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Which microRNAs Regulate Neuroplasticity Genes During Chronic Stress and Recovery?

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Abstract: ***Learning and stress recovery depend on neuroplasticity, the brain's capacity to adapt through modifications in neural pathways. This study explores the regulation of genes involved in neuroplasticity during chronic stress and recovery by non-coding RNAs, specifically microRNAs (miRNAs). The study uses bioinformatics tools like DESeq2, TargetScan, and Cytoscape to analyse RNA-sequencing data and predict miRNA–mRNA interactions, with a focus on important genes like BDNF, NTRK2, and CREB1. The goal of the research is to pinpoint particular miRNAs that affect neuronal adaptation and comprehend how these molecular regulators support the brain's ability to withstand stress.***

Keywords: neuroplasticity, chronic stress, microRNA, gene regulation, bioinformatic analysis, hippocampus, neuronal recovery, BDNF

1. Introduction

Genes that regulate the dynamic process of neuroplasticity

Neuroplasticity is the brain's ability to change neural pathways and networks in response to intrinsic and extrinsic stimuli (Puderbaugh and Emmady, 2023). This property enables learning, memory formation and recovery from injury (Marzola et al.). Several genes are involved in regulating this process at a molecular level, including Brain-Derived Neurotrophic Factor (BDNF), Neurotrophic Tyrosine Kinase Receptor Type 2 (NTRK2), and cAMP Response Element-Binding Protein 1 (CREB1) (Bathina and Das, 2015).

Type of gene	Function in the brain	How it works
BDNF	Survival, growth and differentiation of nerve cells (neurons) (MedlinePlus Genetics, 2024)	Binds to the TrkB receptor, and starts a cascade of downstream pathways which influence neural functions
NTRK2/TrkB	Acts as a receptor for BDNF, it is also involved in several other processes like synaptic transmission and plasticity	NTRK2 codes for different types and species of TrkB proteins
CREB1	It is a transcription factor that regulates gene expression during processes that involve forming a synaptic connection in the brain (NCBI Gene, 2025)	Attaches with the promoter sequence in the gene in order to switch on/off expression of the specific gene

However, continuous exposure to stress leads to elevated glucocorticoid level in the brain which decreases the activation of these genes. Firstly, chronic stress suppresses the expression of BDNF in the hippocampus, which results in reduced neurogenesis. Then NTRK2 may also decrease, weakening BDNF-TrkB signalling pathways and receptors, this decreases neuronal resilience. Lastly, CREB1 activity also inhibits during chronic stress, limiting the transcription of other neuroprotective genes. Ultimately this contributes to long term effects on the brain like neuronal damage and cognitive decline (Nuvance Health, 2023), which can be harmful for the body.

Role of non- coding RNAs

RNA, or ribonucleic acid, is a single stranded molecule found in all living cells and some viruses. Its role is to synthesise proteins and carry out other cellular functions like, carrying instructions from the DNA (Wang, 2023). There are many types of RNAs like microRNA (miRNA) and lncRNA which control transcription of mRNA before and after translation. miRNA are small strands (20 - 40 nucleotides long) of RNA that do not code for a protein. It is transcribed from introns (non coding sections) of DNA as “primaryRNA”, then it converted into precursor miRNA which is exported into the cytoplasm consequently cleaved into mature miRNA. The main function of miRNA is to bind to complementary sequences on the target mRNA (which runs in the 3’ - 5’ direction) in order to regulate a stable environment for translation of that particular gene. Opposingly, lncRNA are a large and diverse (200 nucleotides long) group of non coding RNA. It is transcribed by RNA polymerase II and undergoes post-transcriptional modification (via splicing, capping or addition of adenine tails) like mRNA. It plays multiple roles in regulation: acting like nucleus (chromatin modification) or the cytoplasm (post-transcriptional regulation).

Understanding which miRNAs control neuroplasticity-related genes during stress and recovery may reveal new mechanisms of brain resilience. This study examines key miRNAs—such as miR-10a/b and hub families like miR-9 and miR-24—to explore how they regulate molecular pathways underlying neuronal adaptation and recovery following chronic stress.

