THE NEUROBIOLOGICAL PERSPECTIVE OF SUICIDE: APPLYING BASIC SCIENCE RESEARCH TO DIAGNOSIS AND TREATMENT

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Disclosure

Nothing to disclose

MAGNITUDE OF THE PROBLEM

- ~40,000 deaths per year due to suicide in the USA and is the 2nd leading cause of death in 15-34 years olds
- >One million people die by suicide every year world-wide
- 10-20 times more suicide attempts

SUICIDAL BEHAVIOR

VULNERABILITY FACTORS

- Stress plays a very important role in suicide, but suicide is not a normal response to stress.
- It is a complication of psychiatric illnesses in the vulnerable person.

RELATIONSHIP TO PSYCHIATRIC ILLNESSES

- Unipolar depression: 50% depressed patients have thought of suicide; mortality rate 15%
- Bipolar disorder: Accounts for 15-20% of all completed suicides
- Schizophrenia: Accounts for 10-15 % of all suicides

Co-morbidity

- Anxiety disorder: Co-morbid with depression, drug abuse
- Panic disorder: 20% of suicide deaths are due to panic attack
- PTSD: Strongest association with suicidality
- Personality disorder: 4-8% suicidal individual have personality disorder
- Alcohol/drug abuse: 7-25% of suicide are associated with drug abuse

VULNERABILITY FACTORS IN SUICIDAL BEHAVIOR

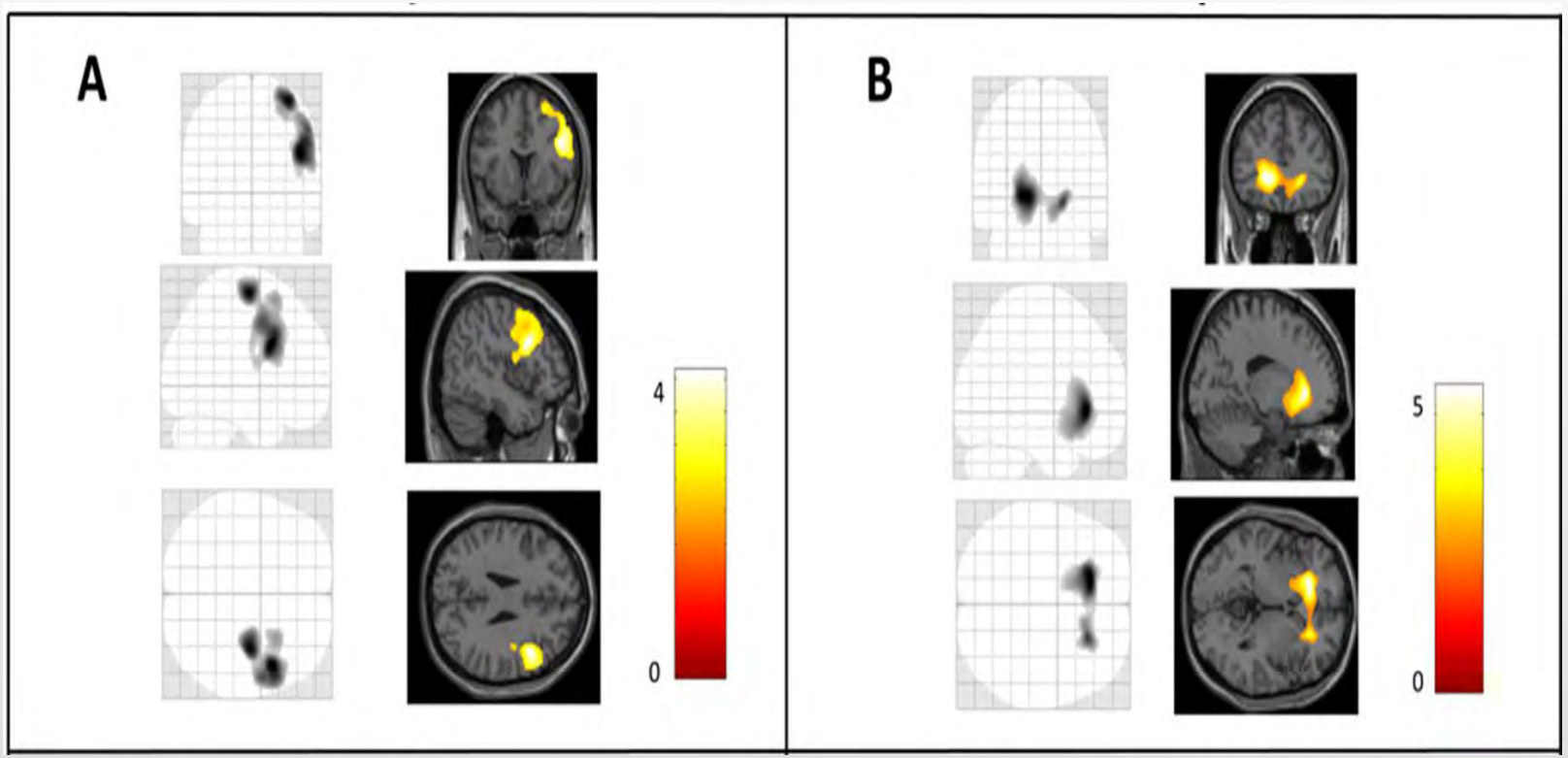
- Most patients with psychiatric illnesses do not attempt suicide.
- What determines whether a patient will attempt or die by suicide?

VULNERABILITY FACTORS IN SUICIDAL BEHAVIOR

- Impulsivity is related to probability.
- Hopelessness or pessimism is related to probability.
- Suicidal intent is related to lethality.

