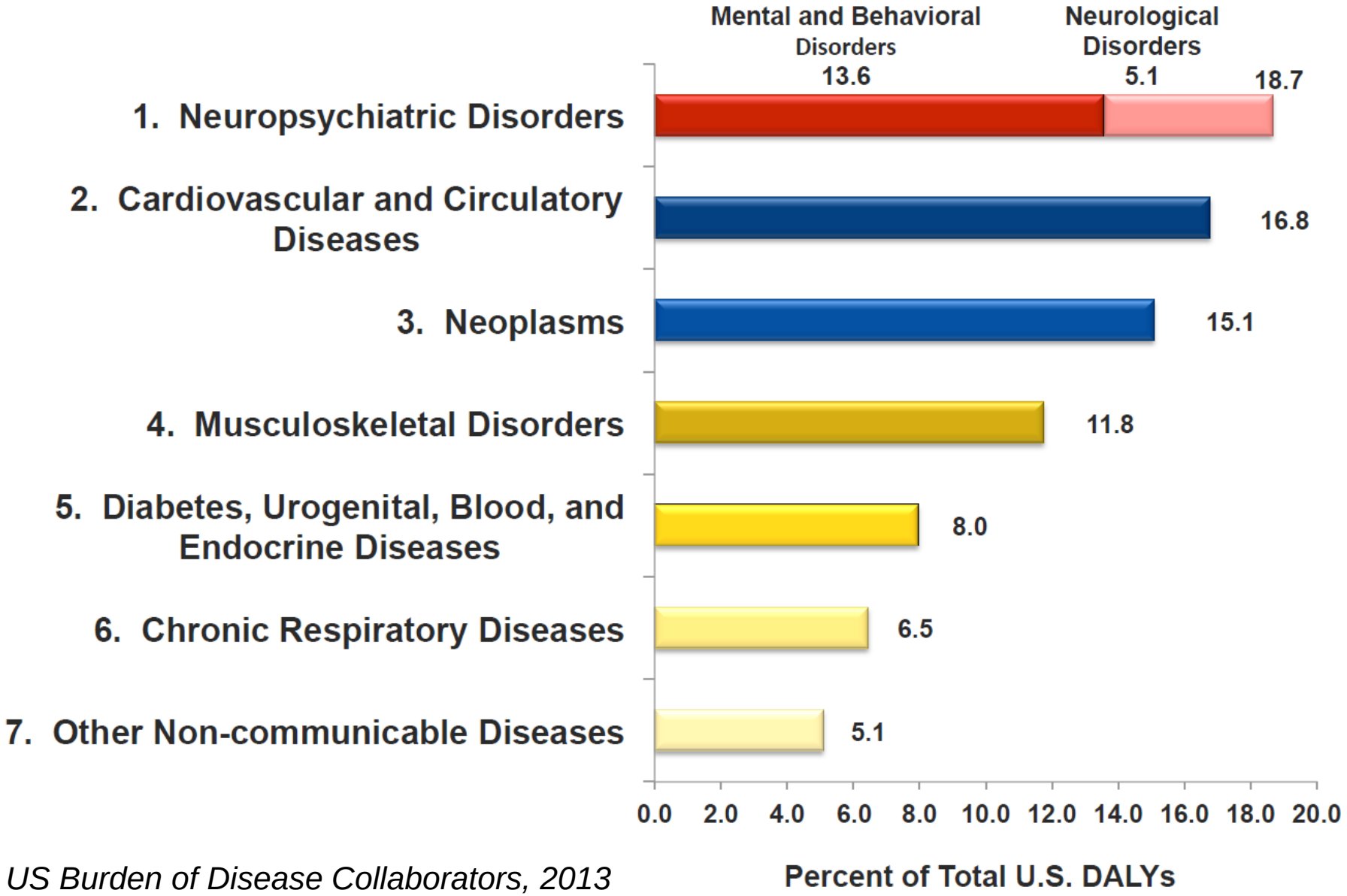
Biomarkers and underlying mechanisms of psychiatric diseases

Will discuss the DSM vs. RDoC approach to study mental health disorders and the related biomarkers and include examples from my research.

(Reading: Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC medicine, 11(1), 126.)

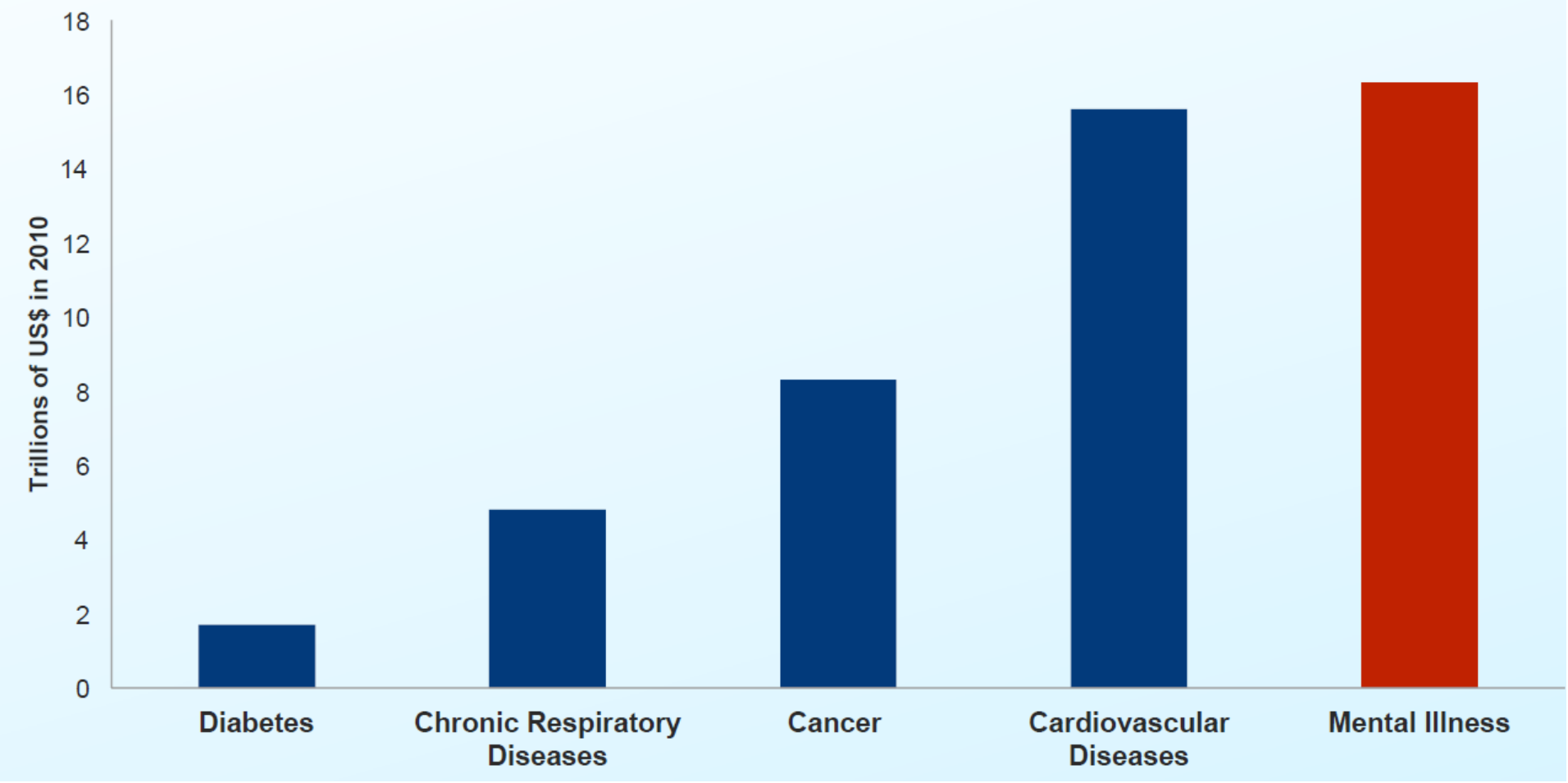
Klára Marečková, Ph.D., M.Sc.

Burden of Diseases: Disability-adjusted Life Years



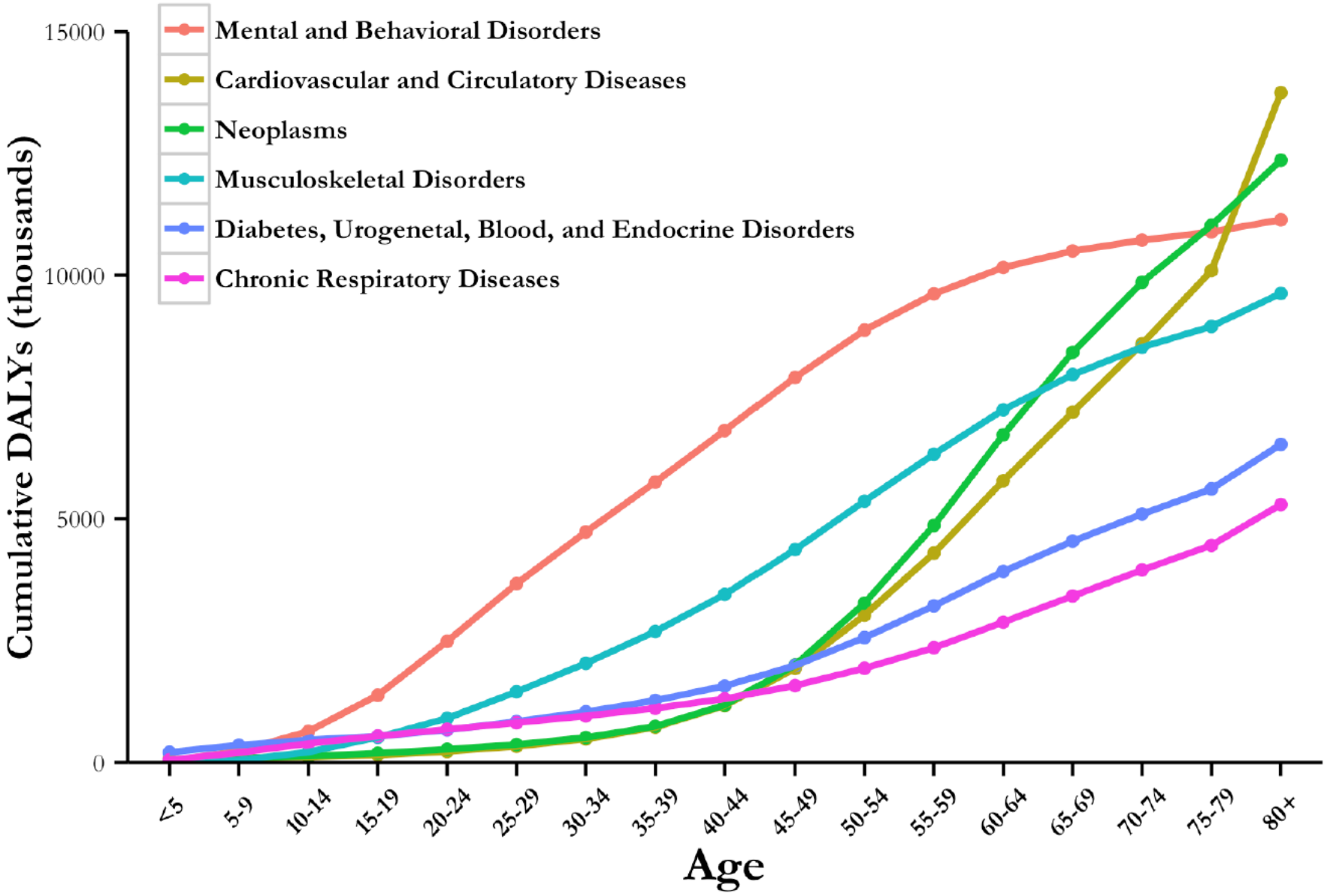
US Burden of Disease Collaborators, 2013

Burden of Diseases: Most Costly Conditions



The Global Economic Burden of Noncommunicable Diseases, WEF, 2011

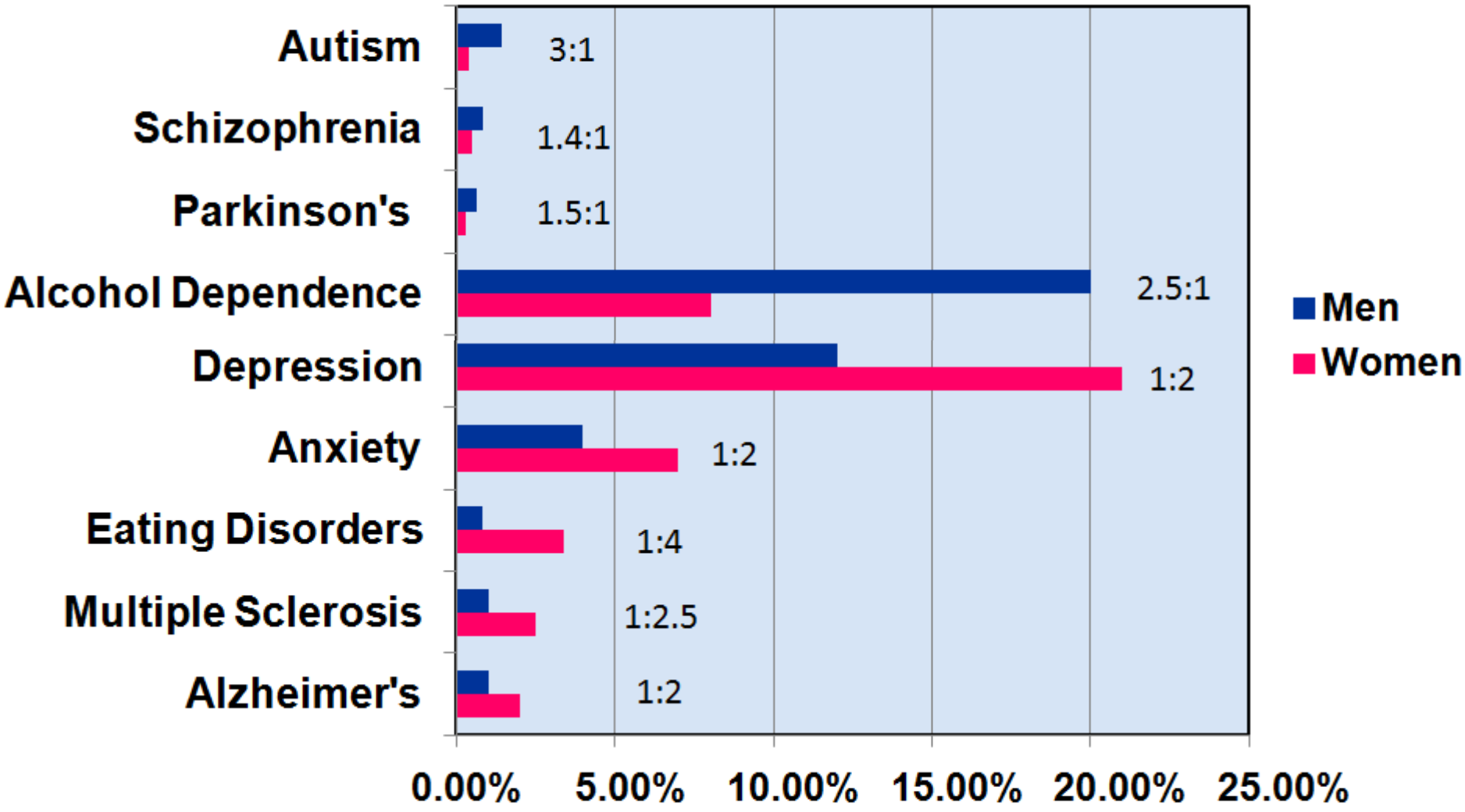
The Most Disabling Disorders before Age 50



Psychiatric diseases are a major health challenge

- $^1/_5$ American
- 2% are on the autistic spectrum
- 1% schizophrenia
- 7% severe depression
- Suicide is the leading causing of death in young people (15 to 29 years)

Sex Differences in Prevalence of Disorders of the Brain



Current diagnostic systems

Published online 13 April 2011 | Nature | doi:10.1038/news.2011.232

News

Schizophrenia 'in a dish'

Researchers are making inroads in the daunting challenge of modelling mental illness, thanks to patients' cells.

Ewen Callaway

Michael Owen: “These disorders are not really disorders. There’s no such thing as schizophrenia. It’s a syndrome. It’s a collection of things psychiatrists have grouped together.”

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Challenges and opportunities for drug discovery in psychiatric disorders: the drug hunters' perspective

Erik H. F. Wong[1], Frank Yocca[1], Mark A. Smith[2] and Chi-Ming Lee[3]

[1] *CNS & Pain Discovery Research, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*
[2] *Early Clinical Development, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*
[3] *Translational Science, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*

"On average, a marketed psychiatric drug is efficacious in approximately half of the patients who take it. One reason for this low response rate is the artificial grouping of heterogeneous syndromes with different pathophysiological mechanisms into one disorder."

Current Diagnostics in Mental Health

- Diagnosis limited to symptoms
  (but symptoms are late manifestations
  of brain disorders)

- Etiology unknown
  (treatments for symptoms not cures)

- Detection late; for most disorders,
  prevention not well developed

Better Treatment through Better Diagnostics

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- **Understand the etiology** through large population-based studies, understand the **mechanisms**
- Focus on **early detection** and prevention (not extreme comparisons of patients vs. controls, study both clinical and pre-clinical populations to identify early biomarkers, use **standardized methods for replication**)
- Move towards **personalized medicine and sex-dependent therapeutics** (take into account one's sex, genes etc.)

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Research Domain Criteria (RDoC)

National Institute of Mental Health

Transforming the understanding and treatment of mental illnesses.

Search the NIMH website

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Research Domain Criteria (RDoC)

The Chronicle Review

Comments (65)

September 9, 2013

A Revolution in Mental Health

Narayan Mahon

Bruce Cuthbert, lead architect of a restructuring of mental-health research.

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Research Domain Criteria (RDoC)

Why Psychiatry's Seismic Shift Will Happen Slowly

+ Comment Now + Follow Comments

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Thomas R. Insel, Director, National Institute of Mental Health. (Photo credit: Wikipedia)

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Home » Monitor on Psychology » July/August 2013 Monitor on Psychology » NIMH funding to shift away from DSM...

UPFRONT

NIMH funding to shift away from DSM categories

July/August 2013, Vol 44, No. 7

Print version: page 10

Cuthbert and Insel *BMC Medicine* 2013, **11**:126
http://www.biomedcentral.com/1741-7015/11/126

BMC Medicine

DEBATE Open Access

Toward the future of psychiatric diagnosis: the seven pillars of RDoC

Bruce N Cuthbert[1,3*] and Thomas R Insel[2,3]

Abstract

Background: Current diagnostic systems for mental disorders rely upon presenting signs and symptoms, with the result that current definitions do not adequately reflect relevant neurobiological and behavioral systems - impeding not only research on etiology and pathophysiology but also the development of new treatments.

Discussion: The National Institute of Mental Health began the Research Domain Criteria (RDoC) project in 2009 to develop a research classification system for mental disorders based upon dimensions of neurobiology and observable behavior. RDoC supports research to explicate fundamental biobehavioral dimensions that cut across current heterogeneous disorder categories. We summarize the rationale, status and long-term goals of RDoC, outline challenges in developing a research classification system (such as construct validity and a suitable process for updating the framework) and discuss seven distinct differences in conception and emphasis from current psychiatric nosologies.

Summary: Future diagnostic systems cannot reflect ongoing advances in genetics, neuroscience and cognitive science until a literature organized around these disciplines is available to inform the revision efforts. The goal of the RDoC project is to provide a framework for research to transform the approach to the nosology of mental disorders.

Keywords: Diagnosis, DSM, ICD, Psychiatric diagnosis, Psychopathology, RDoC, Research domain criteria

Precision Medicine for Mental Disorders

- **2011 US National Academy of Sciences published major report on precision medicine**

  (more individualized treatment, based upon precise specification of the genetic, molecular and cellular aspects of disease)
- For example, in oncology, analysis of genetic variants is used to predict what treatment will be optimal

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- **In contrast to other areas of medicine, the field of mental disorders research lags badly behind the rest of medicine in moving towards precision medicine**
- One syndrom such as MDD involves multiple mechanisms – HPA dysfunction, reward-seeking, emotion regulation, modulatory neurotransmitter systems, epigenetic marks
- One mechanism (e.g. fear circuits or working memory) implicated in multiple disorders
- DSM and ICD categories do not map well onto emerging findings from genetics, systems neuroscience and behavioral science – so it's impossible to translate research findings into systematic understanding of pathology and treatment directed at the mechanisms
- Biological findings that did not map on the current heterogeneous DSM categories of symptom clusters were essentially excluded

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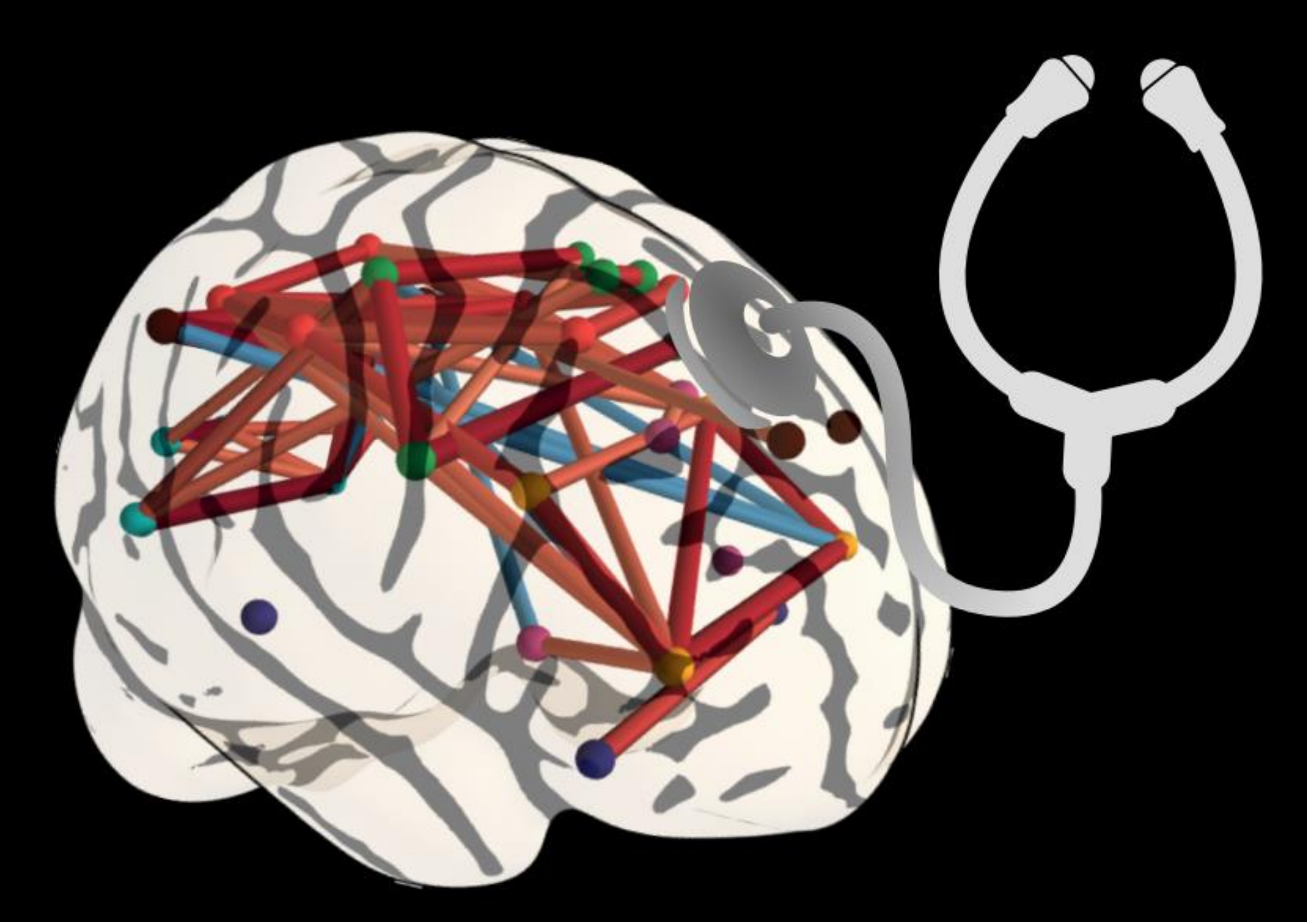
- **2009 NIMH RDoC project - research classification system, NIMH's effort to develop a precision medicine approach for mental disorders**
- New ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures
- Neural circuits and systems are a critical factor in how the brain is organized and functions, and how genetics and epigenetics exert their influence
- Studying full range of variation, from normal to abnormal



