

Early-Life Stress and the Brain

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Overview

1. Effects of ELS. To understand the effects of early-life stress (ELS) on health outcomes in adulthood (e.g., substance use, neuropsychiatric symptoms).
2. Mechanisms of ELS Effects. To understand how ELS exposure creates changes in behavior and brain structure/function, contributing to psychopathology and poor health.
3. Assessment of ELS Exposure. To understand how we measure levels of ELS exposure in adult samples.
 - ▶ Provide an in-depth review of the fundamentals involved in assessing ELS levels in adults. Foster implementation in future research.
4. Assessment of ELS Effects on the Brain. To understand the types of tools we can use to investigate the effects of ELS on cognitive, affective, and neural functions.



Effects of ELS Across the Lifespan

Part 1

Lasting Effects of Adverse Childhood Experiences (ACEs)

ACES can have lasting effects on....



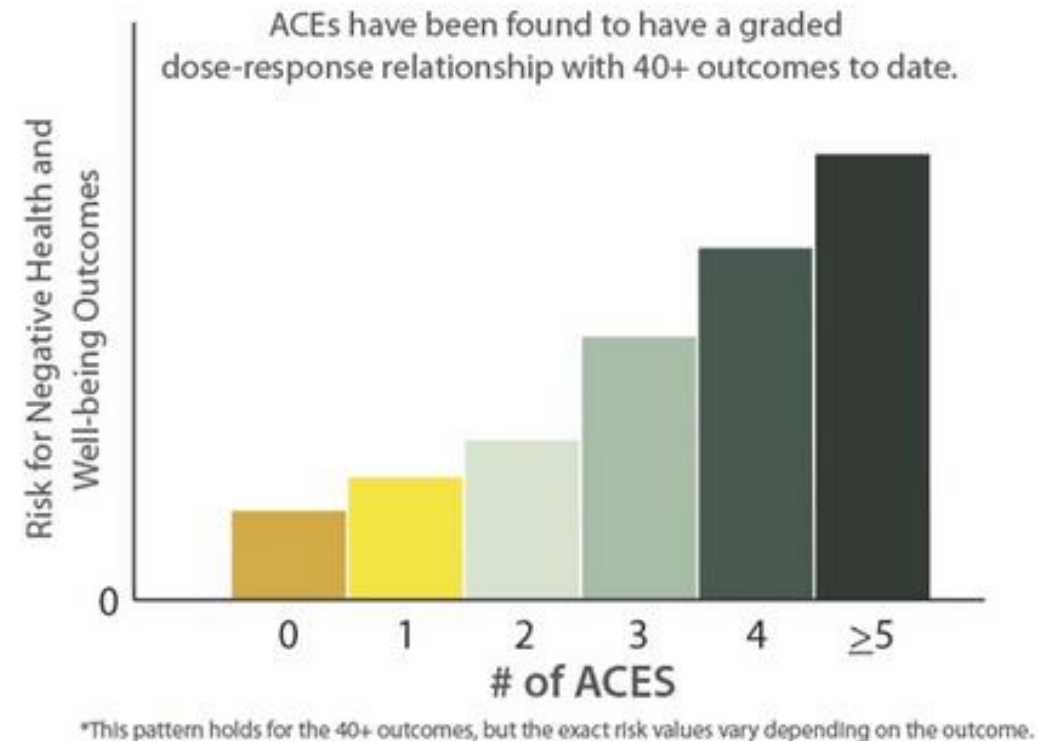
Health (obesity, diabetes, depression, suicide attempts, STDs, heart disease, cancer, stroke, COPD, broken bones)



Behaviors (smoking, alcoholism, drug use)



Life Potential (graduation rates, academic achievement, lost time from work)



Adverse Childhood Experiences

“ACE” Study

- ▶ Purpose: Examine links between the number ACEs experienced and several markers of health (risk behavior, health status, disease).
- ▶ Sample included over 13,000 Kaiser Health Plan members who completed a standardized medical evaluation at Kaiser’s San Diego Health Clinic.
- ▶ Standardized Medical Evaluation:
 - ▶ Medical questionnaire: demographic, biopsychosocial information, previous medical diagnoses, and family medical history.
 - ▶ Medical exam, conducted by health care provider: medical history, physical examination, and review of laboratory tests.
- ▶ 1 week after visit mailed questionnaire assessing ACE exposure
 - ▶ 9,508 (70.5%) responded

ACE Questionnaire

- ▶ 7 ACE “categories” were assessed:
 - ▶ emotional, physical, and sexual abuse
 - ▶ violence in the home (against the mother)
 - ▶ living with household members who were substance abusers, mentally ill or suicidal, or ever imprisoned.
- ▶ More than 50% of respondents reported at least 1 ACE, and 25% reported experiencing more than 2 ACE categories.
- ▶ Most people who were exposed to 1 type of ACE were also exposed to *at least* one additional type of ACE.
- ▶ The 7 ACE categories were strongly interrelated.

Adverse Childhood Experiences

“ACE” Study

- ▶ Adjusted for the effects of demographic factors (e.g., age, gender, race, and educational attainment).
- ▶ Compared to people who reported 0 ACEs, those who had experienced 4+ ACE categories, experienced:
 - ▶ a 4- to 12-fold increase in alcoholism, drug abuse, depression, and suicide attempts
 - ▶ a 2- to 4-fold increase in smoking, poor self-rated health, and STDs
 - ▶ a 1.4- to 1.6-fold increase in physical inactivity and severe obesity.
- ▶ ACE exposure (number of ACE categories) showed a graded, dose-response, relationship with several adult diseases including:
 - ▶ ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease.
- ▶ Conclusion: the impact of ACEs on adult health status is strong and cumulative.
- ▶ Important to consider the “net effects” or additive effects of a wide range of co-occurring ACEs on health outcomes. >> the concept of “High Early-Life Stress”

Adverse Childhood Experiences

“ACE” Study

Health problem	Number of categories	Sample size (N) ^a	Prevalence (%) ^b	Adjusted odds ratio ^c	95% confidence interval
Considers self an alcoholic	0	3,841	2.9	1.0	Referent
	1	1,993	5.7	2.0	(1.6–2.7)
	2	1,042	10.3	4.0	(3.0–5.3)
	3	586	11.3	4.9	(3.5–6.8)
	4 or more	540	16.1	7.4	(5.4–10.2)
	Total	8,002	5.9	—	—
Ever used illicit drugs	0	3,856	6.4	1.0	Referent
	1	1,998	11.4	1.7	(1.4–2.0)
	2	1,045	19.2	2.9	(2.4–3.6)
	3	589	21.5	3.6	(2.8–4.6)
	4 or more	541	28.4	4.7	(3.7–6.0)
	Total	8,029	11.6	—	—
Ever injected drugs	0	3,855	0.3	1.0	Referent
	1	1,996	0.5	1.3	(0.6–3.1)
	2	1,044	1.4	3.8	(1.8–8.2)
	3	587	2.3	7.1	(3.3–15.5)
	4 or more	540	3.4	10.3	(4.9–21.4)
	Total	8,022	0.8	—	—

Effects of High ELS on Psychological Distress

- ▶ International study examining the relationship between ACE exposure and current psychological symptoms in a sample of over 1,600 adults.
 - ▶ United States, Australia, England, and the Netherlands.
- ▶ Examined exposure to 19 specific ACEs using the self-report Early-Life Stress Questionnaire (ELSQ), in relation to current symptoms of stress, depression, and anxiety.
- ▶ Only 27% of the sample reported experiencing 0 ACEs; 40% reported 1 or 2 ACEs; 33% reported 3 or more ACEs.
 - ▶ High prevalence of high ELS exposure: 33% of the sample with 3 or more ACEs.
- ▶ Rates of most ACEs were quite similar across the three continents.
- ▶ ACEs involving emotional abuse, neglect, and family conflict/violence/separation were strongly associated with rates of emotional distress.

Effects of High ELS on Psychiatric Disorders

- ▶ Assessed a nationally representative sample of over 5,000 adults; examined the relation of ACEs to the onset and persistence of psychiatric diagnoses.
- ▶ Persistence of disorders, the proportion of time since onset that a person with a history of the disorder is in episode (a combined function of episode duration and recurrence risk).
- ▶ ACEs involving physical or sexual abuse, neglect, and family dysfunction (parental mental illness, substance use disorder, criminality, family violence) were significantly associated with persistence of mood, substance abuse, and anxiety disorders.
 - ▶ Consistent with earlier studies indicating that ELS is associated with an increased risk for many psychiatric disorders including major depression, PTSD, and bipolar disorder (Famularo et al., 1992)
- ▶ Associations between ACEs and adult psychiatric diagnoses were largely due to associations with onset of diagnosis, rather than with persistence.
 - ▶ Suggesting that the greatest focus of public health attention on ACEs should be aimed at primary rather than secondary prevention, in order to reduce risk of disease onset altogether.

Effects of High ELS on the Brain

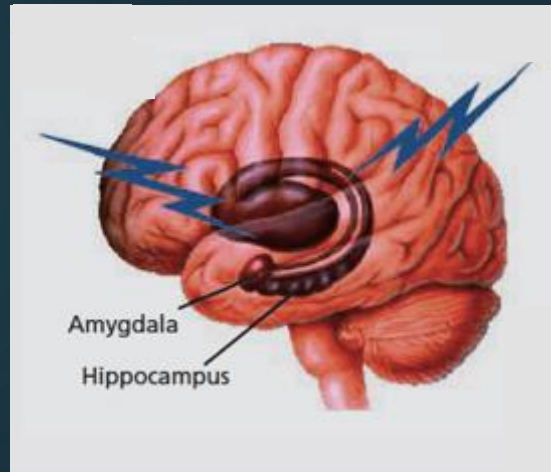
- ▶ High ELS exposure alters the trajectory of brain development.
- ▶ Emotional and sexual abuse, and witnessing domestic violence appear to specifically target brain regions and pathways that process and convey aversive experiences.
 - ▶ auditory, visual, and somatosensory cortices
- ▶ Volumetric alterations in several brain regions:
 - ▶ anterior cingulate, dorsal lateral prefrontal cortex, orbitofrontal cortex, corpus callosum, and hippocampus.
- ▶ Changes in brain function:
 - ▶ E.g., abnormal amygdala response to emotional faces; diminished striatal response to anticipated rewards.
- ▶ These regions appear to have sensitive exposure periods – these regions are most vulnerable to the effects of ELS during these periods in development.

Effects of High ELS on the Brain

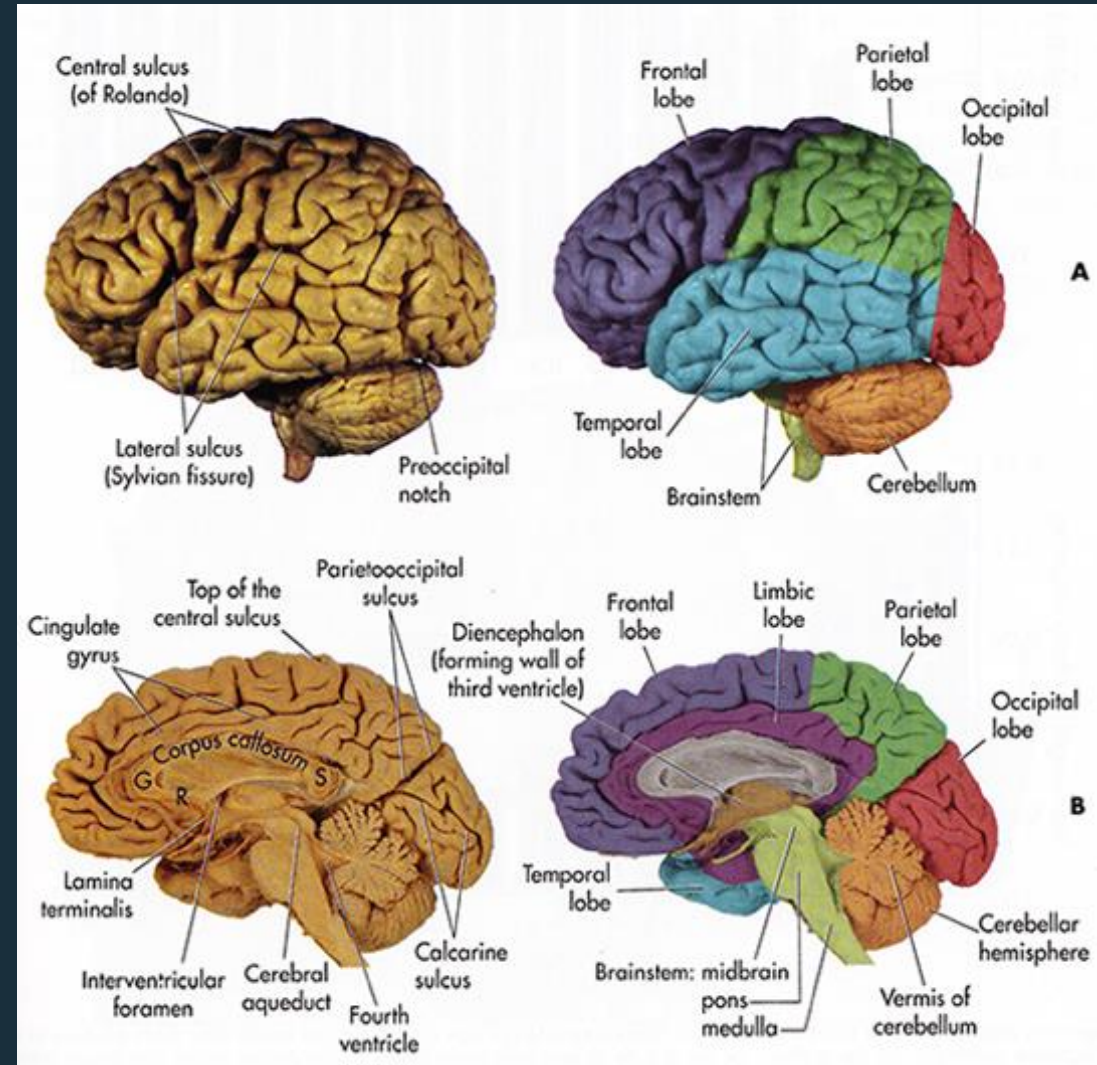
Key Brain Regions

- ▶ anterior cingulate
- ▶ dorsal lateral prefrontal cortex
- ▶ orbitofrontal cortex
- ▶ corpus callosum
- ▶ striatum (basal ganglia)
- ▶ hippocampus
- ▶ amygdala

