Conceptualizing Novel Early Life Interventions for Anxiety and Depression

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Disclosures

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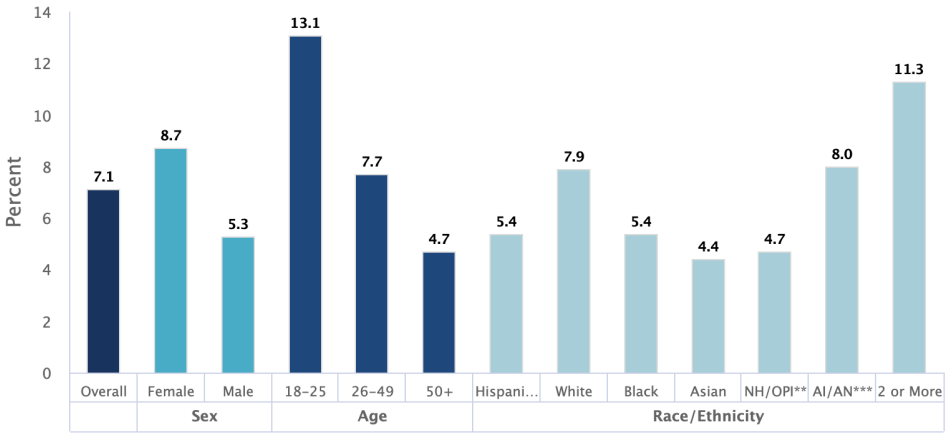
Learning Objective 1

Explore novel early life interventions for anxiety and depression.

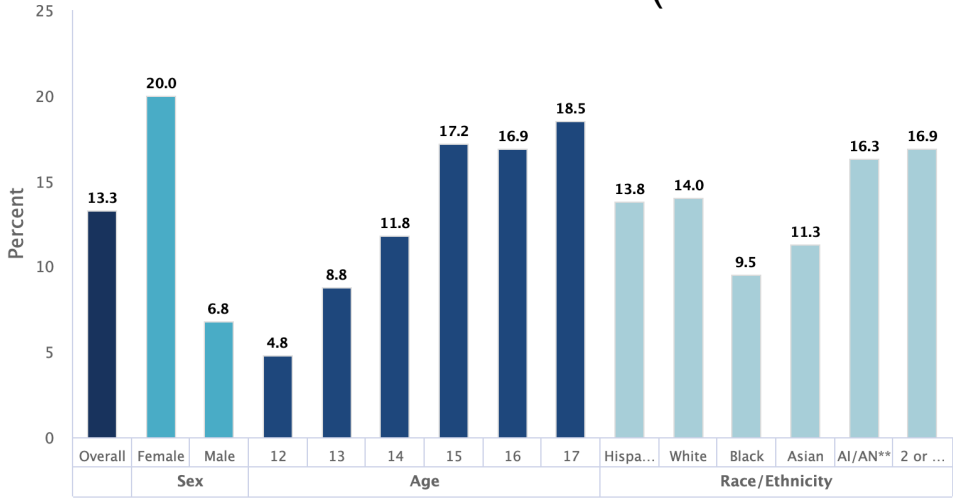
Prevalence of Major Depression in Adults and Adolescents

Past Year Prevalence of Major Depressive Episodes Among U.S. Adults (2017)



*All other groups are non-Hispanic or Latino | **NH/OPI = Native Hawaiian / Other Pacific Islander | ***AI/AN = American Indian / Alaskan Native

Past Year Prevalence of Major Depressive Episodes Among U.S. Adolescents (2017

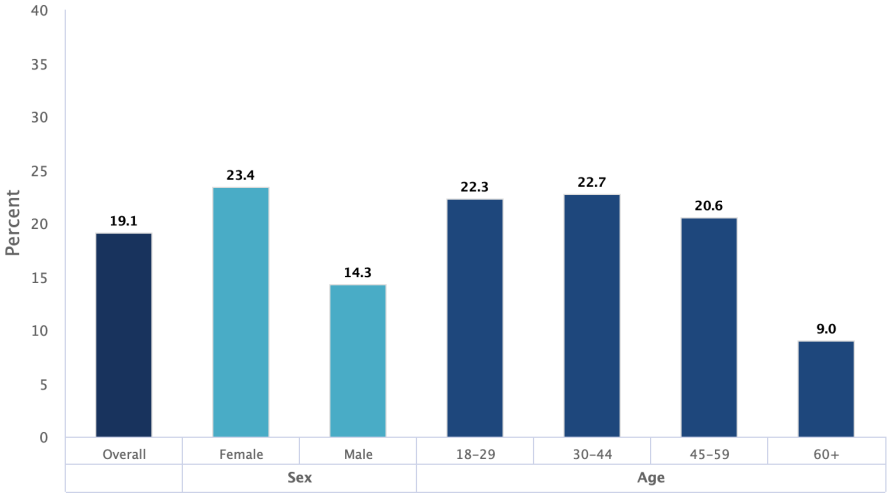


*All other groups are non-Hispanic or Latino / **AI/AN = American Indian/Alaska Native

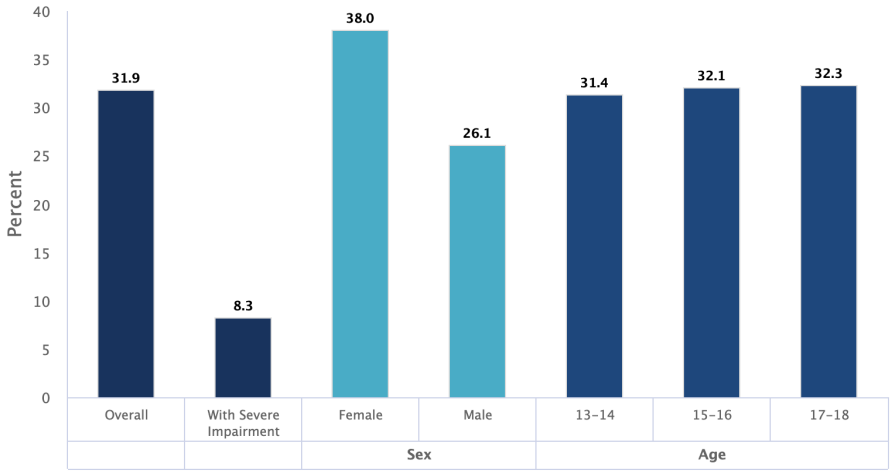
National Institutes of Mental Health. Data courtesy of SAMHSA. Available at https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed February 24, 2020.

Prevalence of Anxiety Disorders in Adults and Adolescents

Past Year Prevalence of Any Anxiety Disorder Among U.S. Adults (2001-2003)[1,2]



Lifetime Prevalence of Any Anxiety Disorder Among Adolescents (2001-2004)[1,3]



1. National Institutes of Mental Health. Data courtesy of SAMHSA. Available at https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml . Accessed February 24, 2020.; 2. Harvard Medical School, 2007. National Comorbidity Survey (NCS). (2017, August 21). Retrieved from https://www.hcp.med.harvard.edu/ncs/index.php. Data Table 2: 12-month prevalence DSM-IV/WMH-CIDI disorders by sex and cohort. 3. Kessler RC, et al. *Arch Gen Psychiatry.* 2005;62(6):617-627.

Lifetime and 12-Month Prevalence of *DSM-III-R* Psychiatric Disorders in the United States

Results From the National Comorbidity Survey

Ronald C. Kessler, PhD; Katherine A. McGonagle, PhD; Shanyang Zhao, PhD; Christopher B. Nelson, MPH; Michael Hughes, PhD; Suzann Eshleman, MA; Hans-Ulrich Wittchen, PhD; Kenneth S. Kendler, MD

- 50% reported 1 disorder
- Most common – depression, alcohol dependence, social phobia, simple phobia
- More than half of all disorders occurred in 14% of the population with a history of 3 or more comorbid disorders

"The prevalence of psychiatric disorders is greater than previously thought to be the case. Furthermore, this morbidity is more highly concentrated than previously recognized in roughly one sixth of the population who have a history of three or more comorbid disorders. This suggests that the causes and consequences of high comorbidity should be the focus of research attention. "

Kessler RC, et al. *Arch Gen Psychiatry*. 1994;51:8-19.

Epidemiology of Major Depressive Disorder

Results From the National Epidemiologic Survey on Alcoholism and Related Conditions

Deborah S. Hasin, PhD; Renee D. Goodwin, PhD; Frederick S. Stinson, PhD; Bridget F. Grant, PhD, PhD

Table 4. Twelve-Month and Lifetime Prevalence of *DSM-IV* Psychiatric Disorders Among Respondents With 12-Month and Lifetime Major Depressive Disorder

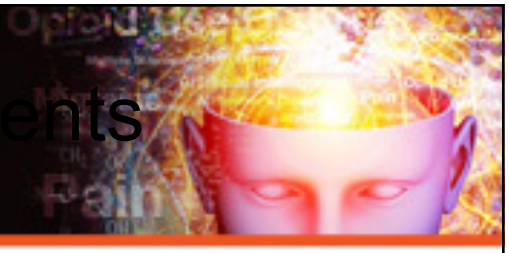
Comorbid Disorder	Major Depressive Disorder, % (SE)	
	12-Month	Lifetime
Any alcohol use disorder	14.1 (0.86)	40.3 (0.89)
Alcohol abuse	5.9 (0.56)	19.4 (0.70)
Alcohol dependence	8.2 (0.78)	21.0 (0.78)
Any drug use disorder	4.6 (0.50)	17.2 (0.64)
Any drug abuse	2.2 (0.34)	11.8 (0.56)
Any drug dependence	2.4 (0.38)	5.5 (0.38)
Nicotine dependence	26.0 (1.11)	30.0 (0.81)
Any anxiety disorder	36.1 (1.27)	41.4 (0.92)
Panic disorder with agoraphobia	2.5 (0.41)	3.1 (0.30)
Panic disorder without agoraphobia	7.9 (0.75)	10.8 (0.55)
Social phobia	10.4 (0.84)	12.8 (0.58)
Specific phobia	17.5 (1.05)	20.4 (0.74)
Generalized anxiety	13.5 (0.87)	15.0 (0.62)
Any personality disorder	37.9 (1.30)	30.8 (0.76)
Avoidant	9.6 (0.77)	6.5 (0.39)
Dependent	2.2 (0.36)	1.2 (0.18)
Obsessive-compulsive	18.3 (1.12)	16.4 (0.69)
Paranoid	15.1 (0.95)	10.0 (0.48)
Schizoid	10.2 (0.82)	7.4 (0.46)
Histrionic	5.3 (0.65)	3.6 (0.38)
Antisocial	8.1 (0.69)	6.3 (0.40)

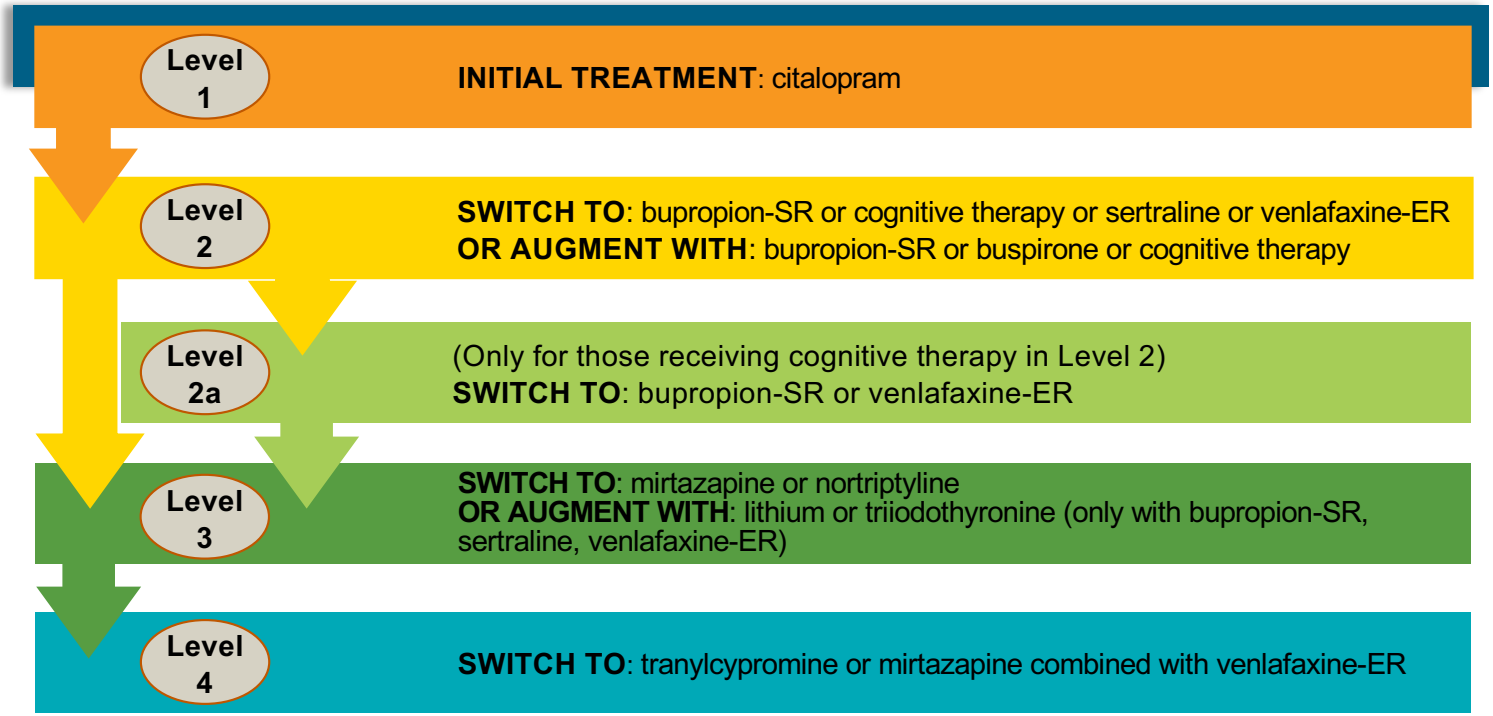
Hasin DS, et al. *Arch Gen Psychiatry*. 2005;62;1097-1106.

Lifetime Comorbidity of Mood with Anxiety Disorders

Kessler et al. Arch Gen Psychiatry 1995; DSM-IV-TR™ 2000; Brawman-Mintzer et al. Am J Psychiatry 1993; Rasmussen et al. J Clin Psychiatry 1992 ; Dunner, Depression and Anxiety 2001

STAR*D Treatment Algorithm Snapshot





STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Trivedi M, et al. *Am J Psychiatry.* 2006;163:28-40.

Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report

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Madhukar H. Trivedi, M.D.

Stephen R. Wisniewski, Ph.D.

Andrew A. Nierenberg, M.D.

Jonathan W. Stewart, M.D.

Diane Warden, Ph.D., M.B.A.

George Niederehe, Ph.D.

Michael E. Thase, M.D.

Philip W. Lavori, Ph.D.

Barry D. Lebowitz, Ph.D.

Patrick J. McGrath, M.D.

Jerrold F. Rosenbaum, M.D.

Harold A. Sackeim, Ph.D.

David J. Kupfer, M.D.

James Luther, M.A.

Maurizio Fava, M.D.

Objective: This report describes the participants and compares the acute and longer-term treatment outcomes associated with each of four successive steps in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

Method: A broadly representative adult outpatient sample with nonpsychotic major depressive disorder received one (N=3,671) to four (N=123) successive acute treatment steps. Those not achieving remission with or unable to tolerate a treatment step were encouraged to move to the next step. Those with an acceptable benefit, preferably symptom remission, from any particular step could enter a 12-month naturalistic follow-up phase. A score of ≤5 on the Quick Inventory of Depressive Symptomatology–Self-Report ($QIDS\text{-}SR_{16}$) (equivalent to ≤7 on the 17-item Hamilton Rating Scale for Depression [$HRSD_{17}$]) defined remission; a $QIDS\text{-}SR_{16}$ total score of ≥11 ($HRSD_{17}$≥14) defined relapse.

Results: The $QIDS\text{-}SR_{16}$ remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively. The overall cumulative remission rate was 67%. Overall, those who required more treatment steps had higher relapse rates during the naturalistic follow-up phase. In addition, lower relapse rates were found among participants who were in remission at follow-up entry than for those who were not after the first three treatment steps.

Conclusions: When more treatment steps are required, lower acute remission rates (especially in the third and fourth treatment steps) and higher relapse rates during the follow-up phase are to be expected. Studies to identify the best multistep treatment sequences for individual patients and the development of more broadly effective treatments are needed.

Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917.

Difference in Treatment Outcome in Outpatients With Anxious Versus Nonanxious Depression: A STAR*D Report

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Stephen R. Wisniewski, Ph.D.

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Andrew Leuchter, M.D.

Robert Howland, M.D.

Diane Warden, Ph.D.

Madhukar H. Trivedi, M.D.

Objective: About half of outpatients with major depressive disorder also have clinically meaningful levels of anxiety. The authors conducted a secondary data analysis to compare antidepressant treatment outcomes for patients with anxious and nonanxious major depression in Levels 1 and 2 of the STAR*D study.

