Addictions are Consequences of Neurodevelopmental Disorders!

How should that change the way we treat persons with addictive disorders?

Dr. Vivek Benegal

Professor of Psychiatry

Centre for Addiction Medicine

Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India

MISSING LINK

Models of Addiction

Moral model
choice made by individuals with low moral standards

- Temperance-
- Prohibition –
- Punishment –
- War on drugs-
- Just say NO

Law & Order
Executive- Judiciary
Prisons – Incarc
Rehab

Medical model
consequence of physiological changes that drugs cause.

- **ncurable disease** with drug addiction as symptom c. Cancer (No guilt)
- Recovery can occur

e.g. Hazelden; AA-NA

Abstinence-based treatment

1. No cure -recovery through peer support and positive change
2. Begin by admitting disease makes him powerless over drugs/ alcohol
3. Personal change -recognizing denial / self-defeating behaviors and replacing with gratitude, honesty, forgiveness, humility
4. Spiritual awakening, faith in higher power, and faith in power of being part of a recovery community.
5. Continued abstinence; person fails if not adherent to precepts

Peers – Long term rehab → Boot camps

Learning model
Conditioned response to the environment - learned behaviour/ habit NOT illness:

- Drug use to cope with stressful environments
- Rewarding behaviour allowing temporary escape from painful reality.
- Drug dependence grows as individuals continue to use drugs to relieve emotional, psychological, or physical suffering.

Relearning skills – habits & cognitions

CBT
Relapse prevention
Motivation Enhancement Therapies

Long term rehab – OP practice

MISSING LINK

Addiction- common complex gene x environment mediated chronic brain disease

- Addiction is a brain disease that develops over time as a result of the initially voluntary behavior of using drugs or engaging in certain behaviors
- Some individuals due to pre-existing brain vulnerabilities are at greater risk
- Both the vulnerability state and the neuroadaptation due to drugs is strongly moderated by effect of environmental factors on gene expression

MISSING LINK

Why do humans use drugs?

- All Drugs of abuse exert initial reinforcing effects by increasing neurotransmitter dopamine [DA]- in Reward circuits in the brain
- Drugs activate same brain areas activated by natural rewards, only more strongly
- *People with lower pre-existing DA activity in reward circuit find DA raising drugs pleasant while those with higher levels find them unpleasant.*
- People with Low DA function →Low hedonic tone (ability to feel pleasure); Low boredom threshold; poor ability to sustain motivation; High novelty seeking
- DA increases - linked to subjective experience of euphoria (or high) during intoxication.

Volkow et al (2010) Bioessays; 32(9): 748–755

MISSING LINK

Drugs initially improve cognitive control in vulnerable individuals

- Dopamine enhancing drugs are also well known to enhance cognitive control.
- Cognitive control helps us attain our goals by resisting distraction and temptations.
- Failures of cognitive control and focus common, in neuropsychiatric disorders - Attention-deficit disorder (ADHD)and addiction but also in healthy states such as fatigue or stress.
- Positive reinforcement encourages regular use (self-medication)

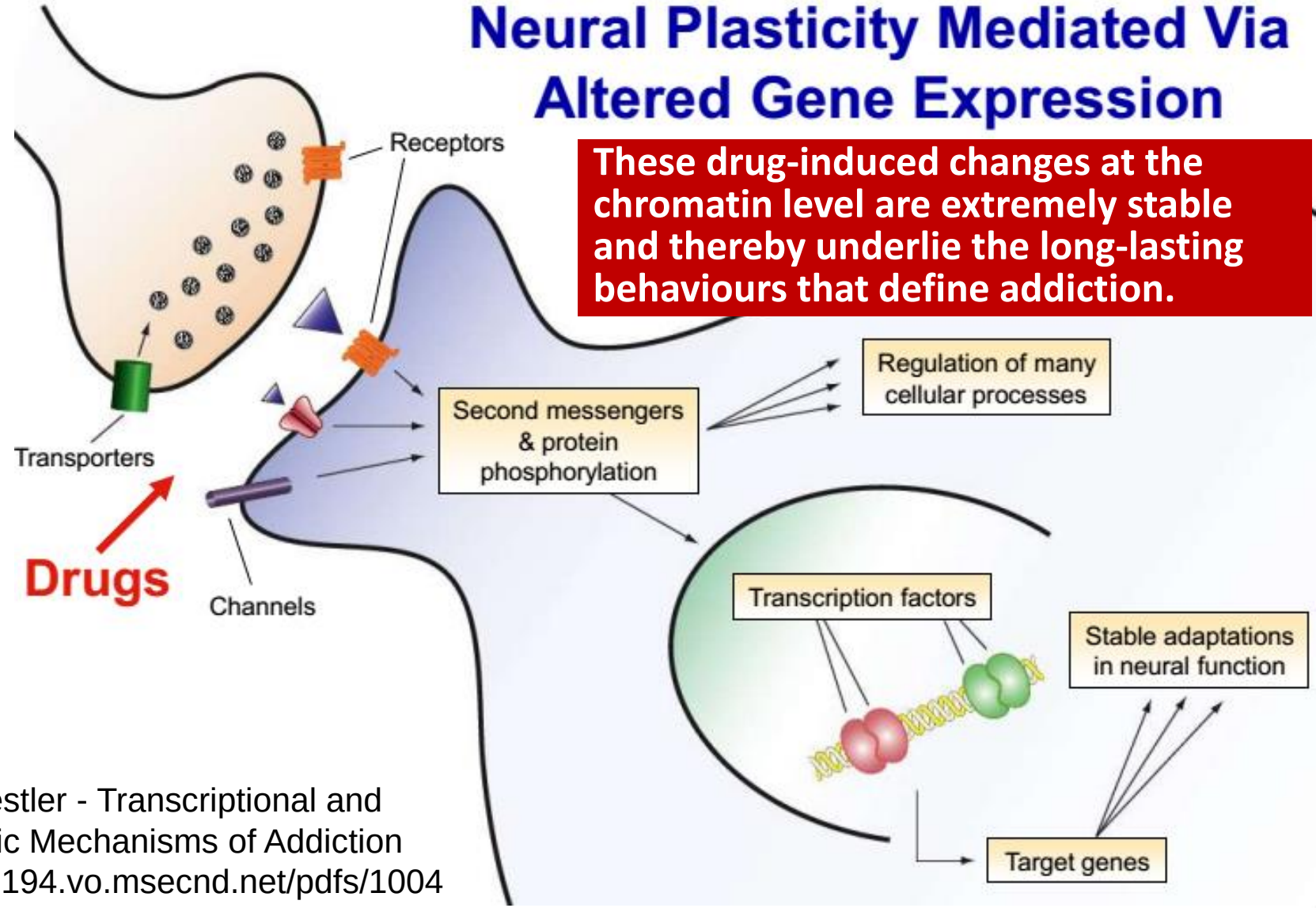
Cools (2016) *The costs and benefits of brain dopamine for cognitive control. Wiley Interdisciplinary Reviews: Cognitive Science, 7(5), 317–329*

Repeated exposure leads to long-lasting neuro-plastic changes

- Drugs modify expression of genes, by switching on/off specific genes, causing long-lasting changes in brain circuits and functions.
- Continued drug use impairs brain function by
  - interfering with the capacity to exert self-control over drug-taking [loss of control] and
  - making the brain more sensitive to stress and negative moods.

Drugs Addiction: Drug-Induced Neural Plasticity Mediated Via Altered Gene Expression

These drug-induced changes at the chromatin level are extremely stable and thereby underlie the long-lasting behaviours that define addiction.



From: Nestler - Transcriptional and Epigenetic Mechanisms of Addiction
http://az9194.vo.msecnd.net/pdfs/100401/EB10L5.pdf

MISSING LINK

Brains of drug users progressed to addiction differ markedly from early or casual users

- Drug abuse alters brain **default-mode network (**DMN) connectivity affecting cognitive - emotional processing.
- Functional connectivity (RSFC) of the anterior DMN, which participates in attribution of personal value and emotional regulation, is decreased
  - Contributes to impaired self-awareness, negative emotions and to ruminations in addiction.
- RSFC of the posterior DMN, which directs attention to the internal world, tends to be increased.
  - disrupted connectivity with cortical regions involved with executive function, memory and emotion could be critical to drug-taking regardless of negative consequences and to stress-triggered relapse

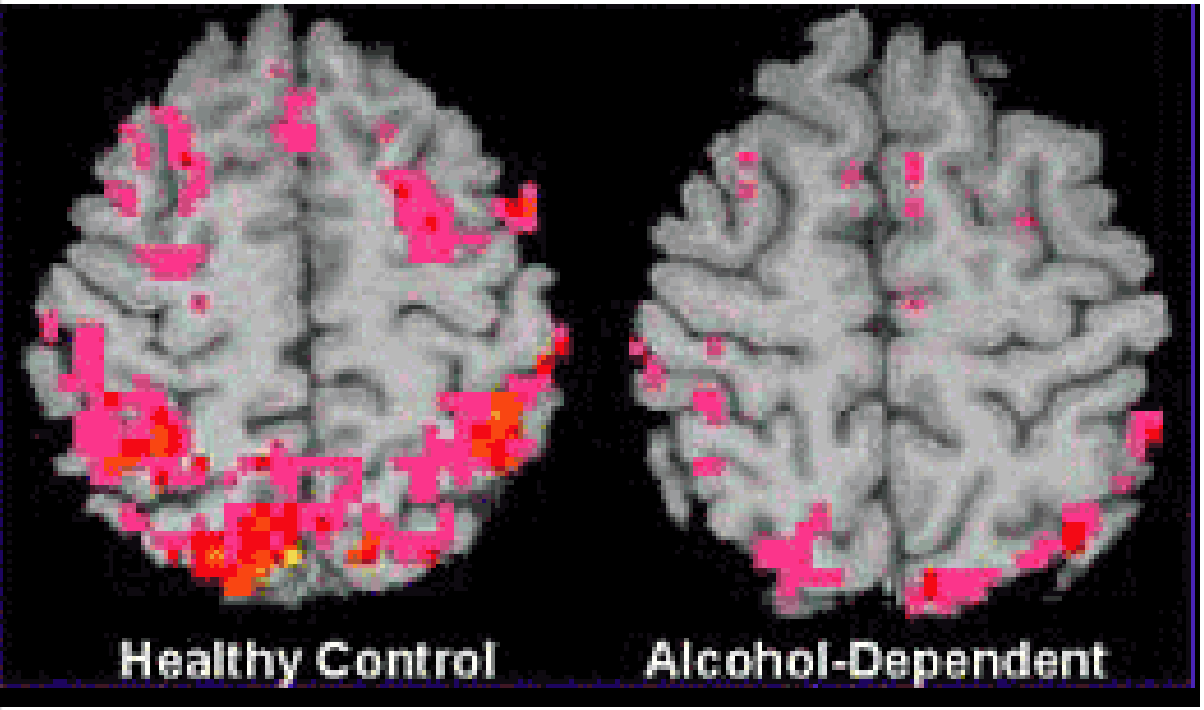
Zhang & Volkow (2019) Brain default-mode network dysfunction in addiction. NeuroImage.

Brains of drug users progressed to addiction differ markedly from early or casual users

- Resting state connectivity best predicts alcohol use severity in moderate to heavy alcohol users
- Network connectivity features between salience network, default mode network, executive control network, and sensory networks explained 33% of the variance associated with AUDIT (machine learning model)

Fede et al (2019). *Resting state connectivity best predicts alcohol use severity in moderate to heavy alcohol users. NeuroImage*

Earlier the onset of use- greater the neuroadaptation
Early drinking →Freezes brain -prolonged neuroadaptations



In young, a dose of alcohol changes activity of neurons in hippocampus, (memory and learning).

Same dose had little or no effect in adult !!

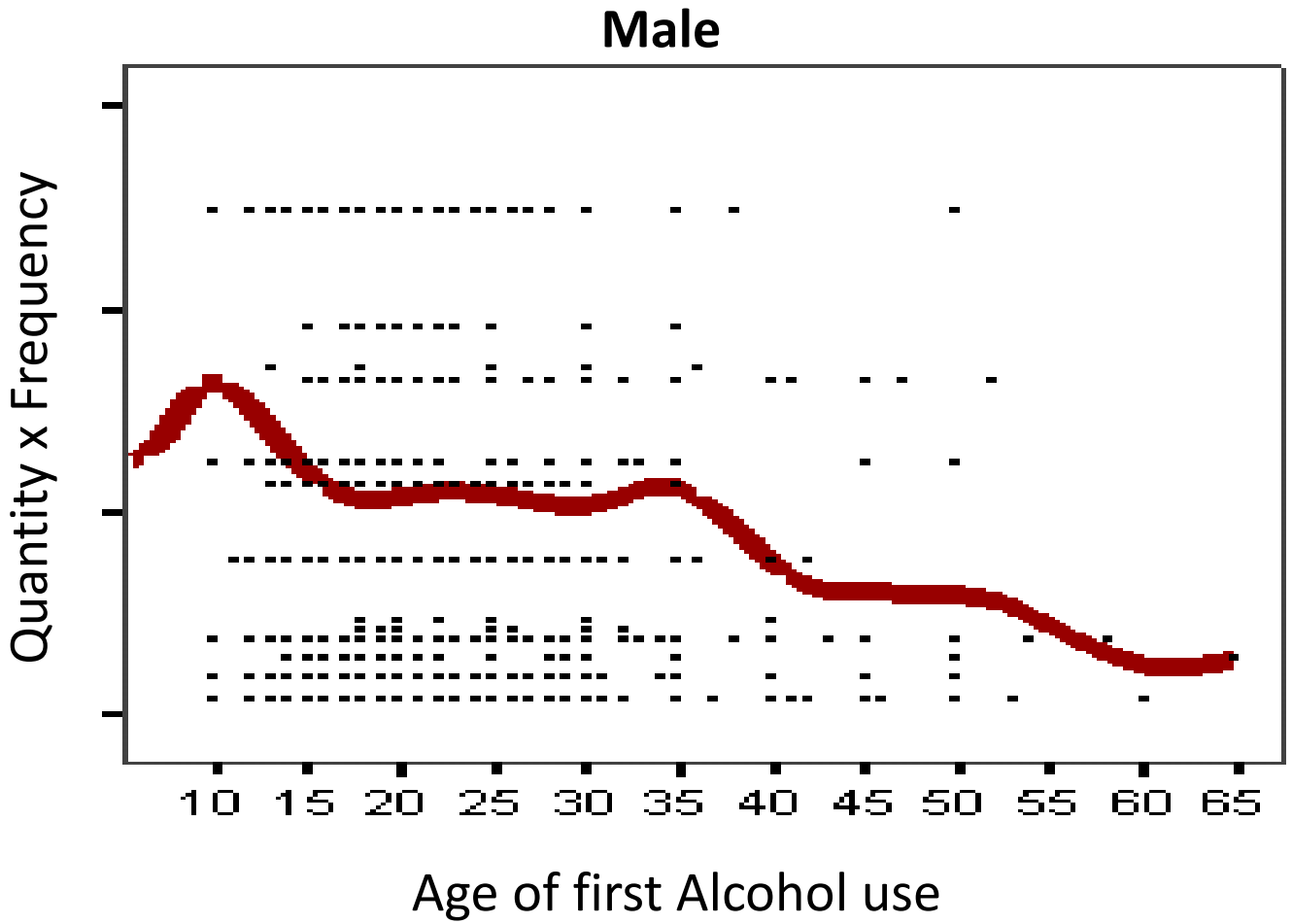
Tapert et al, 2005

MISSING LINK

Who is at risk?