subcortical
regions



Adapted from McEwen 2006



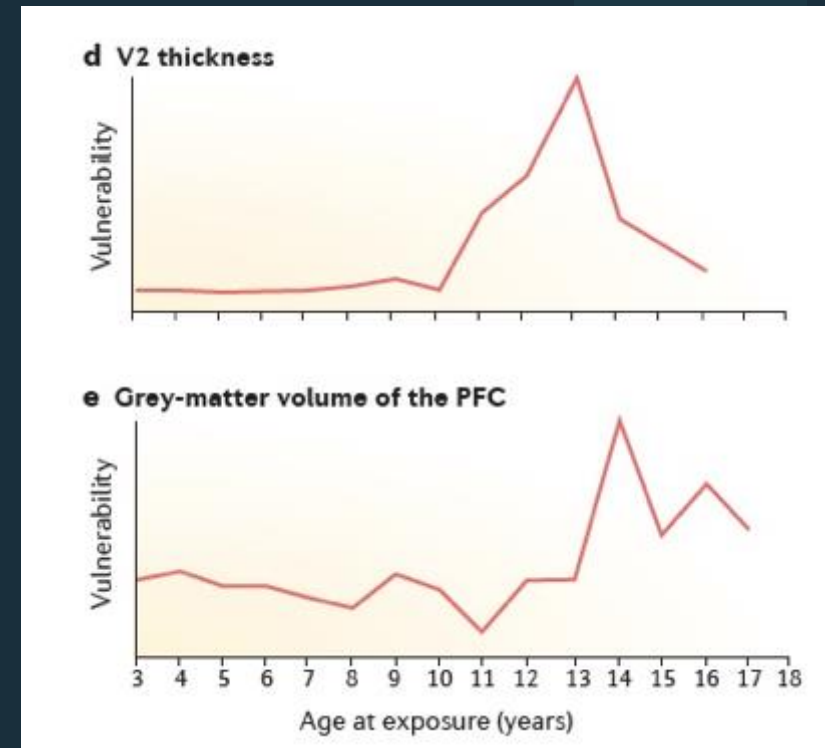
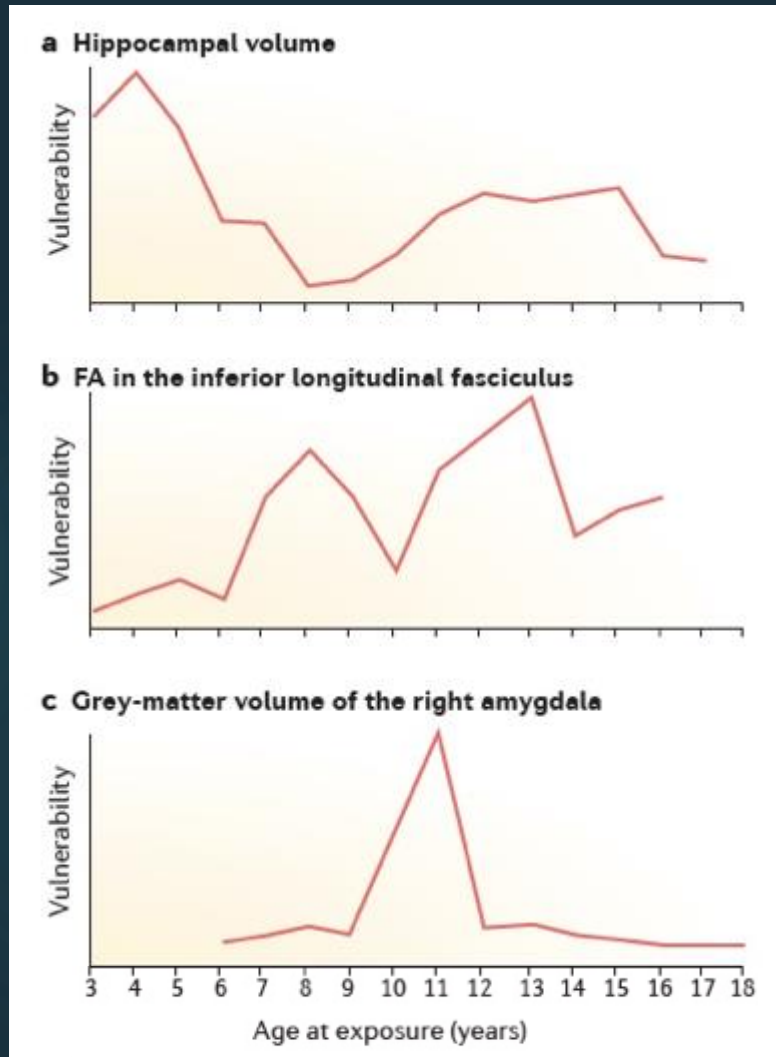
lateral
surface

medial
surface

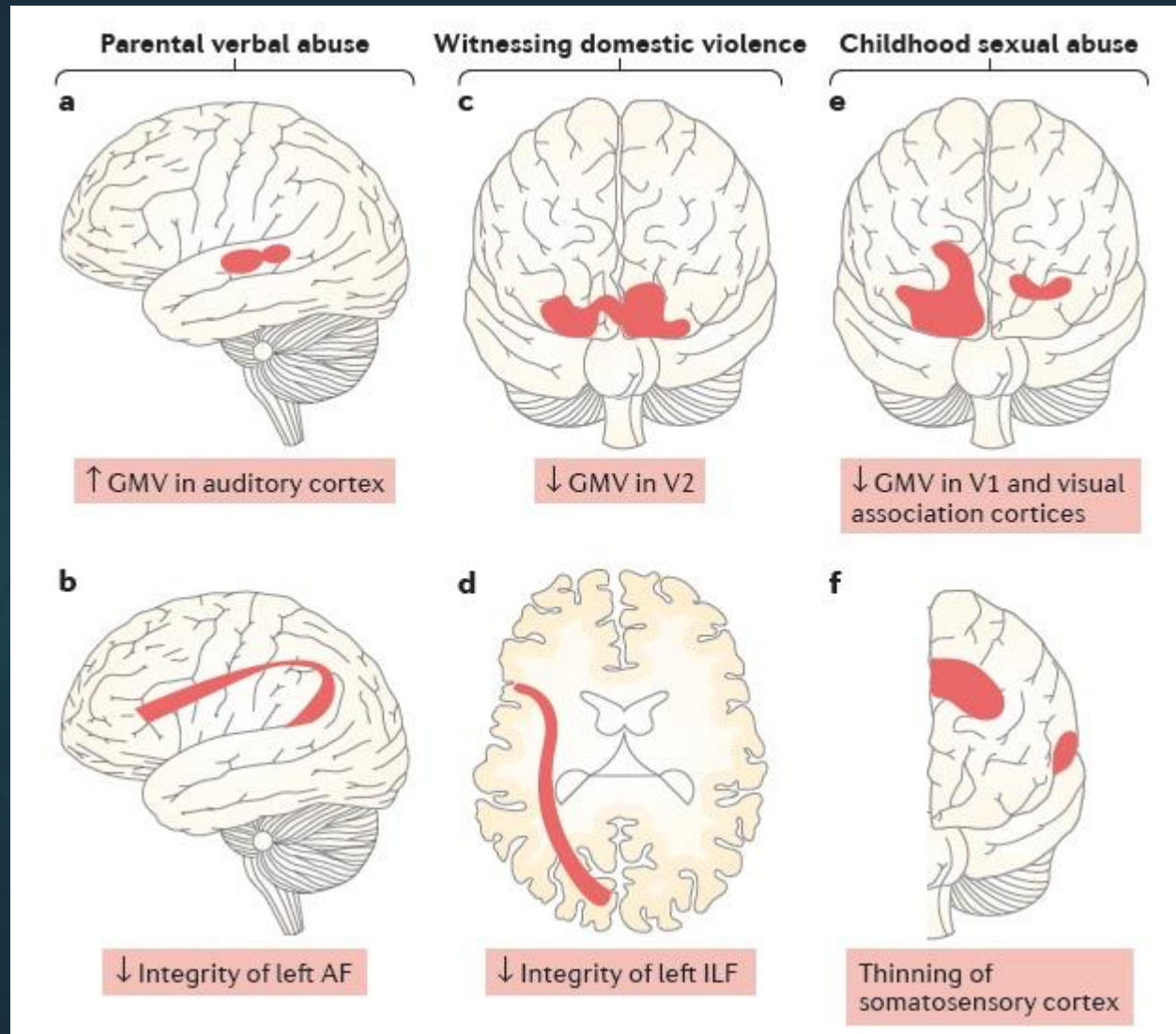
Netter's Atlas of Human Neuroscience

Sensitive Periods

- ▶ Different brain regions may be more vulnerable to the effects of ELS at different points in development.
- ▶ Each brain region undergoes a different trajectory of development.



Type-specific Effects on the Brain



- ▶ Specific types of ACEs may be associated with abnormalities in specific brain regions.
- ▶ Parental verbal abuse has been associated with increased gray matter volume in the auditory cortex and decreased integrity of the left arcuate fasciculus.
- ▶ Regions of the brain that are involved in speech generation and comprehension.

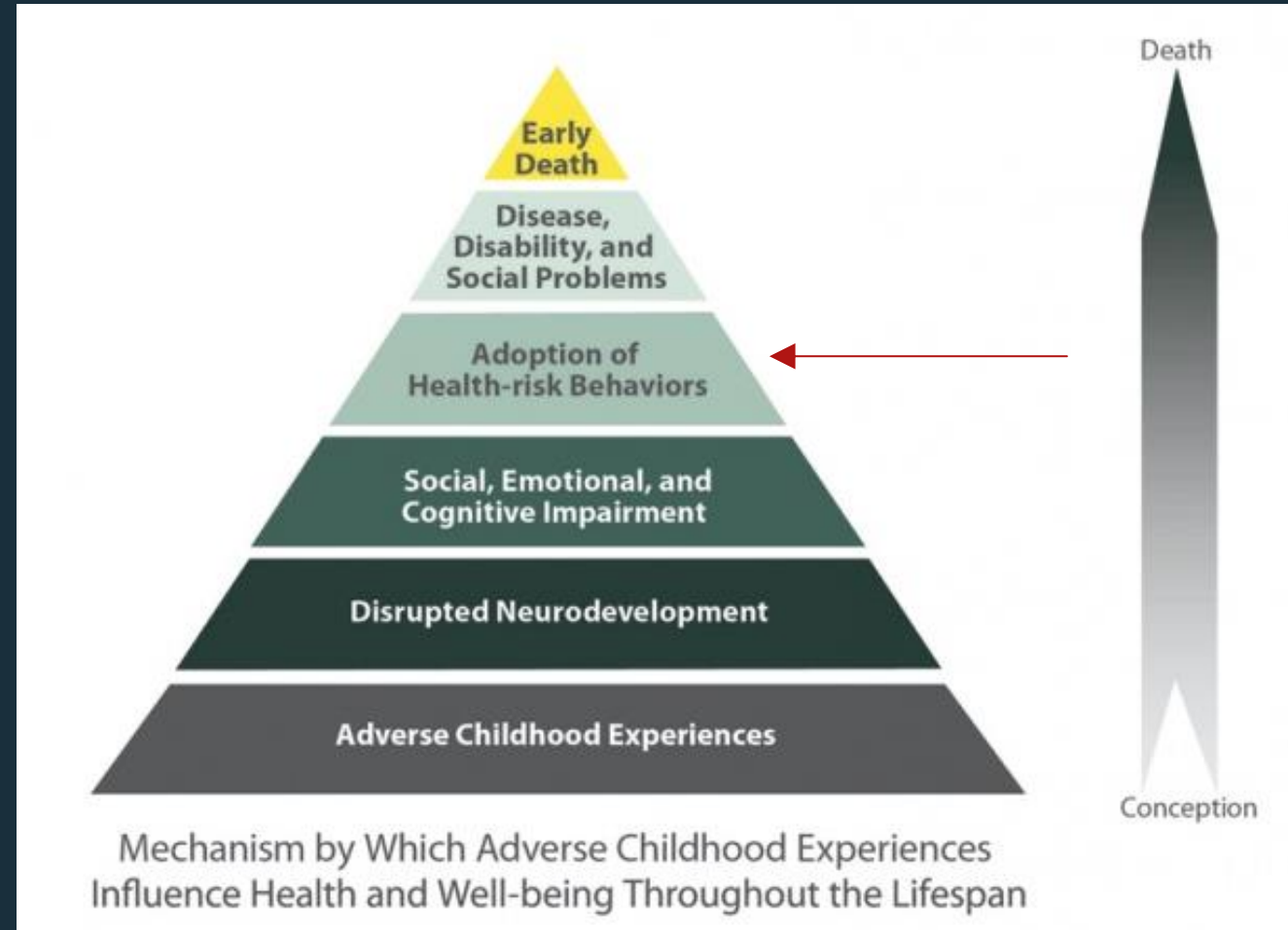


Mechanisms Contributing to ELS Effects on Brain and Behavior

Part 2

Development of Risk Factors for Disease

- ▶ High-Risk Behaviors
 - ▶ Smoking, alcohol/drug abuse, or overeating
- ▶ Provide a short-term “solution” to the negative social, emotional, and cognitive effects of High ELS.
- ▶ Initial benefits (e.g., nicotine antianxiety, antidepressant, anger suppressant, and appetite suppressant properties).
- ▶ Felitti et al., 1998 warned against an incomplete understanding of the initial benefits of these behaviors >> false view that they are irrational and solely negative.
 - ▶ Limit our ability to adequately intervene.