Vulnerability to suicidal behavior involves different brain biology

REGIONAL CEREBRAL METABOLIC RATES OF GLUCOSE UPTAKE IN DEPRESSED SUICIDE ATTEMPTERS VS. NON-ATTEMPTERS



Hypometabolism in Dorsolateral Prefrontal Cortex

Risky decision making, working memory

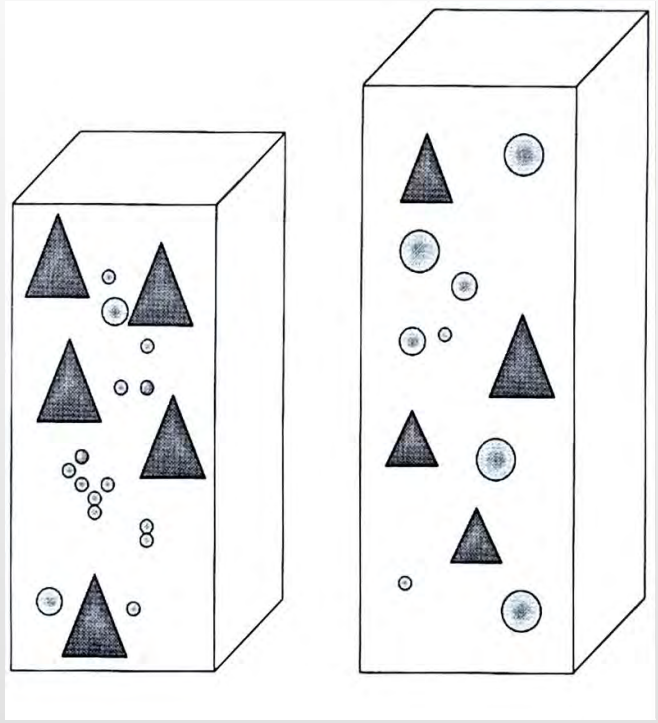
Hypermetabolism in Ventromedial Cortex

Personal and social decision making, emotion

Sublette et al., Arch Suicide Res, 2013

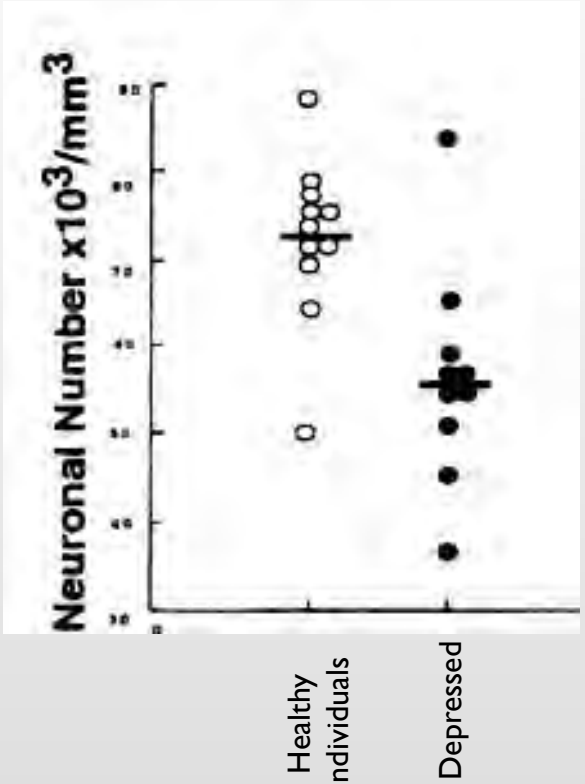
STRUCTURAL ABNORMALITIES IN THE BRAIN

Dorsolateral Prefrontal Cortex

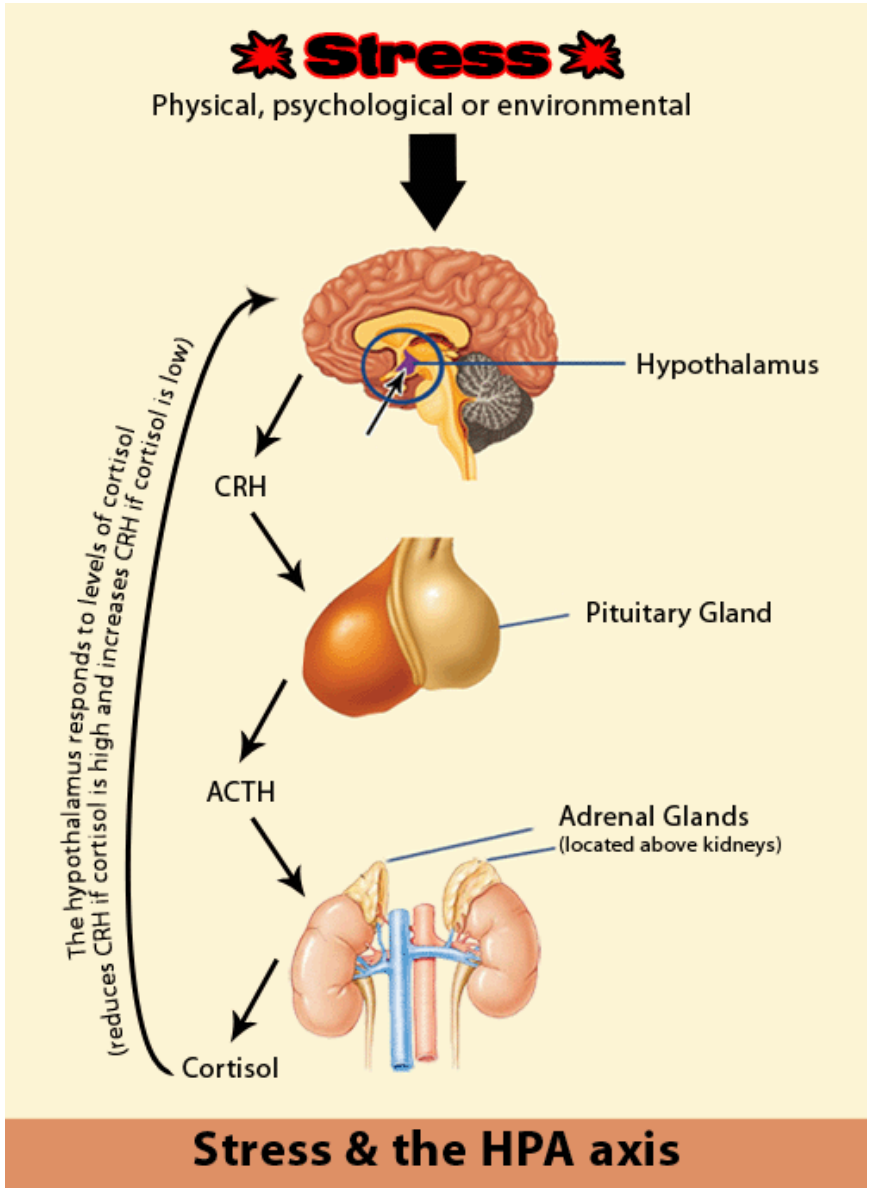


Healthy Individuals

Depressed

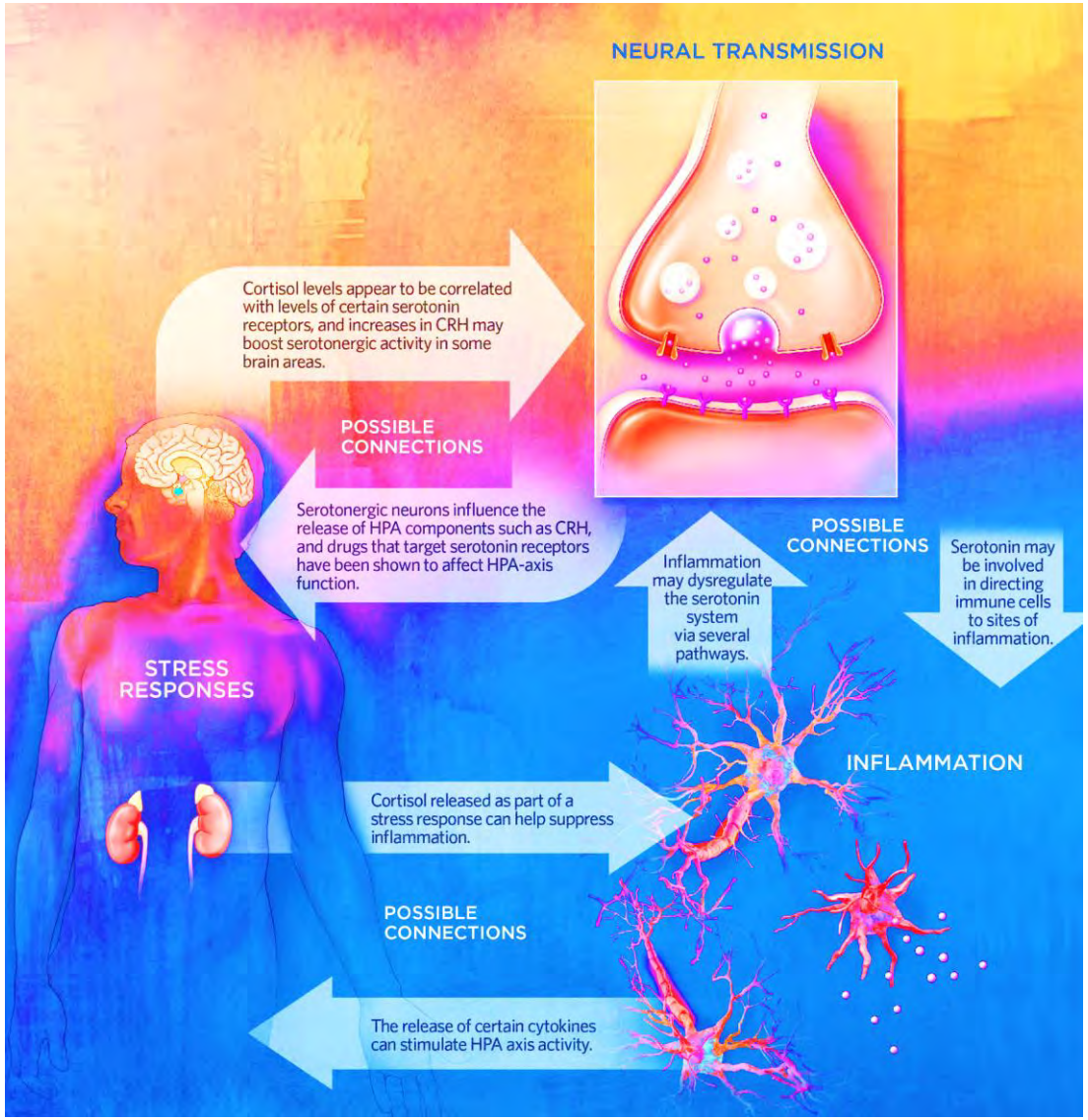


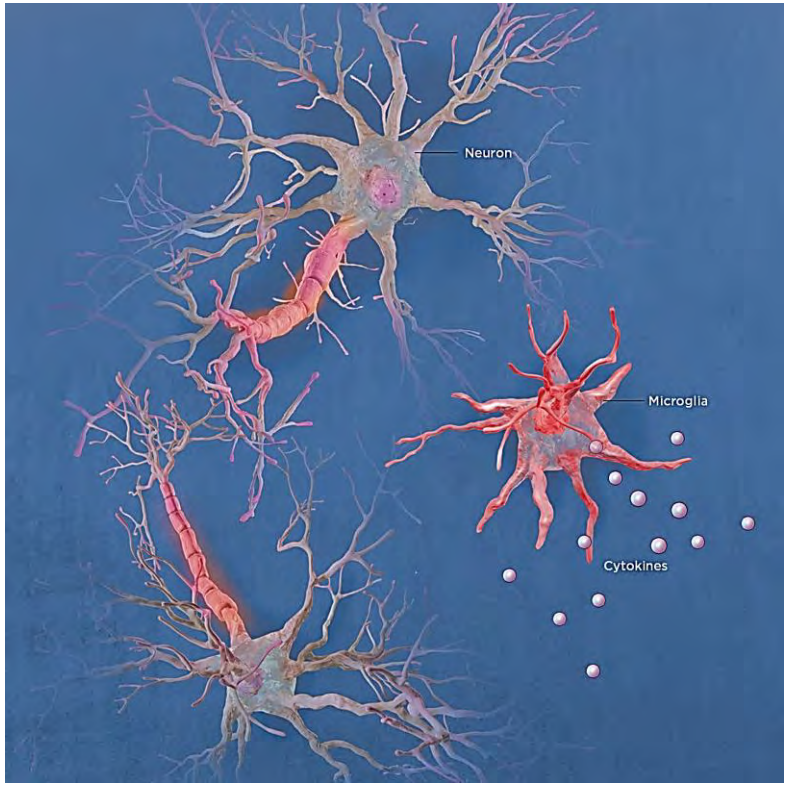
Biological Psychiatry, 2001



Stress & the HPA axis

STRESS CAUSES THE ACTIVATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS





Microglia

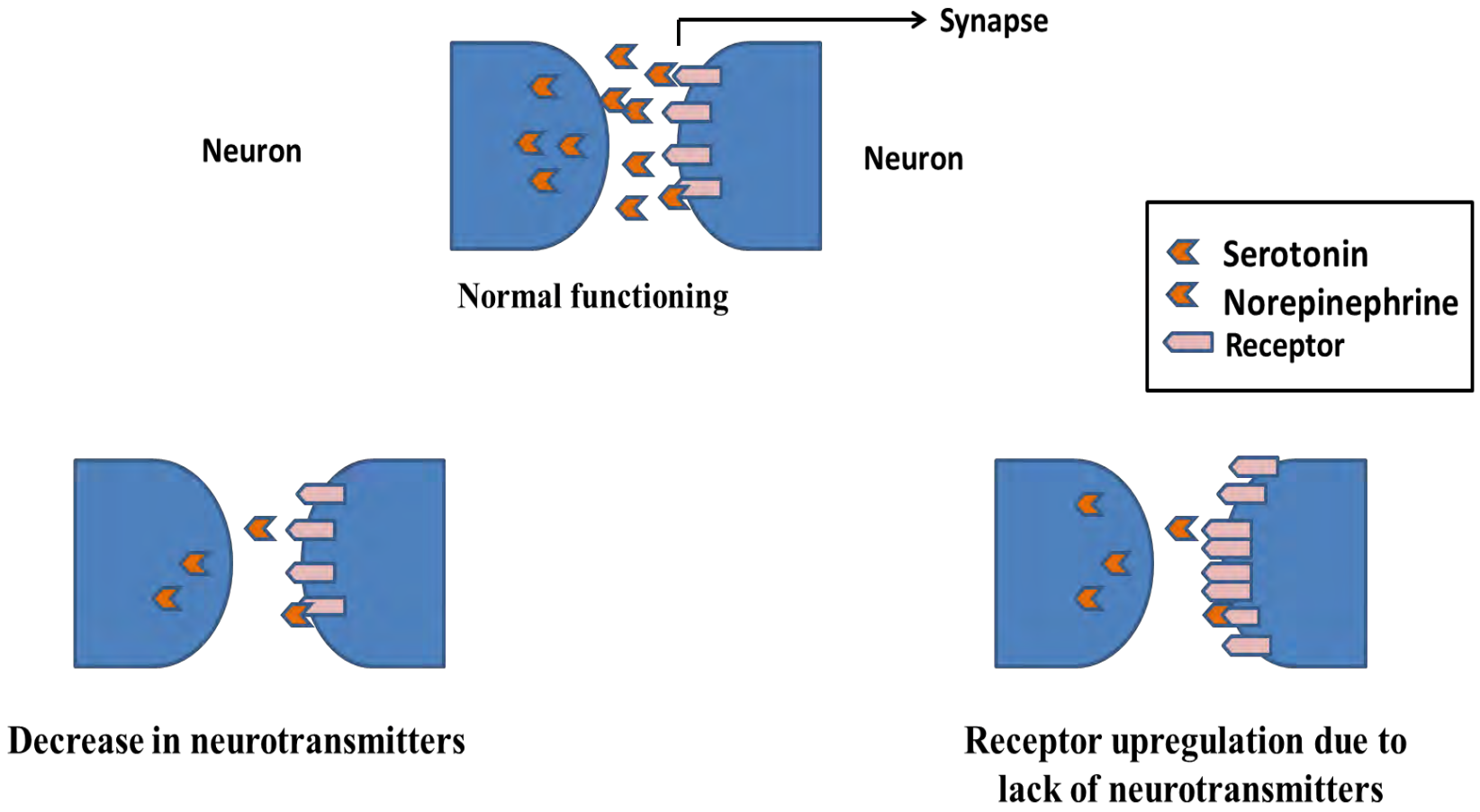
The brains of people who die by suicide show higher levels of microglia activation.

Cytokines

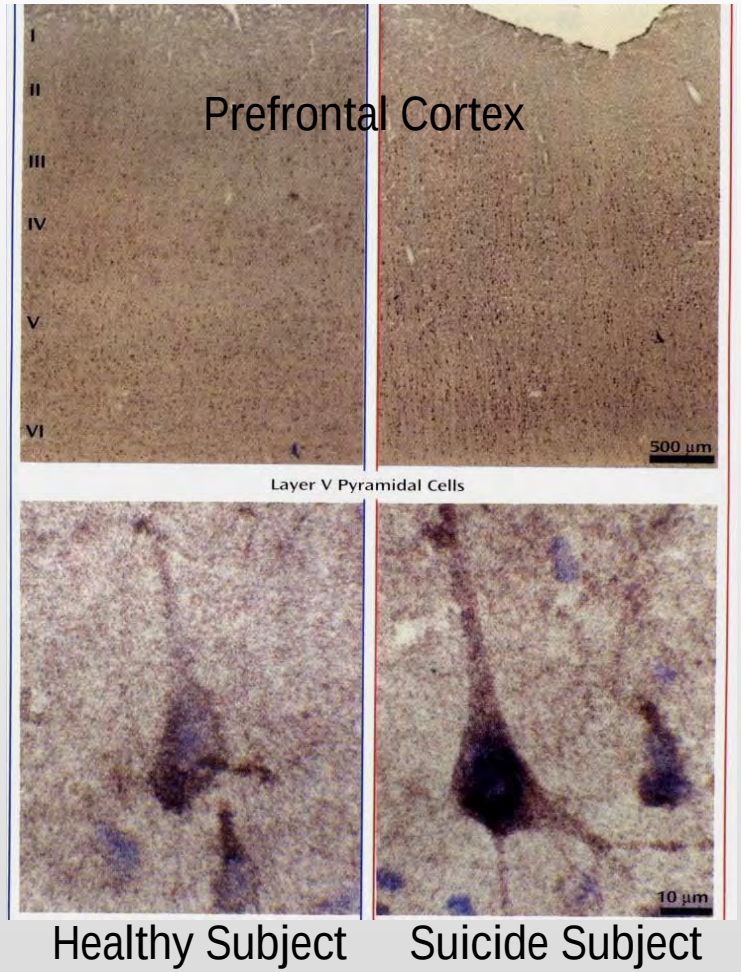
Blood levels of inflammatory cytokines, particularly some types of interleukins, have been found at higher levels in people who attempt suicide.

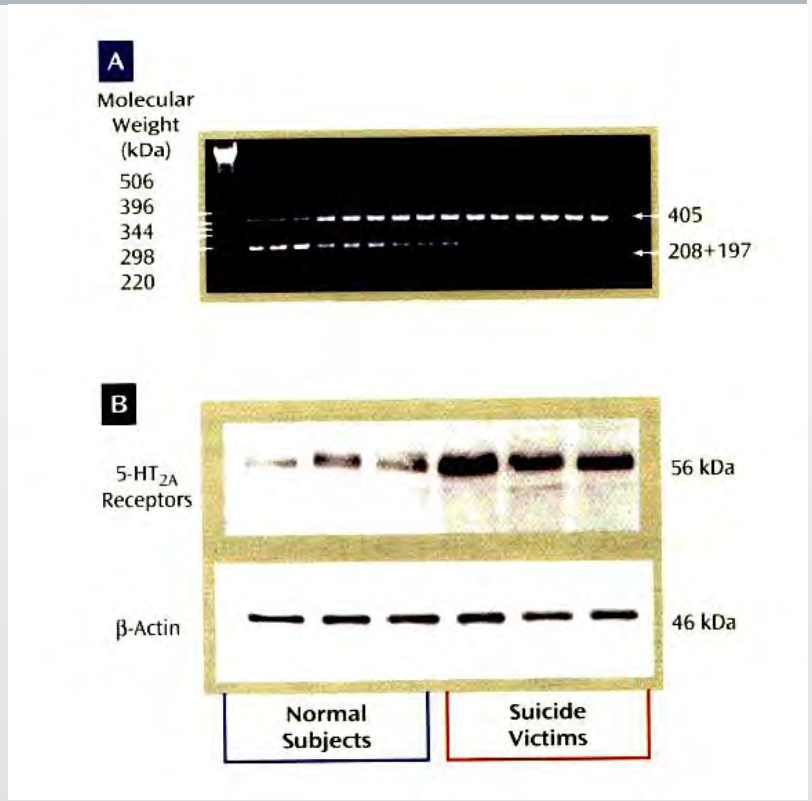
Offord, Scientist, 2020

NEUROTRANSMITTERS IN DEPRESSION AND SUICIDE



HIGHER 5-HT$_{2A}$ RECEPTOR LEVEL IN POSTMORTEM BRAIN OF SUICIDE VICTIMS





SEROTONERGIC ACTIVITY IS RELATED TO AGGRESSION, IMPULSIVITY, AND SUICIDAL BEHAVIOR

Low serotonin is proportional to seriousness of aggression and can predict future aggression

Low serotonin function modulates the intent and impulsive aspects of the suicidal behavior or predisposition

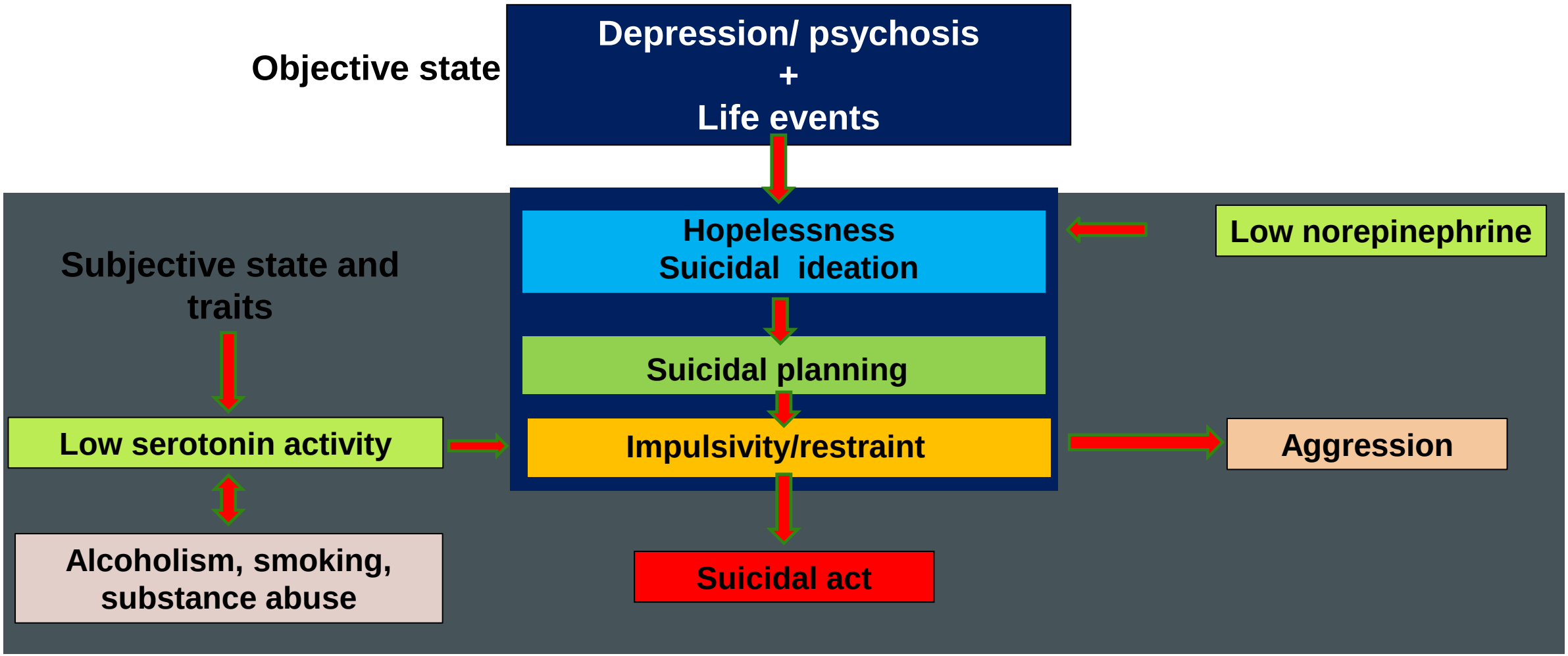
NOREPINEPHRINE RELATES TO HOPELESSNESS

Depleted norepinephrine and can generate despair and giving up

Suicide victims have evidence of marked stress responses in the brain norepinephrine system

Perhaps hopelessness results from NE depletion?

A MODEL OF SUICIDAL BEHAVIOR



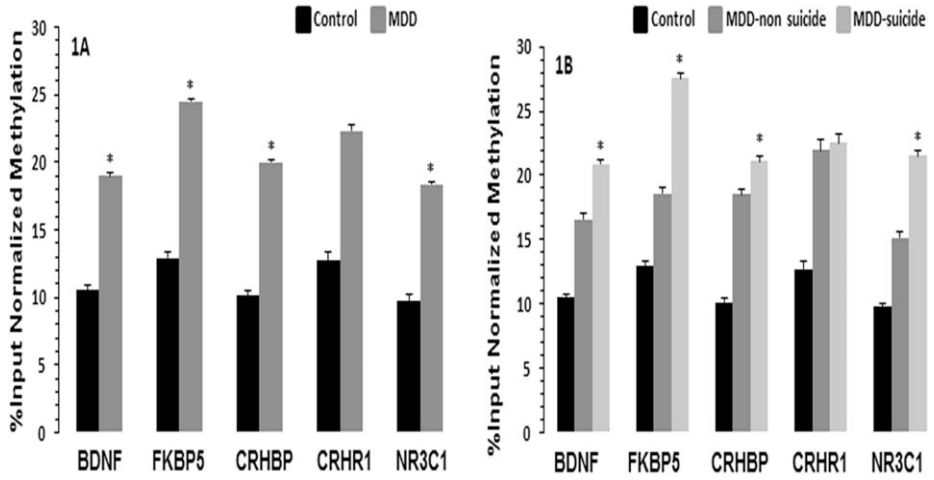
Adapted from Mann et al., 2011

GENETICS OF SUICIDE

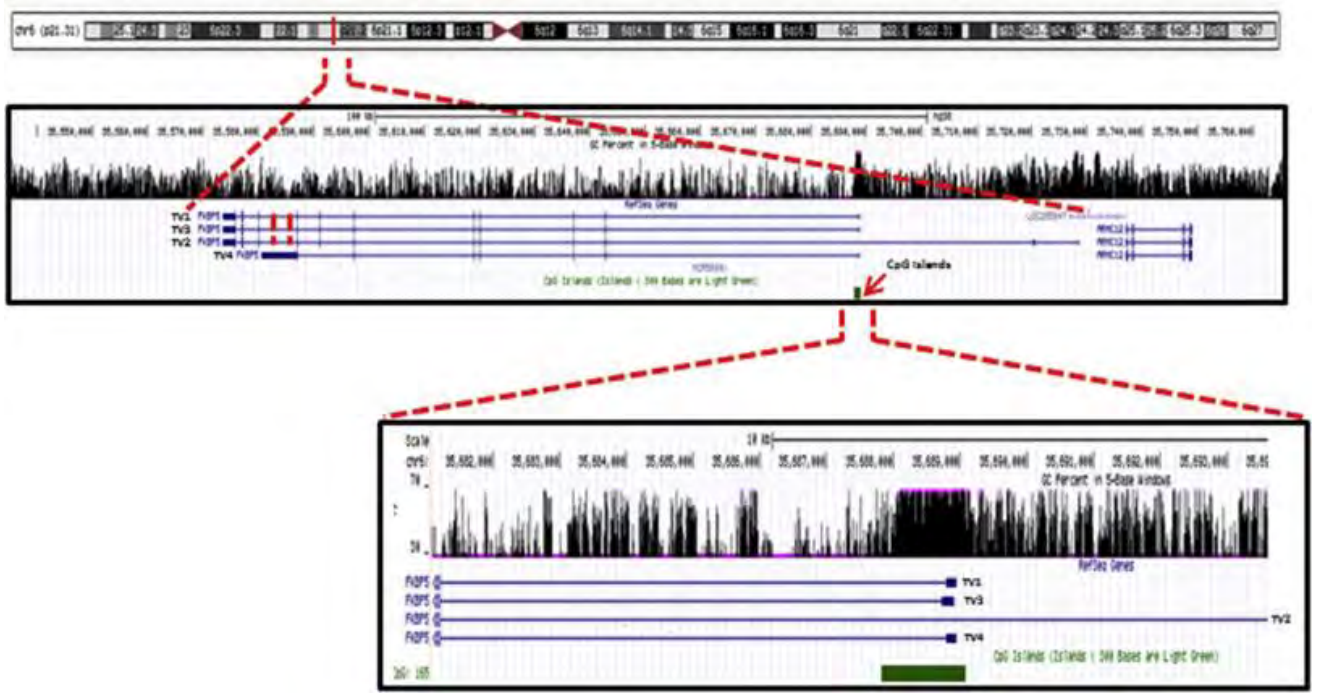
- Twin studies show that 55% of the variance in suicidal behavior can be explained by genetic factors (mono vs. dizygotic; environmental vs. genetic).
- Family studies show a 4- to 10-fold increased risk for suicidal behavior in first-degree relatives.
- 50% increase in the risk for suicidal ideation or attempt relative to offspring whose mothers had never attempted suicide.
- Familial transmission may be independent of psychiatric disorders.