- Drug use starts off as voluntary acts..some at greater risk of early experimentation!
- Some Individuals at greater risk of transitioning into the automatic and compulsive behaviors that characterize addiction
- Not all persons who use substances are at same risk
- Across multiple birth cohort, longitudinal, and nationally representative studies, we continually see a relatively small subset of individuals (~3-8%) account for most of the problem behavior

Current drinking severity predicted by age at onset
(Andaman & Nicobar 2008)

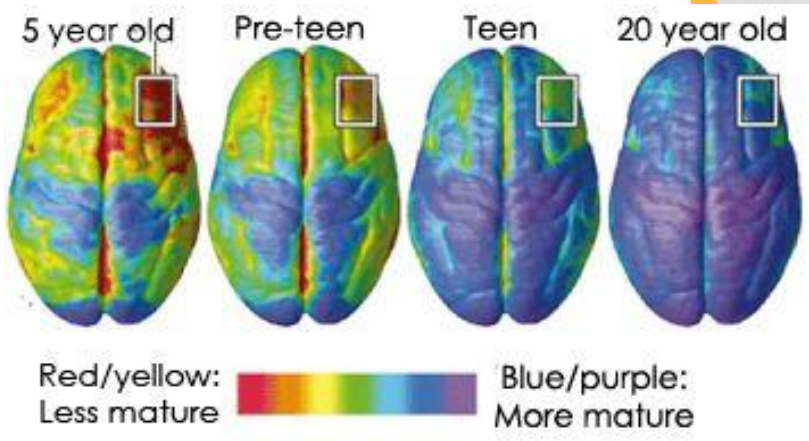


Benegal et al, 2009

SOURCE: 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions

The adolescent brain is "deliberately" set up for risk-taking

- Prefrontal cortex —involved in "executive functions" that support careful decision-making (self-monitoring and impulse control) —not fully developed until mid-20s, long after maturation of emotional processing and reward-seeking centers in limbic system.



- Teens seek out highly stimulating and rewarding activities while seeming less wary of potential risks.
- These make adolescents excellent learners, BUT also vulnerable, particularly when it comes to substance use.

Which adolescents are at greater risk? Dispositional liability to SUDS

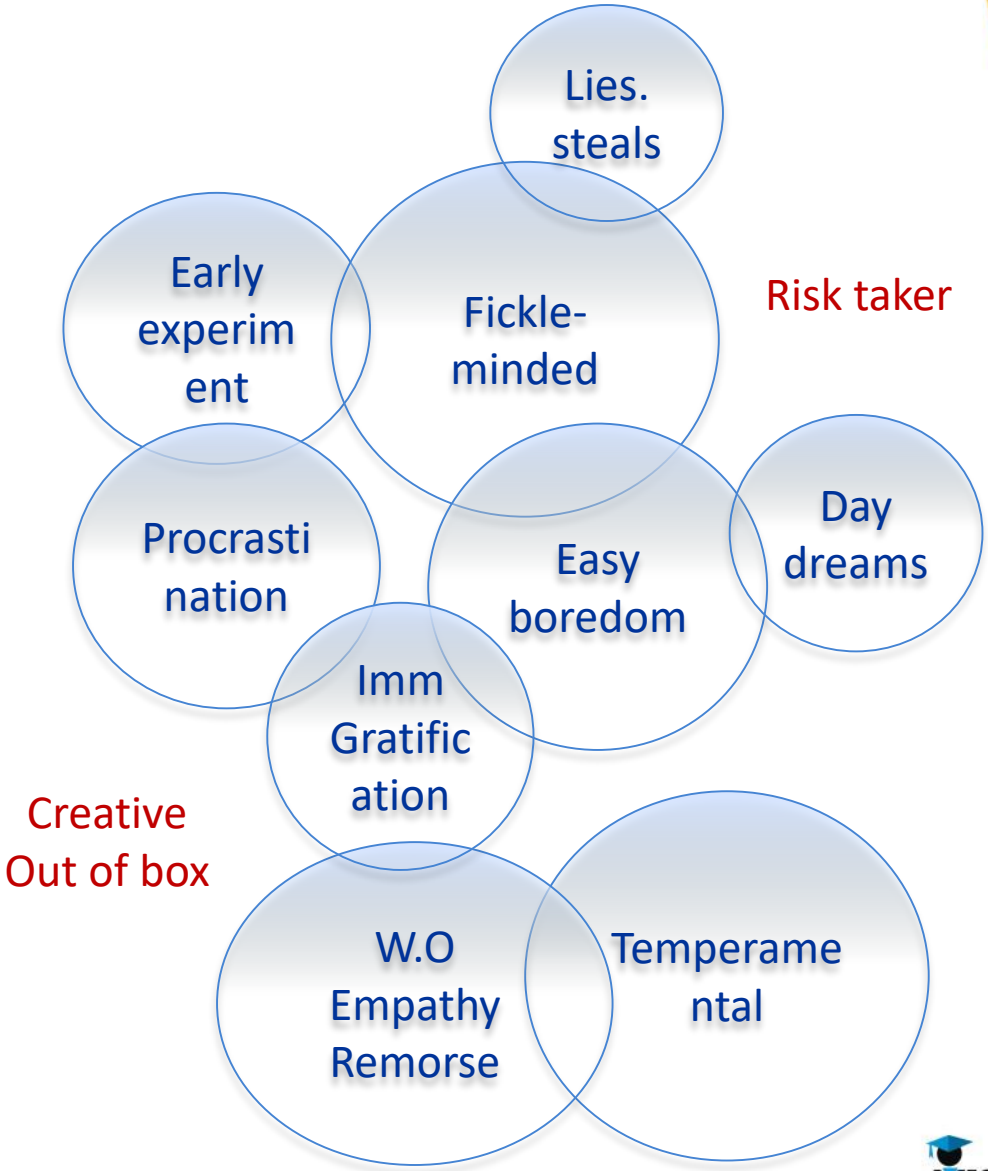
- Broad disposition / liability: impairment in capacity for inhibitory control ("disinhibition") ..contributes to other externalizing problems, incl. childhood disruptive disorders (CD, ODD, ADHD and adult ASPD) and SUDS...which typically occur together
- Highly heritable vulnerability confers broad risk for externalizing problems.
- Disinhibitory liability also contributes to occurrence of certain internalizing problems (anhedonia, dysphoria and distress)

Which adolescents are at greater risk?

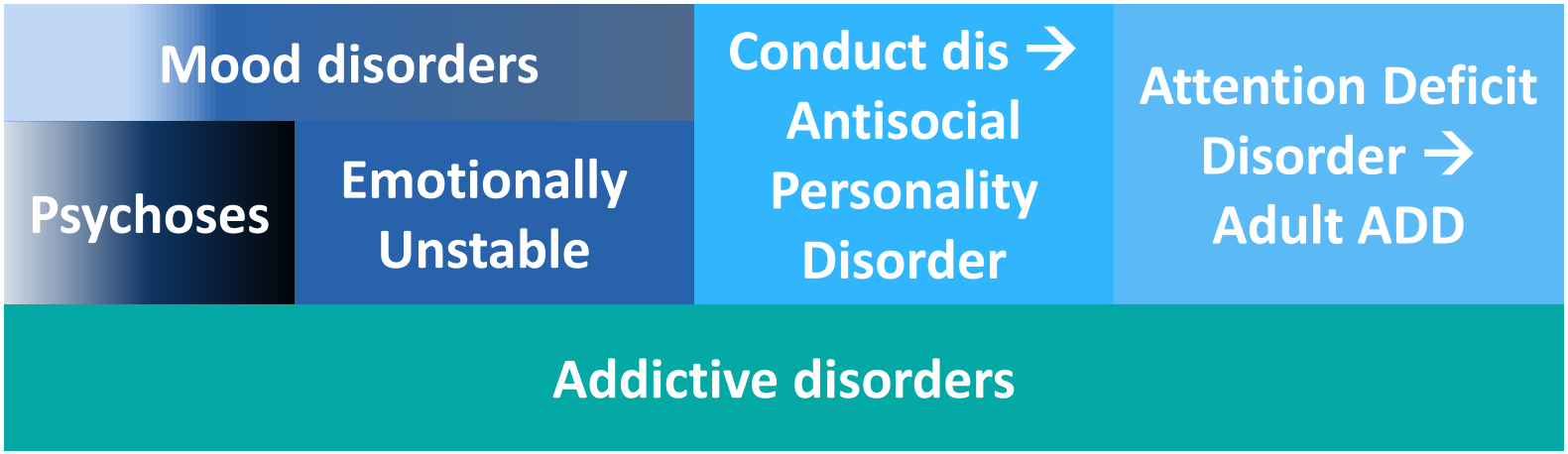
COGNITIVE (Exec) CONTROL
greater Impulsivity
Sustaining Motivational Attn
Reward deficit; Easily Bored
Mind-wandering
Hyper-attending
Hyperactive fidgety

EMOTIONAL REACTIVITY
Poor emo/anger/ control

EMOTIONAL RECOGNITION
ToM -Empathy



Externalizing disorders



Depression & Anxiety Disorders

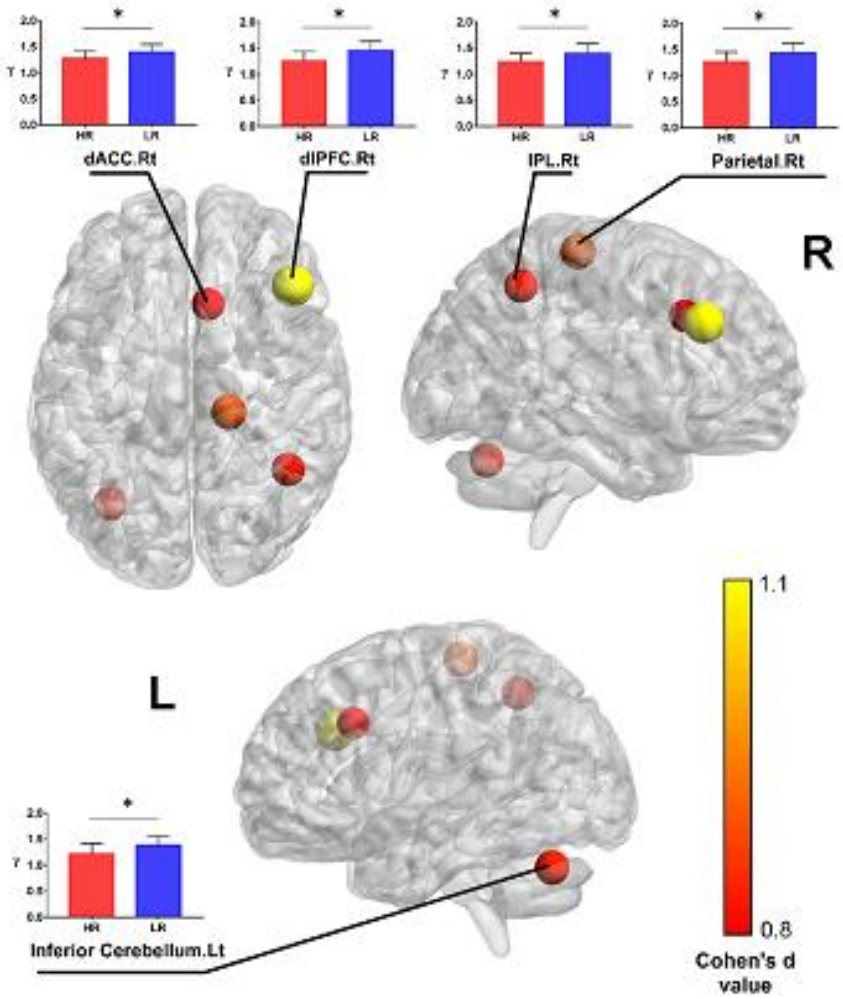
Internalizing disorders

- How Exposure to Environmental Adversities
- Modifies Our Genetic Programming
- To Influence growth of Psychological abilities underlying Vulnerability

WHAT CAUSES THIS VULNERABILITY STATE?

Hi-risk Adol have deficits in functional BR connectivities

CONNECTIVITY



Fronto-parietal, Cingulo-opercular, Sensorimotor and Cerebellar networks exhibited significantly reduced functional segregation.

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

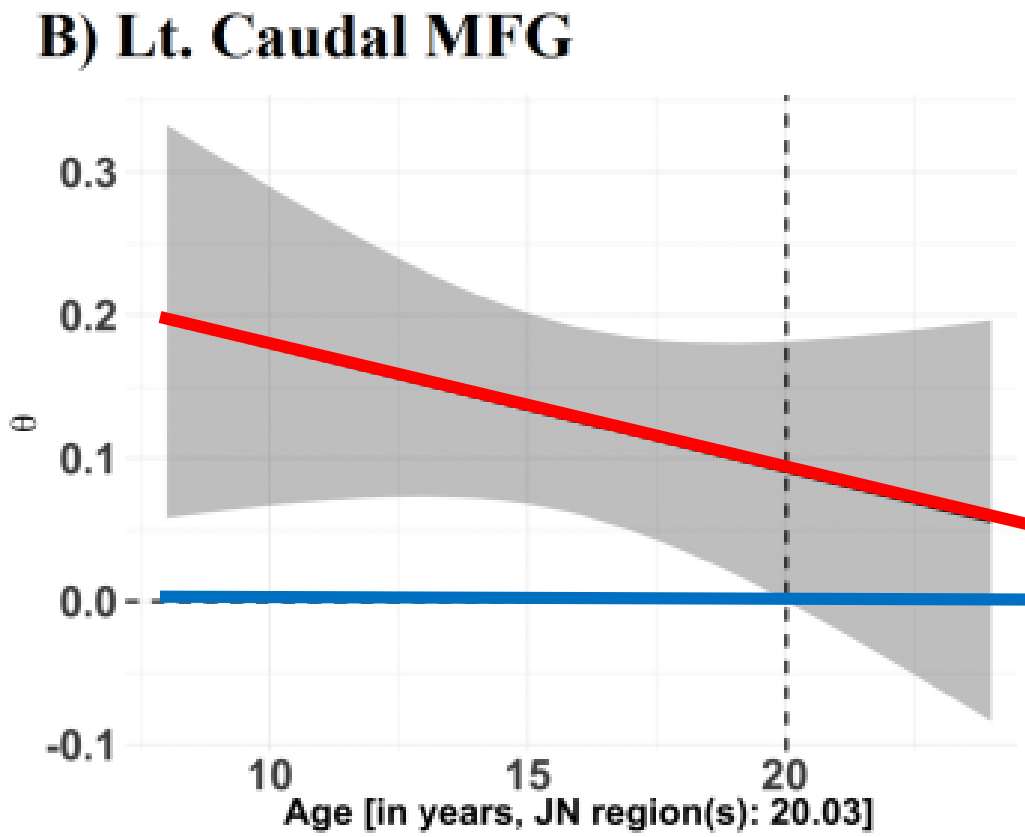
Disrupted resting brain graph measures in individuals at high risk for alcoholism

Bharath Holla[a], Rajanikant Panda[b], Ganesan Venkatasubramanian[c], Bharat Biswal[d], Rose Dawn Bharath[b,*], Vivek Benegal[a,**]

Addiction Biology
ORIGINAL ARTICLE
doi:10.1111/adb.12662

Altered brain cortical maturation is found in adolescents with a family history of alcoholism

Bharath Holla[1], Rose Dawn Bharath[2], Ganesan Venkatasubramanian[3] & Vivek Benegal[1]



Hi Risk (FHP) adolescents show delayed brain maturation

(age related reduction in brain grey matter thickness) in multiple brain areas: precentral & frontal, temporo-parietal junction, inferior-frontal & inferior-temporal gyrus.