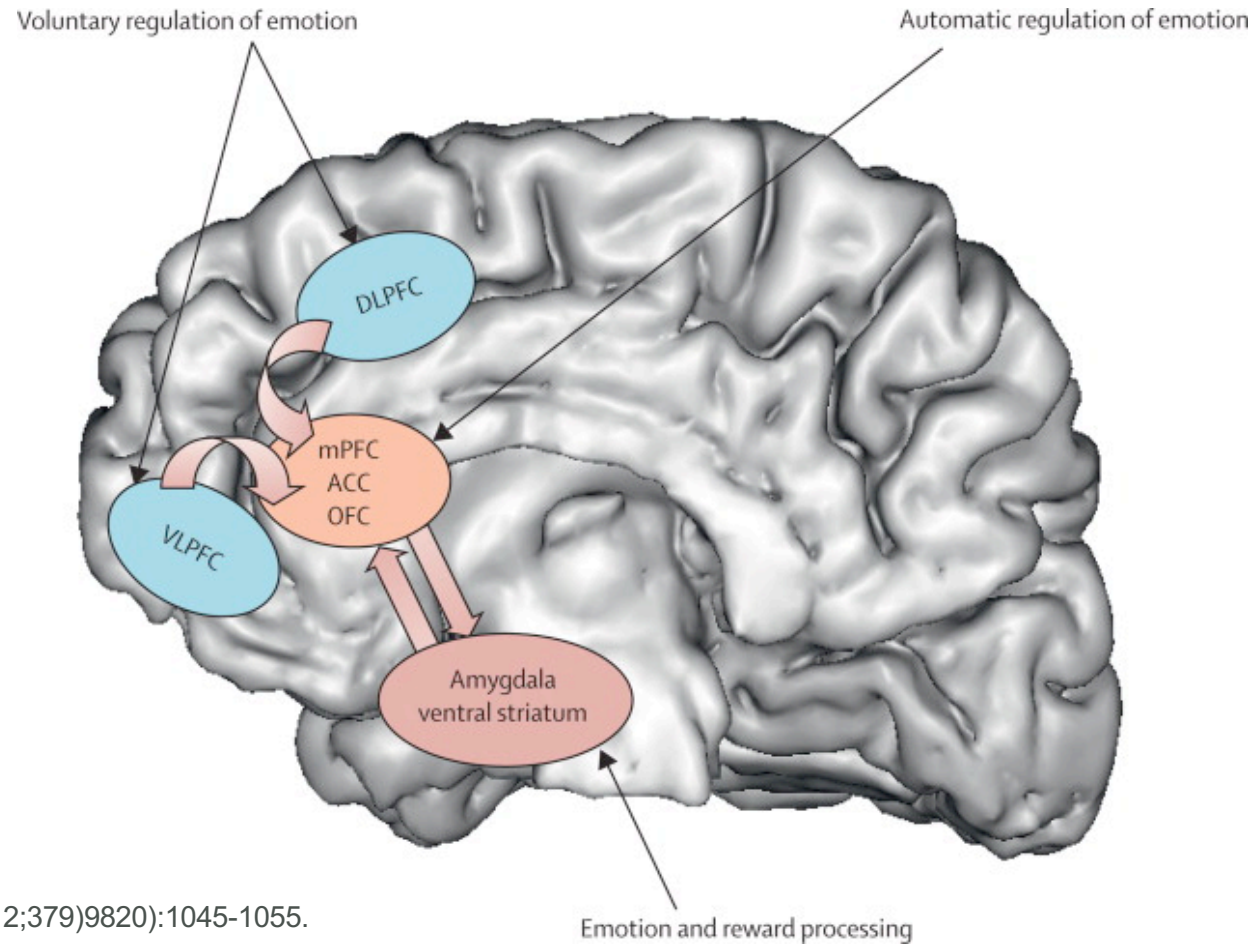
Method: A total of 2,876 adult outpatients with major depressive disorder, enrolled from 18 primary and 23 psychiatric care sites, received citalopram in Level 1 of STAR*D. In Level 2, a total of 1,292 patients who did not remit with or tolerate citalopram were randomly assigned either to switch to sustained-release bupropion (N=239), sertraline (N=238), or extended-release venlafaxine (N=250) or to continue taking citalopram and receive augmentation with sustained-release bupropion (N=279) or buspirone (N=286). Treatment could last up to 14 weeks in each level. Patients were designated as having anxious depression if their anxiety/somatization factor score from the 17-item Hamilton Depression Rating Scale (HAM-D) was 7 or higher at baseline. Rates of remission and response as well as times to remission and response were compared between patients with anxious depression and those with nonanxious depression.

Results: In Level 1 of STAR*D, 53.2% of patients had anxious depression. Remission was significantly less likely and took longer to occur in these patients than in those with nonanxious depression. Ratings of side effect frequency, intensity, and burden, as well as the number of serious adverse events, were significantly greater in the anxious depression group. Similarly, in Level 2, patients with anxious depression fared significantly worse in both the switching and augmentation options.

Conclusions: Anxious depression is associated with poorer acute outcomes than nonanxious depression following antidepressant treatment.

Fava M, et al. *Am J Psychiatry*. 2008;165:342-351.

Stress-related Psychopathology: a Problem of Emotion Regulation



Kufper DJ, et al. *Lancet*. 2012;379)9820):1045-1055.

Cortico-Limbic Interactions Mediate Adaptive and Maladaptive Responses Relevant to Psychopathology

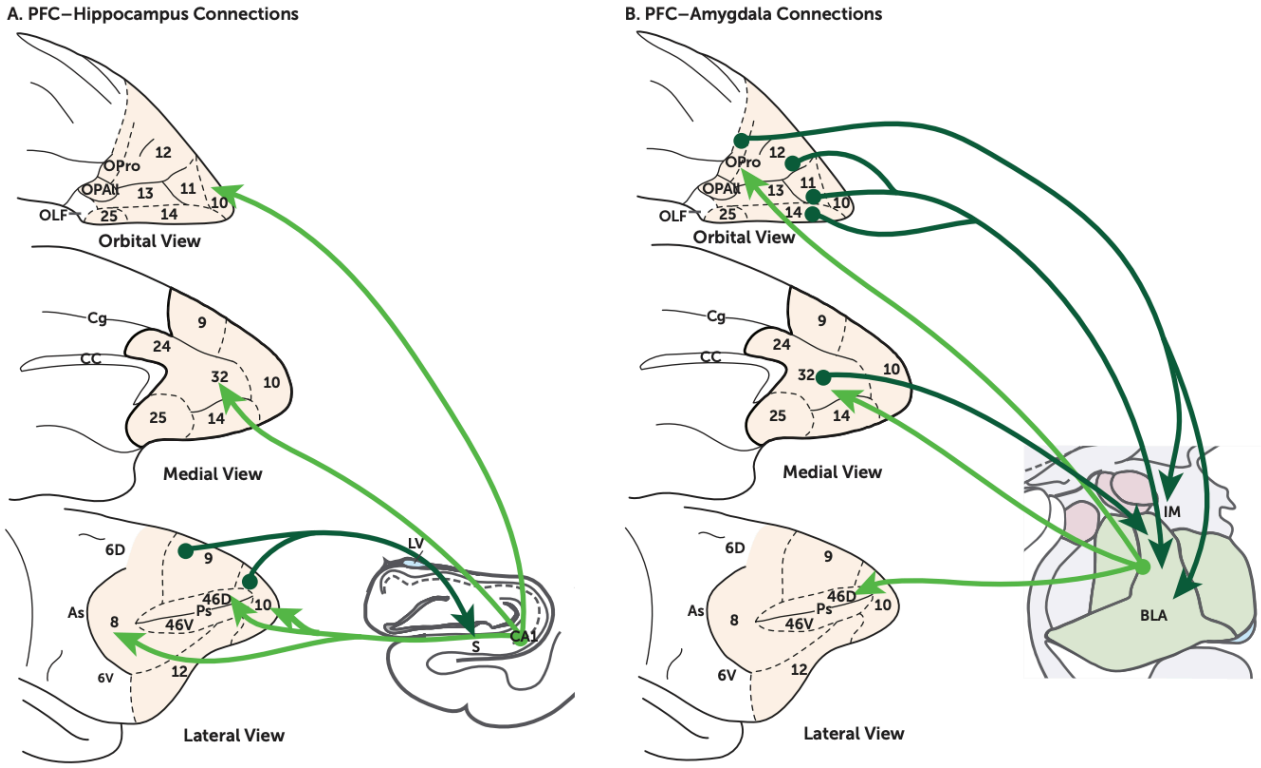
Rothem Kovner, Ph.D., Jonathan A. Oler, Ph.D., Ned H. Kalin, M.D.

Cortico-limbic circuits provide a substrate for adaptive behavioral and emotional responses. However, dysfunction of these circuits can result in maladaptive responses that are associated with psychopathology. The prefrontal-limbic pathways are of particular interest because they facilitate interactions among emotion, cognition, and decision-making functions, all of which are affected in psychiatric disorders. Regulatory aspects of the prefrontal cortex (PFC) are especially relevant to human psychopathology, as the PFC, in addition to its functions, is more recent from an evolutionary perspective and is considerably more complex in human and nonhuman primates compared with other species. This review provides a neuroanatomical and functional perspective of selected regions of the limbic system, the medial temporal lobe structures—the hippocampus and amygdala as well as regions of the PFC. Beyond the specific brain regions, emphasis is placed on the structure and function of critical PFC-limbic circuits, linking alterations in the processing of information across these pathways to the pathophysiology and psychopathology of various psychiatric illnesses.

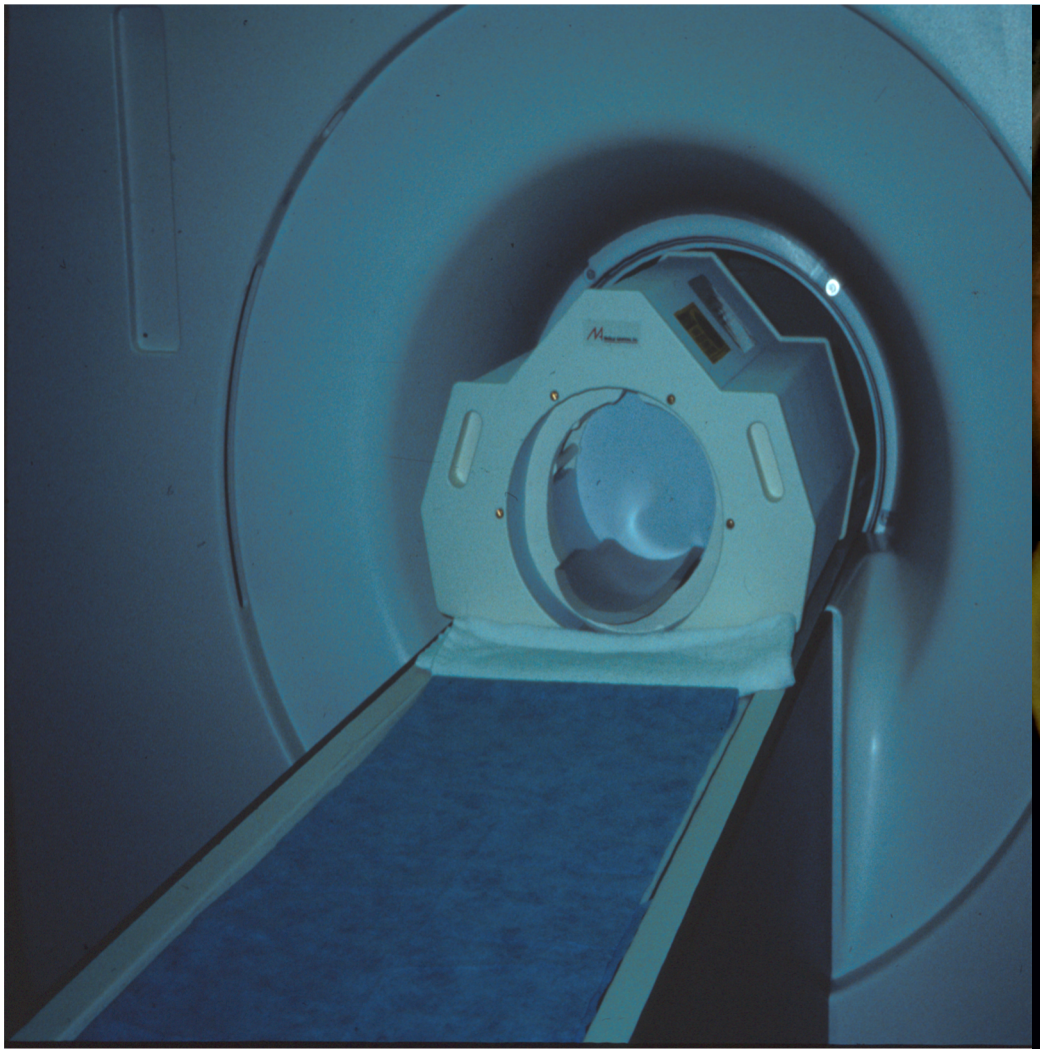
Am J Psychiatry 2019; 176:987–999; doi: 10.1176/appi.ajp.2019.19101064

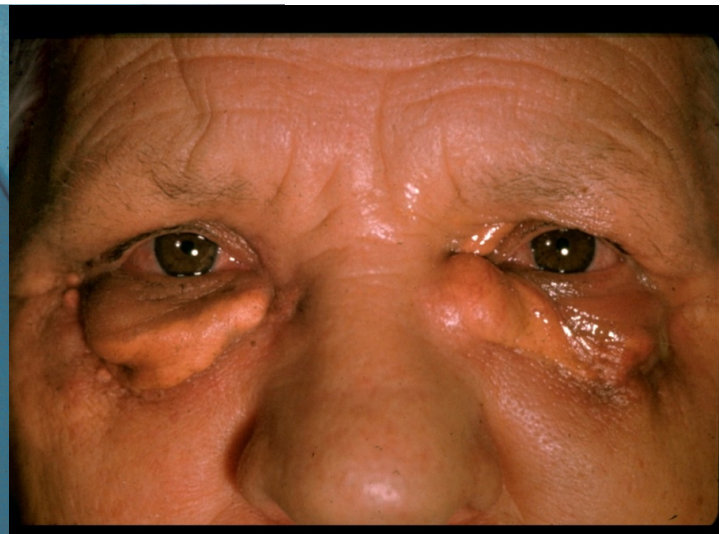
Kovner R, et al. *Am J Psychiatry*. 2019;176:987-999.

Prefrontal Cortex-Limbic Projections Relevant to Psychopathology



Kovner R, et al. *Am J Psychiatriy*. 2019;176(12):987-999





Using Conscious Regulation to Alter Responses to Unpleasant Stimuli

Intensity of unpleasantness

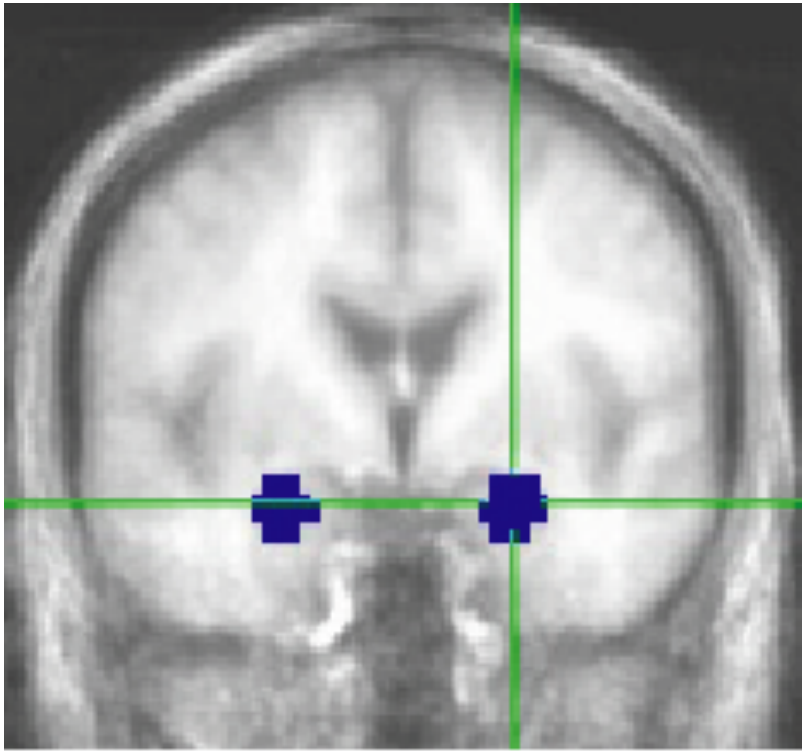
"Fangs plunging in! Legs inching up my arm! Aaargh!!

