D.; Wang, J.; Li, F.; Lu, L.; Gao, Y.; et al. Effects of Panax notoginseng saponin on α , β , and γ secretase involved in A β deposition in SAMP8 mice. *Neuroreport* **2014**, *25*, 89-93, doi:10.1097/wnr.0000000000000048.
79. Huang, J.L.; Jing, X.; Tian, X.; Qin, M.C.; Xu, Z.H.; Wu, D.P.; et al. Neuroprotective Properties of Panax notoginseng Saponins via Preventing Oxidative Stress Injury in SAMP8 Mice. *Evid Based Complement Alternat Med* **2017**, *2017*, 8713561, doi:10.1155/2017/8713561.
80. Ahmed, T.; Gilani, A.U.; Abdollahi, M.; Daglia, M.; Nabavi, S.F.; Nabavi, S.M. Berberine and neurodegeneration: A review of literature. *Pharmacol Rep* **2015**, *67*, 970-979, doi:10.1016/j.pharep.2015.03.002.
81. Cai, Z.; Wang, C.; Yang, W. Role of berberine in Alzheimer's disease. *Neuropsychiatr Dis Treat* **2016**, *12*, 2509-2520, doi:10.2147/ndt.S114846.
82. Zhang, N.; Gao, Y.; Yu, S.; Sun, X.; Shen, K. Berberine attenuates A β 42-induced neuronal damage through regulating circHDAC9/miR-142-5p axis in human neuronal cells. *Life Sci* **2020**, *252*, 117637, doi:10.1016/j.lfs.2020.117637.
83. Jia, E.; Zhou, Y.; Liu, Z.; Wang, L.; Ouyang, T.; Pan, M.; et al. Transcriptomic Profiling of Circular RNA in Different Brain Regions of Parkinson's Disease in a Mouse Model. *Int J Mol Sci* **2020**, *21*, doi:10.3390/ijms21083006.
84. Warre, R.; Thiele, S.; Talwar, S.; Kamal, M.; Johnston, T.H.; Wang, S.; et al. Altered function of glutamatergic cortico-striatal synapses causes output pathway abnormalities in a chronic model of parkinsonism. *Neurobiol Dis* **2011**, *41*, 591-604, doi:10.1016/j.nbd.2010.10.013.
85. Cai, L.; Tu, L.; Li, T.; Yang, X.; Ren, Y.; Gu, R.; et al. Downregulation of lncRNA UCA1 ameliorates the damage of dopaminergic neurons, reduces oxidative stress and inflammation in Parkinson's disease through the inhibition of the PI3K/Akt signaling pathway. *Int Immunopharmacol* **2019**, *75*, 105734, doi:10.1016/j.intimp.2019.105734.
86. Antony, P.M.; Diederich, N.J.; Krüger, R.; Balling, R. The hallmarks of Parkinson's disease. *Febs j* **2013**, *280*, 5981-5993, doi:10.1111/febs.12335.
87. Eriksen, J.L.; Dawson, T.M.; Dickson, D.W.; Petrucelli, L. Caught in the act: alpha-synuclein is the culprit in Parkinson's disease. *Neuron* **2003**, *40*, 453-456, doi:10.1016/s0896-6273(03)00684-6.
88. Salmena, L.; Poliseno, L.; Tay, Y.; Kats, L.; Pandolfi, P.P. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* **2011**, *146*, 353-358, doi:10.1016/j.cell.2011.07.014.
89. Junn, E.; Lee, K.W.; Jeong, B.S.; Chan, T.W.; Im, J.Y.; Mouradian, M.M. Repression of alpha-synuclein expression and toxicity by microRNA-7. *Proc Natl Acad Sci U S A* **2009**, *106*, 13052-13057, doi:10.1073/pnas.0906277106.
90. Choi, D.C.; Yoo, M.; Kabaria, S.; Junn, E. MicroRNA-7 facilitates the degradation of alpha-synuclein and its aggregates by promoting autophagy. *Neurosci Lett* **2018**, *678*, 118-123, doi:10.1016/j.neulet.2018.05.009.
91. Choi, D.C.; Chae, Y.J.; Kabaria, S.; Chaudhuri, A.D.; Jain, M.R.; Li, H.; et al. MicroRNA-7 protects against 1-methyl-4-phenylpyridinium-induced cell death by targeting RelA. *J Neurosci* **2014**, *34*, 12725-12737, doi:10.1523/jneurosci.0985-14.2014.
92. Feng, Z.; Zhang, L.; Wang, S.; Hong, Q. Circular RNA circDLGAP4 exerts neuroprotective effects via modulating miR-134-5p/CREB pathway in Parkinson's disease. *Biochemical and biophysical research communications* **2020**, *522*, 388-394, doi:10.2174/1567202615666180319151244

10.1016/j.bbrc.2019.11.102.

93. Bao, H.; Zhang, Q.; Li, Y.; Nie, C. CircDLGAP4 overexpression ameliorates neuronal injury in Parkinson's disease by binding to EIF4A3 and increasing HMGA2 expression. *J Biochem Mol Toxicol* **2024**, *38*, e23530, doi:10.1002/jbt.23530.
94. Aquilina-Reid, C.; Brennan, S.; Curry-Hyde, A.; Teunisse, G.M.; The Nygc Als, C.; Janitz, M. Circular RNA Expression and Interaction Patterns Are Perturbed in Amyotrophic Lateral Sclerosis. *International journal of molecular sciences* **2022**, *23*, doi:10.3390/ijms232314665.
95. Tsitsipatis, D.; Mazan-Mamczarz, K.; Si, Y.; Herman, A.B.; Yang, J.H.; Guha, A.; et al. Transcriptomic analysis of human ALS skeletal muscle reveals a disease-specific pattern of dysregulated circRNAs. *Aging-Us* **2022**, *14*, 9832-9859.
96. Dolinar, A.; Koritnik, B.; Glavač, D.; Ravnik-Glavač, M. Circular RNAs as Potential Blood Biomarkers in Amyotrophic Lateral Sclerosis. *Mol Neurobiol* **2019**, *56*, 8052-8062, doi:10.1007/s12035-019-1627-x.
97. Glavac, M.R.; Mezzavilla, M.; Dolinar, A.; Koritnik, B.; Glavac, D. Aberrantly Expressed Hsa_circ_0060762 and CSE1L as Potential Peripheral Blood Biomarkers for ALS. *Biomedicines* **2023**, *11*, doi:ARTN 1316 10.3390/biomedicines11051316.
98. Colantoni, A.; Caputo, D.; Alfano, V.; D'Ambra, E.; D'Uva, S.; Tartaglia, G.G.; et al. FUS Alters circRNA Metabolism in Human Motor Neurons Carrying the ALS-Linked P525L Mutation. *International journal of molecular sciences* **2023**, *24*, doi:Artn 3181 10.3390/Ijms24043181.
99. D'Ambra, E.; Santini, T.; Vitiello, E.; D'Uva, S.; Silenzi, V.; Morlando, M.; et al. Circ-Hdgrfp3 shuttles along neurites and is trapped in aggregates formed by ALS-associated mutant FUS. *Iscience* **2021**, *24*, doi:Artn 103504 10.1016/J.Isci.2021.103504.
100. Errichelli, L.; Dini Modigliani, S.; Laneve, P.; Colantoni, A.; Legnini, I.; Caputo, D.; et al. FUS affects circular RNA expression in murine embryonic stem cell-derived motor neurons. *Nat Commun* **2017**, *8*, 14741, doi:10.1038/ncomms14741.
101. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* **1993**, *72*, 971-983, doi:10.1016/0092-8674(93)90585-e.
102. Ayyildiz, D.; Bergonzoni, G.; Monziani, A.; Tripathi, T.; Doring, J.; Kerschbamer, E.; et al. CAG repeat expansion in the Huntington's disease gene shapes linear and circular RNAs biogenesis. *PLoS genetics* **2023**, *19*, e1010988, doi:10.1371/journal.pgen.1010988.
103. Gantley, L.; Stringer, B.W.; Conn, V.M.; Ootsuka, Y.; Holds, D.; Slee, M.; et al. Functional Characterisation of the Circular RNA, circHTT(2-6), in Huntington's Disease. *Cells* **2023**, *12*, doi:10.3390/cells12091337.
104. Morandell, J.; Monziani, A.; Lazioli, M.; Donzel, D.; Doring, J.; Oss Pegorar, C.; et al. CircHTT(2,3,4,5,6) - co-evolving with the HTT CAG-repeat tract - modulates Huntington's disease phenotypes. *Molecular therapy. Nucleic acids* **2024**, *35*, 102234, doi:10.1016/j.omtn.2024.102234.
105. Chen, B.J.; Mills, J.D.; Takenaka, K.; Bliim, N.; Halliday, G.M.; Janitz, M. Characterization of circular RNAs landscape in multiple system atrophy brain. *J Neurochem* **2016**, *139*, 485-496, doi:10.1111/jnc.13752.

