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Impact of early life stress on brain structure and function: biological mechanisms and pathways to resilience

Robert Paul, PhD/ABPP-CN
Director, MIMH
Professor, UMSL

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Presentation outline

MIMH

Review of core research program

Early life stress

- Relation to health
- Mechanisms
- Impact on brain structure
- Moderating variables
- Treatment response
- Pathways to resilience

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A research unit of UMSL

Approx. 50 Principal Investigators and team members

Major Funding Agencies
National Institutes of Health
Department of Defense
Substance Abuse Mental Health Service Administration
Department of Mental Health

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MIMH areas of expertise

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MIMH PI support

Peer Review Program

Mock Review Group

- Full peer review
- Mentor review

Goals

- Identify fatal flaws fast
- Improve technical writing
- Identify methodological confounds
- Improve flow and continuity

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MIMH PI support

Faculty Mentoring Program

- Provide guidance, ongoing career support, and professional development
- Support understanding of unit culture/environment
- Promote job satisfaction and retention

- Build success

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MIMH PI Support

Science Art Collaborative

- Annual program to open minds, unlock creativity, & lead to discovery

- 2016 Visiting Artist: Ms. Heidi Claire

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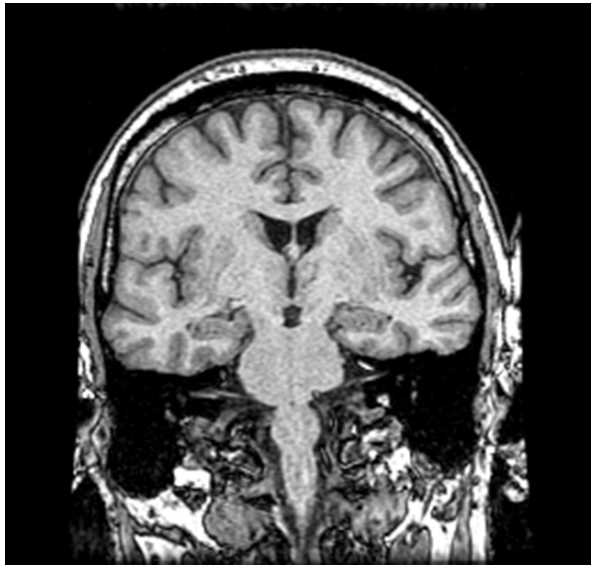
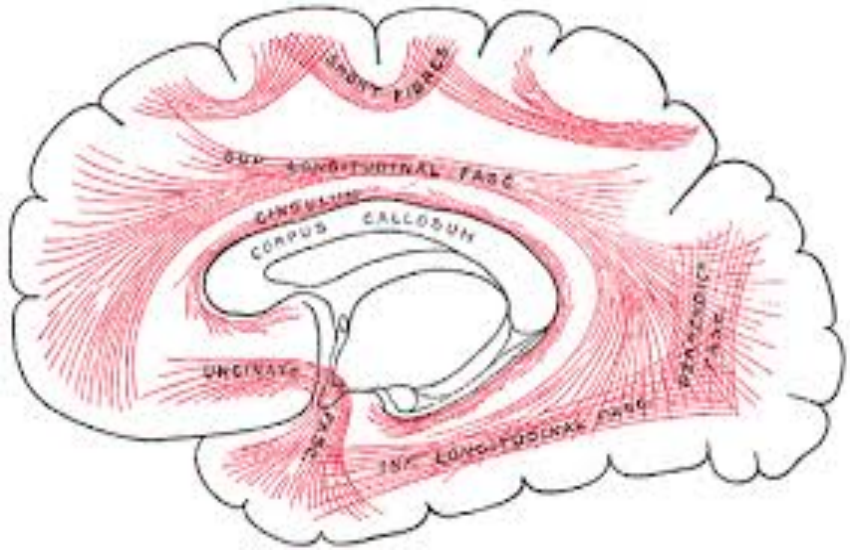
Research program

- Subcortical brain systems

Subcortical nuclei



White matter



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Anatomical circuitry

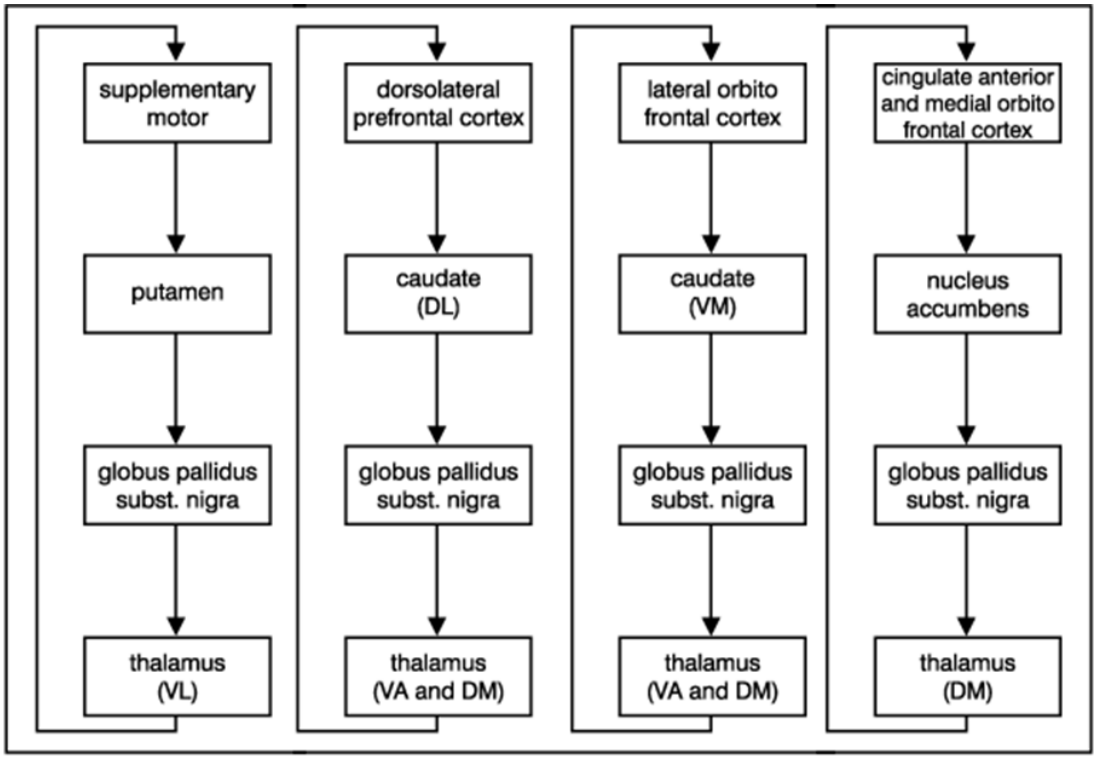

Figure 1 - Frontal-striatal connections.
DL: dorsolateral; DM: dorsomedial; VL: ventrolateral;
VA: ventroanterior; VM: ventromedial.

Nucleus accumbens and apathy. Paul et al 2005

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Research program

- Explain how the brain works.
- Identify mechanisms of brain dysfunction and resiliency.
- Develop (core) mechanism-driven interventions to improve health outcomes.

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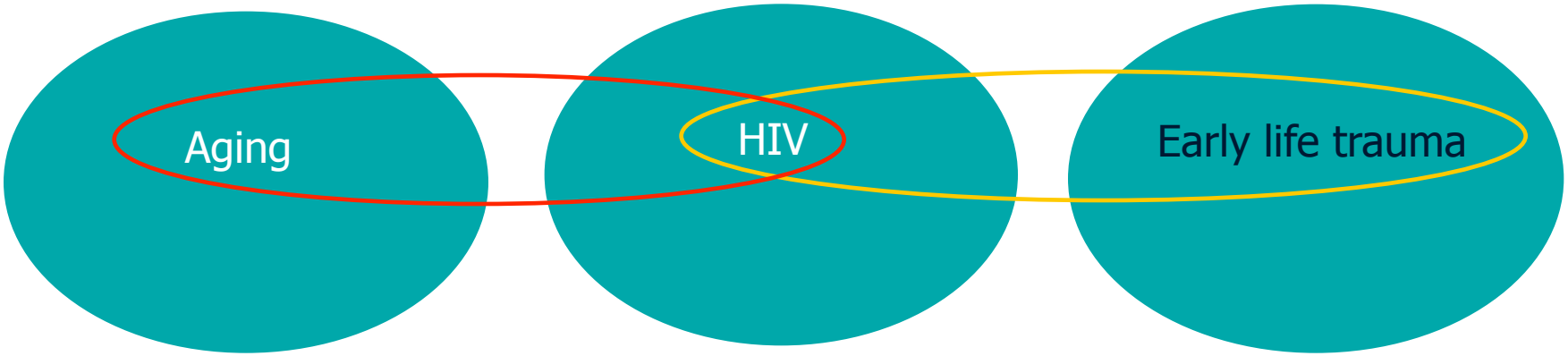
Research program



Targeted involvement of subcortical brain systems (basal ganglia, white matter)

Neuropathogenesis remains undetermined

No current cure

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Relationships to health

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ELS and smoking

- OR of being a current smoker according to number of ACE events:

Number of categories	OR (95% CI)
0	1.0 (referent)
1	1.1 (0.9-1.4)
2	1.5 (1.1-1.8)
3	2.0 (1.5-2.6)
4+	2.2 (1.7-2.9)

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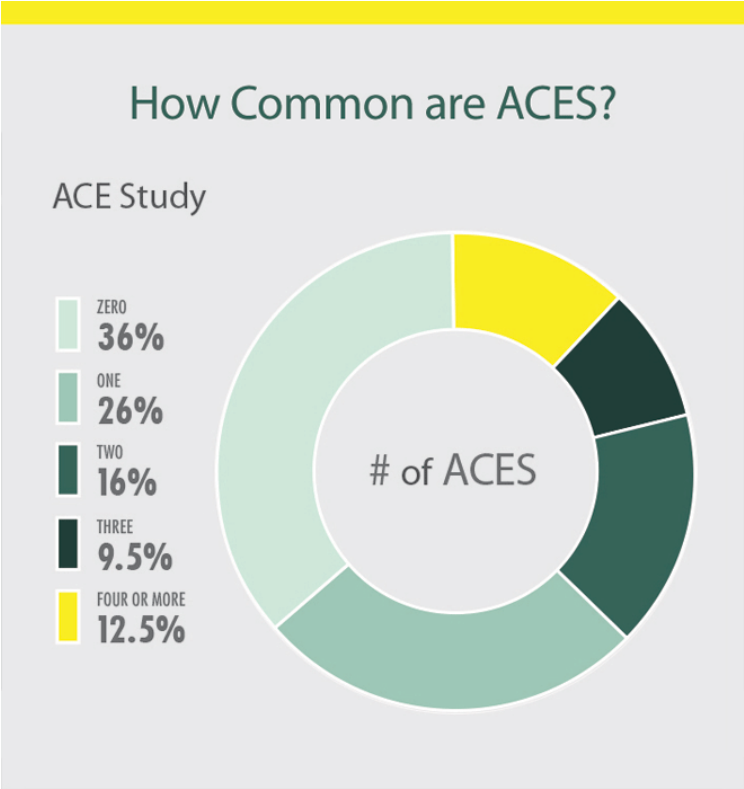
ELS frequency



64% have one or more

CDC, http://www.cdc.gov/violenceprevention/acestudy/

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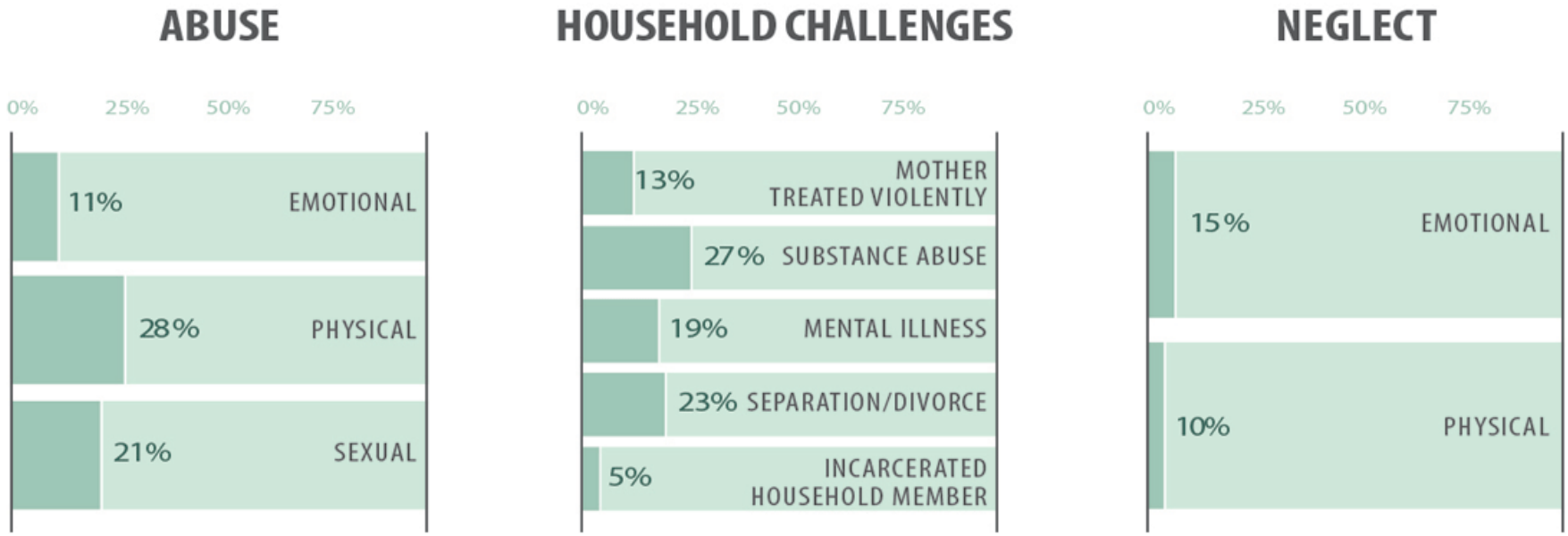
ELS frequency



CDC, http://www.cdc.gov/violenceprevention/acestudy/

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ELS events tend to occur in 'clusters' rather than individual events

Interpersonal violation	Family breakup	Familial health/death	Personal health trauma	Disaster/War
- Emotional abuse - Physical abuse - Neglect or poverty - Sexual abuse - Bullying - Domestic violence - Sustained family conflict	- Domestic violence - Sustained family conflict - Parental divorce or separation - Sibling separation	- Death in family - Family health trauma	- Surgery or hospitalisation - Life-threatening illness or injury	- Warfare - Disasters

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ELS and negative health outcomes

- Dose dependent relationships with negative health outcomes:
  - Alcohol use (OR = 7.4; 5.4-10.2)
  - Injection drug use (OR = 10.3; 4.9-21.4)
  - Diabetes, stroke, emphysema, heart disease, hepatitis, etc

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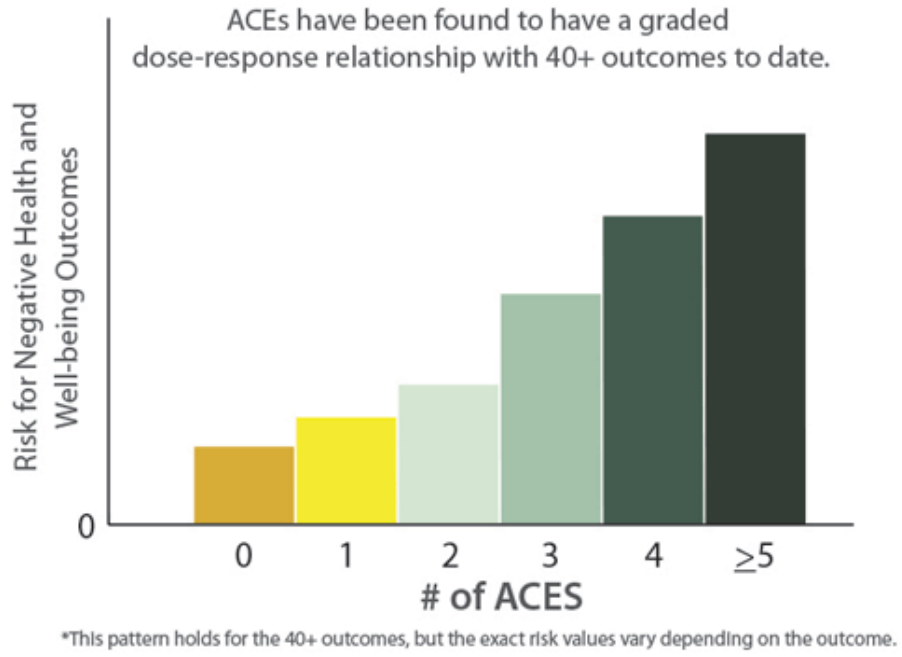
ELS and negative health outcomes

ACES can have lasting effects on….