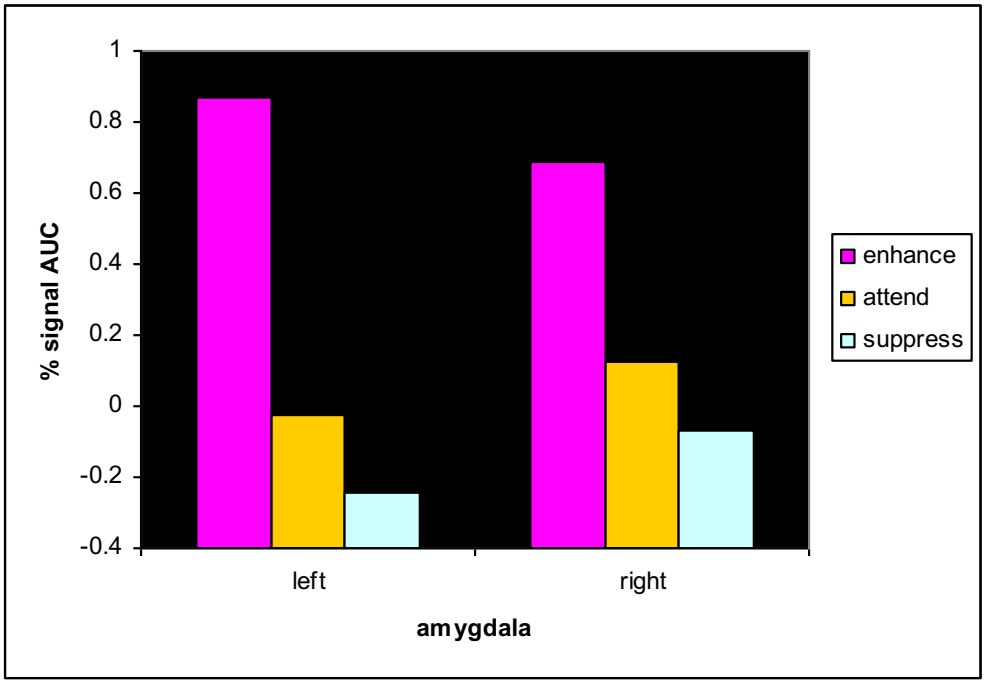
"Eww, creepy!!"

"It's harmless. It'll all be OK."

Time

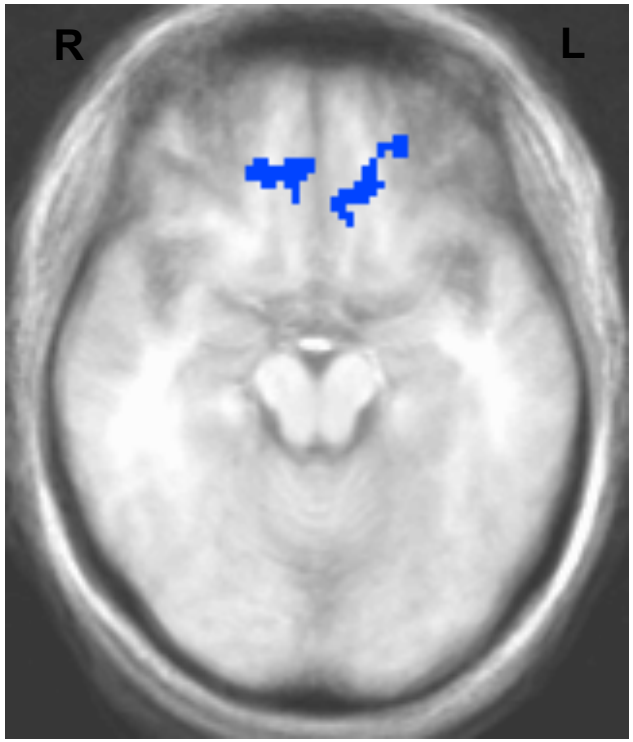
Conscious Emotion Regulation: Modulating Amygdala Activity

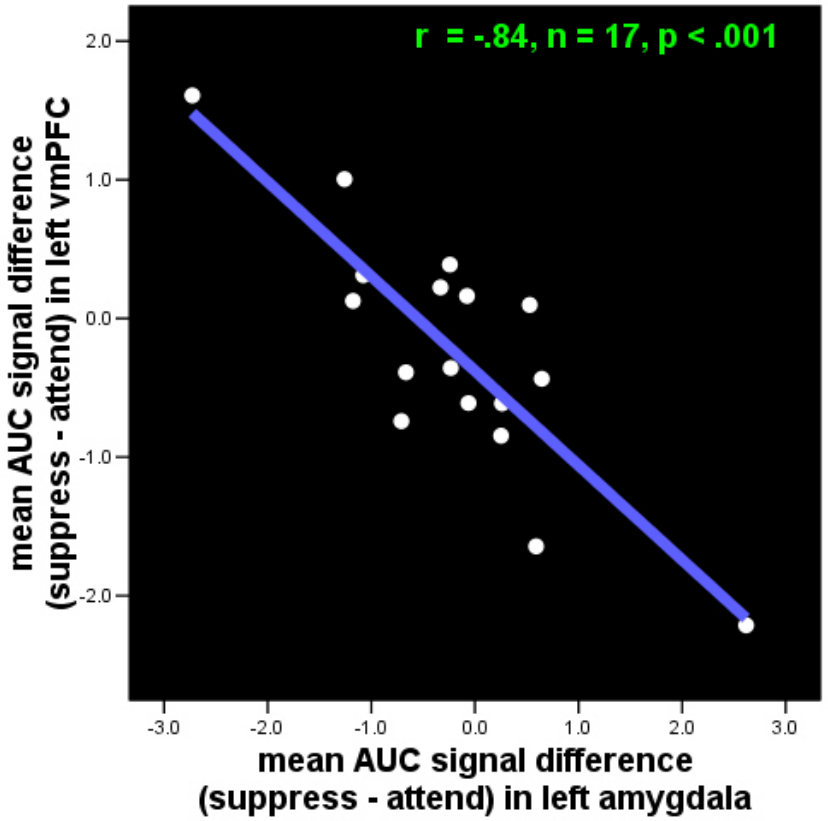




Urry H, et al *J Neurosci.* 2006;26(16):4415-4425.

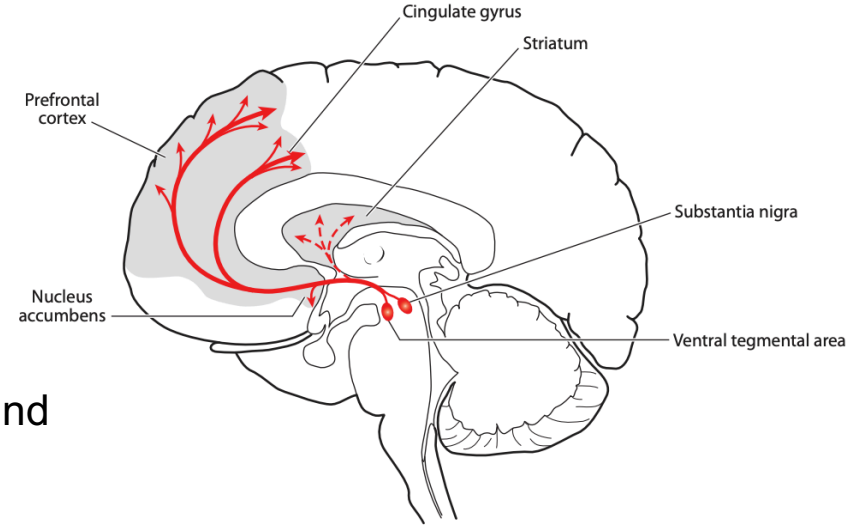
vmPFC and OFC Activity During Conscious Regulation (suppress – attend) Negatively Correlates with Amygdala Activity

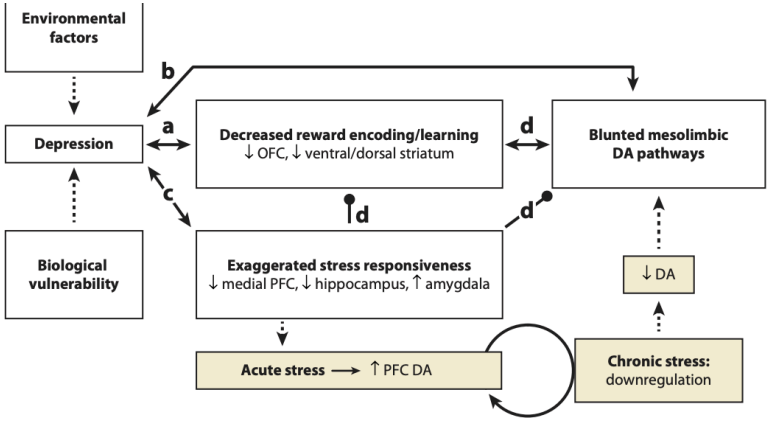




Urry H, et al *J Neurosci.* 2006;26(16):4415-4425.

Dopamine Pathways and Anhedonia





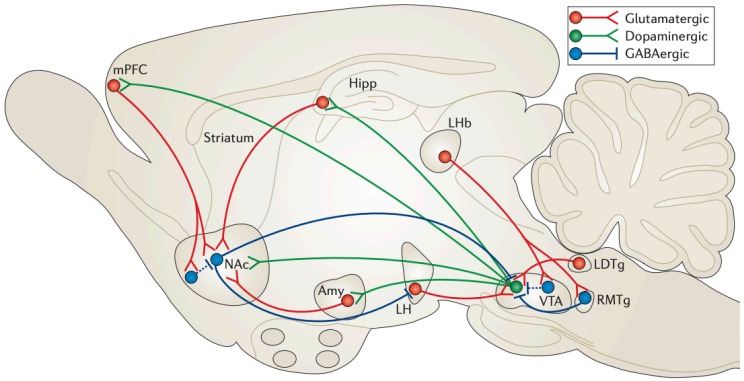


Figure 1 | **VTA–NAc reward circuit.** A simplified schematic of the major dopaminergic, glutamatergic and GABAergic connections to and from the ventral tegmental area (VTA) and nucleus accumbens (NAc) in the rodent brain. The primary reward circuit includes dopaminergic projections from the VTA to the NAc, which release dopamine in response to reward-related stimuli (and in some cases, aversion-related stimuli). There are also GABAergic projections from the NAc to the VTA; projections through the direct pathway (mediated by D1-type medium spiny neurons (MSNs)) directly innervate the VTA, whereas projections through the indirect pathway (mediated by D2-type MSNs) innervate the VTA via intervening GABAergic neurons in the ventral pallidum (not shown). The NAc also contains numerous types of interneurons (FIG. 2). The NAc receives dense innervation from glutamatergic monosynaptic circuits from the medial prefrontal cortex (mPFC), hippocampus (Hipp) and amygdala (Amy), as well as other regions. The VTA receives such inputs from the lateral dorsal tegmentum (LDTg), lateral habenula (LHb) and lateral hypothalamus (LH), as well as both GABAergic and glutamatergic connections from the extended amygdala (not shown). These various glutamatergic inputs control aspects of reward-related perception and memory. The dashed lines indicate internal inhibitory projections. The glutamatergic circuit from the LH to the VTA is also mediated by orexin (not shown). Greater details of these monosynaptic circuits for NAc and VTA are shown in FIG. 2. RTMg, rostromedial tegmentum.

Pizzagalli DA. *Annu Rev Clin Psychol*. 2014;10:393-423.; Russo SJ, Nestler EJ. *Nat Rev Neurosci.* 2013;14(9):609-625.

Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation

Aaron S. Heller[a,b], Tom Johnstone[c], Alexander J. Shackman[a,b], Sharee N. Light[a,b], Michael J. Peterson[d], Gregory G. Kolden[b,d], Ned H. Kalin[b,d,e], and Richard J. Davidson[a,b,d,e,f,1]

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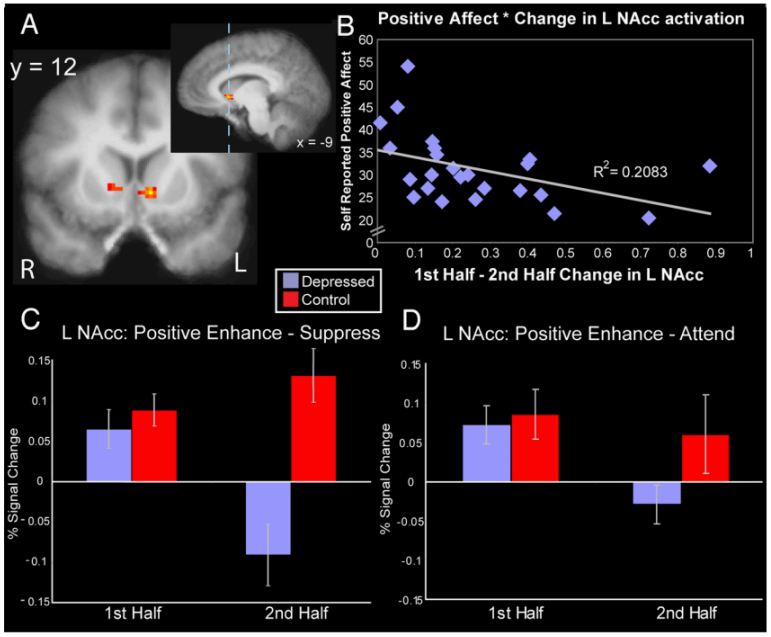
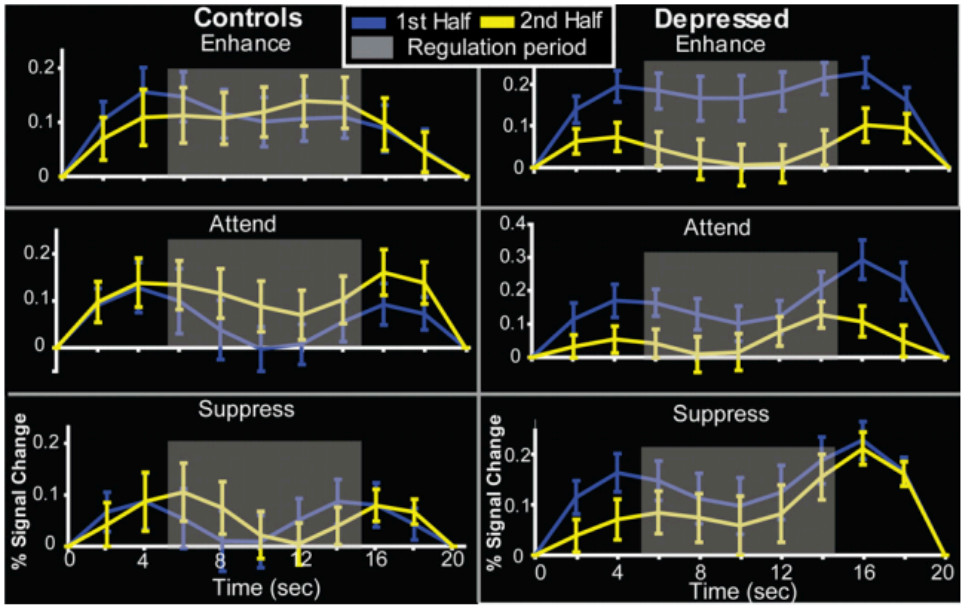
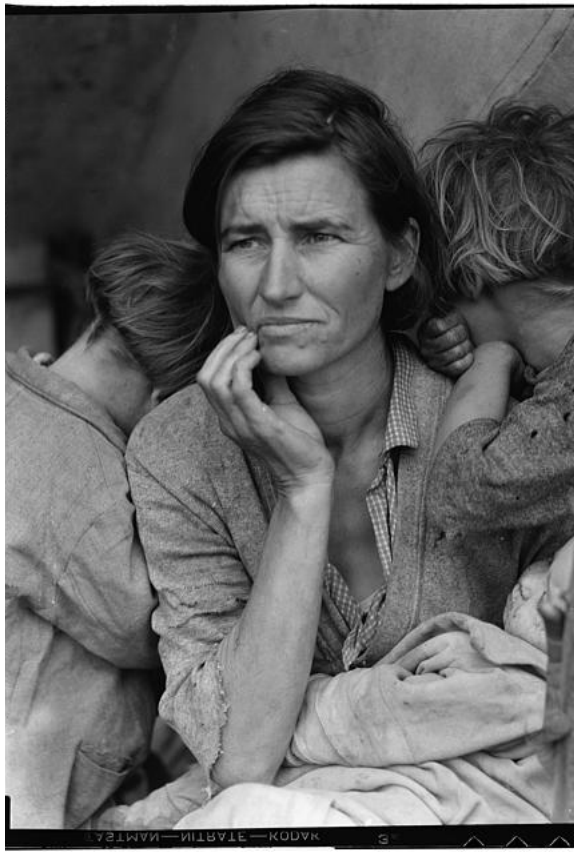




Heller AS, et al. *Proc Natl Acad Sci U S A.*. 2009;106(52):22445-11450.