106. Xu, C.M.; Jun, E.S.; Okugawa, Y.; Toiyama, Y.; Borazanci, E.; Bolton, J.; et al. A Circulating Panel of circRNA Biomarkers for the Noninvasive and Early Detection of Pancreatic Ductal Adenocarcinoma. *Gastroenterology* **2024**, *166*, doi:10.1053/j.gastro.2023.09.050.
107. Nemeth, K.; Bayraktar, R.; Ferracin, M.; Calin, G.A. Non-coding RNAs in disease: from mechanisms to therapeutics. *Nat Rev Genet* **2024**, *25*, 211-232, doi:10.1038/s41576-023-00662-1.
108. Zhang, D.D.; Ji, Y.; Chen, X.J.; Chen, R.S.; Wei, Y.X.; Peng, Q.; et al. Peripheral Blood Circular RNAs as a Biomarker for Major Depressive Disorder and Prediction of Possible Pathways. *Frontiers in neuroscience* **2022**, *16*, doi:Artn 844422
10.3389/Fnins.2022.844422.
109. Bu, T.Y.; Qiao, Z.X.; Wang, W.B.; Yang, X.X.; Zhou, J.W.; Chen, L.; et al. Diagnostic Biomarker Hsa_circ_0126218 and Functioning Prediction in Peripheral Blood Mononuclear Cells of Female Patients With Major Depressive Disorder. *Frontiers in cell and developmental biology* **2021**, *9*, doi:Artn 651803
10.3389/Fcell.2021.651803.
110. Shi, Y.C.; Song, R.Z.; Wang, Z.; Zhang, H.X.; Zhu, J.L.; Yue, Y.P.; et al. Potential clinical value of circular RNAs as peripheral biomarkers for the diagnosis and treatment of major depressive disorder. *EBioMedicine* **2021**, *66*, doi:Artn 103337
10.1016/J.Ebiom.2021.103337.
111. Zhou, T.; Li, M.M.; Xiao, Z.J.; Cai, J.; Zhao, W.W.; Duan, J.J.; et al. Chronic Stress-Induced Gene Changes in Vitro and in Vivo : Potential Biomarkers Associated With Depression and Cancer Based on circRNA- and lncRNA-Associated ceRNA Networks. *Front Oncol* **2021**, *11*, doi:Artn 744251
10.3389/Fonc.2021.744251.
112. Yu, X.Y.; Fan, Z.Y.; Yang, T.T.; Li, H.; Shi, Y.C.; Ye, L.; et al. Plasma circRNA HIPK2 as a putative biomarker for the diagnosis and prediction of therapeutic effects in major depressive disorder. *Clin Chim Acta* **2024**, *552*, doi:10.1016/j.cca.2023.117694.
113. Zhang, Y.; Huang, R.; Cheng, M.; Wang, L.; Chao, J.; Li, J.; et al. Gut microbiota from NLRP3-deficient mice ameliorates depressive-like behaviors by regulating astrocyte dysfunction via circHIPK2. *Microbiome* **2019**, *7*, 116, doi:10.1186/s40168-019-0733-3.
114. Cui, X.; Niu, W.; Kong, L.; He, M.; Jiang, K.; Chen, S.; et al. hsa_circRNA_103636: potential novel diagnostic and therapeutic biomarker in Major depressive disorder. *Biomark Med* **2016**, *10*, 943-952, doi:10.2217/bmm-2016-0130.
115. Song, R.Z.; Bai, Y.; Li, X.R.; Zhu, J.L.; Zhang, H.X.; Shi, Y.C.; et al. Plasma Circular RNA DYM Related to Major Depressive Disorder and Rapid Antidepressant Effect Treated by Visual Cortical Repetitive Transcranial Magnetic Stimulation. *Journal of affective disorders* **2020**, *274*, 486-493, doi:10.1016/j.jad.2020.05.109.
116. Zhang, Y.; Du, L.; Bai, Y.; Han, B.; He, C.; Gong, L.; et al. CircDYM ameliorates depressive-like behavior by targeting miR-9 to regulate microglial activation via HSP90 ubiquitination. *Molecular psychiatry* **2020**, *25*, 1175-1190, doi:10.1038/s41380-018-0285-0.
117. Li, X.; Sun, X.J.; Xie, J.N.; Wan, H. CircDYM ameliorates CUMS mice depressive-like behavior and inhibits hippocampal neurons injury via miR-497a-5p/NR3C1 axis. *Brain research* **2022**, *1787*, doi:ARTN 147911
10.1016/j.brainres.2022.147911.

118. Yu, X.Y.; Bai, Y.; Han, B.; Ju, M.Z.; Tang, T.C.; Shen, L.; et al. Extracellular vesicle-mediated delivery of circDYM alleviates CUS-induced depressive-like behaviours. *J Extracell Vesicles* **2022**, *11*, doi:ARTN e12185
10.1002/jev2.12185.
119. Mahmoudi, E.; Fitzsimmons, C.; Geaghan, M.P.; Shannon Weickert, C.; Atkins, J.R.; Wang, X.; et al. Circular RNA biogenesis is decreased in postmortem cortical gray matter in schizophrenia and may alter the bioavailability of associated miRNA. *Neuropsychopharmacology* **2019**, *44*, 1043-1054, doi:10.1038/s41386-019-0348-1.
120. Zimmerman, A.J.; Hafez, A.K.; Amoah, S.K.; Rodriguez, B.A.; Dell'Orco, M.; Lozano, E.; et al. A psychiatric disease-related circular RNA controls synaptic gene expression and cognition. *Mol Psychiatry* **2020**, *25*, 2712-2727, doi:10.1038/s41380-020-0653-4.
121. Mahmoudi, E.; Green, M.J.; Cairns, M.J. Dysregulation of circRNA expression in the peripheral blood of individuals with schizophrenia and bipolar disorder. *J Mol Med* **2021**, *99*, 981-991, doi:10.1007/s00109-021-02070-6.
122. Yao, G.F.; Niu, W.; Zhu, X.L.; He, M.J.; Kong, L.M.; Chen, S.D.; et al. hsa_circRNA_104597: a novel potential diagnostic and therapeutic biomarker for schizophrenia. *Biomarkers in medicine* **2019**, *13*, 331-341, doi:10.2217/bmm-2018-0447.
123. Tan, G.F.; Wang, L.M.; Liu, Y.Y.; Zhang, H.; Feng, W.H.; Liu, Z.L. The alterations of circular RNA expression in plasma exosomes from patients with schizophrenia. *J Cell Physiol* **2021**, *236*, 458-467, doi:10.1002/jcp.29873.
124. Huang, H.H.; Luo, J.; Qi, Y.J.; Wu, Y.Z.; Qi, J.H.; Yan, X.P.; et al. Comprehensive analysis of circRNA expression profile and circRNA-miRNA-mRNA network susceptibility to very early-onset schizophrenia. *Schizophrenia-Uk* **2023**, *9*, doi:ArtN 70
10.1038/S41537-023-00399-0.
125. Liao, F.P.; Zhu, L.L.; Yang, J.L.; Wu, X.L.; Zhao, Z.; Xu, B.Y.; et al. Whole Transcriptome Sequencing Identified CircRNA Profiles and the Related Networks in Schizophrenia. *J Mol Neurosci* **2022**, *72*, 1622-1635, doi:10.1007/s12031-022-02013-x.
126. Li, W.S.; Xue, X.; Li, X.H.; Wu, X.L.; Zhou, P.; Xia, Y.R.; et al. Ancestral retrovirus envelope protein ERVWE1 upregulates circ_0001810, a potential biomarker for schizophrenia, and induces neuronal mitochondrial dysfunction via activating AK2. *Cell and Bioscience* **2024**, *14*, doi:ARTN 138
10.1186/s13578-024-01318-1.
127. Maass, P.G.; Glazar, P.; Memczak, S.; Dittmar, G.; Hollfinger, I.; Schreyer, L.; et al. A map of human circular RNAs in clinically relevant tissues. *J Mol Med (Berl)* **2017**, *95*, 1179-1189, doi:10.1007/s00109-017-1582-9.
128. Lin, R.X.; Lopez, J.P.; Cruceanu, C.; Pierotti, C.; Fiori, L.M.; Squassina, A.; et al. Circular RNA circCCNT2 is upregulated in the anterior cingulate cortex of individuals with bipolar disorder. *Translational psychiatry* **2021**, *11*, 629, doi:ARTN 629
10.1038/s41398-021-01746-4.
129. Luykx, J.J.; Giuliani, F.; Giuliani, G.; Veldink, J. Coding and Non-Coding RNA Abnormalities in Bipolar Disorder. *Genes (Basel)* **2019**, *10*, doi:10.3390/genes10110946.