Differences diminished with age by young adulthood.

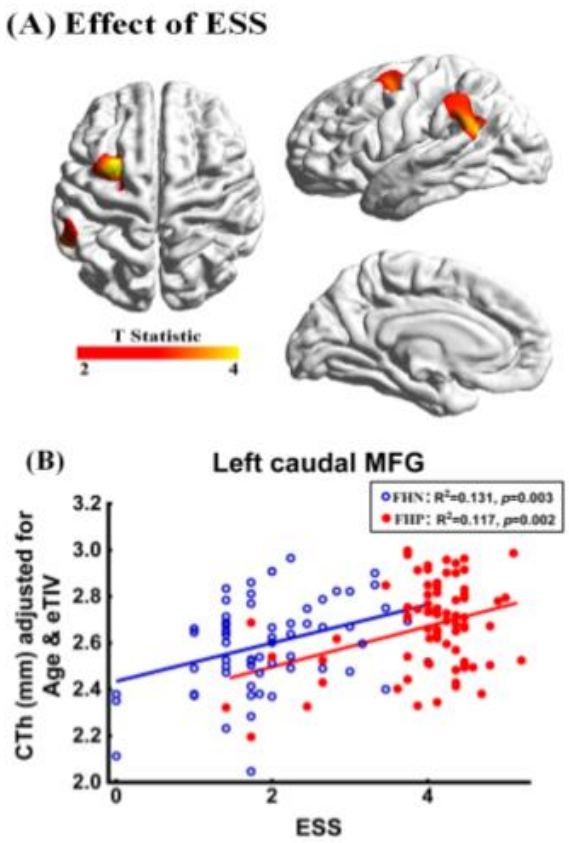
Highlight the crucial role for interventions that target delay in initiation of alcohol use during adolescence in high-risk vulnerable populations.

MISSING LINK

Addiction Biology

Delayed Brain maturation Predicts Higher Externalizing symptoms

In Adolescents with Family History Of Alcoholism"



Thicker cortices associated with greater Externalizing Symptom Scores.

- Familial AUD risk is associated with age-related differences in maturation of several higher order association cortices – which are critical to ongoing development in executive function, emotion regulation and social cognition during adolescence.

Holla et al (2018) Altered Brain Cortical Maturation Is Found In Adolescents With A Family History Of Alcoholism. Addiction Biology

MISSING LINK

Most influential predictors of externalizing behaviors in adolescence

- Parenting
  - Involvement, inconsistent disciplining, and poor monitoring
- Attachment
  - Anger, distress, availability and partnership
- School climate
  - Safety and order
- Physical environment exposures
  - Neighborhood/living characteristics in terms of
    - Water (availability and hygiene)
    - Sanitation
    - Ventilation
    - Toxic exposures (fuel, tobacco smoke, traffic smoke)
    - Electromagnetic exposure
    - Pesticide exposure
    - Noise

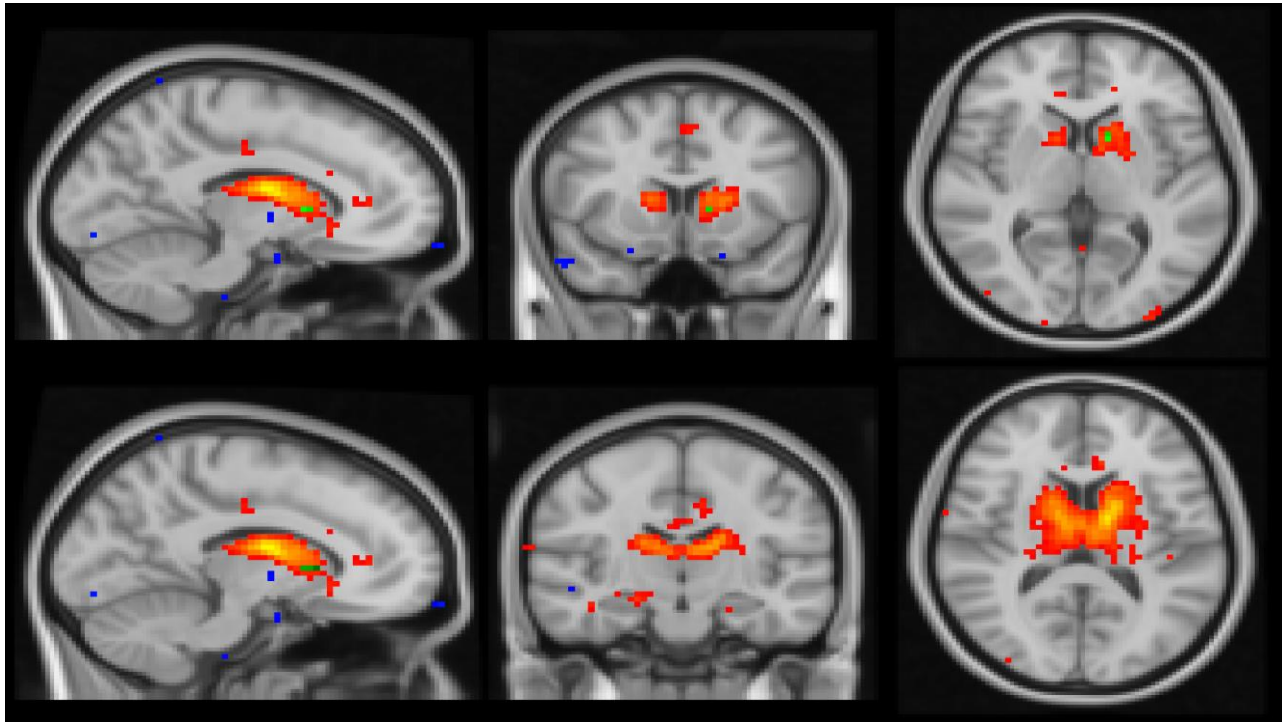
Combination of physical and psycho-social environmental (parenting, school climate, adverse experiences) used to generate a model for problem behavior scores in 5000 adolescents, using machine learning methods at 75% accuracy

MISSING LINK

Low Birth Weight Affects Brain Development (functional connectivity) and Down stream Vulnerability to Mental Illness

Adolescents & young adults with h/o LBW vs Normal Birth Weight had **lower functional connectivity (rsfMRI) in the thalamo-caudate network**

LBW



NormBW

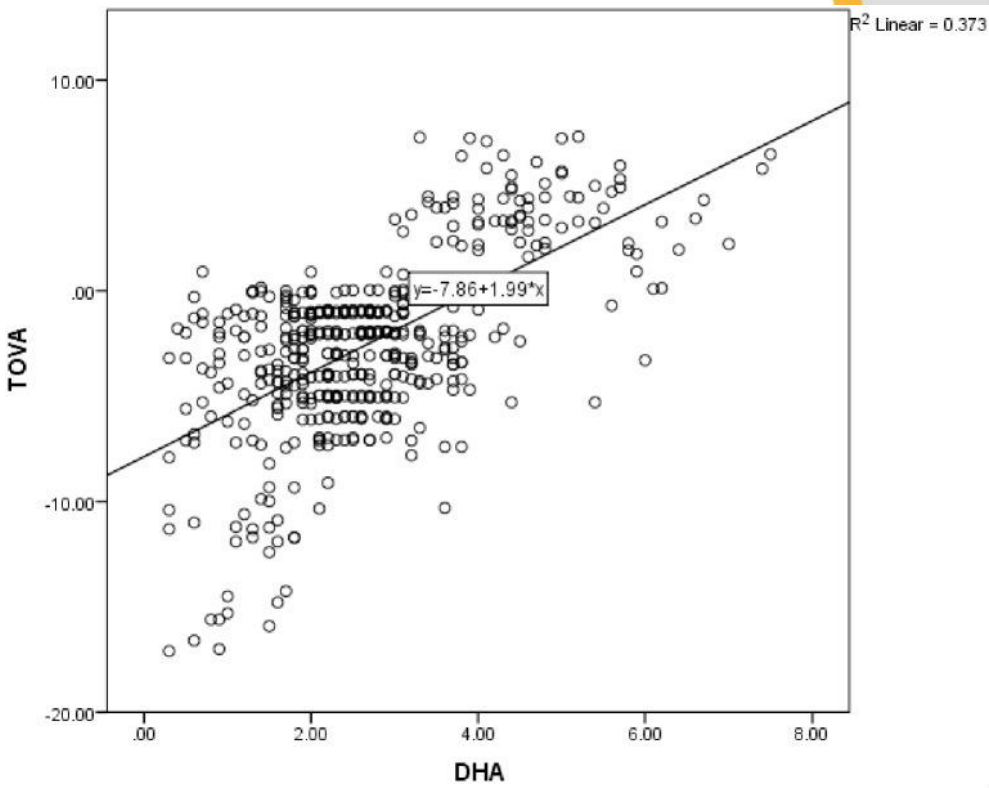
Bharath et al. In prep

Network activity correlates with with emotional recognition task.

In LBW –reduced emotional recognition (empathy): Anger (AN), Disgust (DI), Happiness (HA)

Nutritional deficiency (PUFA) and dev illnesses

- Children with ADHD and ASD have lower n-3 PUFA levels compared with controls
- ω-3 PUFAs supplementation useful in three major neuropsychiatric disorders: psychosis, ASD, and ADHD

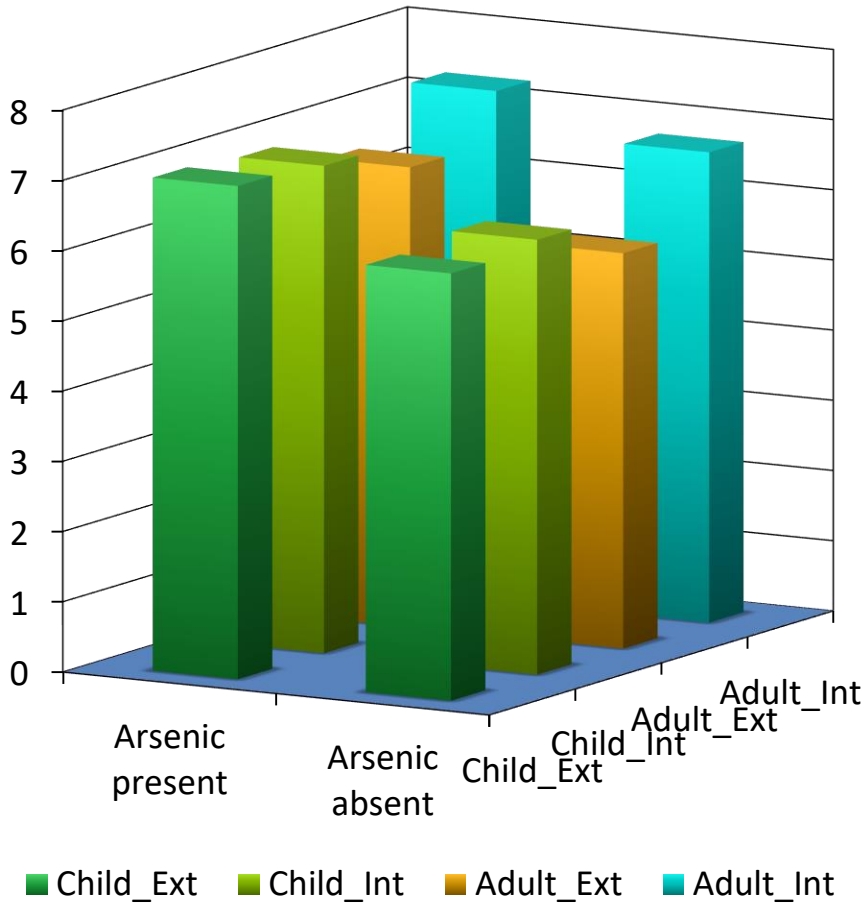


1] Parletta et al (2016) Omega-3 and Omega-6 Polyunsaturated Fatty Acid Levels and Correlations with Symptoms in Children with Attention Deficit Hyperactivity Disorder, Autistic Spectrum Disorder and Typically Developing Controls. *PloS one*

2] Agostoni et al (2017) The Role of Omega-3 Fatty Acids in Developmental Psychopathology: A Systematic Review on Early Psychosis, Autism, and ADHD. *International journal of molecular sciences*

MISSING LINK

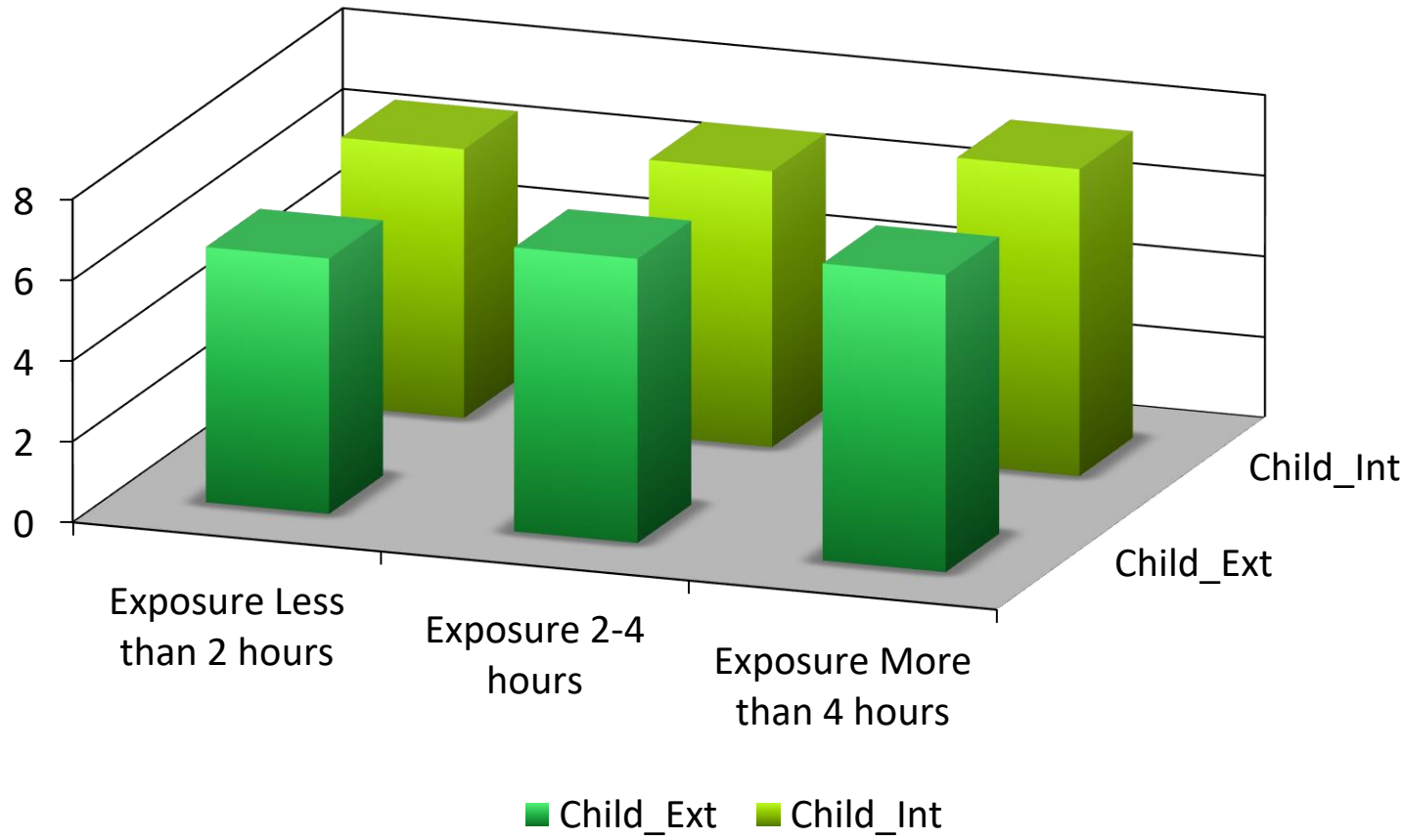
Arsenic contamination in drinking water – associated with problem behaviors in children and adults