Vulnerability to Develop Depression

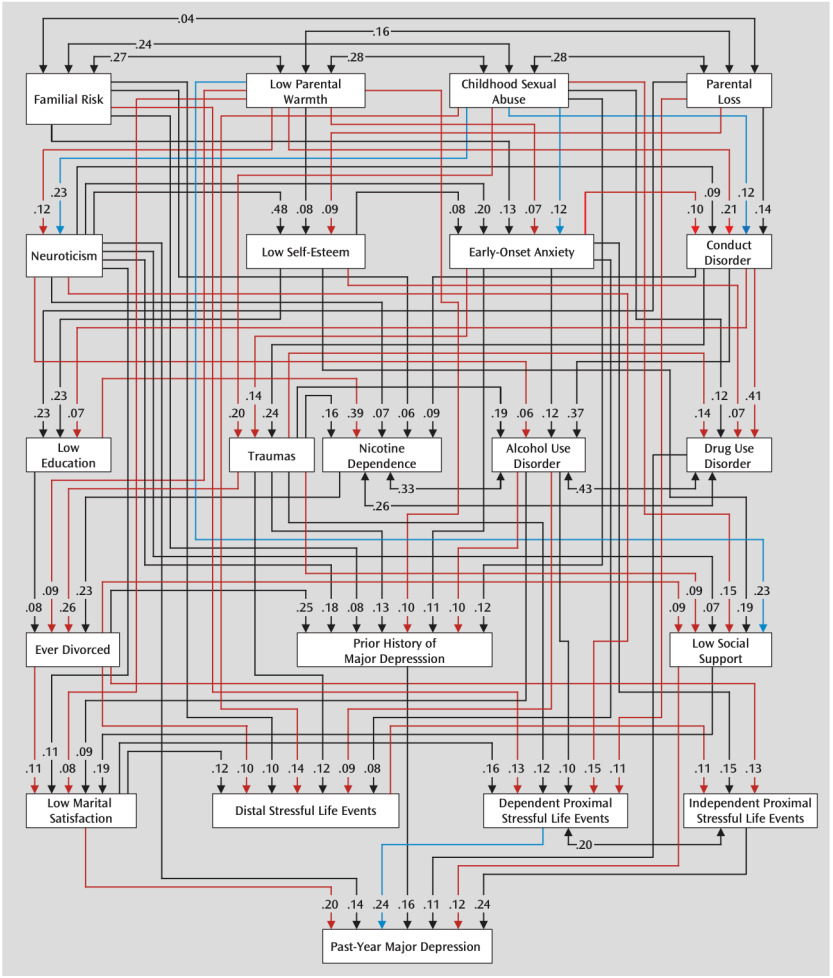
- Genetic
- Early life stress/trauma
- Current stress
- Childhood temperament, personality traits (neuroticism)



Dorothea Lange, Migrant Mother, 1936

Interactions Among Genes, Early Stress, Temperament, and Current Stress

FIGURE 1. Path Estimates for Best-Fit Model for Causal Pathways to Major Depression in Females[a]



[a] Parameters estimated to be equal across sexes, greater in females than males, and greater in males than females are depicted in black, red, and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II in the online data supplement contains the best-fit model estimates for all these paths, along with their statistical significance and the equality or nonequality of that path across sexes. The test of equality across sexes was based on raw path coefficients. However, for ease of interpretation and a consistent measure of effect size, we report standardized path coefficients. Thus, paths that are depicted as equal (using raw coefficients) can differ slightly using standardized paths.

Kendler KS, Gardner CO, *Am J Psychiatry.* 2014;171(4):426-435.

nature neuroscience

ARTICLES

https://doi.org/10.1038/s41593-018-0326-7

Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions

Major depression is a debilitating psychiatric illness that is typically associated with low mood and anhedonia. Depression has a heritable component that has remained difficult to elucidate with current sample sizes due to the polygenic nature of the disorder. To maximize sample size, we meta-analyzed data on 807,553 individuals (246,363 cases and 561,190 controls) from the three largest genome-wide association studies of depression. We identified 102 independent variants, 269 genes, and 15 genesets associated with depression, including both genes and gene pathways associated with synaptic structure and neurotransmission. An enrichment analysis provided further evidence of the importance of prefrontal brain regions. In an independent replication sample of 1,306,354 individuals (414,055 cases and 892,299 controls), 87 of the 102 associated variants were significant after multiple testing correction. These findings advance our understanding of the complex genetic architecture of depression and provide several future avenues for understanding etiology and developing new treatment approaches.

Howard DM, et al. *Nat Neurosci.* 2019;22(3):343-352.

Independent Variants in the Prefrontal Regions

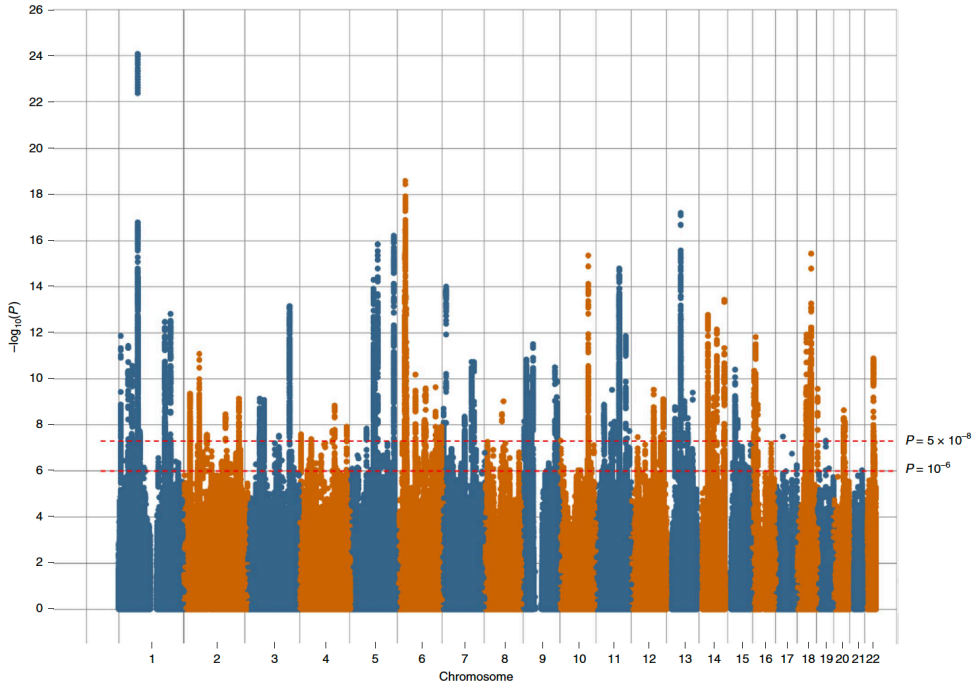


Fig. 1 | Manhattan plot of the observed $-\log_{10} P$ values of each variant for an association with depression in the meta-analysis (n =807,553; 246,363 cases and 561,190 controls). Variants are positioned according to the GRCh37 assembly.

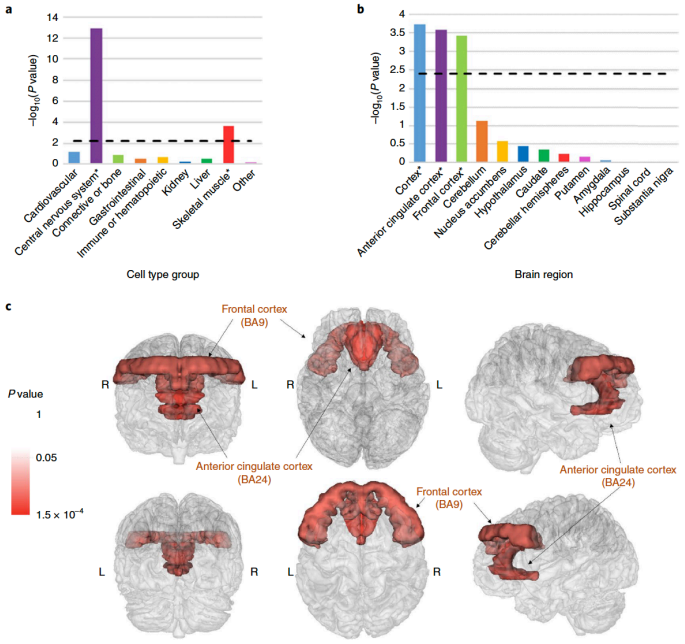


Fig. 2 | Significance of enrichment using a partitioned heritability approach. a, Significance of cell-type enrichment using a partitioned heritability approach. The dashed line represents statistical significance after Bonferroni correction ($-\log_{10}P = 2.36$) and asterisks (*) indicate significant enrichment for that cell type. **b**, Significance of enrichment estimates, based on genetic summary statistics, for brain regions using GTEx. The dashed line represents the Bonferroni cutoff for statistical significance ($-\log_{10}P = 2.41$) and asterisks (*) indicate significant enrichment for that brain region. **c**, Significant enrichment P values, based on genetic summary statistics, for brain cell regions using GTEx overlaid on a physical representation of brain anatomy. The pseudocoloring in **c** (red) highlights the P values of the regions of the brain that were significantly enriched ($P < 0.05$) for depression variants.

Howard DM, et al. *Nat Neurosci.* 2019;22(3):343-352.

Polygenic Risk: Predicting Depression Outcomes in Clinical and Epidemiological Cohorts of Youths

Thorhildur Halldorsdottir, Ph.D., Charlotte Piechaczek, M.S., Ana Paula Soares de Matos, Ph.D., Darina Czamara, Ph.D., Verena Pehl, Ph.D., Petra Wagenbuechler, Lisa Feldmann, M.S., Peggy Quickenstedt-Reinhardt, Dipl.-Psych., Antje-Kathrin Allgaier, Ph.D., Franz Joseph Freisleder, Ph.D., Ellen Greimel, Ph.D., Tuomas Kvist, M.A., Jari Lahti, Ph.D., Katri Räikkönen, Ph.D., Monika Rex-Haffner, Eiríkur Örn Arnarson, Ph.D., W. Edward Craighead, Ph.D., Gerd Schulte-Körne, Ph.D., Elisabeth B. Binder, M.D., Ph.D.

Objective: Identifying risk factors for major depression and depressive symptoms in youths could have important implications for prevention efforts. This study examined the association of polygenic risk scores (PRSs) for a broad depression phenotype derived from a large-scale genome-wide association study (GWAS) in adults, and its interaction with childhood abuse, with clinically relevant depression outcomes in clinical and epidemiological youth cohorts.

Methods: The clinical cohort comprised 279 youths with major depression (mean age=14.76 years [SD=2.00], 68% female) and 187 healthy control subjects (mean age=14.67 years [SD=2.45], 63% female). The first epidemiological cohort included 1,450 youths (mean age=13.99 years [SD=0.92], 63% female). Of those, 694 who were not clinically depressed at baseline underwent follow-ups at 6, 12, and 24 months. The replication epidemiological cohort comprised children assessed at ages 8 (N=184; 49.2% female) and 11 (N=317; 46.7% female) years. All cohorts were genome-wide genotyped and completed measures for major depression, depressive symptoms, and/or childhood abuse. Summary statistics from the largest GWAS to date on depression were used to calculate the depression PRS.

Results: In the clinical cohort, the depression PRS predicted case-control status (odds ratio=1.560, 95% CI=1.230–1.980), depression severity (β=0.177, SE=0.069), and age at onset (β=−0.375, SE=0.160). In the first epidemiological cohort, the depression PRS predicted baseline depressive symptoms (β=0.557, SE=0.200) and prospectively predicted onset of moderate to severe depressive symptoms (hazard ratio=1.202, 95% CI=1.045–1.383). The associations with depressive symptoms were replicated in the second epidemiological cohort. Evidence was found for an additive, but not an interactive, effect of the depression PRS and childhood abuse on depression outcomes.

Conclusions: Depression PRSs derived from adults generalize to depression outcomes in youths and may serve as an early indicator of clinically significant levels of depression.

Am J Psychiatry 2019; 176:615–625; doi: 10.1176/appi.ajp.2019.18091014

Halldorsdottir T, et al. *Am J Psychiatry.* 2019;176:615-625.

The Devastating Clinical Consequences of Child Abuse and Neglect: Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders

Elizabeth T.C. Lippard, Ph.D., Charles B. Nemeroff, M.D., Ph.D.

A large body of evidence has demonstrated that exposure to childhood maltreatment at any stage of development can have long-lasting consequences. It is associated with a marked increase in risk for psychiatric and medical disorders. This review summarizes the literature investigating the effects of childhood maltreatment on disease vulnerability for mood disorders, specifically summarizing cross-sectional and more recent longitudinal studies demonstrating that childhood maltreatment is more prevalent and is associated with increased risk for first mood episode, episode recurrence, greater comorbidities, and increased risk for suicidal ideation and attempts in individuals with mood disorders. It summarizes the persistent alterations associated with childhood maltreatment, including alterations in the hypothalamic-pituitary-adrenal axis and inflammatory cytokines, which may contribute to disease vulnerability and a more pernicious disease course. The authors discuss several candidate genes and environmental factors (for example, substance use) that may alter disease vulnerability and illness course and neurobiological associations that may mediate these relationships following childhood maltreatment. Studies provide insight into modifiable mechanisms and provide direction to improve both treatment and prevention strategies.

AJP in Advance (doi: 10.1176/appi.ajp.2019.19010020)

Lippard ETC, Nemeroff CB. *Am J Psychiatry*. 2020;177(1):20-36.

A Population-Based Twin Study of the Relationship Between Neuroticism and Internalizing Disorders

John M. Hettema, M.D., Ph.D.

Michael C. Neale, Ph.D.

John M. Myers, M.S.

Carol A. Prescott, Ph.D.

Kenneth S. Kendler, M.D.

Objective: The anxiety and depressive disorders exhibit high levels of lifetime comorbidity with one another. The authors examined how genetic and environmental factors shared by the personality trait neuroticism and seven internalizing disorders may help explain this comorbidity.

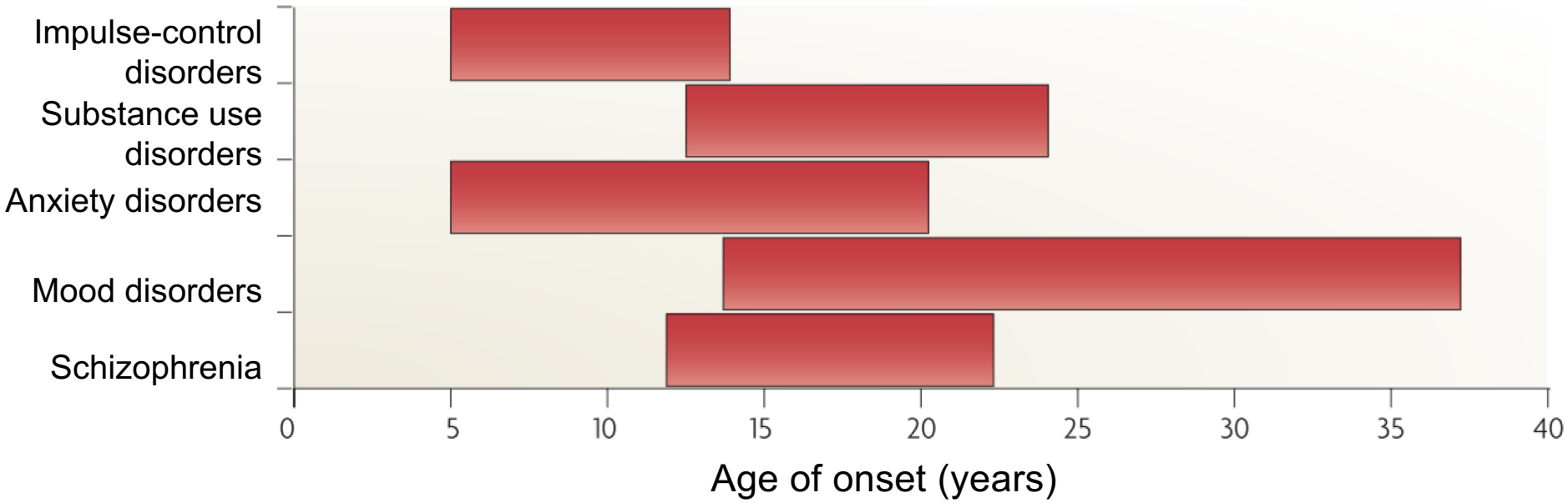
Method: Lifetime major depression, generalized anxiety disorder, panic disorder, agoraphobia, social phobia, animal phobia, situational phobia, and neuroticism were assessed in over 9,000 twins from male-male, female-female, and opposite-sex pairs through structured diagnostic interviews. Multivariate structural equation models were used to decompose the correlations between these phenotypes into genetic and environmental components, allowing for sex-specific factors.

Results: Genetic factors shared with neuroticism accounted for between one-third and one-half of the genetic risk across the internalizing disorders. When nonsignificant gender differences were removed from the models, the genetic correlations between neuroticism and each disorder were high, while individual-specific environmental correlations were substantially lower. In addition, the authors could identify a neuroticism-independent genetic factor that significantly increased risk for major depression, generalized anxiety disorder, and panic disorder.

Conclusions: There is substantial, but not complete, overlap between the genetic factors that influence individual variation in neuroticism and those that increase liability across the internalizing disorders, helping to explain the high rates of comorbidity among the latter. This may have important implications for identifying the susceptibility genes for these conditions.

Hettema JM, et al. *Am J Psychiatry*. 2006;163:857-864.

Why Study Early-Life Risk?