130. Dines, M.; Lamprecht, R. EphrinA4 mimetic peptide targeted to EphA binding site impairs the formation of long-term fear memory in lateral amygdala. *Transl Psychiatry* **2014**, *4*, e450, doi:10.1038/tp.2014.76.
131. Attwood, B.K.; Bourgognon, J.M.; Patel, S.; Mucha, M.; Schiavon, E.; Skrzypiec, A.E.; et al. Neuropsin cleaves EphB2 in the amygdala to control anxiety. *Nature* **2011**, *473*, 372-U553, doi:10.1038/nature09938.
132. Fu, Y.H.; He, W.F.; Zhou, C.X.; Fu, X.; Wan, Q.G.; He, L.; et al. Bioinformatics Analysis of circRNA Expression and Construction of "circRNA-miRNA-mRNA" Competing Endogenous RNAs Networks in Bipolar Disorder Patients. *Frontiers in genetics* **2021**, *12*, doi:Artn 718976
10.3389/Fgene.2021.718976.
133. Xie, X.Q.; Li, K.; Liang, X.T.; Tian, L.; Lin, B.C.; Yan, J.; et al. Identification and characterization of circular RNA in the model of autism spectrum disorder from PM exposure. *Frontiers in genetics* **2023**, *14*, doi:Artn 970465
10.3389/Fgene.2023.970465.
134. He, X.; Yang, Y.Y.; Zhou, S.; Wei, Q.H.; Zhou, H.; Tao, J.Y.; et al. Alterations in microbiota-metabolism-circRNA crosstalk in autism spectrum disorder-like behaviours caused by maternal exposure to glyphosate-based herbicides in mice. *Ecotox Environ Safe* **2024**, *285*, doi:Artn 117060
10.1016/J.Ecoenv.2024.117060.
135. Wang, J.; Yang, Z.X.; Chen, C.M.; Xu, Y.; Wang, H.G.; Liu, B.; et al. Comprehensive circRNA Expression Profile and Construction of circRNAs-Related ceRNA Network in a Mouse Model of Autism. *Frontiers in genetics* **2021**, *11*, doi:Artn 623584
10.3389/Fgene.2020.623584.
136. Gasparini, S.; Del Vecchio, G.; Gioiosa, S.; Flati, T.; Castrignano, T.; Legnini, I.; et al. Differential Expression of Hippocampal Circular RNAs in the BTBR Mouse Model for Autism Spectrum Disorder. *Mol Neurobiol* **2020**, *57*, 2301-2313, doi:10.1007/s12035-020-01878-6.
137. McFarlane, H.G.; Kusek, G.K.; Yang, M.; Phoenix, J.L.; Bolivar, V.J.; Crawley, J.N. Autism-like behavioral phenotypes in BTBR T+tf/J mice. *Genes Brain Behav* **2008**, *7*, 152-163, doi:10.1111/j.1601-183X.2007.00330.x.
138. Blanchard, D.C.; Defensor, E.B.; Meyza, K.Z.; Pobbe, R.L.; Pearson, B.L.; Bolivar, V.J.; et al. Addendum to 'BTBR T+tf/J mice: autism-relevant behaviors and reduced fractone-associated heparan sulfate' [Neurosci. Biobehav. Rev. 36(1) (2012) 285-296]. *Neurosci Biobehav Rev* **2012**, *36*, 2370, doi:10.1016/j.neubiorev.2012.09.005.
139. Meyza, K.Z.; Defensor, E.B.; Jensen, A.L.; Corley, M.J.; Pearson, B.L.; Pobbe, R.L.; et al. The BTBR T+tf/J mouse model for autism spectrum disorders-in search of biomarkers. *Behav Brain Res* **2013**, *251*, 25-34, doi:10.1016/j.bbr.2012.07.021.
140. Gokool, A.; Anwar, F.; Voineagu, I. The Landscape of Circular RNA Expression in the Human Brain. *Biol Psychiatry* **2020**, *87*, 294-304, doi:10.1016/j.biopsych.2019.07.029.
141. Parikshak, N.N.; Swarup, V.; Belgard, T.G.; Irimia, M.; Ramaswami, G.; Gandal, M.J.; et al. Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. *Nature* **2016**, *540*, 423-427, doi:10.1038/nature20612.
142. Mai, T.L.; Chen, C.Y.; Chen, Y.C.; Chiang, T.W.; Chuang, T.J. Trans-genetic effects of circular RNA expression quantitative trait loci and potential causal mechanisms in autism. *Molecular psychiatry* **2022**, *27*, 4695-4706, doi:10.1038/s41380-022-01714-4.