- Health (obesity, diabetes, depression, suicide attempts, STDs, heart disease, cancer, stroke, COPD, broken bones)
- Behaviors (smoking, alcoholism, drug use)
- Life Potential (graduation rates, academic achievement, lost time from work)



CDC, http://www.cdc.gov/violenceprevention/acestudy/

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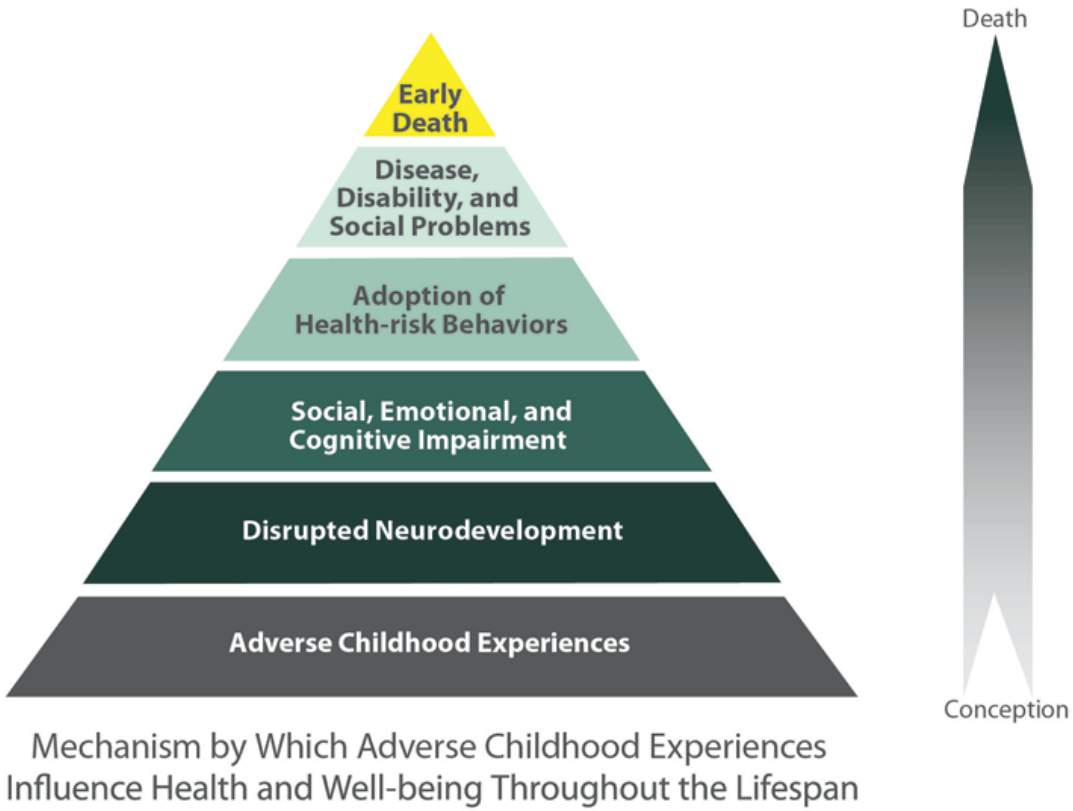
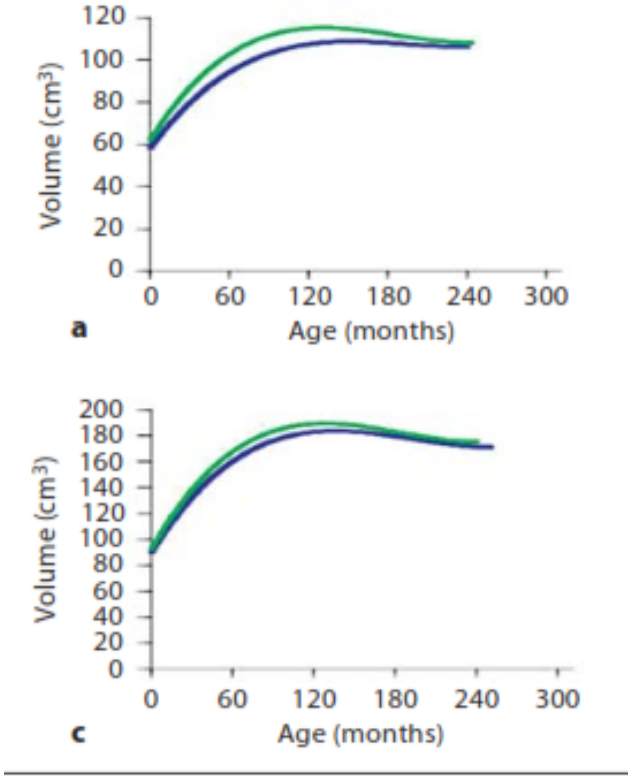
Model of ELS and health



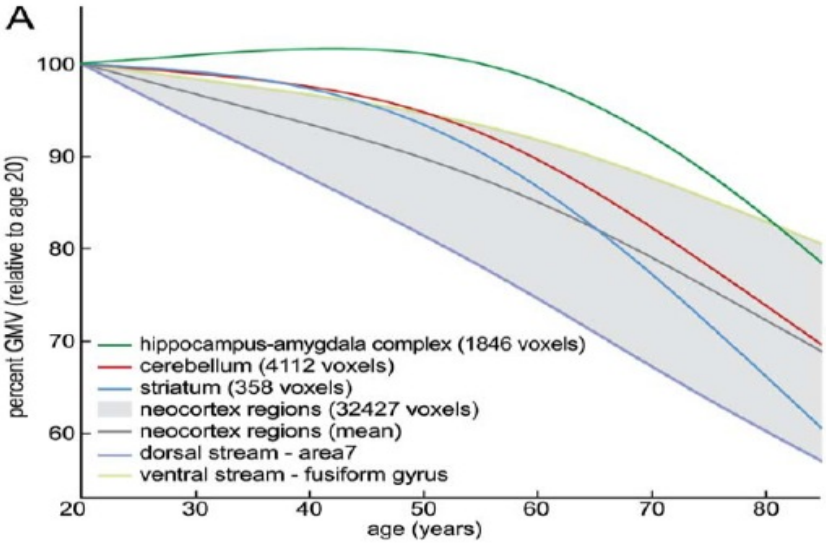
Mechanism by Which Adverse Childhood Experiences Influence Health and Well-being Throughout the Lifespan

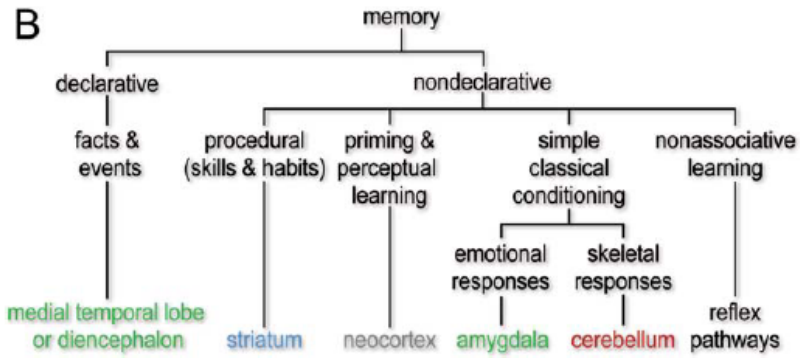
CDC, http://www.cdc.gov/violenceprevention/acestudy/

Early years are critical for brain development



Brain volume: temporal (top), frontal (bottom). Tanaka et al, 2012





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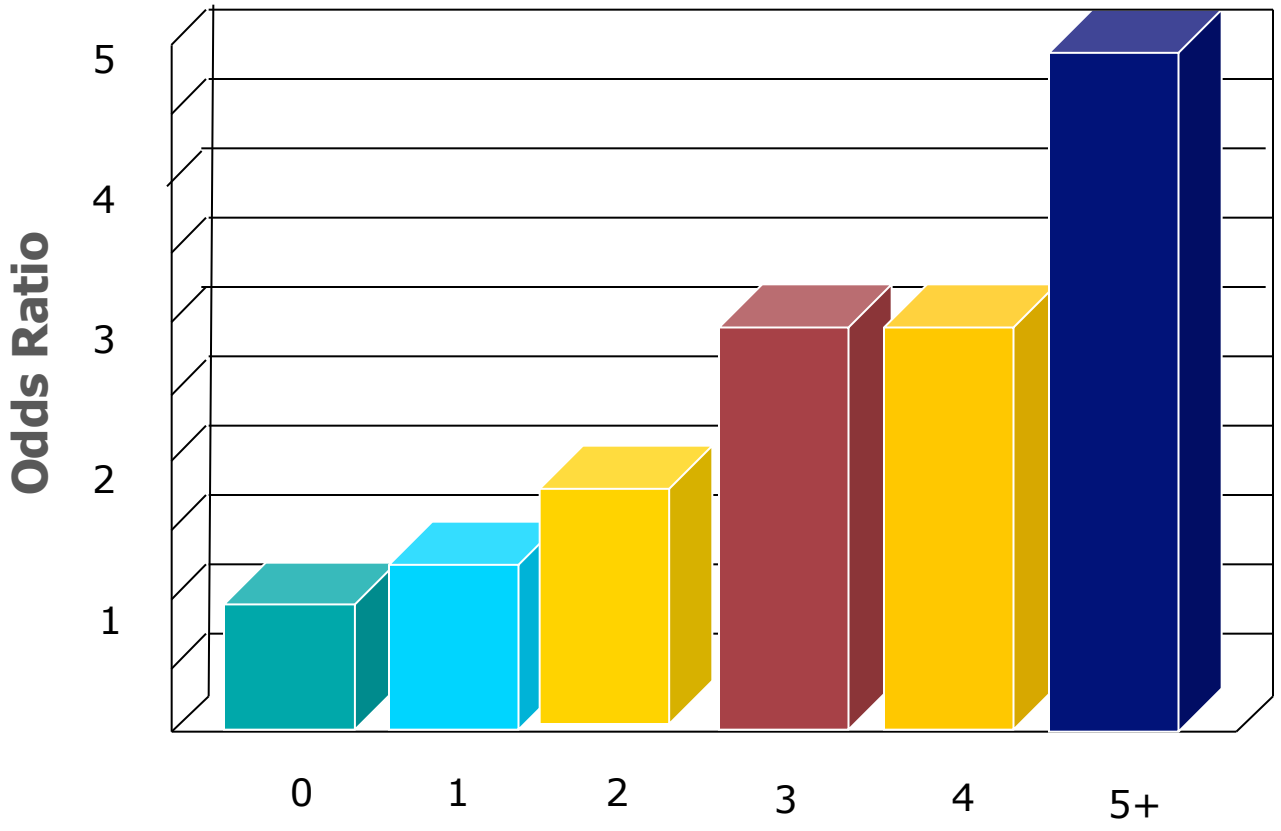
Risk of depression increases with # of ELS events



Source: Chapman et al,
J. Affective Disorders, 2004

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Impact of child/adult trauma on depression & anxiety symptoms

Journal of Psychiatric Research 47 (2013) 23–32

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Early life trauma predicts self-reported levels of depressive and anxiety symptoms in nonclinical community adults: Relative contributions of early life stressor types and adult trauma exposure

Denise A. Chu [a,b,*], Leanne M. Williams [a,b,1], Anthony W.F. Harris [a,b], Richard A. Bryant [a,c], Justine M. Gatt [a,b,1]

[a] *Brain Dynamics Centre, Westmead Millennium Institute & Discipline of Psychiatry, University of Sydney Medical School, Westmead, NSW 2145, Australia*
[b] *Discipline of Psychiatry, Sydney Medical School, University of Sydney, NSW 2006, Australia*
[c] *School of Psychology, University of New South Wales, Randwick, NSW 2052, Australia*

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Childhood exposure has higher risk than adult trauma

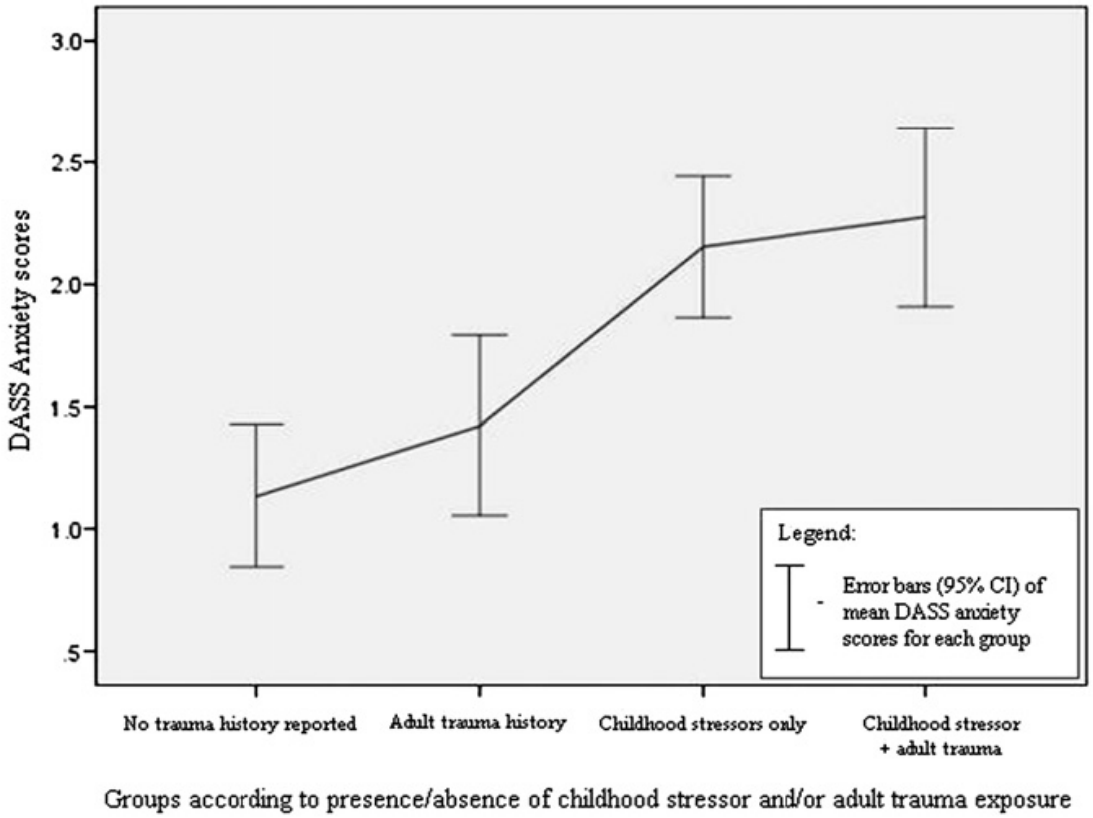

Fig. 2. Graph of mean DASS anxiety scores in nonclinical community adults according to self-reported early life stressor and adult trauma exposure ($n = 1088$).