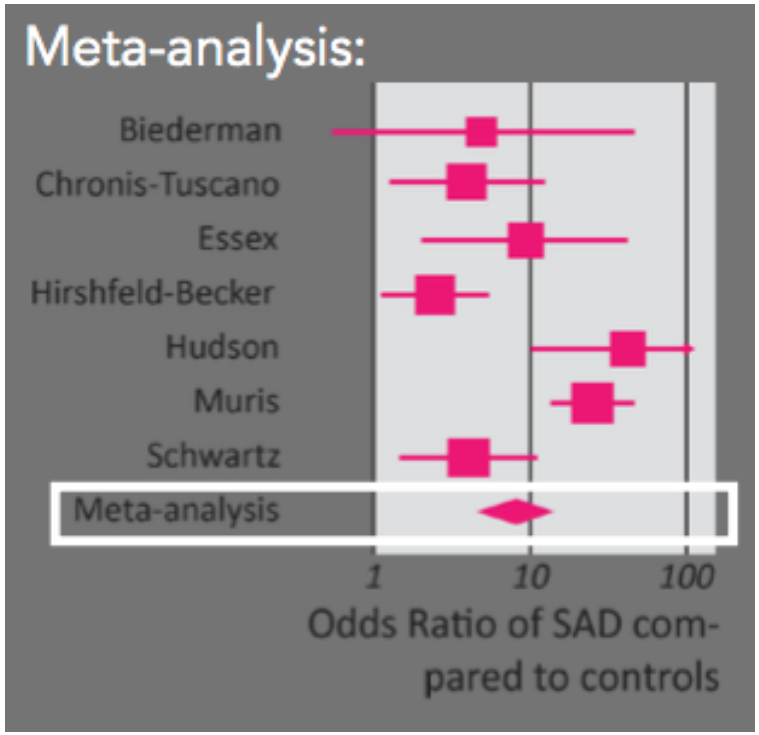


Paus T, et al. *Nat Rev Neurosci*. 2008;9(12):947-957.


Angel Soft
UW Health
uwhealth.org

Inhibited or Anxious Temperament (AT): Risk Phenotype That Precedes Anxiety and Depressive Disorders

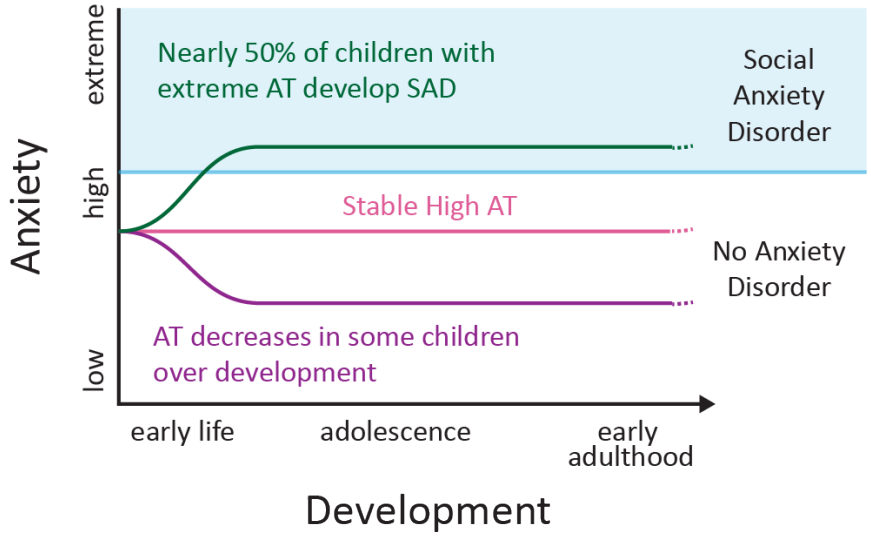
- Extreme behavioral inhibition to novel situations or strangers
- Predicts development of anxiety disorders, depression, and co-morbid drug abuse
- 3-4 fold risk to develop social anxiety disorder
- Can be identified early in life
- Inhibited monkeys and humans share behavioral and physiological features



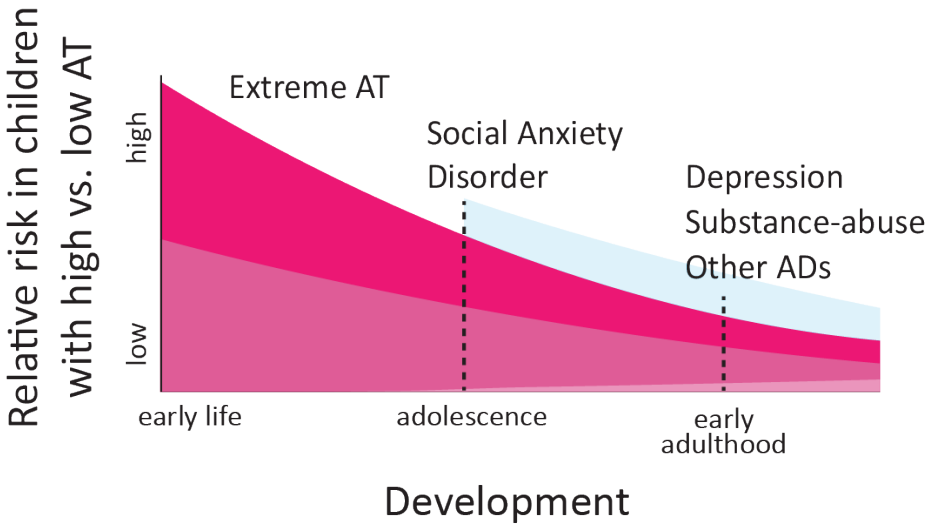
Clauss JA, Blackford JU. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):1066-1075.

Proposed Anxiety Trajectories for Children with High Anxious Temperament

a) Pathological Anxiety: Trajectories for Children with High AT



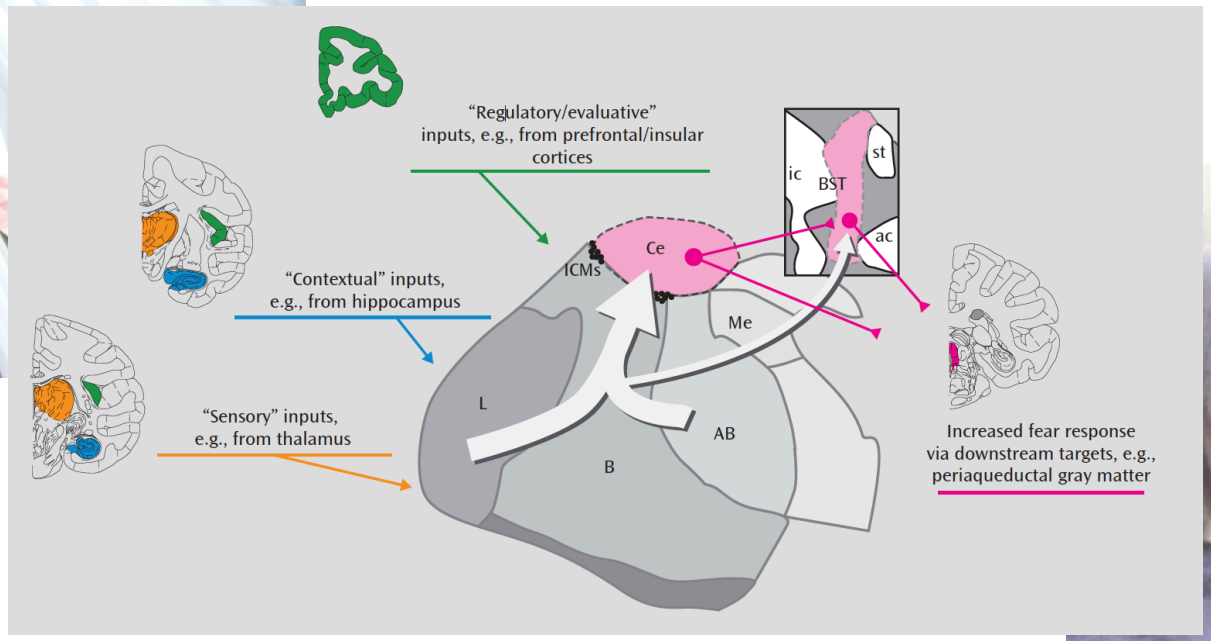
b) Extreme AT children are at risk for psychopathology across the lifespan



Fox AS, Kalin NH. *Am J Psychiatry*. 2014;171(11):1162-1173.

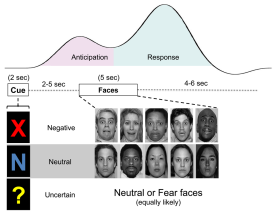
Nonhuman Primates Provide a Unique Opportunity for Studying Human Psychopathology

Validation of the Nonhuman Primate Model: Altered Prefrontal-Amygdala Function in Pre-adolescent Children with Anxiety Disorders and Young Rhesus Monkeys

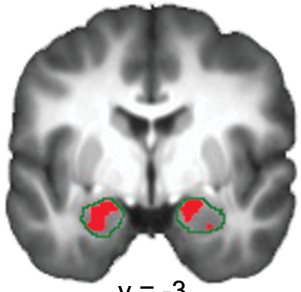


Fox AS, Kalin NH. *Am J Psychiatry*. 2014;171(11):1162-1173.

Elevated Dorsal Amygdala/Ce Activation During Uncertain Anticipation in Preadolescent Children with Anxiety Disorders

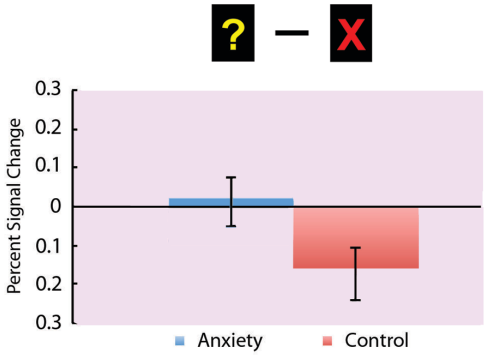


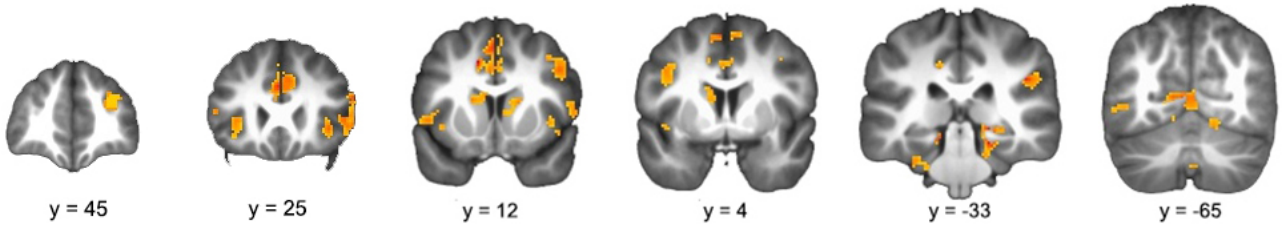
Anxiety Disorder vs Control



y = -3

p < .05 corrected



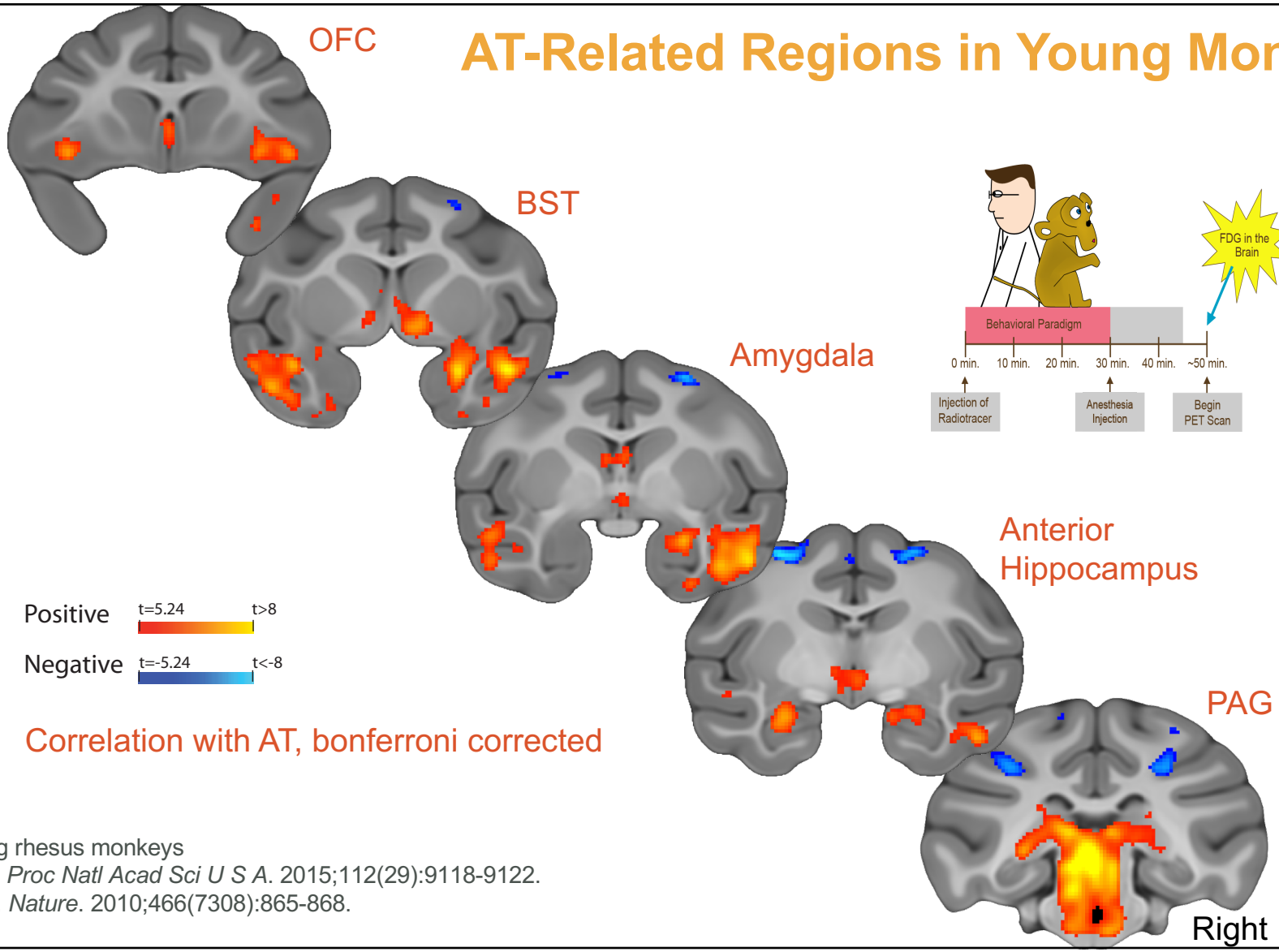


P < .005, uncorrected

n = 33 anxiety disorder, 28 control

Builds on sample from Williams LM, et al. *Neuropsychopharmacology*. 2015;40(10):2398-2408.

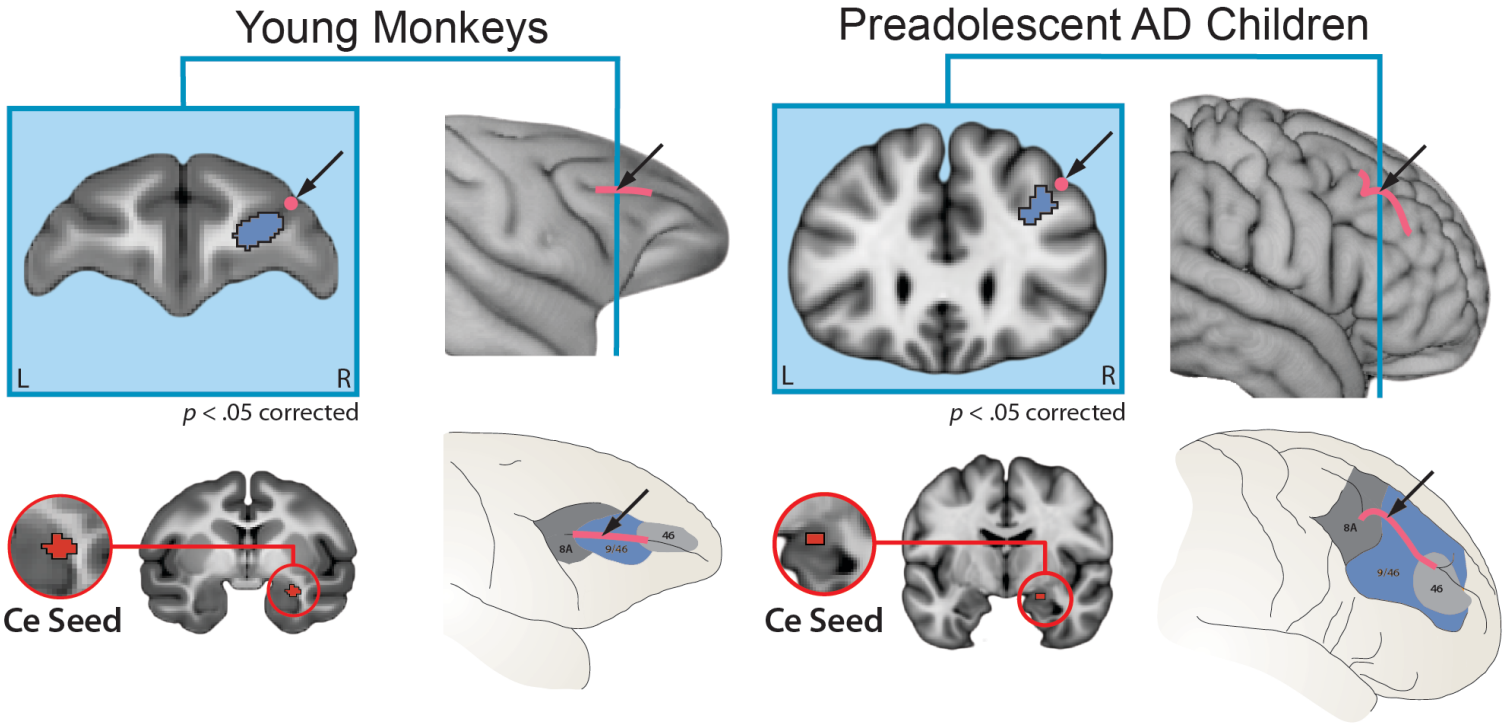
AT-Related Regions in Young Monkeys



n = 592 young rhesus monkeys

Fox AS, et al. *Proc Natl Acad Sci U S A*. 2015;112(29):9118-9122.
Oler JA, et al. *Nature*. 2010;466(7308):865-868.