Research Domain Criteria (RDoC)

NIMH National Institute of Mental Health

Goal: To understand psychiatric dysfunction in terms of biological and behavioral underpinnings

NIMH RDoC Workshops focused on Five Domains:

- Negative Valence
- Positive Valence
- Cognitive Systems
- Systems for Social Processes
- Arousal/Modulatory Systems

	Units of analysis							
Domains/constructs	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports	Paradigms
Negative valence systems								
Active threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive valence systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for social processes								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/regulatory systems								
Arousal and regulation (multiple)								
Resting state activity								

Morris, Bruce, & Cuthbert, 2012

What about symptoms?

v. 5.1, 07/15/2012	RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
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Positive Valence Systems								
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Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social Communication								
Perception/Understanding of Self								
Perception/Understanding of Others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

- Elevated Stress Reactivity
- Problems with emotion regulation

- Lack of pleasure in usual activities
- Lack of energy for productive tasks

- Memory problems
- Problems with executive function

- Social withdrawal
- Poor relationships

- Problems with arousal-modulating systems
- Sleep problems

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Review

Application of Research Domain Criteria to childhood and adolescent impulsive and addictive disorders: Implications for treatment

Sarah W. Yip [a,b], Marc N. Potenza [a,b,c,d,*]

Domains

Negative Valence Systems

Positive Valence Systems

Constructs / Subconstructs	Units of Analysis: Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Approach Motivation								
Reward Learning								
Habit								
Sustained Responsiveness to Reward Attainment								
Initial Responsiveness to Reward Attainment	**DRD2, DAT, (TREK1),** *DRD4, OPRM1*	**Mu and delta opioids, orexin, glutamate, plasticity-related genes (CREB; FosB), endo-cannabinoids,** *dopamine*	*Dopamine neurons*	**NAcc, mOFC vmPFC, dorsal ACC, VTA, ventral pallidum, anterior insula, lateral hypo-thalamus**	*BOLD*	**Taste reactivity,** *behavioral response to reward (e.g., gambling task performance, response to drug challenge)*	**PANAS (state version), consum-matory subscale of TEPS**	**MID, gambling/ guessing tasks, taste reactivity,** *drug challenge*

Cognitive Systems

Arousal and Regulatory Systems

Systems for Social Processes

RDoC **Systems** and Constructs	Genes	Molecules	Circuits	Physiology	Behavior	Self-Report	Paradigm
Negative Valence							
Active threat ("fear")							
Potential threat ("anxiety")	5HT-LPR	SNRI	amygdala -ACC	Startle modulation	Threat bias RT	Hamilton-A STAI	Viewing fear faces
Sustained threat							
Loss							
Frustrative nonreward							
Positive Valence							
Reward Seeking							
Reward/habit Learning							
Cognitive							
Attention							
Perception							
Working memory		Vortioxetine	DLPFC-parietal		Accuracy		N-back
Language behavior							
Cognitive (effortful) control		Stimulants	dACC		Accuracy		Go-NoGo
Social Processes							
Imitation, theory of mind		Oxytocin	mPFC-TPJ		Accuracy		ToM task
Social dominance							
Facial expression identif'n							
Attachment/separation fear							
Self-representation areas							
Arousal/Regulatory							
Arousal & regulation		Neurofeedback		Resting EEG		Emotion regulation?	Explicit regulation
Resting state activity							

Three differentiating principles

- 1) Dimensional approach (translation of basic functional dimensions)
  - Psychopathology = the extreme of a normal dimension
  - Future implication: cut-points to define disorder
- 2) Different units of analysis that can be independent variables
- 3) Agnostic to current DSM/ICD categories
- **NOT a** competitor to DSM or ICD

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- **NOT a** competitor to DSM or ICD

! Orthogonal dimensions: Developmental aspects, Environmental aspects

What does RDoC mean for clinical trials now?

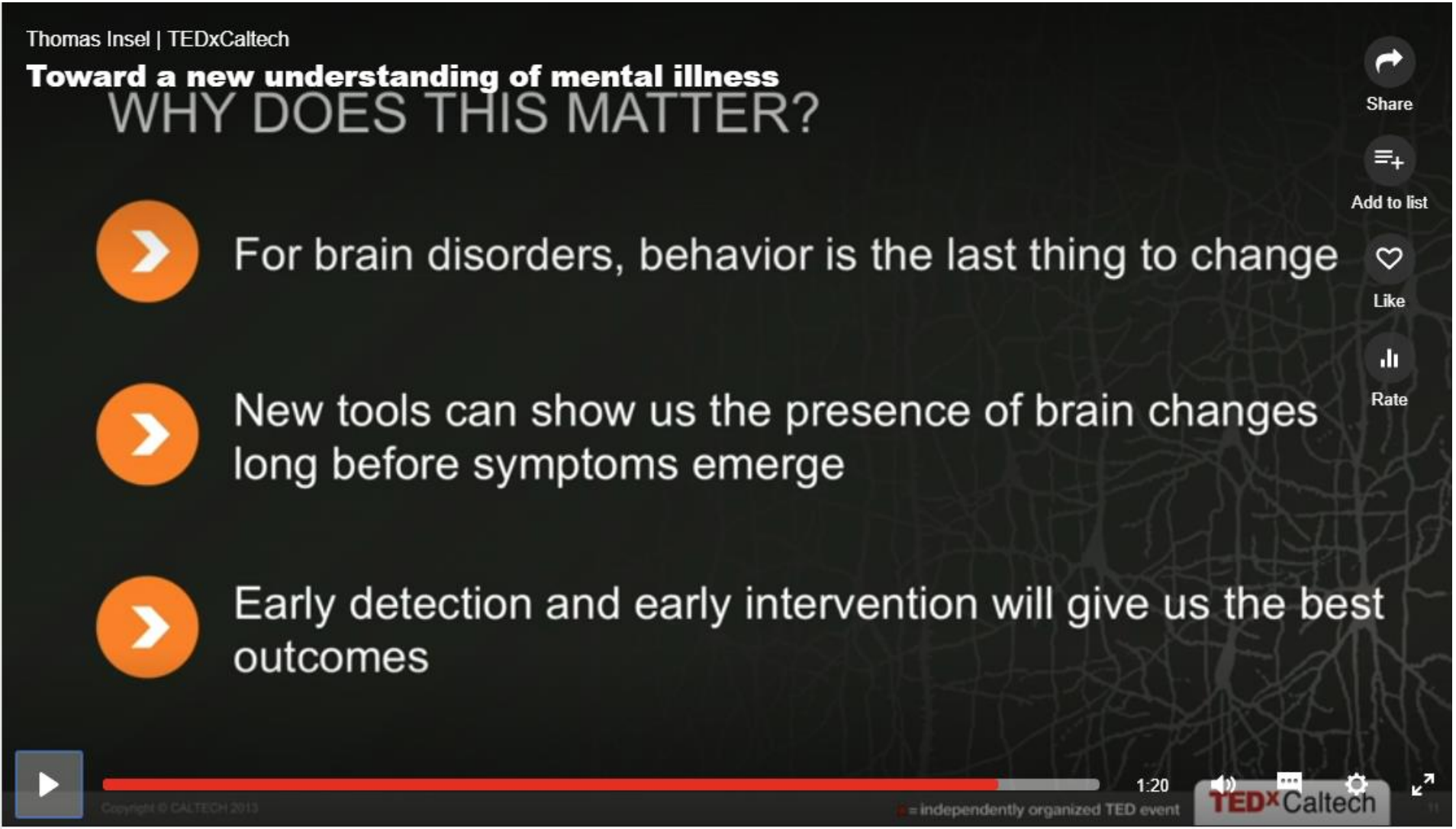
NIMH National Institute of Mental Health

Heterogeneous DSM categories confound studies of mechanism:

- No 1:1 relationship between a DSM diagnosis and a particular mechanism (e.g., not all schizophrenia patients have cognitive deficits)
- 1 feature can appear in multiple DSM disorders (e.g., cognitive deficits are seen in some schizophrenia, bipolar and depressed patients)

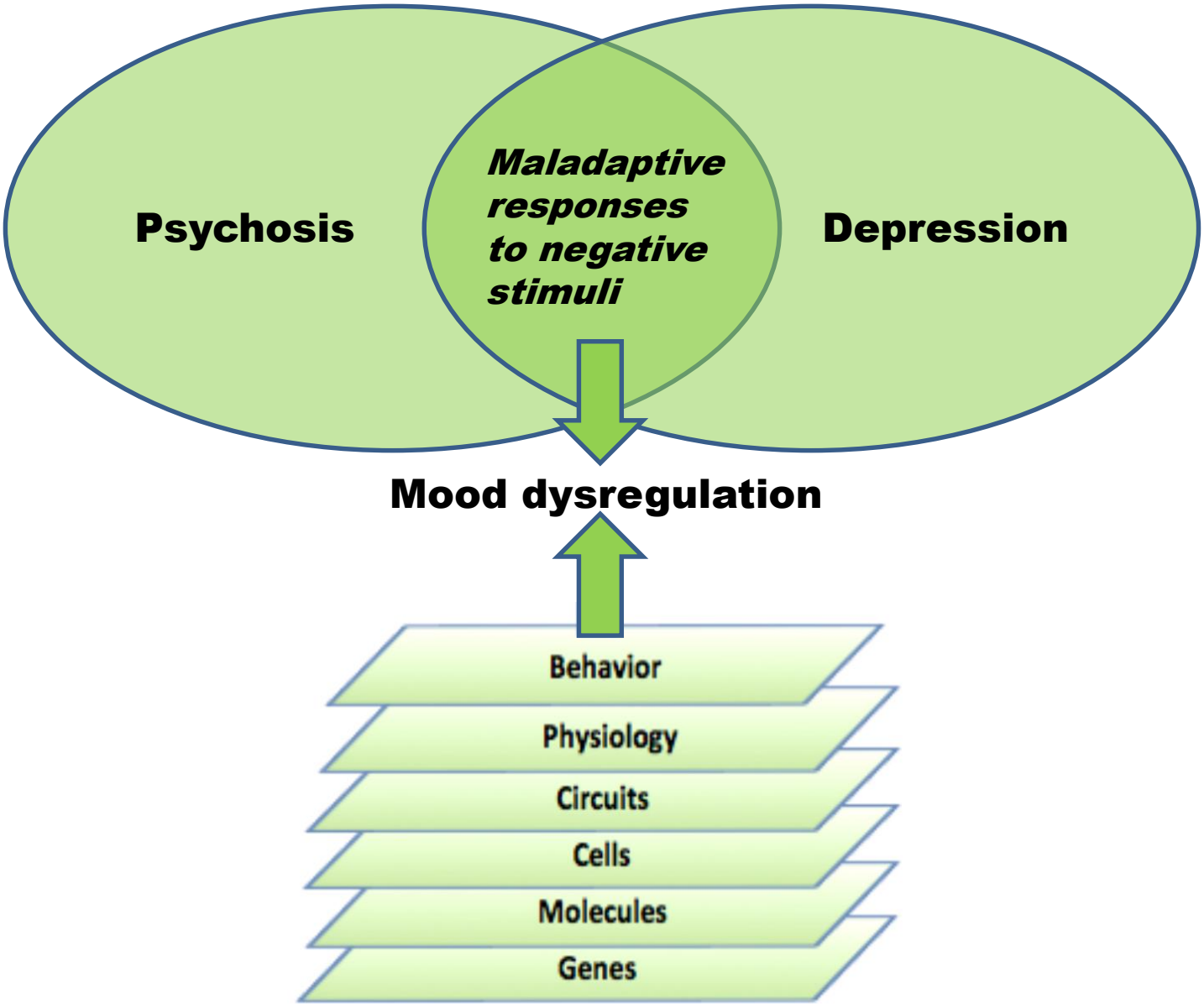
RDoC considerations for early phase clinical trials:

1. Focus on a novel mechanism relevant to a clinical problem regardless of DSM diagnosis (e.g., anhedonia, working memory)
2. Enroll patients based on deficits in the mechanism, not DSM diagnosis
3. Trial outcomes should reflect the changes in the target mechanism
4. The matrix is evolving: new mechanisms can be proposed for study



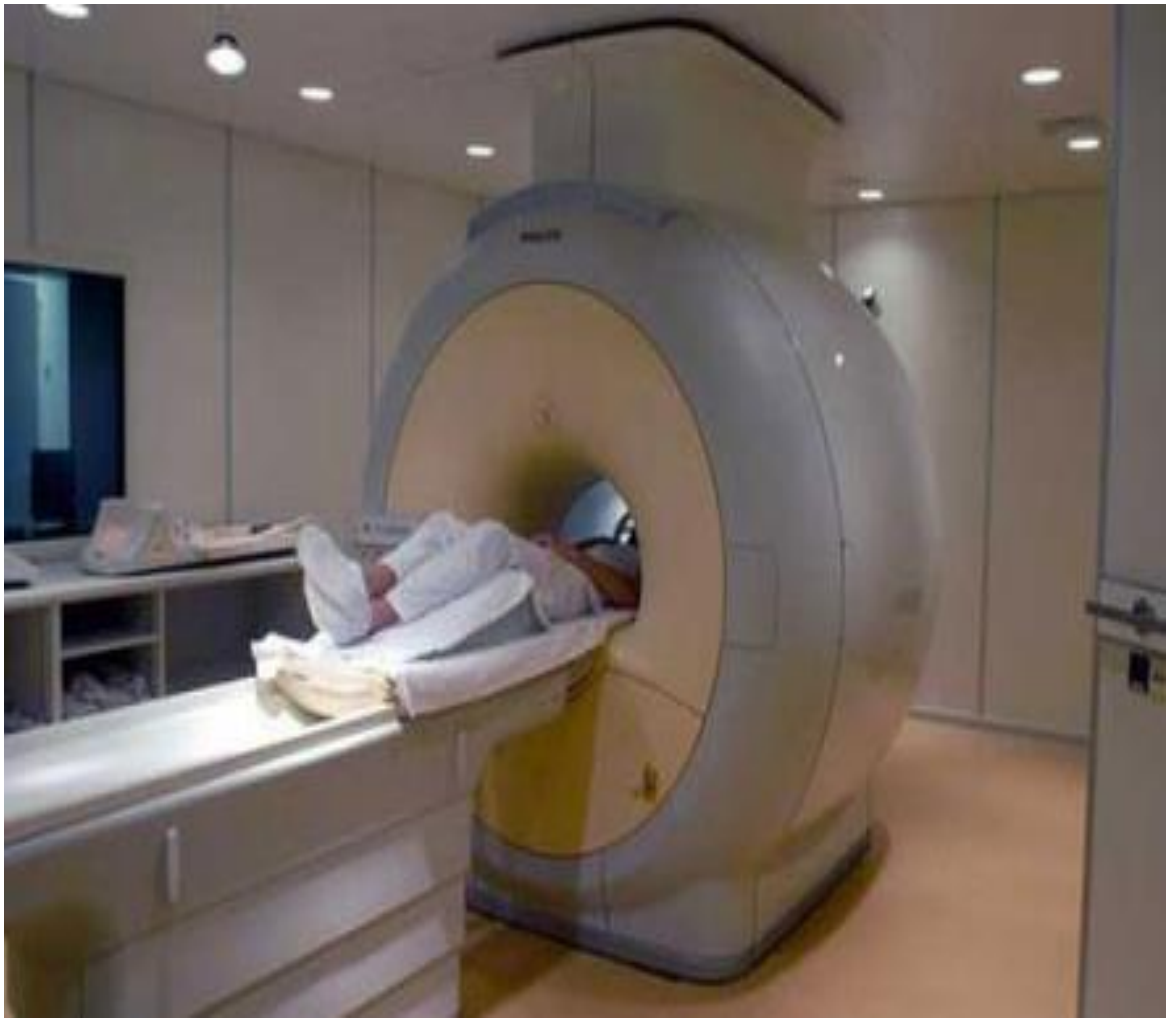
https://www.ted.com/talks/thomas_insel_toward_a_new_understanding_of_mental_illness

NIMH Research Domain Criteria (RDoC)



Functional Magnetic Resonance Imaging

- 99 participants scanned on 3T Siemens scanner



15 F and 16 M with PSY
14 F and 13 M with MDD
19 F and 22 M were CTRL

CPP

CPP

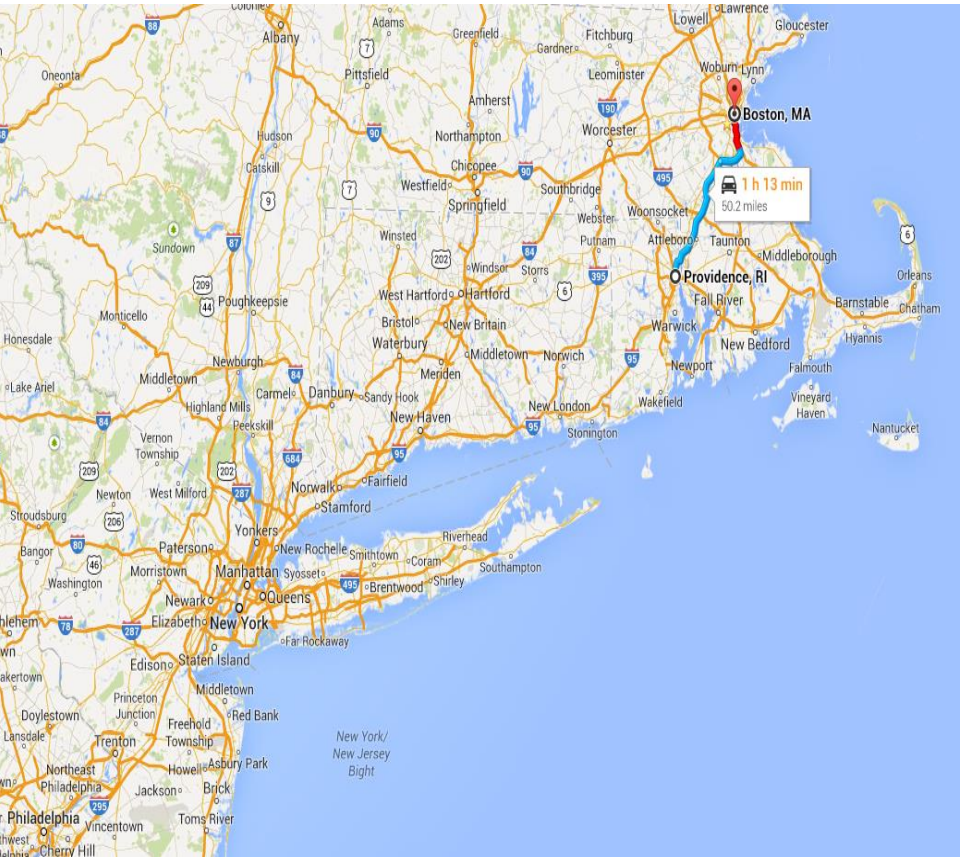
CPP

- a cohort of 17 000 pregnant mothers and their offsprings, born between 1959 – 1966, who were followed up
  - 1/month during the first 7 months of pregnancy
  - 2/month during the 8th month of pregnancy
  - 1/week during the 9th month and neonatal stage
  - at 4, 8, and 12 months
  - at 4 and 7 years

The final assessment at the age of 7 was completed by 80 % of the initial cohort.

NEFS

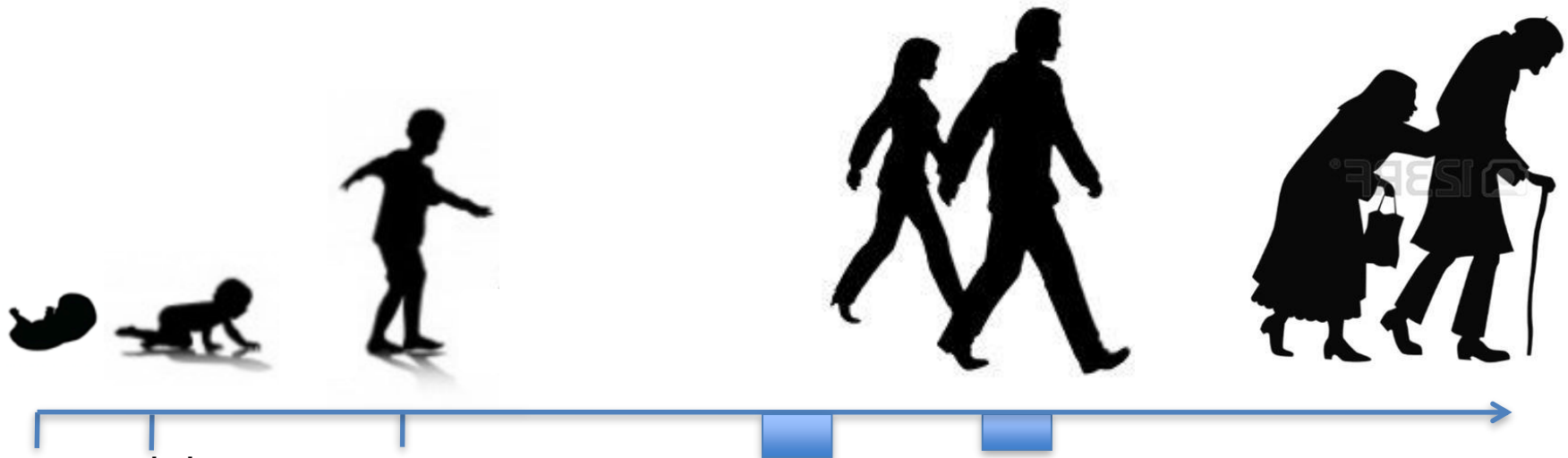
NEW ENGLAND FAMILY STUDY



- In 2000, Dr. Stephen Buka along with Dr. Jill M. Goldstein, Larry J. Seidman and Ming T. Tsuang started New England Family Study (NEFS), aimed to follow up the adults from CPP cohort.
- They successfully located cca 85% of the CPP sample.
- Over 90% of the successfully located individuals decided to participate in further studies focused on prenatal and early life antecedents of neuropsychiatric, physical and behavioral conditions such as schizophrenia, substance use, heart disease, learning disabilities, attention deficit disorder, depression or suicide.
- Actual study sites are located in Boston, MA (Harvard Medical School, Harvard School of Public Health, Massachusetts General Hospital and Massachusetts Mental Health Center) and Providence, RI (Brown University).