	Arsenic contamination present	Arsenic contamination absent	F	Sig
SDQ Parent EXT	396	1477		
	6.14 (3.576)	6.07 (3.733)	0.091	0.7630
SDQ Parent INT	396	1477		
	5.41 (3.646)	5.14 (3.353)	1.939	0.164
SDQ Child EXT	231	958		
	7.02 (3.156)	6.08 (3.444)	14.216	0.0000
SDQ Child INT	231	958		
	6.94 (3.101)	6.19 (3.558)	8.723	0.0030
SDQ Adult EXT	99	987		
	6.55 (3.176)	5.63 (3.339)	6.852	0.0090
SDQ Adult INT	99	987		
	7.27 (3.298)	6.7 (3.889)	1.98	0.1600

Vaidya et al (unpub) cVEDA Study

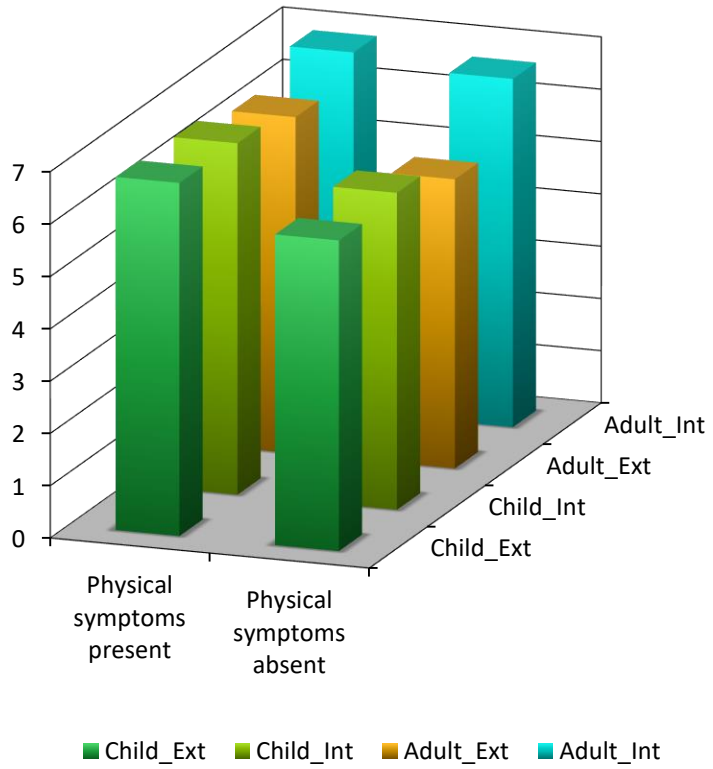
Exposure to coal/coke/firewood smoke incrementally associated with behavior problem scores in children and adolescents



Vaidya et al (unpub) cVEDA Study

MISSING LINK

Physical symptoms associated from exposure to traffic smoke associated with problem behavior scores in children and adults



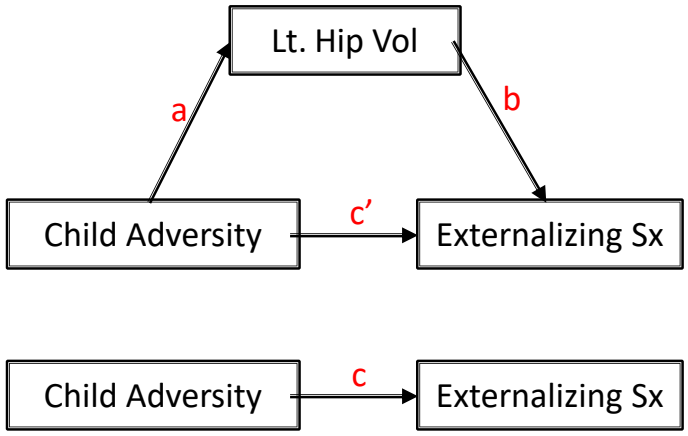
	Physical symptoms from exposure to traffic exhaust smoke	N	Mean	Std. Deviation	t	Sig
SDQ Parent EXT	Yes	1182	6.25	3.794		
	No	2055	6.29	3.738	-0.246	0.8060
SDQ Parent INT	Yes	1182	5.57	3.651		
	No	2055	5.24	3.424	2.482	0.0130
SDQ Child EXT	Yes	683	6.75	3.394		
	No	1127	5.94	3.415	4.866	0.0000
SDQ Child INT	Yes	683	6.72	3.292		
	No	1127	6.06	3.622	3.995	0.0000
SDQ Adult EXT	Yes	431	6.43	3.368		
	No	996	5.53	3.418	4.6	0.0000
SDQ Adult INT	Yes	432	6.88	3.717		
	No	991	6.66	3.887	0.992	0.3210

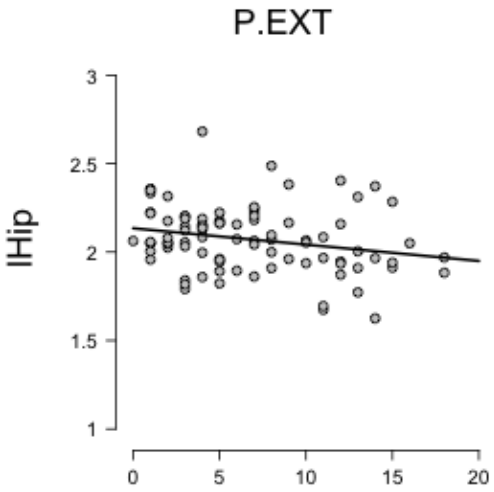
Exposure to air pollutants during pregnancy contribute to childhood abnormalities in brain

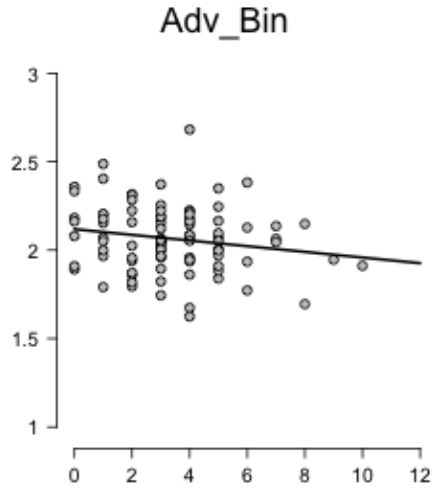
- Prenatal exposure to polycyclic aromatic hydrocarbons (PAH)
- Children assessed at 3-7 yrs
- Exposure associated with:
  - ADHD and other cognitive -behavioural problems incl. reduced IQ, anxiety and depression
  - Reduced white matter maturity in the brain
- Growing body of literature on air pollution and associations with ASD, schizophrenia and cognitive impairment.

Peterson et al. (2015) *JAMA Psychiatry.*

Environmental exposures mediate psychopathology through variations in brain development







Total effect (c) of X on Y

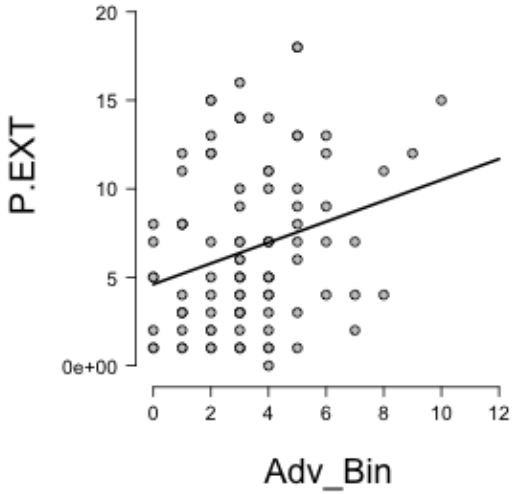
Effect	SE	t	p	LLCI	ULCI
.5523	.2245	2.4607	.0158	.1062	.9985

Direct effect (c') of X on Y

Effect	SE	t	p	LLCI	ULCI
.4114	.2207	1.8641	.0657	-.0273	.8500

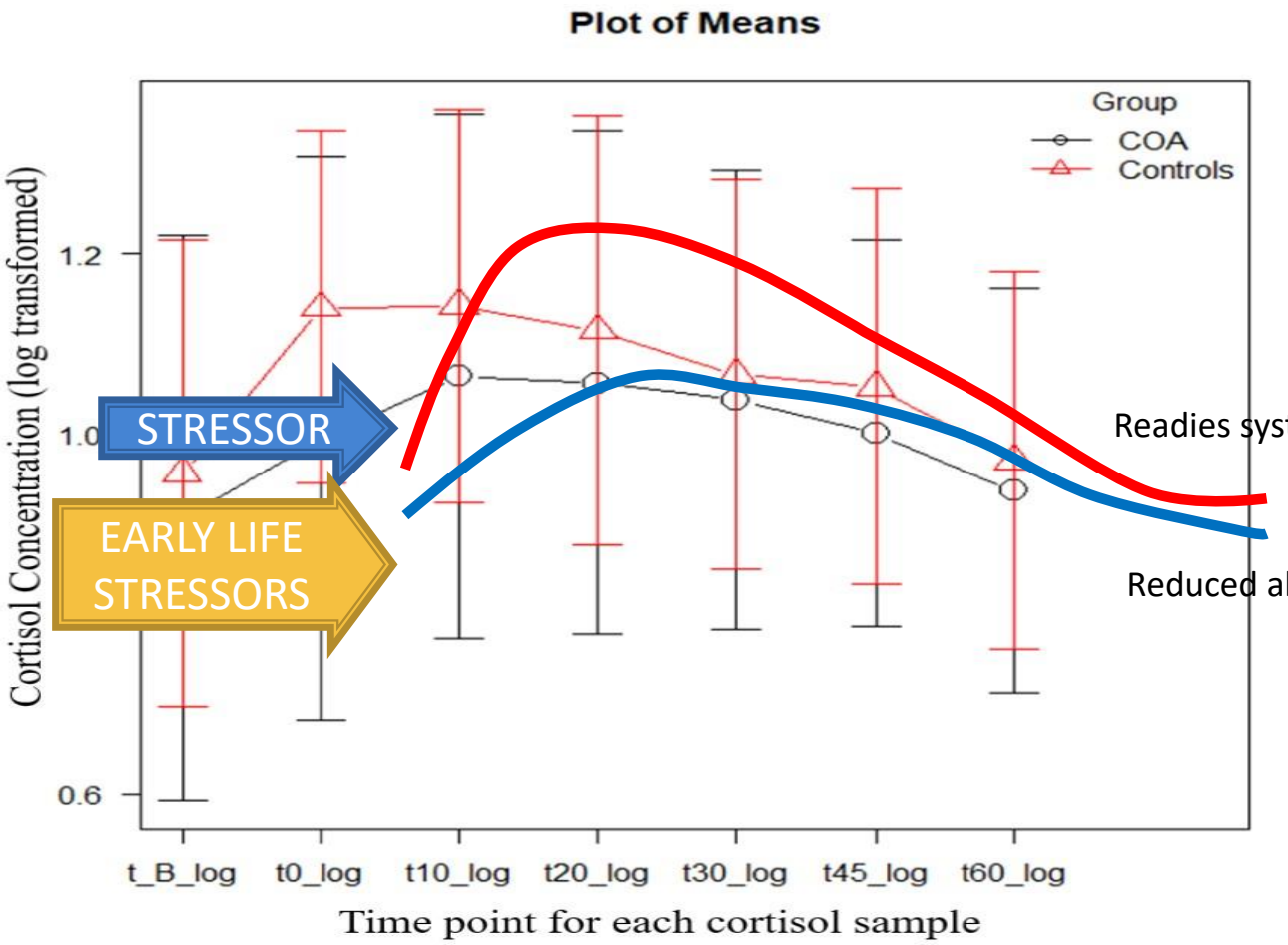
Indirect effect (a*b) of X on Y

	Effect	Boot SE	Boot LLCI	Boot ULCI
lHip	.1410	.0812	.0190	.3525



MISSING LINK

Blunting of cortisol response to social stress



STRESSOR

EARLY LIFE STRESSORS

Readies system to handle threat

Reduced ability to handle env demands

- Greater blunting in children of alcoholics - who have greater early life stress
- Greater blunting predicts EXT behaviors which underlie risk of suds

Timothy et al, 2019

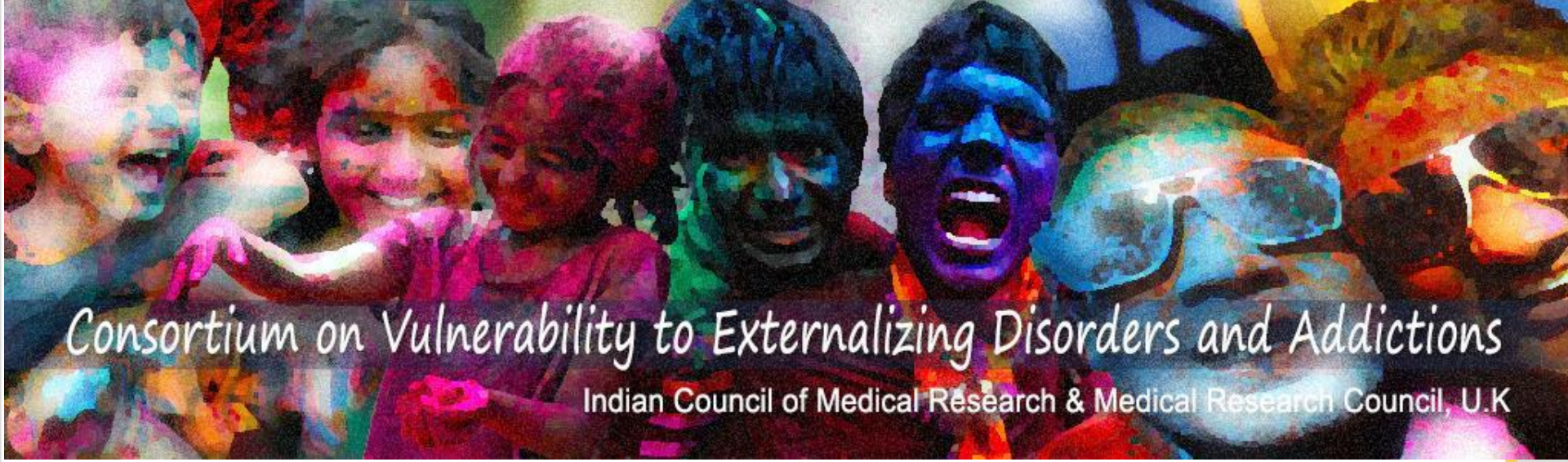
MISSING LINK

ENV. Exposures switch genes off/on to cause longstanding changes in function

- Children exposed to Early Life Stress had Increased Methylation (SWITCH OFF) of Serotonin (SL6A4) Gene important for Stress Response

Anurag Timothy, Vivek Benegal, Bhagya Lakshmi, Sachin Saxena, Sanjeev Jain, Meera Purushottam **(2019) Influence of early adversity on cortisol reactivity, SLC6A4 methylation and externalizing behavior in children of alcoholics.** *Progress in Neuropsychopharmacology & Biological Psychiatry*

MISSING LINK



- Increased understanding of effects of substance use on normal brain development, the harmful effects of adverse environments, and the role of innate vulnerabilities will allow for the development of personalized intervention to reverse or mitigate some of these deficits.
- Adverse social environments during early childhood delays normal brain development associated with impulsivity. In turn, impulsivity predicts greater vulnerability for substance use disorder
  - However, children can be trained to improve their self-regulation and hence control impulsivity
- Research -identifying changes in brain development triggered by early exposure to drugs
  - Development of early interventions to mitigate developmental vulnerabilities or counteract negative neuroadaptations.
- cVEDA study, studying 10,000 children with brain imaging, genotyping, and deepphenotyping across the transition from childhood into adulthood, will provide valuable data for determining normal human variability in brain development and how it is disrupted by drug use and mental illnesses

MISSING LINK

TO CUT A LONG STORY SHORT>>>>

- Rapid & Prolonged Neuro Adaptations, to
- Repeated Exposures of Substances or Addictive Behaviors
- Greater risk in Vulnerable Individuals (Delayed neurodevelopmental maturity)
- Impulsivity → Experimentation
- Low boredom threshold → Higher reinforcement from drug reward
- Difficulty in Learning from Mistakes → chasing the high discounting the low
- Relatively less insulated → Greater & prolonged neuroadaptations

MISSING LINK

High Recidivism (Treatment Resistance)

- Revolving Door Phenomenon
- Therapeutic Nihilism

Why Treatments Fail

Unreal Assumptions

- Abstinence –Only Goal
- One treatment should secure healing – Fracture vs Diabetes
- All Addictions/ Addicted people are the same
- There is one Universal treatment strategy

Why People Fail Treatments

- Treatments Target The Visible Tip
  - Underlying Vulnerabilities [The Cough analogy]
  - Treatments are Stigmatizing
  - Treatments implicitly Defeatist (Once an Alcoholic….)
  - Need for Reframing according to recent knowledge

What can we learn about "PALLIATIVE" & PRE-EMPTIVE management & from these findings?