Evolutionarily-Conserved Decrease in dlPFC-Ce Functional Connectivity in Young Anxious Monkeys and Children

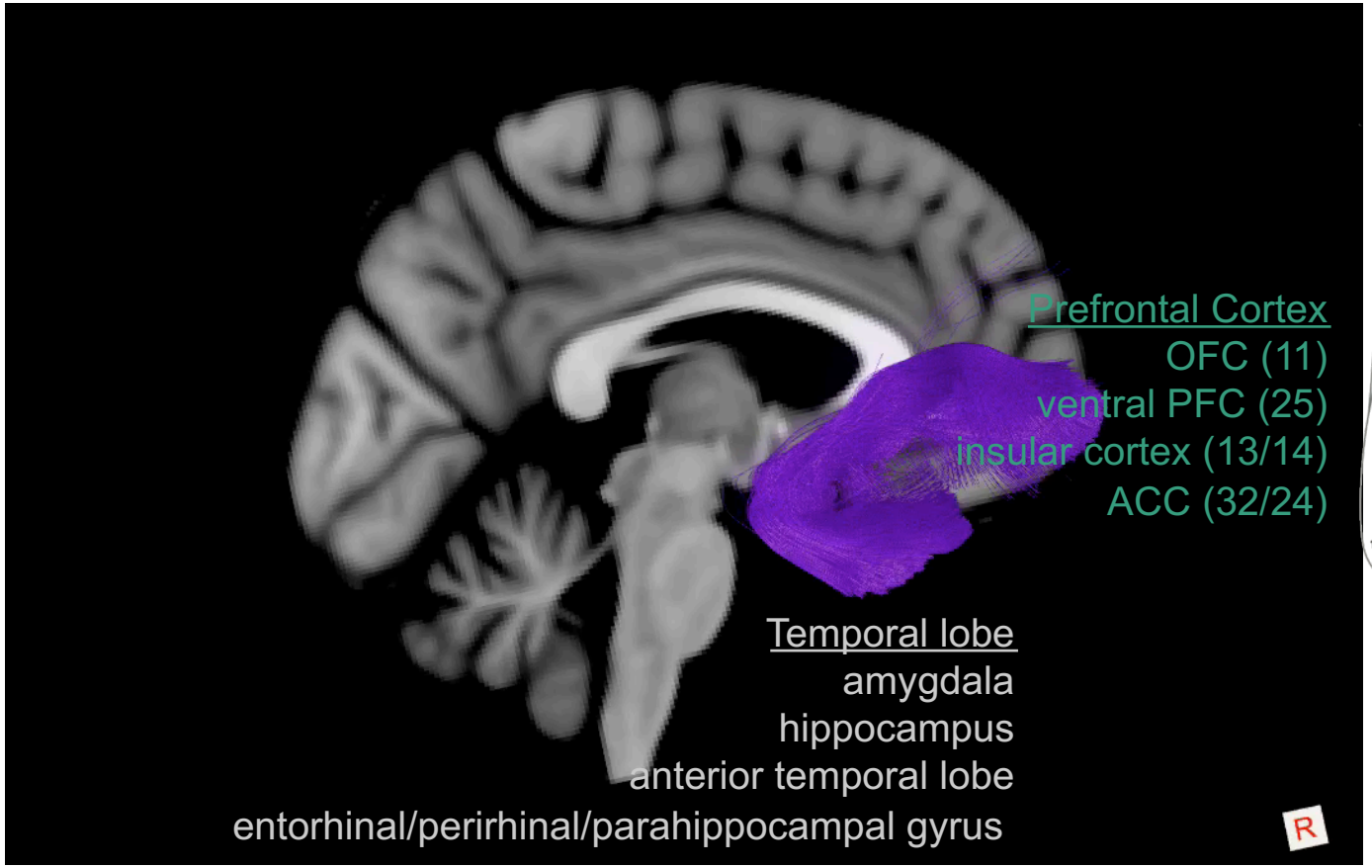


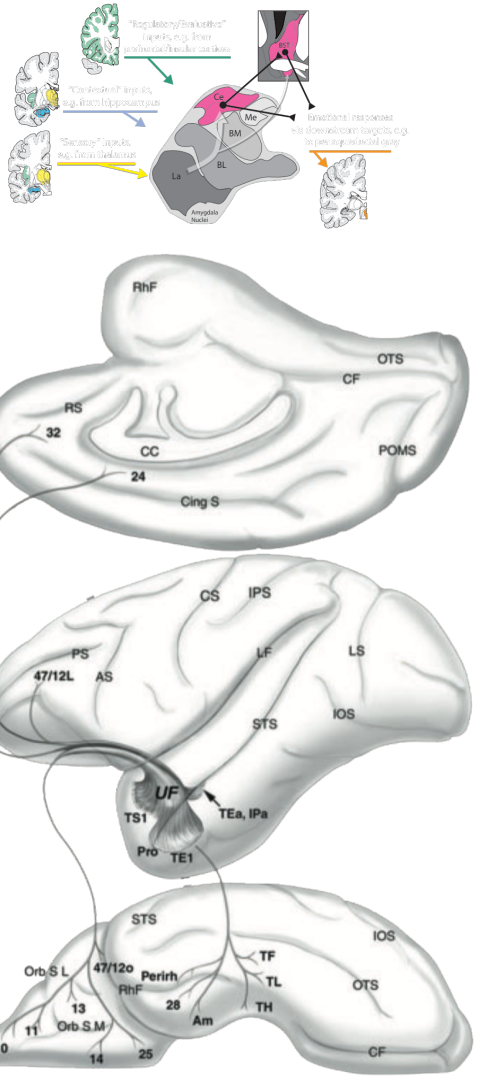
n = 89

n = 14 anxiety disorder, 14 control

Birn RM, et al. *Mol Psychiatry*. 2014;19(8):853.

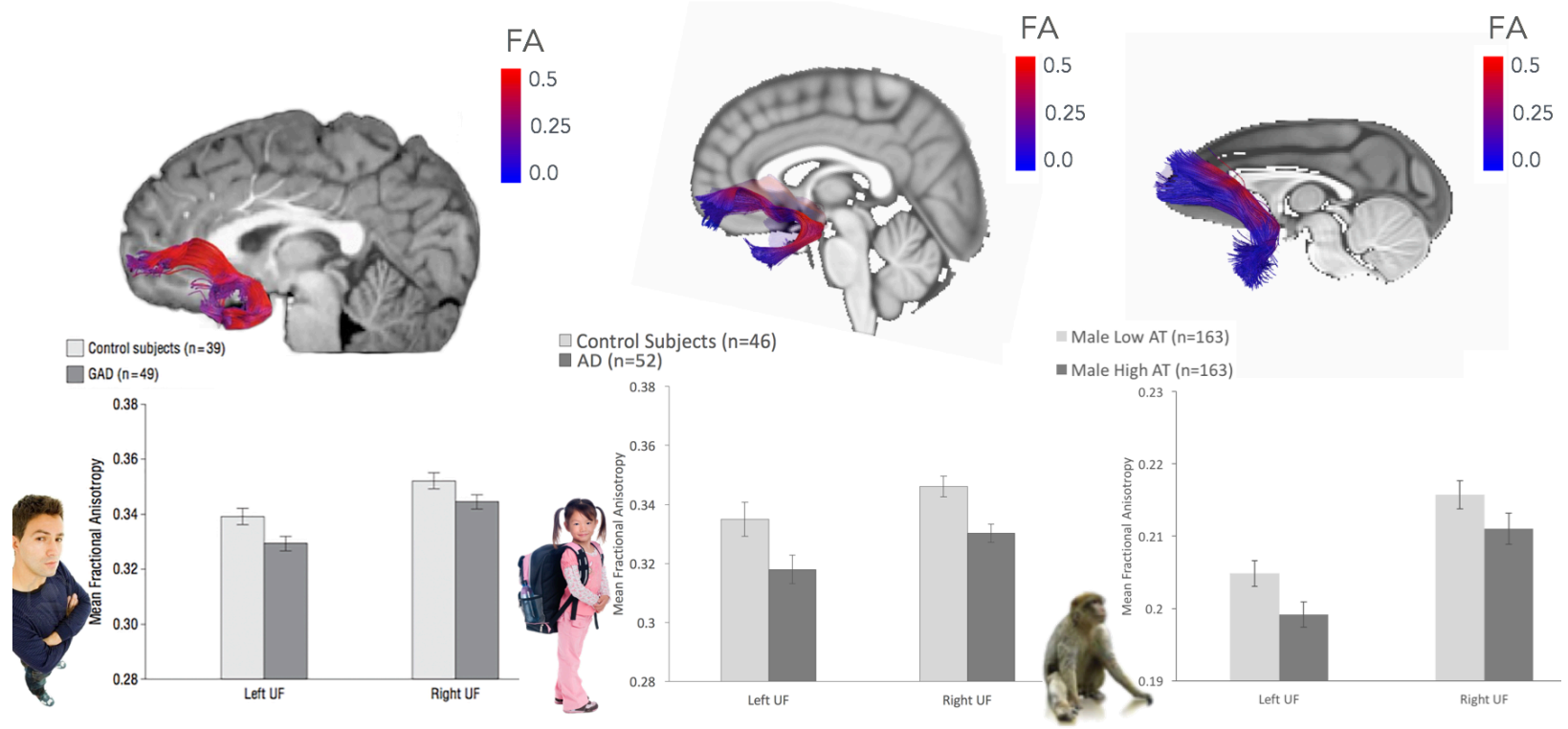
Altered Prefrontal Cortical and Amygdala Interactions Via Uncinate Fasciculus May Underlie Anxiety





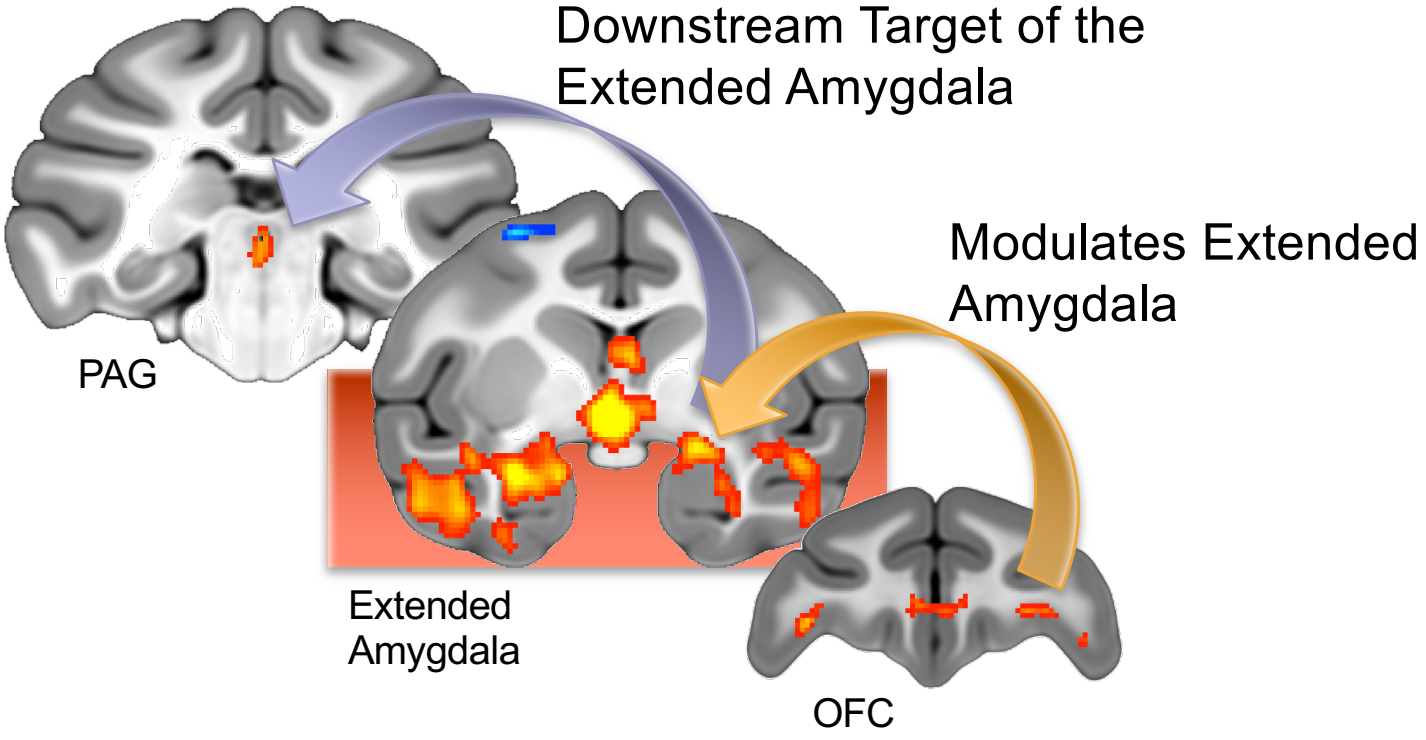
Schmahmann JD, Pandya DN. *J Hist Neurosci* 2007;16(4):362-377.

Decreased White Matter Integrity (FA) in the UF Associated with Higher Anxiety Across Age and Species

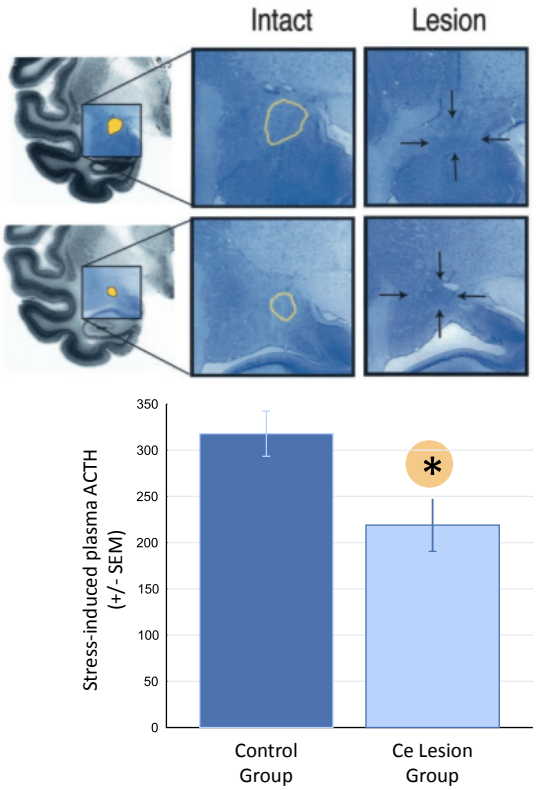


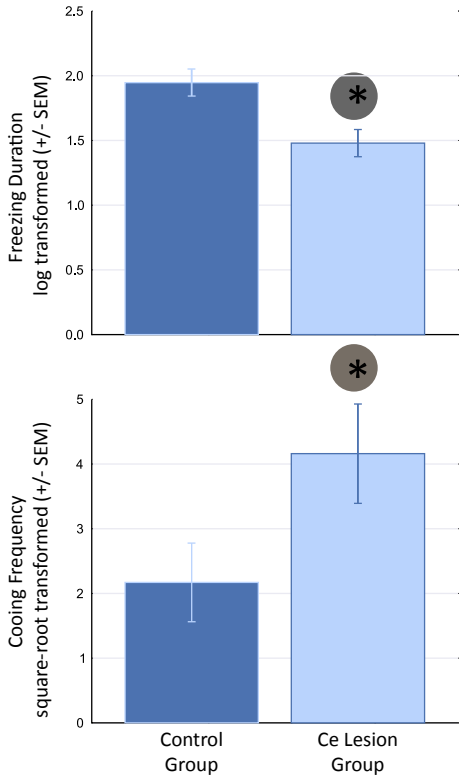
Tromp DP, et al. *Arch Gen Psychiatry*. 2012;69(9):925-934.
Tromp DP, et al. *Am J Psychiatry.* 2019 Jan:appiajp201818040425. doi: 10.1176/appi.ajp.2018.18040425. [Epub ahead of print]

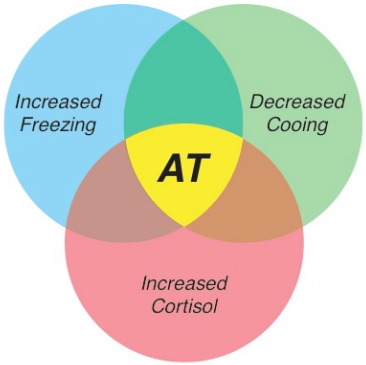
Extended Amygdala is a Core Component of AT with Downstream and Upstream Partners