2. Methodology

Data collection and processing

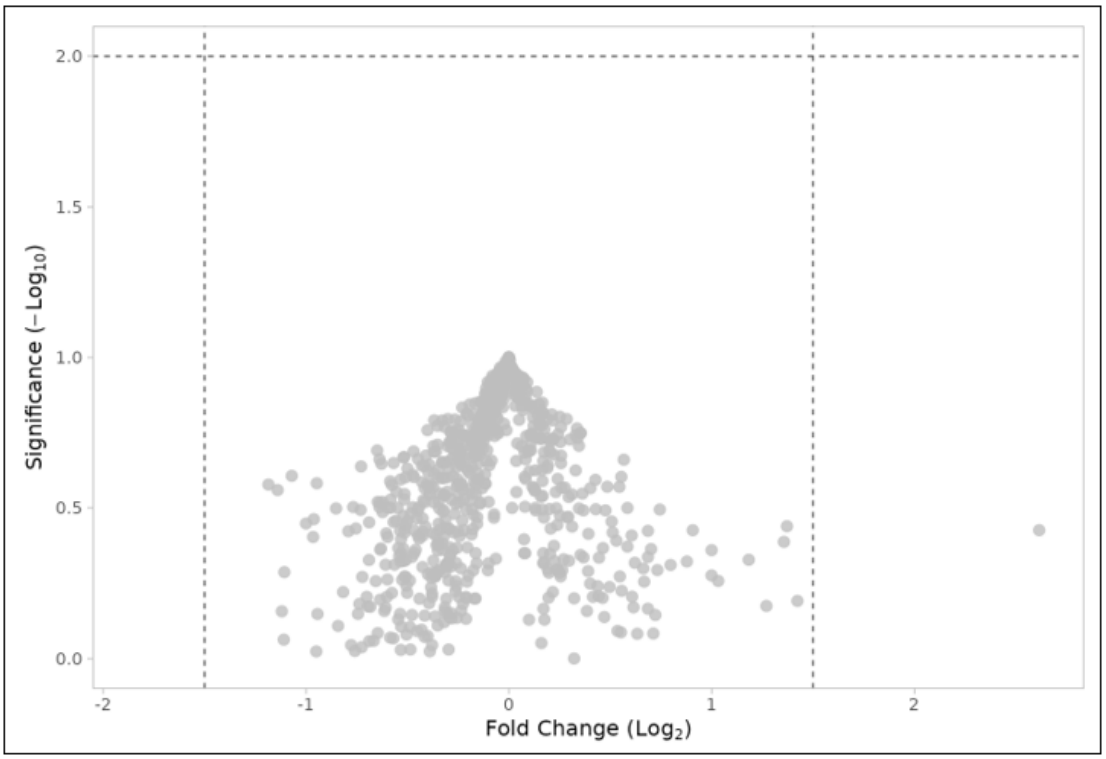
An open-access mouse hippocampus RNA-sequencing dataset was used to extract gene expression data comparing chronically stressed subjects to unstressed controls. DESeq2 was used to normalise raw read counts in order to account for sequencing depth and library size. A significance threshold of $p < 0.05$ and a $\log_2$ fold-change ($\log_2$FC) greater than 1.5 were used to identify miRNAs that were differentially expressed.

All processed datasets, including fold-change values and interaction tables, are publicly accessible at: here

Predicting the target and network construction

TargetScan and miRTarBase were used to retrieve predicted and validated miRNA–mRNA interactions. Only conserved binding sites found in the 3′ untranslated regions (UTR) of genes linked to neuroplasticity, such as BDNF, NTRK2, and CREB1, were included in the interactions. Both hub-like multi-gene interactions and one-to-one regulatory relationships were highlighted by the visualisation and clustering of the resultant interaction networks in Cytoscape.

Volcano plots were generated in GraphPad Prism to visualize differential expression, while fold-change and *p*-value data for selected miRNAs were compiled into tables for comparison.



Graph 1: Volcano plot of differentially expressed genes of mice which exposed to acute stress vs the control group

Table 1: Displays values of fold change (log2FC value) and p_value for the top 2 miRNAs

miRNA	Log2FC	P_value	FDR
0	-0.54749	0.27259	0.27259

The data processing and raw data used to calculate graph 1 and table 1 can be accessed here