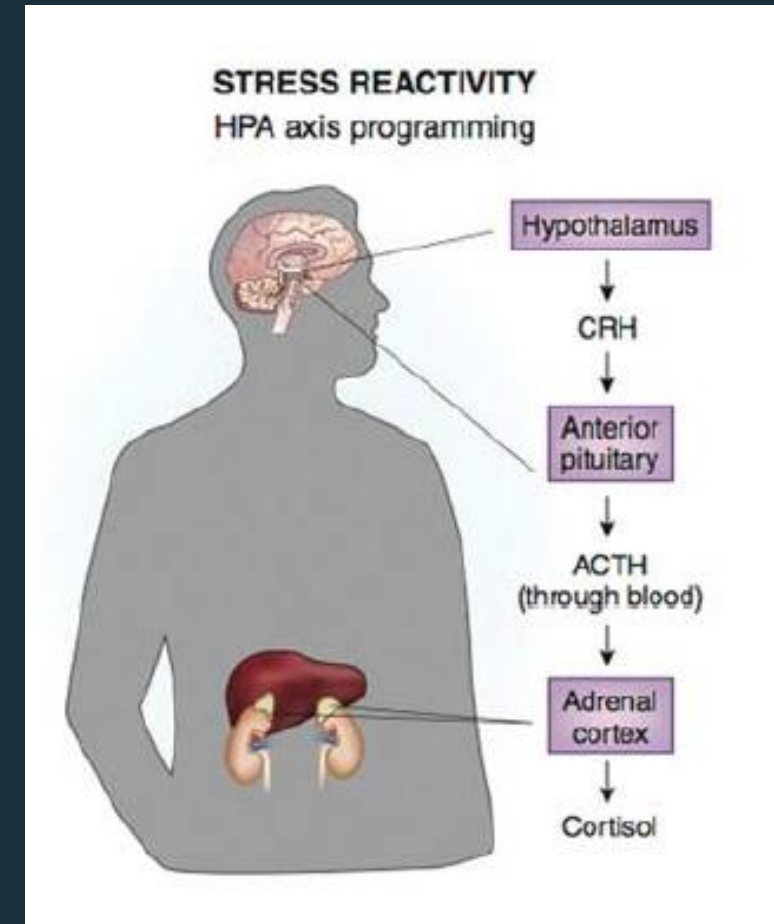


Mechanism of ELS

- ▶ ACEs contribute to poor health through 2 broad mechanisms (Felitti, 2009)
 1. Disease is the delayed consequence of various coping strategies like overeating, smoking, and alcohol/drug use
 - ▶ For example: ELS-related depression > overeating > type 2 diabetes > heart disease > early death
 2. Disease is caused by a cycle of potentiated and chronic stress, which is mediated by chronic hypercortisolemia (cortisol dysregulation) and pro-inflammatory cytokines
 - ▶ For example: chronic headache/back pain, primary pulmonary fibrosis, coronary artery disease.

The HPA axis

- ▶ The sympathetic nervous system functions like a gas pedal in a car. It triggers the fight-or-flight response, providing the body with a burst of energy so that it can respond to perceived dangers.
- ▶ The hypothalamic-pituitary-adrenal (HPA) axis consists of the hypothalamus, the pituitary gland, and the adrenal glands.
- ▶ The HPA axis relies on a series of hormonal signals to keep the sympathetic nervous system – the "gas pedal" – pressed down.
- ▶ In the context of extended stressors, the hypothalamus releases corticotropin-releasing hormone (CRH), which travels to the pituitary gland, triggering the release of adrenocorticotrophic hormone (ACTH).
- ▶ ACTH travels to the adrenal glands, prompting them to release the glucocorticoids, e.g., cortisol.
- ▶ This system functions to keep the body in a state of "high alert."
- ▶ In animal studies, glucocorticoid administration result in increased depressive and anxiety-like symptoms (e.g., McEwen, 1997; Mitra & Sapolsky, 2008; Mitra et al., 2006; Vyas et al., 2003).



Adapted from Danese & Lewis, 2017

HPA axis Contributions to Chronic Inflammation in the Context of High ELS

- ▶ ELS may be indirectly linked to inflammation because of primary neuroendocrine abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis.
 - ▶ Evidence of hyperactive HPA axis functioning in later life in those with ELS (e.g., Danese & McEwen, 2012;), which is thought to be due to glucocorticoid receptor abnormalities.
 - ▶ ELS is also known to be associated with epigenetic changes, which lead to insufficient glucocorticoid signaling (e.g., disruptions in glucocorticoid-receptor-mediated signaling; Weaver et al., 2004; Klengel et al., 2013).
- ▶ These changes might then induce resistance to the anti-inflammatory properties of cortisol >> high inflammation levels (Heim et al., 2000; Miller et al., 2002; Raison & Miller, 2003).
- ▶ Yet, because of the bi-directional association between HPA axis functioning and inflammation, it is also possible that primary inflammatory abnormalities could stimulate HPA axis activity (Besedovsky et al., 1986) and induce glucocorticoid resistance (GCR) (Barnes & Adcock, 2009).
 - ▶ GCR – a decrease in the sensitivity of immune cells to glucocorticoid hormones that normally terminate the inflammatory response.

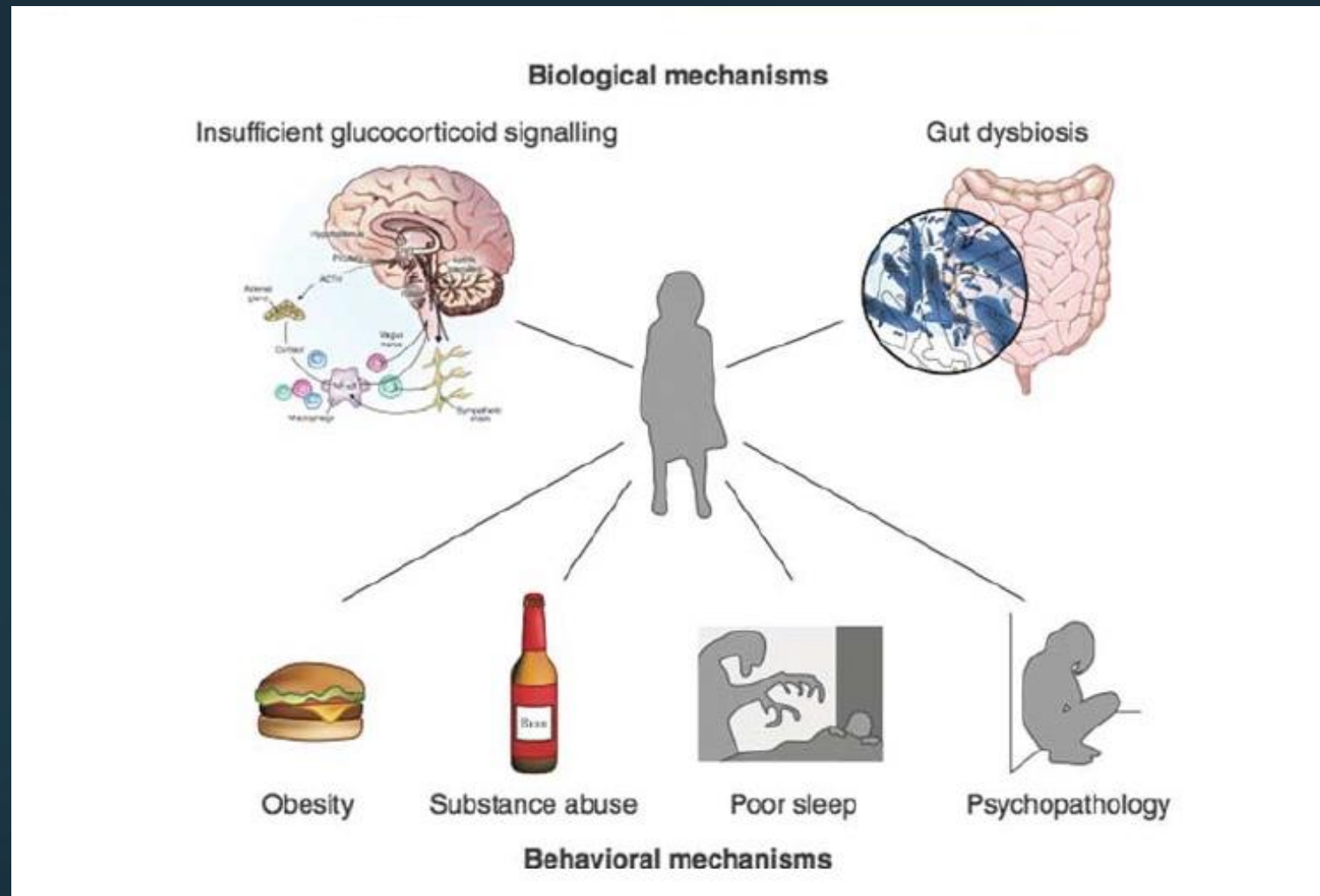
Additional Biological & Behavioral ELS-Related Mechanisms Leading to Chronic Inflammation

1. ELS can influence the composition of the gut microbiome (Bailey & Coe, 1999; O'Mahony et al., 2009).
 - ▶ Changes in the microbiome could influence brain function through stimulation of the vagus nerve and other metabolic (and inflammatory) effects (Cryan & Dinan, 2012).
2. ELS is associated with hormonal and brain abnormalities that could contribute to a 'thrifty' phenotype characterized by increased energy intake and storage >> obesity (Danese & Tan, 2014; Danese et al., 2014).
 - ▶ Obesity is associated with high systemic inflammation through the production of pro-inflammatory cytokines by adipose cells (Gregor and Hotamisligil, 2011).
3. High ELS is associated with increases in alcohol and substance use (Dube et al, 2003; Anda et al., 1999).
 - ▶ Alcohol/substance use can also contribute to increased inflammation levels (Crews et al., 2006; Shiels et al., 2014).

Additional Biological & Behavioral ELS-Related Mechanisms Leading to Chronic Inflammation

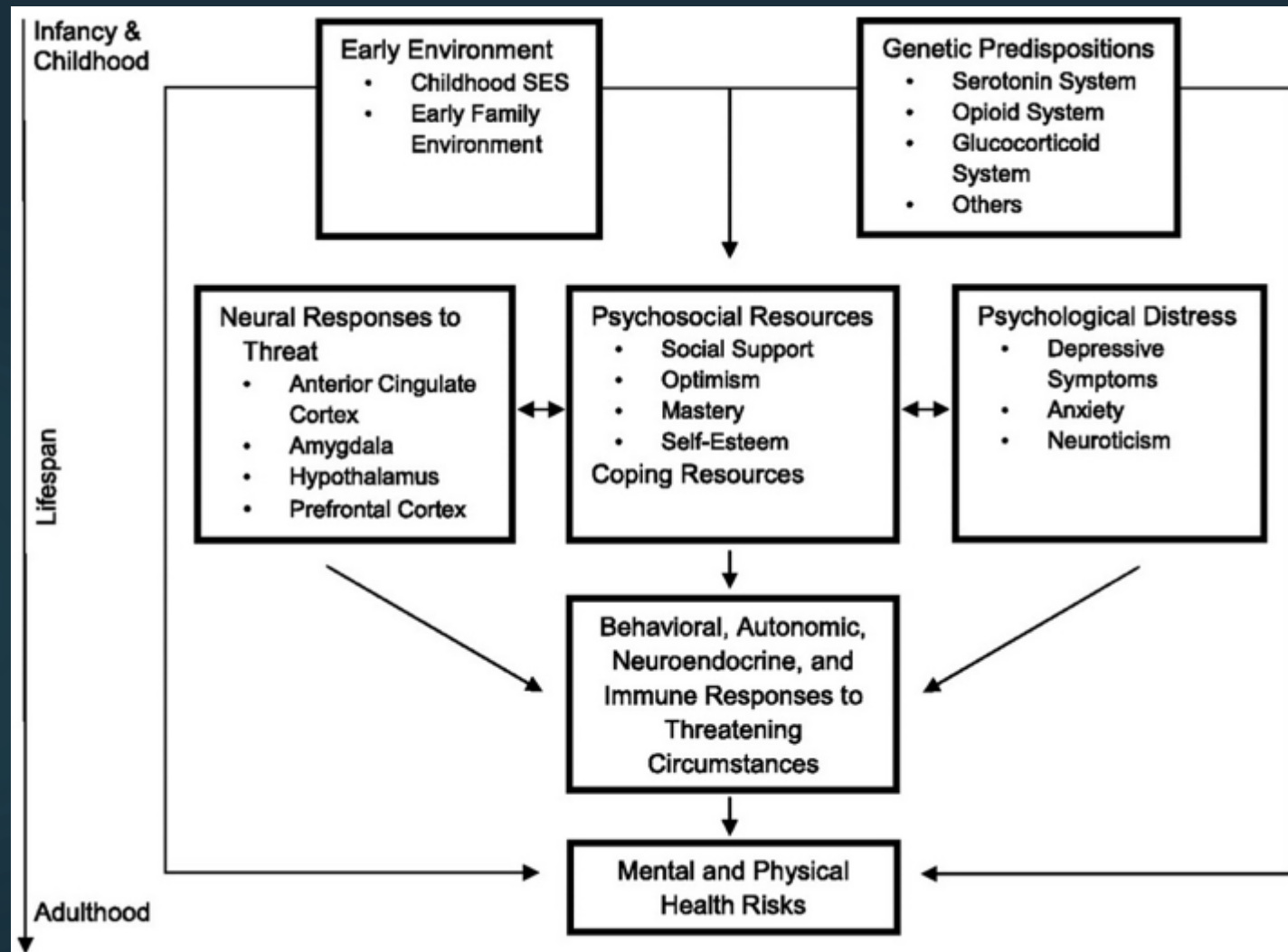
4. ELS is associated with sleep disruption (duration, quality, architecture), both in rodents (Feng et al., 2007; Mrdalj et al., 2013; Tiba et al., 2004) and humans (Gregory & Sadeh, 2016; Kajeeepeta et al., 2015).
 - ▶ Sleep deprivation is associated with an increase in pro-inflammatory cytokines in humans (Irwin et al., 2006) and elevated levels of inflammatory biomarkers (e.g., higher interleukin-6, IL-6, and high-sensitivity C-reactive protein, hs-CRP, in women with poor sleep; Miller et al., 2009).
5. ELS is associated with later abnormalities in brain functioning and behavior, such as elevated reactivity to psychosocial stressors (Carpenter et al., 2010; Danese & McCrory, 2015).
 - ▶ Continued and/or recurrent distress could contribute to elevated inflammation levels through adulthood (Cohen et al., 2012; Molina, 2005).