New England Family Studies: 50 year follow-up

ORWH-NIMH P50 MH082679; NIMH R01s MH56956, MH074679, MH090291



N = 17,741
1959 - 1966
Maternal prenatal sera assayed for early immune and hormonal biomarkers

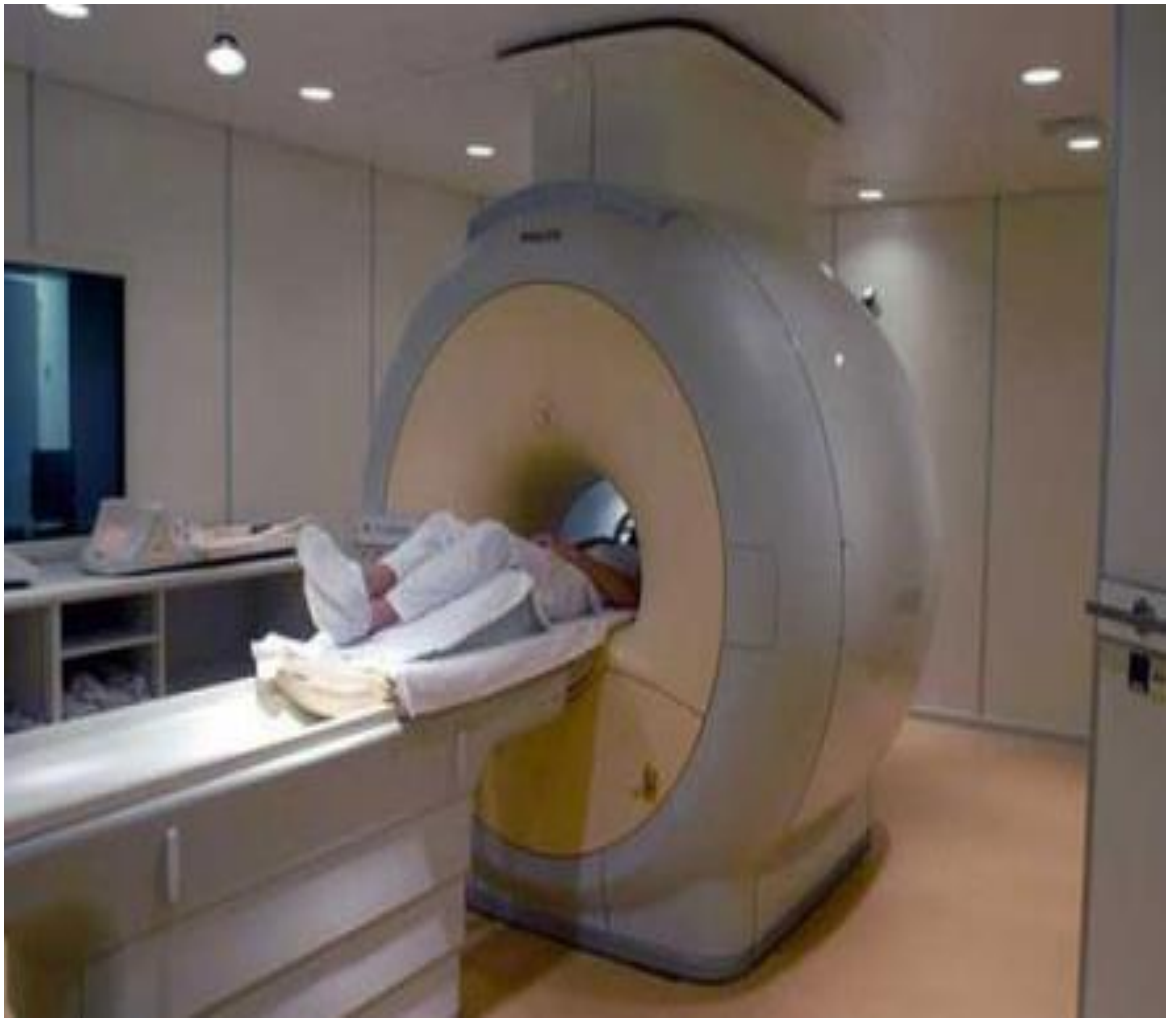
Childhood Assessments
up to age 7

ADULT PHENOTYPING / BIOMARKERS

- Clinical & Cognitive Assts.
- Structural and functional Imaging
- Hormonal Assessments
- EKG & cardiometabolic exams
- Blood and cell collection for genetics/genomics/transcriptomics

Functional Magnetic Resonance Imaging

- 99 participants scanned on 3T Siemens scanner



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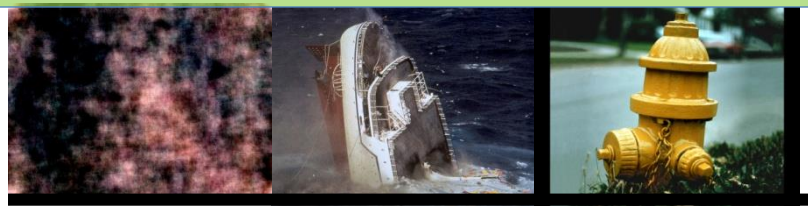
Negative affective stimuli from IAPS (Mild Visual Stress Task)

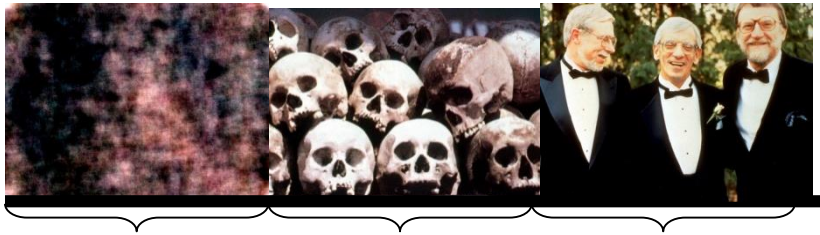


Fixation (30s) Negative (30s) Neutral (30s) + 4 Repetitions of 90s Blocks

Run 1 (6 min)

Fixation (30s) Negative (30s) Neutral (30s) + 4 Repetitions of 90s Blocks

Run 2 (6 min)

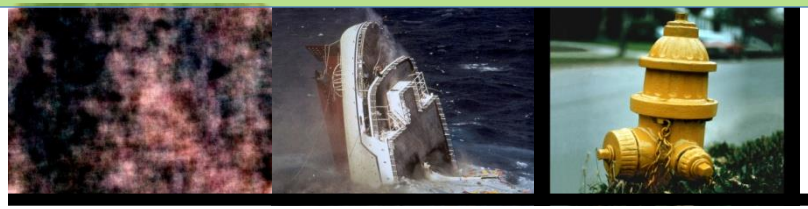


Fixation (30s) Negative (30s) Neutral (30s) + 4 Repetitions of 90s Blocks

Run 3 (6 min)

Negative affective stimuli from IAPS (Mild Visual Stress Task)

with Real-Time Hormone Response



Fixation (30s) | Negative (30s) | Neutral (30s) + 4 Repetitions of 90s Blocks

Time 00 Blood Draw

Run 1 (6 min)

Fixation (30s) | Negative (30s) | Neutral (30s) + 4 Repetitions of 90s Blocks

Run 2 (6 min)

Fixation (30s) | Negative (30s) | Neutral (30s) + 4 Repetitions of 90s Blocks

Time 15 Blood Draw

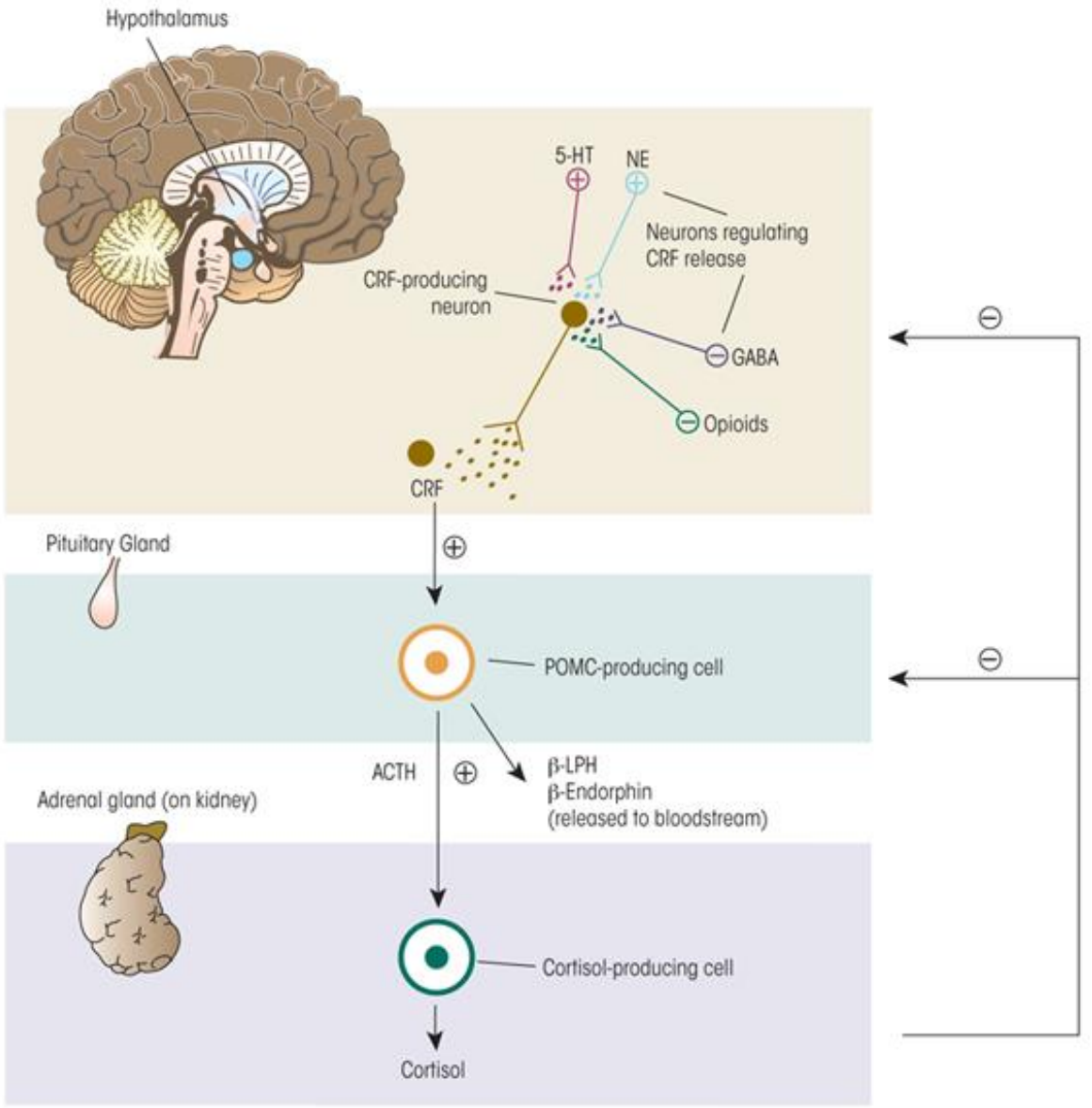
Run 3 (6 min)

Time 30, 60, 90 Blood Draws

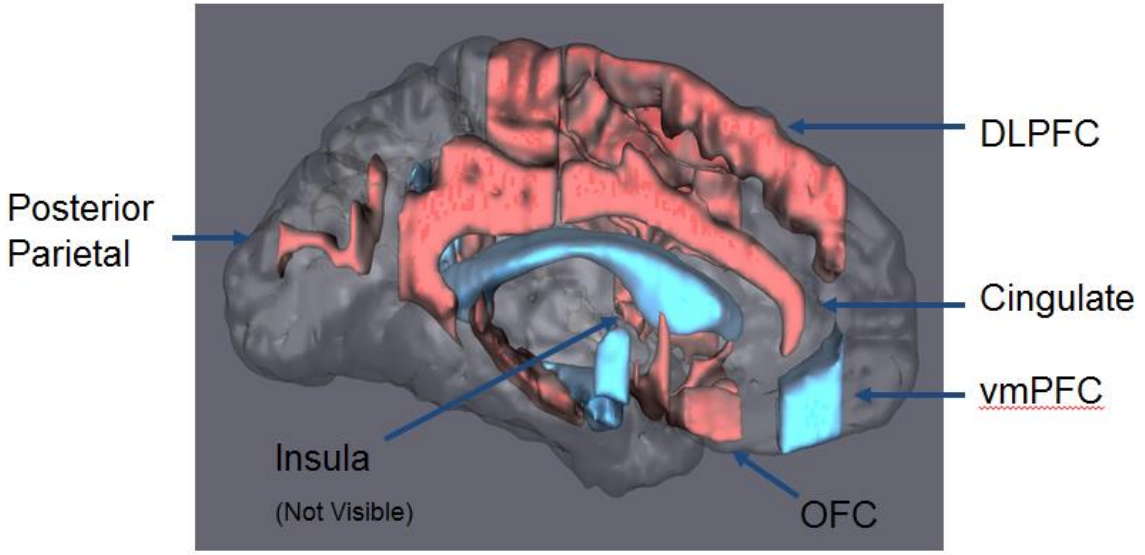
Stress Response Circuitry And The HPA Axis

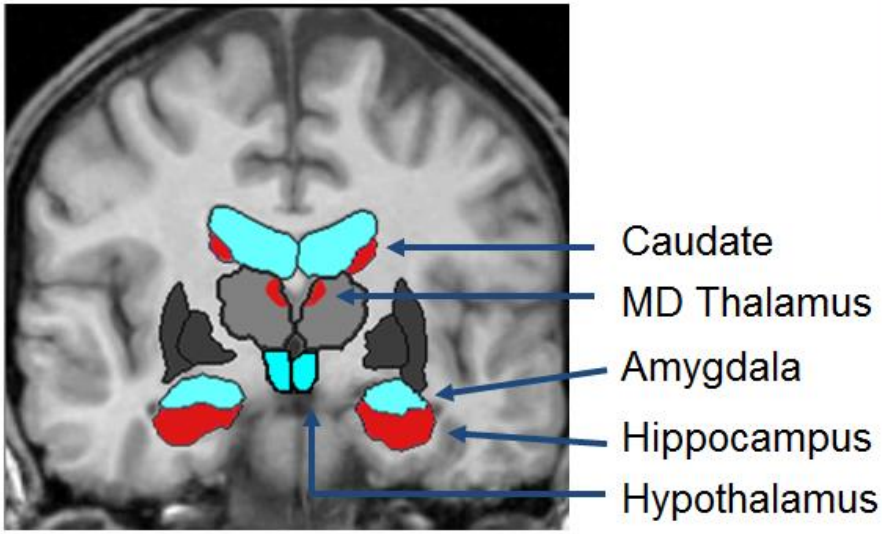
Stress Response Circuitry

- Brainstem
- Amygdala
- Hypothalamus
- Hippocampus
- Ant. Cingualte
- Medial and Orbitofrontal Cortex



Sex Differences in The Healthy Human Brain





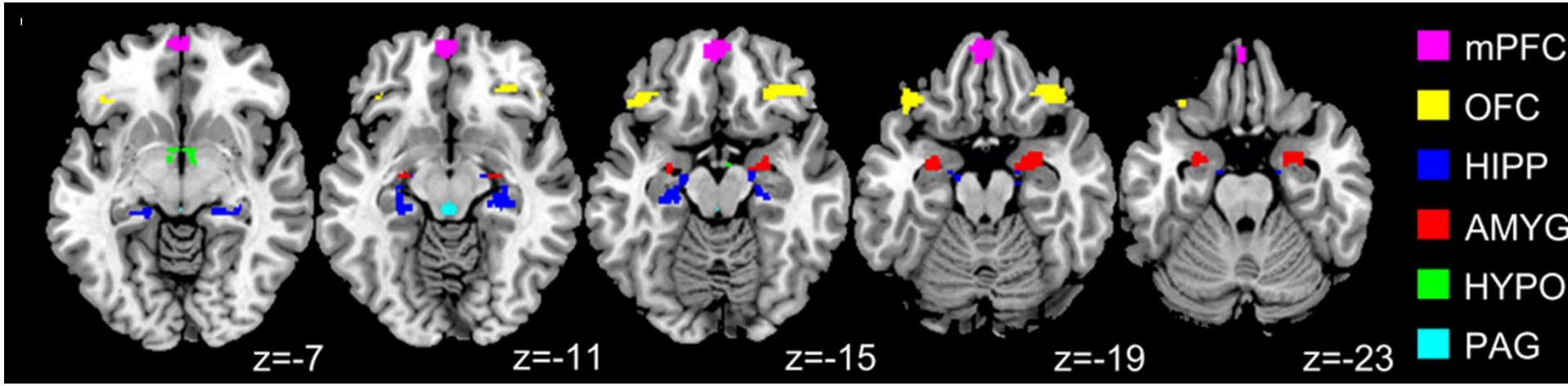
Larger in the female brain, relative to cerebrum size

Larger in the male brain, relative to cerebrum size

Goldstein et al., 2001

BOLD response to negative affective stimuli

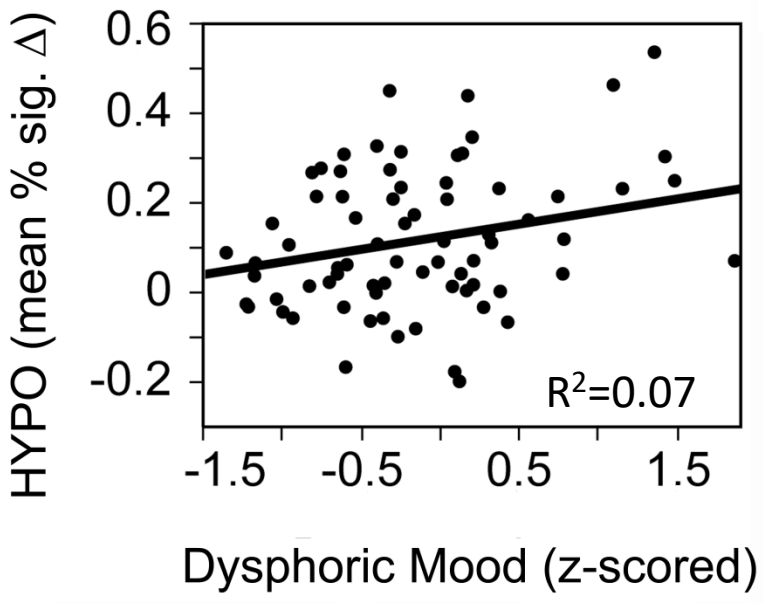
- n= 99 (31 PSY; 27 MDD; 41 HC, equally divided by sex, women in midcycle)

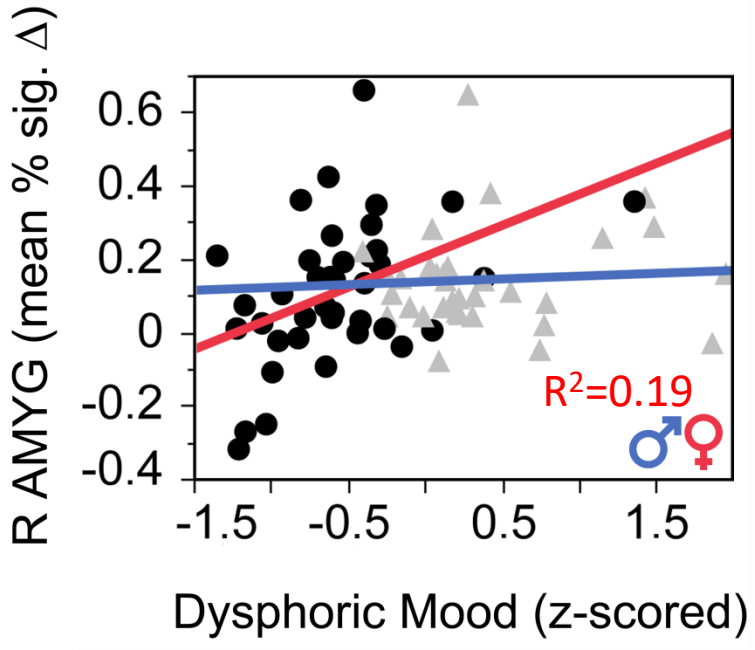


FWE p<0.05

Mareckova et al, Human Brain Mapping, 2016

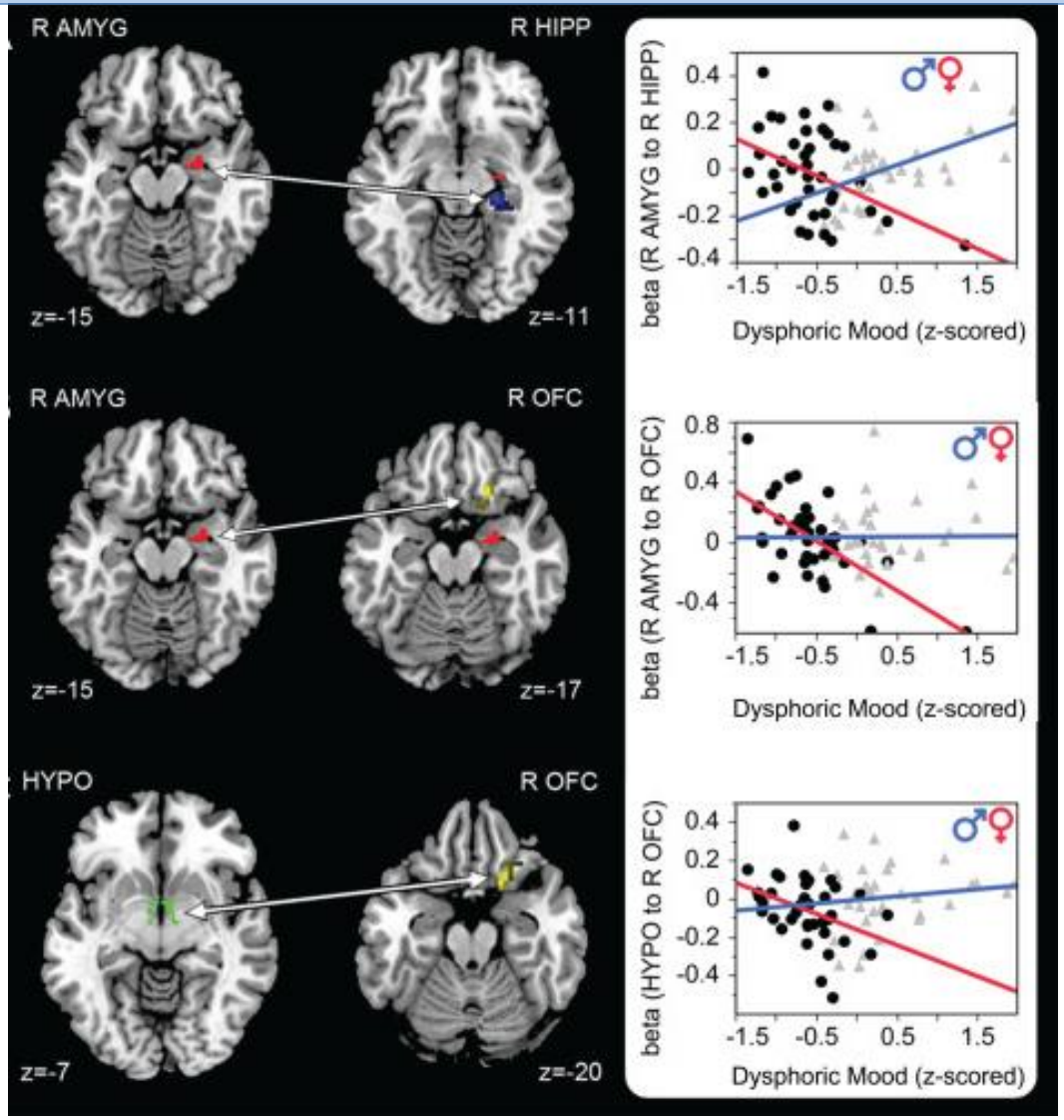
Dysphoric mood predicted increased BOLD in HYPO and AMYG in response to negative affective stimuli