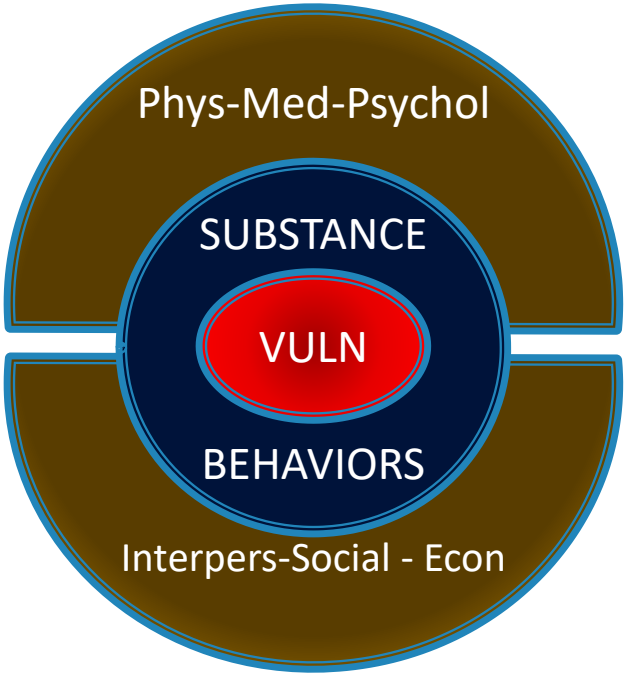
- Treating the diathesis- critical for treatment of addictive behaviors
- Opens up possibilities for early interventions for addictive disorders, externalizing and other psychopathologies

Planning Treatment

Acute	Short Term	Long Term
Crisis Mgt/Motivn	Prevent Relapse	Improve Vulnerability
Withdrawal Mgt		

- Relapse Prev Tx
- Craving Mgt Sgy
- Lapse Mgmt Strgy
- Anti-Relapse Rx

- Rx –Externalizing -Bx
- Rx –DepAnxLoss -Bx
- Rx–Mood Dis/EUPD-Bx
- Indiv-Family Tx
- Voc/Self Mgt Tx
- Self Improv – Pos Psych, Self Help Gr etc.



IMMEDIATE Intervention – Withdrawal & Crisis states

- LOCUS – Out-patient/In-patient; Medical-Support-Respite
- Withdrawal
  - Substitution – BZD-Alc; BUP-Opi; NIC-Tob
  - Symptomatic – Cann; Inhal; AmpLike
- Targeted treatment of crisis states:
  - Medical
  - Psychol
  - Interpersonal

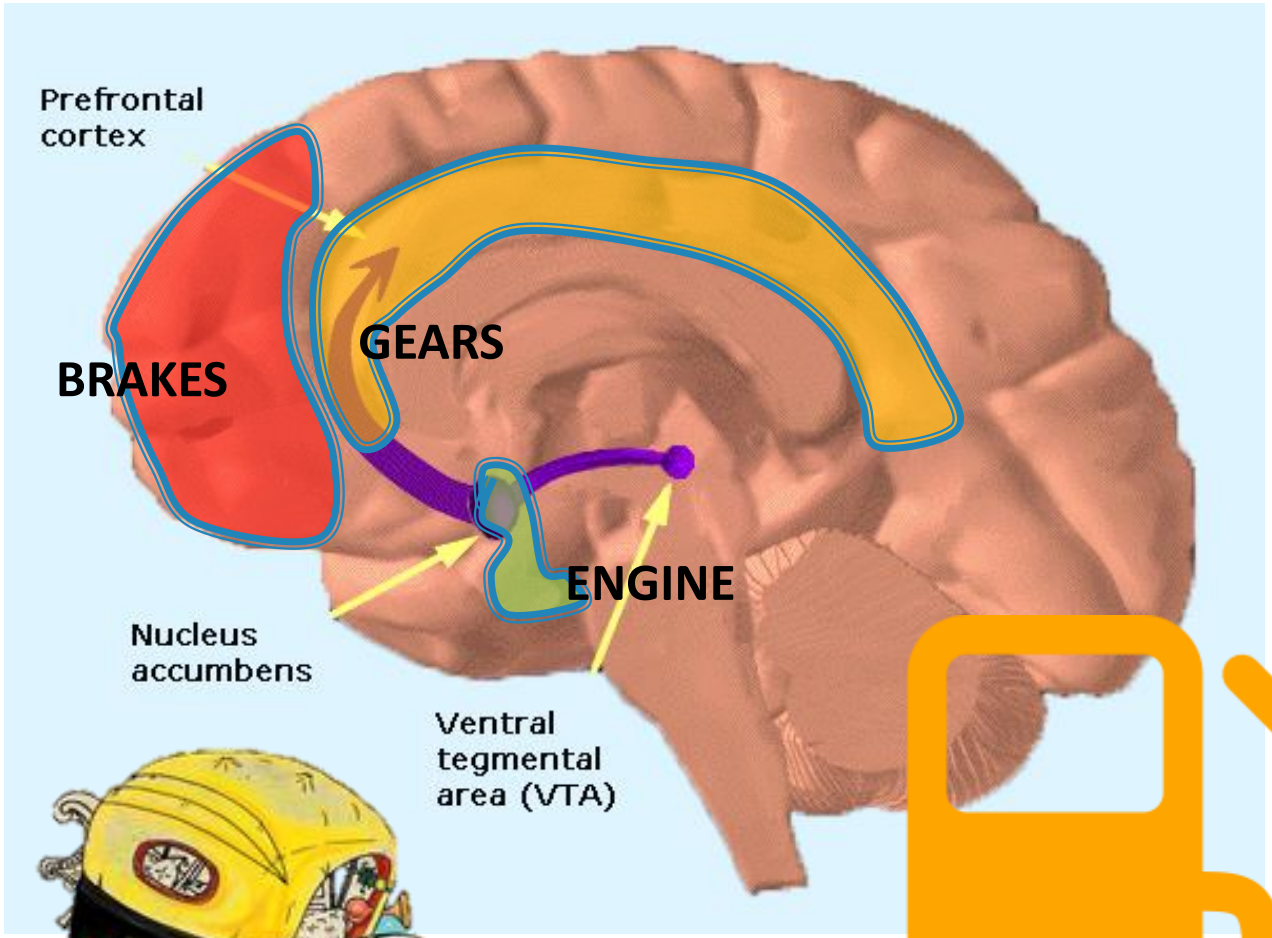
Long term

- Treat vulnerability diathesis
- Prepare to handle lapse/relapse
- Strengthen resilience

Prevent Lapse from Becoming A Relapse

- Lapse & Relapse are Expected and Natural Elements of recovery
- Lapses – When not Why?
- Prevent Lapse from converting to Relapse?
- Early Intervention
- REMEMBER: Diabetes, HT

Reframing

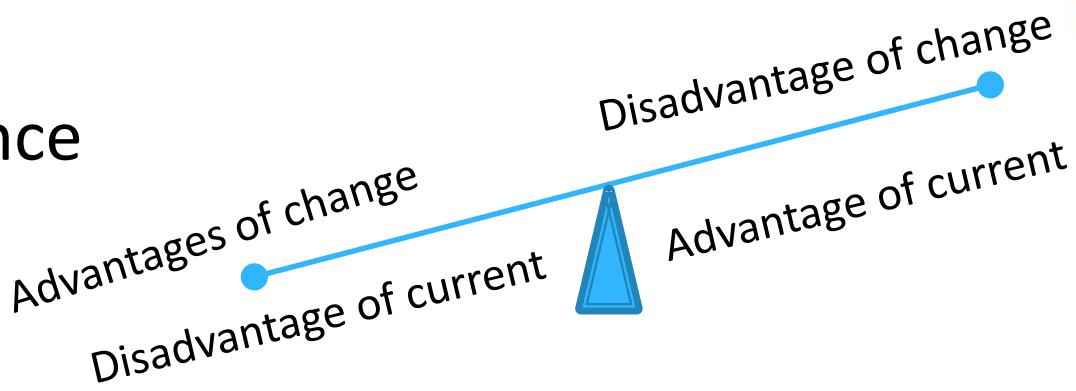


Using Kersosene for Immediate Gratification

MISSING LINK

Motivate for change

- Motivational Balance



- Reframing –Alt Explanatory Model

- **S**pecific, **M**easurable, **A**ttainable, **R**ealistic and **T**imely (SMART) Menu

Strategies for Long lasting Neuroadaptations (Controversies)

- Recurrent/Relapsing disorder → Reframe as chronic disease
- ? Utility of long term stays in protective environments → ??reinforces addict identity & further reduces functioning abilities (Early restoration of ecologically relevant functioning)
- Reversal/ Mitigation :
  - Learning new adaptation strategies
  - Building protective structured life-style
  - Safety net- preventing lapse → relapse
  - **Long term pharmacological supports [substitution/ anticraving/ harm reduction]**

What can we learn about "PALLIATIVE" & PRE-EMPTIVE management & from these findings?

- Treating the diathesis- critical for treatment of addictive behaviors
- Opens up possibilities for early interventions for addictive disorders, externalizing and other psychopathologies

Strategies for Long lasting Neuroadaptations (Controversies)

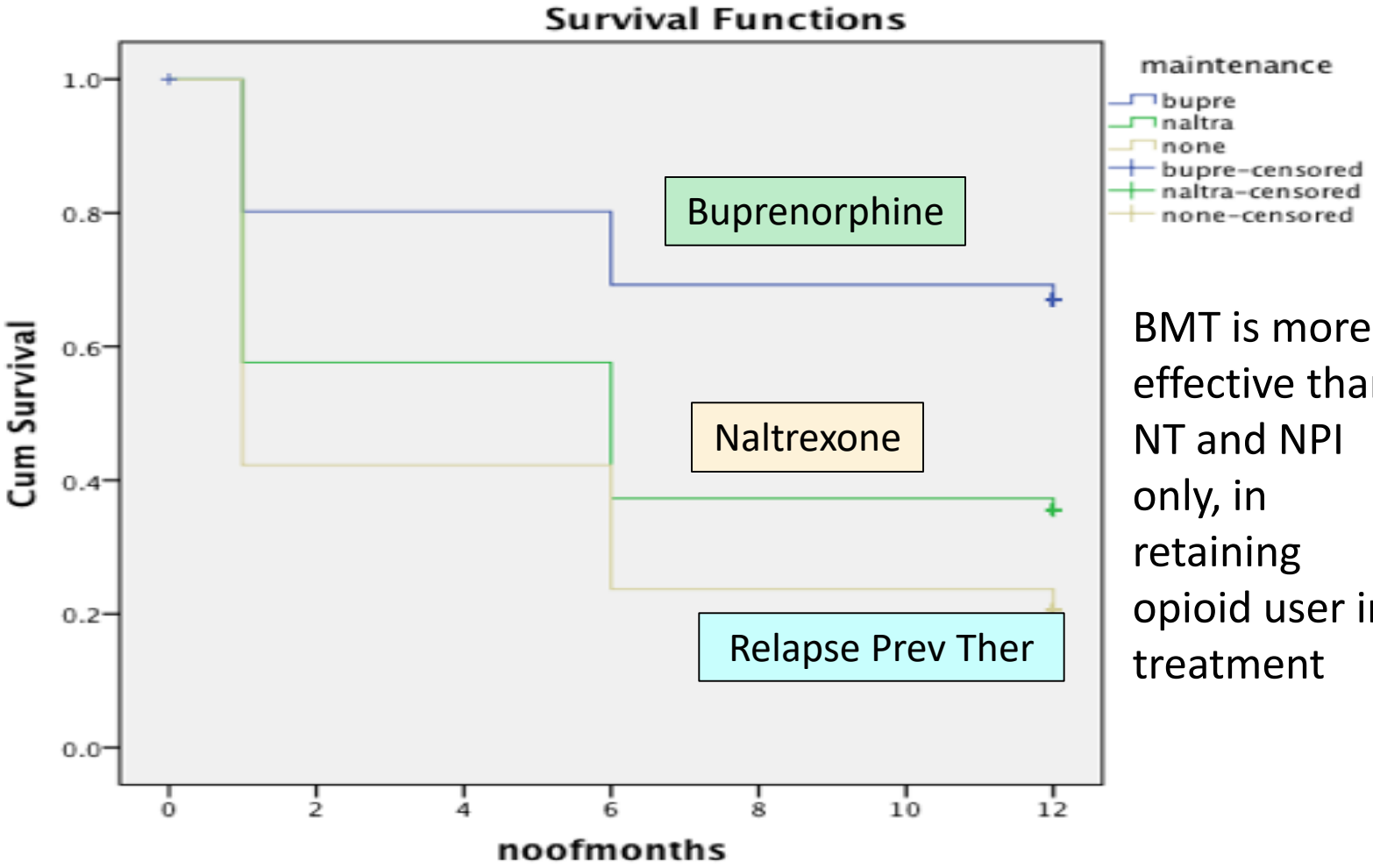
- Recurrent/Relapsing disorder → Reframe as chronic disease
- ? Utility of long term stays in protective environments →??reinforces addict identity & further reduces functioning abilities (Early restoration of ecologically relevant functioning)
- Reversal/ Mitigation :
  - Learning new adaptation strategies
  - Building protective structured life-style
  - Safety net- preventing lapse→relapse
  - **Long term pharmacological supports [substitution/ anticraving/ harm reduction]**

Aims of Treatment-4 [MODUS] PHARMACOLOGICAL MANAGEMENT

CLASS	AGENTS
Aversive	Disulfiram, Alcohol vaccine [experimental]
Substitution	Methadone, Buprenorphine, Nicotine
Blocking agents	Naltrexone, Naloxone, Nalorphine, Varenicline
Anti-craving	Baclofen, Acamprosate, Topiramate, Ondansetron, N Acetyl Cysteine, Pregabalin, Gabapentin, Tiagabine, Modafinil, Ibudilast,
Antagonists	Naloxone, Naltrexone, Flumazenil
Vaccines	Cocaine, Nicotine [experimental]
Physical	rTMS; tDCS; DBS [experimental]
Externalizing syndrome	Atomoxetine, Methylphenidate, desVenlafaxine
Mood syndromes	Lamotrigine, Valproate
Schiz; anx dis	Clozapine, olanz, quetiapine, aripiprazole