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Interpersonal trauma is strongest predictor of depression/anxiety scores

Interpersonal violation	Family breakup	Familial health/death	Personal health trauma	Disaster/War
- Emotional abuse - Physical abuse - Neglect or poverty - Sexual abuse - Bullying - Domestic violence - Sustained family conflict	- Domestic violence - Sustained family conflict - Parental divorce or separation - Sibling separation	- Death in family - Family health trauma	- Surgery or hospitalisation - Life-threatening illness or injury	- Warfare - Disasters

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Mechanisms of ELS

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ELS and the brain – HPA axis

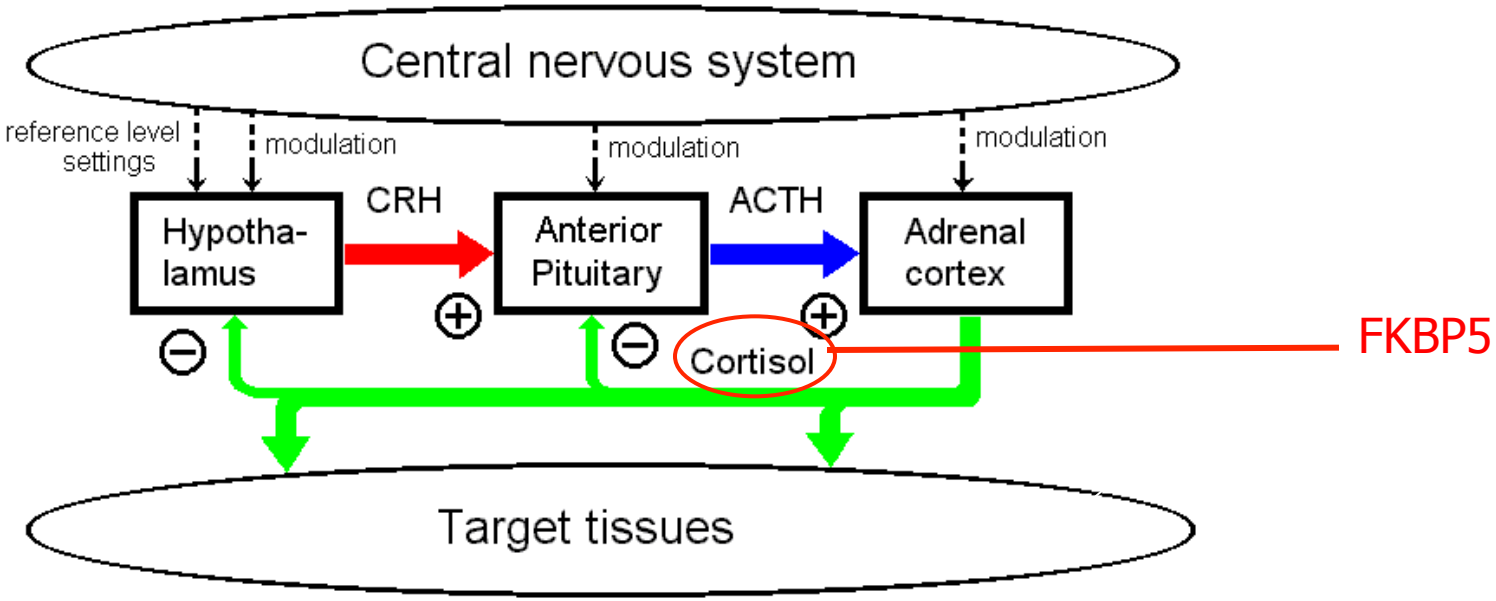

Fig 1. Structure diagram of the HPA axis

http://www.sfu.ca/~vkyrylov/Research/Physiology/HPA_model.html

ELS and the brain – Immune

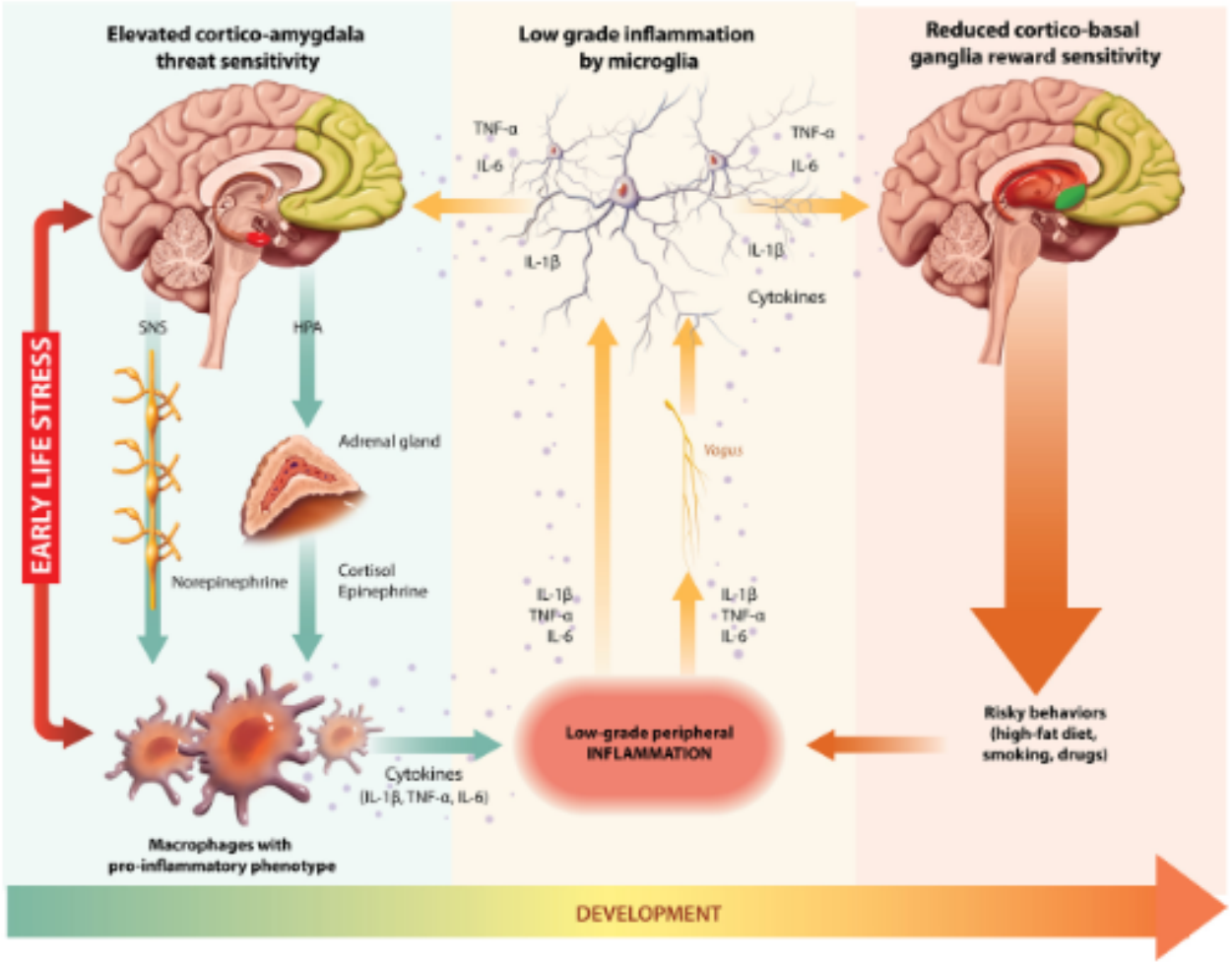

Figure 1. Depiction of neuroimmune network hypothesis. HPA, hypothalamic-pituitary-adrenocortical; IL-1β, interleukin-1β; IL-6, interleukin-6; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-alpha. Illustration by Chi-Chun Liu and Qingyang Chen.

Nusslock et al 2015

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ELS and brain integrity

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ELS and the brain

- MS increases plasma cortisol and ACTH
- MS downregulates glucocorticoid receptor protein

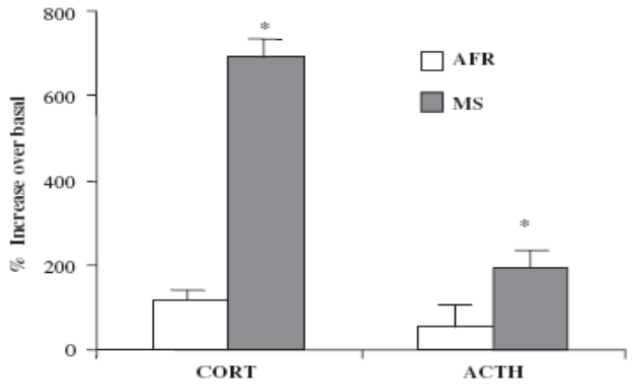

Fig. 3 Effect of maternal separation (MS) on plasma corticosterone and ACTH responses to an acute stressor (15 min swimming). Data are presented as percentage increase over basal values; $^{*}p<0.001$ vs control (AFR) rats, Student's *t*-test. Basal levels were 68.45±6.30 and 70.19±5.59 ng/ml (corticosterone) and 178.05±28.08 and 165.52±48.28 pg/ml (ACTH) for AFR and MS groups, respectively.

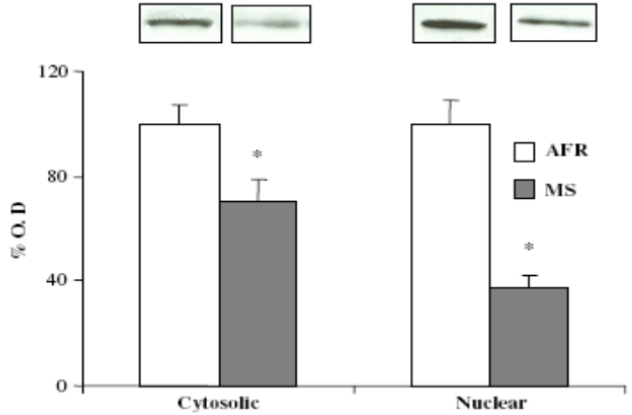

Fig. 4 Distribution of glucocorticoid receptor protein, in nuclear and cytosolic extracts from hippocampus of stressed AFR and MS rats. Data are expressed as percentage of optical density (OD) values of control rats (AFR). MS: maternal separation rats. $^{*}p<0.01$ vs AFR rats, Student *t*-test.

Aisa et al., 2007

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ELS and the brain

- 10-22% reduction in astrocyte density in hippocampus, prefrontal cortex, cingulate cortex, and basolateral amygdala (Leventopoulos et al., 2007).
- Reduced N-acetylaspartate (NAA) in anterior cingulate of monkeys 10 years after exposure to ELS (Mathew et al., 2003).
- Reduced spine densities in pyramidal cells of anterior cingulate and frontal cortex of rats exposed to prenatal stress (Murmu et al., 2006).
- Dendritric atrophy in CA3 pyramidal cells (prevented by NMDA antagonists – Gould et al., 1997).
- Reduced LTP in hippocampus (Yang et al., 2007).

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Harlow's studies of maternal attachment

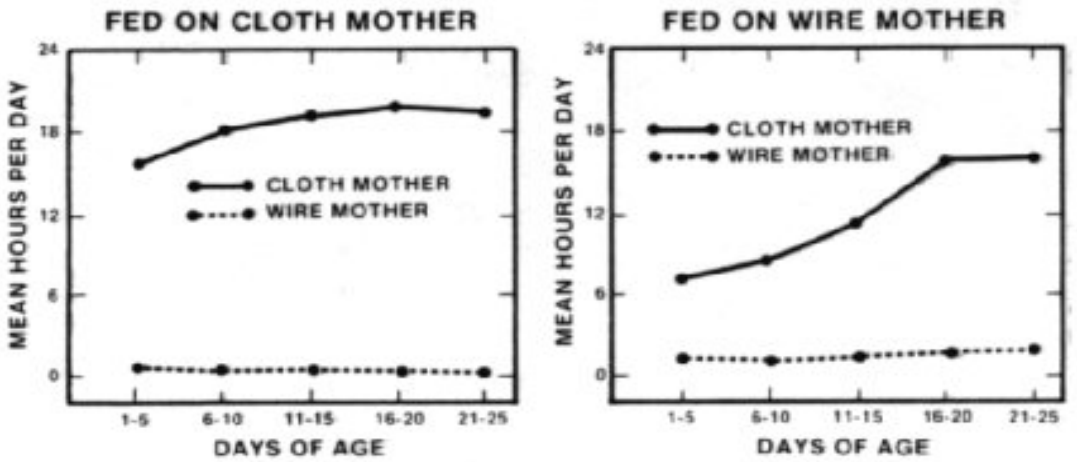

Figure 5. Time spent on cloth and wire mother surrogates.

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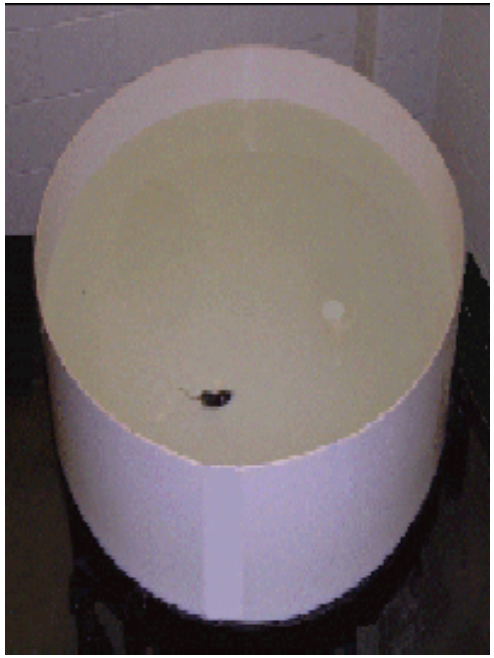
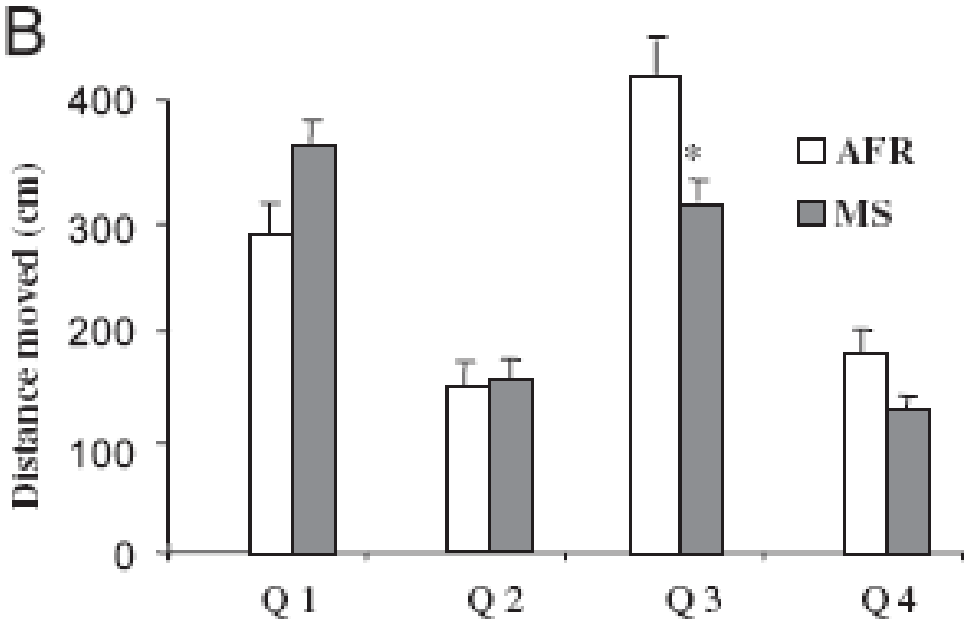
MS and Morris WMT



Morris WMT



Distance swam in each quadrant – platform used to be in quadrant 3.

Aisa et al., 2007

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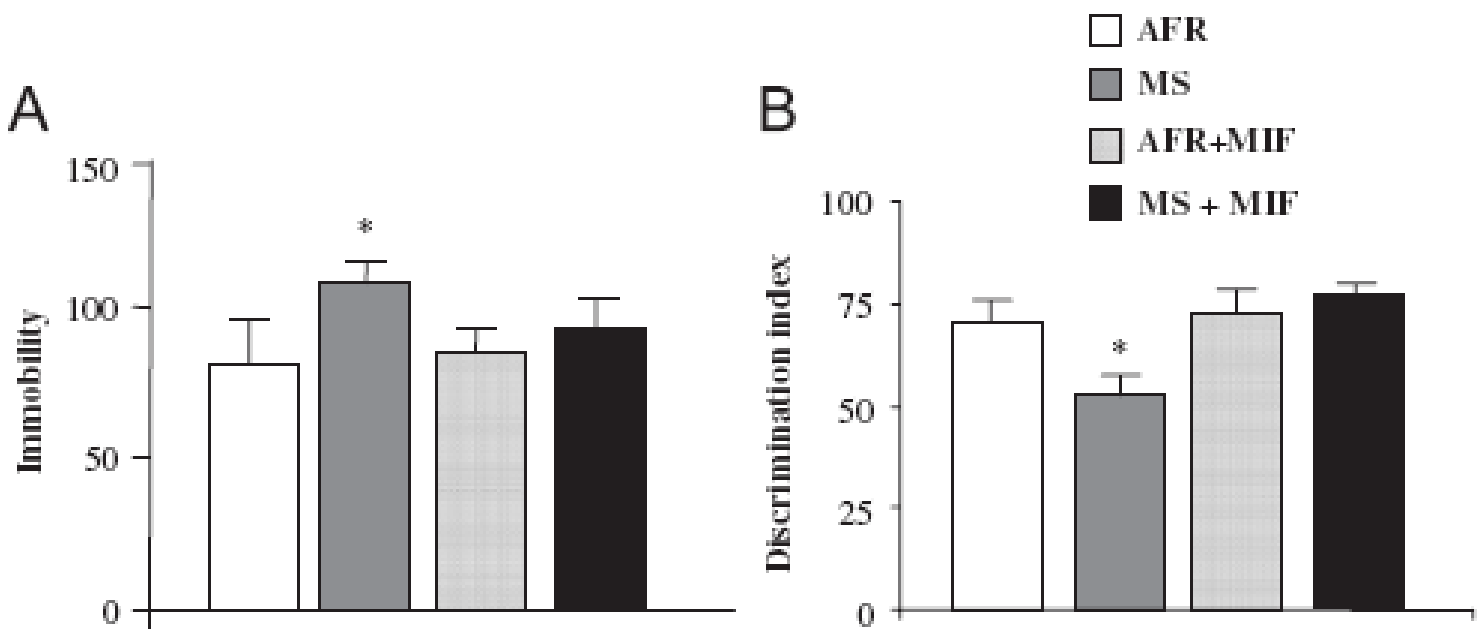
Mifeprestone treatment



A) Forced swimming test (immobility time); B) novel object

Aisa et al., 2007

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ELS and clinical populations

- Individuals with PTSD exhibit:
  - Reduced volume of the hippocampus (Bremmer, 1995, Gurvits et al., 1996; DeBellis et al., 1999)
  - Reduced volume of the corpus callosum (DeBellis et al., 1999, Teicher et al., 2004)
  - Reduced volume of anterior cingulate (Kitayama et al., 2006), and reduced NAA in anterior cingulate (De Bellis, 2000)
  - Elevated CRH in CSF (de Kloet et al., 2006)

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ELS and clinical populations

Table 1. Prevalence and Co-occurrence of Adverse Childhood Events (ACE)

ACE	% Of Total	ACEs (Total)	%
Divorce	22.2	0	31.8
Severe Family Conflict	20.3	1	22.3
Separated from Family	16.1	2	15.3
Premature Birth	15.6	3	9.2
Major Illness in Family	14.9	4	5.1
Bullied	17.4	5	4.0
Death in Family	11.3	6	2.8
Emotional Abuse	12.3	7	2.2
Domestic Violence	11.8	8 or more	2.0
Hospitalization/Surgery	9.4		
Natural Disaster	7.6		
Major Illness (Self)	7.4		
Physical Abuse	5.2		
Sexual Abuse	4.6		
War	4.1		
Poverty/Neglect	3.7		
Fire Destroyed Home	1.5		
Adoption	1.2		

ACEs-Total excludes premature birth.