Mareckova et al, Human Brain Mapping, 2016

Dysphoric mood and sex predicted regulation of stress response



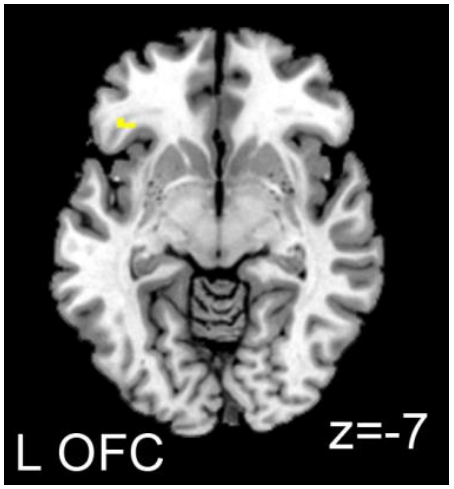
R^2=0.23
R^2=0.19

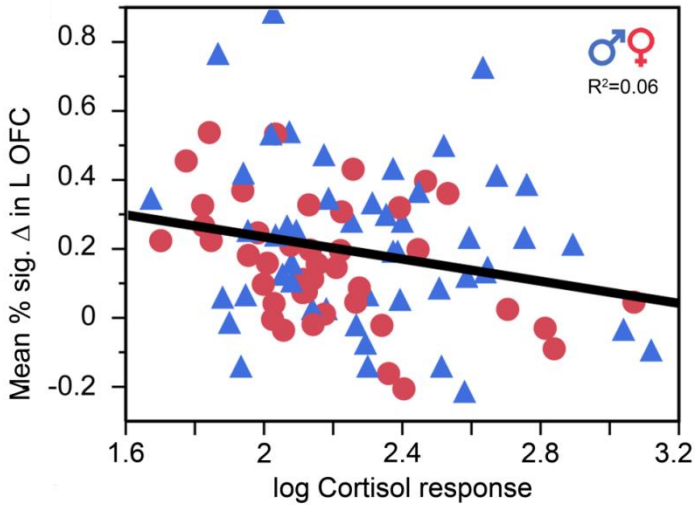
R^2=not sig.
R^2=0.42

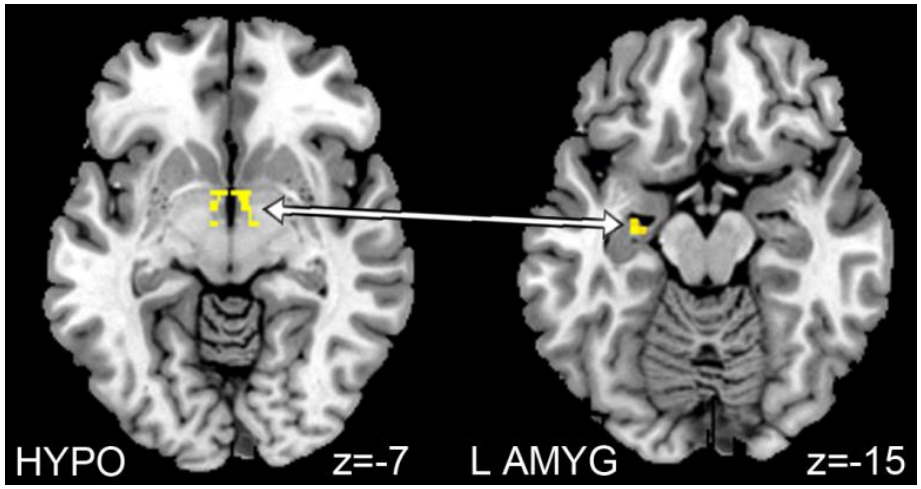
R^2=not sig.
R^2=0.37

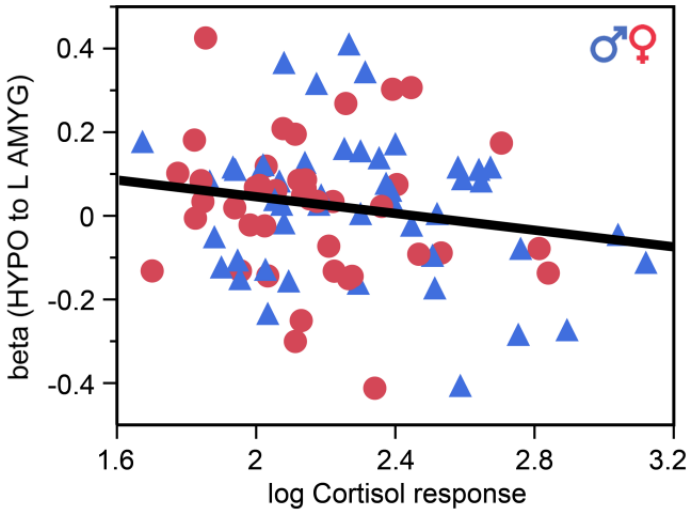
Mareckova et al, Human Brain Mapping, 2016

Elevated cortisol response predicted lower activity in OFC and low HYPO-AMYG connectivity



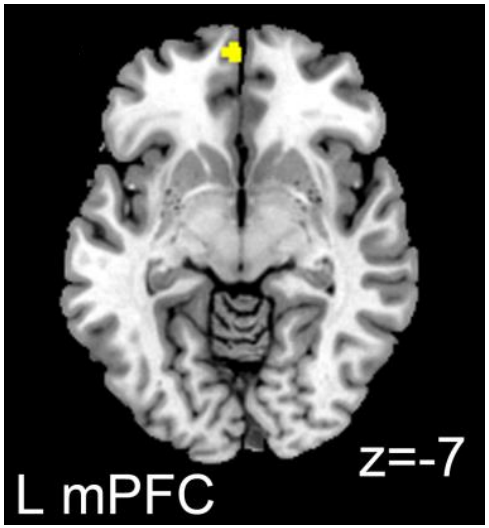


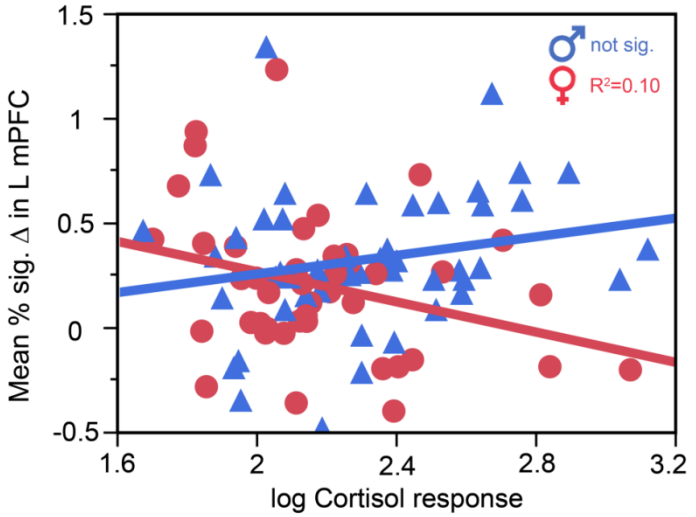


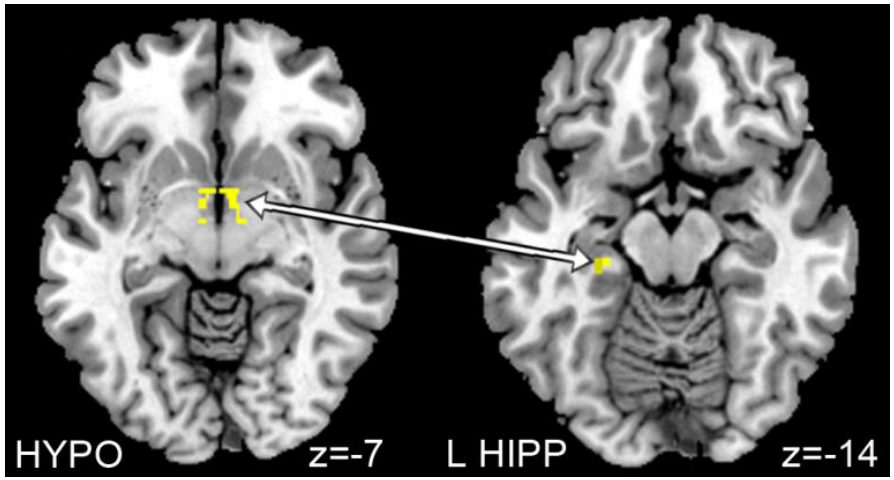


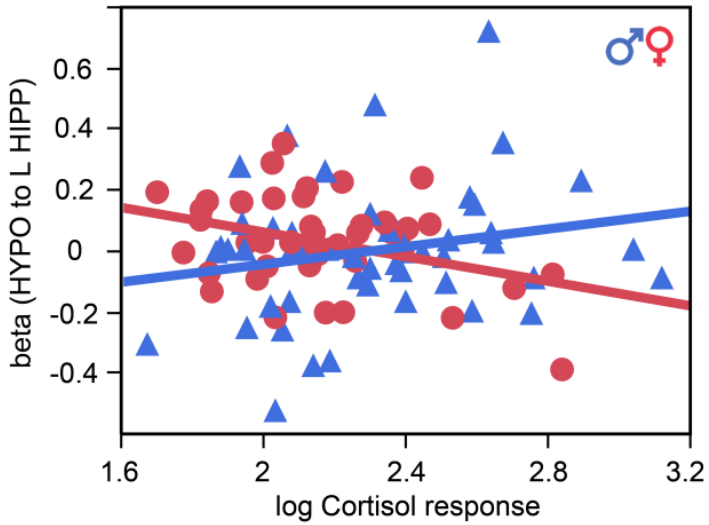
z=3.36, FWE p=0.01

In women, elevated cortisol response predicted lower activity in mPFC and low HYPO-HIPP connectivity









z=4.39, *FWE* p=0.001

Conclusions

- We demonstrated a transdiagnostic impact of cortisol response to mild visual stress on brain function in the stress circuitry (independent of diagnosis or medication).

- Even under mild stress, females with more severe mood symptomatology were unable to regulate arousal by inhibitory regions. This might possibly explain why are females at higher risk to develop mood disorders.

Better Treatment through Better Diagnostics

- Diagnosis limited to symptoms
  (but symptoms are late manifestations of brain disorders)
- Etiology unknown
  (treatments for symptoms not cures)
- Detection late; for most disorders, prevention not well developed

- Mental disorders are disorders of brain circuits, focus on **brain-based biomarkers,** whole **biosignatures**
- **Understand the etiology** through large population-based studies, understand the **mechanisms**
- Focus on **early detection** and prevention (not extreme comparisons of patients vs. controls, study both clinical and pre-clinical populations to identify early biomarkers, use **standardized methods for replication**)
- Move towards **personalized medicine and sex-dependent therapeutics** (take into account one's sex, genes etc.)

Developmental Risk Factors

Schizophrenia

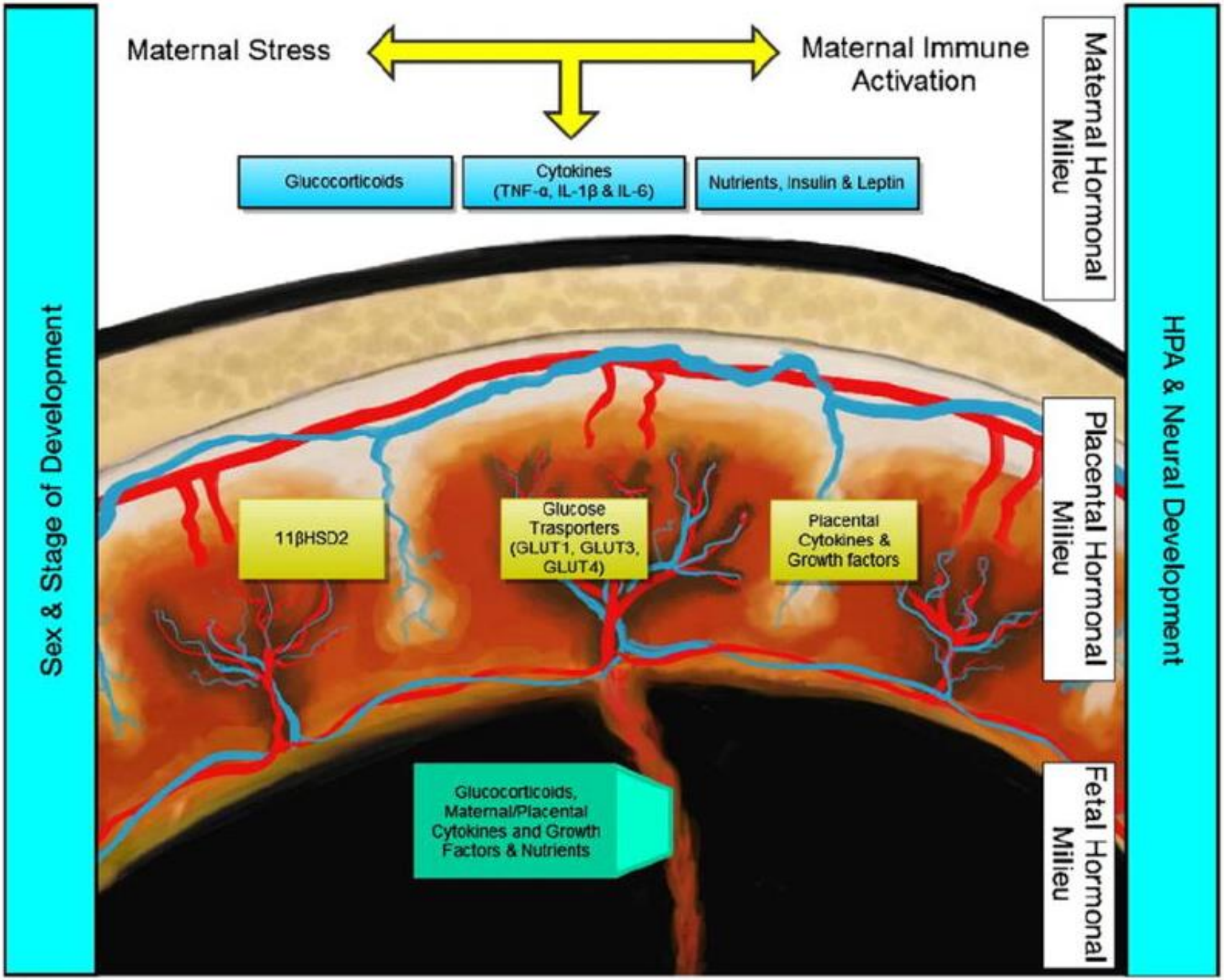
Fetal/Birth Risk Factors	Relative Risk
Low birthweight	1.6 – 3.9
Obstetric complicaitons (preeclampsia, hypoxia)	2.4 – 2.8
Maternal malnutrition	2.0
Maternal herpes simplex	3.4 – 4.4
Maternal rubella	5.2
Maternal hypertension	2.6
Maternal diabetes	5.4

Buka et al., 1998; 2002; Susser et al. 1996; Sacker, 1995; Dalman et al., 1999; Hultman et al., 1999; Brown et al. 2000; Cannon, 2002; Goldstein et al, 2012

Depression

Fetal/Birth Risk Factors	Relative Risk
Low birthweight	3.5
Obstetric complicaitons (preeclampsia, hypoxia)	1.4
Maternal malnutrition	1.6
Influenza	1.7

Kinney, 1998; Sacker, 1995; Preti, 2000; Bellingham-Young, 2003; van Os, 1997; Machon, 1997; Brown, 2000; Costello et a.,2007



Howerton & Bale, 2012

Sex Effects in Timing of Fetal Risk Factors for Psychiatric Disorders

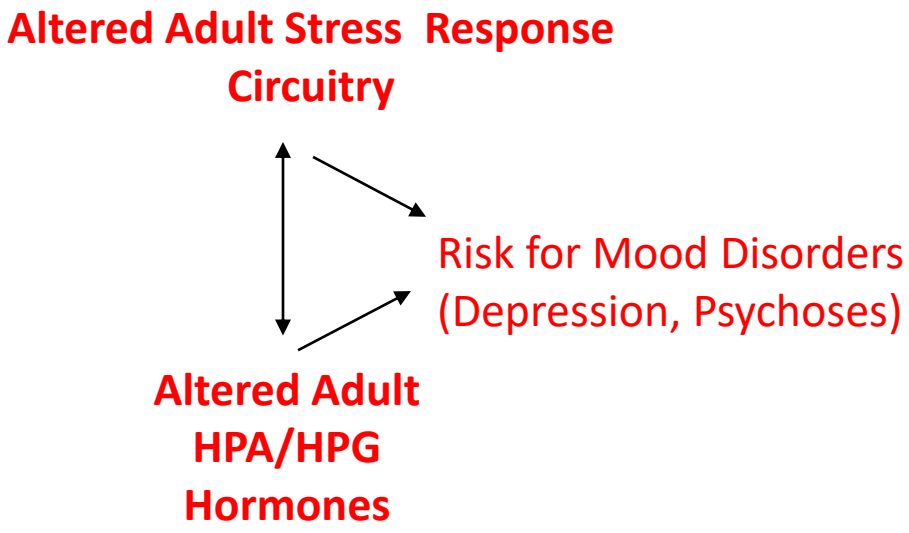
	Males	Females
1st Trimester		
- Malnutrition; Influenza	≈	≈
2nd & 3rd Trimesters		
- Hypoxia	↑	↓
- Preeclampsia	↑	↑
- Influenza	↑	↑
- Maternal Cortisol	↑	↑
- Maternal Diabetes	--	↑

↑ = significant ↑ = trend

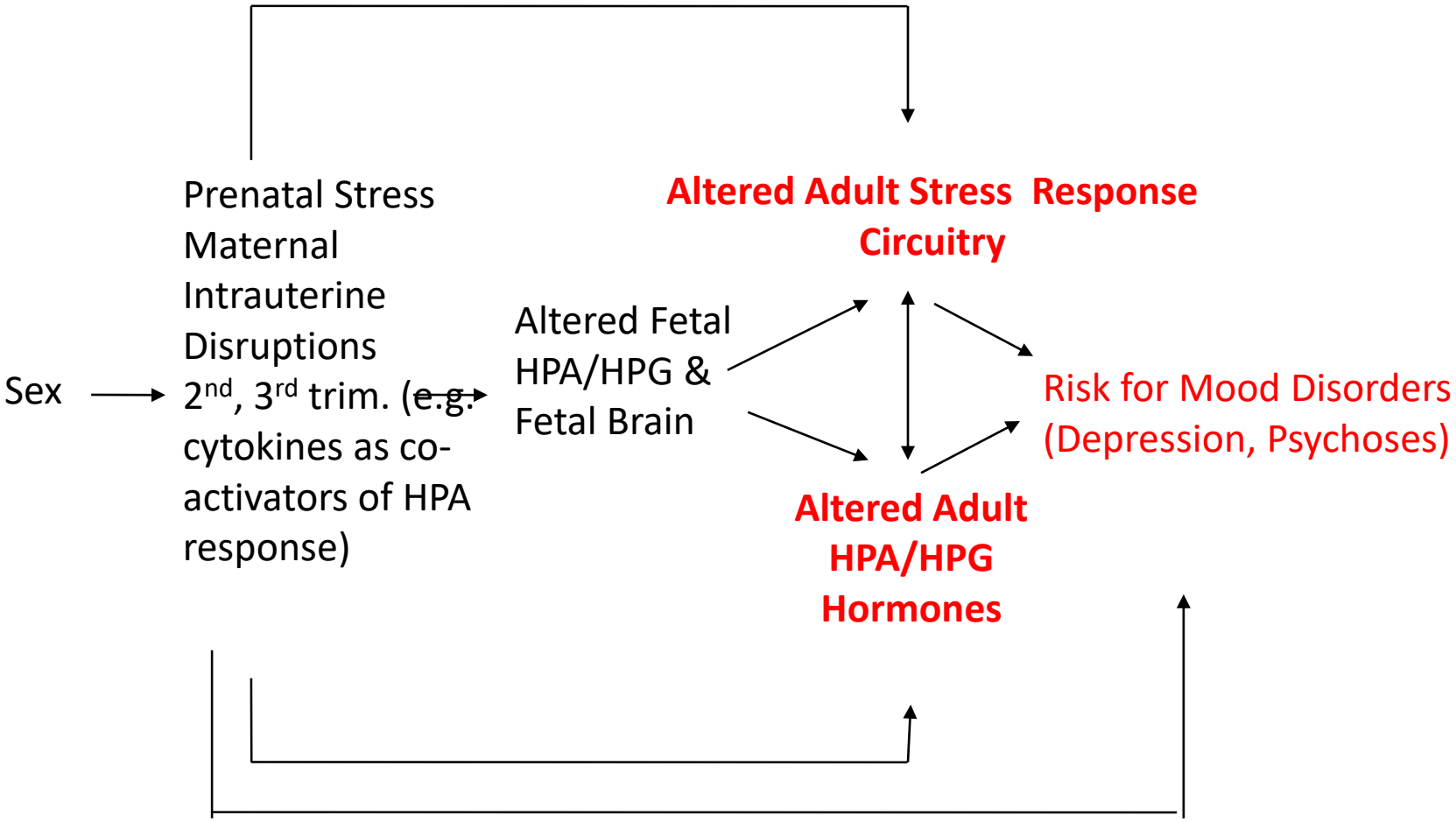
Organizaitonal Effects of Gonadal Steroids on Fetal Brain Development

- ***Mid-gestation***: Active period of sexual differentiation; e.g., testes begin to secrete T
- ***Testosterone***: Direct effects and indirect effects through aromatization into estradiol
- ***Estradiol & Androgens***: Major impact on neuronal growth and development

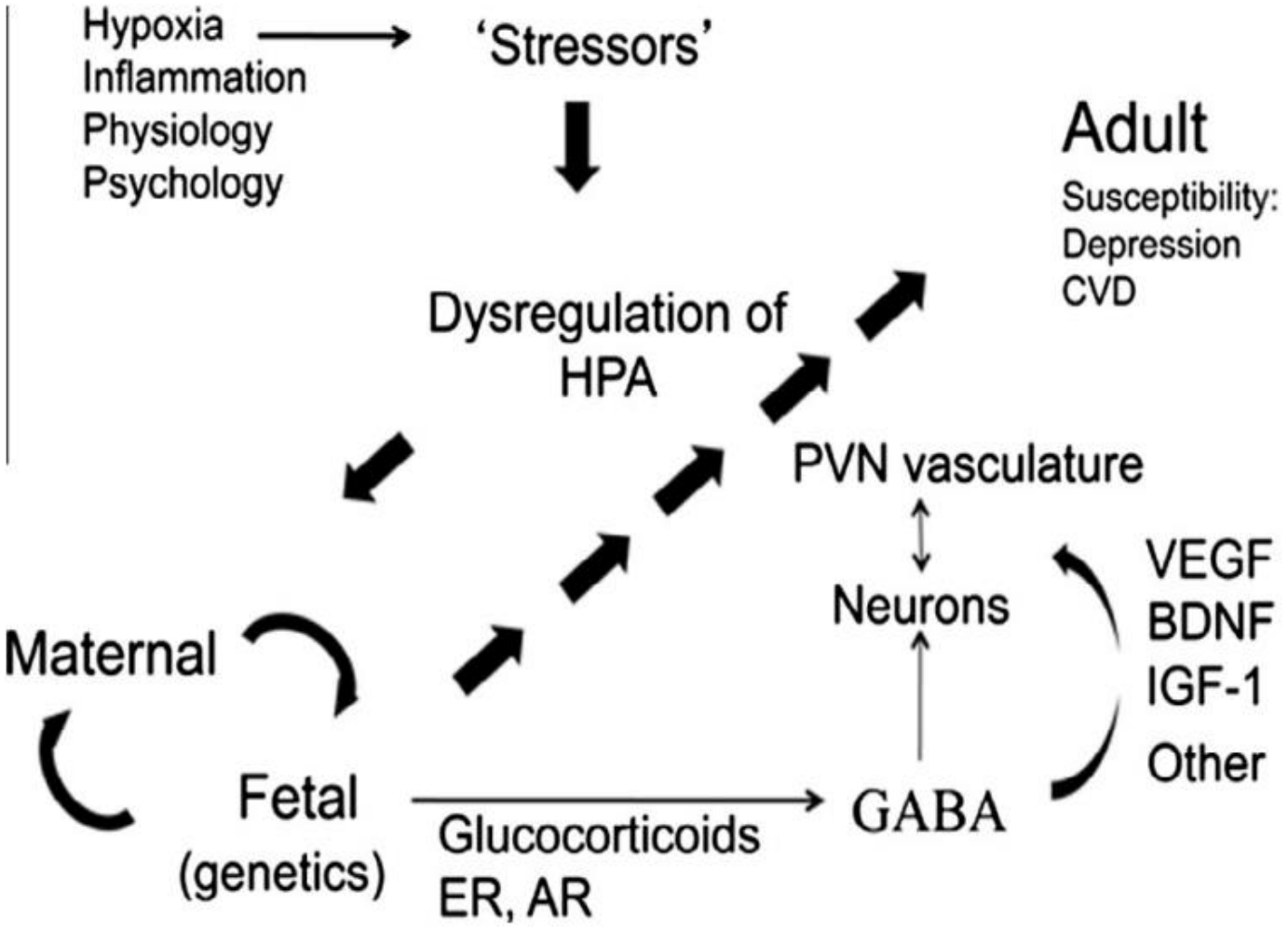
Prenatal maternal immune programming of offspring adult stress response circuitry



Prenatal maternal immune programming of offspring adult stress response circuitry



Prenatal stress model



Goldstein et al., 2014

Fetal Hormonal Programming of Sex Differences in Depression and Psychoses

- We are testing hypothesis of shared etiologies to understanding *sex differences* in MDD and SCZ.

- Focus on maternal TNF-α, IL-1β, and IL-6, pro-inflammatory cytokines, primary co-activators of HPA response, whose receptors are located in the sex-specific regions of the stress-response circuitry
- Focus on the 2^{nd} and 3^{rd} trimestr , as the period of sexual differentiation of the brain.

- Are disruptions in fetal hormonal programming associated with *sex differences* in stress circuitry and endocrine function and development of depression and psychoses in adulthood?