Multiple Biological & Behavioral Routes to Chronic Inflammation Associated with ELS



Additional Biological Effects of ELS:

Multiple Interactions Across Systems & Throughout the Lifespan



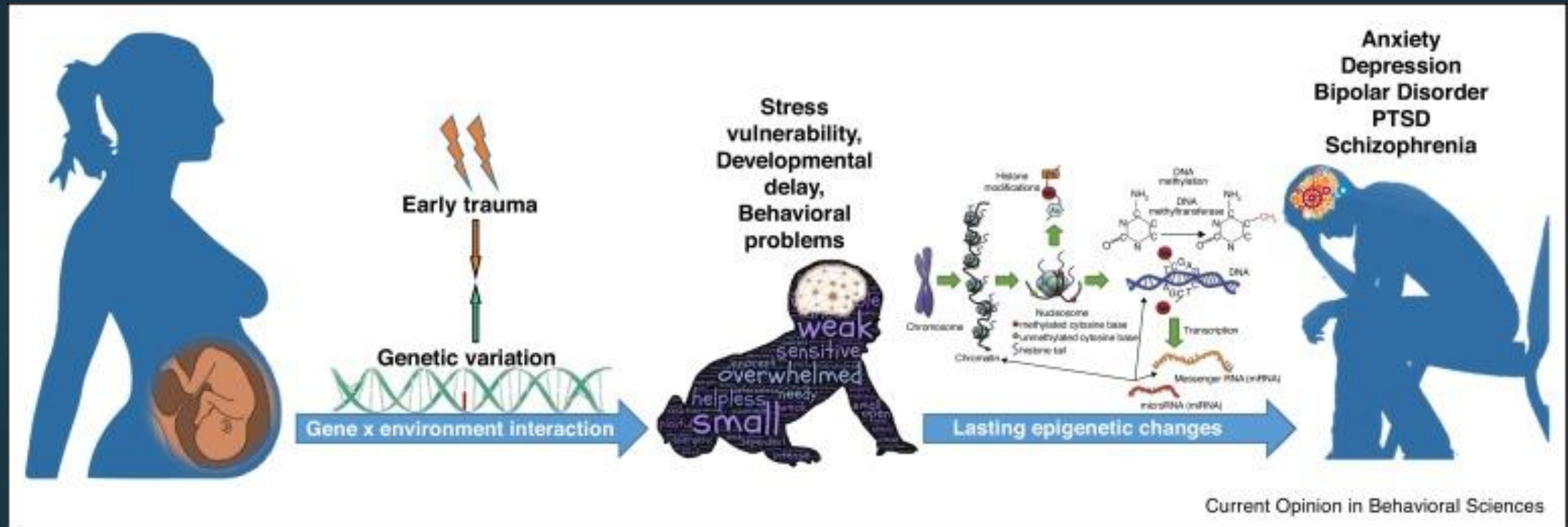
1. ACE Exposure Impacts Multiple Biological Systems

2. Interactions Between Biological & Behavioral Consequences of ACE Exposure Across the Lifespan

3. Changes in the Biological Response the Threat

4. Mental & Physical Health Risks

Additional Biological Effects of ELS: Epigenetic Mechanisms



Mechanism of ELS-Related Brain Effects

- ▶ The brain is not fully formed at birth; permits optimal adaptation to environment; vulnerable to environment effects.
- ▶ Repeated exposure to ACEs induce a cascade of stress-mediated effects on hormones and neurotransmitters.
 - ▶ This includes stress-induced programming of several systems (glucocorticoid, noradrenergic, and vasopressin-oxytocin stress response systems), which alter the stress response.
- ▶ These effects impact several aspects of brain development:
 - ▶ neurogenesis, synaptic over-production and pruning of synapses, and myelination.
- ▶ Strongest effects observed in “vulnerable” brain regions.
 1. Protracted postnatal development
 2. A high density of glucocorticoid receptors
 3. Some degree of postnatal neurogenesis
- ▶ “Stress vulnerable” brain regions: hippocampus, amygdala, neocortex, cerebellum, WM tracts.
- ▶ Resulting alterations may initially be adaptive in stressful environments (e.g., hypervigilance), but long-term a mismatch occurs between brain/environment leads to psychopathology.



Assessment of ELS in Adult Samples

Part 3

Measurement of ELS

1. Longitudinal assessments of trauma exposure can be used in prospective cohort studies of children/teens (e.g., CTAPS). Superior approach, methodologically; time intensive.
 - ▶ YLSI - Youth Life Stress Interview (Rudolph & Flynn, 2007, as applied by Birn et al., 2017)
2. Retrospective analyses of institutional records (e.g., open records from the child protection agency) can be used to assess ELS exposure (e.g., McGee et al 1995).
 - ▶ Permits assessment of:
 - ▶ physical and emotional abuse/neglect, sexual abuse, and exposure to family violence
 - ▶ Labor intensive; Records may be incomplete; Restricts sample to those with documented histories
3. Retrospective questionnaires are the most common and efficient method of assessing ELS exposure in adults.
 - ▶ ACE, ACE Study Questionnaire; CTQ, Childhood Trauma Questionnaire; ELSQ, Early-Life Stress Questionnaire; ACE-IQ, Adverse Childhood Experience International Questionnaire
 - ▶ Validity?
 - ▶ Ability to accurately recall childhood?
 - ▶ Potential for biased reports, particularly in those with high current stress levels?
 - ▶ Longitudinal follow-up of adults whose childhood abuse was well documented suggest that retrospective reports of childhood abuse are generally accurate, and may actually underestimate actual occurrences (Femina et al., 1990; Williams, 1994, 1995).

ACE Study Questionnaire

- ▶ Described by Felitti et al. in the 1998 ACE Study
 - ▶ American Journal of Preventive Medicine, 1998, Vol. 14(4) 245-258
- ▶ Designed for administration to adults age 18 and older.
- ▶ Adapted from the Conflicts Tactics Scale (Straus et al., 1990)
 - ▶ emotional and physical abuse
 - ▶ violence against mother (or stepmother)
- ▶ Added additional questions from
 - ▶ a study of the prevalence of child sexual abuse in the US (Wyatt, 1985)
 - ▶ 1988 National Health Interview Survey; assessed exposure to adults using alcohol/drugs.
- ▶ Structure: Self-report questionnaire that assesses whether respondents were exposed to specific adverse childhood experiences (ACEs) before age 18.

ACE Study Questionnaire

- ▶ 17 questions, assessing 7 “categories” of childhood abuse
 1. Psychological abuse
 2. Physical abuse
 3. Sexual abuse
 4. Parental substance abuse
 5. Mental illness in the home
 6. Domestic abuse (physical) in the home
 7. Exposure to criminal behavior in the home
- ▶ Example item: “Did you live with someone who used street drugs?” (substance abuse)
- ▶ Scoring: If any ACE was experienced within a category, the respondent receives a score of 1 for that category.
- ▶ Scores are summarized, with a range of 0 to 7.

Behavioral Risk Factor Surveillance System (BRFSS) ACE Module

- ▶ Shorter version of the ACE Study Questionnaire – 11 items
 - ▶ CDC, 2015. Behavioral Risk Factor Surveillance System Survey ACE Data, 2009-2014. Atlanta, Georgia: U.S. Department of Health and Human Services.
- ▶ Adapted from the original ACE Study.
 - ▶ 8 categories assessed (7 ACE + parental separation/divorce).
- ▶ Used primarily in a cross-sectional telephone survey organized by the CDC to collect national information about child abuse and neglect in the US.
 - ▶ Survey data are available for download from the CDC.
- ▶ Scale is free, and available in English and Spanish:
 - ▶ https://www.cdc.gov/violenceprevention/acestudy/ace_brfss.html

Childhood Trauma Questionnaire (CTQ)

- ▶ 28-items; asks respondents to recall the frequency of childhood experiences of abuse and neglect using a 5-point Likert-type scale
- ▶ 5 categories of maltreatment are assessed:
 - ▶ emotional, physical, and sexual abuse; emotional and physical neglect
- ▶ Unique component – compared to ACE, the CTQ expands its assessment beyond abuse and adds a focus on neglect
 - ▶ Example item: “I felt loved.” (emotional neglect; reverse scored)
 - ▶ “never true,” “rarely true,” “sometimes true,” “often true,” or “very often true”
- ▶ High internal consistency and test-retest reliability (Bernstein & Fink, 1994)
 - ▶ Cronbach's alpha for factors are between 0.79 to 0.94; intraclass correlation = 0.88

Childhood Trauma Questionnaire (CTQ)

- ▶ Scoring: Respondents rate each statement on a 1-5 scale, from:
 - ▶ “never true” = 1 to “very often true” = 5
 - ▶ Scores range from 5 to 25 for each maltreatment category.
 - ▶ 5 categories: emotional, physical, and sexual abuse; emotional and physical neglect
 - ▶ Total CTQ scores range from 25 to 125.
 - ▶ Determine percentiles, based on normative data (Scher et al., 2001).
- ▶ Published cut-off scores are used to determine severity of exposure for each of the 5 categories of maltreatment (Bernstein and Fink, 1994):
 - ▶ Severity ratings: “none to minimal,” “low to moderate,” “moderate to severe,” or “severe to extreme”
- ▶ Severity ratings generate subscale severity scores for each category.
 - ▶ none/minimal = 0; low to moderate = 1; moderate to severe = 2; severe to extreme = 3
- ▶ A CTQ severity summary score can also be generated from each of the 5 subscales, ranging from 0 to 15.

Early-Life Stress Questionnaire (ELSQ)

- ▶ Described by Cohen et al. in 2006
 - ▶ International Journal of Psychiatry in Medicine, 2006, Vol. 36(1) 35-52.
- ▶ Created for use in adult samples.
- ▶ Adapted from the Child Abuse and Trauma Scale (Sanders et al., 1995), which has strong internal consistency, test-retest reliability, and validity.
- ▶ Assesses the occurrence of 19 adverse childhood experiences (ACEs) before age 18.
 - ▶ Example item: “How often did you not have enough to eat?” (poverty/neglect)
 - ▶ 5 additional items, identical to the CTQ, that focus on emotional neglect.
- ▶ Unique component – asks about age and duration of ACE exposure.
 - ▶ Allows you to assess whether the ACE occurred within a known “sensitivity period”

ELSQ – 19 Individual ACEs

1. Adopted
 2. Surgery/hospital
 3. Life-threatening illness/injury (self)
 4. Life-threatening illness/injury (family)
 5. Family member died
 6. Divorce/parents separated
 7. Child separated from family
 8. Family conflict
 9. Bullied
 10. House destroyed (e.g., by fire)
 11. Natural disaster
 12. Witness warfare
 13. Poverty/neglect
 14. Domestic abuse
 15. Emotional abuse
 16. Physical abuse
 17. Sexual abuse
 18. Other traumatic event (self-described)
 - ▶ often excluded; too broad
 - ▶ not standardized domain – types of trauma not consistently assessed across participants
 19. Premature birth
 - ▶ often excluded from studies that examine ELS effects on brain structure or cognitive function
 - ▶ potential impact on brain development and cognition, which could artificially bias effects associated with high ELS
 - ▶ could be used as a covariate in analyses
- ▶ Scoring: 1 point is given for every ACE endorsed; range: 0 - 17
 - ▶ For some ACEs we consider the frequency of exposure (event occurred often or very often, etc.); method that parallels original ACE studies.

Adverse Childhood Experiences International Questionnaire (ACE-IQ)

- ▶ Designed for administration to people age 18 and older.
- ▶ Developed by the International ACE Research Network; their goal is to enable ELS measurement in all countries and to foster cross-country comparisons.
- ▶ Currently being validated internationally by World Health Organization (WHO) investigators/collaborators.
 - ▶ Based on an earlier version tested in several countries (China, Macedonia, Philippines, Saudi Arabia, South Africa, Thailand, and Vietnam).
- ▶ Pilot phase; strength for those conducting international studies
- ▶ Free to download:
 - ▶ www.who.int/violence_injury_prevention/violence/activities/adverse_childhood_experiences/en/

Adverse Childhood Experiences International Questionnaire (ACE-IQ)

- ▶ Assesses several ACEs; grouped into 13 categories of maltreatment
 1. emotional abuse
 2. physical abuse
 3. sexual abuse
 4. emotional neglect
 5. physical neglect
 6. bullying
 7. domestic abuse
 8. household member who was abusing substances
 9. household member who was mentally ill or suicidal
 10. household member who was imprisoned
 11. one or no parents, parental separation/divorce
 12. community violence
 13. collective violence
- ▶ Unique component – focus on community violence and collective violence
 - ▶ Example item: “Were you beaten up by soldiers, police, militia, or gangs?” (collective violence)
- ▶ Two scoring methods:
 - ▶ Binary scoring – 1 point is given for every category with an endorsed item
 - ▶ Frequency scoring – as above, but considers frequency of exposure (event occurred often or very often, etc.); method that parallels original ACE studies
- ▶ Scores range from 0 to 13 for both scoring systems

Which scale to choose?