~ 50% females

Sexual/emotional abuse > in females

Bullying > in males.

Cohen et al. Biol. Psychiatry, 2006
n=1045 from community sample
Chu et al. J Psychiatric Research, 2013
n=1209 from community sample

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ELS and gray matter

- 265 healthy controls
  - ELS defined as high (2 or more) vs. none

Table 2. Volume of Brain Structures as a Function of Early Life Stress

Brain Structure	ACE-None	ACE-High
ACC		
Right	3.667 ± .537	3.518 ± .571
Left	4.744 ± .702	4.602 ± .734
Amygdala		
Right	1.27 ± 1.40	1.26 ± 1.43
Left	1.16 ± 1.28	1.15 ± 1.36
Caudate Nucleus		
Right	2.773 ± .309	2.681 ± .310
Left	2.941 ± .348	2.875 ± .351
Hippocampus		
Right	3.166 ± .390	3.079 ± .400
Left	3.380 ± .400	3.279 ± .406

Measurements in mm^3 for each structure bilaterally. Bold indicates between-group differences ($p < .05$). ACE, adverse childhood event; ACC, anterior cirgulate cortex.

BIOL PSYCHIATRY 2006;59:975–982

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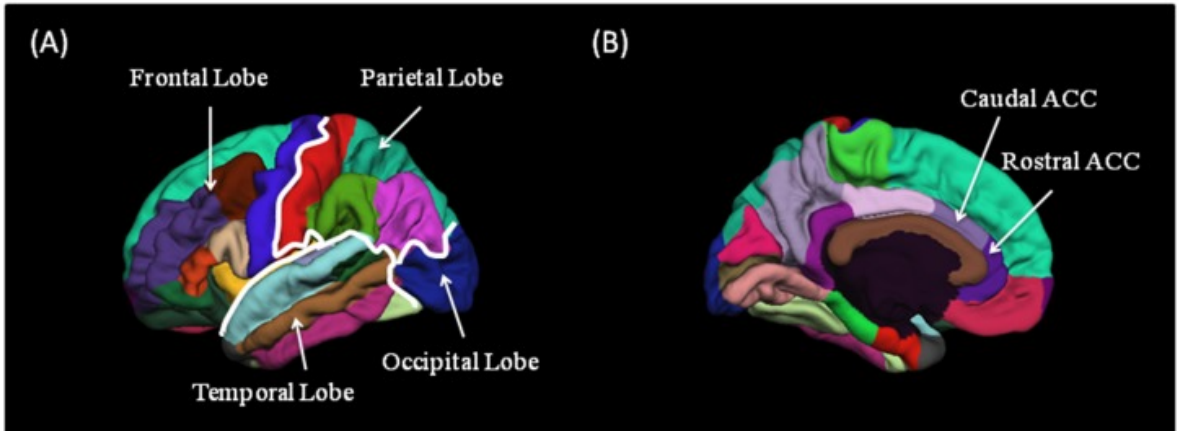
Early Exposure to Traumatic Stressors Impairs Emotional Brain Circuitry

Mayuresh S. Korgaonkar[1,2*], Cassandra Antees[1], Leanne M. Williams[1,2,3], Justine M. Gatt[1,2], Richard A. Bryant[4], Ronald Cohen[5], Robert Paul[6], Ruth O'Hara[3], Stuart M. Grieve[1,7]



ACC and amygdala are *reduced* in adolescents 13-18 years w/ >2 ELS events

Summary: cortical gray matter is affected.

Korgaonkar et al. PLOS ONE, 2013

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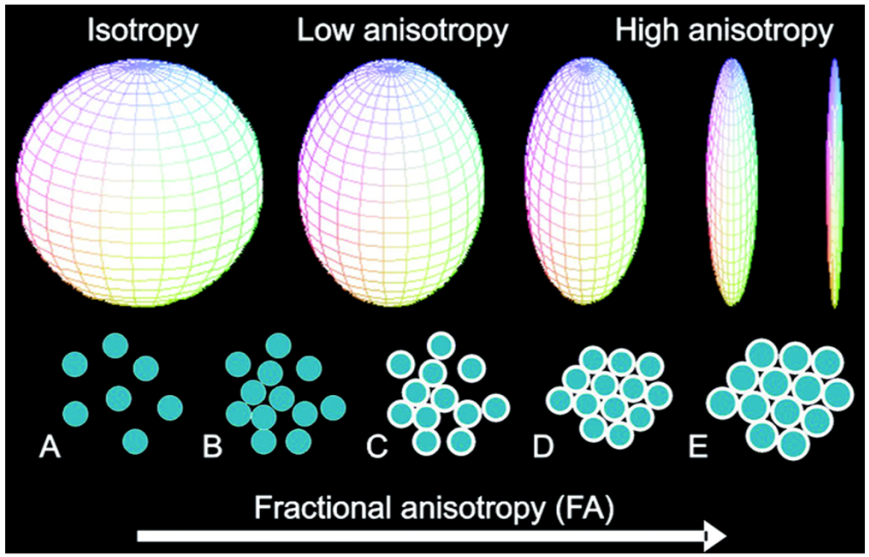
White matter: diffusion tensor

- Mean Diffusivity (MD)
  - The amount of total diffusion in a given voxel

- Fractional Anisotropy (FA)
  - The non-uniformity of diffusion with direction
  - FA is highly sensitive to microstructural changes, it is less specific to the type of change.



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White matter: diffusion tensor

Table 2 DTI outcomes among those with either ELS low or ELS high across the three age groups

Age group	ELS high *n*	ELS low *n*	ELS high FA	ELS low FA
8–12	6	3	0.19 (.16)	0.38 (0.06)
18–50	62	10	0.44 (.10)	0.46 (0.07)
51–73	21	5	0.30 (.13)	0.40 (0.08)

FA, fractional anisotropy (range is 0–1.0).

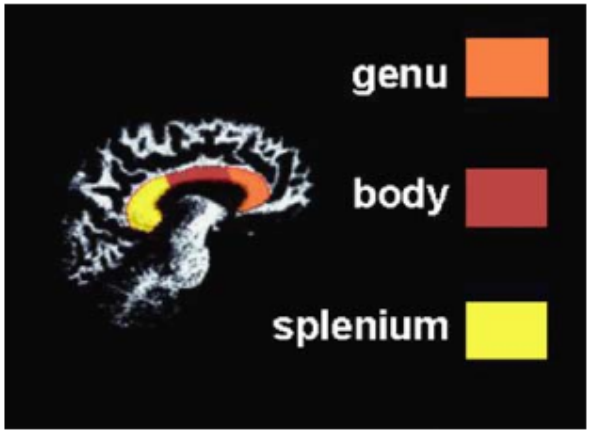

Fig. 1 Demarcated regions of the corpus callosum. For the present study only the region of the genu was included in analyses

Brain Imaging and Behavior (2008) 2:49–58
DOI 10.1007/s11682-007-9015-y

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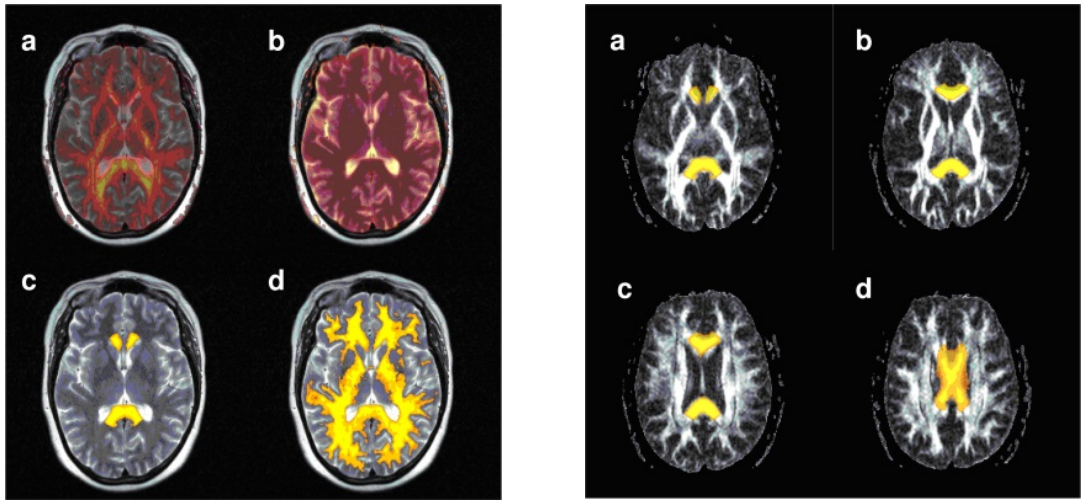
ELS and DTI

- n=116 participants with histories of ELS



	Age	Education
ELS-high:	41.0 (16.5)	14.6 (2.7)
ELS-none:	38.1 (17.2)	13.6 (2.6)

Neuropsychiatric Disease and Treatment 2008:4(1) 193–201

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ELS and DTI

Table 1

	ELS total	ELS high	ELS none
Age	38.5 (16.1)	41.0 (16.5)	38.1 (17.2)
Education	13.8 (2.7)	14.6 (2.7)	13.6 (2.6)
Handedness	R (91%), L (9%)	100%	R (93%), L (7%)
Gender	54% female, 46% male	60% female, 40% male	53% female, 47% male
DASS depression	4.9 (9.6)	3.3 (3.0)	2.2 (3.0)
DASS anxiety	2.6 (3.6)	1.7 (1.8)	1.1 (1.8)
DASS stress	7.0 (6.4)	4.6 (4.2)	3.3 (2.9)

Neuropsychiatric Disease and Treatment 2008:4(1) 193–201

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ELS and DTI

Table 3 FA values and gross morphometry for the whole group and ELS-high vs. ELS-none

Variable	Whole group	ELS-High	ELS-None
Mean FA Value – Whole CC	0.54 (0.09)	0.49 (0.13)	0.54 (0.08)
Mean FA Value – Genu*	0.45 (0.09)	0.39 (0.13)	0.45 (0.07).
Mean FA Value – Body	0.56 (0.11)	0.50 (0.16)	0.57 (0.09)
Mean FA Value – Splenium	0.58 (0.10)	0.55 (0.12)	0.58 (0.10)
Mean volume – Whole CC	18.3 (2.9)	17.8 (3.5)	18.3 (2.7)
Mean Volume – Genu	5.6 (1.0)	5.5 (1.3)	5.5 (0.95)
Mean Volume – Body	4.4 (0.71)	4.3 (0.77)	4.3 (0.71)
Mean Volume – Splenium	8.4 (1.3)	8.0 (1.7)	8.4 (1.2)

* = Significant differences ($p < .05$); FA = fractional anisotropy

Neuropsychiatric Disease and Treatment 2008:4(1) 193–201

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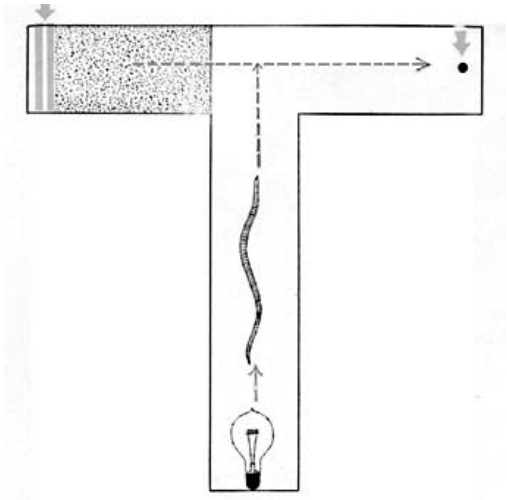
Age of onset

- We next wanted to understand if critical windows of development existed that would influence the effects of ELS on brain integrity.

- "infantile amnesia"



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ELS and DTI

Table 2 Mean volume of brain structures as a function of early life stress

Brain structure	No ELS	Early childhood ELS (Ages 1 month–7 years)	Later childhood ELS (Ages 8–17 years)	P value
ACC	5304.98 ± 691.41	5088.16 ± 642.01	5046.27 ± 594.07	.061
*Right	5139.32 ± 677.85	4941.91 ± 618.97	4894.01 ± 576.51	.018
*Left	5470.64 ± 704.96	5234.41 ± 665.05	5198.53 ± 611.63	.031
Amygdala	1219.12 ± 128.45	1194.16 ± 129.94	1209.53 ±115.87	.237
Right	1277.76 ± 138.46	1243.35 ± 137.79	1267.71 ± 125.45	.181
Left	1160.47 ± 124.80	1135.22 ± 117.61	1151.34 ± 111.82	.354
Caudate nucleus	3256.08 ± 336.47	3134.11 ± 349.40	3169.67 ± 357. 69	.079
Right	3289.55 ± 356.77	3148.47 ± 352.34	3214.37 ± 386.48	.077
Left	3222.62 ± 337.46	3093.27 ± 330.11	3124.97 ± 339.38	.097
Hippocampus	3943.20 ± 454.42	3887.05 ± 418.47	3843.47 ± 387.72	.558
Right	3860.04 ± 451.57	3792.72 ± 409.40	3575.45 ± 380.63	.531
Left	4026.36 ± 473.78	3956.82 ± 428.71	3929.50 ± 405.76	.608
Insula	8286.63 ± 1032.23	8025.02 ± 941.17	7890.26 ± 887.92	.053
Right	8212.37 ± 1084.66	7982.27 ± 884.89	7835.26 ± 903.88	.155
*Left	8360.55± 1004.84	7980.72 ± 909.42	7945.26 ± 897.19	.018

Mean ± Standard deviation shown in table, Measurements in mm^3 for each structure bilaterally. *Between-group differences ($p < .05$)

Brain Imaging and Behavior (2013) 7:196–203

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Genetic variables

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BDNF met as 'risk' allele in brain but no direct impact on depression symptoms

Brain Derived Neurotrophic Factor (BDNF)
BDNF Val66Met polymorphism

BDNF is involved in brain plasticity.
It has a direct effect on plasticity of
amygdala and on frontal-hippocampal circuits

The Met allele is present in about 20% of people and is linked to reduced plasticity