New England Family Study: 50 year follow-up

ORWH-NIMH P50 MH082679 (depression); NIMH RO1 MH56956 (psychoses)

In utero Birth 7 33-45 46-54 Future follow-ups…

N = 17,741

Maternal prenatal sera assayed for early immune and hormonal biomarkers

Childhood Assessments up to age 7

ADULT PHENOTYPING / BIOMARKERS

- Clinical & Cognitive Assts.
- Structural and functional Imaging
- Hormonal Assessments
- EKG & cardiometabolic exams
- Blood and cell collection for genetics/genomics/transcriptomics

Maternal Immune Activity and Sex-Dependent Risk for Psychosis in The Offspring

Psychological Medicine, Page 1 of 13.
doi:10.1017/S0033291714000683

ORIGINAL ARTICLE

Prenatal maternal immune disruption and sex-dependent risk for psychoses

J. M Goldstein[1,2,3]*, S. Cherkerzian[1,2], L. J. Seidman[3,4], J.-A. L. Donatelli[5], A. G. Remington[1], M. T. Tsuang[6,7,8], M. Hornig[9,10] and S. L. Buka[5]

Results. There were higher prenatal IL-6 levels among male SCZ than male controls, and lower TNF-α levels among female SCZ than female controls. The results were supported by deviant subgroup analyses with significantly more SCZ males with high IL-6 levels (>highest quartile) compared with controls [odd ratio $(OR)_{75}$=3.33, 95% confidence interval (CI) 1.13–9.82], and greater prevalence of low TNF-α levels (<lowest quartile) among SCZ females compared with their controls (OR_{25}=6.30, 95% CI 1.20–33.04) and SCZ males. Higher levels of IL-6 were only found among SCZ compared with AP cases. Lower TNF-α levels (non-significant) also characterized female AP cases *versus* controls, although the prevalence of the lowest levels was higher in SCZ than AP females (70% *v.* 40%), with no effect in SCZ or AP males.

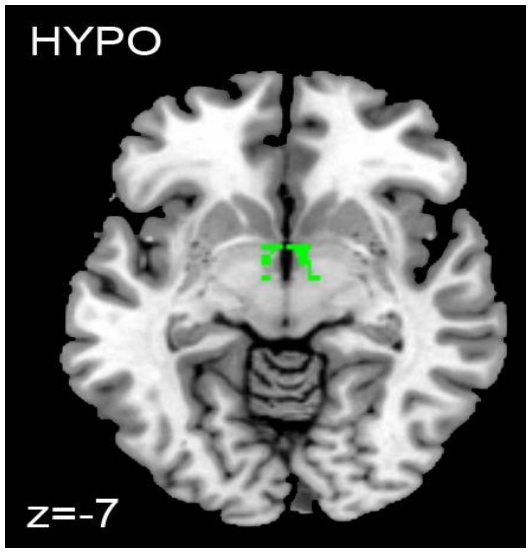
Maternal Immune Activity And Sex-Dependent Risk for MDD in The Offspring

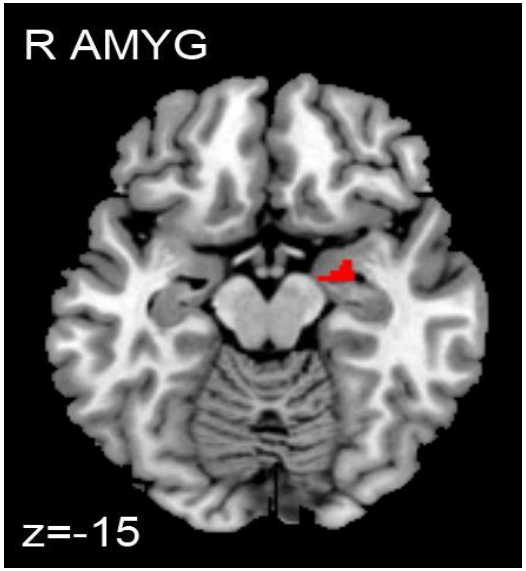
Abstract

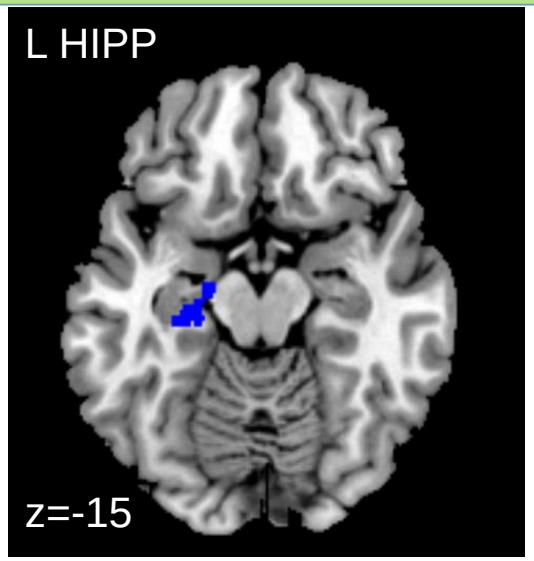
Maternal immune functioning during pregnancy contributes to sex-dependent deficits in brain development, alters behaviors associated with affective traits in preclinical studies, and has indirectly been linked with offspring depression in epidemiologic studies. We therefore investigated the association between maternal immune activity during pregnancy and the risk of depression in male and female offspring. We conducted a case-control study of depression (n=484 cases and n=774 controls) using data from the New England Family Study, a pregnancy cohort enrolled from 1959-1966 that assessed psychiatric outcomes in adult offspring (mean age=39.7 years). We assayed concentrations of three pro-inflammatory cytokines, interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, and the anti-inflammatory cytokine, IL-10, in mid-gestational maternal serum. High maternal TNF-α was associated with a lower odds of depression among both male and female offspring (OR=0.68; CI=0.48, 0.98). However, when considering the TNF-α to IL-10 ratio, a measure of pro- vs. anti-inflammatory loading, maternal immune effects on offspring depression differed significantly by sex (χ^2=13.9, df=4, p=0.008). Among females, higher maternal TNF-α:IL-10 was associated with a lower odds of depression (OR=0.51; CI=0.32, 0.81); in contrast, among males, high maternal TNF-α:IL-10 was associated with a higher odds of depression (OR=1.86; CI=1.02, 3.39). Thus, the balance between TNF-α and IL-10 in maternal serum was associated with depression in a sex-dependent manner. These findings are consistent with the role of TNF-α in the maturation of the sexually dimorphic fetal brain circuitry that regulates stress and affective responses, and support a prenatal stress-immune interaction model of depression pathogenesis.

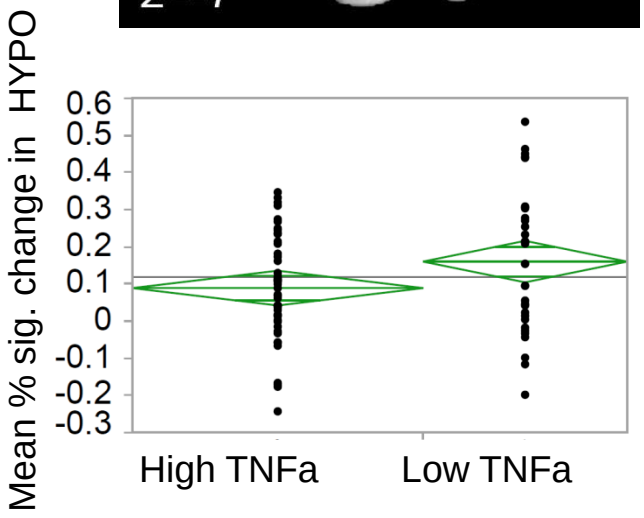
Gilman et al., under review

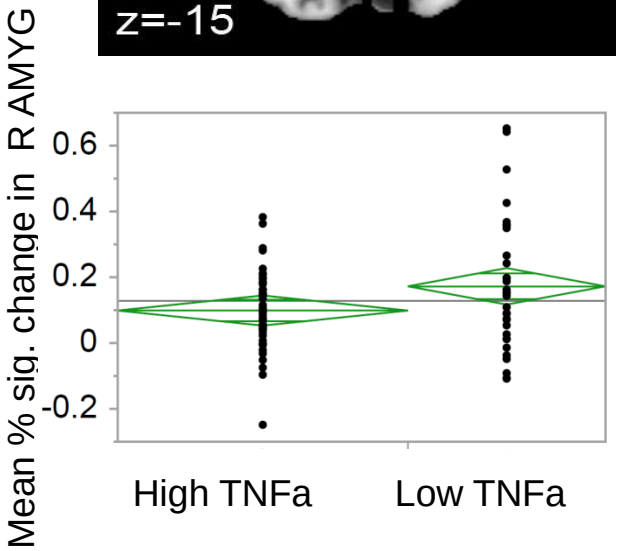
Low Exposure to TNFa Prenatally Associated with Hyperactive Subcortical Regions

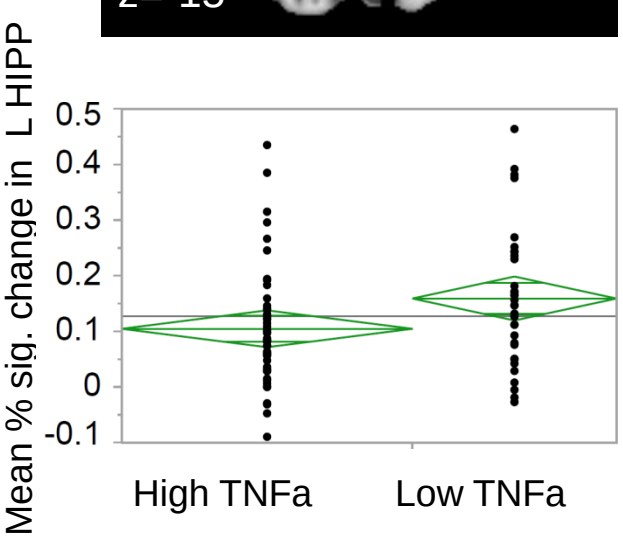










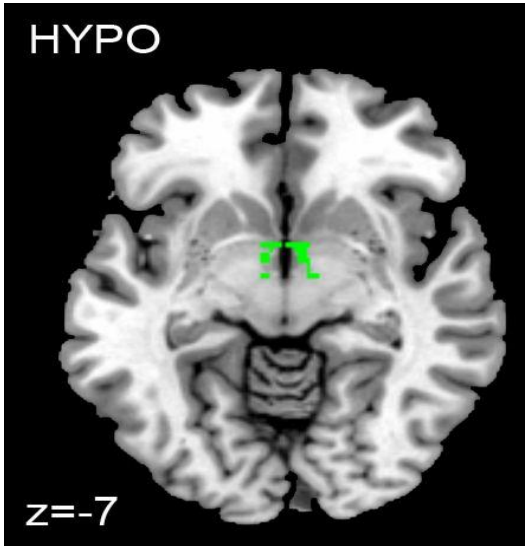


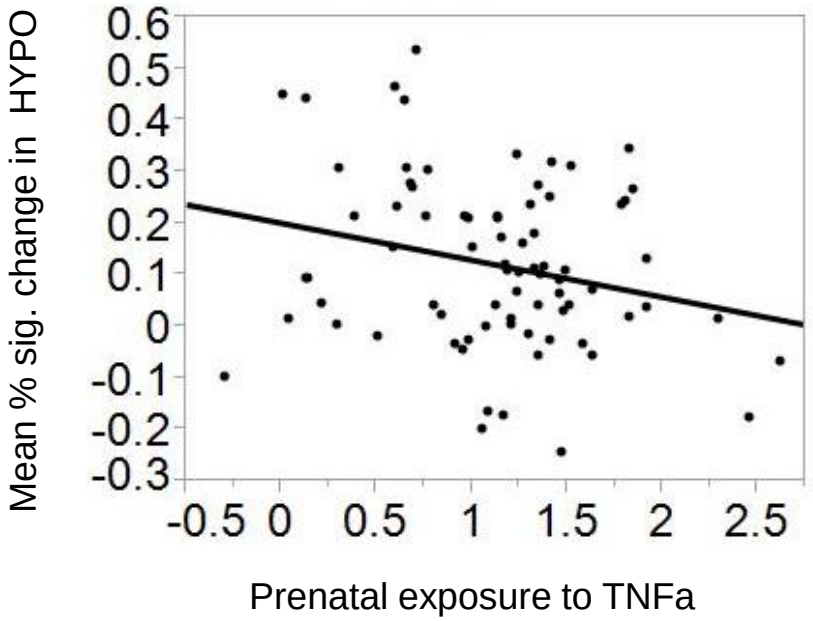
$t(79)=1.94$, $p=0.05$, $R^2=0.05$

$t(78)=2.04$, $p=0.045$, $R^2=0.05$

$t(79)=2.1$, $p=0.04$, $R^2=0.05$

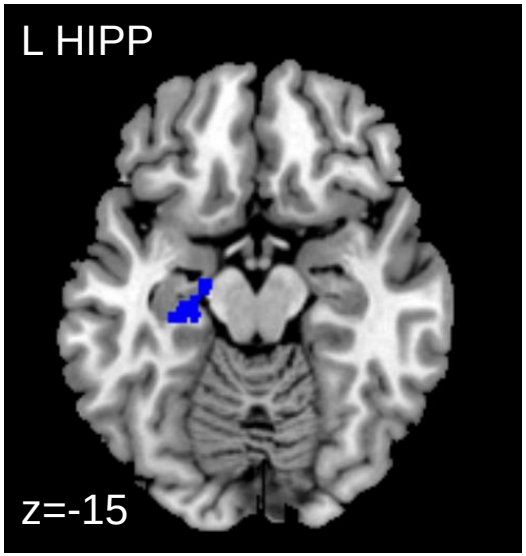
Low Exposure to TNFa Prenatally Predicts High BOLD in HYPO and Low BOLD in mPFC

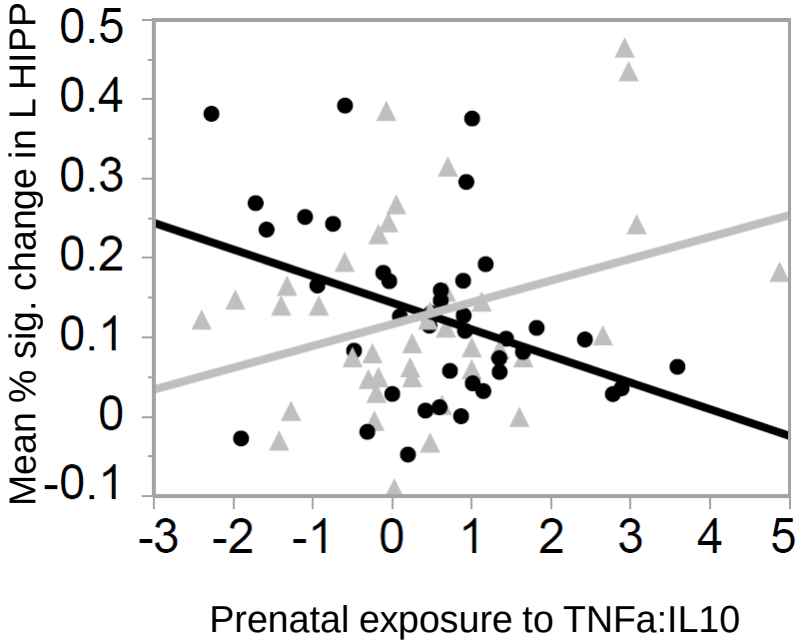




All: $t(76)=-2.22$, $p=0.03$, $R^2=0.06$

Sex Differences in The Effects of Prenatal Exposure to TNFa:IL10 on Stress Circuitry





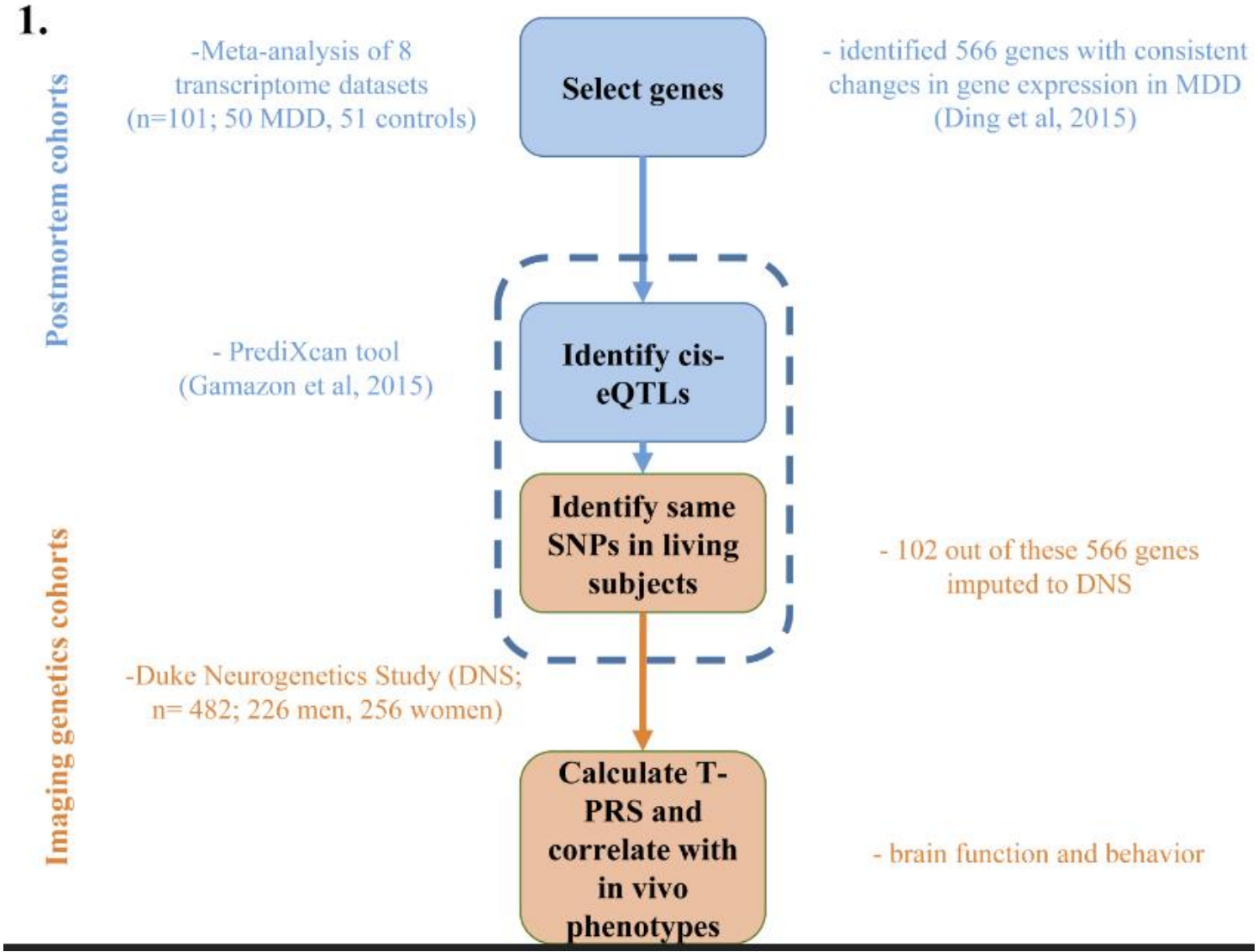
Males:
t(39)=2.13, p=0.04, R^2=0.11

Females:
t(39)=-2.59, p=0.01, R^2=0.15

Conclusions

- Prenatal stress-immune pathways predict brain function and vulnerability to psychiatric disorders 50 years later.

Novel transcriptome-based polygenic risk score for depression predicts brain function during face processing



Novel transcriptome-based polygenic risk score for depression predicts brain function during face processing

K. Marečková[1], C. Hawco[1], A. Bakht[1], E. Sibille[1], A.R. Hariri[2], Y.S. Nikolova[1]

[1] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

[2] Laboratory of NeuroGenetics, Department of Psychology & Neuroscience, Duke University, Durham, NC, 27708, USA

INTRODUCTION

- Depression is a complex disorder with moderate heritability and a polygenic nature.
- Imaging and postmortem gene expression studies converge to suggest that dysregulation of cortico-limbic circuitry (CLC) might be one of the underlying pathophysiological mechanisms of depression.
- ➢ Number of imaging studies reported altered amygdala reactivity in vivo (both higher[1,2] and lower[3,4])
- ➢ Prior postmortem gene expression studies reported depression-related changes in the amygdala, subgenual anterior cingulate (sgACC) and the dorsolateral prefrontal cortex (dlPFC), suggesting reduced neurotrophic support, neuronal signaling and GABA function in these key CLC nodes[5].
- ➢ These altered molecular pathways overlap with age-related processes[5], consistent with prior conceptualization of depression as accelerated brain aging[6,7].

MAIN OBJECTIVE

- This study aimed to determine whether SNPs which cause subtle shifts towards a more depression-like transcriptome in postmortem CLC brain tissue might also impact in vivo CLC circuit response and related depression risk in young healthy adults.

METHODS

PARTICIPANTS

- 485 non-hispanic Caucasian young adults (228 men; age 19.78+/-1.23) participating in the Duke Neurogenetics Study.

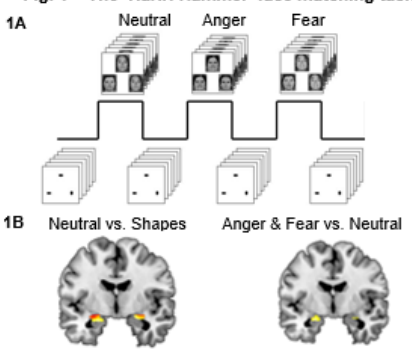
PROCEDURES

- PrediXcan[5] was used to "impute" cortical expression levels based on common cis-eQTL SNPs of 102 out of the 566 genes identified by previous research[6].
- A Polygenic risk score (PRS) was created as a sum of these imputed expression values, weighted by previously reported effect size and direction[6], such that higher PRS reflects a more depression-like CLC transcriptome.
- Mood and Anxiety Symptoms Questionnaire (MASQ[9]).
- Functional magnetic resonance imaging (fMRI) during a face matching task (Fig. 1A) conducted using General Electric MR750 3T scanner.

ANALYSIS

- fMRI data were processed in SPM8, ROI-based analyses focused on anatomically defined amygdala, estimates surviving FWE p<0.05 statistical threshold were extracted (see Fig. 1B for contrasts of interest), and relationships between PRS, sex, and amygdala response were assessed.
- Additional exploratory analyses used partial least square (PLS) regression to complement the hypothesis-driven ROI approach and to assess the impact of the novel transcriptome-based PRS on BOLD response in the whole brain.

Fig. 1 – The 'Hariri Hammer' face matching task.



RESULTS

Polygenic risk and amygdala response

Fig. 2 – The PRS interacted with sex to predict BOLD response in left amygdala only during the neutral faces vs. shapes contrast. Higher PRS was associated with lower response in the left amygdala in men but not women.

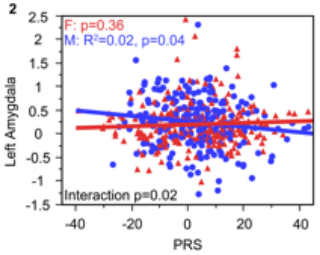


Fig. 3 - Lower response in left amygdala to neutral faces was associated with greater self-reported anhedonia. This effect remained significant when correcting for sex and other MASQ domains.

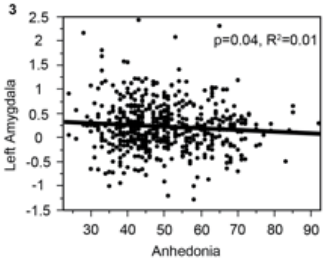
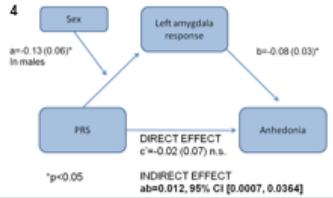


Fig. 4 - The relationship between the PRS and anhedonia was mediated by BOLD response in left amygdala during the Neutral faces vs. Shapes contrast.



Polygenic risk and whole brain response

- PLS analysis identified one latent variable (LV) significantly correlated with the transcriptome-based PRS. This LV accounted for 39.45% of crossblock covariance.

Fig. 5 - Brain regions correlated with the novel transcriptome-based PRS. Clusters (n=69) negatively correlated with polygenic risk that survived the 2.5 bootstrap ratio (corresponding to 95% reliability) included key CLC nodes and are illustrated in blue. There were no clusters positively correlated with polygenic risk that survived the 2.5 bootstrap ratio.