143. Chen, Y.J.; Chen, C.Y.; Mai, T.L.; Chuang, C.F.; Chen, Y.C.; Gupta, S.K.; et al. Genome-wide, integrative analysis of circular RNA dysregulation and the corresponding circular RNA-microRNA-mRNA regulatory axes in autism. *Genome Res* **2020**, *30*, 375-391, doi:10.1101/gr.255463.119.
144. Meng, P.; Zhang, X.; Liu, T.T.; Liu, J.; Luo, Y.; Xie, M.X.; et al. A whole transcriptome profiling analysis for antidepressant mechanism of Xiaoyaosan mediated synapse loss via BDNF/trkB/PI3K signal axis in CUMS rats. *BMC Complement Med Ther* **2023**, *23*, 198, doi:10.1186/s12906-023-04000-0.
145. Lo, I.; Hill, J.; Vilhjálmsdóttir, B.J.; Kjems, J. Linking the association between circRNAs and Alzheimer's disease progression by multi-tissue circular RNA characterization. *RNA Biol* **2020**, *17*, 1789-1797, doi:10.1080/15476286.2020.1783487.
146. Ilieva, M.S. Non-Coding RNAs in Neurological and Neuropsychiatric Disorders: Unraveling the Hidden Players in Disease Pathogenesis. *Cells* **2024**, *13*, doi:10.3390/cells13121063.
147. Caba, L.; Florea, L.; Gug, C.; Dimitriu, D.C.; Gorduza, E.V. Circular RNA-Is the Circle Perfect? *Biomolecules* **2021**, *11*, doi:10.3390/biom11121755.
148. Moreno-García, L.; Moreno-Martínez, L.; de la Torre, M.; Macías-Redondo, S.; García-Redondo, A.; Osta, R.; et al. Circular RNA expression in ALS is progressively deregulated and tissue-dependent. *BMC Genomics* **2025**, *26*, 576, doi:10.1186/s12864-025-11725-4.
149. Hatzimanolis, O.; Sykes, A.M.; Cristino, A.S. Circular RNAs in neurological conditions - computational identification, functional validation, and potential clinical applications. *Mol Psychiatry* **2025**, *30*, 1652-1675, doi:10.1038/s41380-025-02925-1.
150. Shi, Z.X.; Chen, Z.C.; Zhong, J.Y.; Hu, K.H.; Zheng, Y.F.; Chen, Y.; et al. High-throughput and high-accuracy single-cell RNA isoform analysis using PacBio circular consensus sequencing. *Nat Commun* **2023**, *14*, 2631, doi:10.1038/s41467-023-38324-9.
151. Awan, F.M.; Yang, B.B.; Naz, A.; Hanif, A.; Ikram, A.; Obaid, A.; et al. The emerging role and significance of circular RNAs in viral infections and antiviral immune responses: possible implication as theranostic agents. *RNA Biol* **2021**, *18*, 1-15, doi:10.1080/15476286.2020.1790198.
152. Wang, A.Z.; Langer, R.; Farokhzad, O.C. Nanoparticle delivery of cancer drugs. *Annu Rev Med* **2012**, *63*, 185-198, doi:10.1146/annurev-med-040210-162544.
153. Singh, S.; Narang, A.S.; Mahato, R.I. Subcellular fate and off-target effects of siRNA, shRNA, and miRNA. *Pharm Res* **2011**, *28*, 2996-3015, doi:10.1007/s11095-011-0608-1.
154. Li, S.; Li, X.; Xue, W.; Zhang, L.; Yang, L.Z.; Cao, S.M.; et al. Screening for functional circular RNAs using the CRISPR-Cas13 system. *Nat Methods* **2021**, *18*, 51-59, doi:10.1038/s41592-020-01011-4.
155. Zhang, Y.; Nguyen, T.M.; Zhang, X.O.; Wang, L.; Phan, T.; Clohessy, J.G.; et al. Optimized RNA-targeting CRISPR/Cas13d technology outperforms shRNA in identifying functional circRNAs. *Genome Biol* **2021**, *22*, 41, doi:10.1186/s13059-021-02263-9.
156. Kulkarni, J.A.; Witzigmann, D.; Chen, S.; Cullis, P.R.; van der Meel, R. Lipid Nanoparticle Technology for Clinical Translation of siRNA Therapeutics. *Acc Chem Res* **2019**, *52*, 2435-2444, doi:10.1021/acs.accounts.9b00368.
157. El-Andaloussi, S.; Lee, Y.; Lakhal-Littleton, S.; Li, J.; Seow, Y.; Gardiner, C.; et al. Exosome-mediated delivery of siRNA in vitro and in vivo. *Nat Protoc* **2012**, *7*, 2112-2126, doi:10.1038/nprot.2012.131.

158. Oliveira, A.C.N.; Fernandes, J.; Gonçalves, A.; Gomes, A.C.; Oliveira, M. Lipid-based Nanocarriers for siRNA Delivery: Challenges, Strategies and the Lessons Learned from the DODAX: MO Liposomal System. *Curr Drug Targets* **2019**, *20*, 29-50, doi:10.2174/1389450119666180703145410.
159. Chen, L.; Wang, C.; Sun, H.; Wang, J.; Liang, Y.; Wang, Y.; et al. The bioinformatics toolbox for circRNA discovery and analysis. *Brief Bioinform* **2021**, *22*, 1706-1728, doi:10.1093/bib/bbaa001.
160. Zhou, Y.; Cui, H.; Liu, D.; Wang, W. MSTCRB: Predicting circRNA-RBP interaction by extracting multi-scale features based on transformer and attention mechanism. *Int J Biol Macromol* **2024**, *278*, 134805, doi:10.1016/j.ijbiomac.2024.134805.
161. Liu, X.; Xiao, H.; Peng, X.; Chai, Y.; Wang, S.; Wen, G. Identification and comprehensive analysis of circRNA-miRNA-mRNA regulatory networks in osteoarthritis. *Front Immunol* **2022**, *13*, 1050743, doi:10.3389/fimmu.2022.1050743.
162. Wang, G.; Han, B.; Shen, L.; Wu, S.; Yang, L.; Liao, J.; et al. Silencing of circular RNA HIPK2 in neural stem cells enhances functional recovery following ischaemic stroke. *EBioMedicine* **2020**, *52*, 102660, doi:10.1016/j.ebiom.2020.102660.
163. Piwecka, M.; Glazar, P.; Hernandez-Miranda, L.R.; Memczak, S.; Wolf, S.A.; Rybak-Wolf, A.; et al. Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. *Science* **2017**, *357*, eaam8526, doi:10.1126/science.aam8526.
164. Qi, Y.; Ma, N.N.; Chen, X.F.; Wang, Y.; Zhang, W.; Wan, J. CircRtn4 Acts as the Sponge of miR-24-3p to Promote Neurite Growth by Regulating CHD5. *Frontiers in molecular neuroscience* **2021**, *14*, doi:Artn 660429
10.3389/Fnmol.2021.660429.
165. Lukiw, W.J. Circular RNA (circRNA) in Alzheimer's disease (AD). *Front Genet* **2013**, *4*, 307, doi:10.3389/fgene.2013.00307.
166. Zhao, Y.; Alexandrov, P.N.; Jaber, V.; Lukiw, W.J. Deficiency in the ubiquitin conjugating enzyme UBE2A in Alzheimer's disease (AD) is linked to deficits in a natural circular miRNA-7 sponge (circRNA; ciRS-7). *Genes* **2016**, *7*, 116, doi:10.3390/genes7120116.
167. Shi, Z.; Chen, T.; Yao, Q.; Zheng, L.; Zhang, Z.; Wang, J.; et al. The circular RNA ciRS-7 promotes APP and BACE1 degradation in an NF- κ B-dependent manner. *Febs j* **2017**, *284*, 1096-1109, doi:10.1111/febs.14045.
168. Lu, Y.; Tan, L.; Wang, X. Circular HDAC9/microRNA-138/Sirtuin-1 Pathway Mediates Synaptic and Amyloid Precursor Protein Processing Deficits in Alzheimer's Disease. *Neurosci Bull* **2019**, *35*, 877-888, doi:10.1007/s12264-019-00361-0.
169. Zhang, N.; Gao, Y.; Yu, S.; Sun, X.; Shen, K. Berberine attenuates Abeta42-induced neuronal damage through regulating circHDAC9/miR-142-5p axis in human neuronal cells. *Life sciences* **2020**, *252*, 117637, doi:10.1016/j.lfs.2020.117637.
170. Wu, L.; Du, Q.; Wu, C. CircLPAR1/miR-212-3p/ZNF217 feedback loop promotes amyloid beta-induced neuronal injury in Alzheimer's Disease. *Brain research* **2021**, *1770*, 147622, doi:10.1016/j.brainres.2021.147622.
171. Xiong, W.; Li, D.; Feng, Y.; Jia, C.; Zhang, X.; Liu, Z. CircLPAR1 Promotes Neuroinflammation and Oxidative Stress in APP/PS1 Mice by Inhibiting SIRT1/Nrf-2/HO-1 Axis Through Destabilizing GDF-15 mRNA. *Molecular neurobiology* **2023**, *60*, 2236-2251, doi:10.1007/s12035-022-03177-8.