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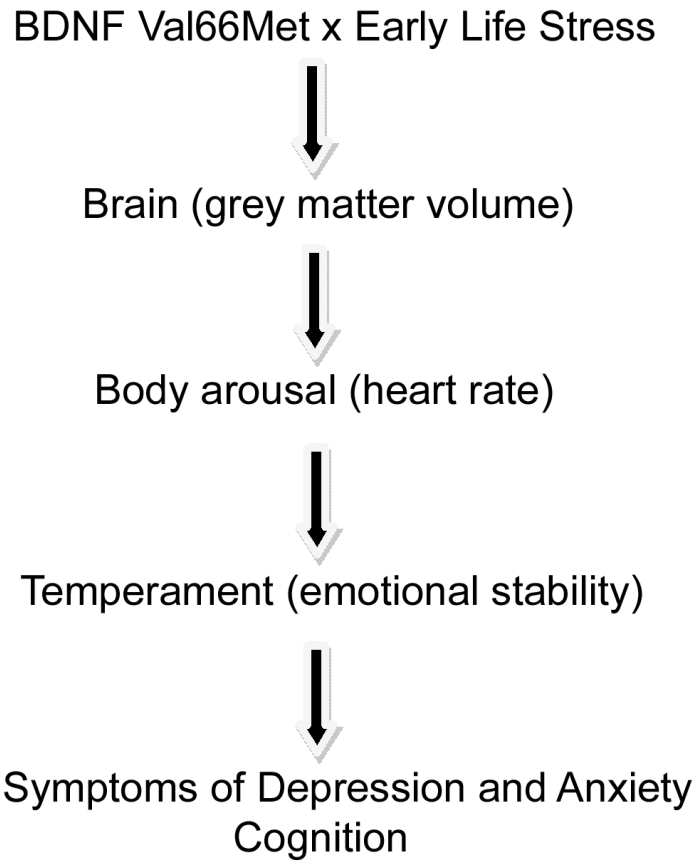
BDNF met as 'risk' allele in brain but no direct impact on depression symptoms



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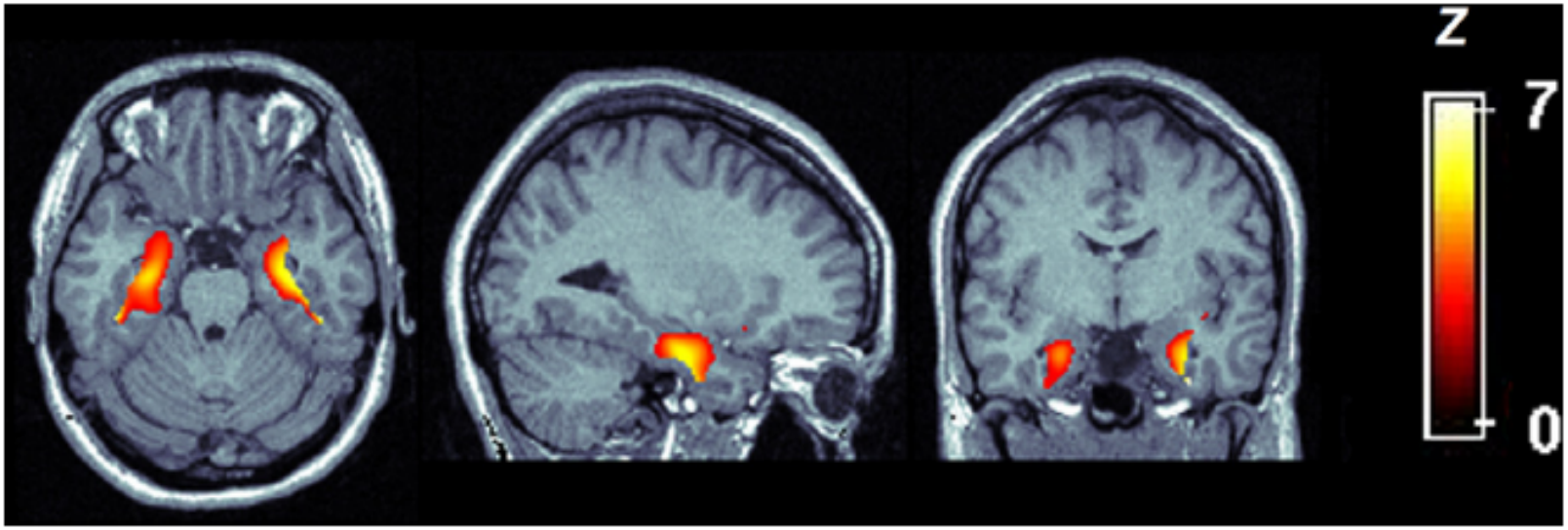
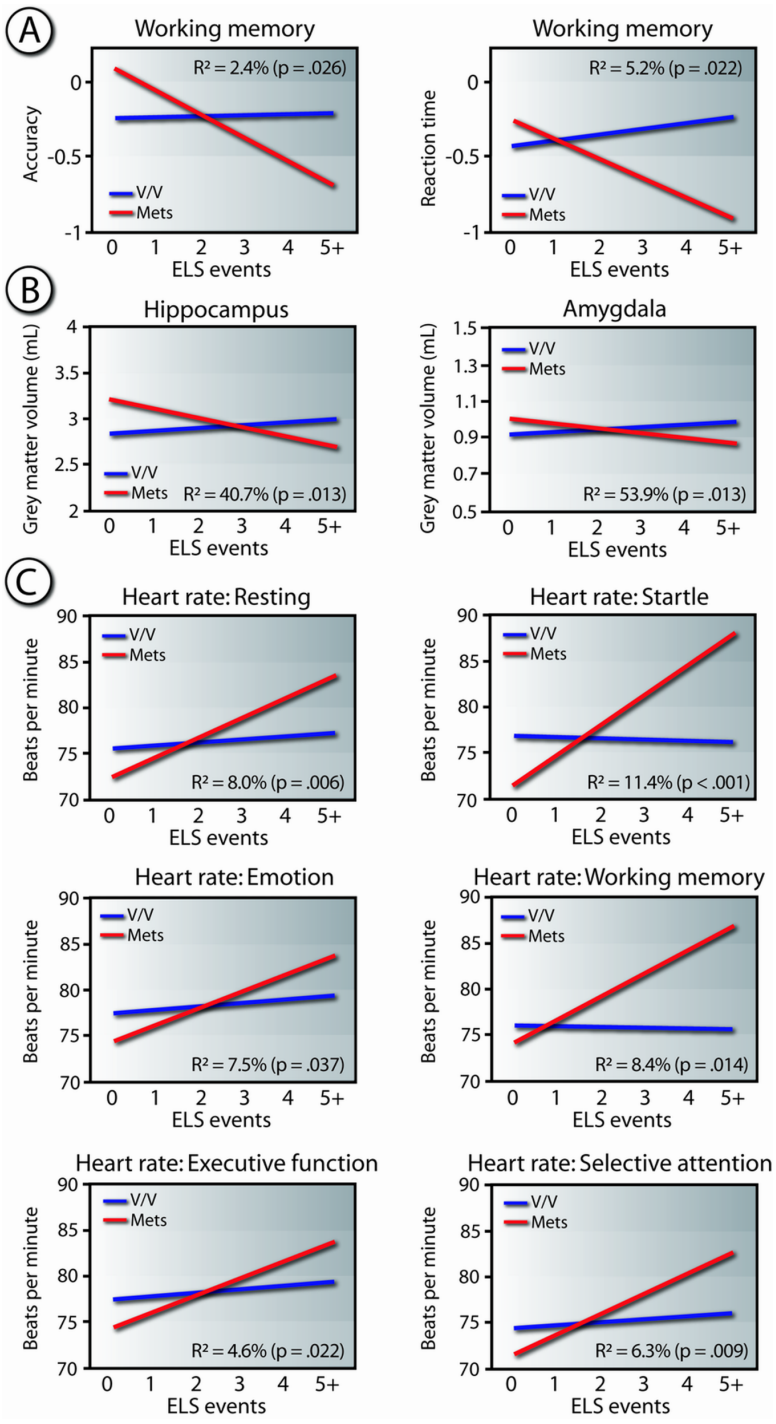
BDNF Mets as 'risk' allele in brain but no direct impact on depression symptoms



- BDNF Met allele carriers show reductions in grey matter volume of hippocampus, relative to VV genotypes

Schofield et al., 2009, Biol Psychol, 80



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Serotonin transporter gene

5HT Transporter Gene

People with the Short allele variant of the 5HT Transporter have a higher risk for depression, especially when coupled with stress

The Short allele is present in about 40% of people

Dunedin birth cohort in New Zealand

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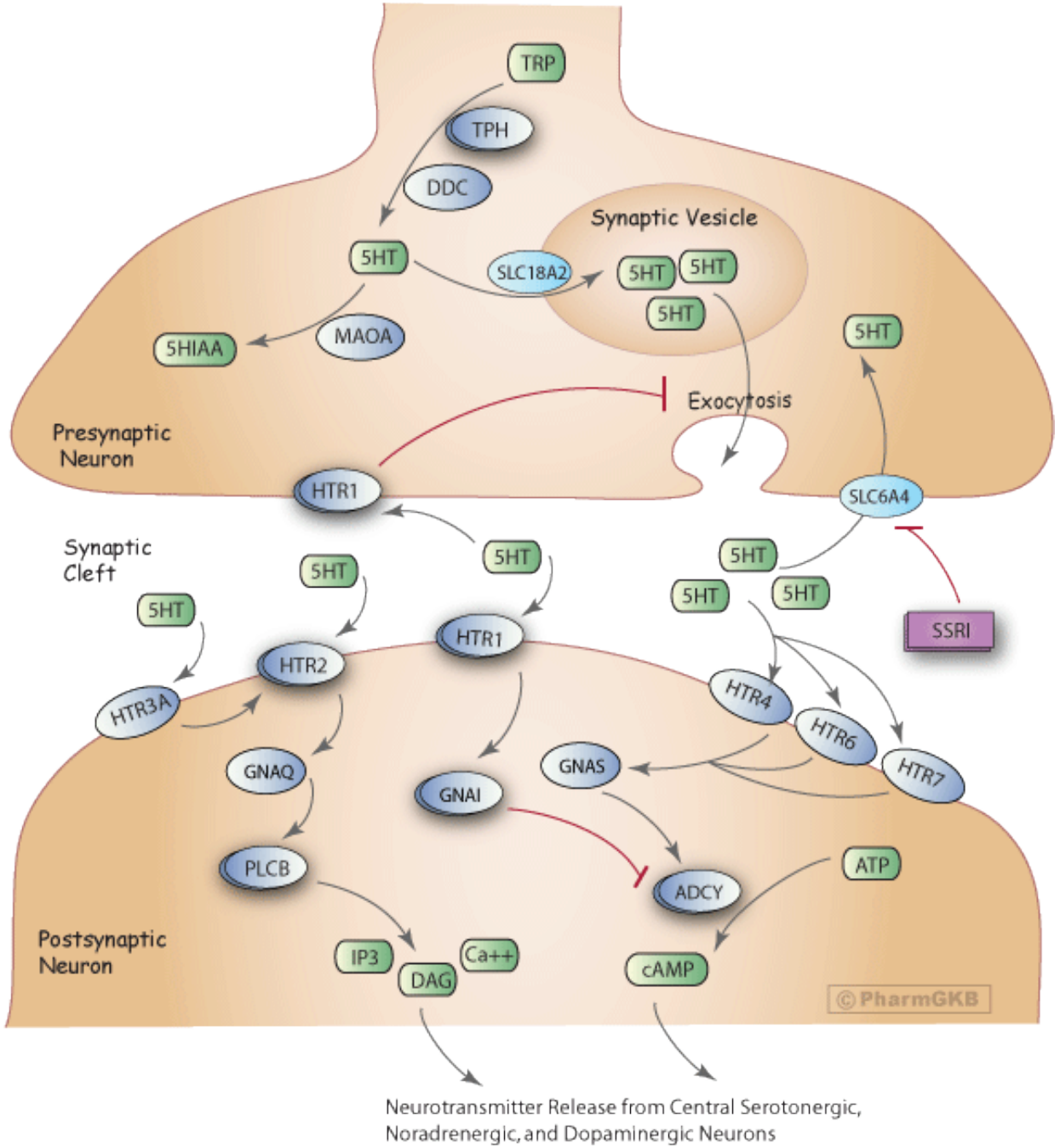

Neurotransmitter Release from Central Serotonergic, Noradrenergic, and Dopaminergic Neurons

https://www.pharmgkb.org/pathway/PA161749006

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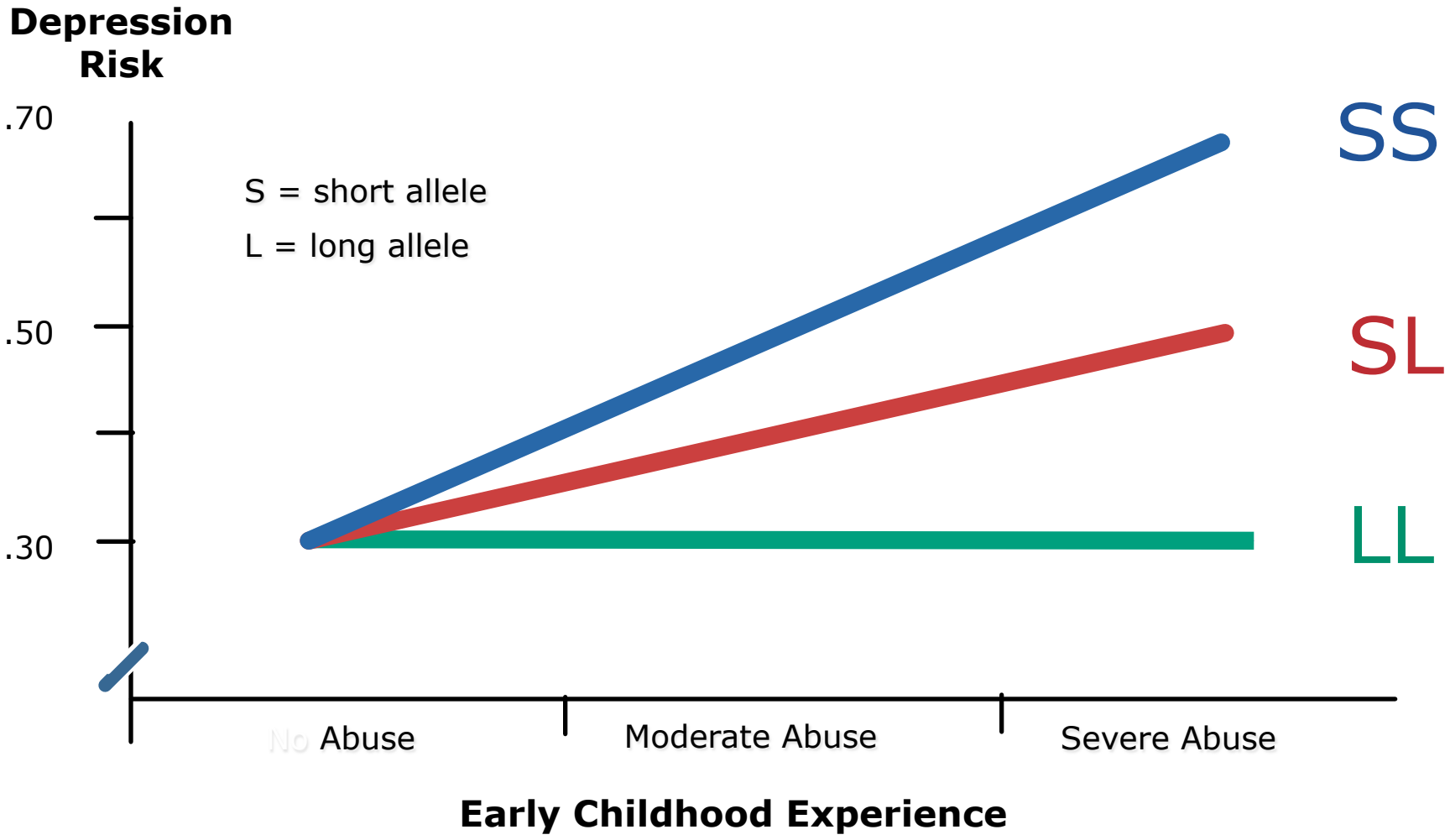