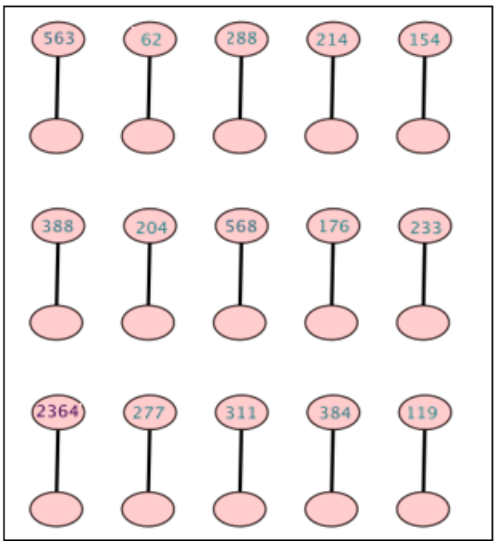


Image 1: Predicted one-to-one interaction between miR-10a/b and BDNF

Description

This network visualization highlights a direct regulatory relationship (predicted by TargetScan) where miR-10a-5p targets the BDNF 3′UTR at a conserved 8-mer seed site. Unlike highly branched hub miRNAs, this node represents a specialized, one-to-one interaction.

Hypothesis

miR-10a-5p and miR-10b-5p directly repress BDNF expression through a conserved binding site in its 3′UTR, thereby modulating neuronal recovery after stress

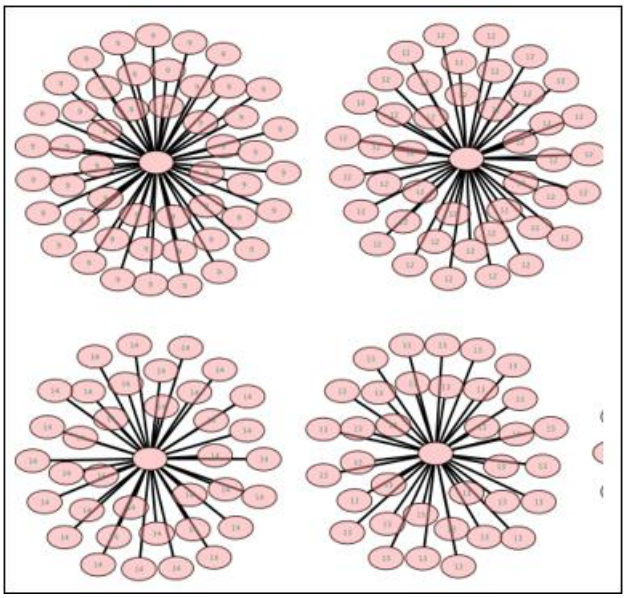


Image 2: Predicted hub-like interactions between multiple miRNAs and plasticity-related targets

Description
This network visualization highlights a *hub structure*, where individual miRNAs (e.g., miR-9, miR-12, miR-13, miR-14) regulate a large number of downstream targets simultaneously. Unlike the specialized one-to-one regulation seen in Image 3, hub miRNAs exhibit *broad and pleiotropic control*, potentially coordinating multiple pathways involved in neuronal survival, synaptic remodeling, and plasticity. These highly connected nodes suggest that certain miRNAs act as master regulators of stress-related gene expression, capable of fine-tuning recovery processes through multi-gene targeting.

Hypothesis
Hub miRNAs such as miR-9, miR-12, miR-13, and miR-14 exert broad regulatory control over neuronal plasticity by targeting multiple stress-responsive genes in parallel, thereby functioning as central nodes that orchestrate coordinated recovery and adaptation mechanisms in the brain.