172. Li, Y.; Wang, H.; Chen, L.; Wei, K.; Liu, Y.; Han, Y.; et al. Circ_0003611 regulates apoptosis and oxidative stress injury of Alzheimer's disease via miR-383-5p/KIF1B axis. *Metabolic brain disease* **2022**, *37*, 2915-2924, doi:10.1007/s11011-022-01051-z.
173. Pan, W.; Hu, Y.; Wang, L.; Li, J. Circ_0003611 acts as a miR-885-5p sponge to aggravate the amyloid-beta-induced neuronal injury in Alzheimer's disease. *Metabolic brain disease* **2022**, *37*, 961-971, doi:10.1007/s11011-022-00912-x.
174. Li, Y.L.; Fan, H.; Sun, J.; Ni, M.; Zhang, L.; Chen, C.; et al. Circular RNA expression profile of Alzheimer's disease and its clinical significance as biomarkers for the disease risk and progression. *The international journal of biochemistry & cell biology* **2020**, *123*, 105747, doi:10.1016/J.Biocel.2020.105747.
175. Urdanoz-Casado, A.; Sanchez-Ruiz de Gordo, J.; Robles, M.; Roldan, M.; Macias Conde, M.; Acha, B.; et al. circRNA from APP Gene Changes in Alzheimer's Disease Human Brain. *International journal of molecular sciences* **2023**, *24*, doi:10.3390/ijms24054308.
176. Mo, D.; Li, X.; Raabe, C.A.; Rozhdestvensky, T.S.; Skryabin, B.V.; Brosius, J. Circular RNA Encoded Amyloid Beta peptides-A Novel Putative Player in Alzheimer's Disease. *Cells* **2020**, *9*, doi:10.3390/cells9102196.
177. Urdanoz-Casado, A.; de Gordo, J.S.; Robles, M.; Roldan, M.; Zelaya, M.V.; Blanco-Luquin, I.; et al. Profile of TREM2-Derived circRNA and mRNA Variants in the Entorhinal Cortex of Alzheimer's Disease Patients. *International journal of molecular sciences* **2022**, *23*, doi:10.3390/ijms23147682.
178. Wang, H.F.; Li, Y.B.; Liu, Z.Y.; Xie, W.M.; Liu, Q.; Zhang, R.J.; et al. Circ-Bptf Ameliorates Learning and Memory Impairments via the miR-138-5p/p62 Axis in APP/PS1 Mice. *Molecular neurobiology* **2024**, doi:10.1007/s12035-024-04066-y.
179. Meng, S.; Wang, B.; Li, W. CircAXL Knockdown Alleviates Abeta(1-42)-Induced Neurotoxicity in Alzheimer's Disease via Repressing PDE4A by Releasing miR-1306-5p. *Neurochemical research* **2022**, *47*, 1707-1720, doi:10.1007/s11064-022-03563-7.
180. Li, Y.; Han, X.; Fan, H.; Sun, J.; Ni, M.; Zhang, L.; et al. Circular RNA AXL increases neuron injury and inflammation through targeting microRNA-328 mediated BACE1 in Alzheimer's disease. *Neuroscience letters* **2022**, *776*, 136531, doi:10.1016/j.neulet.2022.136531.
181. Zhang, Y.C.; Chen, D.Q.; Tian, R.; Yan, X.Y.; Zhou, Y.W. Resveratrol alleviates amyloid β -induced neuronal apoptosis, inflammation, and oxidative and endoplasmic reticulum stress by circ_0050263/miR-361-3p/PDE4A axis during Alzheimer's disease. *Chem Biol Drug Des* **2023**, *102*, 1121-1132, doi:10.1111/cbdd.14313.
182. Li, N.; Zhang, D.; Guo, H.; Yang, Q.; Li, P.; He, Y. Inhibition of circ_0004381 improves cognitive function via miR-647/PSEN1 axis in an Alzheimer disease mouse model. *Journal of neuropathology and experimental neurology* **2022**, *82*, 84-92, doi:10.1093/jnen/nlac108.
183. Meng, T.; Chen, Y.; Wang, P.; Yang, L.; Li, C. Circ-HUWE1 Knockdown Alleviates Amyloid-beta-Induced Neuronal Injury in SK-N-SH Cells via miR-433-3p Release-Mediated FGF7 Downregulation. *Neurotoxicity research* **2022**, *40*, 913-924, doi:10.1007/s12640-022-00523-5.
184. Hanan, M.; Simchovitz, A.; Yayon, N.; Vaknine, S.; Cohen-Fultheim, R.; Karmon, M.; et al. A Parkinson's disease CircRNAs Resource reveals a link between circSLC8A1 and oxidative stress. *EMBO Mol Med* **2020**, *12*, e11942, doi:10.15252/emmm.201911942.

185. Zhou, Y.; Liu, Y.; Kang, Z.; Yao, H.; Song, N.; Wang, M.; et al. CircEPS15, as a sponge of MIR24-3p ameliorates neuronal damage in Parkinson disease through boosting PINK1-PRKN-mediated mitophagy. *Autophagy* **2023**, *19*, 2520-2537, doi:10.1080/15548627.2023.2196889.
186. Lin, X.; Mao, L.; Chen, Q.; Wang, T.; Tao, T.; Pan, L. CircHIVEP2 alleviates Parkinson's nerve damage and inflammatory response by targeting miR-485-3p. *Exp Gerontol* **2024**, *188*, 112387, doi:10.1016/j.exger.2024.112387.
187. Liu, Q.; Li, Q.; Zhang, R.; Wang, H.; Li, Y.; Liu, Z.; et al. circ-Pank1 promotes dopaminergic neuron neurodegeneration through modulating miR-7a-5p/ α -syn pathway in Parkinson's disease. *Cell Death Dis* **2022**, *13*, 477, doi:10.1038/s41419-022-04934-2.
188. Wang, W.; Lv, R.; Zhang, J.; Liu, Y. circSAMD4A participates in the apoptosis and autophagy of dopaminergic neurons via the miR-29c-3p-mediated AMPK/mTOR pathway in Parkinson's disease. *Mol Med Rep* **2021**, *24*, doi:10.3892/mmr.2021.12179.
189. Cheng, Q.; Wang, J.; Li, M.; Fang, J.; Ding, H.; Meng, J.; et al. CircSV2b participates in oxidative stress regulation through miR-5107-5p-Foxk1-Akt1 axis in Parkinson's disease. *Redox Biol* **2022**, *56*, 102430, doi:10.1016/j.redox.2022.102430.
190. Cao, X.; Guo, J.; Mochizuki, H.; Xu, D.; Zhang, T.; Han, H.; et al. Circular RNA circ_0070441 regulates MPP(+)-triggered neurotoxic effect in SH-SY5Y cells via miR-626/IRS2 axis. *Metab Brain Dis* **2022**, *37*, 513-524, doi:10.1007/s11011-021-00869-3.
191. Wang, Q.; Wang, H.; Zhao, X.; Han, C.; Liu, C.; Li, Z.; et al. Transcriptome sequencing of circular RNA reveals the involvement of hsa-SCMH1_0001 in the pathogenesis of Parkinson's disease. *CNS Neurosci Ther* **2024**, *30*, e14435, doi:10.1111/cns.14435.
192. Zhou, Z.; Ye, Q.; Ren, H.; Zhang, Y.; Han, B.; Yao, H.; et al. CircDYM attenuates microglial apoptosis via CEBPB/ZC3H4 axis in LPS-induced mouse model of depression. *Int J Biol Macromol* **2024**, *254*, 127922, doi:10.1016/j.ijbiomac.2023.127922.
193. Yu, X.; Bai, Y.; Han, B.; Ju, M.; Tang, T.; Shen, L.; et al. Extracellular vesicle-mediated delivery of circDYM alleviates CUS-induced depressive-like behaviours. *J Extracell Vesicles* **2022**, *11*, e12185, doi:10.1002/jev2.12185.
194. Ju, M.; Zhang, Z.; Gao, F.; Chen, G.; Zhao, S.; Wang, D.; et al. Intranasal Delivery of circATF7IP siRNA via Lipid Nanoparticles Alleviates LPS-induced Depressive-Like Behaviors. *Adv Healthc Mater* **2024**, e2402219, doi:10.1002/adhm.202402219.
195. Bai, Y.; Chang, D.; Ren, H.; Ju, M.; Wang, Y.; Chen, B.; et al. Engagement of N(6)-methyladenosine methylation of Gng4 mRNA in astrocyte dysfunction regulated by CircHECW2. *Acta Pharm Sin B* **2024**, *14*, 1644-1660, doi:10.1016/j.apsb.2024.01.011.
196. Fan, C.; Li, Y.; Lan, T.; Wang, W.; Long, Y.; Yu, S.Y. Microglia secrete miR-146a-5p-containing exosomes to regulate neurogenesis in depression. *Mol Ther* **2022**, *30*, 1300-1314, doi:10.1016/j.ymthe.2021.11.006.
197. Cai, Y.; Ji, Y.; Liu, Y.; Zhang, D.; Gong, Z.; Li, L.; et al. Microglial circ-UBE2K exacerbates depression by regulating parental gene UBE2K via targeting HNRNPU. *Theranostics* **2024**, *14*, 4058-4075, doi:10.7150/thno.96890.
198. Huang, R.; Zhang, Y.; Bai, Y.; Han, B.; Ju, M.; Chen, B.; et al. N(6)-methyladenosine modification of fatty acid amide hydrolase messenger RNA in circular RNA STAG1-regulated astrocyte dysfunction and depressive-like behaviors. *Biological psychiatry* **2020**, *88*, 392-404, doi:10.1016/j.biopsych.2020.02.018.