- ▶ Points to consider:
 - ▶ What types of traumas/maltreatment do you want to assess?
 - ▶ Consider the most frequent types of traumas experienced in your population.
 - ▶ Input from the literature. Expand beyond what has been examined in the literature.
 - ▶ Do you want to focus on a specific type of trauma/maltreatment?
 - ▶ Emotional neglect, poverty, community violence, immigration-related traumas (e.g., forced family separations), etc.
 - ▶ All ACE scales are not created equal.
 - ▶ Make sure that these types of ACEs included in your scale.
 - ▶ Are you interested in a broad assessment of many different types of ACEs?
 - ▶ ELSQ, ACE-IQ
 - ▶ Do you want to assess information about age of exposure, duration of exposure?
 - ▶ ELSQ; Modify an already existing scale to include these assessments?
 - ▶ Administration time
 - ▶ ELSQ and ACE-IQ are the longest; BRFSS is the shortest (11 items)

Overview of ELS Measures

	Example Items	ACE Study	BRFSS ACE	CTQ	ELSQ	ACE-IQ
Number of Categories Assessed		7	8	5	13	13
<i>Abuse</i>		47%	45%	60%	21%	28%
Emotional Abuse	Insulted, put down by family member/family said hurtful things	2	1	5	2	2
Physical Abuse	Hit hard enough to leave marks/had to visit doctor/others noticed	2	1	5	2	2
Sexual Abuse	Touched, fondled; was threatened to comply with sexual request	4	3	5	4	4
Peer Violence	Bullied/rejected by peers				1	1
<i>Other Physical Threats</i>		0%	0%	0%	13%	24%
Bodily Harm	Major surgery/repeated hospitalizations				2	
Witness Traumatic Events	Natural disaster (earthquake, flood); warfare				3	
Community Violence	See/hear someone get beaten up/stabbed/shot (in real life)					3
Collective Violence	Beaten up by solders, police, militia, gangs					4
<i>Household Dysfunction</i>		53%	55%	0%	44%	28%
Substance Abuse	Live with problem drinker/who misused street or prescription drugs	2	2		2	1
Mental Illness	Household member depressed/mentally ill/attempted suicide	2	1		2	1
Domestic Abuse	Mother/household member pushed, grabbed, slapped	4	1		5	3
Other Household Discord	Live with someone who was in/went to prison	1	1		1	1
Family Separations/Traumas	Parents separated/divorced; foster care; family member died		1		7	2
<i>Deprivation</i>		0%	0%	40%	21%	17%
Poverty/Physical Neglect	Parent/guardian too drunk/high to care; wear dirty clothes			5	3	3
Emotional Neglect	Parents/guardians don't understand problems/worries			5	5	2

Administration Issues: Literacy

- ▶ What is the literacy level of your population?
 - ▶ Make the decision to read the questionnaire to all participants or none of the participants prior to beginning the study.
 - ▶ Reading questionnaires to participants can impact the information you obtain.
 - ▶ Verbally admitting that you have experienced trauma to another person is very different from (privately) endorsing these experiences on a questionnaire.
 - ▶ The interpersonal interaction changes the nature of the assessment and could impact willingness to report sensitive traumas (e.g., sexual abuse).
 - ▶ Any systematic differences in administration which impact a specific sub-sample of your cohort (low literacy/SES respondents) should be avoided.
 - ▶ Record any deviations in administration.
 - ▶ Take deviations into account when determining which data to include in your analyses.
 - ▶ Could impact how data are analyzed: depending on sample size, use as covariate.

Administration Issues: Rapport

- ▶ Rapport building will enhance the integrity of the data you collect.
- ▶ Consider placement of ELS assessments in your test battery.
 - ▶ Should be placed later in the interview/battery. Avoid having this assessment be the first interaction with participants, before you have a chance to build rapport.
- ▶ ELS interviews should be as natural as possible and conducted politely, like a normal conversation.
- ▶ Remind participants that we will maintain the confidentiality of their information.
- ▶ Empathic responses are natural, but those who administer these scales should remember not to be judgmental or express shock at a participant's response.
- ▶ Don't rush the assessment.
 - ▶ If pressured, people may respond with anything that crosses their mind.
- ▶ Administrators are encouraged to respect a person's right not to respond.
 - ▶ Some participants may refuse to answer certain or all items. Others may not refuse outright but may express hesitancy, reservation, or hostility. We must always respect a person's right to refuse.

Comorbid Conditions

- ▶ Important to consider how to handle conditions that commonly covary with high ELS if our goal is to reveal the unique impact of high ELS on neural/cognitive/behavioral outcomes.
- ▶ ELS exposure is commonly associated with higher levels of current stress, PTSD symptoms, and depression.
 - ▶ These factors have known impacts on several outcomes of interest:
 - ▶ Brain structure, Brain function, Cognition, Behavior, Affective response
- ▶ Consider excluding those with current PTSD and/or MDD diagnoses; or covary for their occurrence.
 - ▶ E.g., PTSD and MDD are associated with cognitive dysfunction and aberrant brain response
- ▶ If MRI study, consider excluding those taking psychoactive medications which impact brain function (e.g., amygdala response).
- ▶ High ELS is a risk factor for substance use, which can also impact brain structure, function, and cognition.
 - ▶ Consider whether to exclude those with current AUD/SUD and/or how to control for levels of past use.

Assessment of Comorbid Conditions

- ▶ history of current/past Psychiatric Diagnoses (MDD, Anxiety, OCD, PTSD, AUD/SUD)
 - ▶ MINI - Mini-International Neuropsychiatric Interview; SCID; CIDI
- ▶ current Stress levels
 - ▶ PSS - Perceived Stress Scale (Cohen et al., 1983)
- ▶ current levels of Depression
 - ▶ CES-D - Center for Epidemiological Studies-Depression Scale (Radloff, 1977);
 - ▶ BDI - Beck Depression Inventory
- ▶ current Anxiety symptoms
 - ▶ BAI - Beck Anxiety Inventory
 - ▶ STAI - State-Trait Anxiety Inventory
- ▶ current PTSD symptoms
 - ▶ PCL-C - Posttraumatic Stress Disorder Checklist-Civilian (Weathers et al., 1993)
- ▶ quantify lifetime levels of Alcohol and Substance Use
 - ▶ KMSK - The Kreek-McHugh-Schluger-Kellogg scale (Kellogg et al., 2003)
- ▶ assess for history of Learning Disability, exclude those with ADHD
 - ▶ MINI, SCID, etc.
- ▶ Several of these measures can be used as covariates in analyses – unique contribution of ELS.



Assessment of ELS Effects on the Brain

Part 4

Effects of ELS on Cognition Functions

- ▶ Brain structures that develop during childhood, such as the frontal lobes, are more likely to be impacted by ELS exposure (Pechtel & Pizzagalli, 2011).
 - ▶ High ELS exposure has been linked to reductions in frontal lobe (OFC) and anterior cingulate volumes (Bachi et al., 2018; Cohen et al., 2006).
 - ▶ The frontal lobes support higher-order, cognitive abilities.
- ▶ Deficits in **higher-order cognitive abilities** are commonly observed in adults with high ELS exposure (Bos et al., 2009; Colvert et al., 2008; Pollak et al., 2010; Guyer et al., 2006).
 - ▶ **Executive functions; Planning; Inhibitory control; Attention; Decision-making**
- ▶ Postnatal hippocampal development begins at a very early age and continues into adulthood (Gogtay et al., 2006).
 - ▶ Reduced hippocampal volumes have been observed in adults with high ELS exposure (Karl et al., 2006; Woon & Hedges, 2008; Woon et al., 2010; but see also Bellis et al. 2010).
 - ▶ Hippocampus contributes to memory functions.
- ▶ Adults with high ELS demonstrate impairments in **verbal, visual, and global memory** (Bos et al., 2009; Bremner et al., 2003; De Bellis et al., 2010; Navalta et al., 2006; Tomoda et al. 2010).

Assessment of Cognition Functions

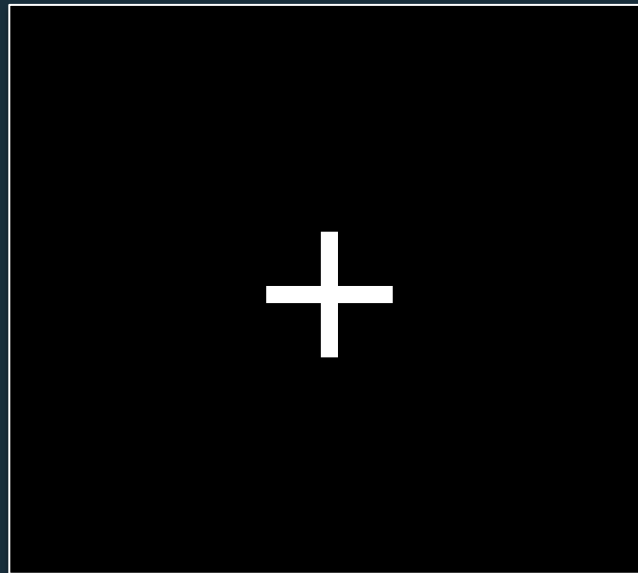
- ▶ Assess domains known to be impacted by ELS exposure (e.g., executive functions, memory).
- ▶ In developing a battery of neurocognitive tests, it can be helpful to work with a psychologist who has specialized training in this area (e.g., Neuropsychologist).
- ▶ Executive functions
 - ▶ Cognitive Flexibility
 - ▶ WCST – Wisconsin Card Sorting Test
 - ▶ CANTAB IED – Intra-Extra Dimensional Set Shift
 - ▶ EXAMINER Set Shifting
 - ▶ Trail Making Test, Part B
 - ▶ Verbal Fluency (FAS)
 - ▶ Working Memory
 - ▶ EXAMINER Dot Counting
 - ▶ WAIS Letter-Number Sequencing
 - ▶ N-Back Task
 - ▶ Planning
 - ▶ EXAMINER Unstructured Task
 - ▶ DKEF-S The Tower Test
 - ▶ Attention
 - ▶ CPT - Continuous Performance Test
 - ▶ Trail Making Test, Part B
 - ▶ Inhibitory Control
 - ▶ Go/No-Go
 - ▶ Stop Signal Task
 - ▶ Delayed Reward Discounting

Assessment of Cognition Functions

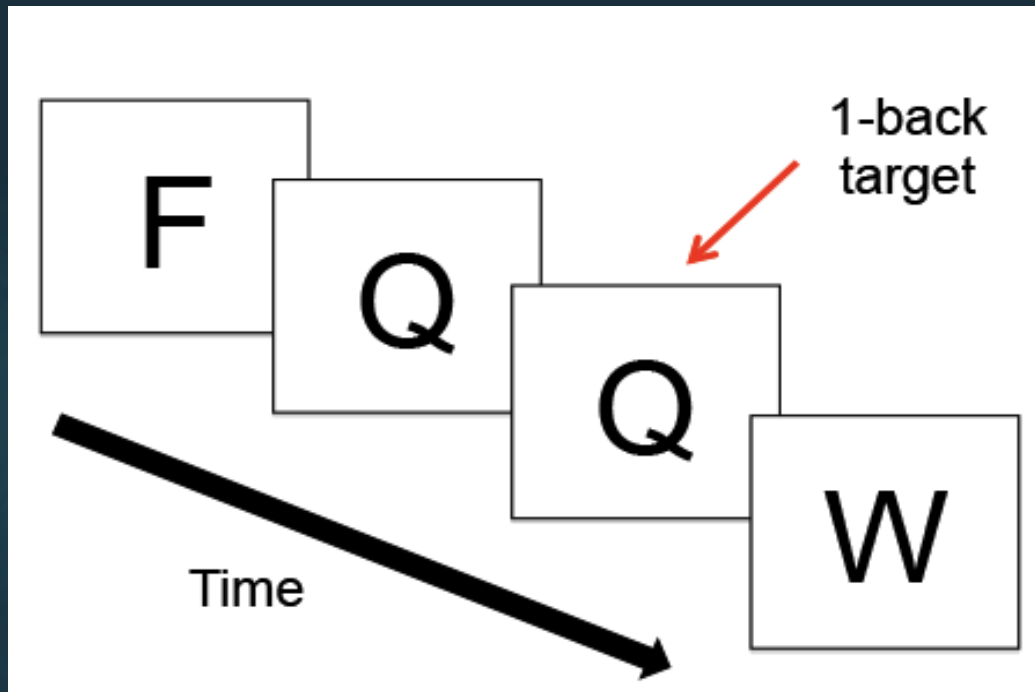
- ▶ Learning/Memory
 - ▶ HVLT - Hopkins Verbal Learning Test-Revised
 - ▶ CVLT-II – California Verbal Learning Test (2nd edition)
 - ▶ BVMT - Brief Visuospatial Memory Test
 - ▶ WMS - Wechsler Memory Scale
- ▶ Decision-Making Abilities
 - ▶ Iowa Gambling Task (reward-related decision-making)
- ▶ Helpful to assess factors that covary with ELS and impact cognitive performance:
 - ▶ Overall intelligence (e.g., De Bellis et al., 2009)
 - ▶ WASI - Wechsler Abbreviated Scale of Intelligence (2 test; 4 tests)
 - ▶ WTAR - The Wechsler Test of Adult Reading (reading test)
 - ▶ Education quality
 - ▶ WRAT - Wide Range Achievement Test
 - ▶ Socioeconomic Status (SES)
 - ▶ Hollingshead Index of Socioeconomic Status

Hands-on Activity:

The N-Back task, 1-Back condition



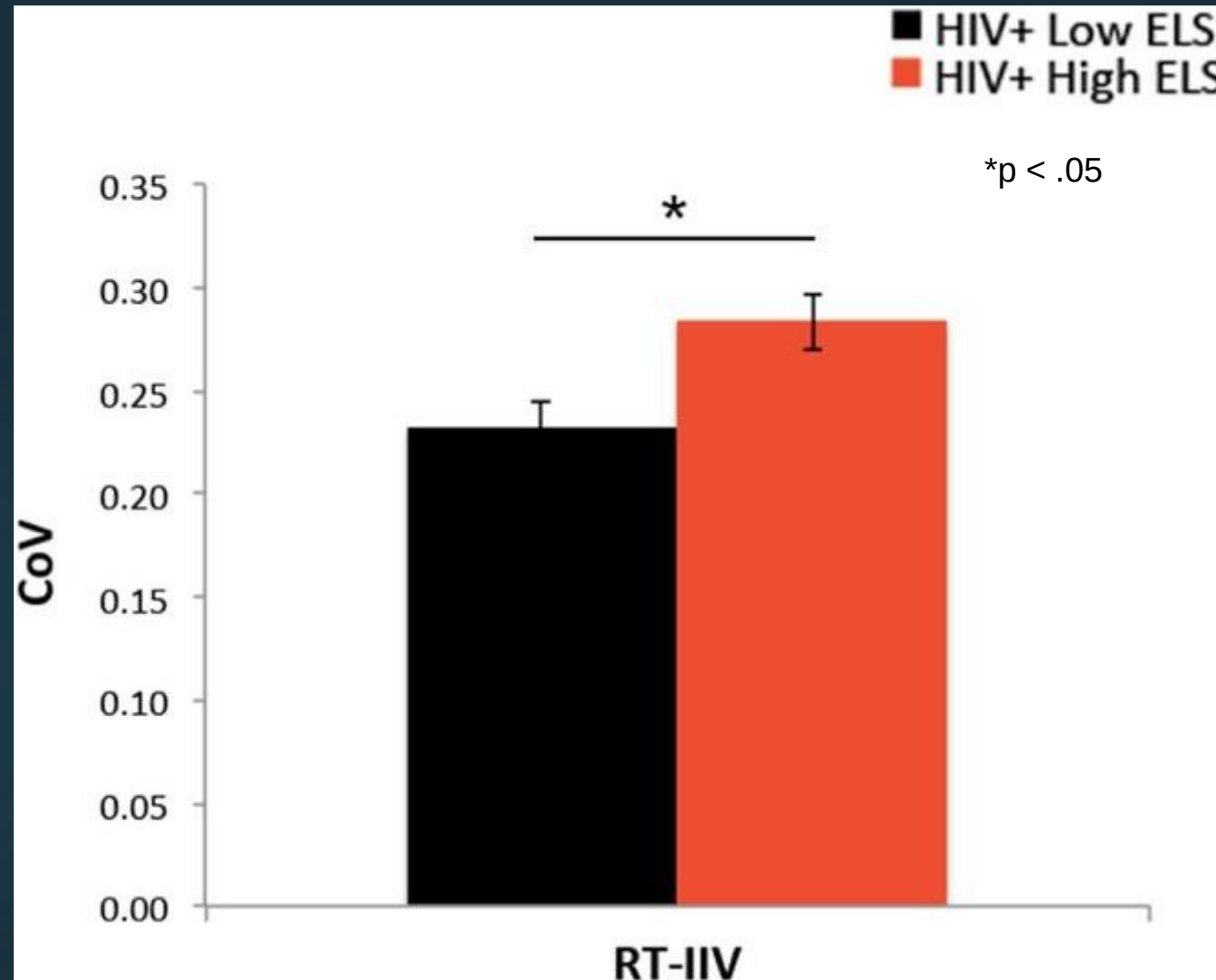
Application of the N-Back in a study of High ELS effects in an HIV+ sample