Mechanistic Role of Ce: Neurotoxic Lesions Alter Components of AT



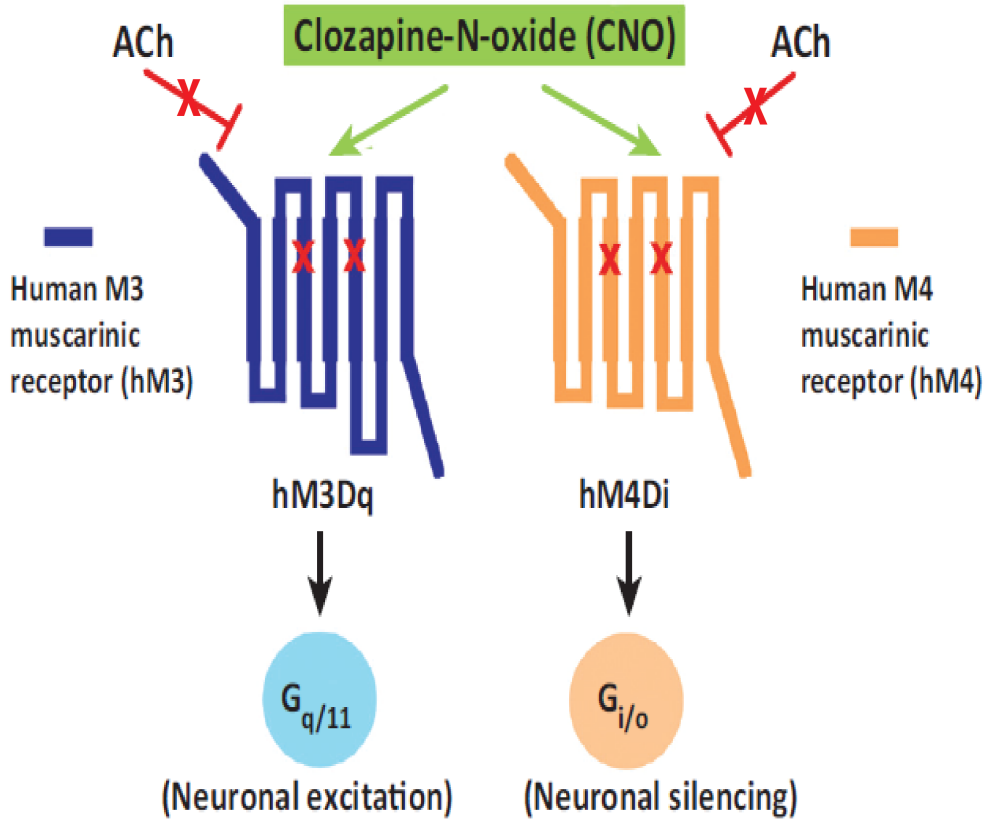




* = Control vs. Lesion p<.05

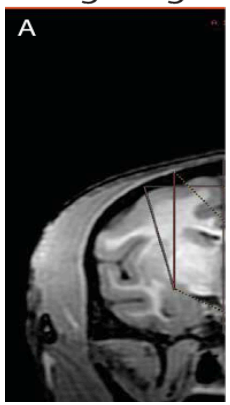
Kalin NH, et al. *J Neurosci.* 2004;24(24):5506-5515.

Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) Technology

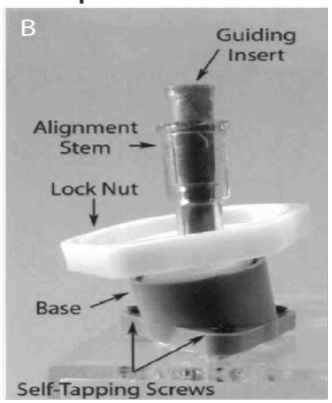


Real time MRI for Site Specific Delivery of Viral Vector (AAV2)

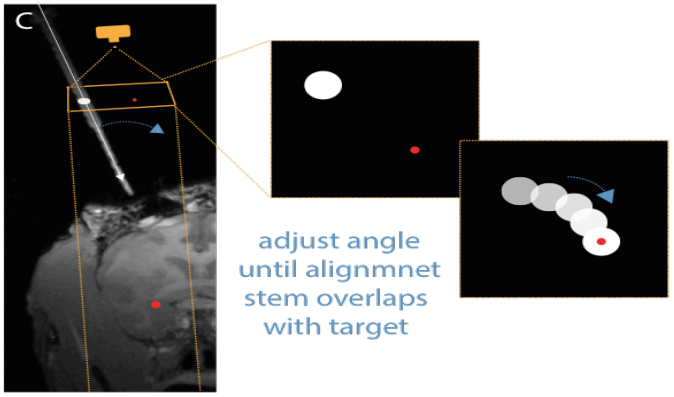
presurgical targeting



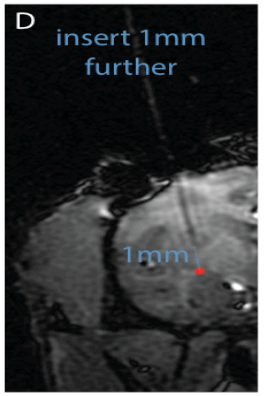
Navigus port placement



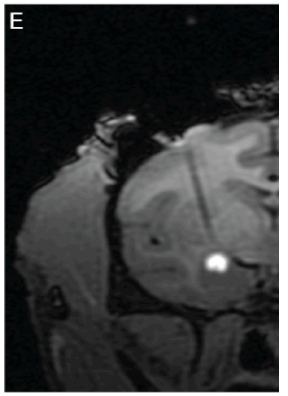
alignment guide & intraoperative trajectory planning



depth assessment



infusion monitoring

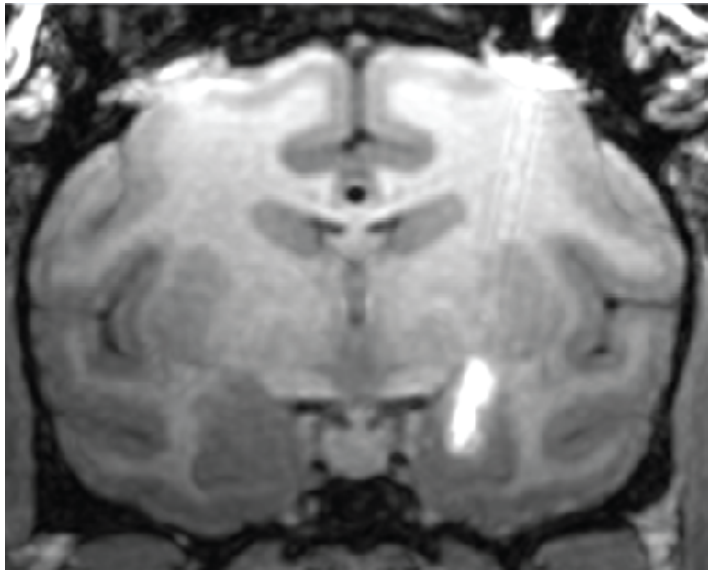


In Vivo PET Assessment of DREADDs: Clozapine Binding

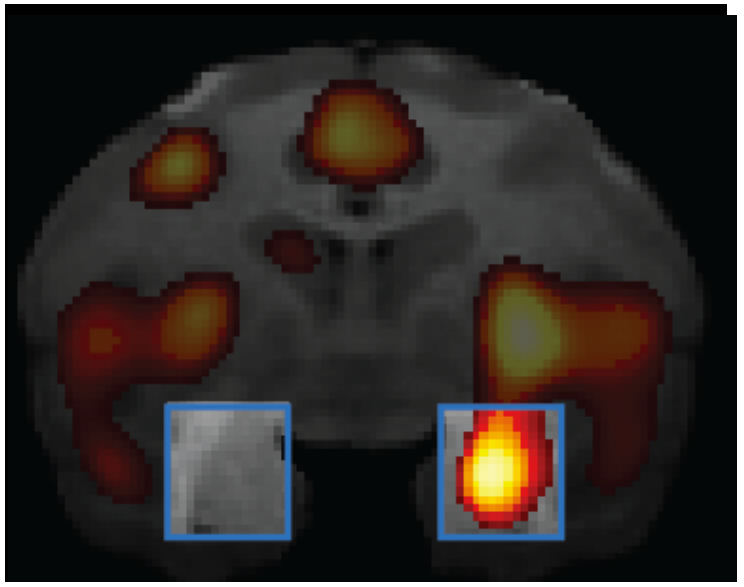
Right hemisphere injections: Amygdala (24 µL) and Putamen (24 µL)

AAV2/5-hSyn-hM4Di – 6.95 x 10^{13} gc/ml

iMRI

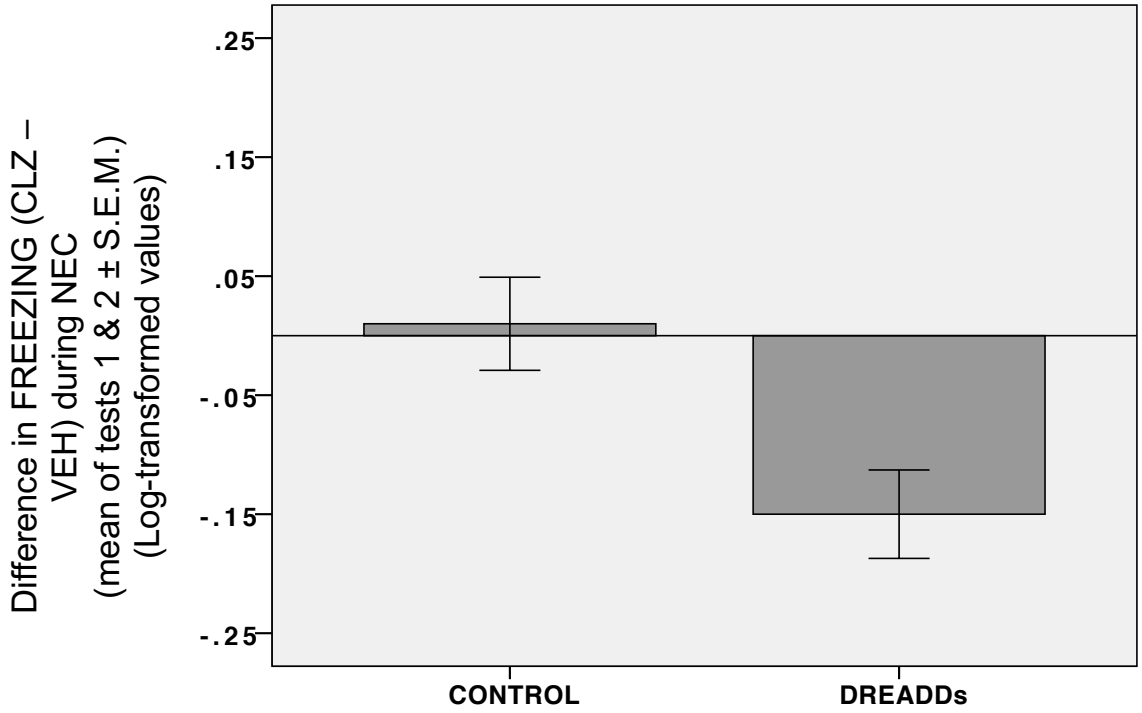


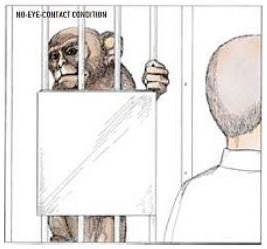
[^{11}C]clozapine PET



Subject 43

Effect of hM4Di DREADDs activation on Freezing during NEC condition





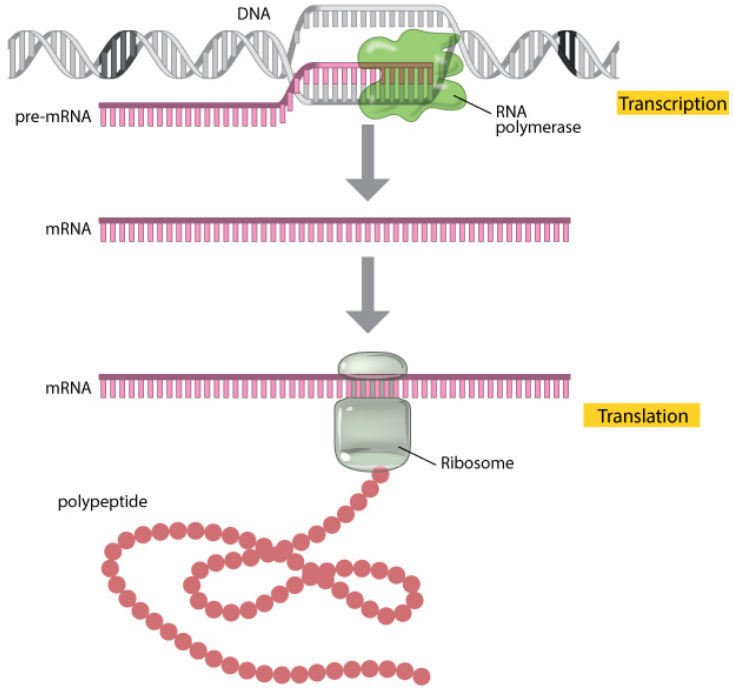
group T-test on difference score

$t_8 = 2.966$, ***p* = 0.018***

N = 10, 5 Control and 5 Experimental

Performing Post-Mortem Transcriptome Studies to Identify Novel Molecular Targets

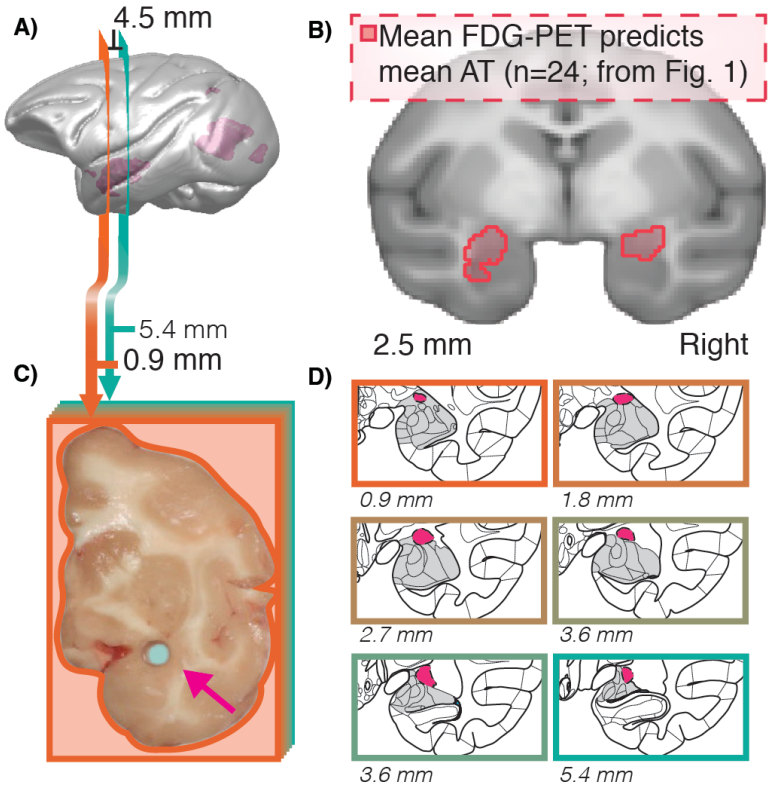
Assessing gene function measuring mRNA

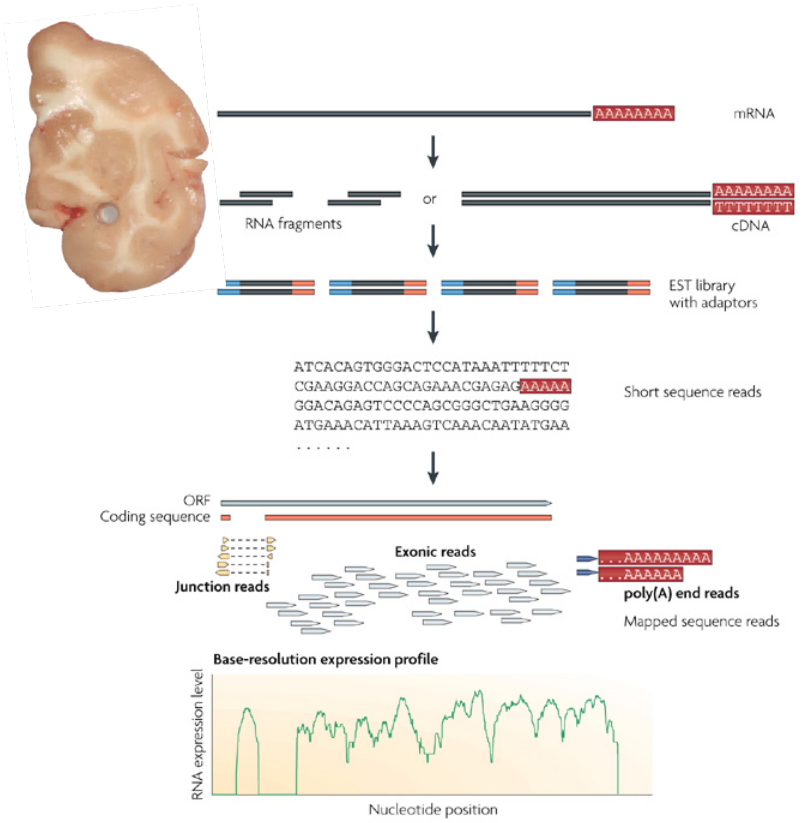


Why Study RNA?