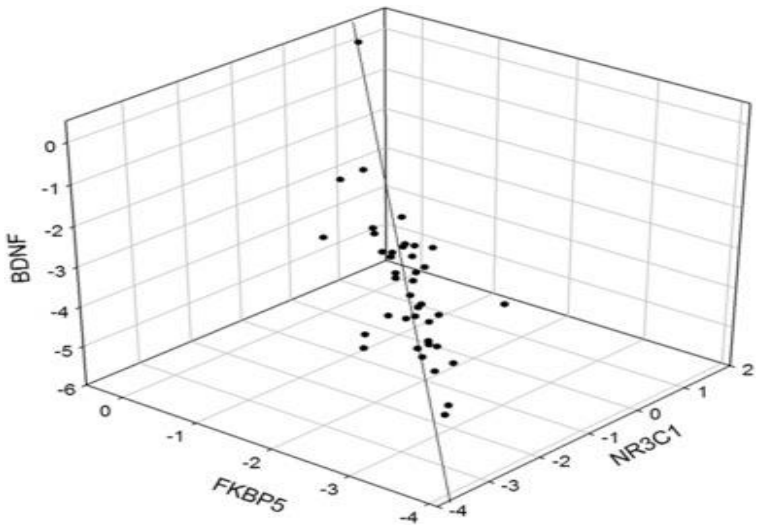
CHILDHOOD ABUSE AND SUICIDE

- Parental abuse is associated with suicide attempts in adulthood
- Childhood abuse may affect suicidal behavior in adulthood due to impulsivity (less serotonin)
- Maternal deprivation in monkey resets serotonin system function; deficiency persists into adulthood and is associated with more impulsive, aggressive behavior in adulthood
- Childhood abuse causes epigenetic modifications in brain



Roy et al., J Psych Res. 2017



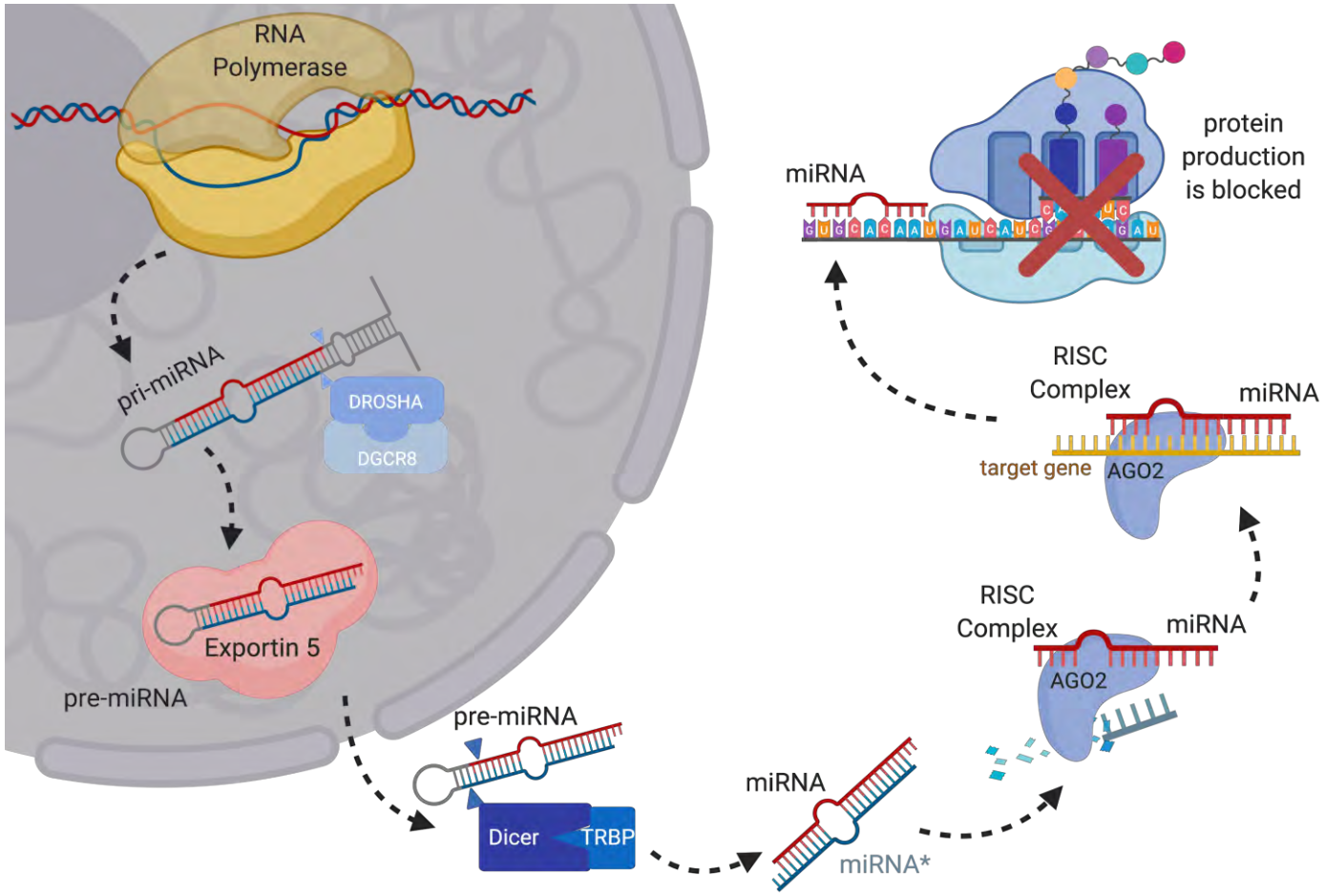


DNA METHYLATION AND EXPRESSION OF STRESS RELATED GENES IN PBMC OF MDD PATIENTS WITH AND WITHOUT SERIOUS SUICIDAL IDEATION

BRAIN-DERIVED EXOSOME BASED BIOMARKER DISCOVERY IN PATIENT POPULATION

A Novel Method To Identify Suicidality and Treatment Response

miRNA Biogenesis



Allen, Dwivedi, Mol. Psych., 2020

What are miRNAs?

- miRNAs are non-coding RNAs
- ~22 nt in length and play an important role in regulating expression of specific mRNAs post-transcriptionally
- Only partial sequence complementarity is required for translational repression via miRNA
- One miRNA can potentially regulate several mRNAs or one mRNA can be regulated by multiple miRNAs
- About 60% genes are regulated by miRNAs

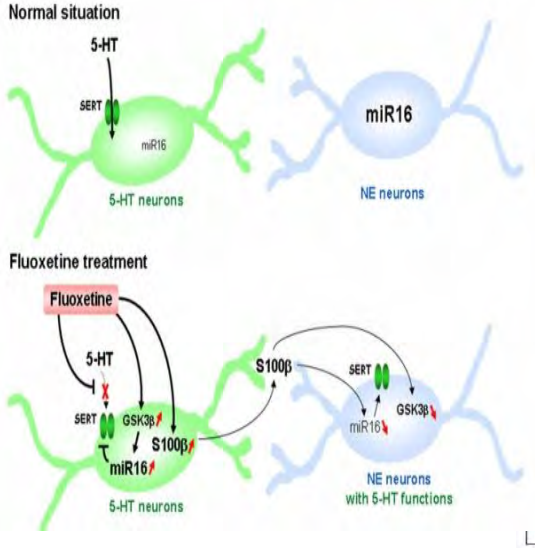
Science 2010 Sep 17;329:1537

Neuron 2014 Jul 16;83:344

MiR-16 Targets the Serotonin Transporter: A New Facet for Adaptive Responses to Antidepressants

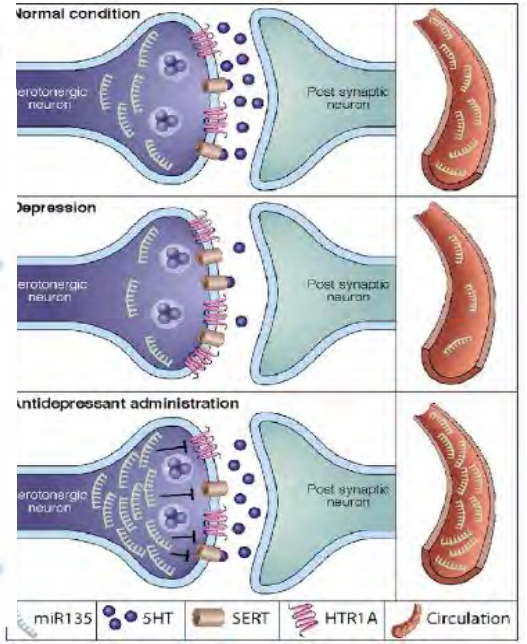
Anne Baudry,[1] Sophie Mouillet-Richard,[1] Benoît Schneider,[1] Jean-Marie Launay,[2,3]* Odile Kellermann[1]*

The serotonin transporter (SERT) ensures the recapture of serotonin and is the pharmacological target of selective serotonin reuptake inhibitor (SSRI) antidepressants. We show that SERT is a target of microRNA-16 (miR-16). miR-16 is expressed at higher levels in noradrenergic than in serotonergic cells; its reduction in noradrenergic neurons causes de novo SERT expression. In

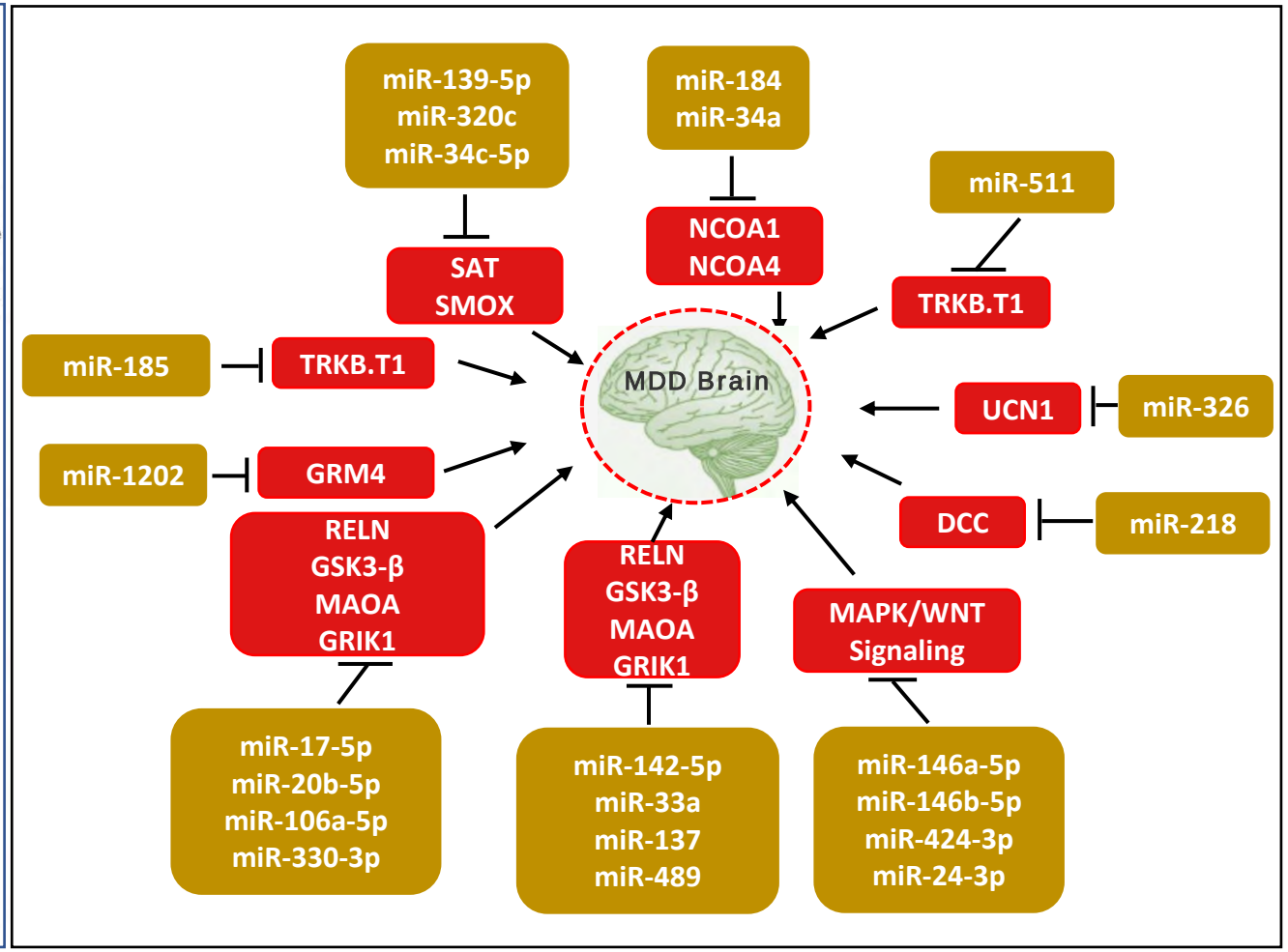


MicroRNA 135 Is Essential for Chronic Stress Resiliency, Antidepressant Efficacy, and Intact Serotonergic Activity

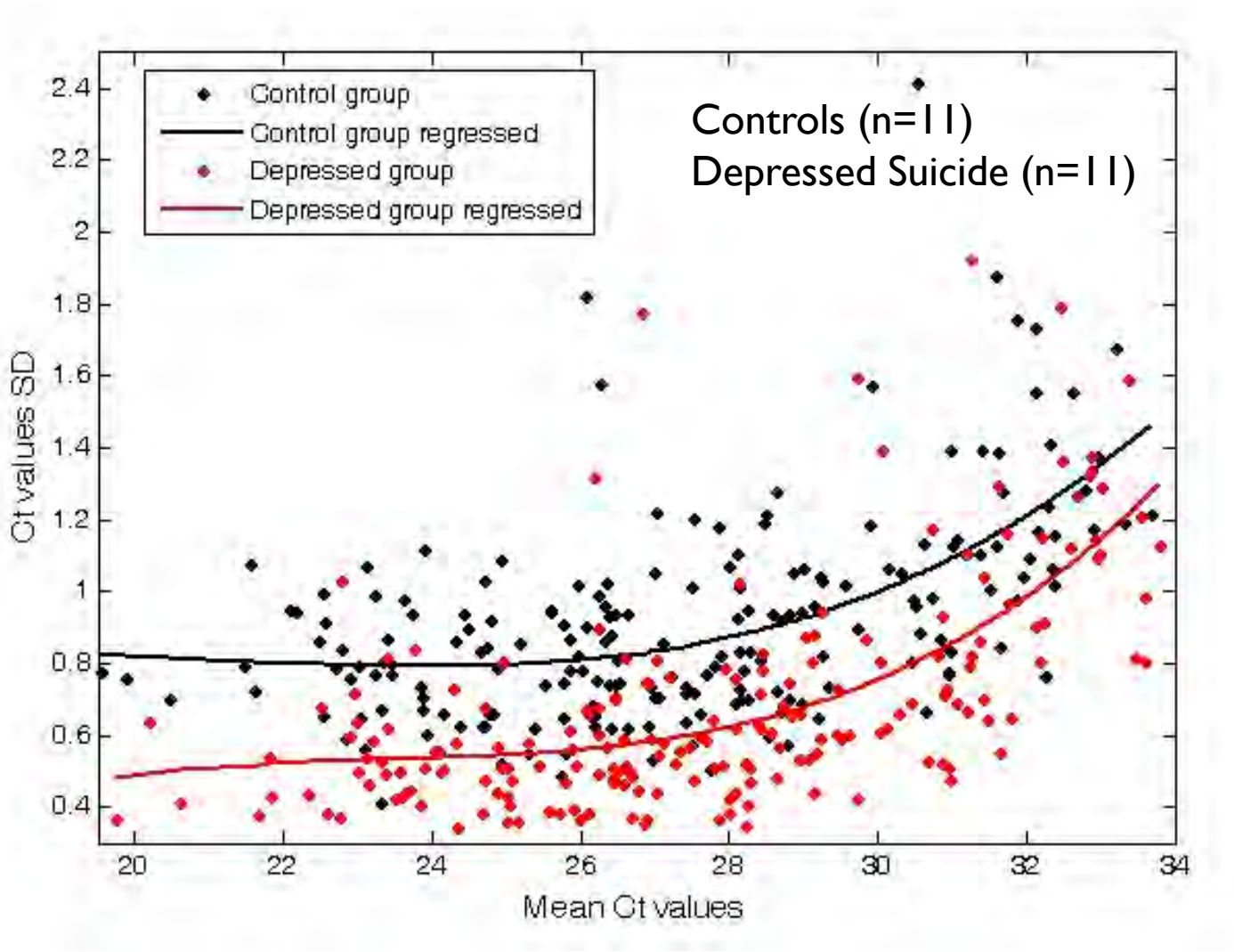
Orna Issler,[1,2] Sharon Haramati,[1] Evan D. Paul,[3] Hiroshi Maeno,[4] Inbal Navon,[1] Rayya Zwang,[1] Shosh Gil,[1] Helen S. Mayberg,[5] Boadie W. Dunlop,[5] Andreas Menke,[6] Rajeshwar Awatramani,[7] Elisabeth B. Binder,[5,6] Evan S. Deneris,[4] Christopher A. Lowry,[3] and Alon Chen[1,2,*]
[1]The Ruhman Family Laboratory for Research on the Neurobiology of Stress, Department of Neurobiology, Weizmann Institute 76100 Rehovot, Israel
[2]Department of Stress Neurobiology and Neurogenetics, Max-Planck Institute of Psychiatry, 80804 Munich, Germany
[3]Department of Integrative Physiology and Center for Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA



Overview of NeuromiR in MDD Brain



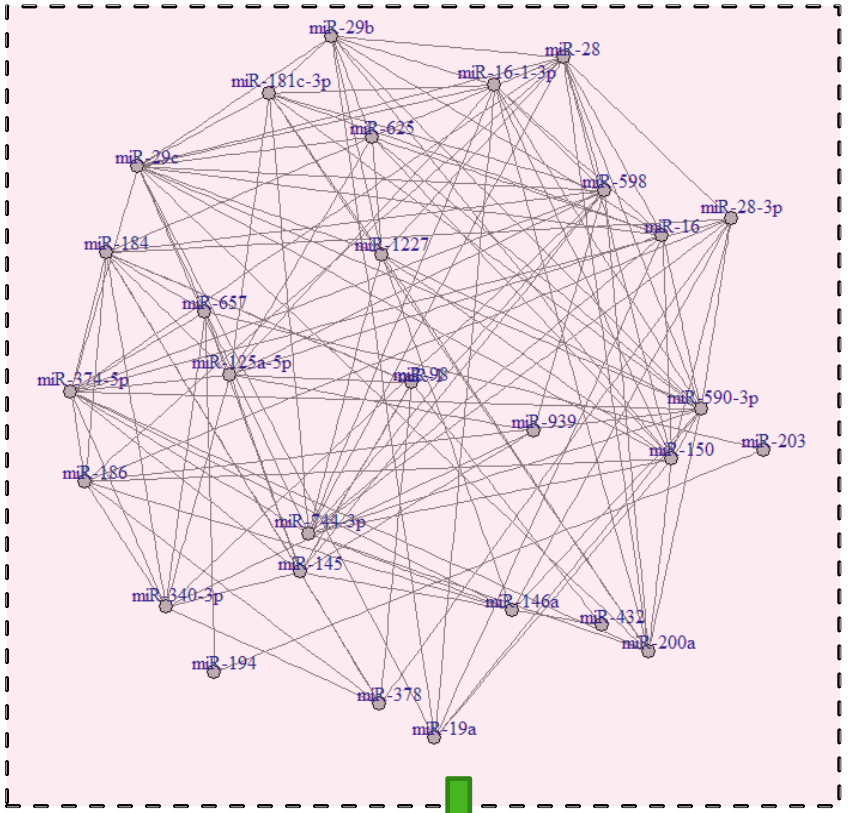
miRNA Expression Changes in the dlPFC of Depressed Suicide Subjects



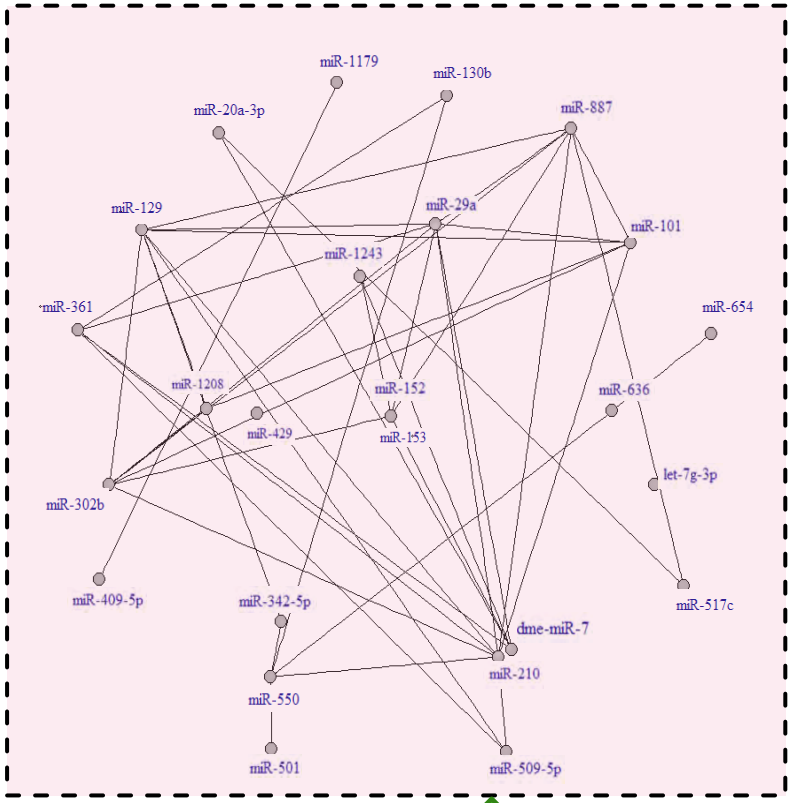
Smalheiser et al., PlosOne, 2012

microRNAs IN THE BRAIN OF SUICIDE SUBJECTS

miRNA Network in Healthy Brain

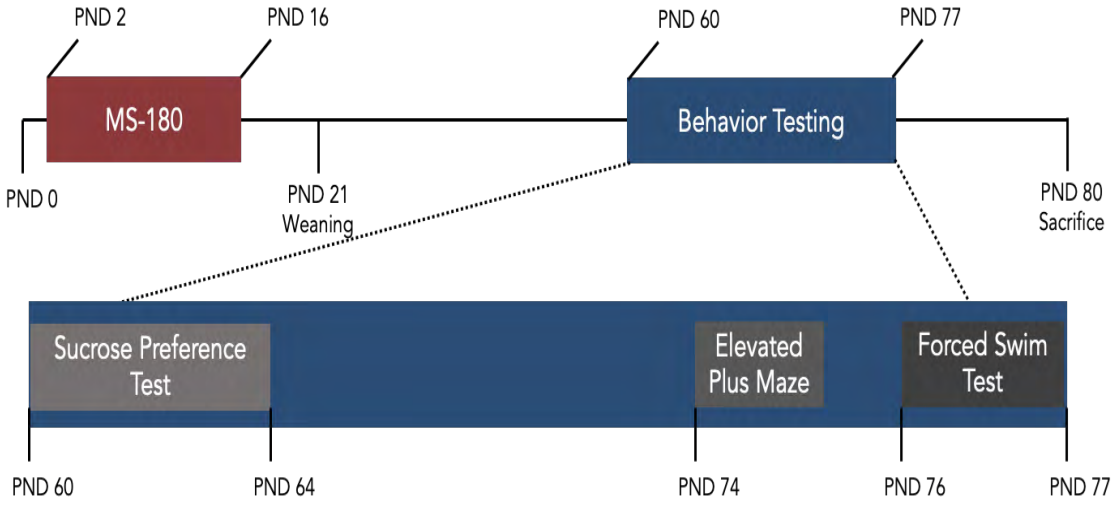


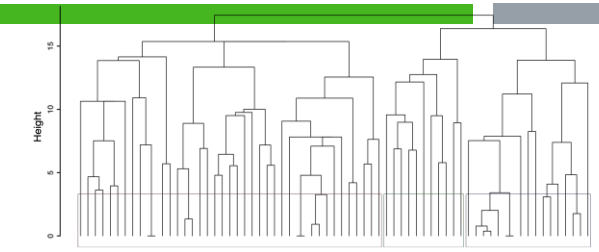
miRNA Network in MDD-suicide Brain

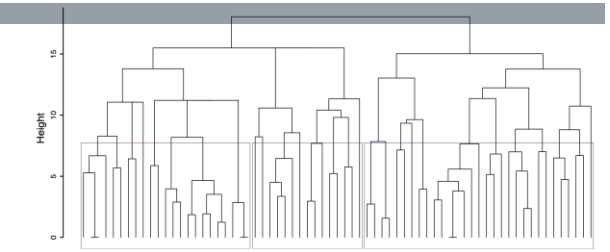


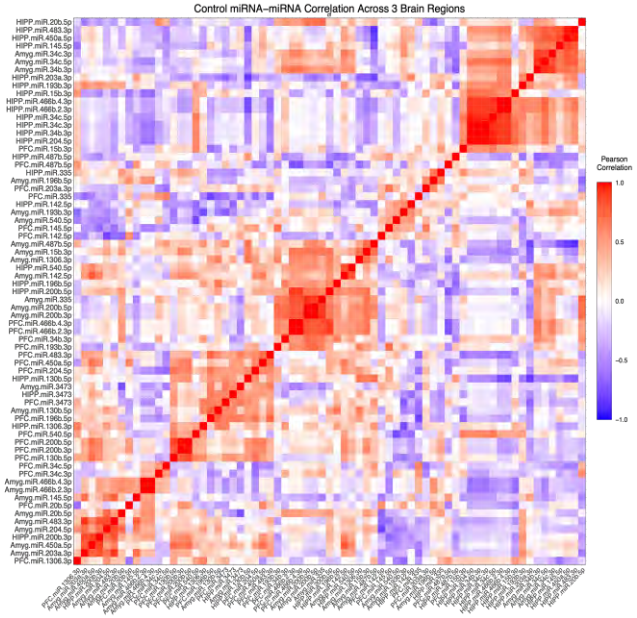
Roy, Dwivedi, Nature Sci. Rep., 2017

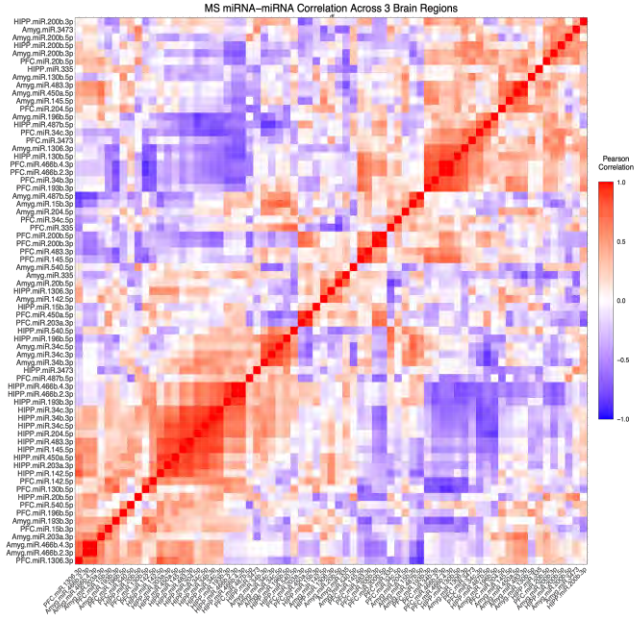
miRNA-miRNA Expression Correlation of Significantly Altered miRNAs Across the PFC, Amygdala, and Hippocampus in Maternally Separated Rats

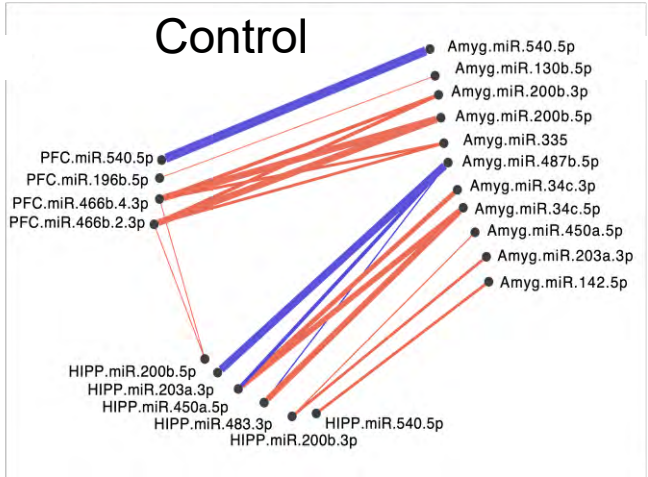


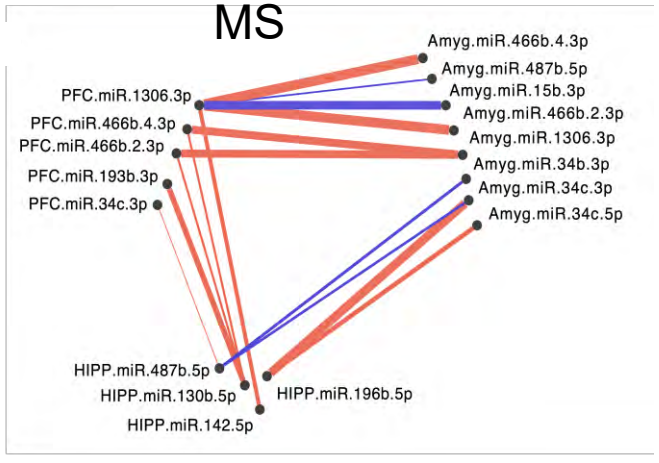






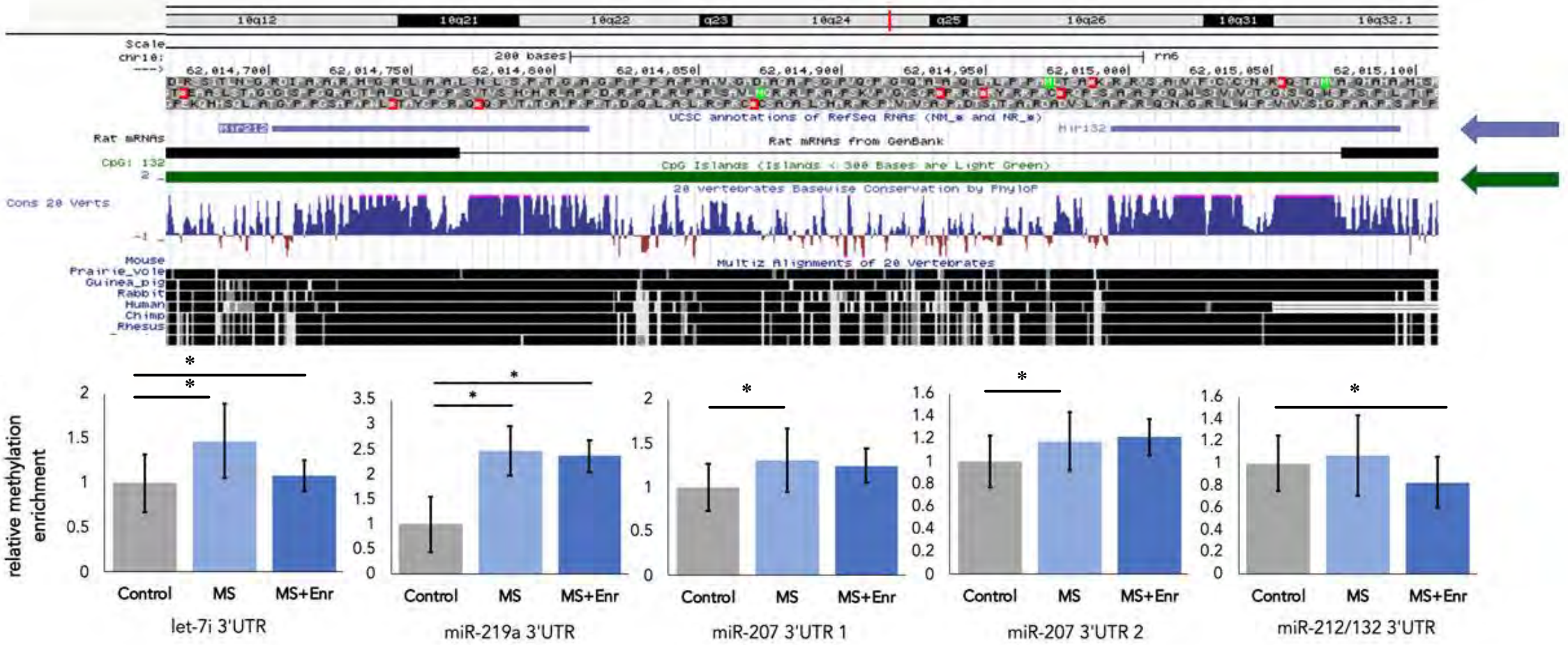






Allen and Dwivedi, 2021 (submitted)