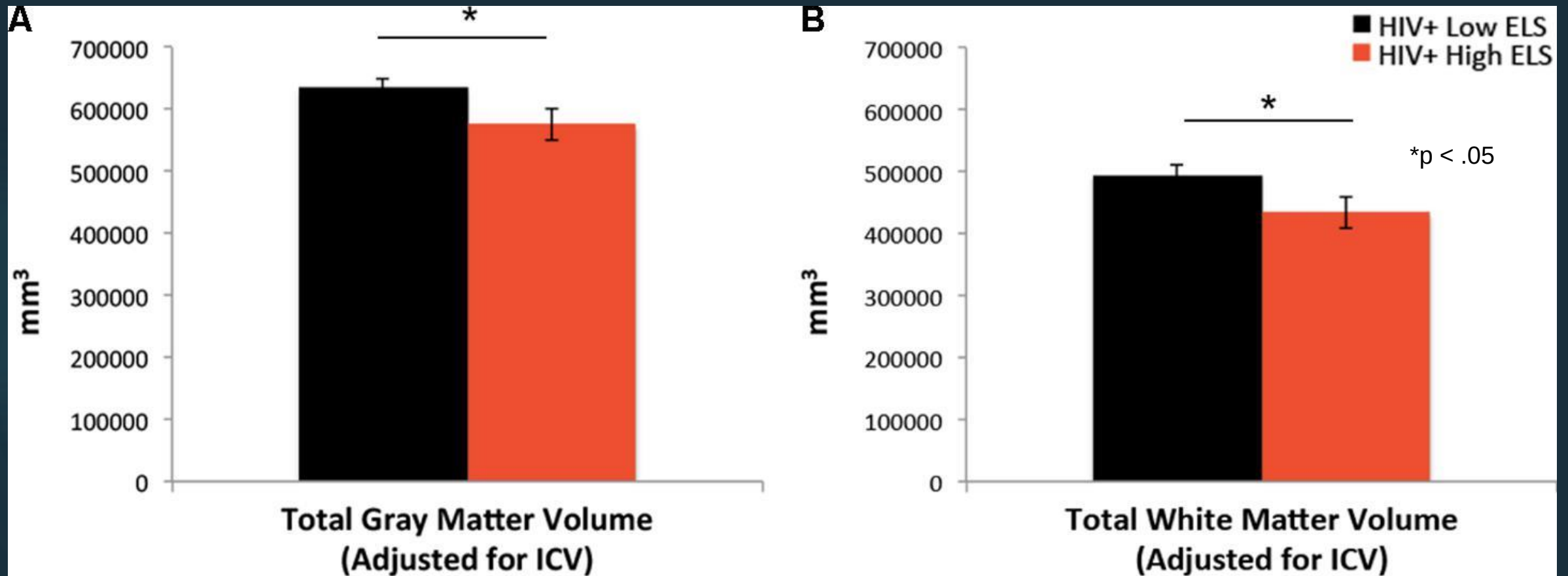
1-Back Task: *Indicate Yes/No whether the letter on the screen is the same as the one presented just before.*

- ▶ Performance Measure – Reaction Time Variability (RT-IIV)
- ▶ A measure of an individual's variability in response times, summarized across a number of trials in a task.
- ▶ A marker of cognitive ability; exhibits strong correlations with cognitive functions in HIV+ adults (Ettenhofer et al., 2010) and in non-HIV samples (Dixon et al., 2007).
- ▶ Sensitive to elevations in psychological symptoms (Swick et al., 2012) and brain volume abnormalities (Jackson et al., 2012) in non-HIV samples.

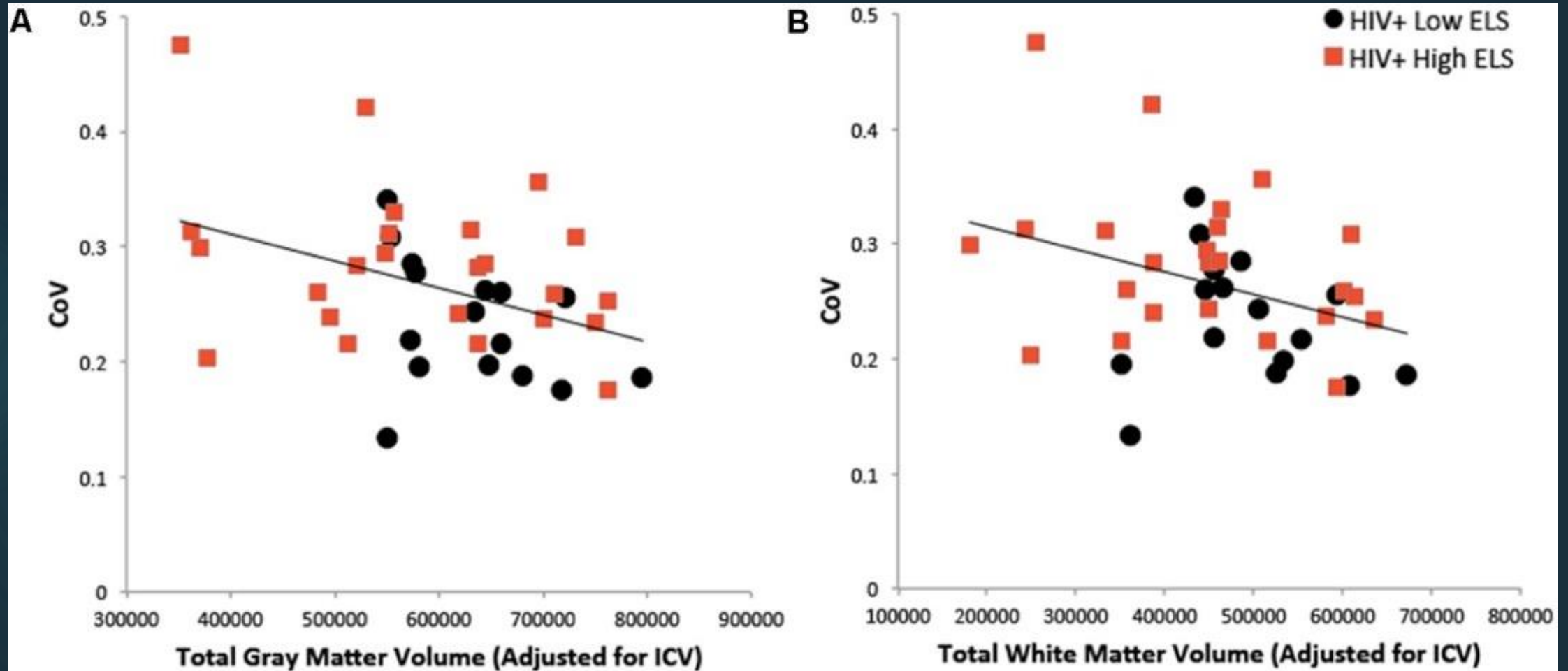
On the 1-Back, HIV+ adults with high ELS exhibit greater RT-IIV than those with low ELS



HIV+ adults with high ELS exhibit smaller gray and white matter volumes than those with low ELS



RT-IIV correlates with ELS-related reductions in global gray and white matter volume in HIV+ adults, even when controlling for ELS-related elevations in depression and current stress.



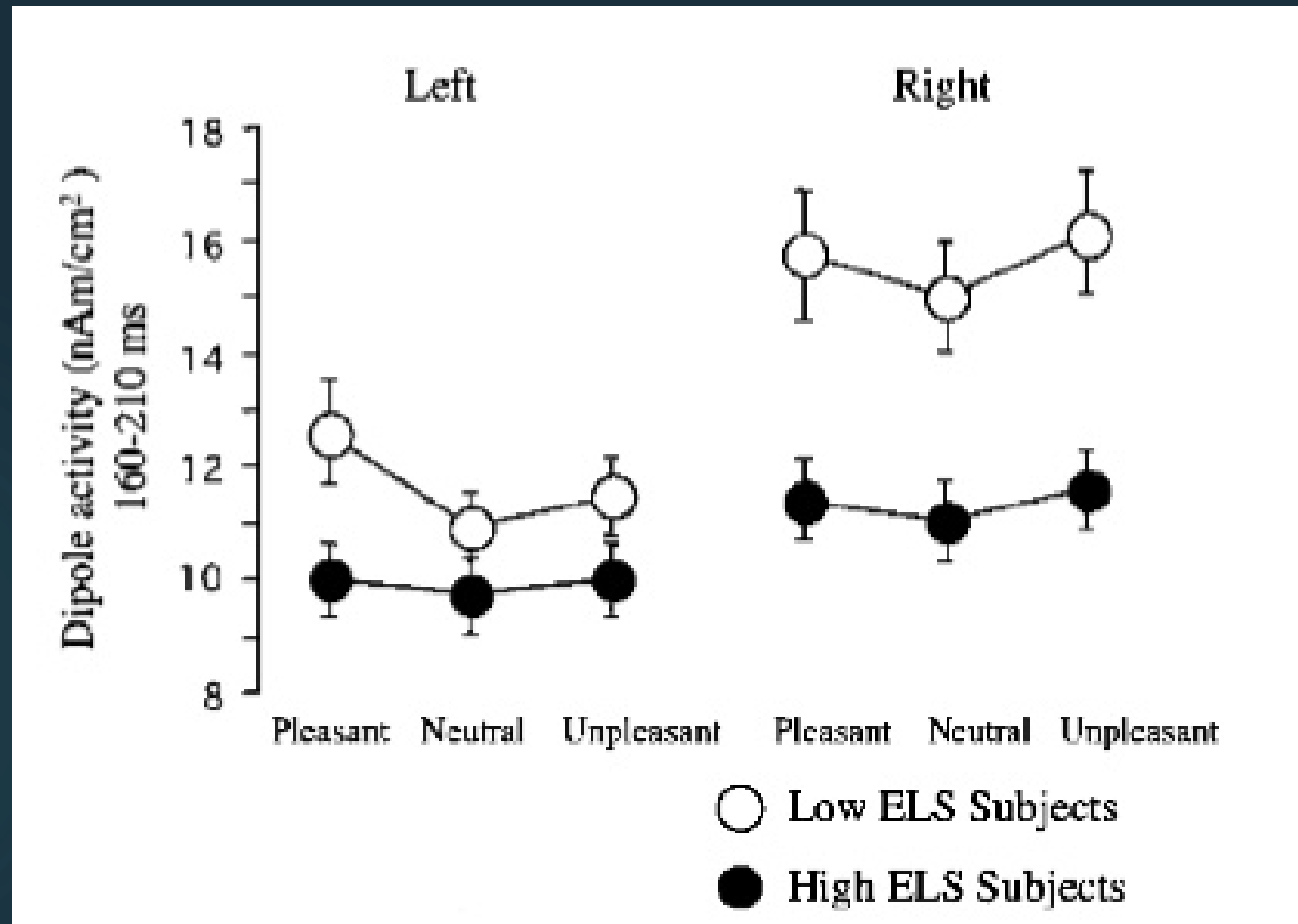
Effects of ELS on Affective Functions

- ▶ ELS is a risk factor for increased psychiatric symptoms (e.g., depression, anxiety) (Clark et al., 2017; Felitti et al., 1998; Kaufman & Charney, 2001; McFarlane et al., 2005; Pesonen & Raikkonen, 2012; Repetti et al., 2002; Taylor, 2010).
- ▶ The amygdala undergoes a period of rapid development after birth extending into childhood (Shaw et al., 2008).
- ▶ The amygdala appears to be more reactive during childhood than adulthood; childhood might represent a sensitive period in which stress exposure can disrupt maturation (Tottenham et al., 2010).
 - ▶ Children exposed to high ELS exhibit increased amygdala volumes (Tottenham et al., 2009; Mehta et al., 2009).
- ▶ The amygdala is involved in learning about, and responding to, social and affective stimuli.
- ▶ In those with high ELS histories, aberrant amygdala development might impact response thresholds (to affective stimuli) and contribute to psychopathology (Tottenham & Sheridan, 2010; Kim & Whalen, 2009).