Substitution

Follow up rates in Opioid dependence Syndrome



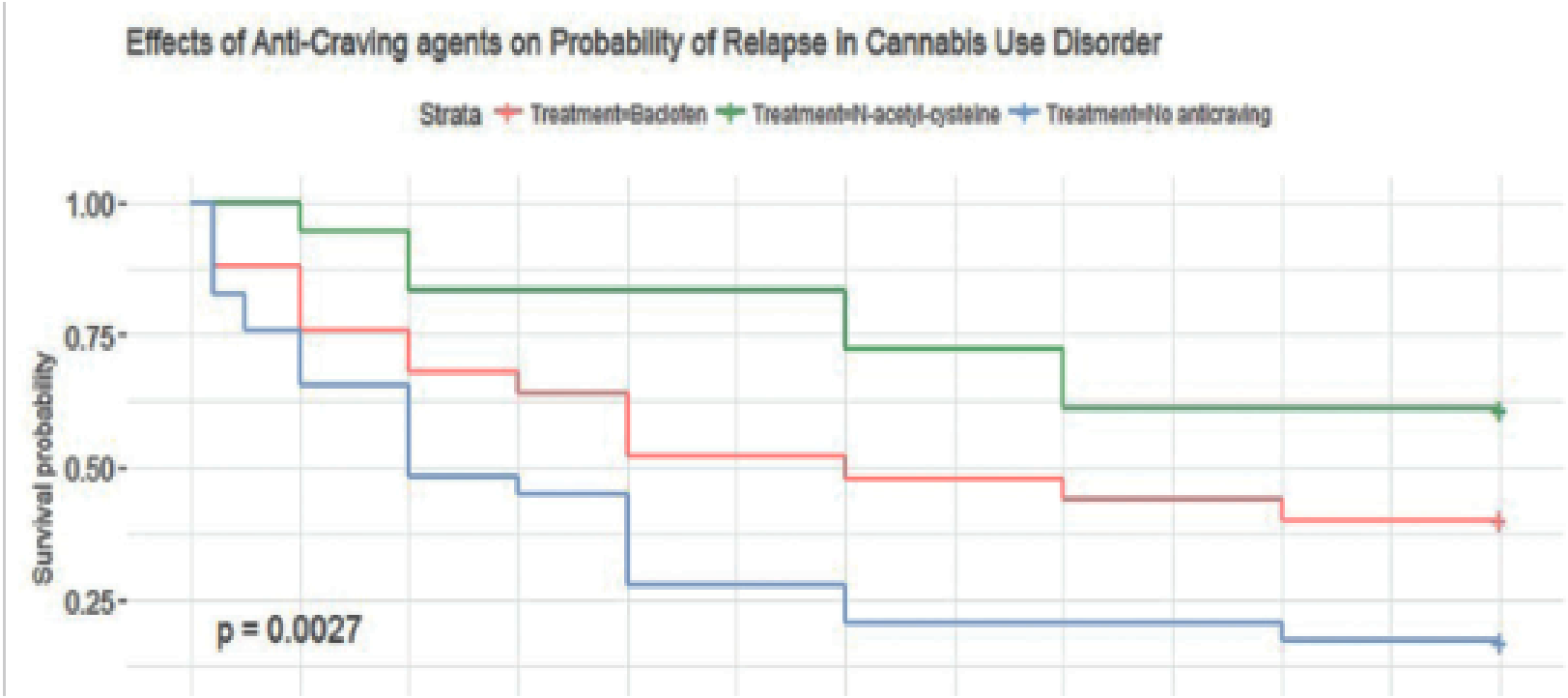
BMT is more effective than NT and NPI only, in retaining opioid user in treatment

Bandawar et al (2015) Follow Up Rates In Opioid Dependence Syndrome: A Case Control Study From India. IJPM

Long term anti-craving Rx

Relative effectiveness of N-acetylcysteine and baclofen as anticraving agents in cannabis dependence – A retrospective study with telephonic follow-up

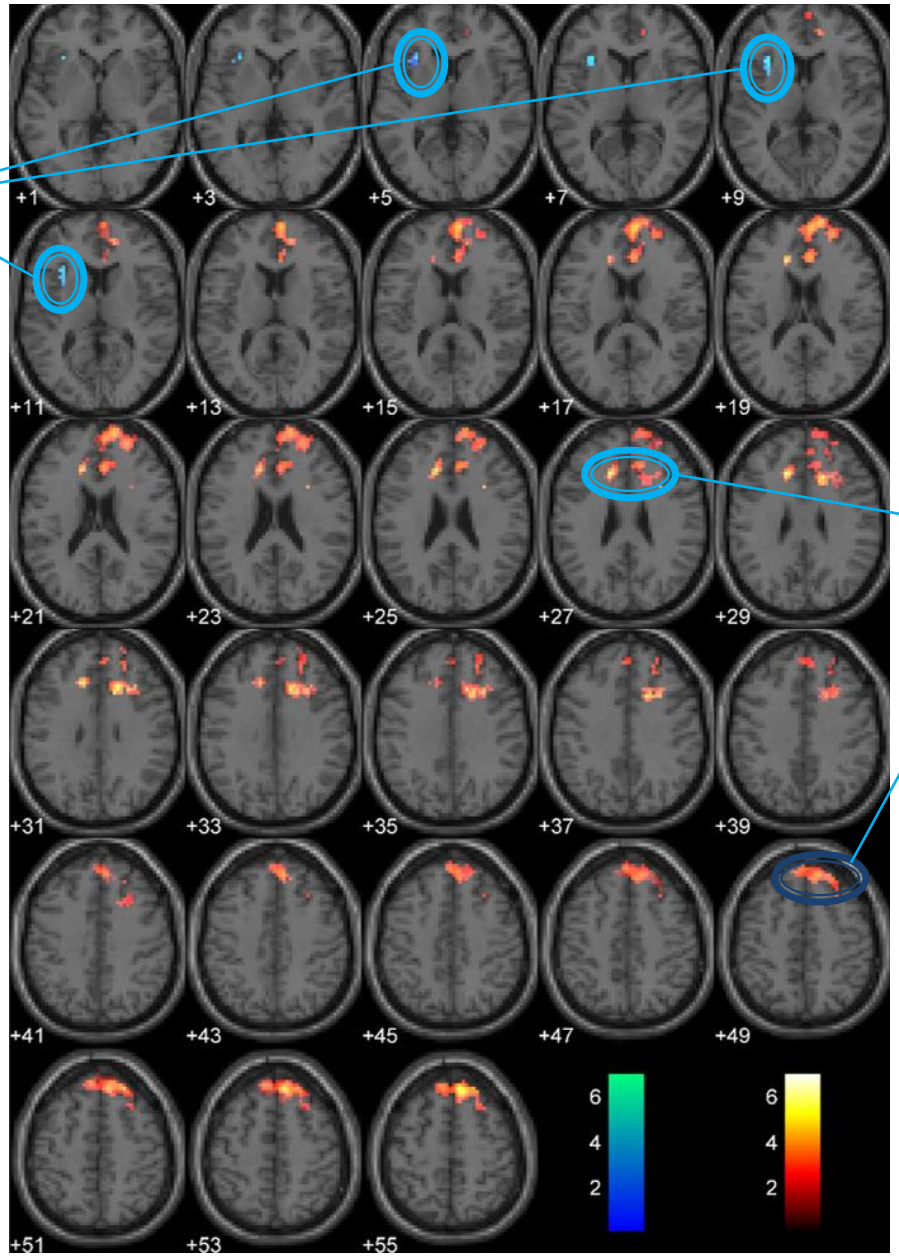
Venkata Lakshmi Narasimha, Lekhansh Shukla, R. P. S. Shyam[1], Arun Kandasamy, Vivek Benegal



Survival curves -psychosocial intervention vs. baclofen vs. N-acetylcysteine - NAC gr had better survival and less relapse compared to baclofen and to psychosocial intervention

Deactivation of Insula

Baclofen reduces activation due to craving imagery



BACLOFEN REDUCES EMOTIONAL VALUATION & INCREASES JUDGEMENTAL PROCESSES

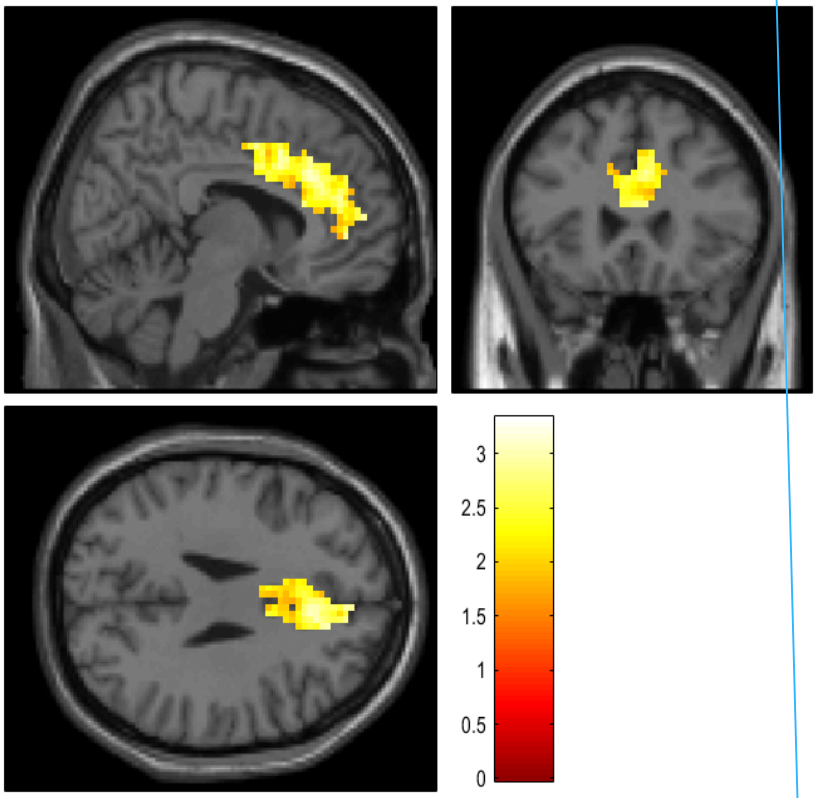
Activation of ACC & DLPFC

Holla et al, 2017. Clinical Psycho-pharmacology and Neuro-science [In press]

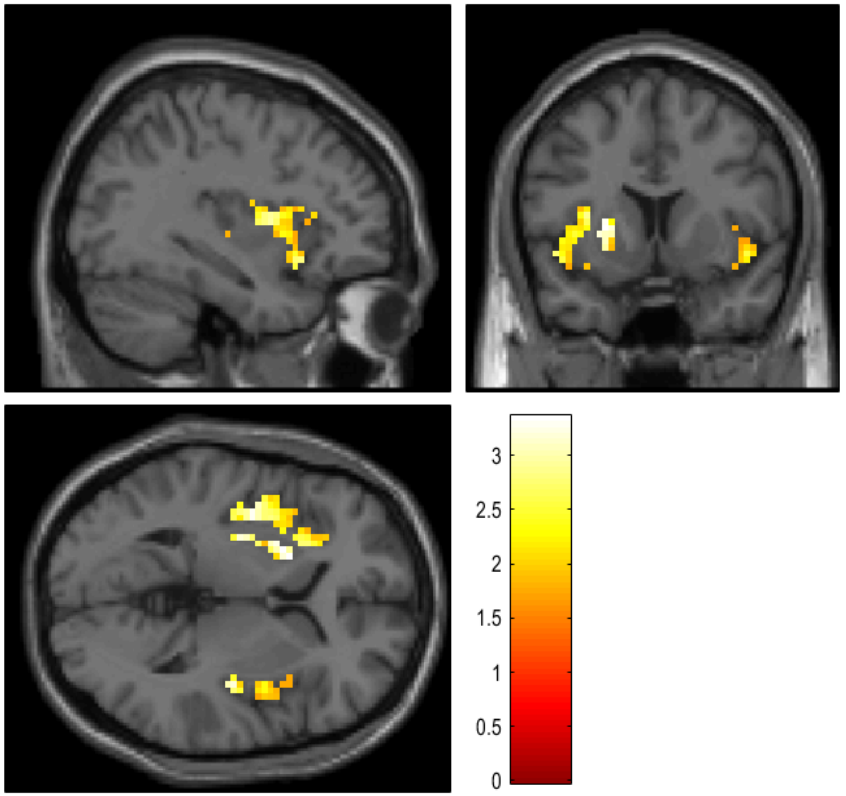
MISSING LINK

Activity of insula and dorsal striatum predicts time to relapse - BACLOFEN

Areas getting activated after 2 weeks treatment with baclofen (Bilateral ACC)



Areas getting deactivated after 2 weeks treatment with baclofen (bilateral insula)



Karthik et al; unpub

MISSING LINK

Efficacy review of Baclofen in Long-Term Mntn ce of Alc Dep

- 348 Male subjects, with mean age 39.2 ±10.4yrs; age at onset of dep: 26.1 ± 8.4years
- Duration of dep: 13.1 ± 9.1years
- Family history of alcohol dependence in FDR present in 61.5%
- Daily intake : 14.6 ±7.8 units (10.8 gms ETOH
- Baclofen dosage: 50.8 ± 21.7 mg /dy
- Time to first drink : 4.4 ± 3.8 months

Multiple linear regression –
Dependent variable: 'time to first drink'
6 Predictor variables: 1) avg daily alc units, 2) curr age, 3) age at onset of dep, 4) family history, 5) durn of dependence and 6)dose of baclofen in mg/day.

- Significant correlation of outcome variable with only two predictor variables :
  - Dose of baclofen and
  - Average daily intake.
- Using hierarchical method - 'dose of baclofen' and 'avg alcohol intake' explain sig variance in 'time to first drink'.
  ($F(1, 345) = 182.8$, $p < 0.001$, $R2 = 0.52$, $R2$ adjusted $= 0.51$).