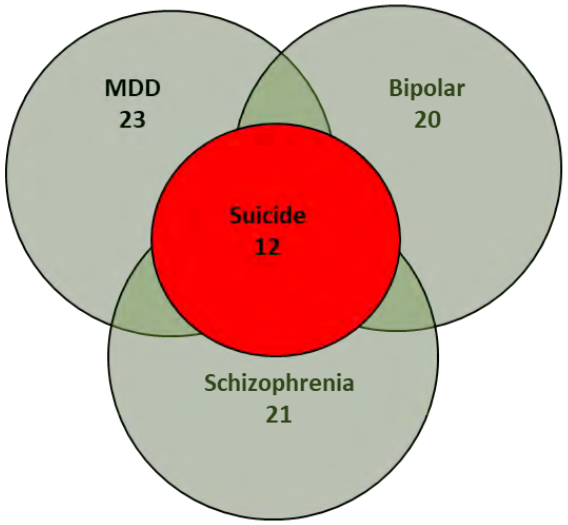
miRNA CpG Methylation in Maternal Separation and Environment Enrichment

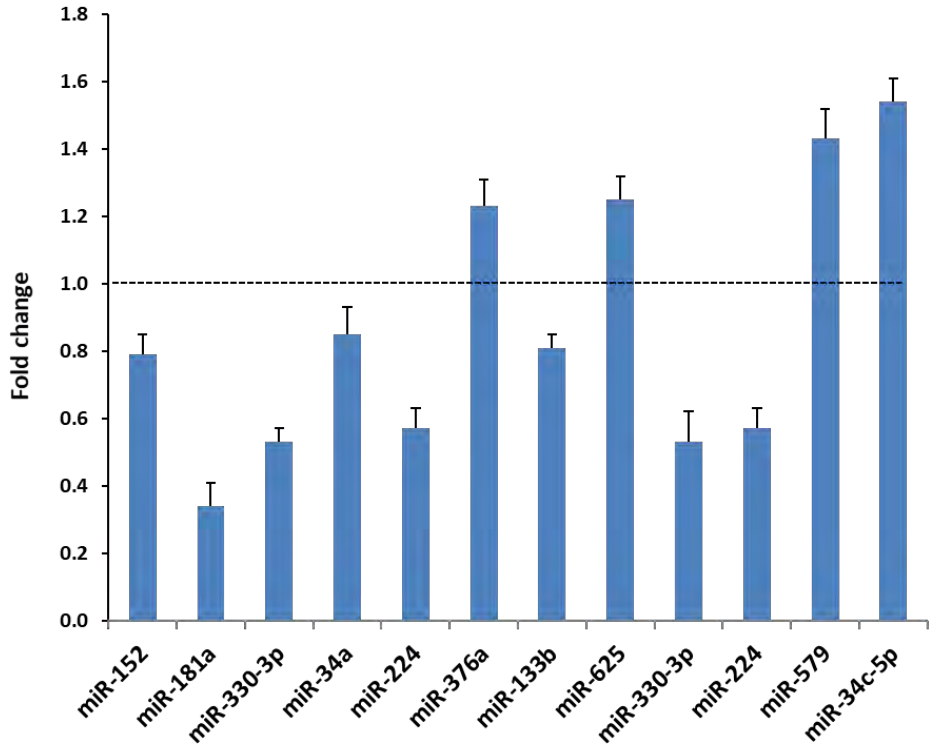


Allen and Dwivedi, 2021 (submitted)

MS= Maternally separated
Enr= Environment enrichment

Suicide-Specific Changes in miRNAs in dlPFC of MDD, Bipolar, and Schizophrenia Subjects





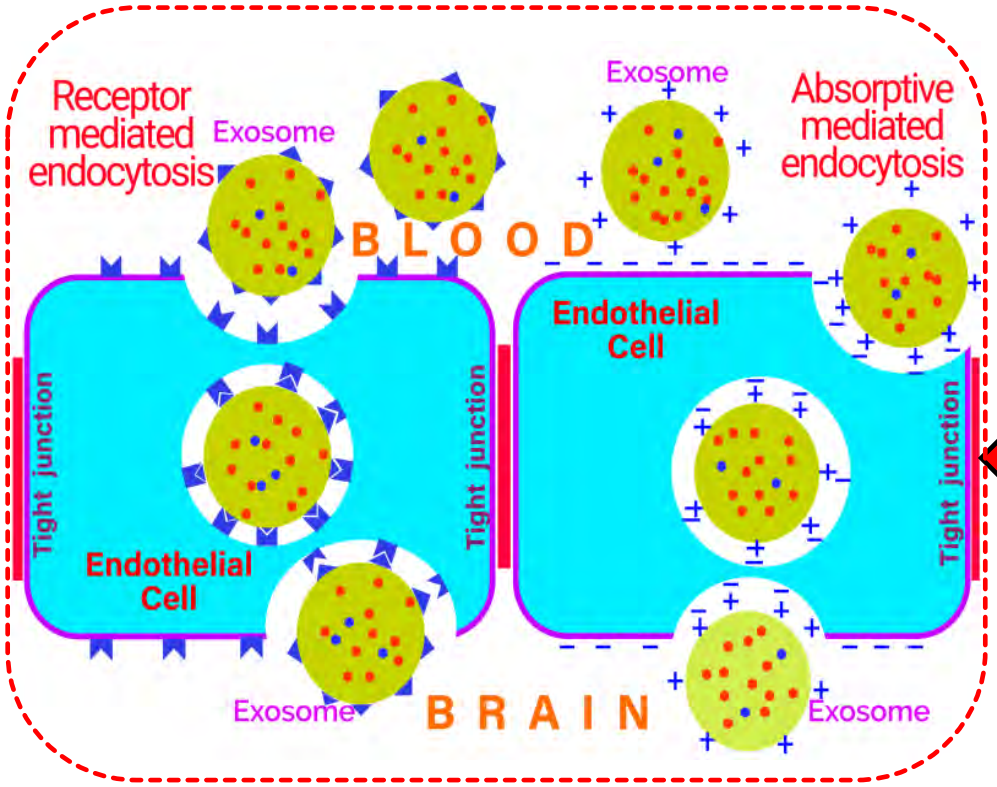
Can miRNAs be Developed as Biomarkers for Disease Pathogenesis and Treatment Response?

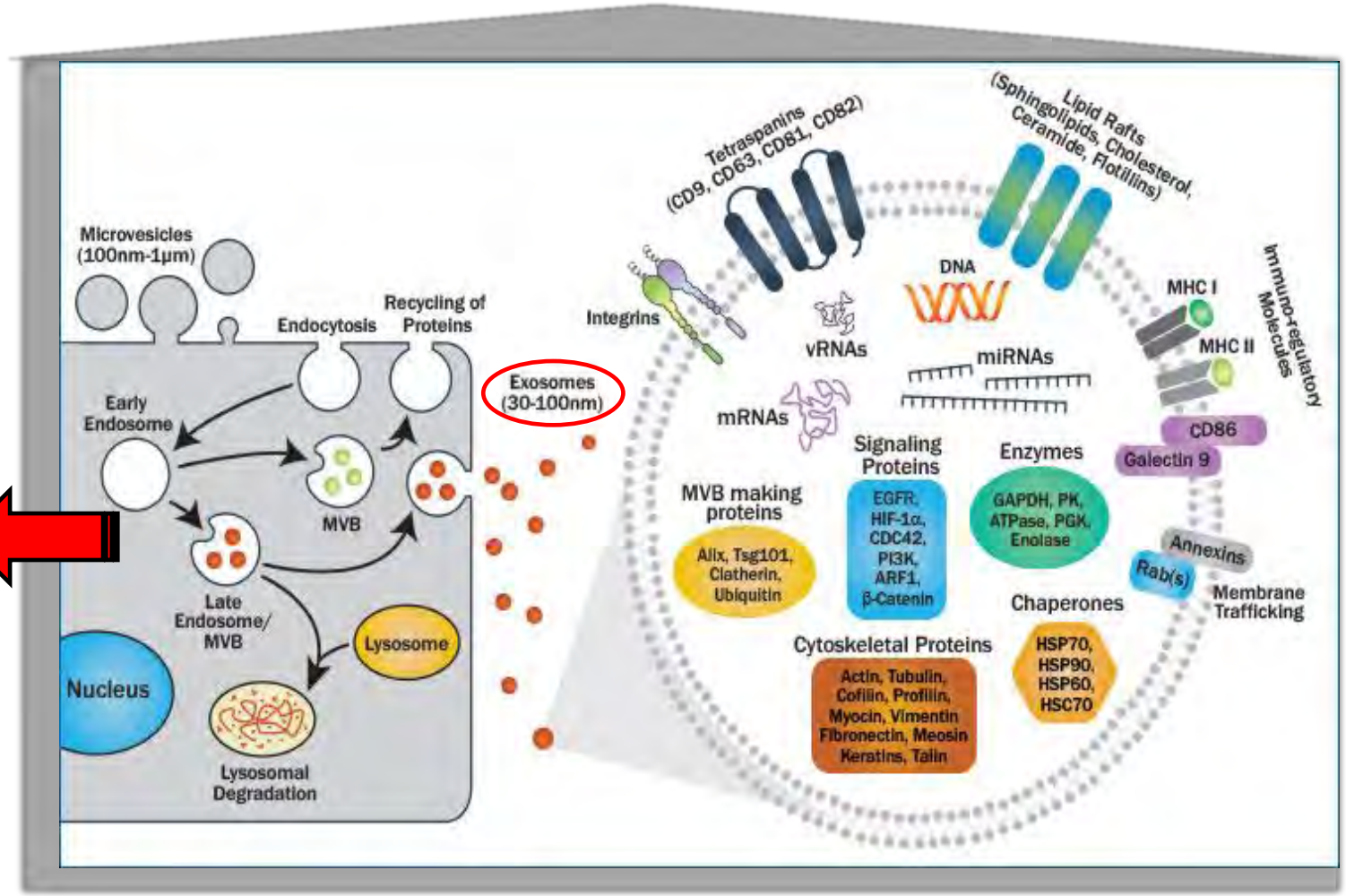
miRNAs are Present in Biological Fluids

- Plasma
- Serum
- Saliva
- CSF
- Urine

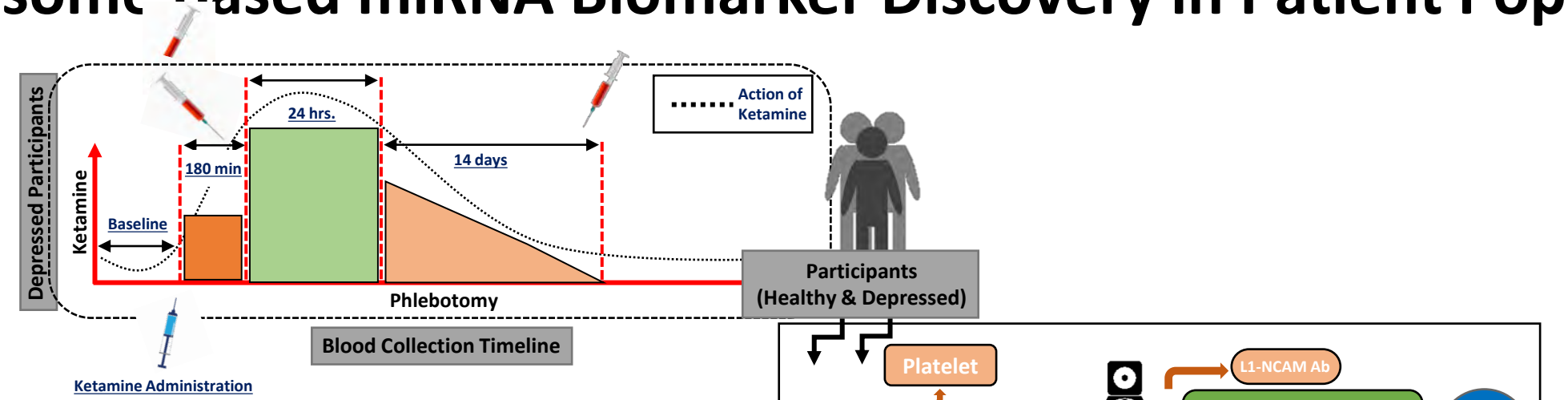
Exosomes: Cargo for Molecular Transportation

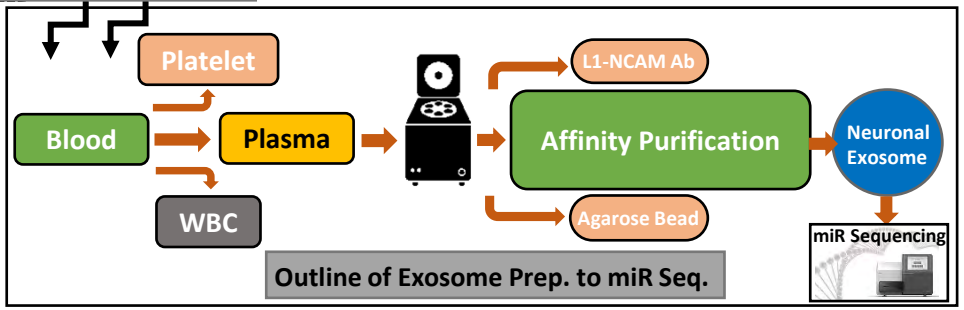
Exosomes: From Brain to Blood

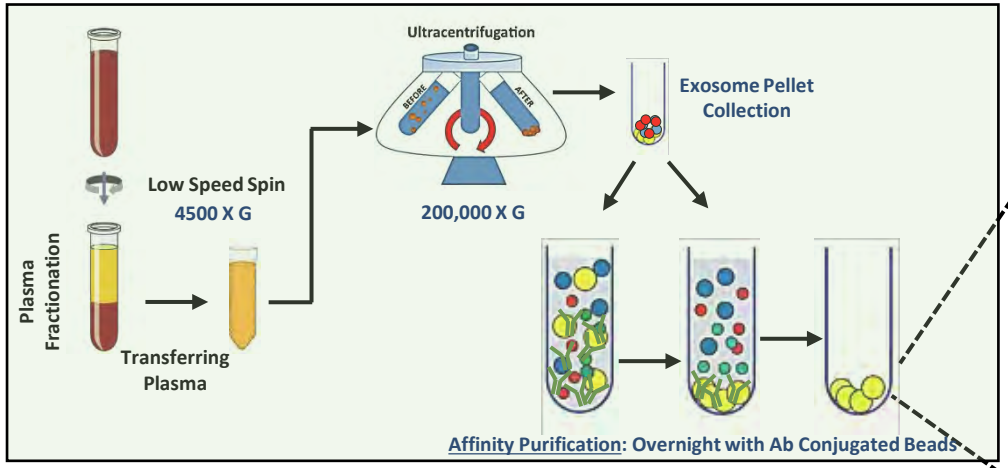


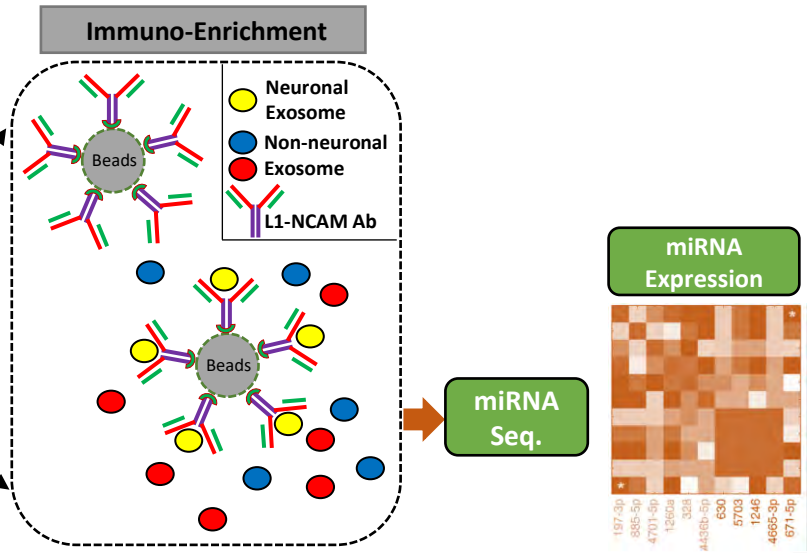


Exosome Based miRNA Biomarker Discovery in Patient Population



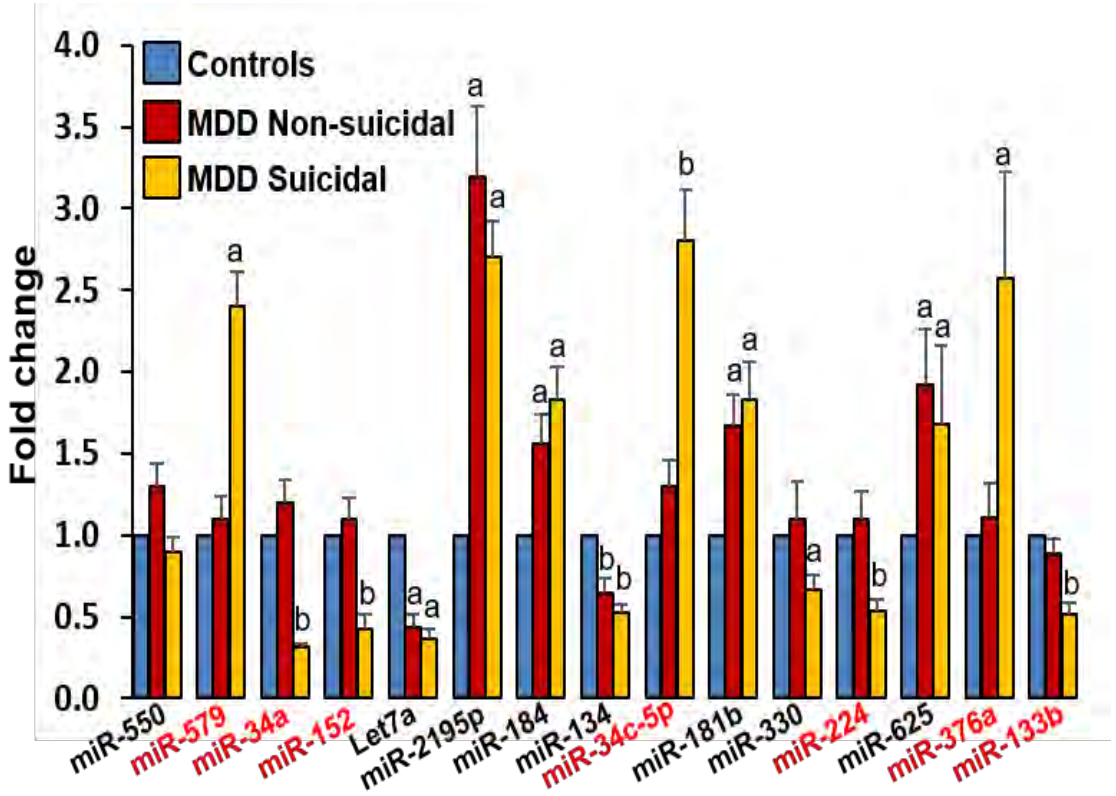






Ratio of Brain-Enriched miRNAs in Neural-Derived vs. Total Plasma Exosomes.