- Reflection of the regulated step between DNA and protein
- Deficits in RNA expression and regulation is linked to numerous diseases

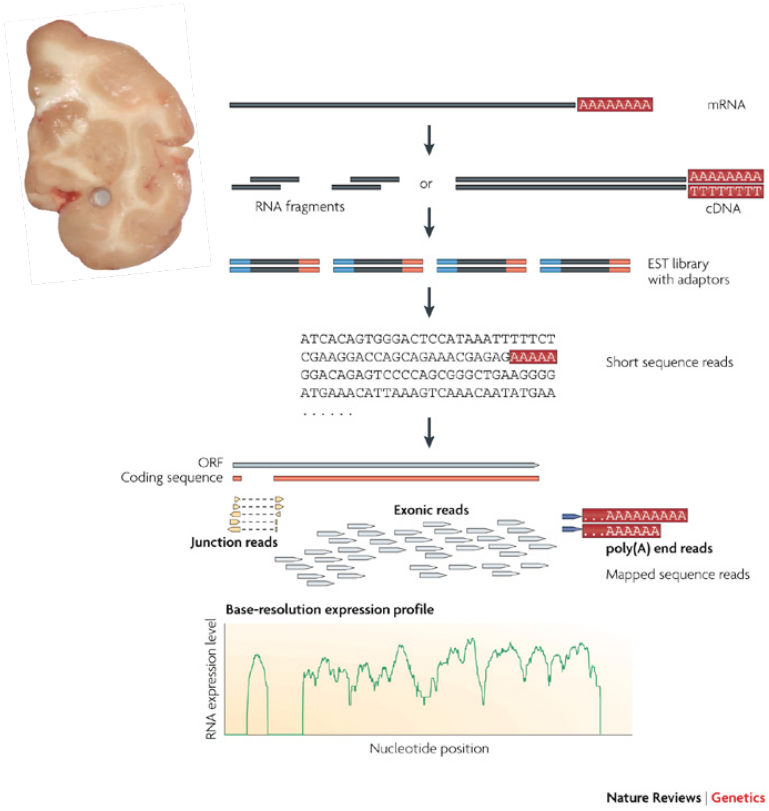
Identifying Alterations in Gene Expression Relevant to AT: At-Related Ce Gene Expression





Fox AS, et al. *Proc Natl Acad Sci U. S. A.* 2012;109(44):18108-18113.

RNA-seq in Ce in 46 Young Monkeys



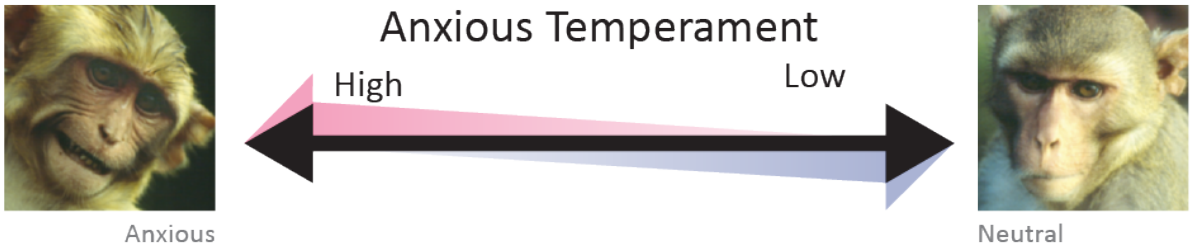
Tade Souaiaia

James Knowles

RNA-Seq was performed using NuGEN Ovation RNA-Seq v2 libaries on Illumina DNA sequencers with ~30 million 100bp reads per animal.

1. Fox AS, et al. *Proc Natl Acad Sci U. S. A.* 2012;109(44):18108-18113.; 2. FoxAS, Souaiaia T, et al. In prep.

Expression of Neuroplasticity-Related Genes in Ce is Negatively Associated with AT



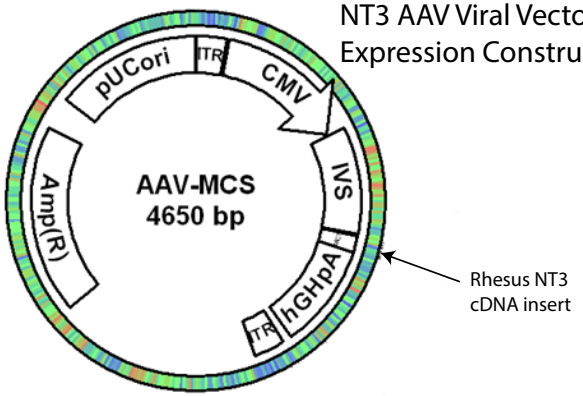
Decreased Neuroplasticity in AT-regions

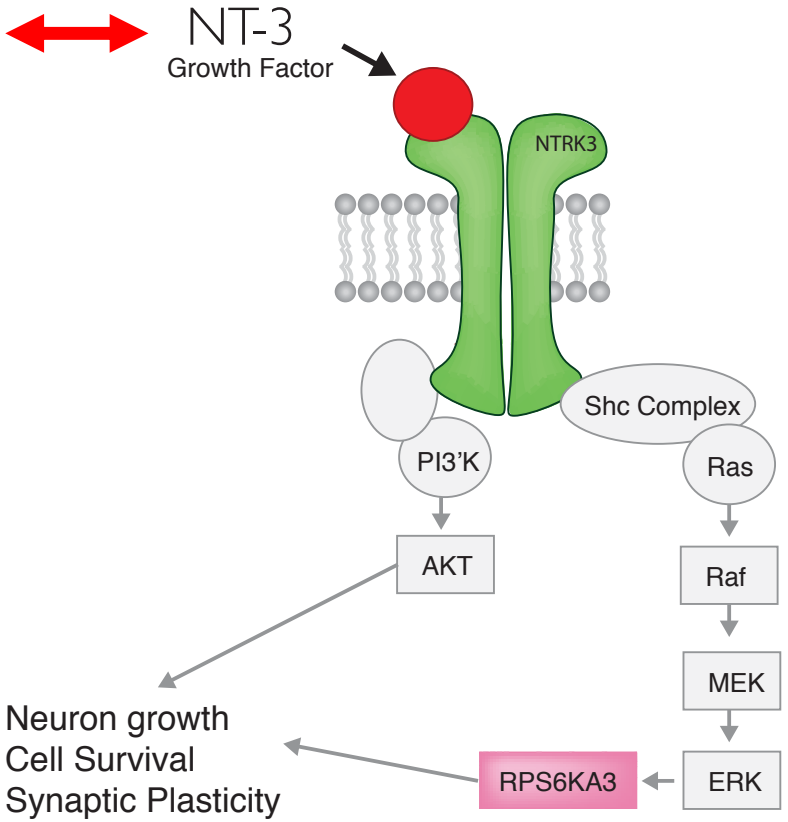
Increased Neuroplasticity in AT-regions

- 217 negatively associated with AT ($p<.05$)
  - Actin filament-based process (GO:0030029)
  - mRNA processing (GO:0006397)
  - Neurotrophin TRK receptor signaling pathway (GO:0048011)
  - Axon guidance (GO:0007411)

1. Fox AS, Souaiaia T, et al. Presented at Society of Biological Psychiatry, 70th Annual Meeting. May 14-16, 2015.; 2. Fox AS, et al. *Proc Natl Acad Sci U. S. A.* 2012;109(44):18108-18113.*; 3.* Fox AS, Kalin NH. *Am J Psychiatry.* 2014;171(11):1162-1173.

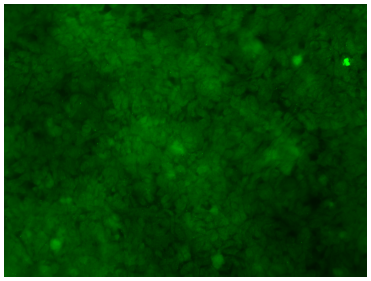
Testing the Neuroplasticity Hypothesis: AAV5 Virus to Overexpress NT-3



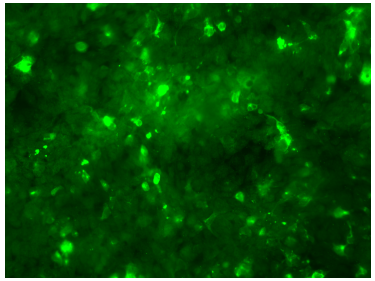


Kalin NH, et al. *Biol Psychiatry*. 2016;80(5):345-355.

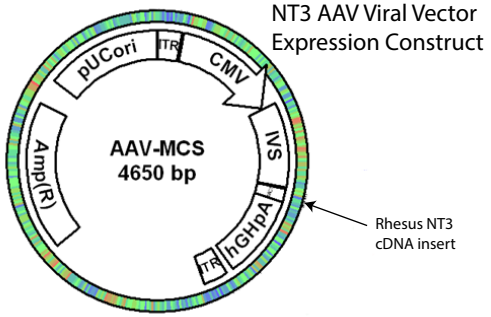
NT-3 Overexpression



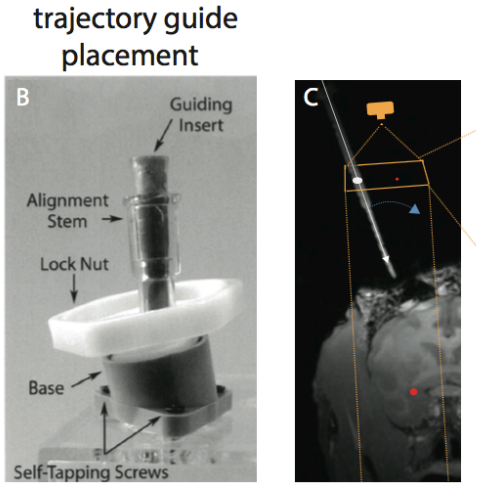
Control

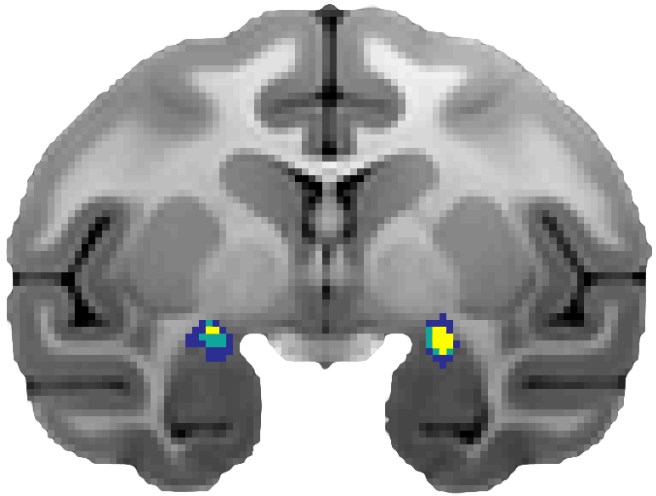


AAV5-NT3



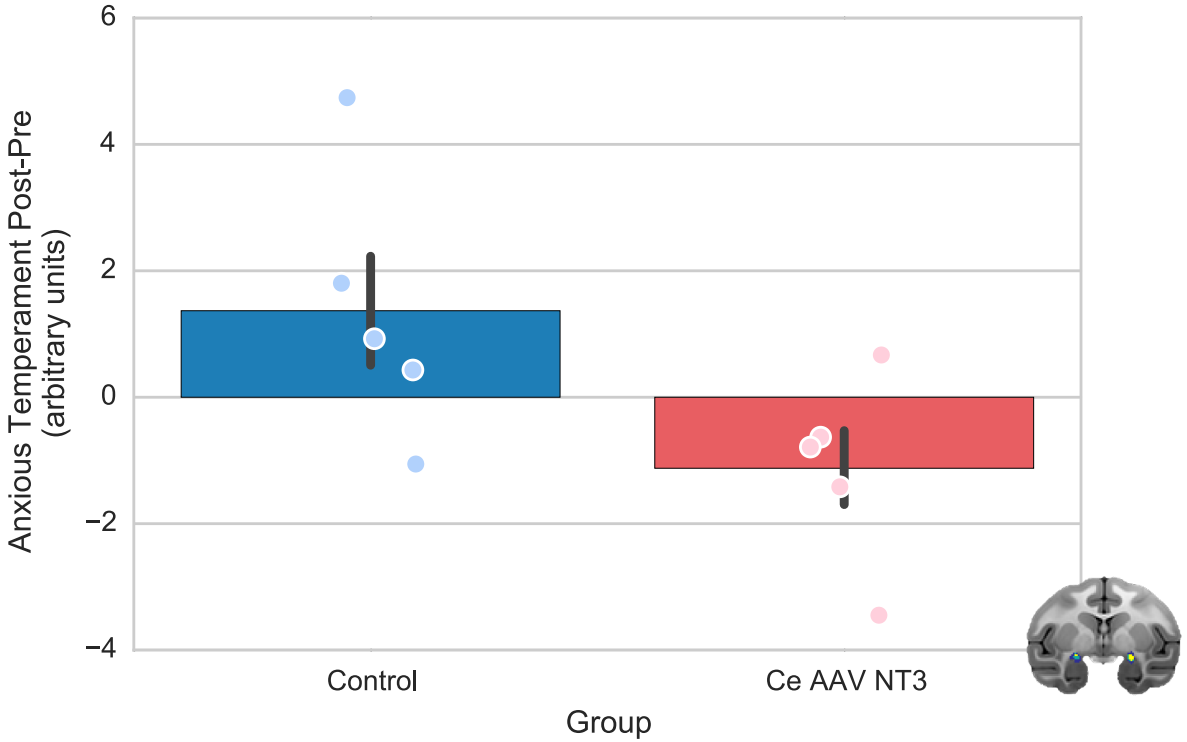
Infusion Overlap (n = 4/5)





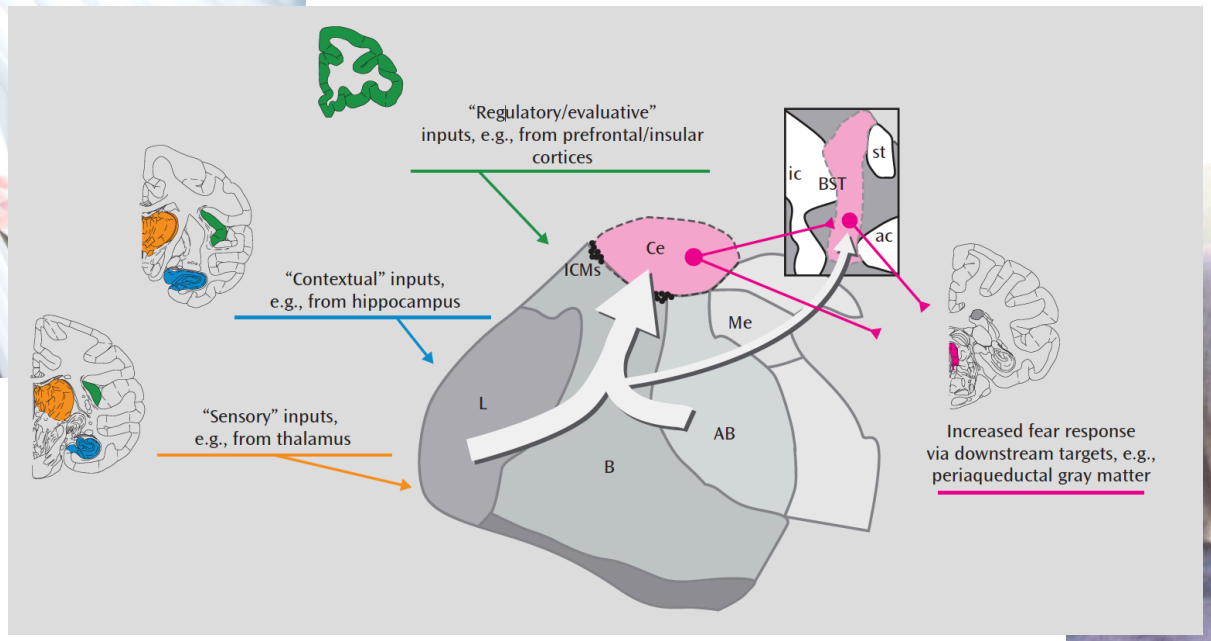
Kalin NH, et al. *Biol Psychiatry*. 2016;80(5):345-355.

Ce AVV5 NT3 Decreases AT



AT is significant p<.05 one-tailed significant, t=-2.515, p=0.066; t=-3.013, p=0.039, two-tailed paired t-test
Fox AS, et al. *Biol Psychiatry*. 2019;86(12):881-889.

Translational Studies to Yield Circuit Based Molecular Approaches to Develop New Treatments



Fox AS, Kalin NH. *Am J Psychiatry*. 2014;171(11):1162-1173.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- In treating stress-related psychopathology, it is critical to understand the early factors contributing to each individual's presentation
- Recognize that alterations underlying anxiety and depression involve prefrontal cortical-limbic circuits
- Early interventions have the potential to change the course of anxiety and depressive disorders

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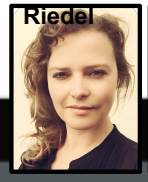
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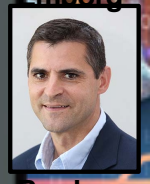
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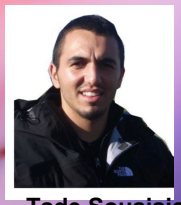
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Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.