Baclofen may be more effective in patients with:
1.Severe alc dependence &
2.Higher daily intake

Shukla, Shukla, Bokka, Kandasamy, Chand, Murthy, Benegal (2015) IJPM

MISSING LINK

Cannabis & Baclofen

- Baclofen has been shown to reduce cannabis withdrawal symptoms and the subjective effects of cannabis. Few studies

Biological Psychiatry
A Journal of Psychiatric Neuroscience and Therapeutics

Baclofen in Cannabis Dependence Syndrome

(2010) Subodh Bhagyalakshmi Nanjayya,Madhusudhan Shivappa, Prabhat Kumar Chand, Pratima Murthy, Vivek Benegal Volume 68, Issue 3, Pages e9–e10

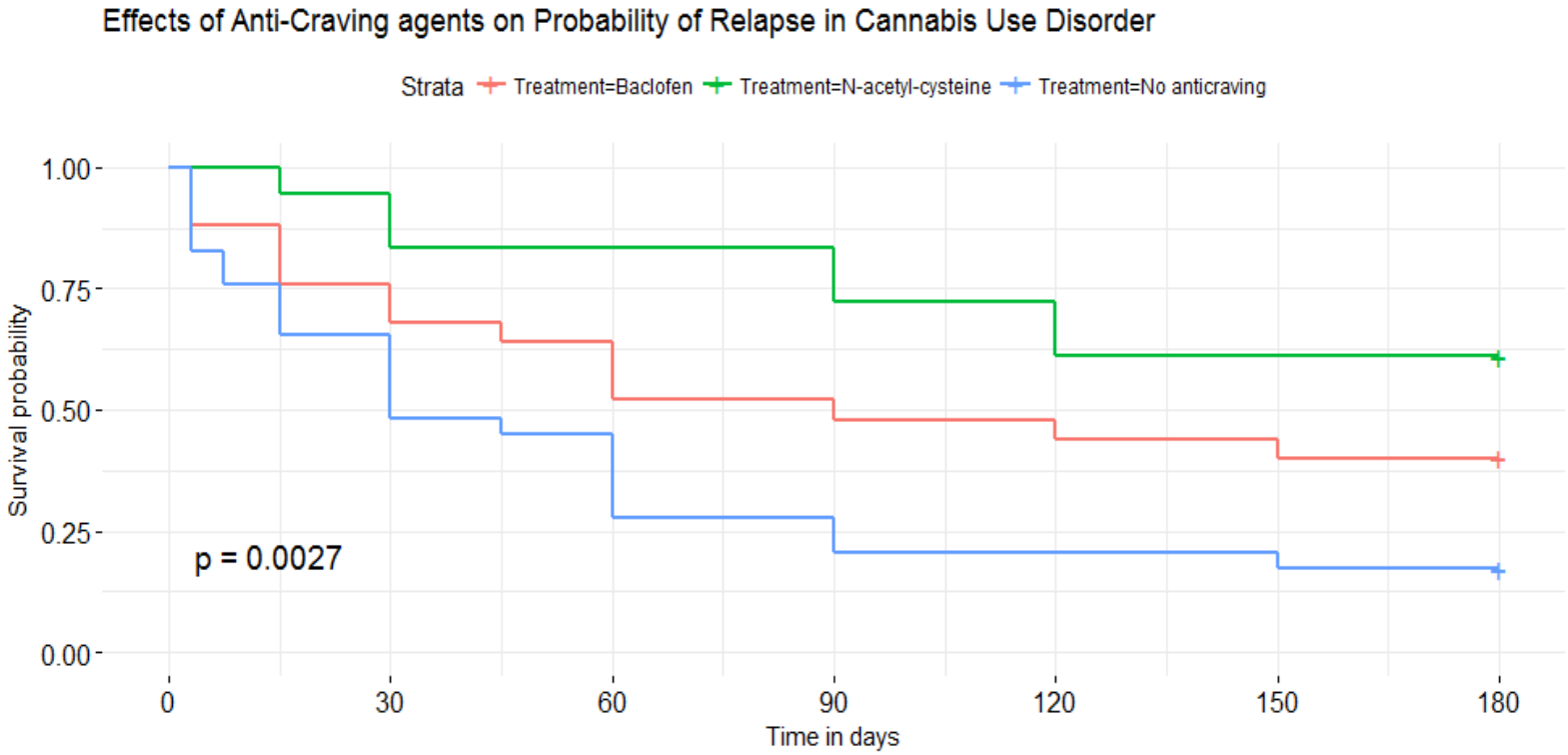
Therapeutic Advances in Psychopharmacology SAGE

Baclofen in the management of cannabis dependence syndrome

Bruce Imbert, Nathalie Labrune, Christophe Lancon, and Nicolas Simon. Ther Adv Psychopharmacol. 2014; 4(1): 50–52.

MISSING LINK

Relative effectiveness of N-acetylcysteine and baclofen as anticraving agents in cannabis dependence

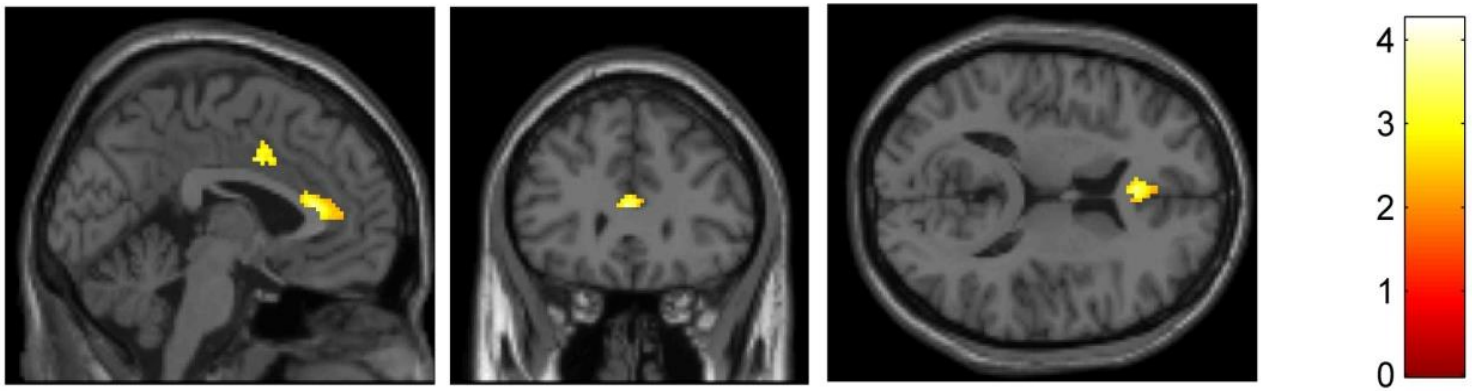


Narasimha VL, Shukla L, Shyam R P, Kandasamy A, Benegal V. (2019) Relative effectiveness of N-acetylcysteine and baclofen as anticraving agents in cannabis dependence. Indian J Psychiatry

Deactivation of "valence" in Ant. Cingulate after **ACAMPROSATE** treatment

- After two weeks of acamprosate treatment there is a significant deactivation of left dorsal and ventral anterior cingulate.

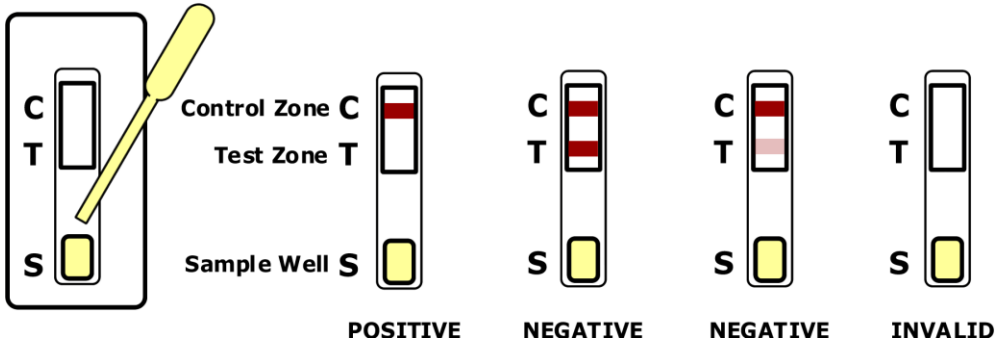
(C) Effect of Acamprosate treatment: Brain regions with significant Deactivation (Pre-Post) for Alcohol versus Neutral cues.



Khadse et al 2015 unpub

Address habits & learnt BX
Centred around drug seeking and taking

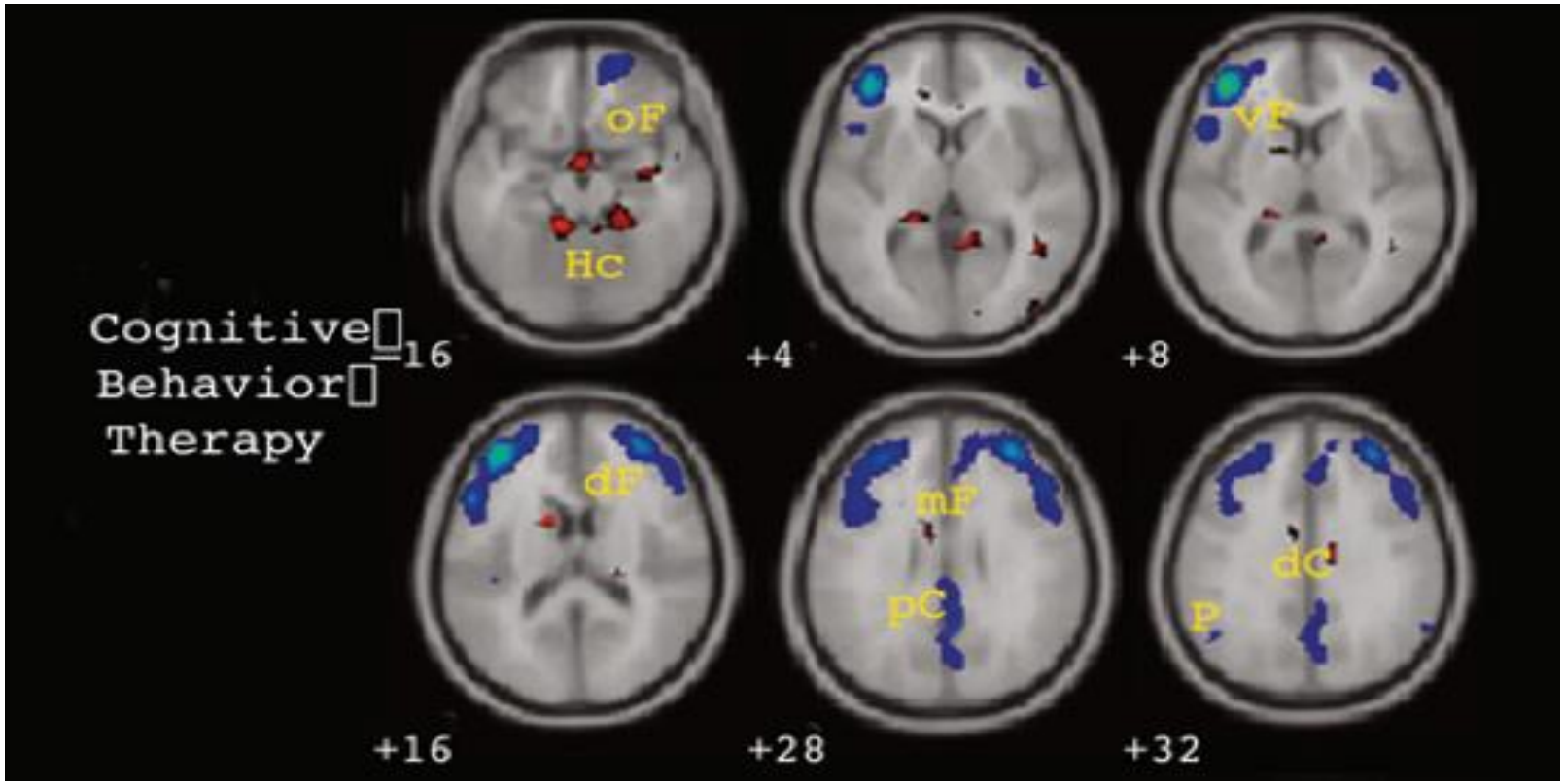
- Reduce deficit behaviors
- Increase adaptive behaviors
- Trust issues (confidence building measures)
  - Urine tox screens
  - Apps and phone ins
  - Behavioral contracts



Neuro-remediation

- Brain Gym [Lumosity/ Captain's Table/ Google…]
- Alpha Theta Biofeedback
- Cognitive Behavioral Therapies
- Exposure Response Therapies
- Psychological interventions specific to Ext syndromes
- Family Tx
- Positive Psychology Interventions

Behavioral Therapies make changes in Brain Function
Changes in neurological metabolic activities post CBT



Neuroimaging showing metabolic changes in the brain after completion of CBT; Red indicates increases and blue indicates decreases

Goldapple et al., 2004

MISSING LINK

First Visit	• Informed consent and Contact information collected • Follow-up dates list collected from the members fed into the Aftercare System
Follow-up	• Missing follow ups – System will alert us • SMS will be sent the patient on the same date
If no follow-up,	• SMS twice over 15 days of missing follow-up
If no response,	• Two phone calls attempted over next 21 days • If patient or family responded, follow-up status as per proforma recorded and patient requested to attend follow-up
If no further response	• Home visit arranged for Bangalore patients if no further response

Strategies for Vulnerability

- Reframe as “core”problem
  - Pts & families suffered for long.. but lumped with drug use behaviors→ sidesteps denial/ambivalence
  - Find it easier to engage with goal of improving cognitive control than emotionally challenging abstinence/addict model
  - If will continue to cause problems/distress even when abstinent (“Dry-Drunk”) and hasten relapse

Treat the vulnerability / Diathesis

Contents lists available at ScienceDirect

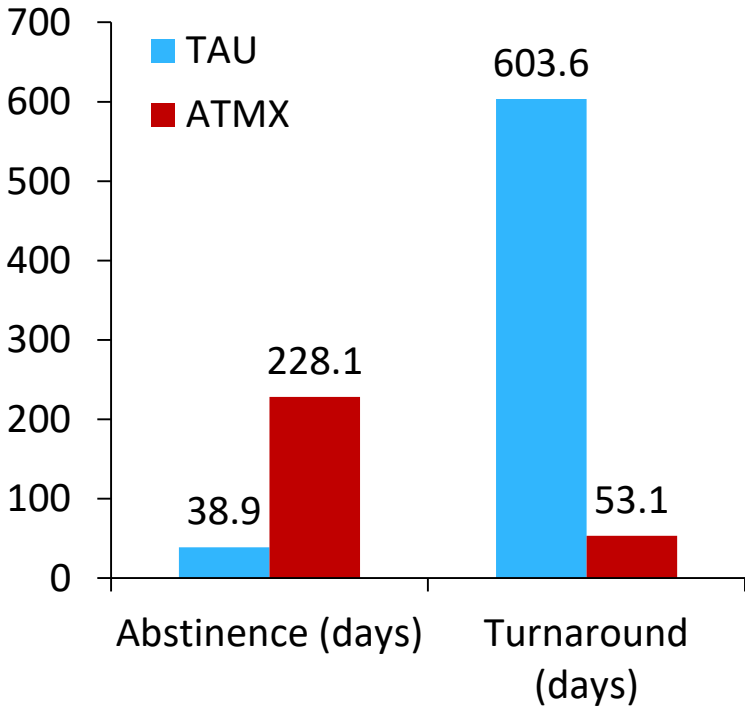
Asian Journal of Psychiatry

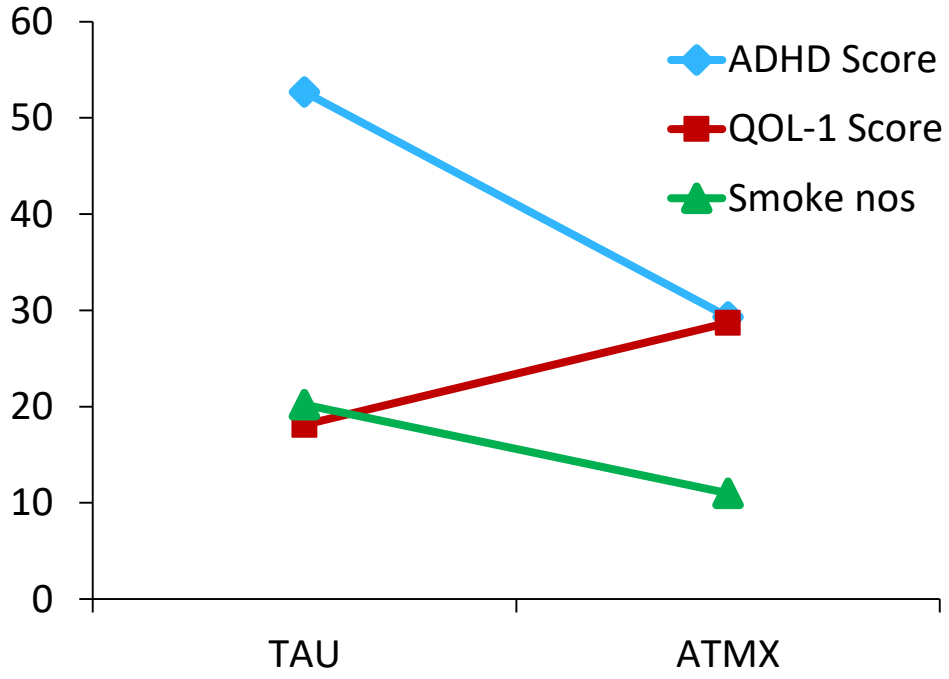
journal homepage: www.elsevier.com/locate/ajp

The efficacy of atomoxetine as adjunctive treatment for co-morbid substance use disorders and externalizing symptoms☆

Vivek Benegal[a], Biju Viswanath[a,*], Janardhanan C. Narayanaswamy[a], Sam P. Jose[b], Vaskar Chakraborty[a], Deepa Sankar[a], Thennarasu Kandavel[a], Muralidharan Kesavan[a]

[a] Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India
[b] Chalmeda Anadarao Institute of Medical Sciences, Karimnagar, Andhra Pradesh, India





Asian Journal of Psychiatry

Volume 24, December 2016, Pages 53–58

The efficacy of atomoxetine in treating adult attention deficit hyperactivity disorder (ADHD): A meta-analysis of controlled trials

Vinutha Ravishankar[1], Suresh Vedaveni Chowdappa[1], Vivek Benegal, Kesavan Muralidharan (Dr.)