hsa-miRNAs	Ratio (neural/ total)	hsa-miRNAs	Ratio (neural/ total)
miR-9	18.7	miR-184	13.5
Let-7a	14.2	miR-195	12.1
Let-7b	12.2	miR-20a	11.4
miR-124a	18.5	miR-214	4.4
miR-126	4.2	miR-219-5p	7.8
miR-128a	16.3	miR-224	3.6
miR-128b	15.2	miR-27b	5.8
miR-132	10.3	miR301a	9.1
miR-133b	4.2	miR-30a-5p	8.9
miR-134	11.6	miR-330-3p	4.9
miR-142-3p	6.9	miR-346	9.3
miR142-5p	8.1	miR-34a	8.3
miR-146a	5.8	miR-34c-5p	4.2
miR146b	4.2	miR-376a	7.1
miR-148b	9.5	miR-376a	7.3
miR-151-3p	7.2	miR-489	4.7
miR-152	4.5	miR-550	3.2
miR-181a	8.3	miR-579	6.1
miR-181b	10.1	miR-625	8.9
		miR-96	12.1



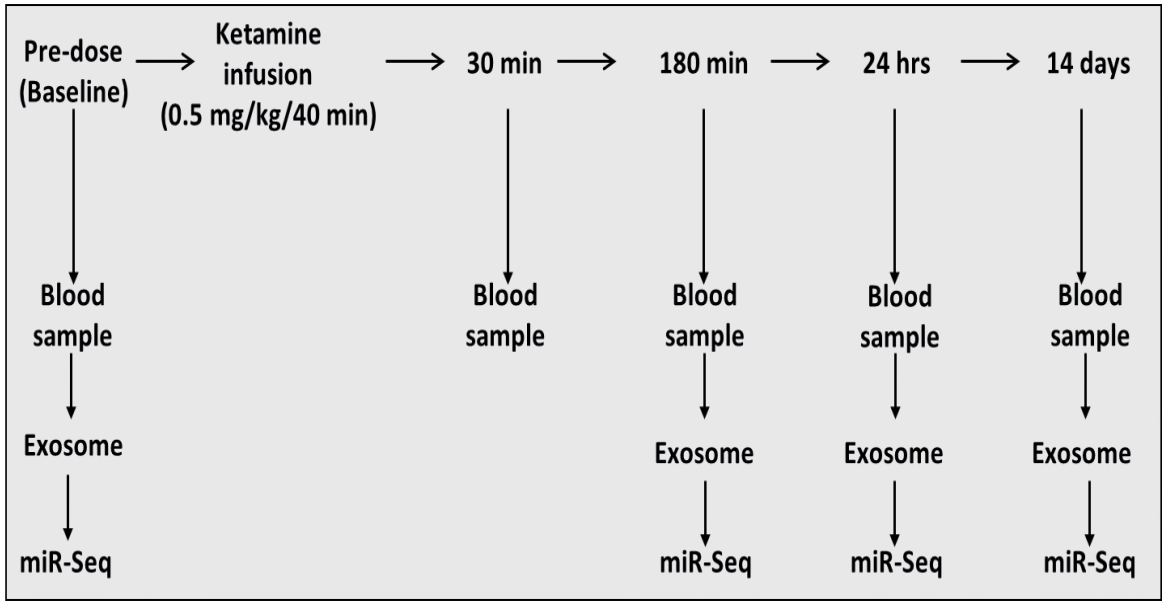
MDD- and suicide-specific miRNA changes in neural-derived plasma exosomes. miRNAs in red letters denote suicide-specific changes. N=25 per group. Data were analyzed by One-way ANOVA followed by Bonferroni corrections. [a]p<0.001; [b]p<0.01.

Neural-Derived Exosomal miRNAs in Suicidality and Treatment Response

Demography

		Control	MDD (-SA)	MDD (+SA)
N		22	30	37
Sex				
	Males	10 (45%)	13 (43.3%)	15 (40.5%)
	Females	12 (54%)	17 (56.7%)	22 (59.5%)
Age (yrs)		39.54	48.27	38.32
Race	Caucasian	14 (63.6%)	25 (83.3%)	29 (78.4%)
	African American	5 (22.7%)	5 (16.7%)	6 (16.2%)
	Asian	2 (9.1%)	0 (0%)	0 (0%)
	Hispanic	1 (4.5%)	0 (0%)	2 (5.4%)

Study Design



Schedule of Assessments

Assessment	Screen	Post ketamine						
		0	30 min	1 hr	2 hr	3 hr	24 hr	14 Days
Informed consent	X							
MINI	X							
Labs (chem.; CBC, TSH, UDS, preg)	X							
ECG	X							
ATRQ-M	X							
HRSD	X							
C-SSRS-R/L	X							
CTQ	X							
PSS	X							
MADRS		X	X	X	X	X	X	X
BDI-II	X	X		X		X	X	X
BAI	X	X		X		X	X	X
BSSI	X	X	X	X	X	X	X	X
HS		X				X	X	X
BDHI	X							
BIS-11	X							
BGHA	X							
SIS	X							
NEO-PI	X							
PAI-BOR	X							
PANSS	X	X	X			X	X	X
DSS	X	X	X			X	X	X
YMRS	X					X	X	X
Vital signs		X	X	X	X	X	X	X
SAFTEE	X			X		X	X	X
Blood draws	X	X	X	X	X	X	X	X

Inclusion Criteria

All Participants:

- Age 18-65 yrs
- Physically healthy and capable of undergoing ketamine infusion
- Willing and able to provide informed consent

MDD participants:

- Diagnosis of MDE as determined by the MINI International Neuropsychiatric Interview
- HAM-D 21 score ≥ 16

MDD with suicidal ideation but without attempt

- Past 7 days, C-SSRS ≥3
- No recent suicide attempts

MDD Participants with Suicide Attempt:

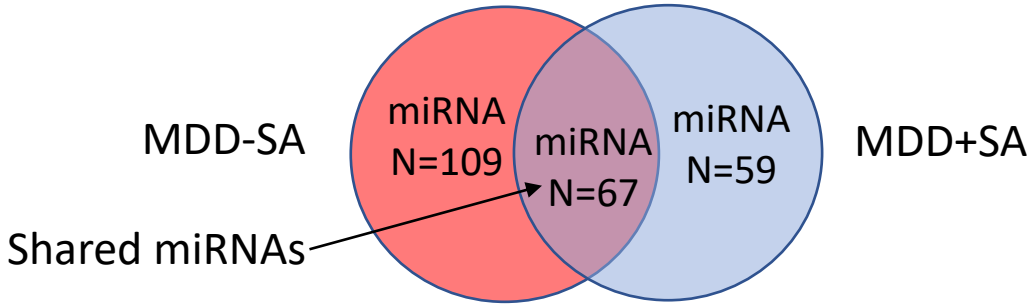
- Suicide attempt occurred within past 2 weeks

Exclusion Criteria

- Pregnancy or lactation Post-partum state (2 months) Homicide risk
- Lifetime history of psychotic disorder
- Any history of dissociation or dissociative disorder
- Bipolar disorder
- Pervasive developmental disorder
- Cognitive disorder
- Cluster A personality disorder
- Anorexia nervosa
- Any medication known to affect the glutamate-NMDA receptor system

  (Lamotrigine, acamprosate, memantine, riluzole, or lithium)
- Alcohol/drug dependence last month
- Any hallucinogen last month
- Ketamine hypersensitivity
- Recent MI/unstable angina
- Cancer in the past 6 months/chemotherapy
- Immunosuppressive or corticosteroid last month
- Head injury/LOC last 6 months.

miRNAs Specific to MDD with and without Suicidal Ideation (SI)/Behavior (SB) OR Shared Between the Two Groups



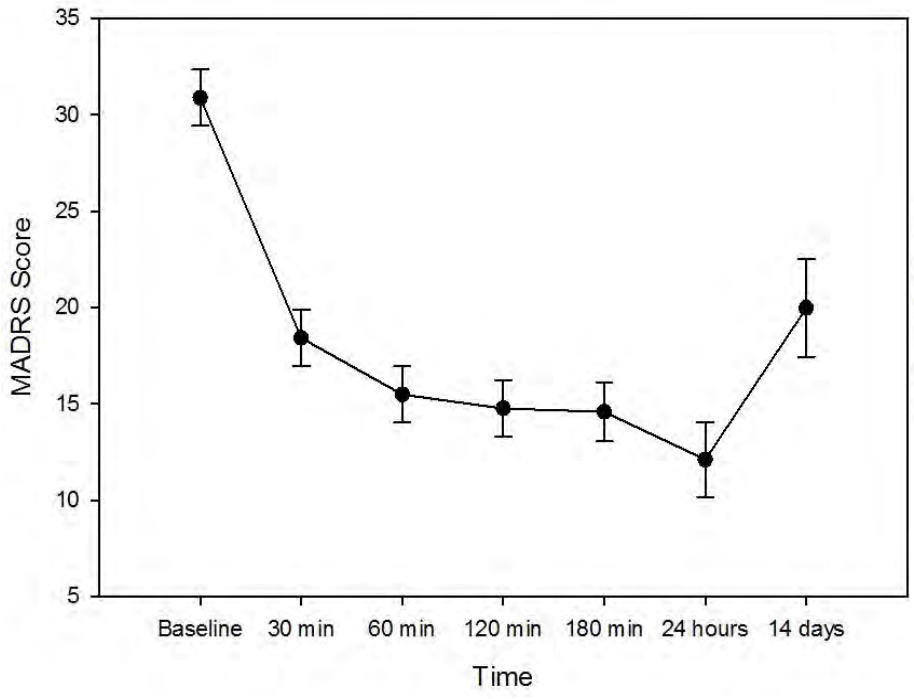
MDD-SA (N=30)
MDD+SA (N=37)

Select significantly altered miRNAs Specific to MDD and Suicide Attempt (fold change >2)

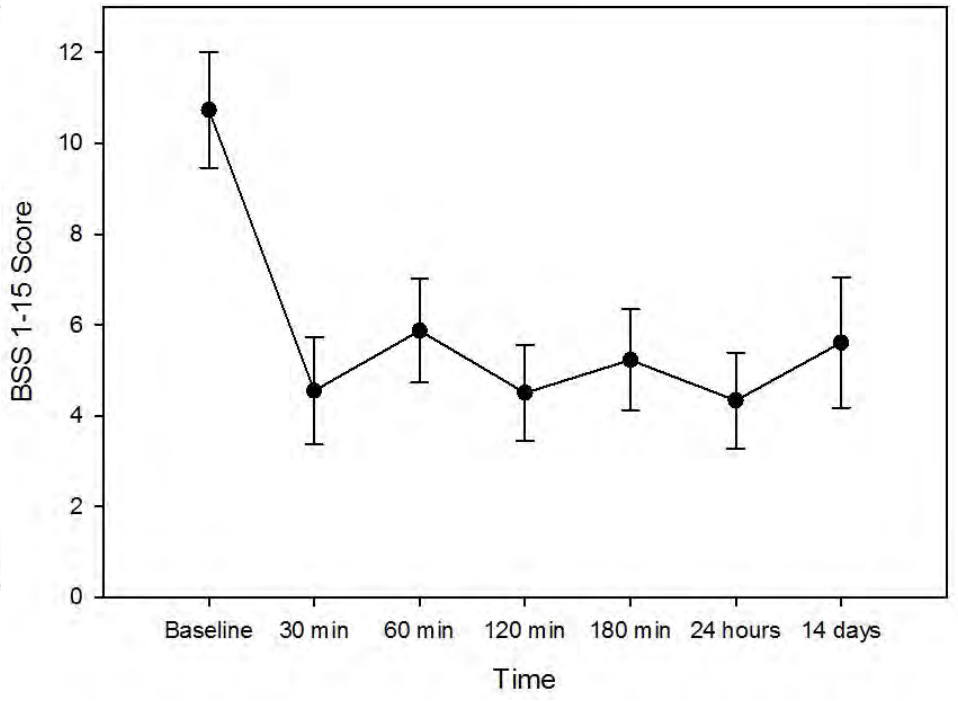
Specific to MDD		Shared between MDD and SA		Specific to SA	
miRNAs	Regulation	miRNAs	Regulation	miRNAs	Regulation
miR-550	Down	Let7a-5p	Down	miR-34c-5p	Up
miR-199a-3p	Up	miR-184	Up	miR-639-3p	Up
miR-92b-3p	Down	miR-134-5p	Down	miR-16-5p	Up
let-7g-5p	Up	miR-625	Up	miR-581	Up
miR-151a-3p	Up	miR-181b	Up	miR-486-5p	Up
miR-1908	Up	miR-584-5p	Up	miR-579	Up
miR-27a-3p	Up	miR-20a-5p	Up	miR-146a	Down
miR-363-3p	Up	miR-17-5p	Up	miR-132-5p	Down
miR-106b-3p	Down	miR-93-5p	Up	miR-224-5p	Down
miR-24-3p	Up	miR-183-5p	Up	miR-330-3p	Down
miR-370	Up	miR-409-3p	Up	miR-26a-5p	Down
miR-22-3p	Up	miR-219-5p	Up	miR-451a	Up
miR-99b-5p	Up	miR-10a-5p	Up	Let-7d-3p	Up
miR-155-5p	Up	miR-1908	Up	miR-103a-3p	Up
miR-223-5p	Up	miR-320c	Up	miR-148b-3p	Up
miR-92a-3p	Up	miR-409-3p	Down	miR-760-5p	Down
miR-150-5p	Up	miR-215	Up	miR-127-3p	Down
miR-1307-3p	Up	miR-101-3p	Up	miR-30c-5p	Down
miR-140-3p	Up	miR-222-3p	Up	miR-432	Down
miR-30d-5p	Up	miR-100-5p	Up	miR-376a	Up

Clinical Assessment of MDD Suicidal Patients after Ketamine Administration (0.5 mg/kg/40 min)

MADRS (Mean ±SEM)

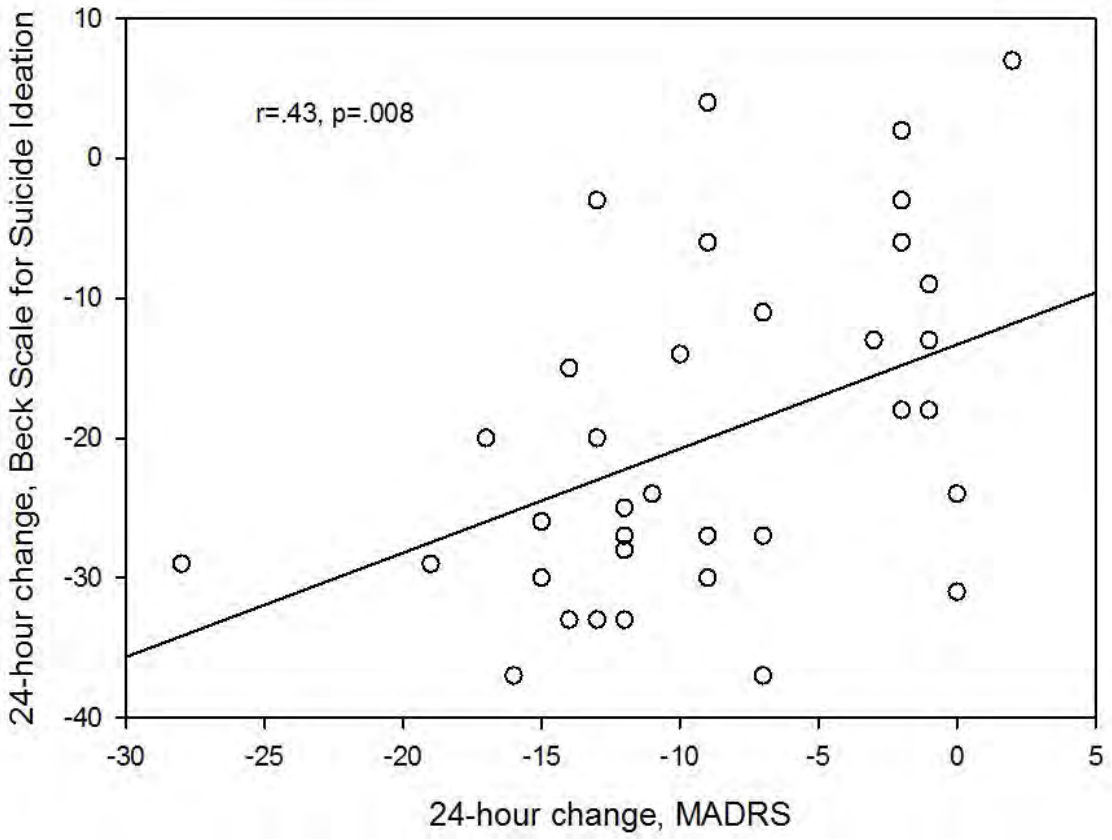


BSS (Mean ±SEM)