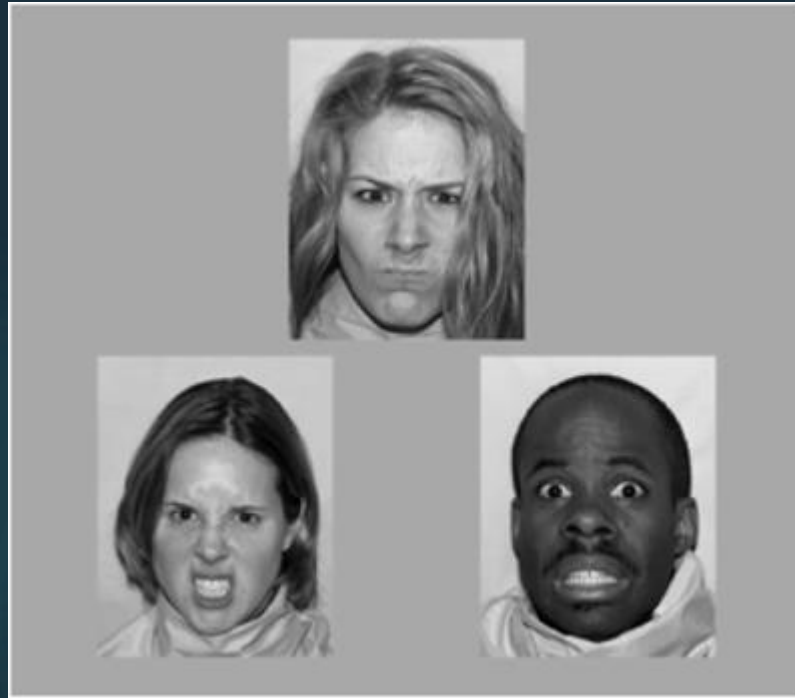
Assessment of Affective Functions

- ▶ Measures used to assess Stress, Depression, Anxiety, PTSD, and other psychiatric symptoms
 - ▶ PSS - Perceived Stress Scale (Cohen et al., 1983)
 - ▶ LSI - UCLA Life Stress Interview (Hammen et al., 1998)
 - ▶ CES-D - Center for Epidemiological Studies-Depression Scale (Radloff, 1977)
 - ▶ BDI - Beck Depression Inventory
 - ▶ BAI - Beck Anxiety Inventory
 - ▶ PCL-C - Posttraumatic Stress Disorder Checklist-Civilian (Weathers et al., 1993)
 - ▶ SCID-5 - Structured Clinical Interview for DSM-5
- ▶ Tasks that elicit an Affective Response (*used in neuroimaging and behavioral studies*)
 - ▶ IAPS - International Affective Picture System (Lang et al., 2008)
 - ▶ Ekman Faces (Ekman & Friesen, 1976)
 - ▶ NimStim - images of facial emotion; modern; racially diverse (Tottenham et al., 2012)

IAPS



Affect Recognition/Observation Tasks

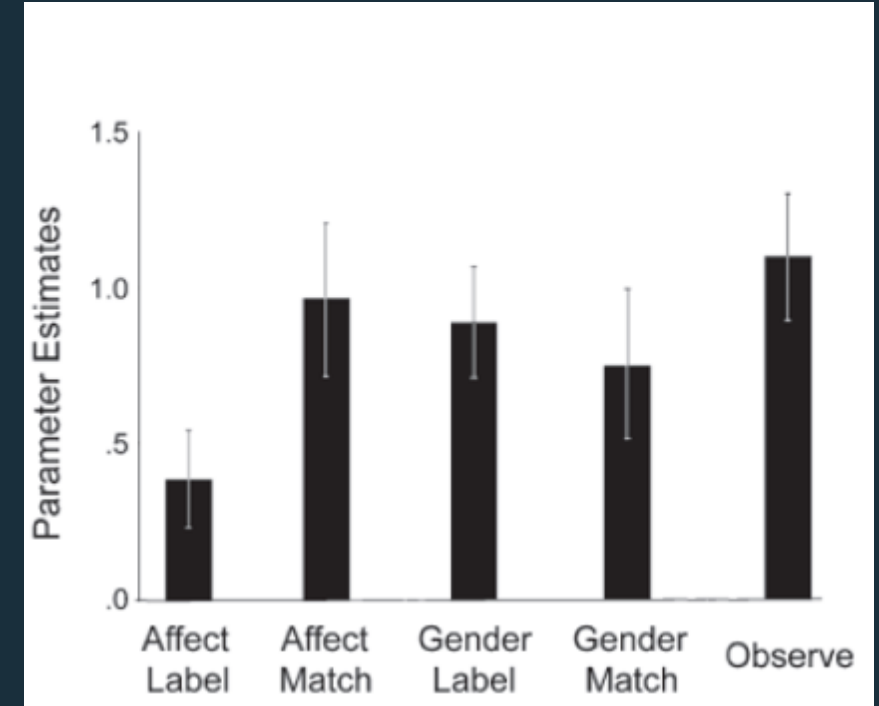


<< Affect Match



Affect Label >>

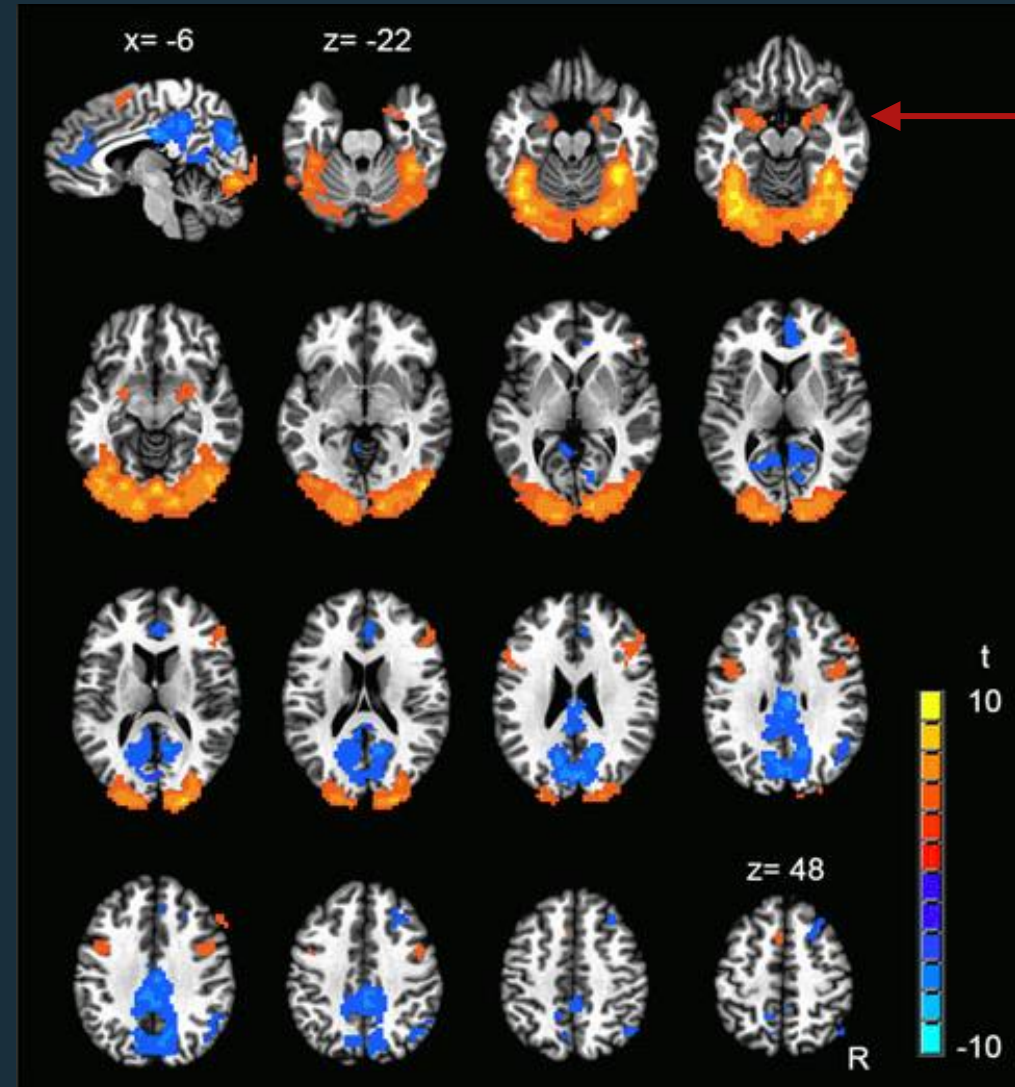
SCARED ANGRY



(from Lieberman et al. 2007;
see also Hariri et al., 2000, 2002)

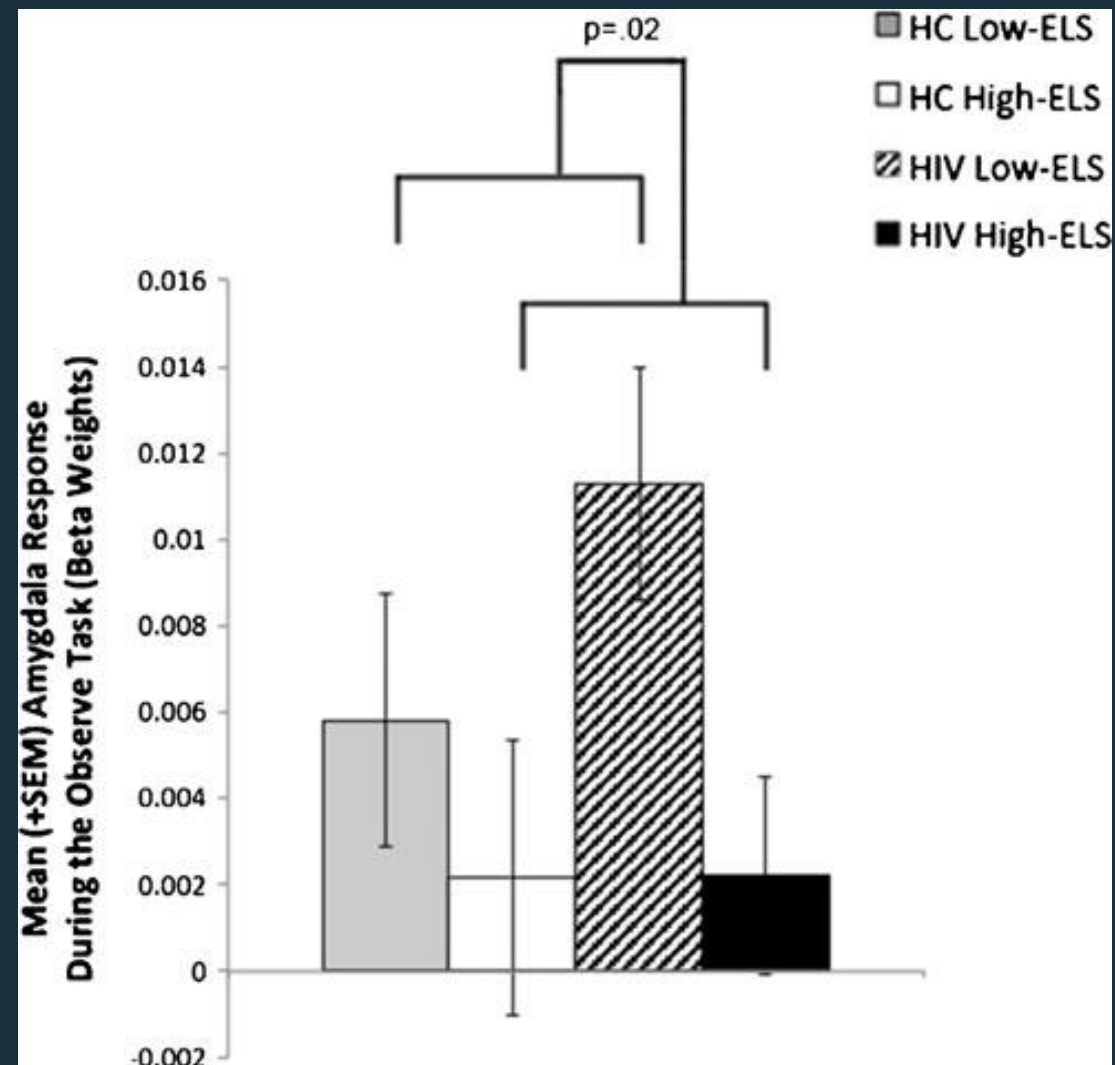
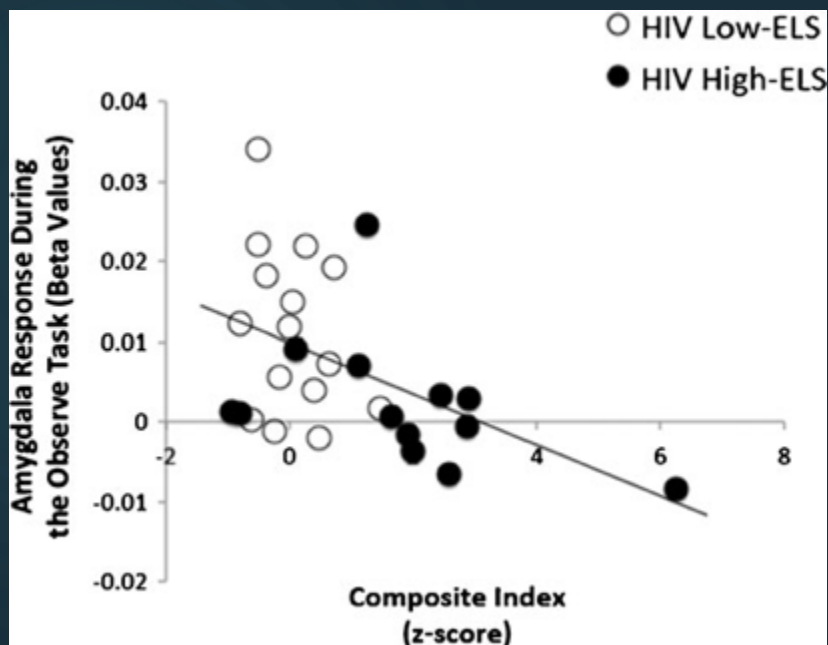
Affect Recognition/Observation Tasks

- ▶ Activation during the Observation task.
- ▶ Robust activation in the bilateral amygdala.
- ▶ Activation of the fusiform face area and other visual regions.



Affect Recognition/Observation Tasks

- ▶ Adults with high ELS demonstrate a blunted amygdala response when viewing images of negative facial affect.
- ▶ Degree of amygdala blunting correlates with levels of psychiatric symptoms in HIV+ adults.



Effects of ELS on Reward Processing & Associated Risk-Taking

- ▶ Several studies have linked ELS to impairments in reward processing and reduced activation in brain regions involved in processing rewards – e.g., basal ganglia.
 - ▶ High ELS participants exhibit decreased anticipatory reward-related activity in the basal ganglia (globus pallidus, putamen) (Dillon et al., 2009).
 - ▶ Adults with high ELS also exhibit reduced basal ganglia (ventral striatum) activation to reward-predicting cues (Mehta et al., 2010).
 - ▶ Adults with high high ELS exhibit lower levels of brain activation when processing cues signaling potential losses and increased responsivity when actually experiencing losses (Birn et al., 2017)
 - ▶ These patterns of brain activity were associated with both laboratory and real-world measures of individuals' risk taking in adulthood (Birn et al., 2017).
 - ▶ These effects were predicted only by ELS levels and not by current stress levels.