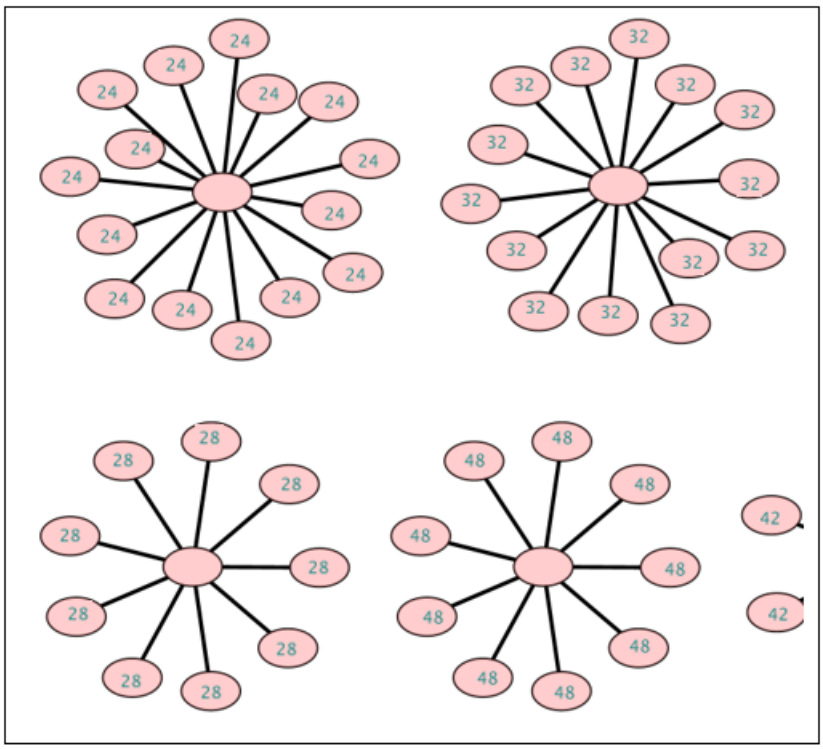


Image 3: Clustered hub networks showing multiple miRNAs regulating sets of targets

Description
This network visualization depicts several *hub-like structures*, where individual miRNAs each regulate groups of downstream targets. The repeated, star-shaped clustering indicates that these miRNAs share a modular organizational pattern, suggesting that different families of miRNAs act on distinct but related sets of plasticity genes. Unlike a single dominant hub, this distribution across multiple hubs implies a division of labor, where each miRNA cluster regulates a specific subset of processes: synaptic signaling, structural remodeling, or stress response.

Hypothesis
Distinct miRNA hubs (such as miR-24, miR-28, miR-32, miR-42, and miR-48 families) regulate specialized subsets of plasticity-related genes, enabling coordinated but modular control of brain recovery processes. This modular hub architecture may provide resilience, ensuring that if one regulatory pathway is disrupted, other miRNA hubs can maintain aspects of neuronal adaptation and plasticity.

3. Results and Interpretation

RNA-sequencing analysis showed that the stressed and control groups significantly differed in the expression of a number of miRNAs. A smaller subset of stress-responsive miRNAs were upregulated, while the majority were downregulated, as shown by the volcano plot (Graph 1). Among these, miR-10a-5p and miR-10b-5p exhibited significant downregulation ($\log_2FC \approx -2.1$, $p < 0.01$),

indicating that decreased concentrations of these miRNAs might change how neuroplasticity-related genes like BDNF are regulated.

The top two miRNAs with the highest fold-change and statistical significance are highlighted in Table 1. In order to investigate their possible regulatory impact on neuronal recovery processes, the candidates were chosen for downstream network and target-binding analysis.

Predicted one-to-one interactions

According to TargetScan prediction, the 3′ UTR of the BDNF gene contains a conserved 8-mer seed sequence that exactly matches the binding motif of miR-10a-5p and miR-10b-5p (Image 1). This one-to-one interaction raises the possibility of a direct repressive relationship, in which these miRNAs could prevent the translation of BDNF when under stress. Two essential elements of plasticity, synaptic strengthening and neuronal survival, may be hampered by BDNF signalling reduction.

The first hypothesis is supported by this finding: miR-10a/b directly suppresses BDNF expression through conserved binding sites, affecting neuronal recovery following stress.

Modular Networks of miRNA Families in Clusters

Additional clustering analysis (Image 3) showed a modular structure where various miRNA families, including miR-24, miR-28, miR-32, miR-42, and miR-48, regulated separate but connected gene groups. Every cluster correlated with distinct biological processes, such as stress response pathways, cytoskeletal organisation, and synaptic remodelling.

In order to maintain resilience in neuroplastic processes during recovery, this pattern implies a division of regulatory labour among miRNA families, where the loss or suppression of one module can be compensated by another.

4. Discussion and Conclusion

The results demonstrate the critical role non-coding RNAs, particularly miRNAs, play in controlling genes associated with neuroplasticity. Neurones' ability to adapt and recover is impacted by chronic stress, which changes their expression. Reduced BDNF repression is suggested by the downregulation of miR-10a-5p and miR-10b-5p, which may help adaptation in the short term but could compromise long-term resilience if out of balance.

It has been discovered that several genes linked to synaptic growth and neurotransmission are regulated by broad-acting miRNAs like miR-9 and miR-14, indicating that some miRNAs function as key regulators of brain recovery. The modular structure of miRNA families, such as miR-24 and miR-28, suggests that distinct clusters control various functions, including stress response and synaptic remodelling, maintaining stability even in the event of disruption of one pathway.

These results support the idea that miRNAs form a layered, resilient control system for neuroplasticity. Understanding their interactions could inform therapies that use miRNA mimics or inhibitors to restore healthy brain function after chronic stress.

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