199. Wang, X.; Song, H.; Du, Y.; Zhao, Y.; Fu, Y.; Meng, Q.; et al. CircSYNDIG1 ameliorates stress-induced abnormal behaviors by suppressing miR-344-5p in mice. *Brain research bulletin* **2023**, *195*, 66-77, doi:10.1016/j.brainresbull.2023.02.010.
200. Zhao, Y.; Zhang, Q.; Yan, Y.; Wang, X.; Shao, Y.; Mei, C.; et al. Antidepressant-like effects of geniposide in chronic unpredictable mild stress-induced mice by regulating the circ_0008405/miR-25-3p/Gata2 and Oip5os1/miR-25-3p/Gata2 networks. *Phytother Res* **2023**, *37*, 1850-1863, doi:10.1002/ptr.7702.
201. Hu, N.; Zheng, Y.; Liu, X.; Jia, J.; Feng, J.; Zhang, C.; et al. CircKat6b Mediates the Antidepressant Effect of Esketamine by Regulating Astrocyte Function. *Mol Neurobiol* **2024**, doi:10.1007/s12035-024-04420-0.

Figure Legends

Figure 1. **CircRNAs Orchestrate Multifaceted Regulation of Brain Development through Molecular Interactions.**

Circular RNAs (circRNAs), generated through back-splicing of pre-mRNA, regulate brain development by modulating brain size, neural stem cell differentiation, and neuronal morphogenesis. Specifically, CDR1as interacts with miR-7 to regulate neural plasticity, thereby influencing brain size of volumes and neuronal network activity. Several circRNAs, including circAcbd6, circHIPK2, and circZNF827, collectively modulate the differentiation trajectory of neural stem cells through interactions with their respective target molecules. Furthermore, circRtn4 regulates both neural stem cell function and the growth of neuronal soma and dendrites via its interaction with CHD5. Additional circRNAs, such as circHomer1, circTulp4, circFat3, and circRmst, have also been implicated in the regulation of neuronal soma and dendritic growth, highlighting the complex regulatory network mediated by circRNAs in brain development.

Figure 2. **CircRNAs Networks Modulate Multifactorial Pathological Mechanisms in the Pathogenesis of Alzheimer's Disease**

The pathogenesis of Alzheimer's disease (AD) involves multiple interconnected pathological processes, including dysregulated apoptosis, neuroinflammation, oxidative stress, and mitochondrial dysfunction. Evidence demonstrates that specific circRNAs, such as CDR1as, circAXL, circATP13A1, circHDAC9, circLPAR1, circARID1B, and circHUWE1, modulate these pathological processes through their interactions with target molecules and downstream signaling pathways. Furthermore, characteristic AD pathologies, including synaptic dysfunction and amyloid- β plaque accumulation, are regulated by the dysregulation of circCwc27, circBptf, and

circRIMS2, which in turn create feedback loops affecting circRNAs expression profiles. These molecular alterations together contribute to the progressive cognitive decline and memory impairment in AD patients.

Figure 3. Cell-Type-Specific circRNAs Dynamics in Stress-Induced Depression Pathogenesis

Stress dynamically modulates circRNAs expression across different cell types in both humans and rodents, particularly in microglia, neurons, and astrocytes. Stress-induced alterations in microglial circRNAs promote activation and neuroinflammation, while dysregulated neuronal circRNAs contribute to apoptosis and synaptic dysfunction. Similarly, aberrant circRNAs expression in astrocytes leads to functional impairment and programmed cell death. These cell type-specific, circRNAs-mediated processes collectively drive the pathogenesis of depression. CircRNAs validated in both human and rodent studies are marked with a red “*” to highlight their translational relevance.

Table 1. The circRNAs in neuron differentiation and plasticity

CircRNAs name	Samples and Model	Targets	Function
circHIPK2	NSCs	SMOX	Silencing of circHIPK2 enhances NSC-differentiated neurons, spine density and the expression of synaptic protein [162].
circSLC45A4	SH-SY5Y cells; mouse embryos	/	Knockdown of circSLC45A4 in human SH-SY5Y cells causes spontaneous differentiation and in developing mouse cortex depletes the basal progenitor pool [34].
CDR1as	Zebrafish embryos; Cdr1as knockout mice	miR-7	Aberrant expression of CDR1as impairs midbrain development, normal brain function, and neuronal plasticity, and regulates the expression of several synaptic plasticity-related genes [15,38,163].
circHomer1	Primary hippocampal neurons and slices	/	CircHomer1 was significantly upregulated both in neuron soma and dendrites, and decreased homeostatic synaptic plasticity [17].
circRtn4	H9 cells; N2a cells; primary cortical neurons	miR-24-3p/CHD5	Nuclear circRtn4 was exported to cytosols to promote neuronal differentiation and neurite outgrowth [49,164].
circAcdb6	NSCs	miR-320-5p/Osbp12	The upregulated circAcdb6 promotes the differentiation of NSCs into cholinergic neurons [50].
circZNF827	L-AN-5 cells	hnRNP-K and -L	CircZNF827 complexes with transcriptional regulators hnRNP-K and -L and ZNF827 and regulates their specific nuclear localization to inhibit neuronal marker expression levels and neuronal differentiation [51].
circTulp4	E14 cultures	/	The expression of circTulp4 regulates the average neurite length and the secondary branch count [32].
circFat3	E14 cultures	/	The expression of circFat3 regulates soma size and nucleic size and the number of TH positive neurons [32].
circEzh2	E14 cultures	/	The expression of circEzh2/circRmst regulates the nucleic size but not soma size

[32].		
circRmst	E14 cultures	/
The expression of circRmst regulates soma size but not nucleic size [32].		

NSCs, Neural stem cells; /, The specific targets involved remain undefined; SMOX, spermine oxidase; TH, tyrosine hydroxylase.