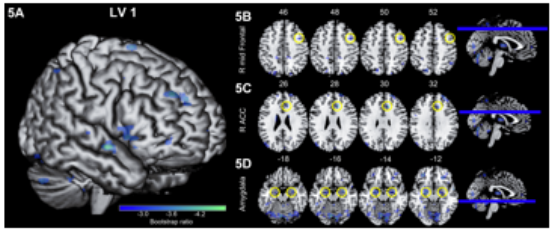
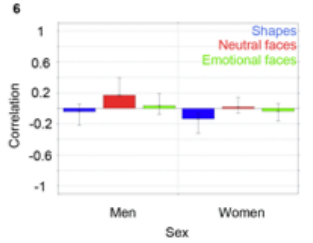


Fig. 6 – Higher levels of polygenic risk were associated with lower activity in the LV1 clusters during the neutral condition in men and higher activity in the LV1 clusters during the shapes condition in women.



CONCLUSIONS

- Genetically driven shifts towards a depression-like transcriptome in the CLC may be associated with a male-specific anhedonic pathway of depression risk characterized by blunted amygdala reactivity to social stimuli.
- This blunting is broadly consistent with CLC reactivity patterns observed in older adults[9] and may reflect overlap between molecular pathways implicated in depression and aging.
- Our PLS analyses extend these results to a broader network of regions.

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Disclosures: Authors declare no conflict of interest.

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Better Treatment through Better Diagnostics

- Diagnosis limited to symptoms
  (but symptoms are late manifestations of brain disorders)
- Etiology unknown
  (treatments for symptoms not cures)
- Detection late; for most disorders, prevention not well developed

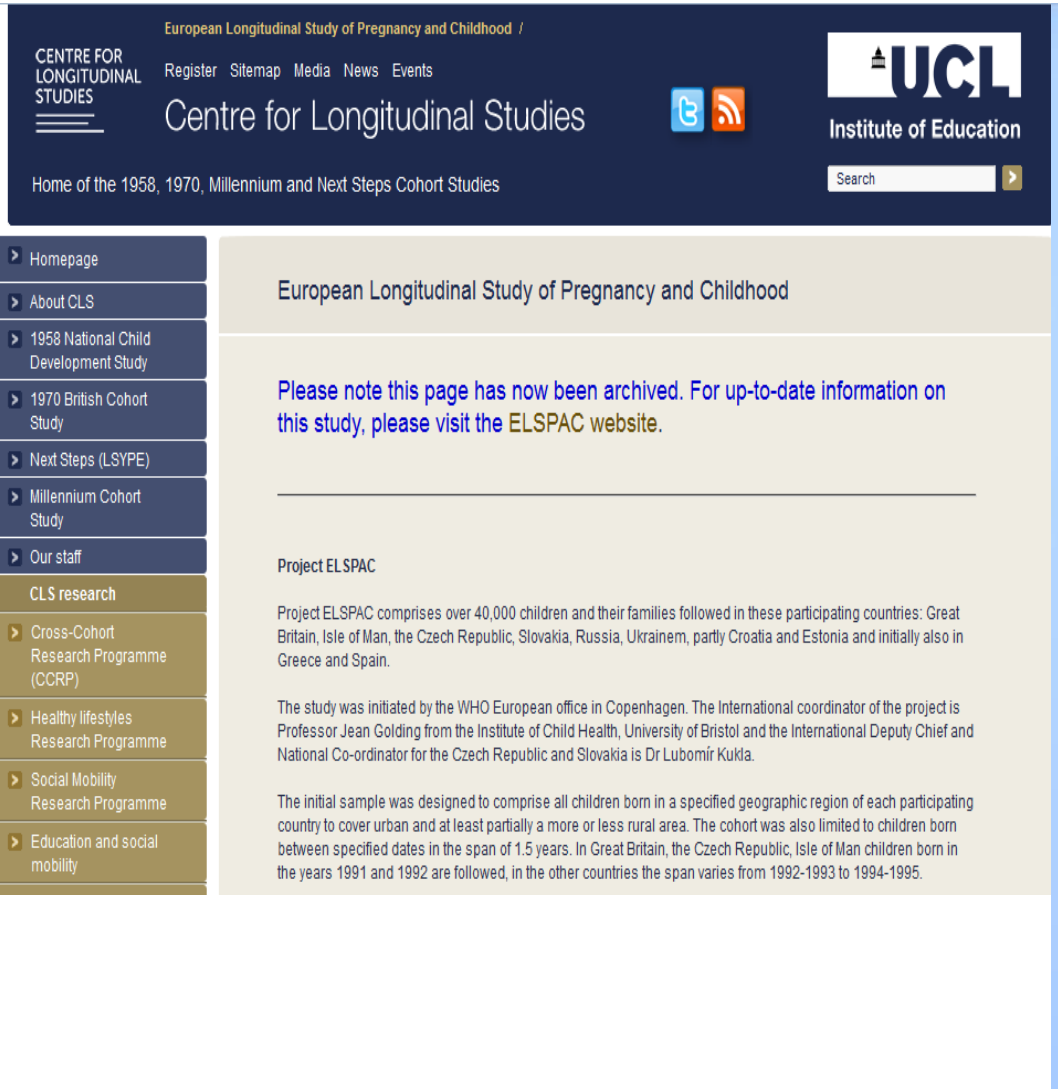
- Mental disorders are disorders of brain circuits, focus on **brain-based biomarkers,** whole **biosignatures**
- **Understand the etiology** through large population-based studies, understand the **mechanisms**
- Focus on **early detection** and prevention (not extreme comparisons of patients vs. controls, study both clinical and pre-clinical populations to identify early biomarkers, use **standardized methods for replication**)
- Move towards **personalized medicine and sex-dependent therapeutics** (take into account one's sex, genes etc.)

Next Steps

Verifying these biosignatures of dysregulated stress circuitry in a pre-clinical sample of typically developing young adults from another birth cohort,

for whom we've recently collected rich neuroimaging and biosmecimen data.

European Longitudinal Study of Pregnancy and Childhood (ELSPAC)



European Longitudinal Study of Pregnancy and Childhood

Evropská dlouhodobá studie těhotenství a dětství

česky

Introduction | About ELSPAC | For study participants | For professionals | Contact

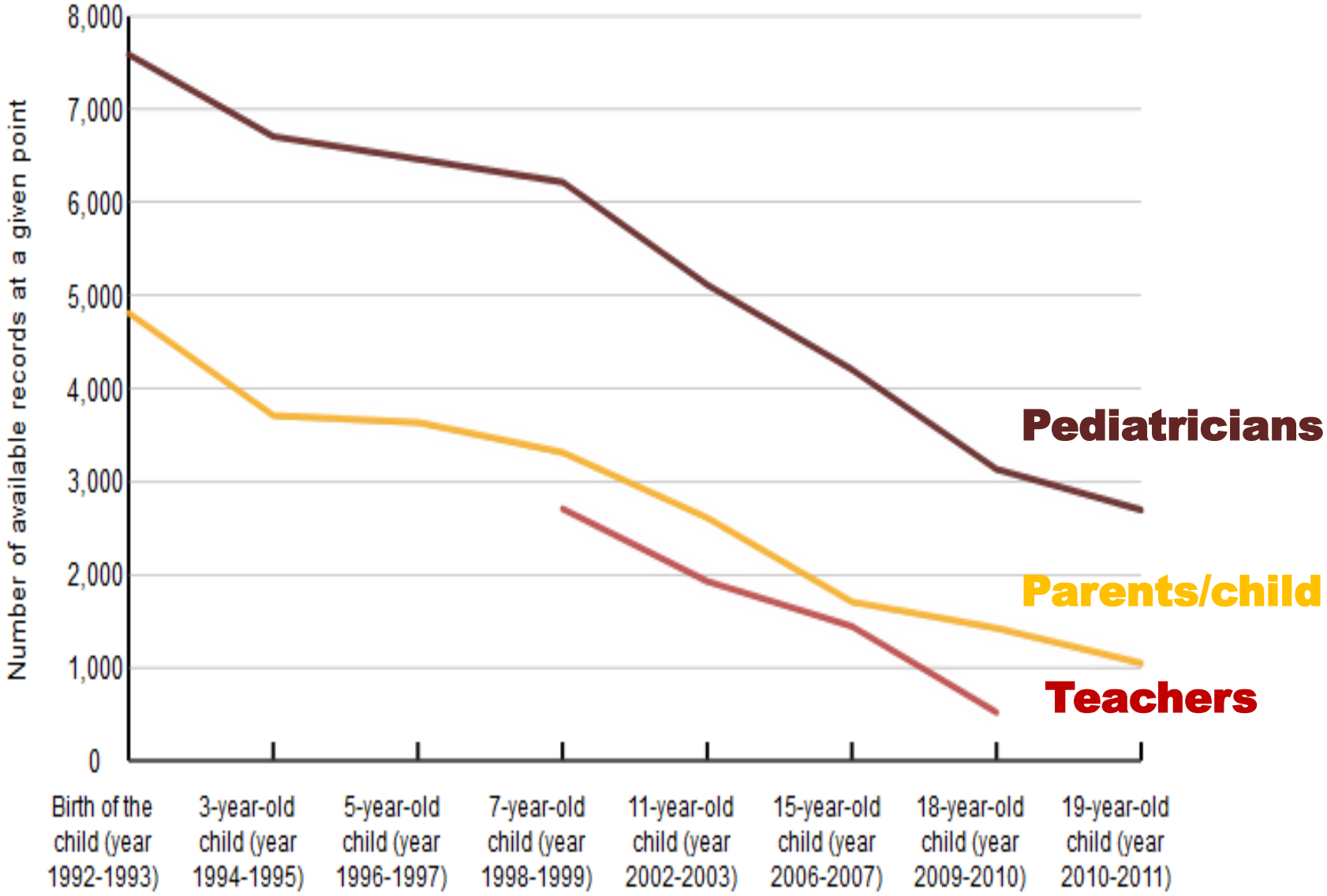
Welcome to the website of the ELSPAC study

... website of a unique scientific study that has been following factors which might influence health of one generation of children in the South Moravian Region for more than 20 years. The study involves 7.589 children, their parents, teachers, paediatricians, psychologists and dentists.

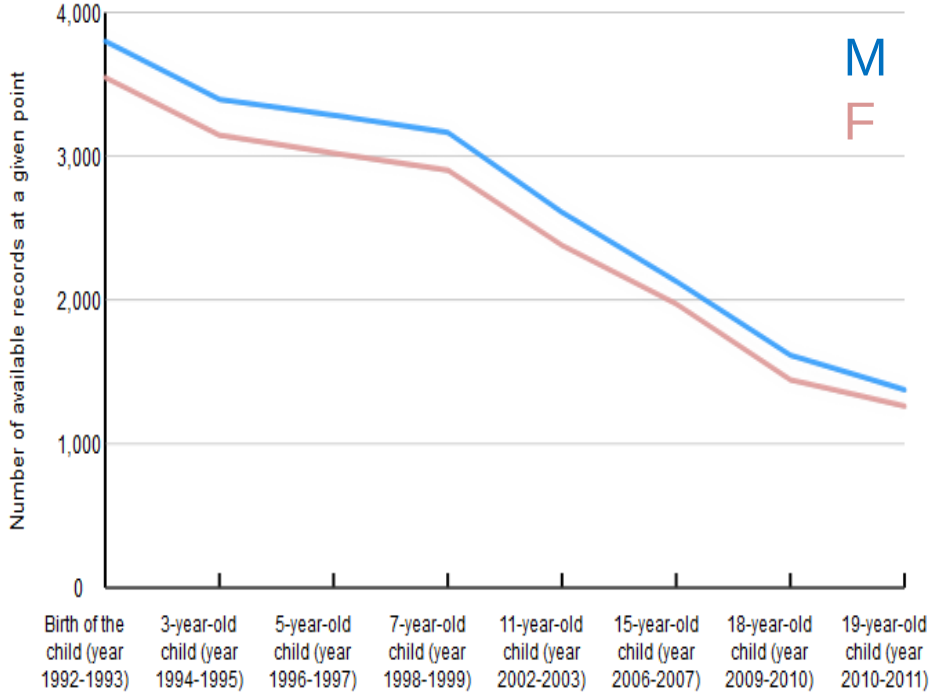
About the ELSPAC study

The European Longitudinal Study of Pregnancy and Childhood (ELSPAC) is a prospective study that was initiated in 1980s by the **World Health Organization (WHO)** in six European countries. In the Czech Republic, the ELSPAC study has followed up **5.738 children born in Brno and 1.851 children born in Znojmo since their birth to their adulthood.**

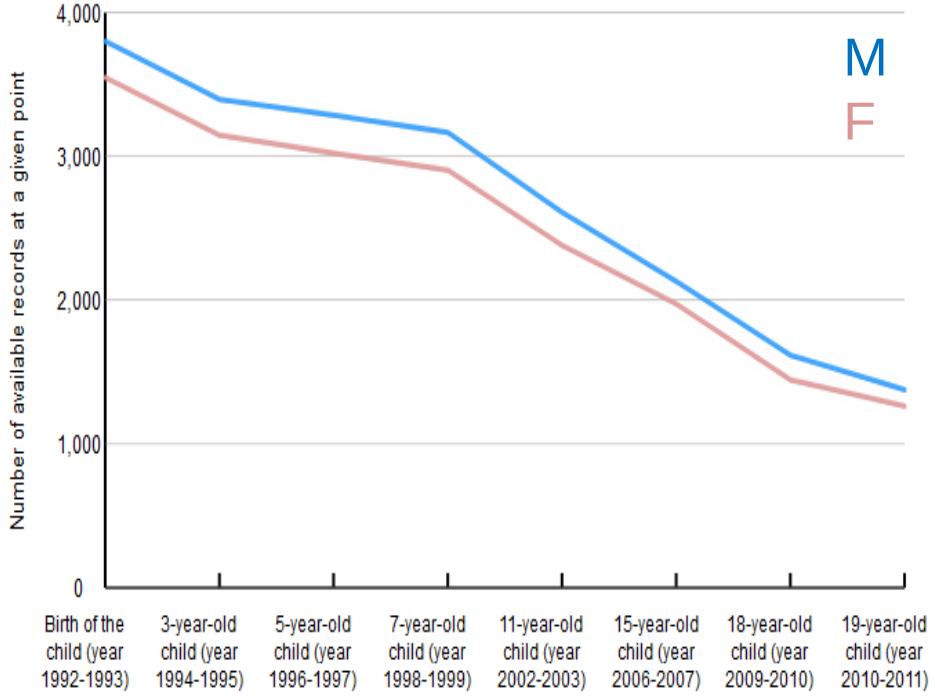
Number of participating families

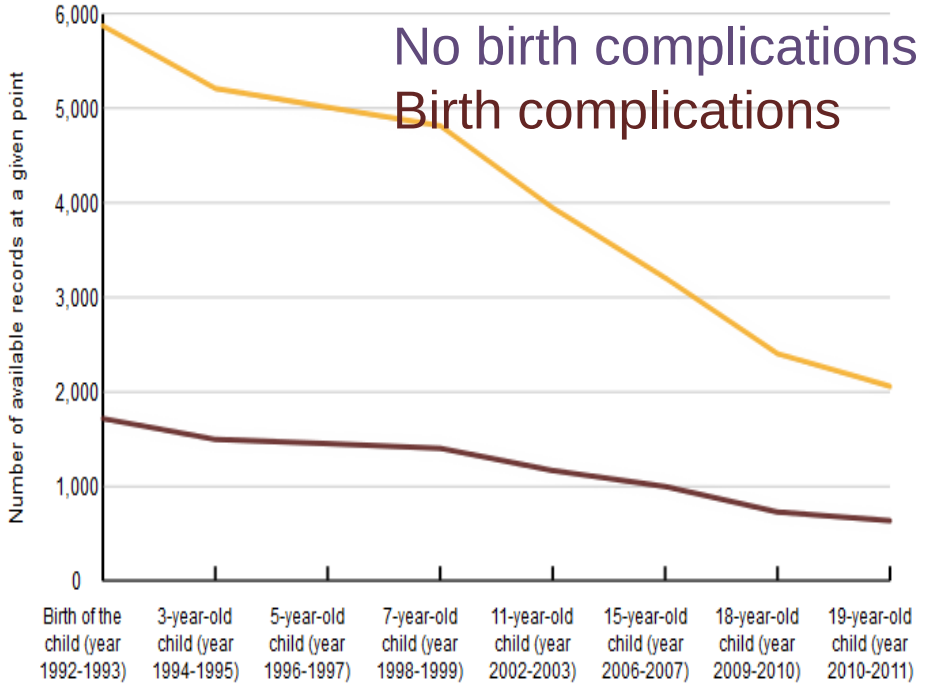


Number of pediatric reports according to child's gender and birth complications



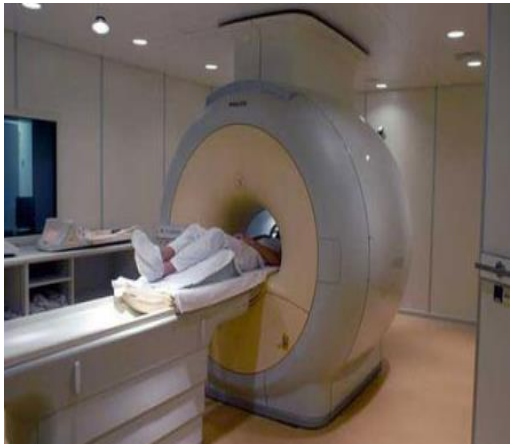
Number of pediatric reports according to child's gender and birth complications



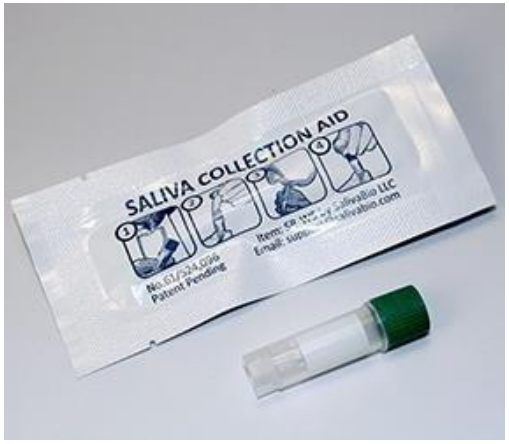


Next steps

- Recruit 120 participants (60 males, 60 females) who previously participated in the European Longitudinal Study of Pregnancy and Childhood (ELSPAC), collect



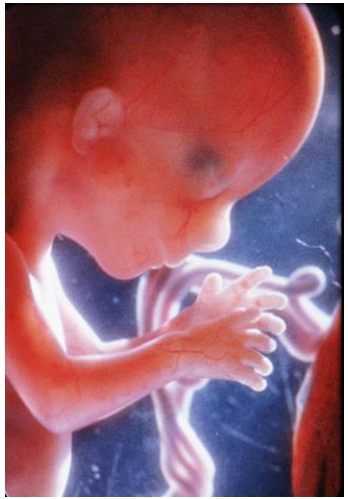
MRI, fMRI, rs-fMRI



Cortisol, Sex hormones, Genes

Questionnaires etc.

- and link these with their longitudinal data from pre/peri-natal period and adolescence.



VULDE data overview (n=131)

- Basic demographics data, medications, drug use
- Depression and Anxiety-related questionnaires (BDI, MFQ, STAI, POMS)
- Neuroimaging data (T1, T2 FLAIR, task fMRI, rs fMRI, DTI)
- Physiological data (ECG, breathing, skin conductance; during task fMRI and rs fMRI)
- Anthropometric & cardio data (blood pressure, heart rate, BMI, bioimpedance, subcut. fat)
- Hormonal data (salivary cortisol, testosterone, estrogen, progesterone), taken by passive drool between 8-9 am, females in late follicular phase (days 10-15 from onset of menstruation), 37% on oral contraception, all analyzed by ELISA kits
- Buccal swaps (will be analysed with genetic and epigenetic chips)
- Longitudinal ELSPAC data (questionnaires from MDs, parents, teachers, child; prenatal till 19)

Demographics

- 131 participants recruited from the ELSPAC cohort
- 61 males, 70 females

- All 23 or 24 years old when VULDE testing (MRI, saliva etc.)
- All White Caucasians of European origin, from South Moravia, Czech Republic

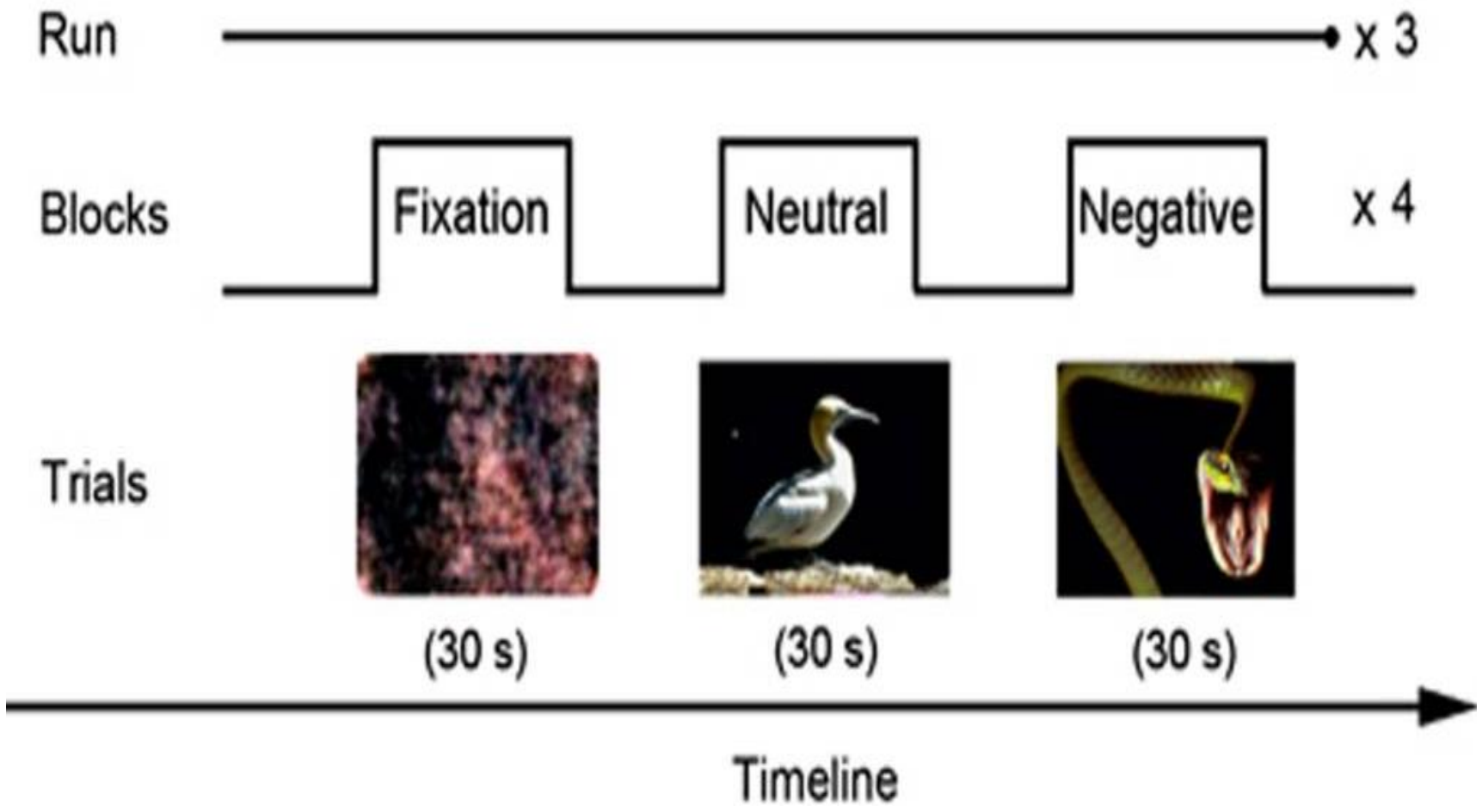
- Females tested during the high estrogen phase (menstrual cycle day 10-15)
- 26 out of the 70 females were on oral contraception

- Majority of them are university students

VULDE research questions

- Can we observe structural and functional changes among VULDE participants who had more depressive symptoms?
- Could we use the altered structure and function in these regions as a potential early biomarker of depressive symptomatology in young adults?
- Would this biomarker differ among males and females?
- Would it be related to prenatal stress or depression during adolescence?

Design of the negative affect fMRI task (International Affective Picture System)



Jacobs et al., 2015

Sex differences in BOLD response to negative affect

- VULDE IAPS fMRI data processed using the same pipeline as in the Mareckova et al (HBM, 2016) paper on NEFS
- extracted BOLD response from the Negative > Netural contrast in the hypothesized ROIs (Mareckova et al, HBM, 2016).