Caspi et al. Science, 2003

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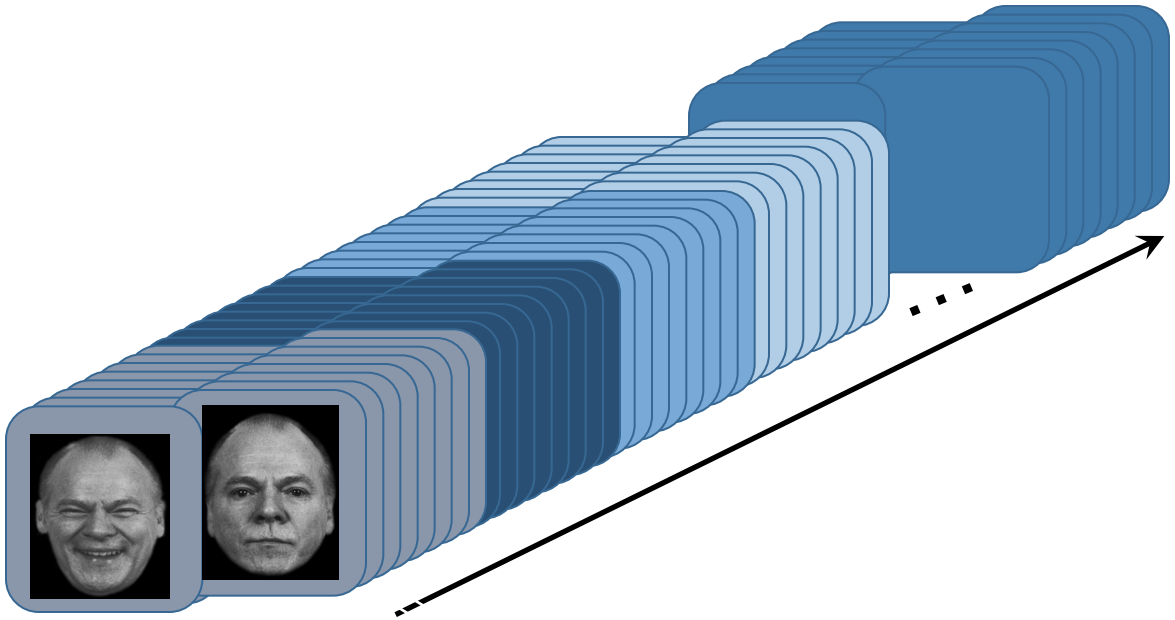
Short allele and emotion processing



Williams et al., Human Brain Mapping, 2004; Williams et al., Human Brain Mapping, 2006; Williams et al., J Neuroscience, 2006a,b; Williams et al., Neuroimage, 2009, 2010; Korgaonkar et al., Neuropsychopharmacology 2013

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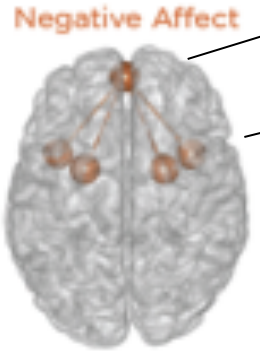
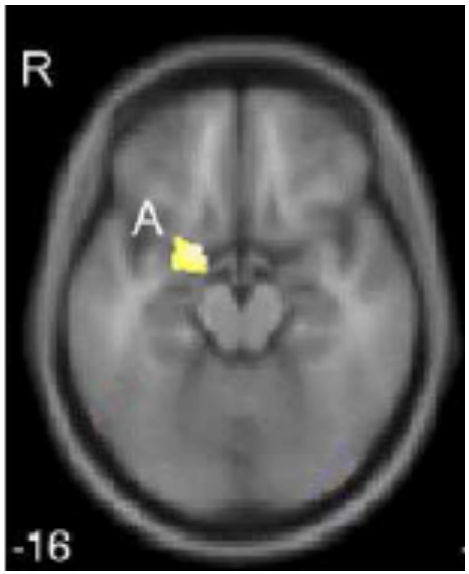
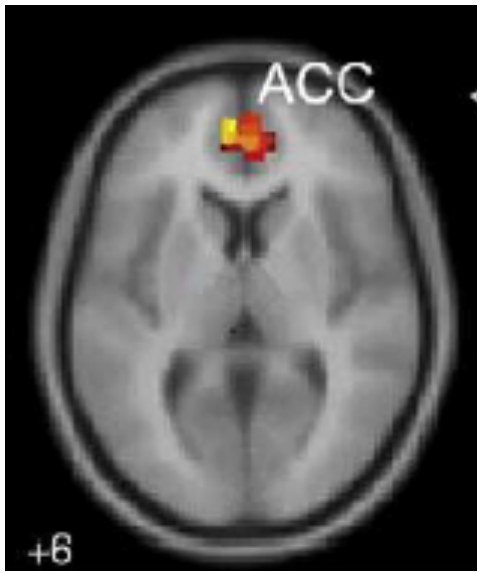
Anterior Cingulate

Amygdala







Amygdala (A) and Anterior Cingulate (ACC) activation is …
•greater in people with the 5HT Transporter Short Allele.
•greatest in Short allele carrriers who also have >2 traumatic events.

This hyper-activation predicts greater symptomatic risk for depression

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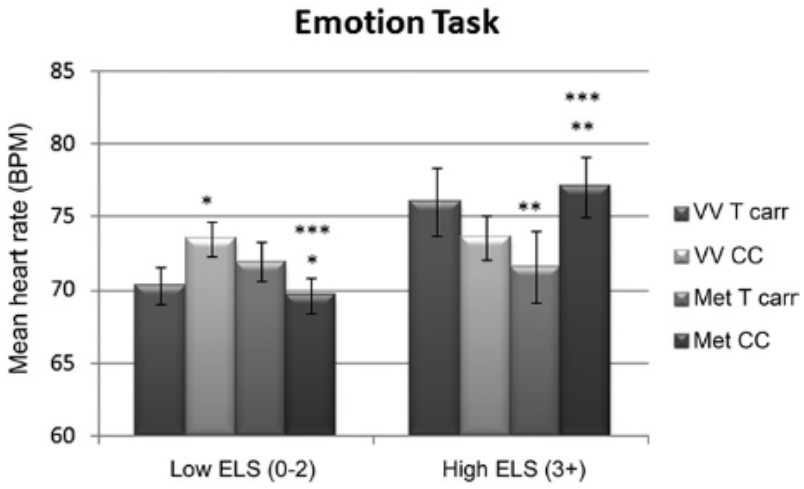
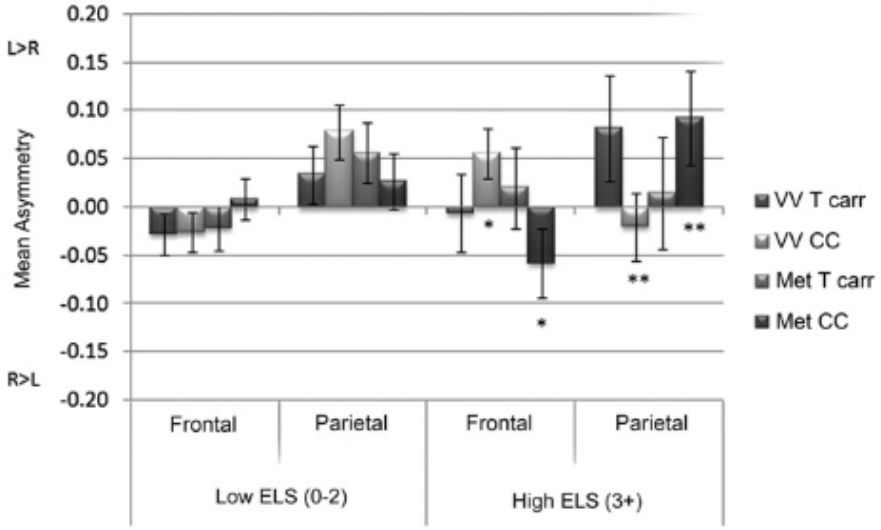
BDNF + serotonin 3A

- Brain derived neurotropic factor, met66val polymorphism. met/met < val/val
- Serotonin 3A, HTR3ACC vs T





Worst outcomes among Met CC: reduced neuroprotection and decreased serotonin 3A receptor expression

Gatt et al. Biological Psychiatry, 2010

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Treatment response

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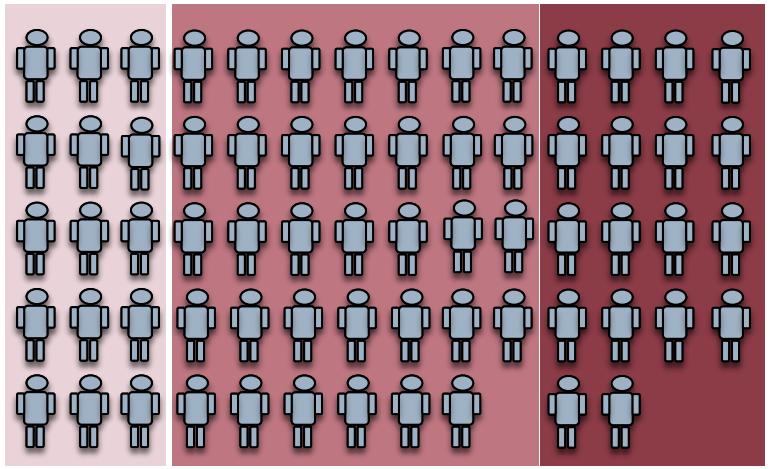
ELS predicts antidepressant treatment response



Low ELS	Mid ELS	High ELS
60%	20.6%	16.7%

Williams et al., Translational Psychiatry, in press

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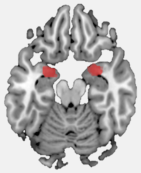
Phase of Study

Pre-Treatment Assessment Week 0

ELS Questionnaire

QIDS
HAM-D
SOFAS



Amygdala Function

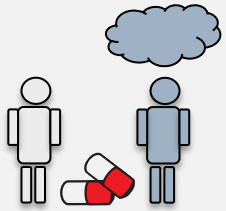
Randomized to

Escitalopram
Sertraline
Venlafaxine-XR

Weeks 2, 4 and 6

Telephone Monitoring

Final Visit Week 8



Primary Outcome: Functional Remission

<= 7 HAM-D >= 61 SOFAS
<= 5 QIDS >= 10 improvement

Naturalistic Follow-up

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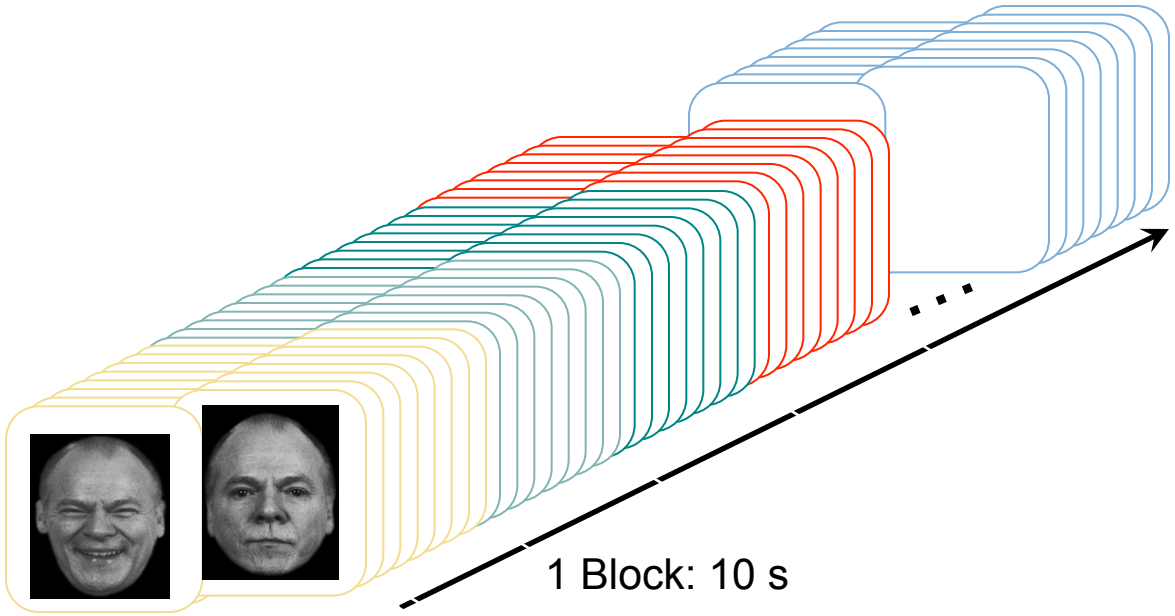
Amygdala test



Williams et al., Human Brain Mapping, 2004; Williams et al., Human Brain Mapping, 2006;
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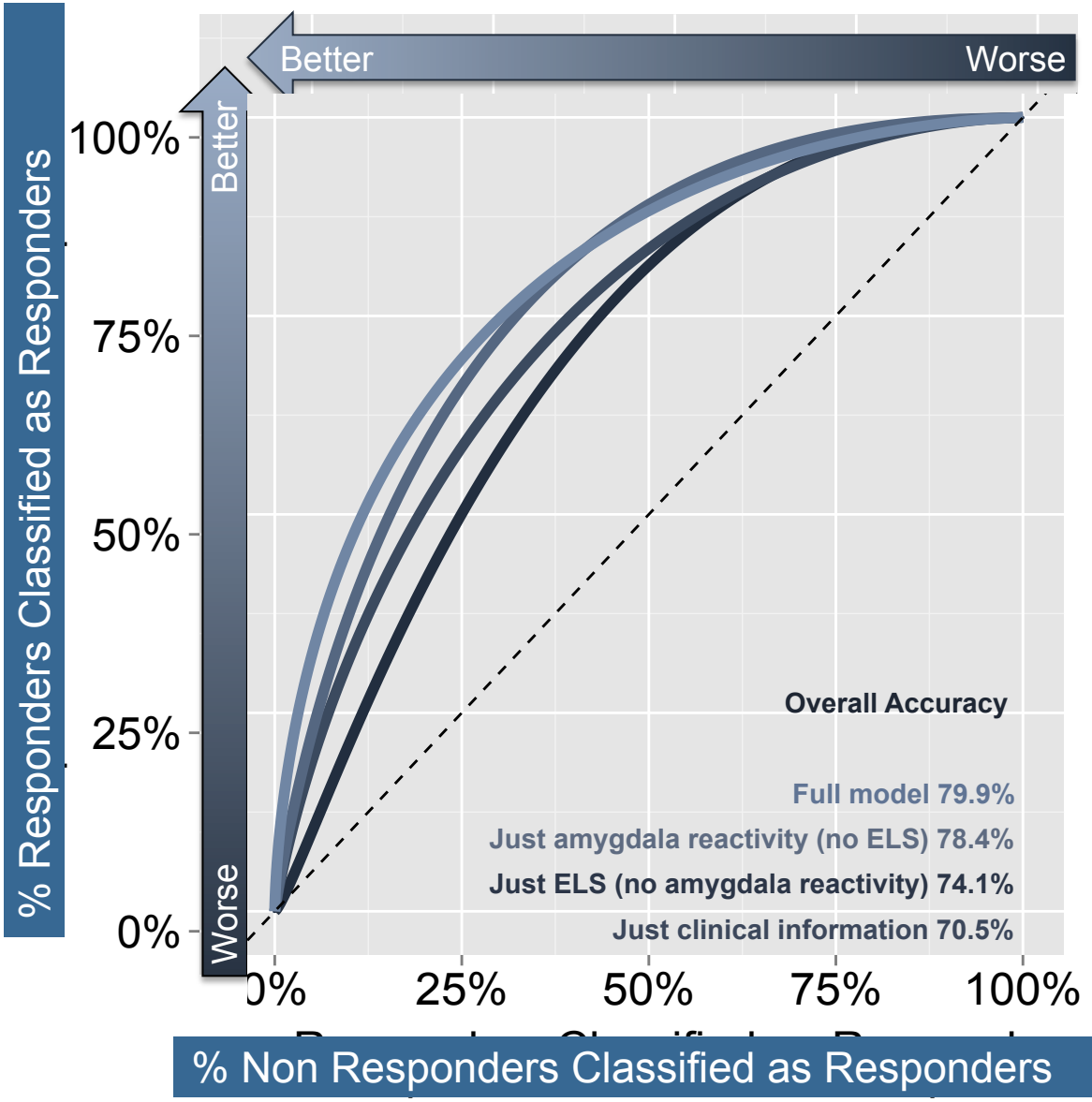
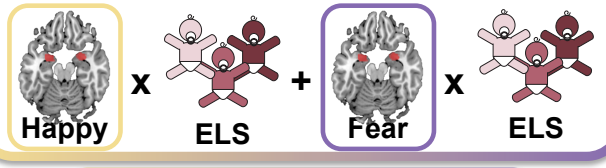