Table 2. The functioned circRNAs in AD

CircRNAs name	Samples and Model	Targets	Function
CDR1as	Human hippocampal CA1 and superior temporal neocortex; SH-SY5Y cells	NF- κ B	The level of CDR1as is significantly reduced in AD compared with control [165,166]. The overexpression of CDR1as depress the expression of UCHL1 depended on the NF- κ B localization, which then promotes the degradation of APP and BACE1 through proteasomes and lysosomes, and reduces the accumulation of A β proteins [167].
circHDAC9	Serum of AD patients; N2a cells; human neuronal cells; APP/PS1 mice	miR-138/ Sirt1 <hr/> miR-142-5p	CircHDAC9 is significantly decreased in AD patients. Overexpression of circHDAC9 can alleviate apoptosis, inflammation and oxidative stress injury and prevent the excessive production of A β to reverse AD-associated synaptic and cognitive impairments [168,169].
circLPAR1	Serum and CSF of AD patients;	miR-885-5p/ KREMEN1	The circLPAR1 was highly expressed in AD patients and A β -treated cells. Silencing circLPAR1 abolishes A β -

	APP/PS1 mice; SK-N-SH cells; SH-SY5Y cells	miR-212-3p /ZNF217	mediated cell proliferation, apoptosis, inflammatory response, oxidative stress, and glycolysis as miRNA sponge or RNA-binding protein to alleviate AD-associated cognitive performance [170-174].
		miR-383-5p/ KIF1B	
		UPF1/GDF-15/SIRT1/Nrf-2/HO-1	
circCwc27	Temporal cortex and plasma of AD patients; APP/PS1 mice	Pur- α	The expression of circCwc27 is significantly upregulated in AD mice and patients. Knockdown of circCwc27 improves AD associated spatial learning and memory ability and prevents A β deposition through directly binding to Pur- α [26].
circRIMS2	APP/PS1 mice	miR-3968/UBE2K	CircRIMS2 is significantly upregulated in AD mice, which was regulated by METTL3-dependent N6-methyladenosine modification. Inhibited circRIMS2 mitigates synaptic and memory impairments [44].
circAPP	AD patients; HEK293 cells	/	The circAPP levels is significantly reduced in entorhinal cortex of AD cases. The circAPP is efficiently translated into a novel A β -containing A β 175 polypeptide causing A β accumulation [175,176].

circTREM2	AD patient entorhinal cortex	/	CircTREM2 levels is significantly upregulated in AD entorhinal cortex. The association between global average area of A β deposits and circTREM2 expression levels shows negative correlation [177].
circBptf	APP/PS1 mice	miR-138-5p/P62	The expression of circBptf shows an age-dependent decrease in the hippocampus of APP/PS1 mice. Overexpressed circBptf significantly reverses AD-associated dendritic spine loss and learning and memory impairment [178].
circAXL	CSF samples from AD patients; SK-SY5Y and SK-N-SH cells	miR-1306-5p/PDE4A miR-328/BACE1	The expression of circAXL is significantly increased in AD patients and AD cellular model. CircAXL functioned as a miRNA sponge to alleviate AD-associated cell cytotoxicity, cell apoptosis, inflammation, oxidative stress and endoplasmic reticulum stress [60,179,180].
circATP13A1	SK-N-SH cells	miR-361-3p/PDE4A	CircATP13A1 expression is increased in A β -treated SK-N-SH cells after A β treatment. Reducing circATP13A1 expression alleviates A β -induced apoptosis, inflammatory response,

			oxidative stress, and endoplasmic reticulum stress [181].
			A β 42-treated hippocampal neurons upregulate the circARID1B expression. Knockdown of circARID1B attenuates A β -42-induced apoptosis, oxidative stress and mitochondrial dysfunction and reverses AD-like spatial learning and memory ability [182].
circARID1B	APP/PS1 mice; primary hippocampal neurons	miR-647/PSEN1	
			CircHUWE1 is aberrantly upregulated in serum samples of AD patients and A β -treated SK-N-SH cells. CircHUWE1 knockdown inhibits viability decrease, apoptosis, and inflammation [183].
circHUWE1	Serum of AD patients; SK-N-SH cells	miR-433-3p/FGF7	

AD, Alzheimer's Disease; /, The specific targets involved remain undefined; NF- κ B, nuclear factor- κ B; APP, β -amyloid precursor protein; BACE1, β -site APP-cleaving enzyme 1; A β , Beta-amyloid; ZNF217, Zinc finger protein 217; Sirt1, sirtuin 1; APP/PS1, APP^{swe} and PSEN1^{dE9}; CSF, cerebrospinal fluid; UPF1, up-frameshift protein 1; GDF-15, growth differentiation factor 15; HO-1, heme oxygenase-1; Pur- α , purine-rich element-binding protein A; PDE4A, Phosphodiesterase 4A; PSEN1, presenilin-1; FGF7, fibroblast growth factor 7.

Table 3. The circRNAs functioned in PD

CircRNAs name	Samples and Models	Targets	Function
circSLC8A1	Human substantia nigra tissues	miR-128	CircSLC8A1 is significantly upregulated in the PD substantia nigra. CircSLC8A1 may mediate PD-induced damage via binding to miR-128 as a neuroprotective agent [184].
circEPS15	Plasma of PD patients,	miR24-3p/	The expression level of circEPS15 is significantly decreased in the PD patients and

	MPTP-induced PD model, SH-SY5Y and primary neurons	PINK1	negatively correlated with the severity of PD motor symptoms. CircEPS15 binds to miR24-3p stabilizing PINK1 expression to maintain mitochondrial homeostasis and subsequent rescue of dopaminergic neurons [185].
circHIVE P2	The serum of PD patients and SH-SY5Y cells	miR-485-3p	Elevated circHIVEP2 partially alleviates the PD-associated inflammation and neuronal apoptosis through directly binding to miR-485-3p [186].
circPank1	PD mice model; MN9D cell model induced by rotenone	miR-7a-5p/ α -syn	Inhibiting CircPank1 expression promotes dopaminergic neuron damage and locomotor dysfunction by sponging miR-7a-5p to regulate the α -syn expression [187].
circSAMD 4A	MPTP-induced PD mice model; SH-SY5Y cells treated with MPP ⁺	miR-29c-3p	The expression of circSAMD4A is upregulated in both PD animal and cellular models. CircSAMD4A directly binding miR-29c-3p participates the apoptosis and autophagy of dopaminergic neurons by modulating the AMPK/mTOR pathway in PD [188].
circSV2b	MPTP-induced PD mice model; Neuro2a	miR-5107-5p/Foxk1	The circSV2b expression is significantly decreased in the PD model. CircSV2b overexpression restores the dopamine synthesis, maintains nigrostriatal function,

	cells;		and improves the motor function by directly sponging miR-5107-5p to regulated Foxk1/Akt1 axis in PD mice [189].
circDLGA P4	MPTP-induced PD mice model; MN9D cells and SH SY5Y cells treated with MPP ⁺	miR-134-5p/CREB	The circDLGAP4 expression is decreased in PD model. Overexpressed circDLGAP4 level exerts neuroprotective effects via modulating miR-134-5p/CREB pathway, including promoting cell viability, reducing apoptosis, decreasing mitochondrial damage, enhancing autophagy [92].
	SK-N-SH cells and MN9D cells treated with MPP ⁺	EIF4A3/HMGA2	The circDLGAP4 expression is reduced in the PD model, while upregulated circDLGAP4 restores cell activity, decreases apoptosis, and reduces inflammatory damage and oxidative stress in PD cell models by recruiting EIF4A3 to maintain mRNA stability of HMGA2 [93].
circSNCA	SH-SY5Y cells treated with MPP ⁺	miR-626/IRS2	The levels of circSNCA are increased in PD model. Inhibiting the expression of circSNCA promotes apoptosis, inflammation and neuron damage induced MPP ⁺ by sponging miR-626 to regulated IRS2 expression [190].
circSCMH 1	Plasma exosome of PD patients	/	The circSCMH1 expression levels are significantly downregulated in PD patients. And its levels is negatively correlated with

the severity of PD cognitive and motor symptoms [191].

/, The specific targets involved remain undefined; PD, Parkinson's disease; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; α -syn, α -synuclein; MPP, 1-methyl-4-phenylpyridinium; EIF4A3, eukaryotic initiation factor 4A3; HMGA2, high mobility group AT-hook 2; IRS2, insulin receptor substrate 2.