- MANOVA showed a significant ROI*Sex interaction ($F=4.71$, $p<0.0001$).
- Posthoc analyses showed that men had greater BOLD to negative affective stimuli than women in PAG, R AMYG, ACC, HIPP, mPFC (viz table on the left).

ROI	Direction of the sig. relationship	R^2
PAG	M>F	0.03
HYPO	-	-
L AMYG	-	-
R AMYG	M>F	0.03
L HIPP	M > F	0.04
R HIPP	M>F	0.06
L sgACC	M>F	0.12
R sgACC	M>F	0.08
L dpgACC	-	-
R dpgACC	M>F	0.04
L OFC	-	-
R OFC	-	-
L mPFC	M>F	0.10
R mPFC	M>F	0.07

Sex differences in BOLD response to negative affect

✓ Goldstein et al (2005) paper demonstrating sex differences in the physiology of the brain but not in the subjective feelings.
✓ Goldstein et al (2010) paper demonstrating larger BOLD response in the stress circuitry in men vs. mid-cycle women.

Sex differences in BOLD response to negative affect

✓ Goldstein et al (2005) paper demonstrating sex differences in the physiology of the brain but not in the subjective feelings.
✓ Goldstein et al (2010) paper demonstrating larger BOLD response in the stress circuitry in men vs. mid-cycle women.

Table 3. Signal change values in hypothesized stress response circuitry regions comparing negative to neutral stimuli in men versus women in early follicular and late follicular/midcycle periods

Hypothesized regions[a]	R/L Hem	Men	EF Women	LF/MC Women	Difference in ES[b]: men versus EF	Difference in ES[b]: men versus LF/MC	Test of different differences in ES[c]
Cortical							
ACG							
BA 24, 32	L	0.20	−0.08	−0.15	0.28*	0.35**	−0.07
	R	0.05	−0.15	−0.16	0.20*	0.21*	−0.01
OFC							
BA 10,11,47	L	0.39	0.15	−0.20	0.24	0.59**	−0.35**
	R	0.29	0.10	−0.19	0.19	0.49**	−0.30**
medPFC							
BA 10, 11	R	0.24	0.26	−0.36	−0.02	0.60**	−0.62***
vmPFC	L	0.31	0.07	−0.29	−0.024	0.61**	−0.37***
	R	0.52	0.52	−0.02	0.00	0.54*	−0.54***
Subcortical							
Amygdala	L	0.36	0.09	0.01	0.27*	0.35*	−0.08
	R	0.06	0.05	−0.09	0.01	0.15	−0.14*
Hippocampus	R	0.25	0.12	−0.05	0.13	0.30***	−0.18**
Hypothalamus							
LHA	L	0.58	0.15	0.17	0.43*	0.41*	−0.02
VMN	L	0.43	0.14	0.12	0.29*	0.31*	−0.03
Brainstem							
Medulla		0.10	0.04	−0.03	0.06	0.13	−0.07
Midbrain		0.19	0.02	−0.06	0.18	0.25*	−0.08
PAG		0.48	0.48	0.08	0.01	0.40*	−0.40*
Pons		0.15	0.07	−0.07	0.08	0.22 +	−0.15

- ✓ VULDE women scanned on days 10-15; NEFS women scanned on days 10-14
- ✓ Both studies demonstrated women's lower BOLD response to negative affective stimuli in the subcortical arousal regions (PAG, AMYG) as well as HIPP and cortical regions that control the arousal (ACC, mPFC).
- ✓ Both studies found the largest effect sizes in mPFC.

Goldstein et al., Journal of Neuroscience, 2010

Conclusions

• We tried to replicate the clinical findings on the effects of sex and depressive symptomatology on brain function during negative affect (Goldstein et al, 2005; Goldstein et al, 2010; Mareckova et al, 2016) in typically developing young adults from a prenatal birth cohort.

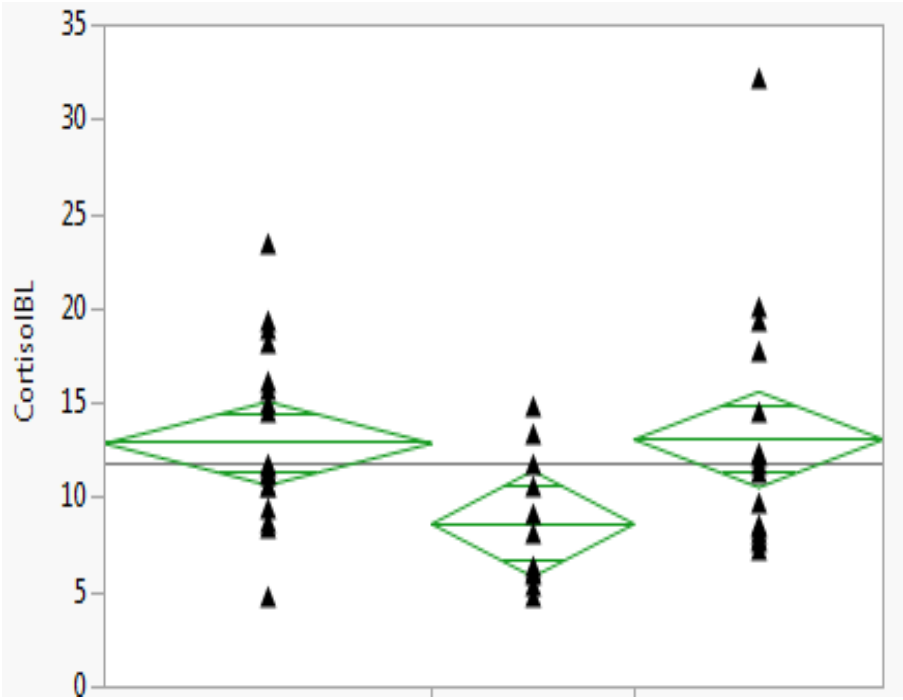
• We conclude that men demonstrated higher BOLD response to negative affect than women and that these sex differences were particularly pronounced in individuals with more depressive symptomatology.

• These findings suggest that during mild stress**, men might recruit the regulatory regions to a greater extent than women, possibly explaining why are women more vulnerable to depression than men.**

• The fact that there were no sex differences in the demographics or the mood-related variables suggests that **vulnerability to mood disorders might be detectable at the level of the brain well before it might manifest in the behavior.**

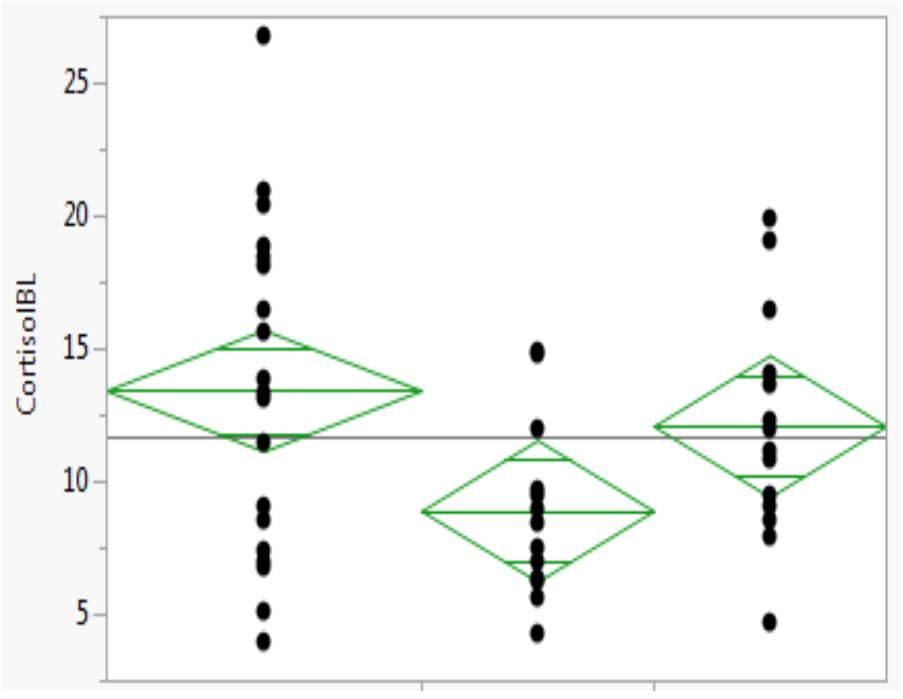
Baseline cortisol in clinical samples (NEFS)

Cortisol in men



$F(2,47)=3.59$, $p=0.04$, $R^2=0.13$

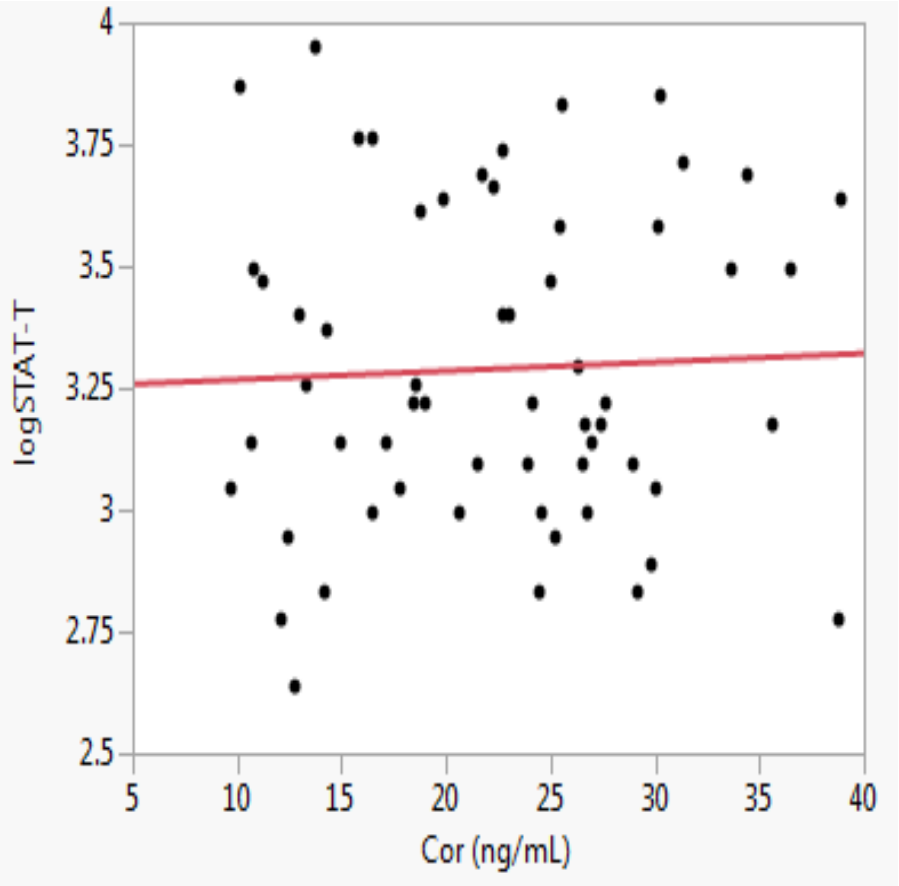
Cortisol in women



$F(2,44)=3.45$, $p=0.04$, $R^2=0.14$

Hormonal biomarker of vulnerability to depression?

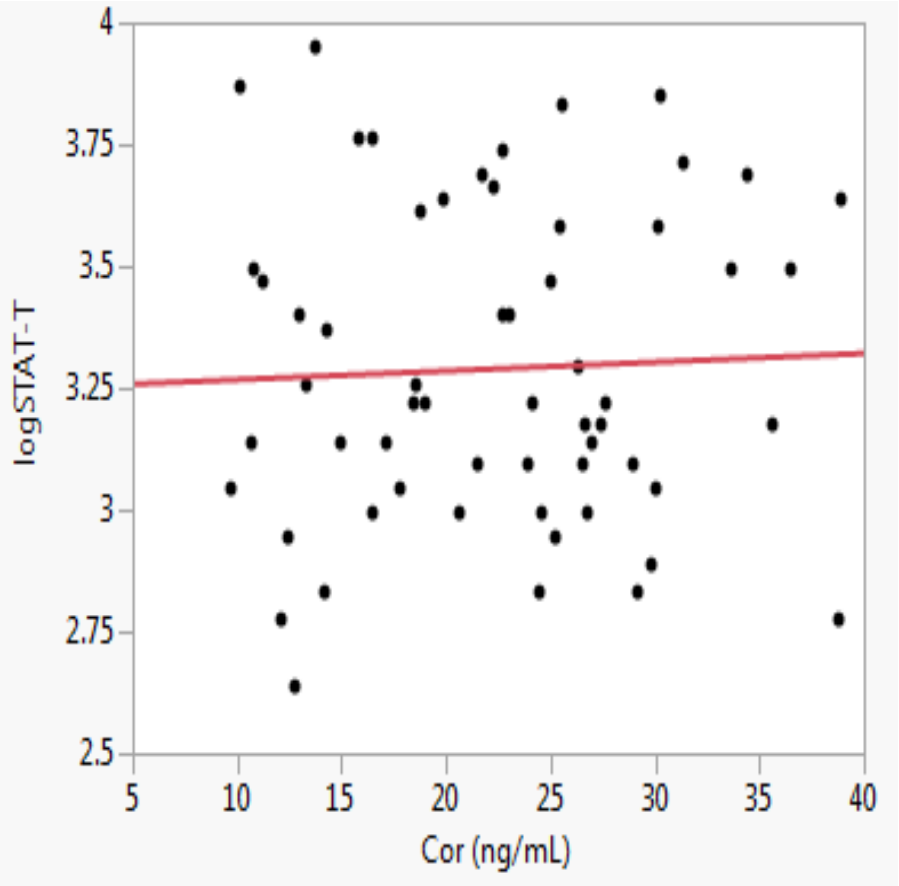
Cortisol & Anxiety trait in men



p=0.75

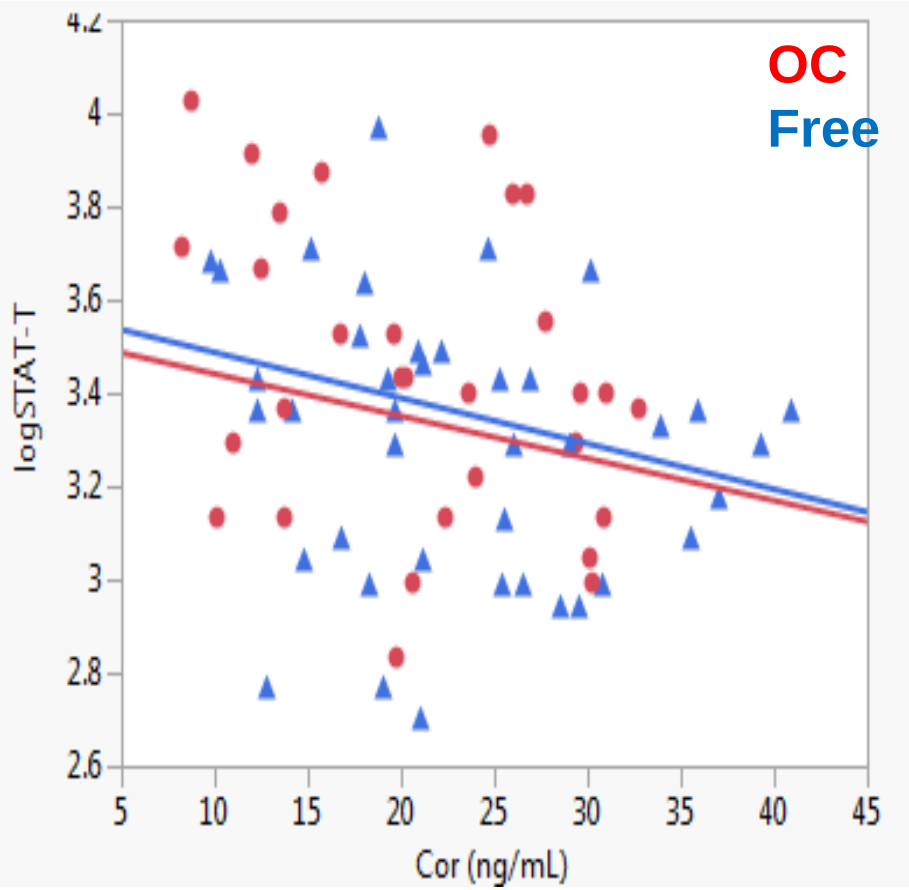
Hormonal biomarker of vulnerability to depression?

Cortisol & Anxiety trait in men



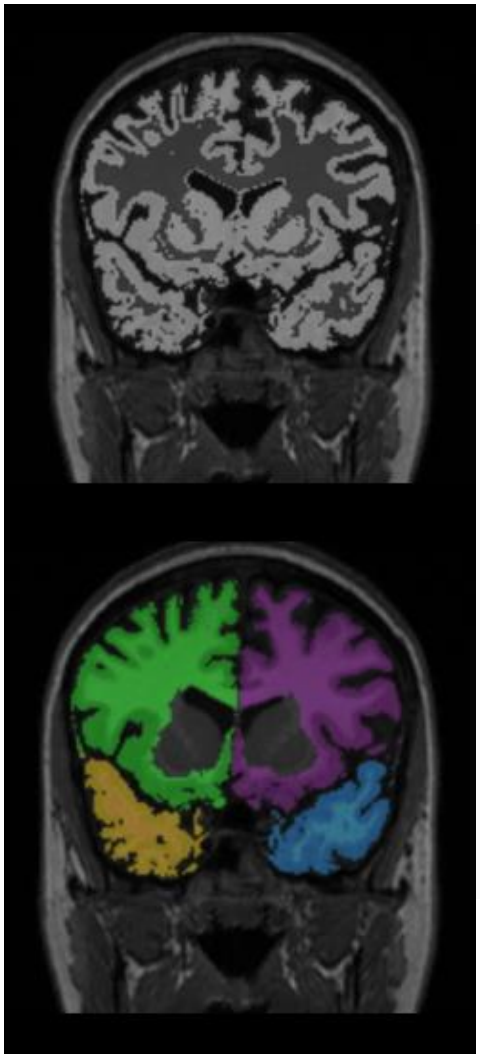
p=0.75

Cortisol & Anxiety trait in women

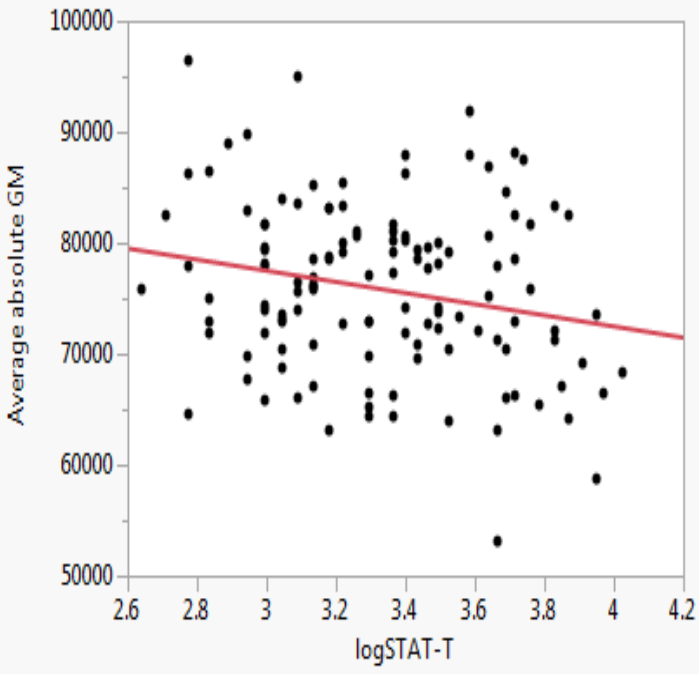


t(69)=-2.14, p=0.036, R^2=0.06

Volume of Grey Matter (GM)

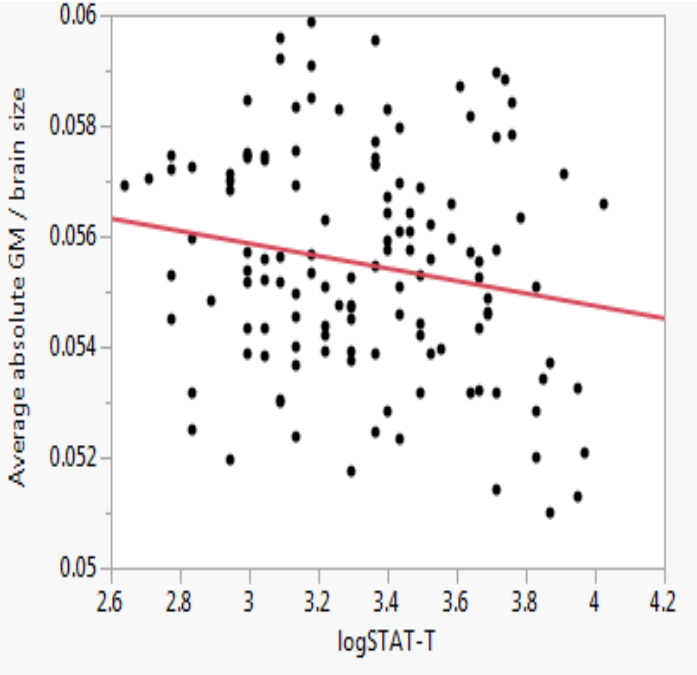


STAI-T & Overall GM



t(128)=-2.46, p=0.02, R^2=0.05

STAI-T & Overall GM/brain size



t(128)=-2.07, p=0.04, R^2=0.03

Volume of Grey Matter in Different Lobes

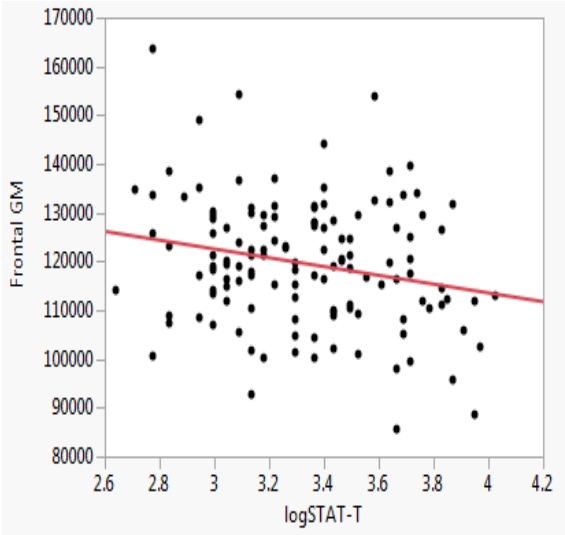
- MANOVA: STAI-T: $F=5.28$, $p=0.02$; Lobe: $F=97.96$, $p<0.001$; STAI-T*Lobe: $F=4.79$, $p=0.003$

Volume of Grey Matter in Different Lobes

- MANOVA: STAI-T: F=5.28, p=0.02; Lobe: F=97.96, p<0.001; STAI-T*Lobe: F=4.79, p=0.003