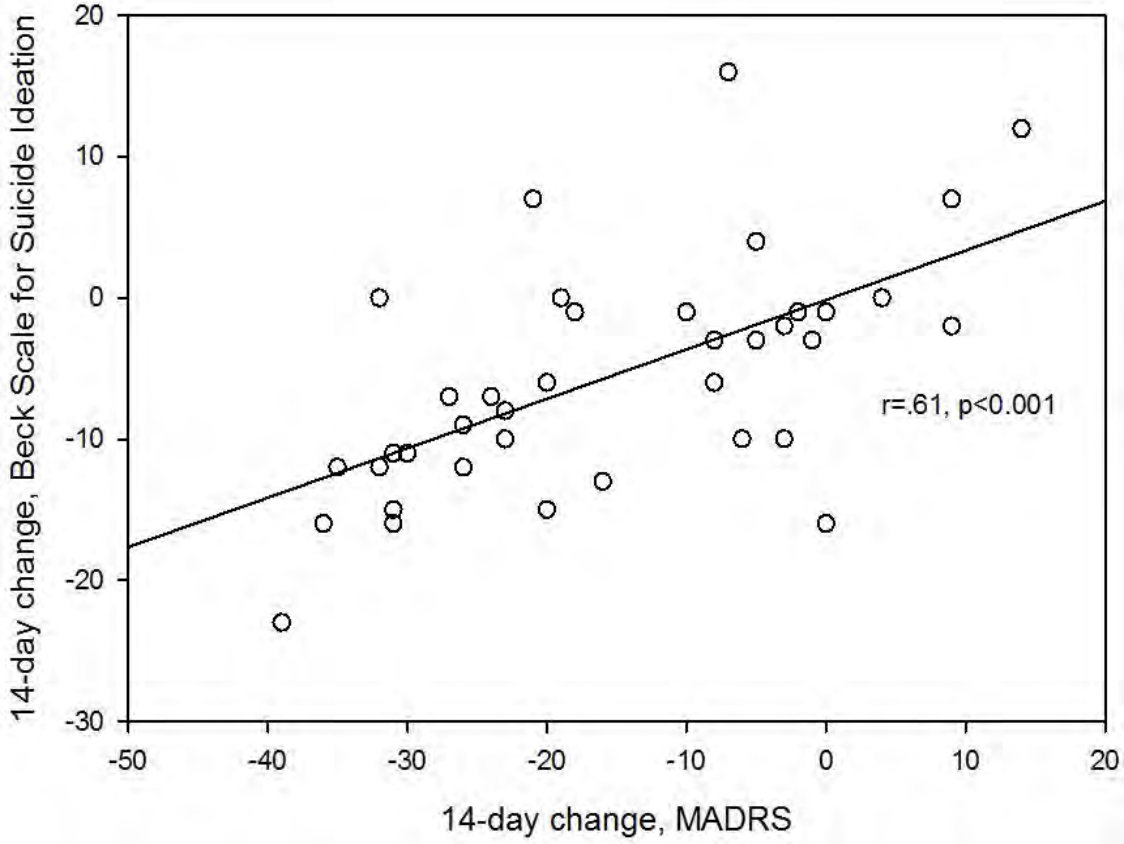


Correlation Between Changes in MADRS and BSS at 24 hours and 14 days Post Ketamine

24 hours

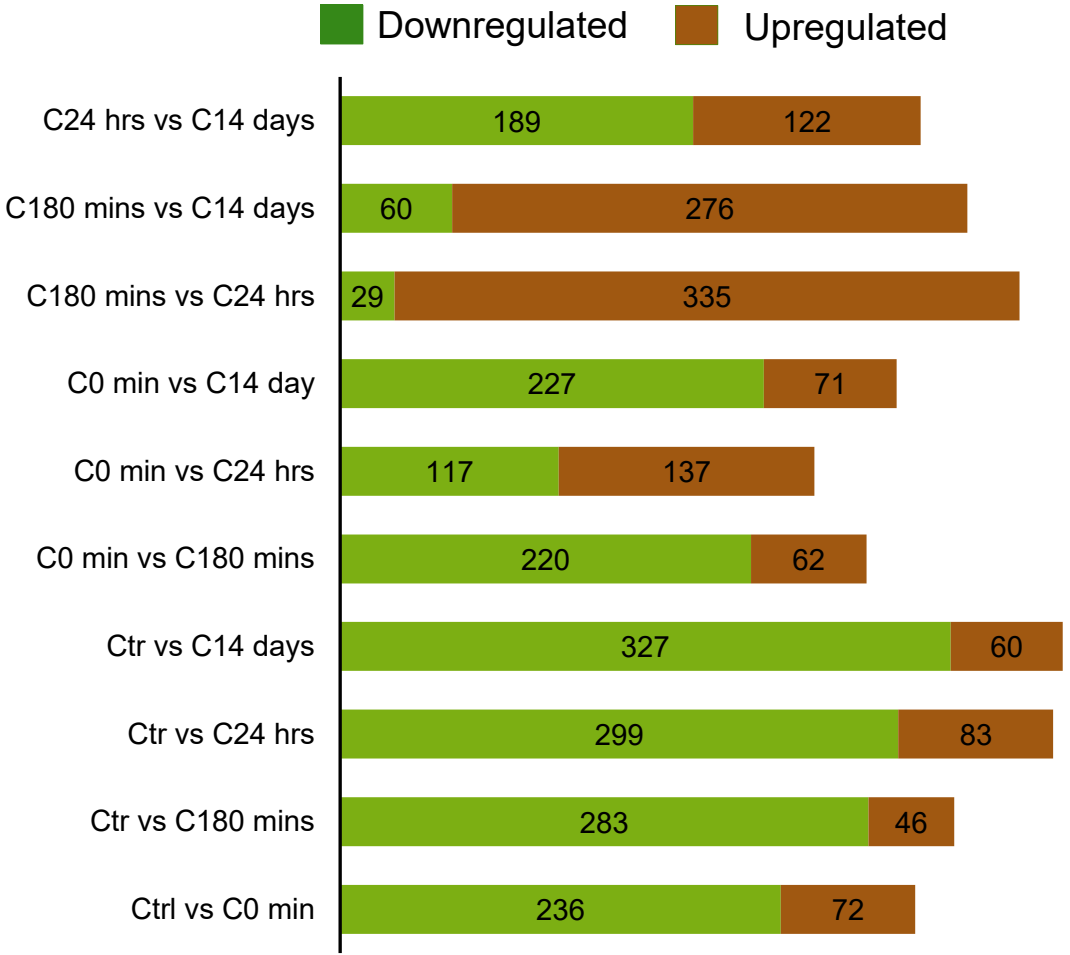


14 days

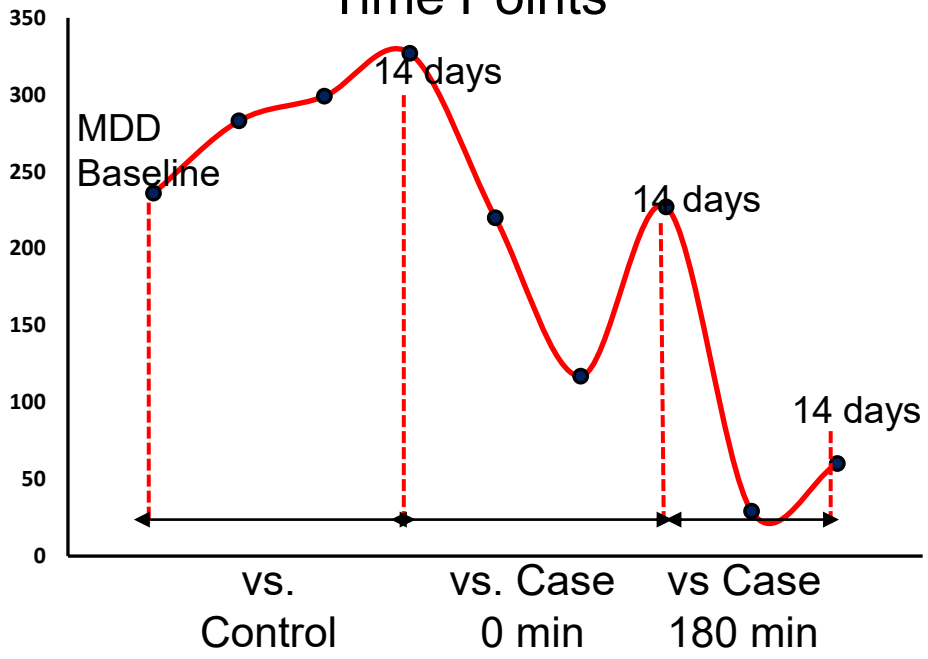


Ketamine-Induced Changes in Exosomal miRNAs Over 14-Day Period in SA Patients

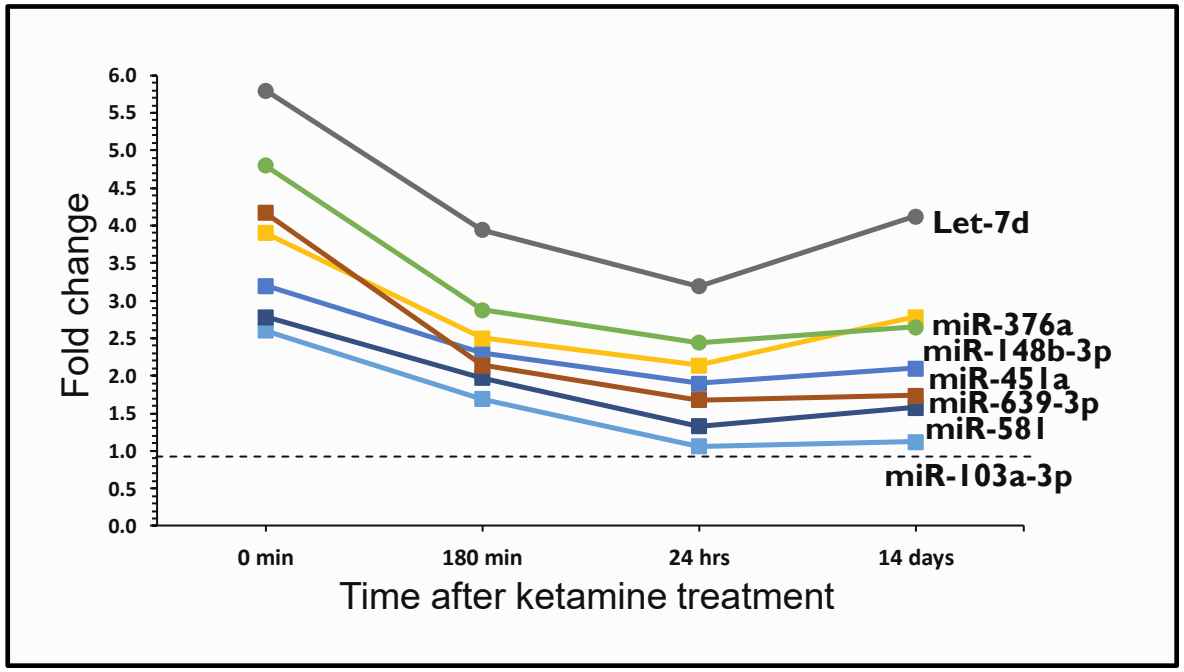
Differential Distribution of miRNAs Over 2 Week Period



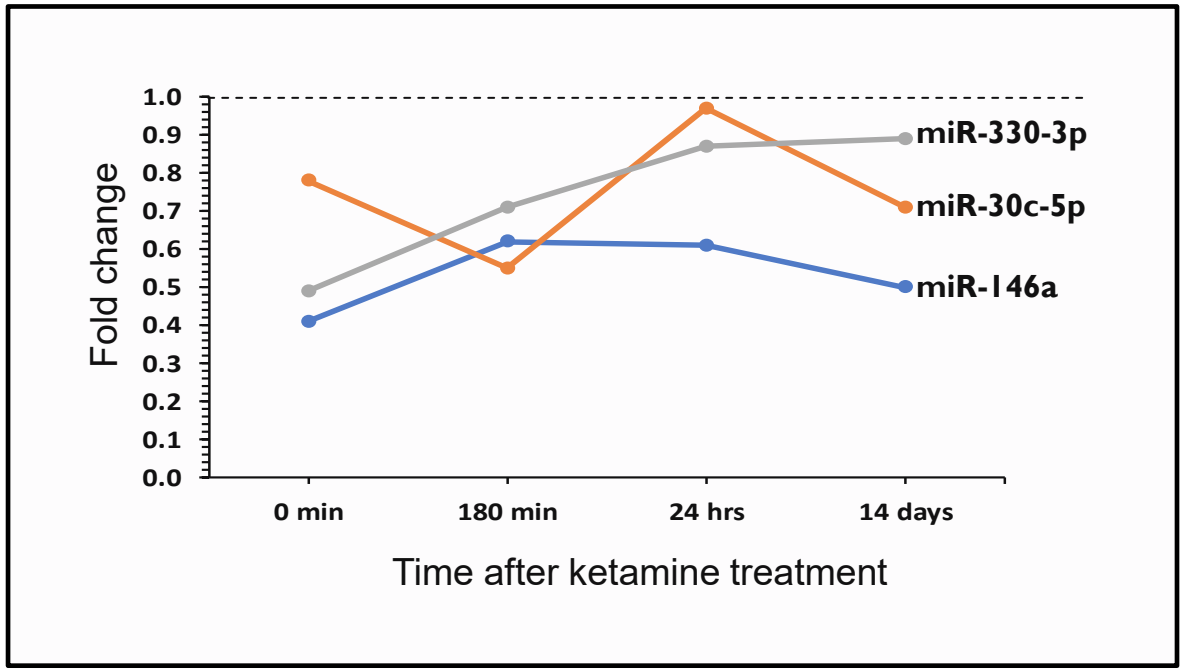
miRNA Change At Various Time Points



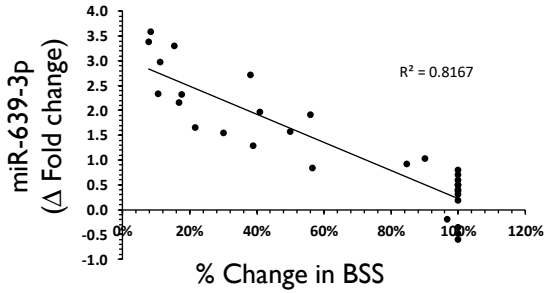
Ketamine-induced reversal of suicide-specific upregulated miRNAs

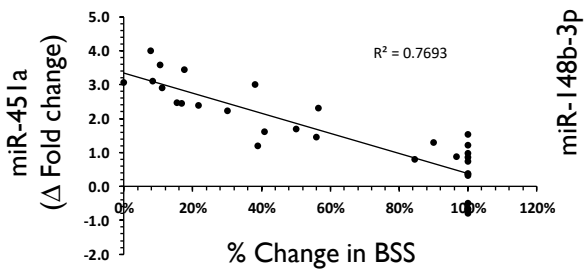


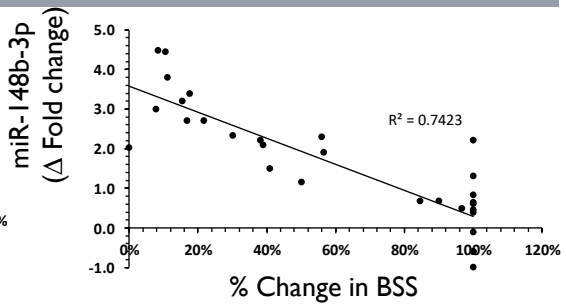
Ketamine-induced reversal of suicide-specific downregulated miRNAs

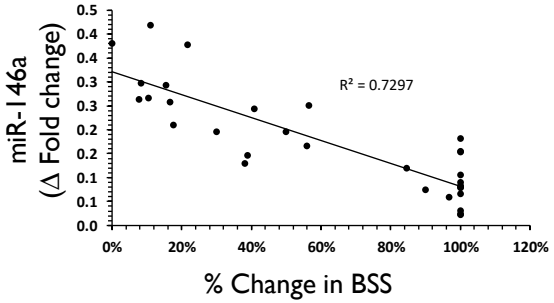


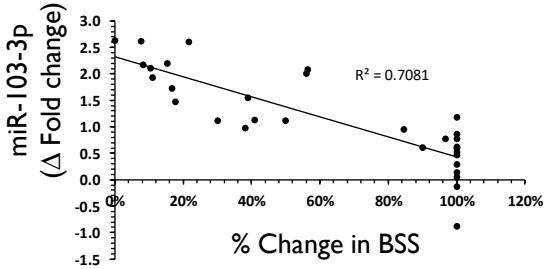
Correlation Between miRNA Response to Ketamine (24 h) and % Change in BSS Scores in MDD+SA Patients