Table 4. The circRNAs functioned in depression

CircRNAs name	Samples and Model	Targets	Function
circDYM	The chronic unpredictable stress and LPS-induced depression mouse model	miR-9/HECTD	The circDYM levels is decreased remarkably in MDD patients and mouse model. Restoration of circDYM inhibits microglial activation and attenuated depressive-like behavior via targeting miR-9/HECTD to regulate HSP90 ubiquitination [116].
	LPS-induced depression mouse model	CEBPB	The circDYM regulates microglial autophagy and apoptosis to ameliorate depressive-like behaviors induced by LPS via CEBPB/ZC3H4 axis [192].
	The chronic unpredictable stress model	TAF1	Engineered extracellular vesicles bearing circDYM can be delivered to the brain and exert therapeutic effects against CUS-induced depressive-like behaviors via binding mechanistically to the transcription factor TAF1 to regulate microglial-induced neuroinflammation [193].
	The chronic	miR-497a-	Overexpressed circDYM alleviates

	unpredictable stress model	5p/NR3C1	depression-like behavior and inhibits hippocampal neurons injury induced by CUS via sponging miR-497a-5p to increase NR3C1 expression[117].
circATF7IP	Plasma of MDD patients; LPS-induced depression mouse model	/	<p>The level of circATF7IP is significantly upregulated in MDD patients and depression mouse model.</p> <p>The knockdown of circATF7IP attenuates microglial activation and alleviates astrocyte loss dysfunction to ameliorate LPS-induced depressive-like behaviors [194].</p>
circHECW2	Plasma of MDD patients; chronic unpredictable stress model	WTAP	<p>The circHECW2 levels are markedly increased in MDD patients and mice models of depression. Increased circHECW2 reveals a positive correlation with the scores of the symptom of MDD and leads to astrocyte dysfunction and depressive-like behavior via directly targeting methylase WTAP to regulate methylation of Gng4 [195].</p>
circHIPK2	Plasma of MDD patients; chronic unpredictable	/	<p>The circHIPK2 levels are significantly increased in MDD patients and depression model mice. Knockdown of circHIPK2 expression ameliorates depressive-like behaviors and astrocyte</p>

	stress model		dysfunction via the microbiota-gut-brain axis [112,113].
circANKS1B	Chronic unpredictable stress model	MiR-146a-5p/KLF4	CircANKS1B is decreased in the DG region of depression model mice. The circANKS1B acts as a miRNA sponge for miR-146a-5p to mediate KLF4 expression and its pathway to maintain neurogenesis and alleviate depression-like behaviors [196].
circUBE2K	The peripheral blood of MDD patients; chronic unpredictable stress model	HNRNPU/UBE2K	The expression of circUBE2K is significantly upregulated in MDD patients and depression model animals. Microglia-specific circUBE2K inhibition ameliorates depressive-like behavior and restores microglial activation via directly interacting with the HNRNPU protein to regulate the expression of the parental gene <i>UBE2K</i> [197].
circSTAG1	The plasma of MDD patients; chronic unpredictable stress model	ALKBH5	The expression of circSTAG1 is decreased in CUS mice and patients with MDD. CircSTAG1 overexpression binding with ALKBH5 in hippocampus notably increases the stability of FAAH mRNA to attenuate astrocyte dysfunction and depressive-like behaviors induced by CUS [198].

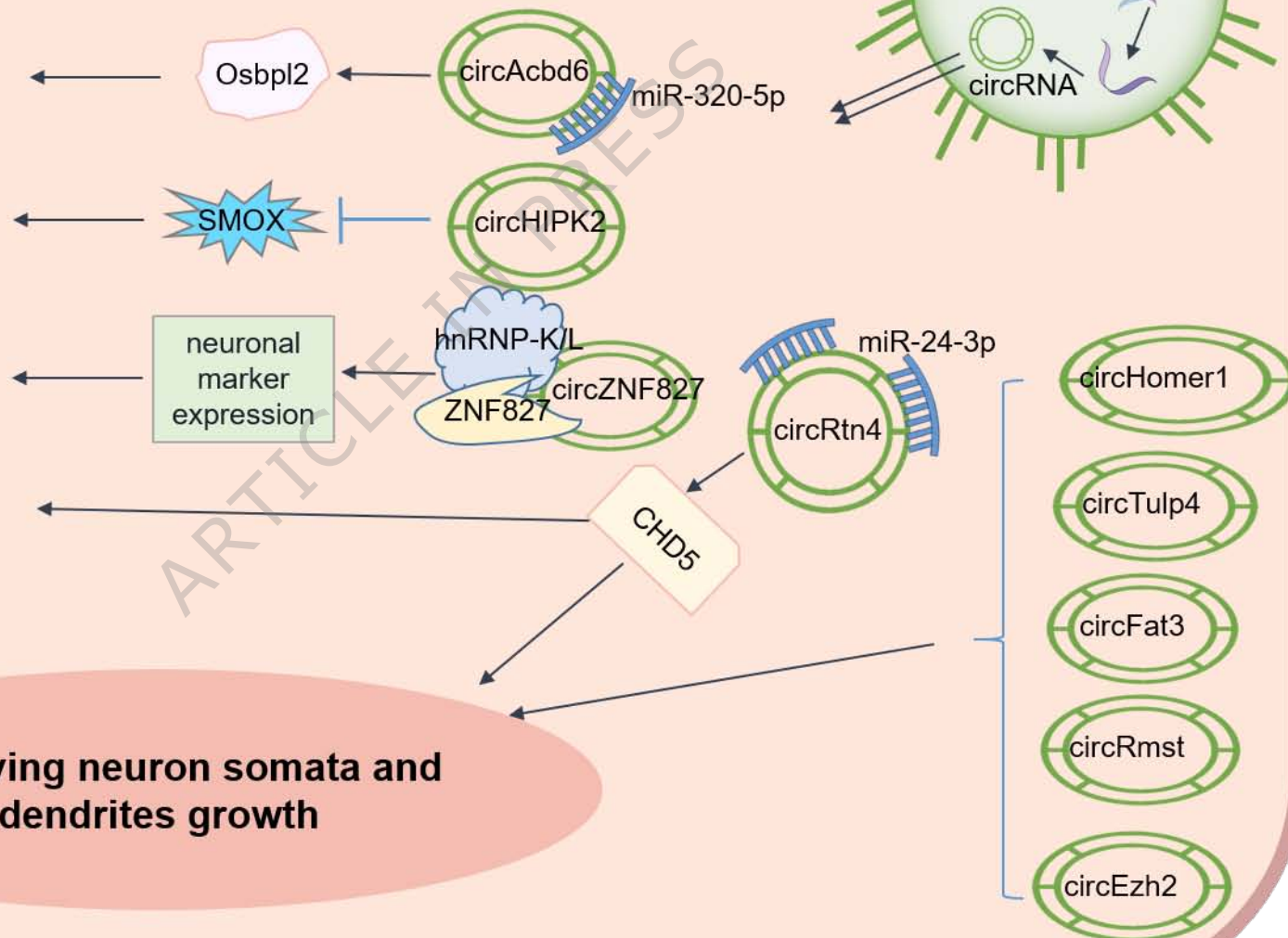
circSYNDIG1	Chronic unpredictable stress model	miR-344-5p	The circSYNDIG1 levels are significantly decreased in the hippocampus of depressive model mice. The circSYNDIG1 functions as a miR-344-5p sponge to regulate dendritic spine density and depressive-like behaviors [199].
circPBX1	Chronic unpredictable stress model	miR-25-3p/Gata2	The expression of circPBX1 is downregulated in the hippocampal of CUS mice, while geniposide treatment in the CUS mice leads to increased circPBX1 levels that exerts a beneficial effect on CUS-induced depression [200].
circKat6b	Chronic unpredictable stress model	/	S-enantiomer of ketamine exerts a rapid and obvious antidepressant effect through overexpressing circKat6b in the hippocampus significantly to decrease p-stat1 expression in astrocytes [201].

MDD, major depressive disorder; CUS, Chronic unpredictable stress; /, The specific targets involved remain undefined; HECTD1, HECT domain E3 ubiquitin protein ligase 1; TAF1, TATA-box binding protein associated factor 1; LPS, Lipopolysaccharide; NR3C1, glucocorticoid receptor; WTAP, Wilms tumor 1 associated protein; KLF4, Krüppel-like factor 4; HNRNPU heterogeneous nuclear ribonucleoprotein U;

size of
volumes and
neural network
activity

Improving the
differentiation of neural
stem cell into neuron

Improving neuron somata and
dendrites growth



Synaptic impairment

Amyloid plaques

Apoptosis

Inflammation

stress

Mitochondrial dysfunction

impair

cognitive

memory