Full Interaction Model



Full Additive Model

ELS Model

+ Covariates

Covariate Model

Age + Education +
MDD Duration/Severity

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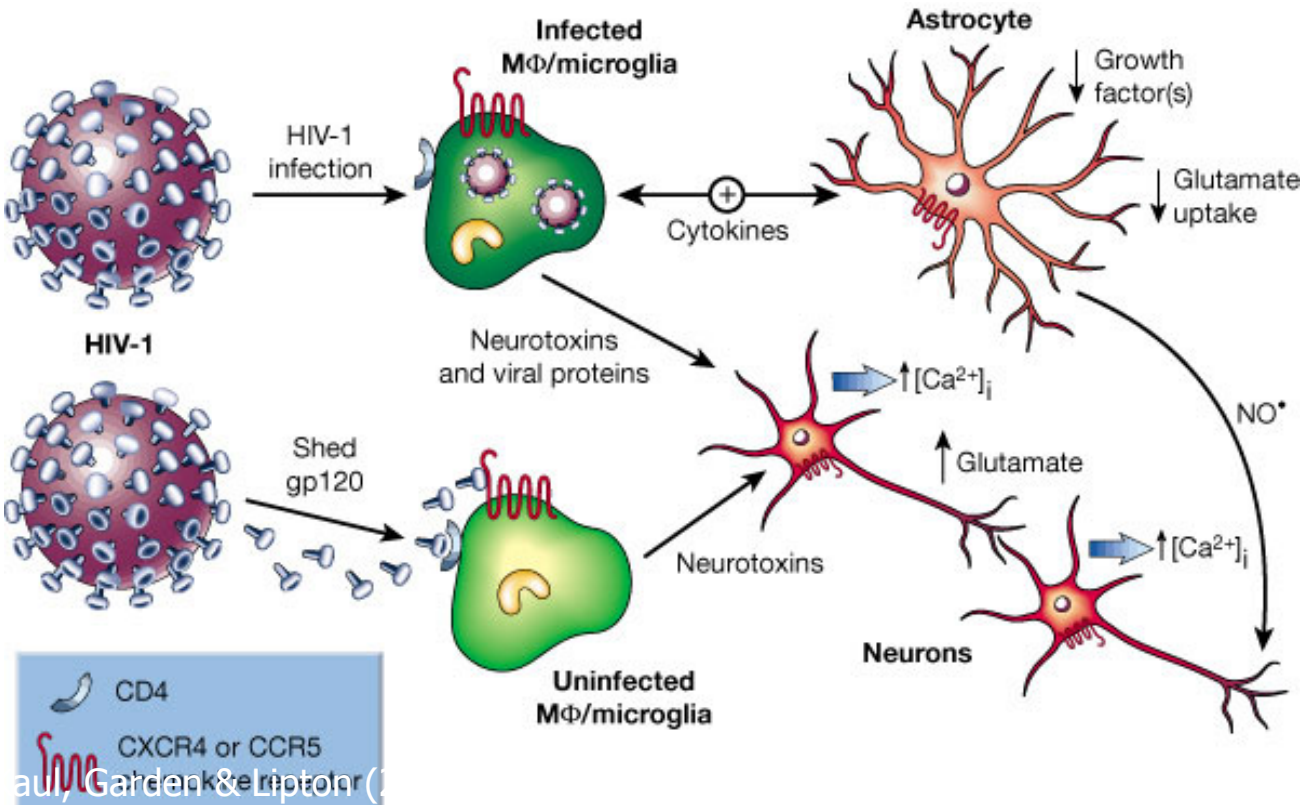
ELS and HIV



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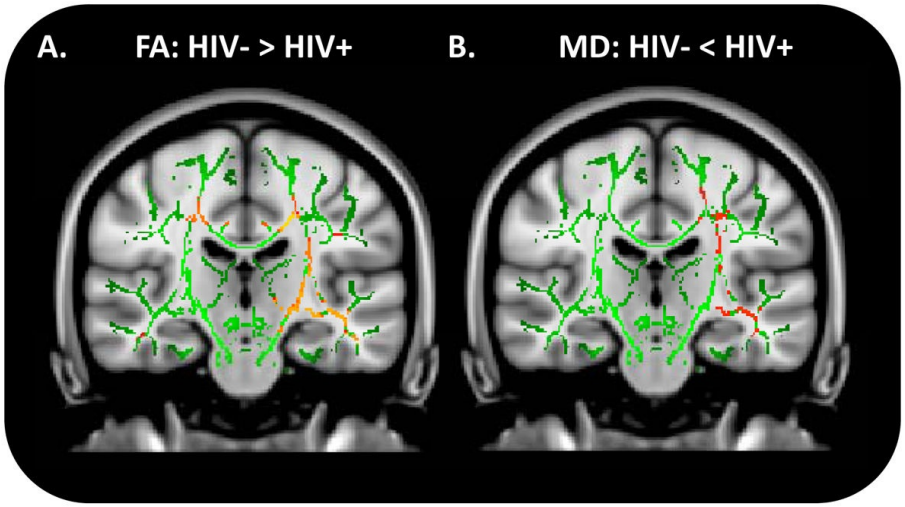
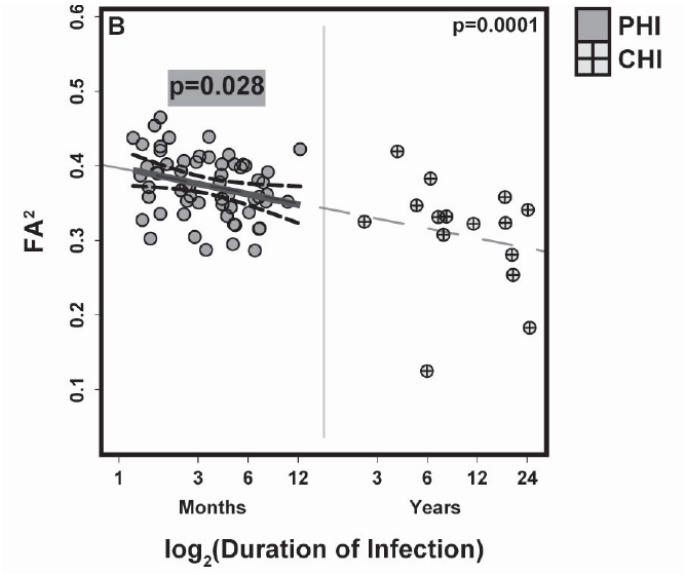
HIV disrupts subcortical white matter integrity



Voxelwise comparisons for FA (A) and MD (B) using Tract-Based Spatial Statistics (TBSS). Red: p=0.05; Orange: p=0.03; Yellow: p=0.01. Ances lab 2014



Scanned 4 months post infection. Significant correlations between FA and CSF protein and CSF serum/albumin ratio.

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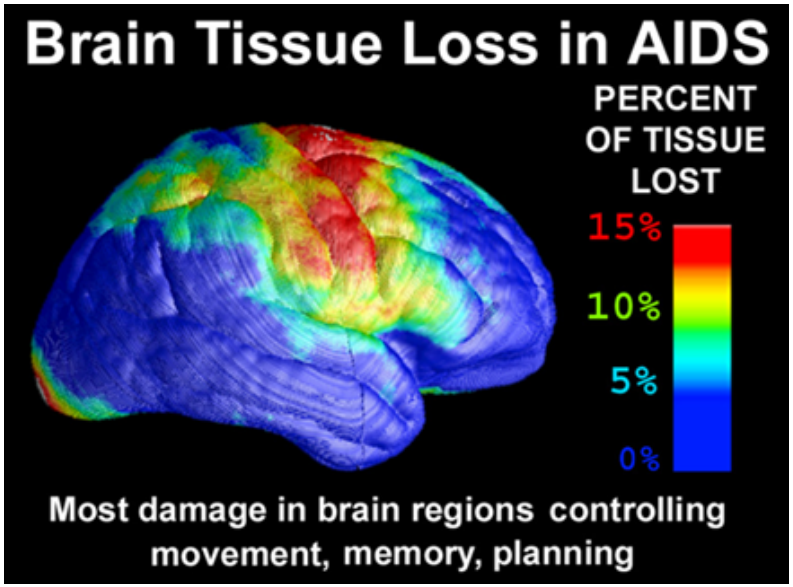
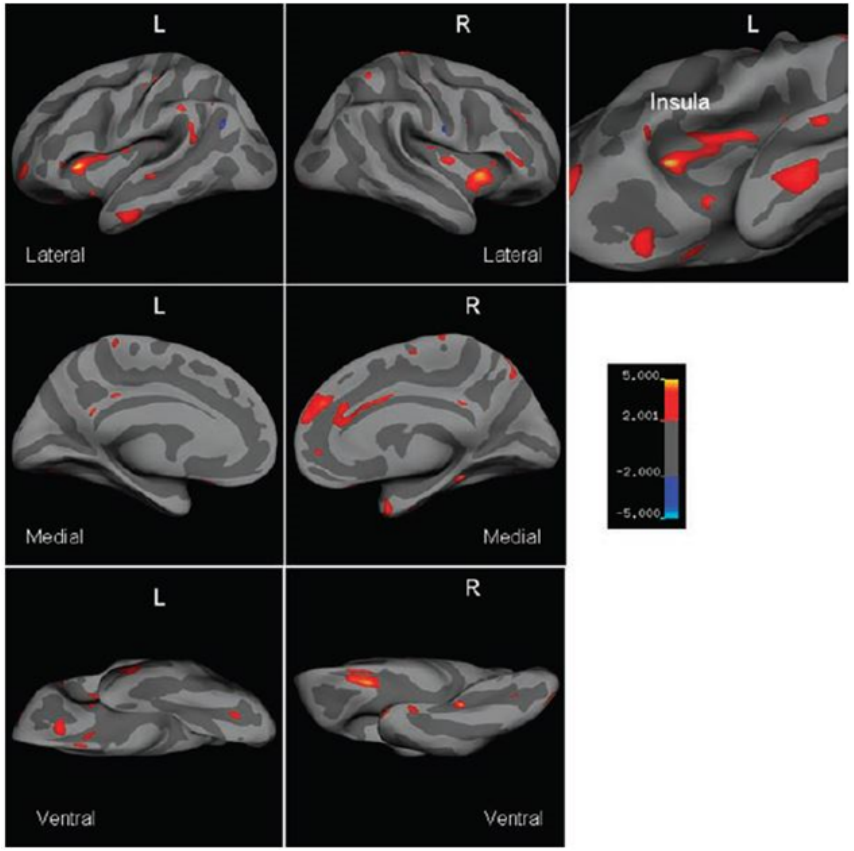
HIV disrupts cortical regions



Thompson et al, 2005



Kallianpur, Valcour, et al. 2012

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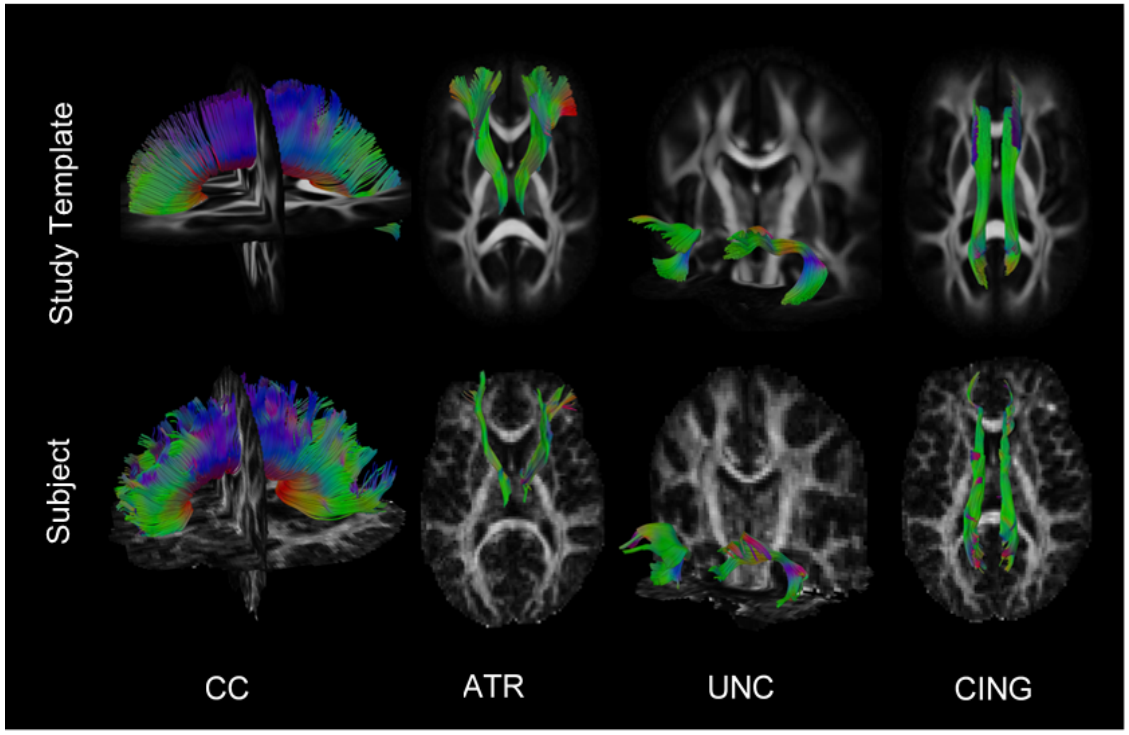
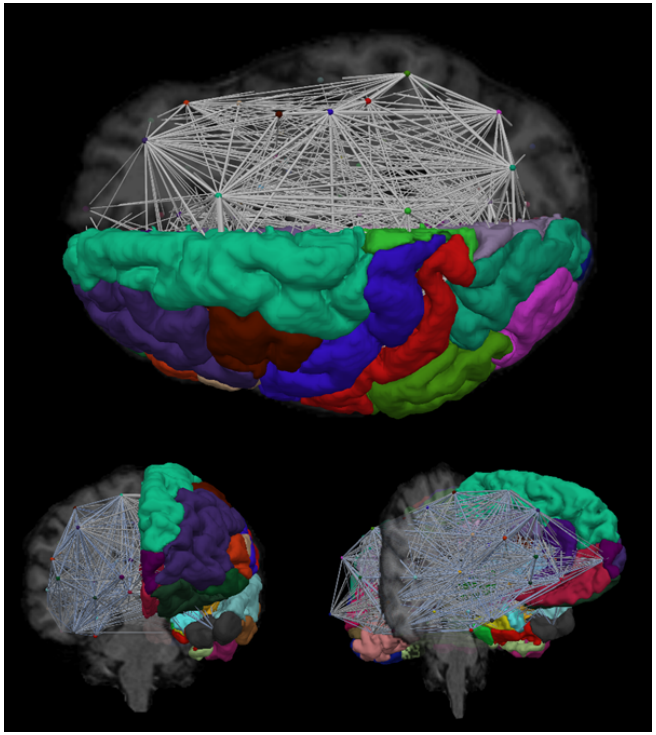
HIV disrupts broad networks





Paul et al, submitted, AIDS

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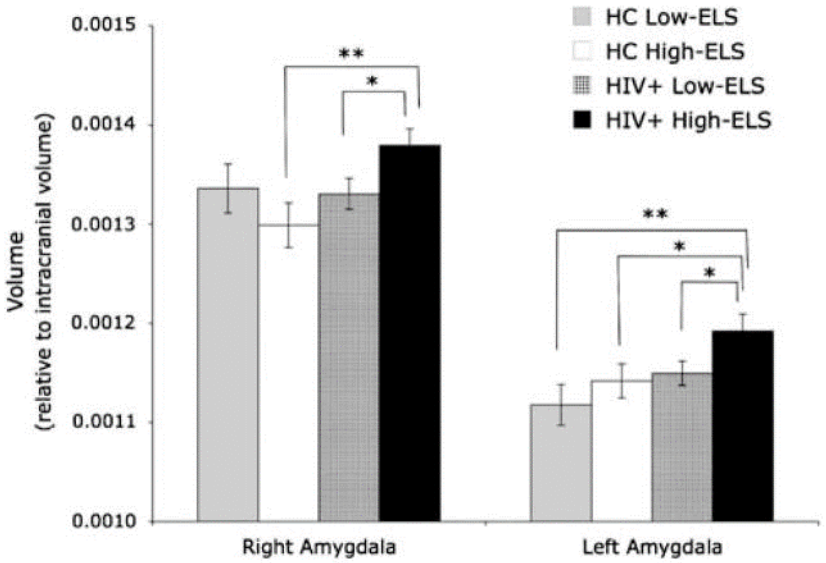
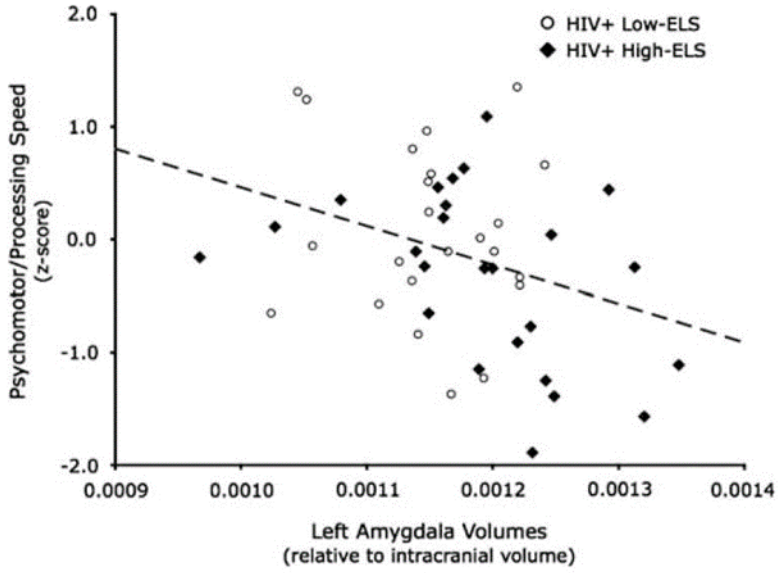
ELS x HIV