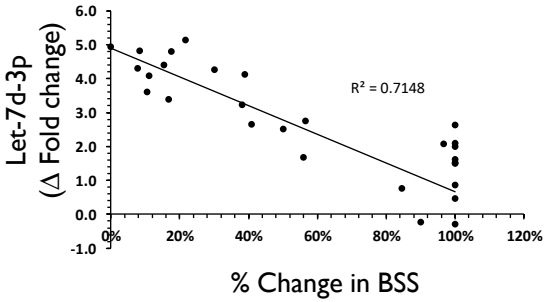


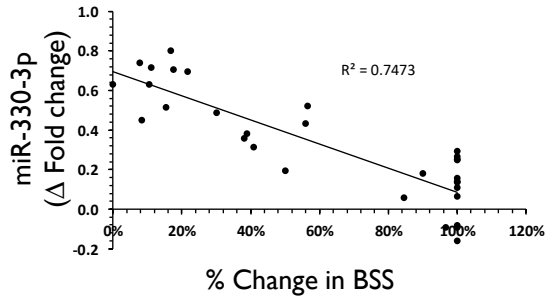


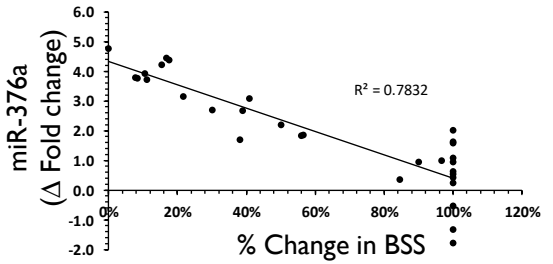


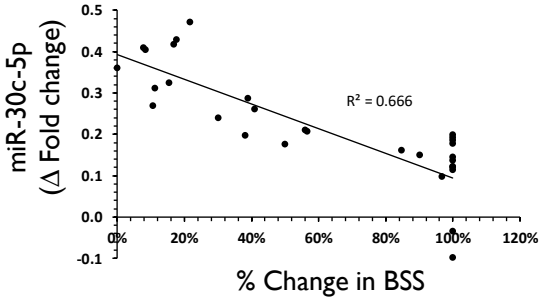


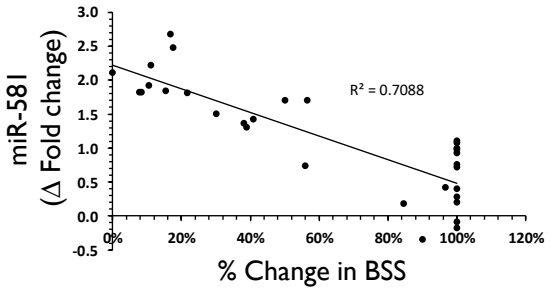




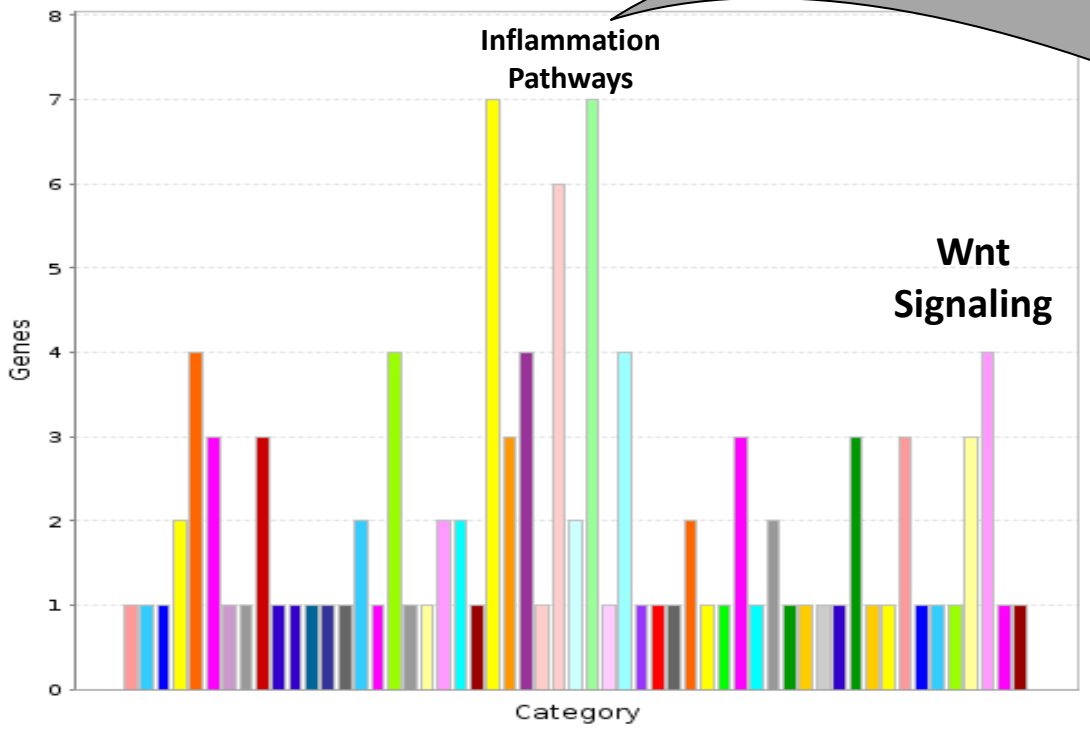




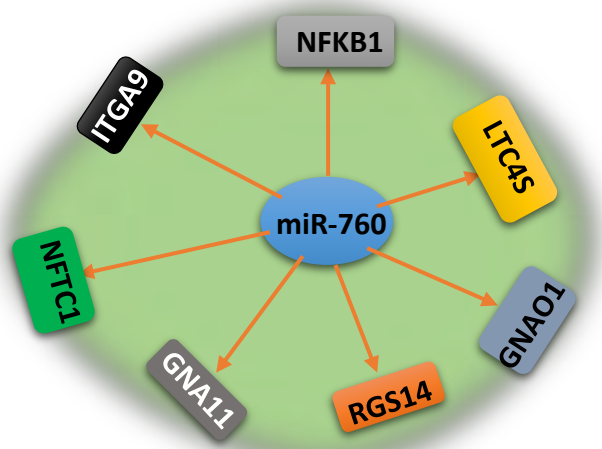




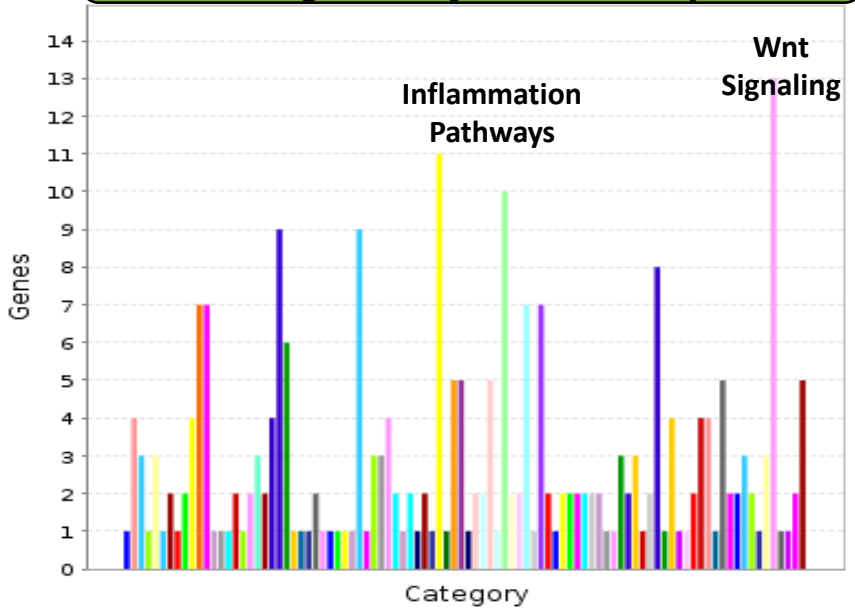
Selective enrichment of Pathways Targeted by miR-760



Inflammation Related Cytokine Pathway



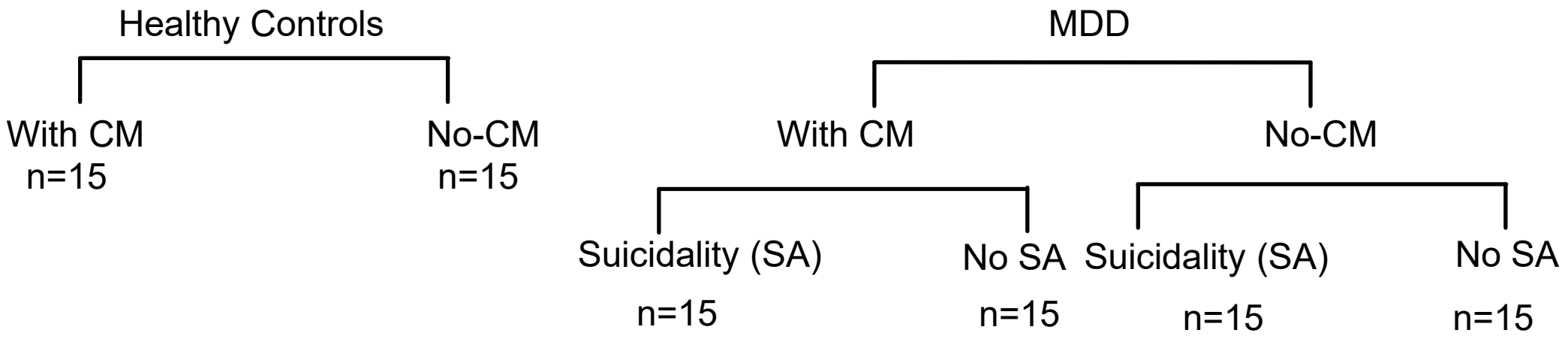
Selective enrichment of Pathways Targeted by miR-432-5p



Gene targets for both the miRNAs enriched for:

- Neuroinflammation
- Wnt signaling

miRNA-Mediated Childhood Maltreatment (CM)-Induced Suicidality in MDD Patients



Inclusion/Exclusion criteria

All participants

- Males and females
- Ages 18-60
- All races/ethnicities
- Physically healthy
- Willing and able to provide informed consent

Non-psychiatric controls

No lifetime history of any major mental illness.

MDD participants

A diagnosis of DSM-V determined by the MINI International Neuropsychiatric Interview

Childhood Maltreatment

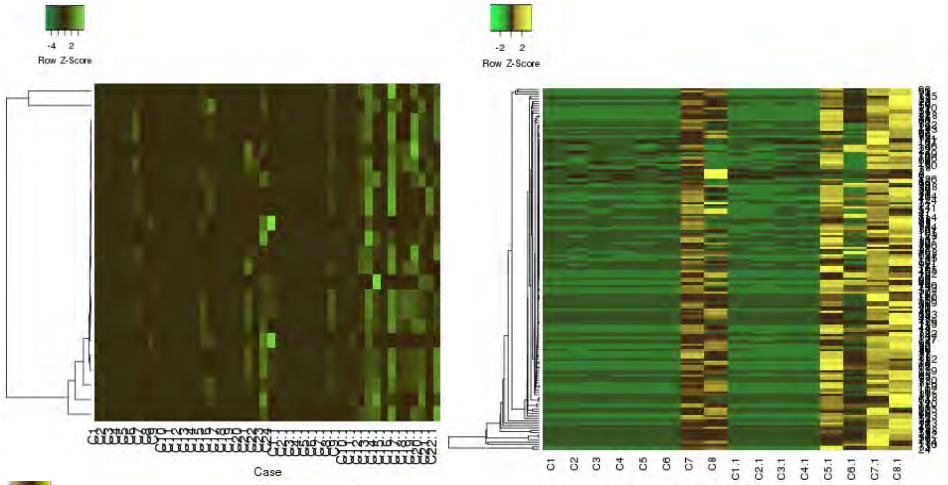
- CM consisted of sexual abuse (SA), emotional neglect (EN), and physical neglect (PN).
- A history of CM as confirmed from CTQ using standard numerical cutoffs (CTQ SA>7, EA>9, PA>9)

Suicide

- Current and past suicidal ideation, plans, intent, and behaviors assessed using the C-SSRS
- The primary assessment tool to determine suicidal severity--Beck Scale for Suicide Ideation (BSS)

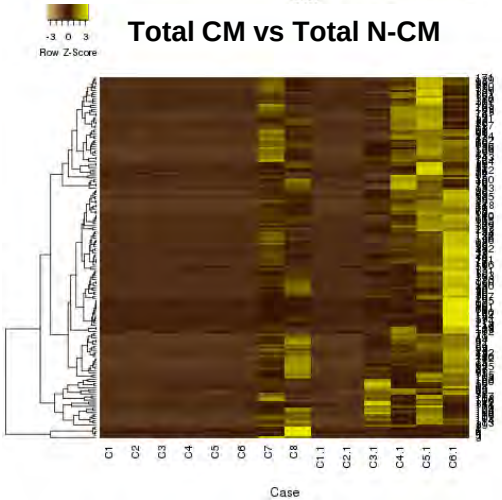
miRNA-Mediated CM-Induced Suicidality in MDD Patients

Differential expression of miRNAs across various groups

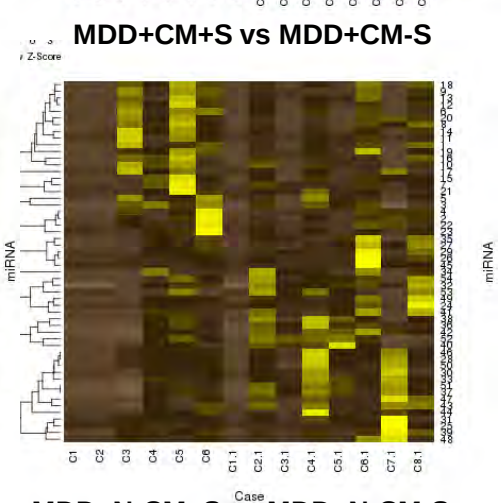


Total CM vs Total N-CM

MDD+CM+S vs MDD+CM-S



MDD+CM+S vs MDD-CM+SI

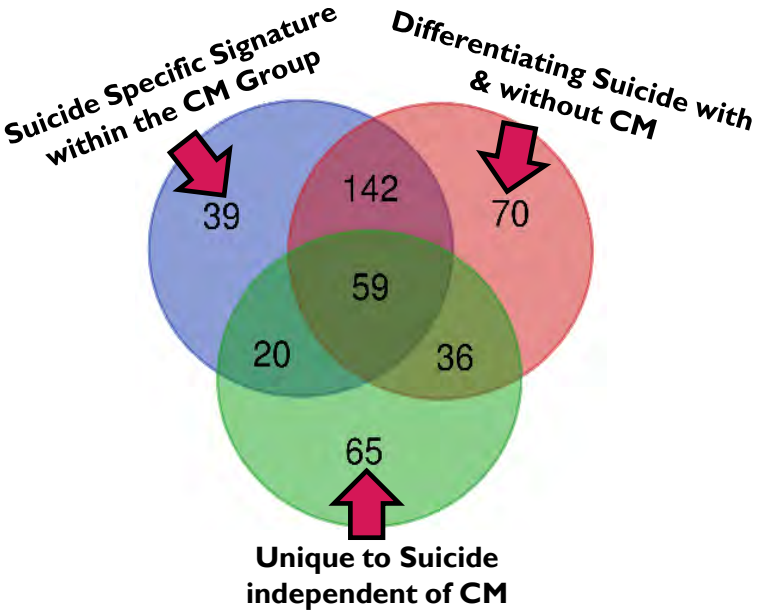


MDD+N-CM+S vs MDD+N-CM-S

Representative miRNAs specific to CM-SA group

miRNAs	Fold Change	Regulation
hsa-miR-34c-5p	0.33	Down
hsa-miR-181a-5p	0.29	Down
hsa-miR-152	0.19	Down
hsa-miR-224-5p	0.45	Down
hsa-miR-639	2.13	Up
hsa-miR-26a-5p	0.27	Down
hsa-miR-146b-5p	0.29	Down
hsa-miR-330-3p	0.37	Down
hsa-miR-190b	1.99	Up
hsa-miR-4707-3p	12.18	Up
hsa-miR-581	8.34	Up
hsa-miR-128	0.28	Down
hsa-miR-4516	7.30	Up
hsa-miR-3151	8.39	Up
hsa-miR-200a-5p	2.51	Up
hsa-miR-1255a	1.50	Up
hsa-miR-3913-5p	5.37	Up
hsa-miR-3151	8.39	Up
hsa-miR-1294	1.78	Up

Venn diagram showing miRNAs across specific groups



CONCLUSIONS

- Prevention starts with recognition of psychiatric illnesses and then recognition of individual patients at higher risk
- Patients at higher risk have a predisposition (vulnerability factors)
- Biological identification and reduction of the predisposition will reduce risk
- Suicidality and treatment response can be identified at biological level