Atomoxetine has significantly superior efficacy to placebo in treating adult ADHD

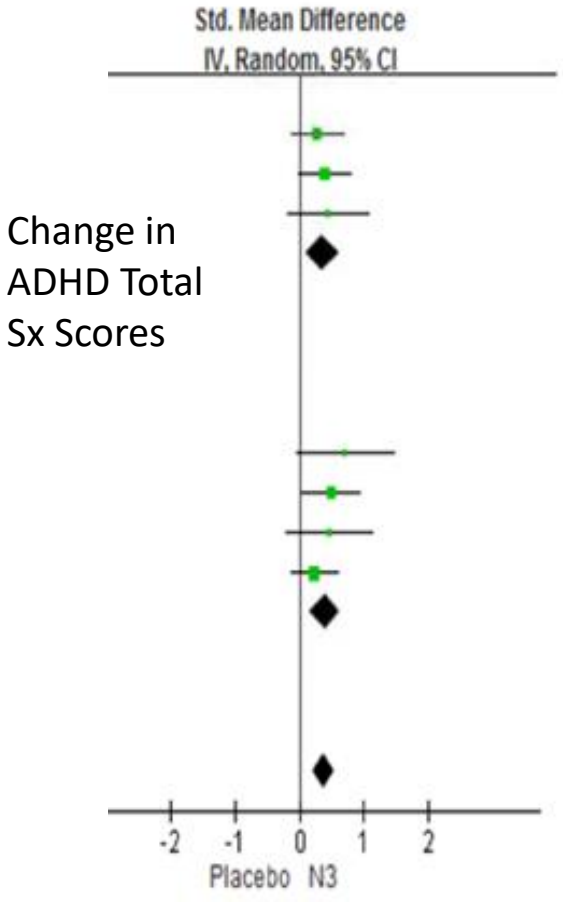
Efficacy of atomoxetine is superior to placebo in treating both inattention and hyperactivity/impulsivity.

Atomoxetine is significantly more efficacious in treating inattention than hyperactivity/impulsivity.

Response rates: most studies report about 60% response rates for 25% drop in ADHD scores.

Interventions: Pre-emptive
PUFA supplementation for ADHD

- Meta-analyses of 7 RCTs: n-3 PUFAs supplementation improves
  - ADHD symptom scores and
  - Cognitive measures –attention
- Children and adolescents with ADHD have lower levels of DHA, EPA
- n-3 PUFAs supplementation monotherapy improves clinical symptoms and cognitive performances in children and adolescents with ADHD



Jane Pei-Chen Chang, Kuan-Pin Su, Valeria Mondelli & Carmine M Parian (2018) **Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: a Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. Neuropsychopharmacology; 43**, 534–45

Role of Exercise in ADHD Intervention Planning

A rapidly growing literature suggests that physical exercise has powerful effects on brain function and structure, and is one avenue by which neural and cognitive development can be impacted over both the short- and longer-term.

Berwid & Halperin 2012 Curr Psychiatry Rep

MISSING LINK

Preventive Interventions for Vulnerability & Neuroadaptations

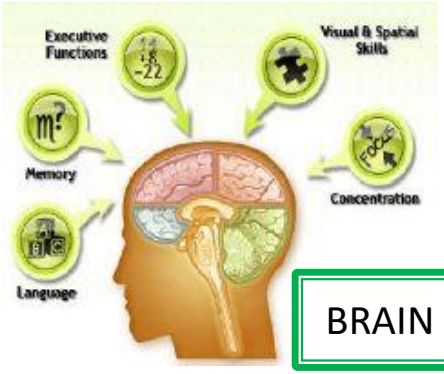
Substance Dependence Theory	Associated Risk Behaviors	Predictions for Vulnerable Adolescents	Affected Neural Substrate(s)	Preventative Interventions
Executive Dysfunction	Inhibitory control, Sustained attention	Decreased	PFC	Meditation/Yoga, Martial Arts, Mindfulness Training
Incentive Salience	Reward cue reactivity, Sensitivity to Reward	Increased	NAc → mPFC, BLA ⟷ mPFC	Novelty, Enrichment
Habit Formation	Automatic behaviors, Insensitive to devaluation	Increased	Dorsal STR	Exercise
Stress Reactivity	Emotional dysregulation, Heightened startle/arousal	Increased	Hypothalamus, Amygdala, Hippocampus, NAc, STR, mPFC	Yoga, Mindfulness, Social Support

Volkow & Boyle, 2018, AJP

MISSING LINK

Intervention strategies for adolescent substance abuse

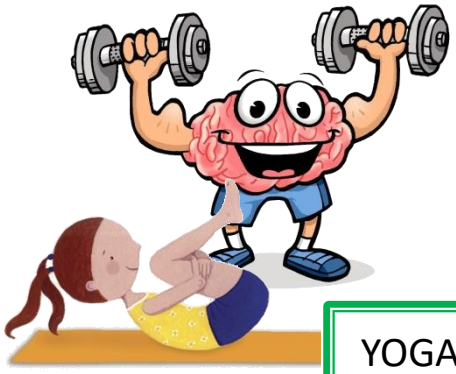
BRAIN TUNING Rx



BRAIN GYM

PARENTING & EDUCATION

BRAIN REPAIRING Rx



YOGA/ GYM

Learn CHANGE BEHAV

DIET SUPPL.

"PROJECT"

MISSING LINK

SUGGESTED TREATMENT ALGORITHMS
Early Onset Dependence

Diathesis Externalizing	Wx sx	Reverse Neuro Adaptation	Relapse Prevention	Dealing with fallout
Atomoxetine **Bupropion** **+** **Behavioral Training** **-Cog train** **-Brain train** **-Prob solving** **-Coping skills**	BZDZ Thiamine H2 blockers Other prn **Acamprosate** –ve Affect state **Baclofen** 30-60 mg/d	**Naltrexone** **Ondansetron** **Baclofen** ***Topiramate*** *+* **Unchain habits** **Structure ADL** **Alternative highs** **Phys. Exercise/ Yoga**	**- Relapse Triggers** **-Social support** **-Monitoring** **-*Safety net*** **-Contingency Contracting** **-Regular F/U** **-Single therapist**	**Involve sig. others** Supportive Therapy ? Directive & Prescriptive Behav. Marital etc.

Bipolar (esp BP II) very common – ask and treat appropriately

MISSING LINK

SUGGESTED TREATMENT ALGORITHMS

Late Onset Dependence

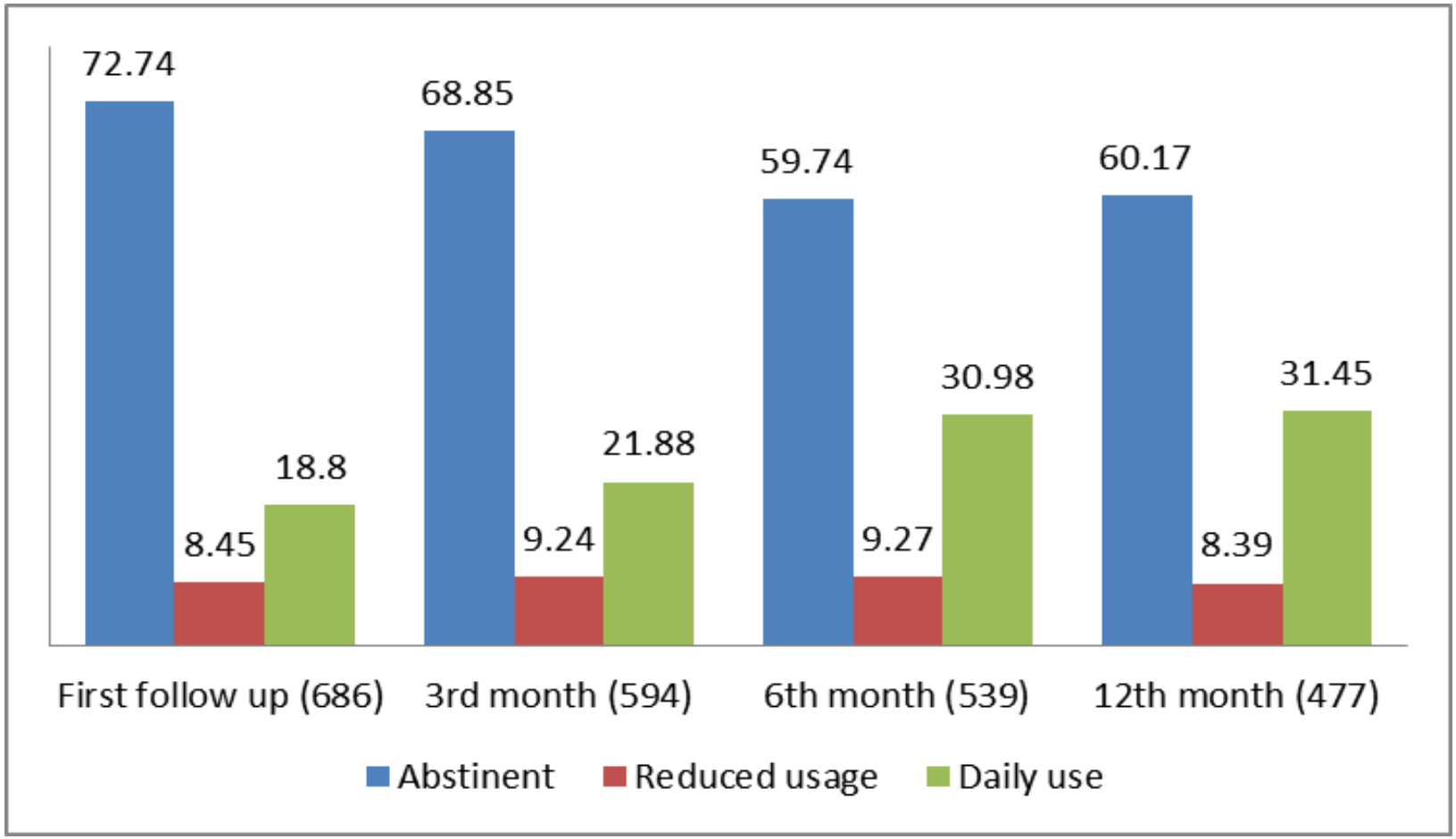
Precursor event / condition	**Wx sx**	Reverse **Neuro Adaptation**	**Relapse Prevention**	Dealing with fallout
Supportive and/ Individual Therapy prn **SSRI's etc.**	BZDZ Thiamine H2 blockers **Acamprosate** –ve Affect state	**SSRI–**Sertraline **Acamprosate** **Topiramate** **Baclofen** *+* **Unchain habits** **Structure ADL** Alternative highs **Yoga/ relaxation tech**	**- Relapse Triggers** **-Social support** **-Monitoring** ***-Safety net*** -Contingency Contracting **-Regular F/U** **-Single therapist**	**Involve sig. others** Supportive Therapy ? Directive & Prescriptive Behav. Marital etc.

Depression and anx dis very common – ask and treat appropriately

MISSING LINK

DOES THIS REALLY WORK?

Alcohol use Status of In-Patients with ADS over 12 m



CAM NIMHANS Data (2017-18)

MISSING LINK

- Criteria for SUD, including loss of control of substance use, continued use despite negative consequences and craving can be explained by abnormalities in brain function
- Addictive behavior is, driven by abnormal functioning in neural circuitry of decision making, impulse control, emotion regulation, stress mitigation, and reward learning and seeking
- Characterized by maladaptive neural plasticity in response to drugs of abuse that persists throughout lifetime of individual
- Susceptibility to addiction due to convergence of genetic predisposition and exposure to environmental risk-factors, which results in dysregulation of specific genes
- Treating withdrawal is important but does not necessarily prevent relapse or qualify as addiction treatment
- Repeated relapses are due to long-lasting neurobiological changes in decision-making networks, and, to be effective, relapse prevention agents need to restore functioning in this circuitry
- To restore functionality and to address causes of initiation and relapse, treatment of both neuroadaptations and vulnerability is essential

To conclude

- Recent research is developing a mechanistic understanding of individual vulnerability and the development of long term brain changes underlying addictive disorders
- Addictive disorders at least in those of young onset appear to be an epiphenomenon of a brain developmental disorder!
- Need to incorporate these learnings to modify our treatment strategies and to expand to both palliative and pre-emptive care

Opioid dependence

	FOCUS	MODUS
1	Wx	Detox –CLON + Ms Relaxant +
		Substitution (short term) –Buprenorphine
2	Long-term	Substitution (Long term) –BUP+NALOX/ METHADONE Or BACLO
3	Reversing neuroadaptation	Baclofen; N-Acetyl cysteine Medication management
4	Treating susceptibility	Atomoxetine/ MPH; other appropriate Behavioral interventions – Cog Enh Th; Alt adds; Exercise-yoga;
5	Preventing Lapse → Relapse	Relapse Prev and Lapse mgt.

Cannabis dependence

	FOCUS	MODUS
1	Cannabis wx – typically mild	No specific treatment ?BZDZ/
2	IF…Cannabis psychosis – longer term-SCZ	2nd gen antipsychotics=CLOZ>QUET=OLANZ=ARIP>>RSP>>>HPL or CPZ
3	Reversing neuroadaptation	Baclofen; N-Acetyl cysteine Medication management
4	Treating susceptibility	Atomoxetine/ MPH; other appropriate Behavioral interventions – Cog Enh Th; Alt adds; Exercise-yoga;
5	Preventing Lapse→ Relapse	Relapse Prev and Lapse mgt.

Gray et al (2012) A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry

Inhalant dependence

	FOCUS	MODUS
1	Withdrawal	No specific; BZDZ or BACLO; Motivational Int; Supportive
2	Psychosis-anger	2nd gen antipsych
3	Neuroadaptn	BACLO
4	Susceptibility	Ext<-- ATMX/MPH>DVNLFX=BUP Behavioral interventions – Cog Enh Th; Alt adds; Exercise-yoga;
5	Preventing Lapse→ Relapse	Relapse Prev and Lapse mgt.