Clark et al., 2014

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Summary

Childhood trauma …

a) is “prevalent”, and confers risk for depression-anxiety

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Summary

b) disrupts the normal maturation of emotional brain circuits during adolescence; especially emotional brain circuits

c) interacts with serotonin system genotypes to increase the effects on emotional brain circuits, and risk for depression-anxiety

d) Is more prevalent with overt depression and interacts with emotional brain function to determine antidepressant response

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Pathways to resilience

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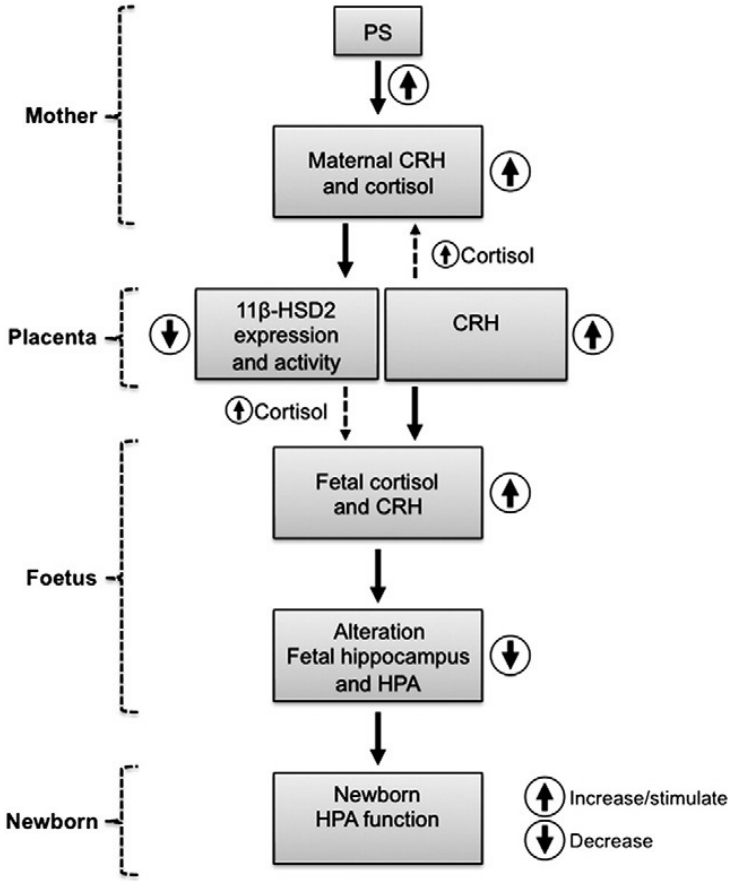
Prenatal stress and the environment



(Yang et al., 2007).

http://www.cerebromente.org.br/n11/mente/eisntein/rats.html

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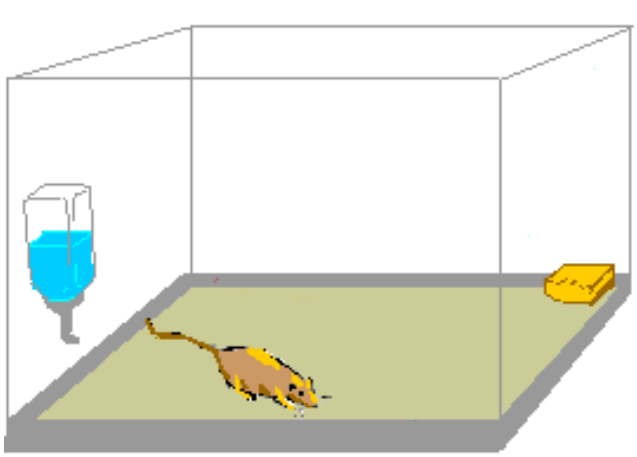
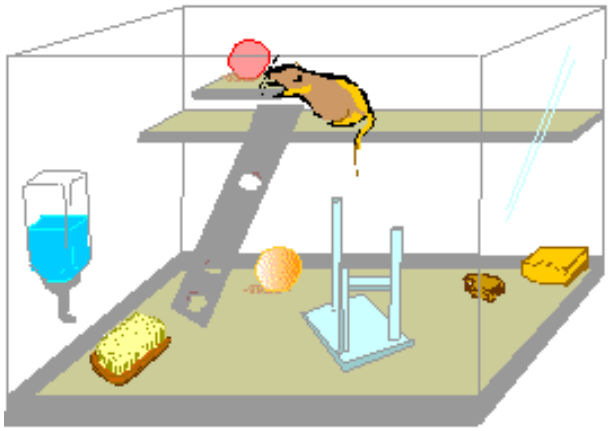
Prenatal stress and the environment

Pregnant rats stressed using foot shock

At PN 22 days, 50% of offspring reared in standard cages, 50% in EE cages.
Remained for 30 days.





(Yang et al., 2007).

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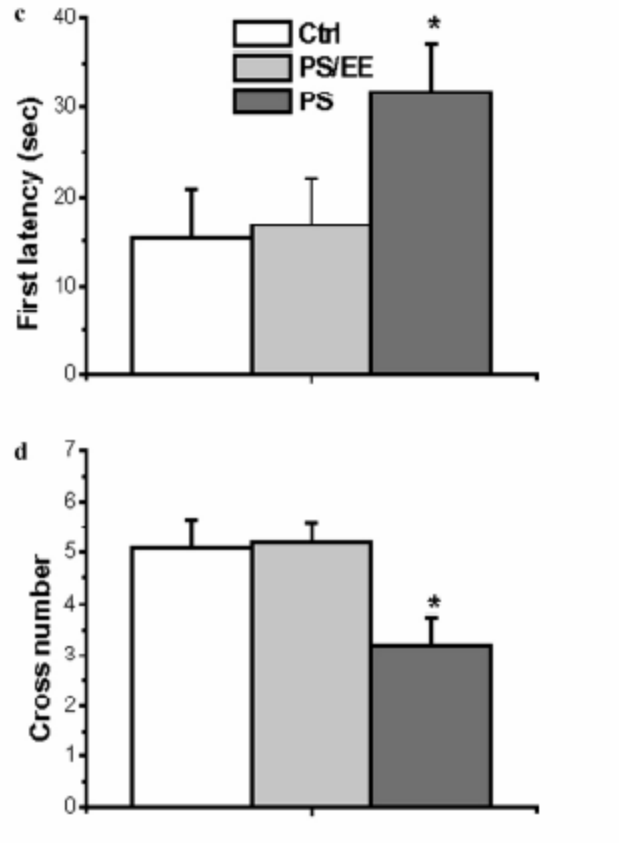
Prenatal stress and the environment



Top) PN stressed offspring showed a longer latency in the first time of crossing the location of the platform compared to controls, but this was reversed by EE.

Bottom) PN stressed animals crossed fewer times, but this was reversed by EE.

Opens the door to interventions.

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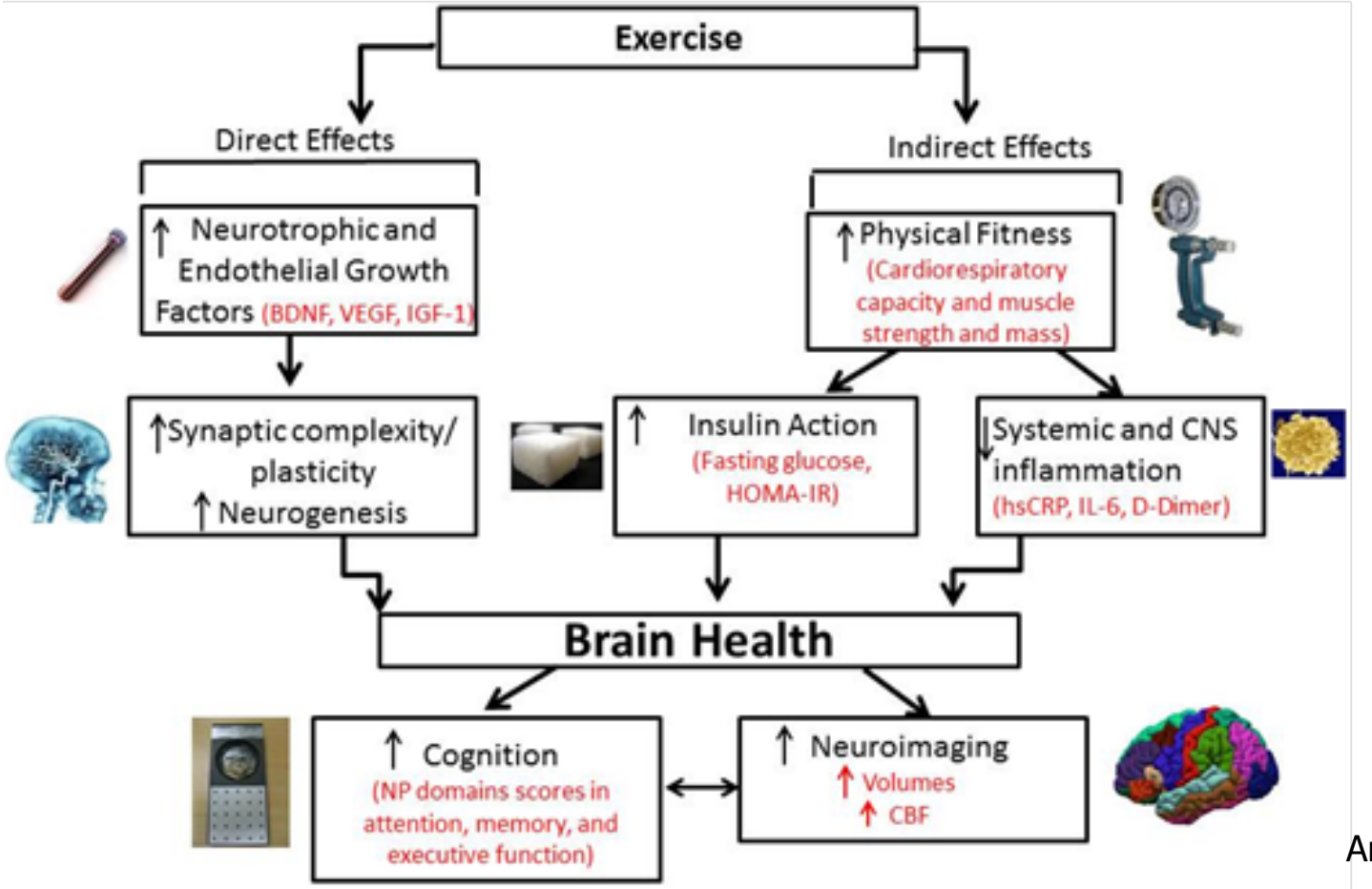
Pathways to resilience- Exercise



Ances, 2016

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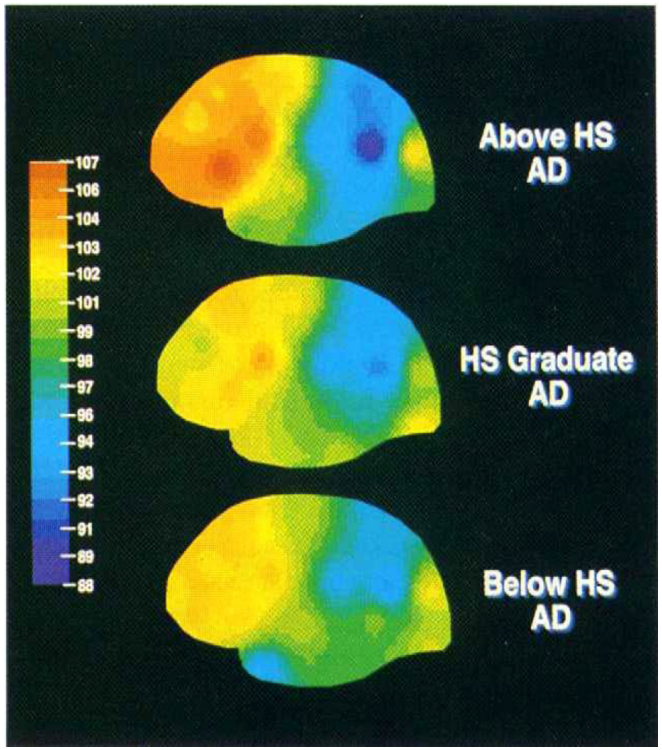
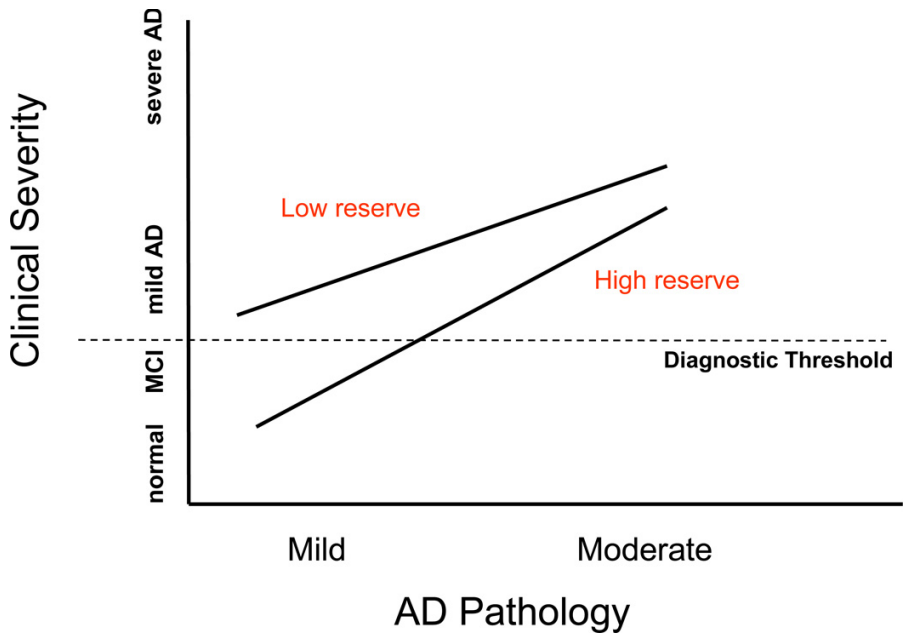
Pathways to resilience- Cognitive Reserve





Stern, 2012

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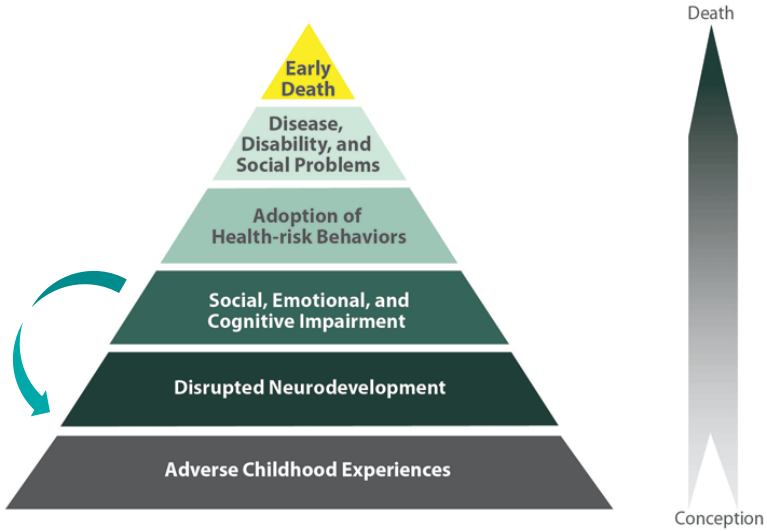
Conclusion

ELS is common, creates a vulnerability that is influenced by genes and the environment.

Postnatal environmental enrichment mitigates prenatal ELS.

Exercise and cognitive/emotion-based interventions have potential to re-configure brain network activity, HPA activity, and immune activation.

Downstream effects on cognition, emotion-regulation and reduced risk behaviors.



Mechanism by Which Adverse Childhood Experiences Influence Health and Well-being Throughout the Lifespan

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Special Thanks

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Ryan Cabeen, PhD	Brown
Charlie Nemeroff, MD	University of Miami