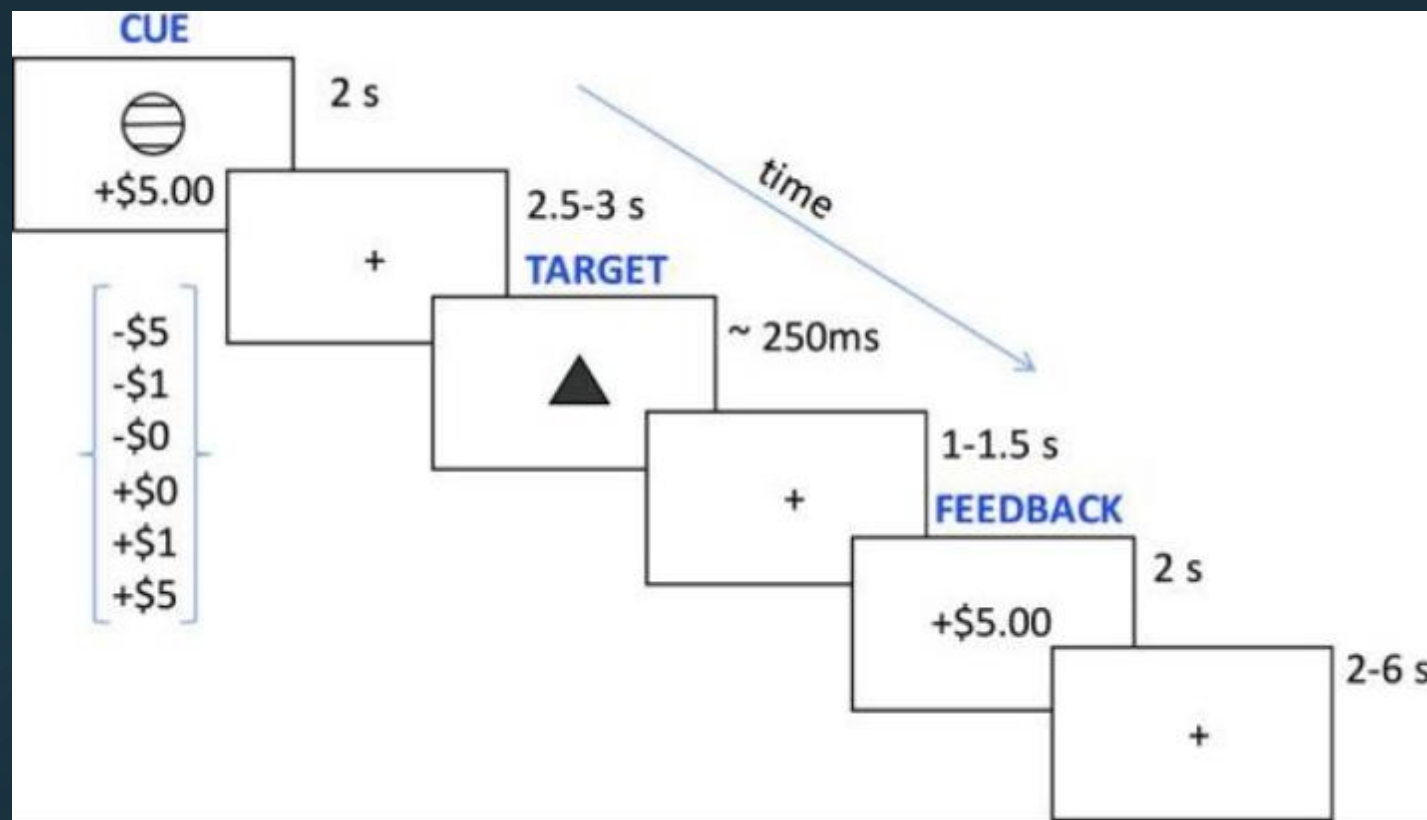
Assessment of Reward Processing & Associated Risk-Taking

- ▶ Reward Processing
 - ▶ Monetary Incentive Delay Task (Knutson et al., 2000)
- ▶ Risk-Taking Behaviors (*surveys*)
 - ▶ Youth Risk Behavior Survey (Eaton et al., 2012, as modified by Birn et al., 2017)
 - ▶ 52 items; queries risky behavior in several areas including driving, weapons, tobacco, alcohol, drugs, sex, health, and crime.
 - ▶ HIV-Risk-Taking Behavior Scale (Darke et al., 1991)
 - ▶ 11 items, used to assess HIV risk among IV drug users
 - ▶ 2 subscales to measure IV drug use and sexual behaviors
- ▶ Risk-Taking Behaviors (*behavioral tasks*)
 - ▶ BART - Balloon Analogue Risk Task (Lejuez et al., 2002)
 - ▶ Risky Gains Task (Paulus et al., 2003)
 - ▶ Iowa Gambling Task (reward-related decision-making)
 - ▶ Cambridge Gambling Task (CANTAB, Cambridge Cognition Ltd; used by Birn et al., 2017)

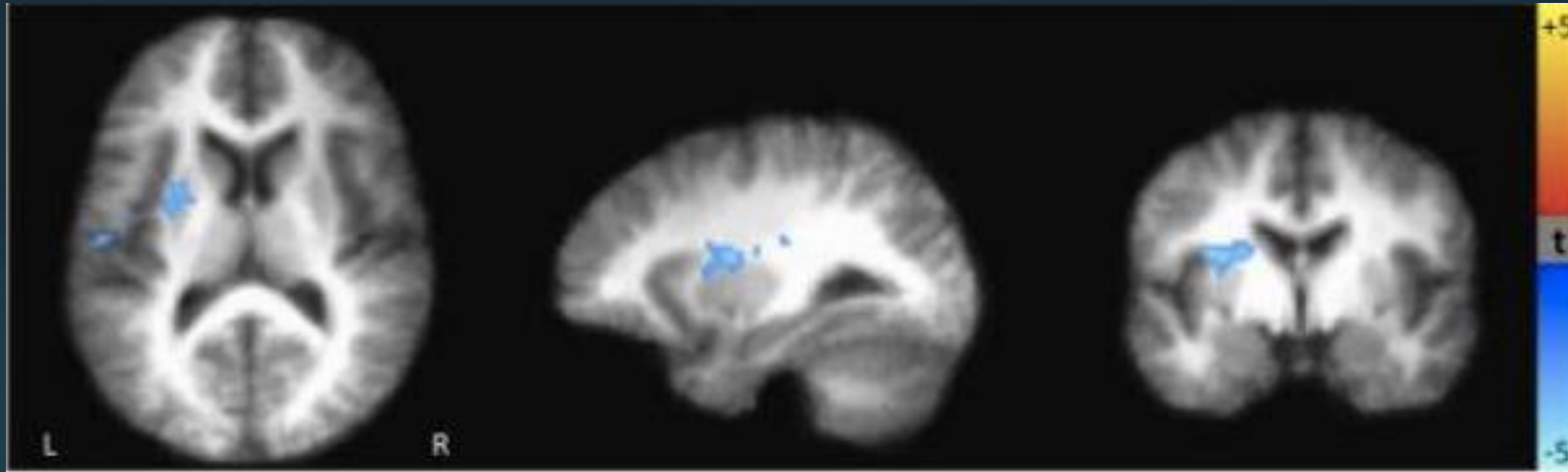
Monetary Incentive Delay Task

- Taps activation of the brain's reward circuitry, including the basal ganglia/ventral striatum, insula, thalamus, and medial prefrontal cortex (Knutson et al., 2000; Knutson et al., *Neuroreport*, 2001; Knutson et al., *J. Neurosci.*, 2001).

Used to assess differences in activation patterns during anticipation of rewards, wins, and losses.

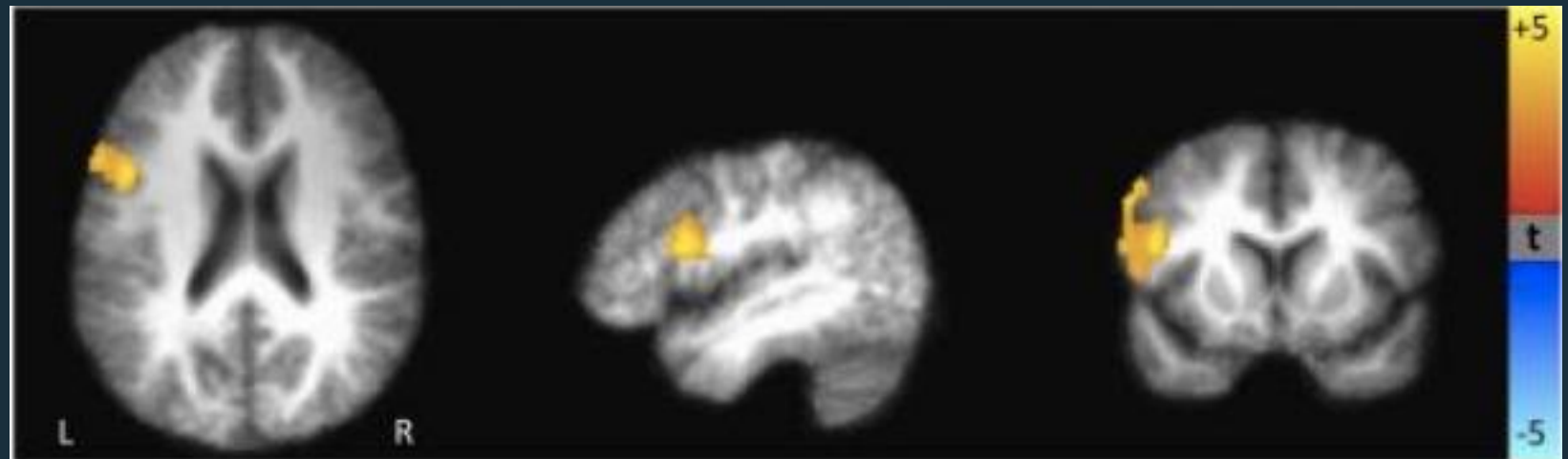


Effects of ELS on Reward Processing & Associated Risk-Taking

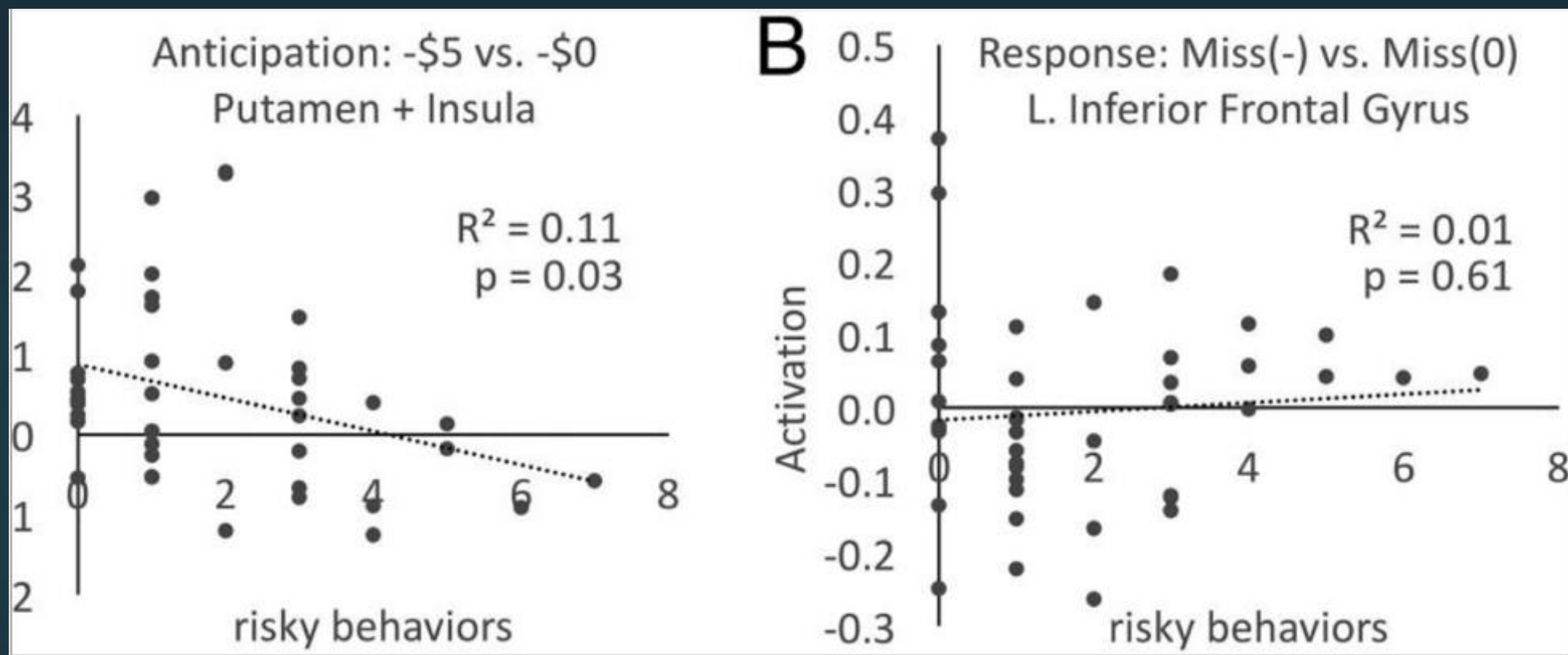


High ELS adults exhibit reduced activation in the putamen and insula during the anticipation of potential losses.

High ELS adults exhibit increased activation in the left inferior frontal gyrus when experiencing an actual loss.



Effects of ELS on Reward Processing & Associated Risk-Taking



Summary

- ▶ Studies highlight the various methods of assessing ELS in order to better understand its contributions to cognitive, affective, and behavioral outcomes.
- ▶ Numerous tools can be used to help reveal the unique contribution of high ELS to cognitive and affective functions.
- ▶ Neuroimaging methodologies can be applied to further refine our understanding of how ELS modulates cognitive and affective processes that govern behavior.
- ▶ If we better understand the underlying mechanisms of ELS, as well as reveal its unique effects on behavior, we will be in a better position to develop strategies capable of preventing and improving ELS-related health risks.

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