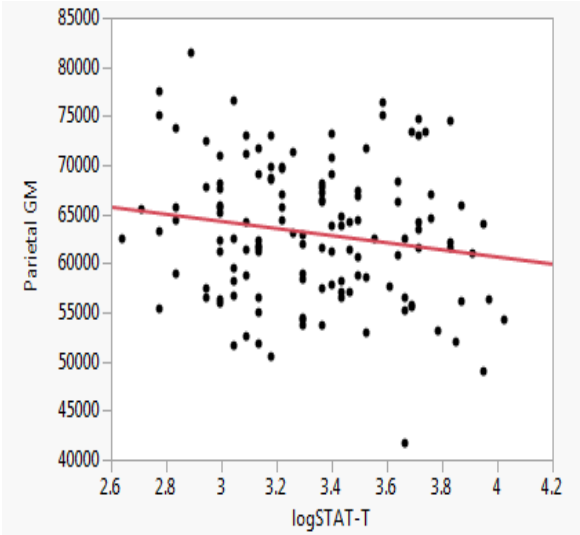
Frontal Lobe

t(129)=-2.56
p=0.01
R^2=0.05



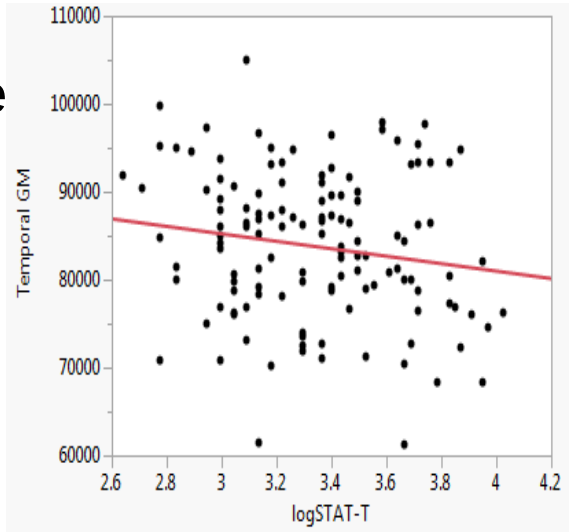
Parietal Lobe

t(129)=-1.91
p=0.06
R^2=0.03



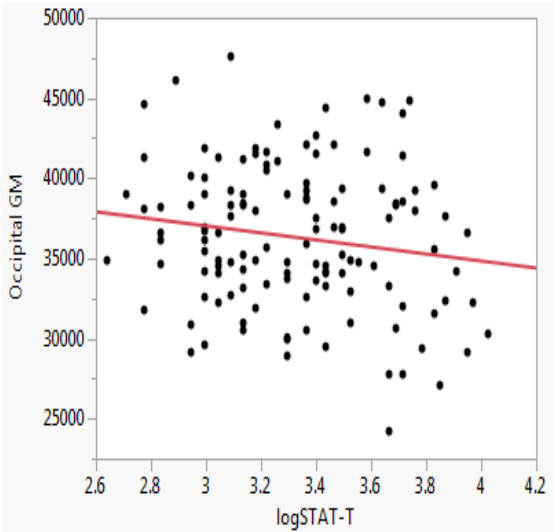
Temporal Lobe

t(129)=-1.86
p=0.07
R^2=0.03

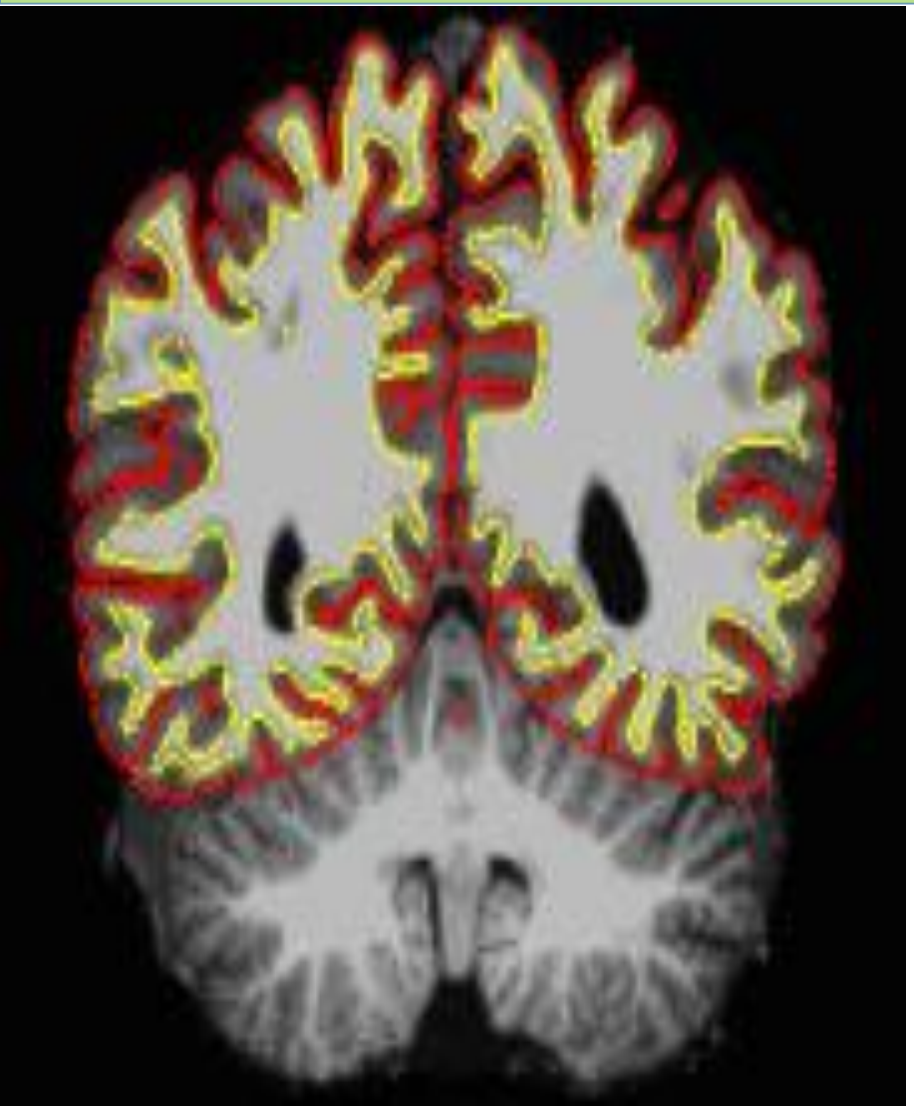


Occipital Lobe

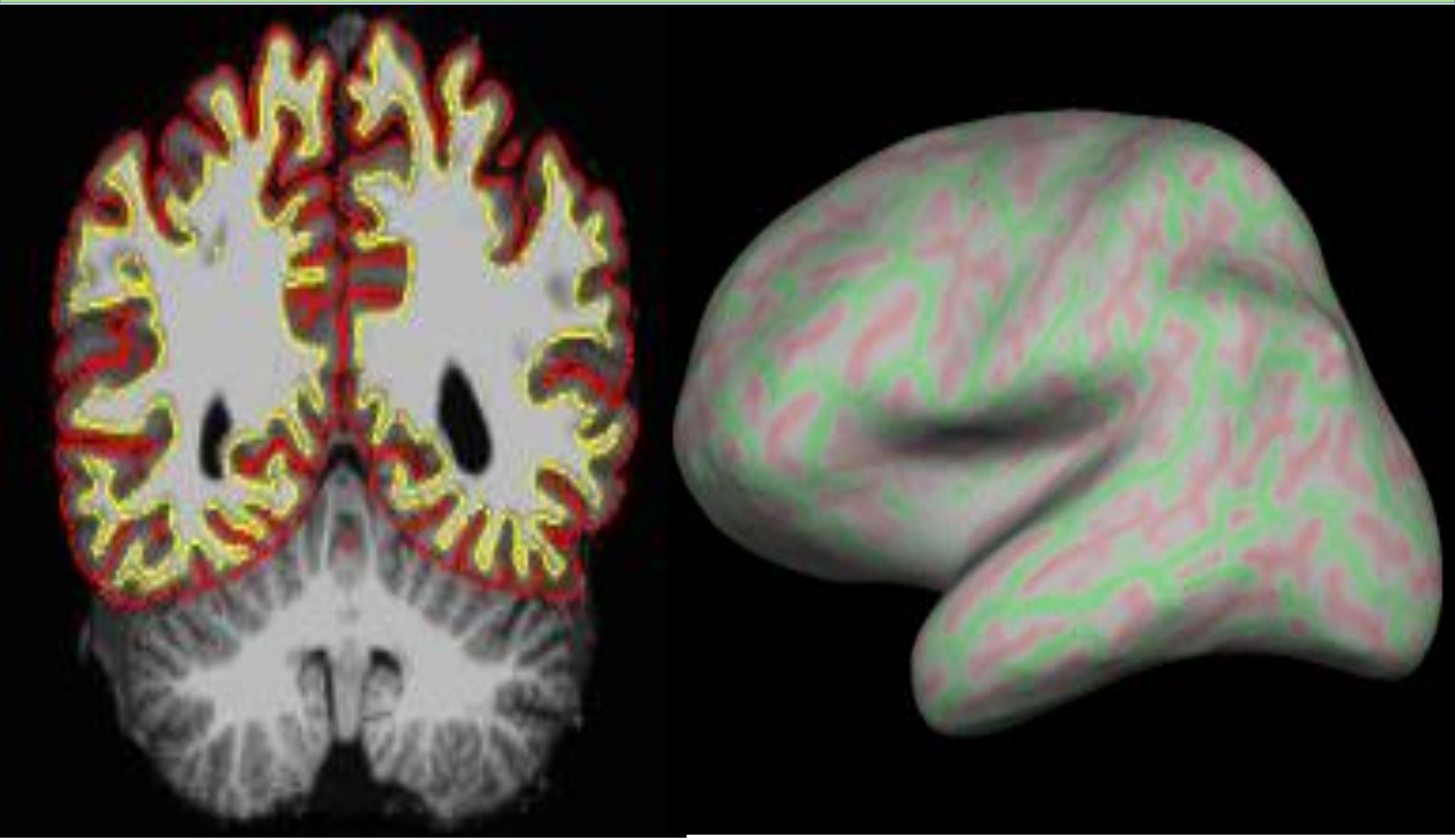
t(129)=-1.79
p=0.08
R^2=0.02



Cortical Volume = Product of Cortical Thickness & Area

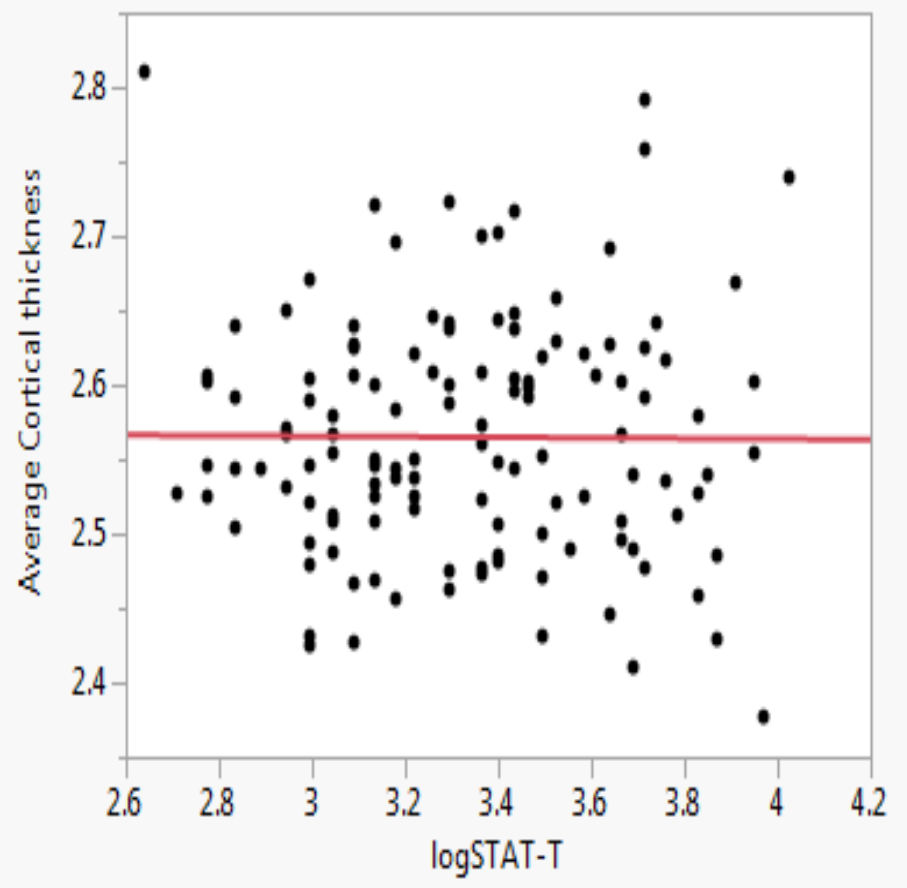


Cortical Volume = Product of Cortical Thickness & Area



Cortical Volume = Product of Cortical Thickness & Area

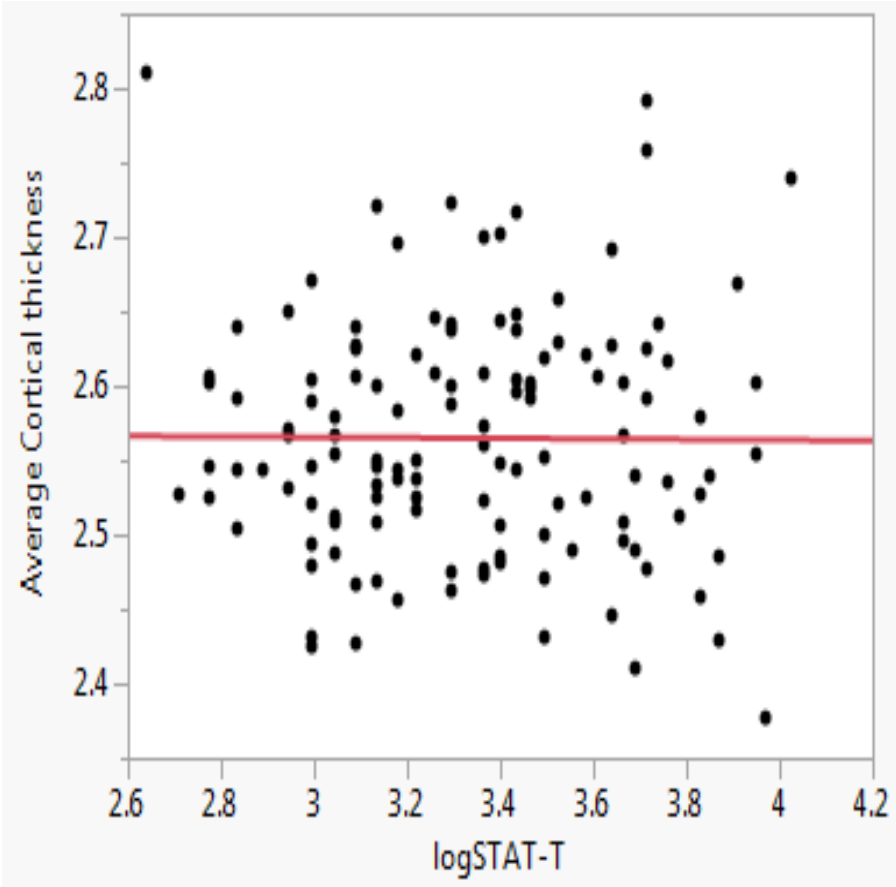
Overall cortical thickness & STAI-T



p=0.93

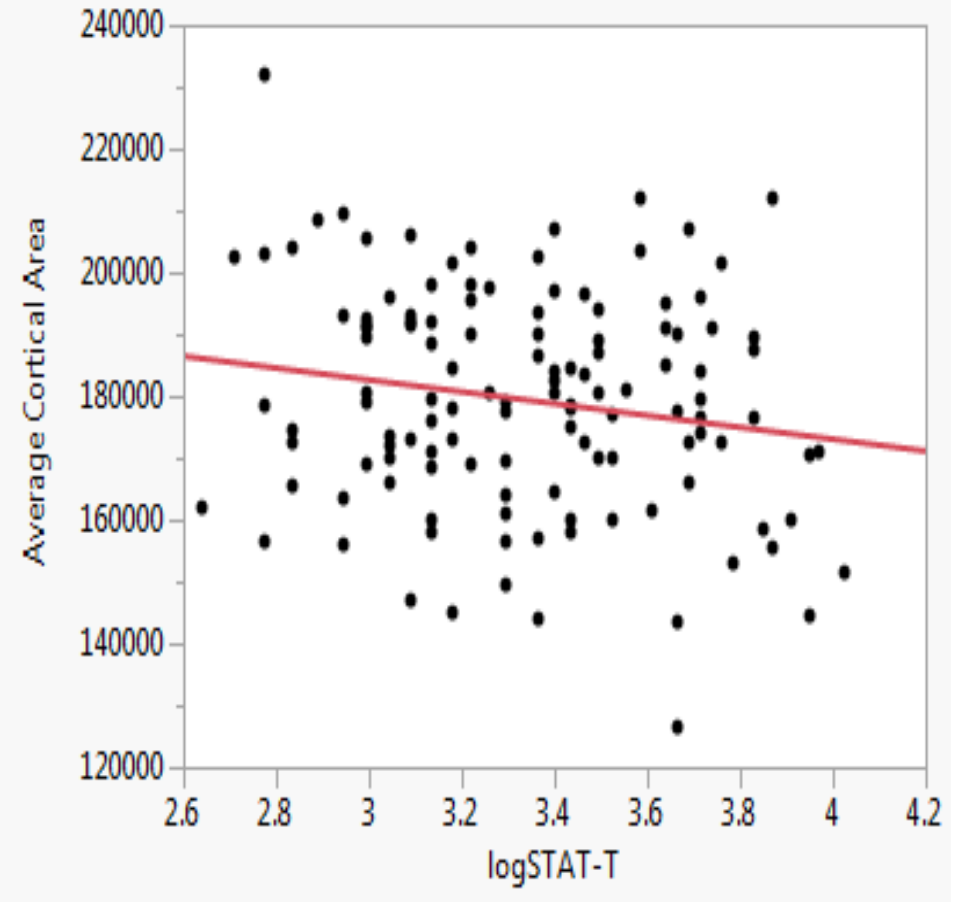
Cortical Volume = Product of Cortical Thickness & Area

Overall cortical thickness & STAI-T



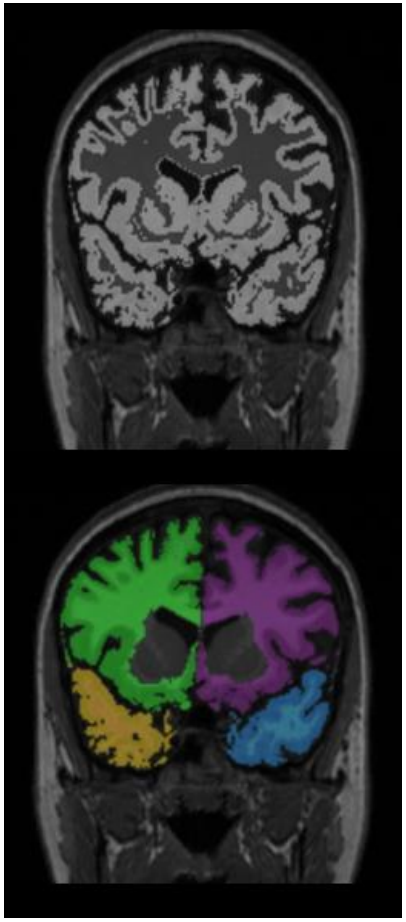
p=0.93

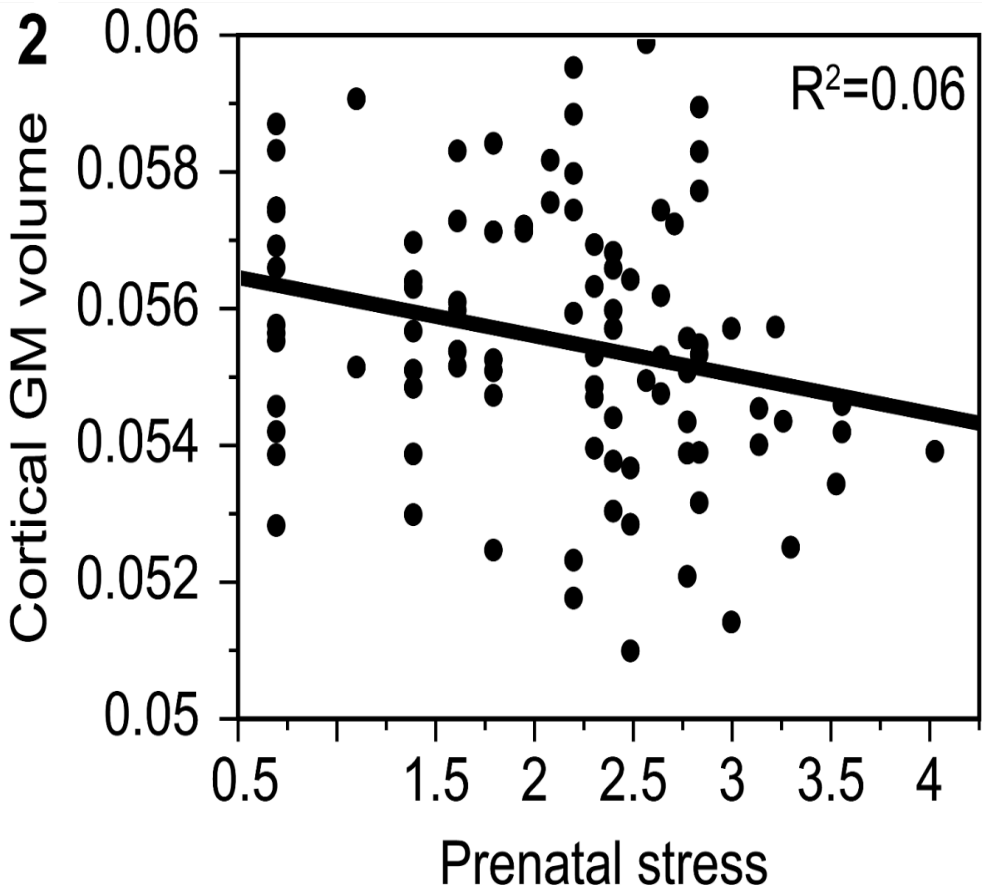
Overall cortical area & STAI-T



t(128)=-1.98, p=0.049, R^2=0.03

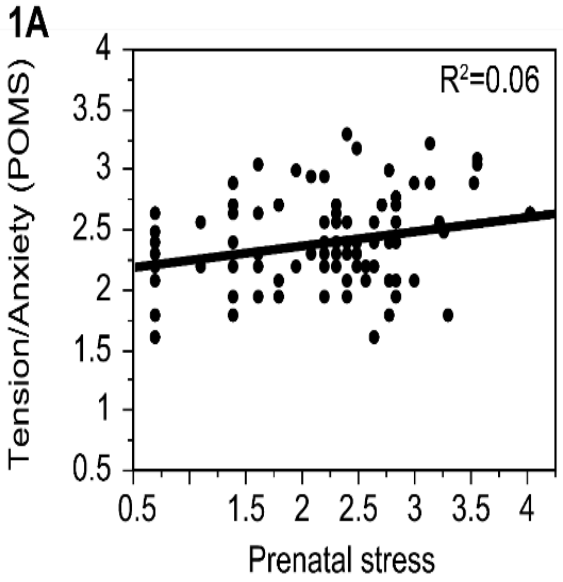
Prenatal stress and gray matter volume in young adulthood

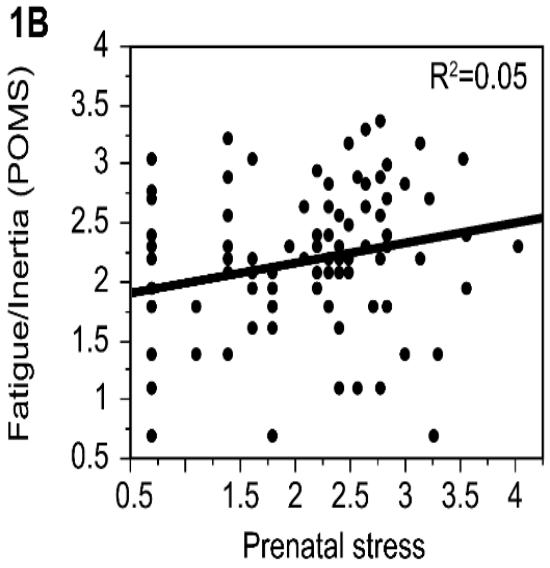


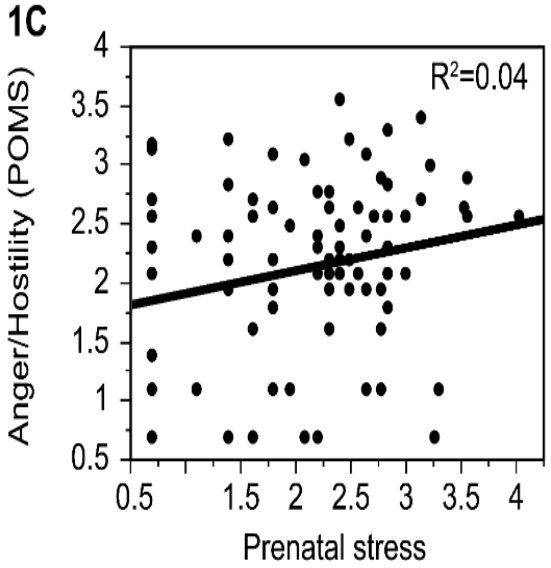


Mareckova et al, Cerebral Cortex, 2018

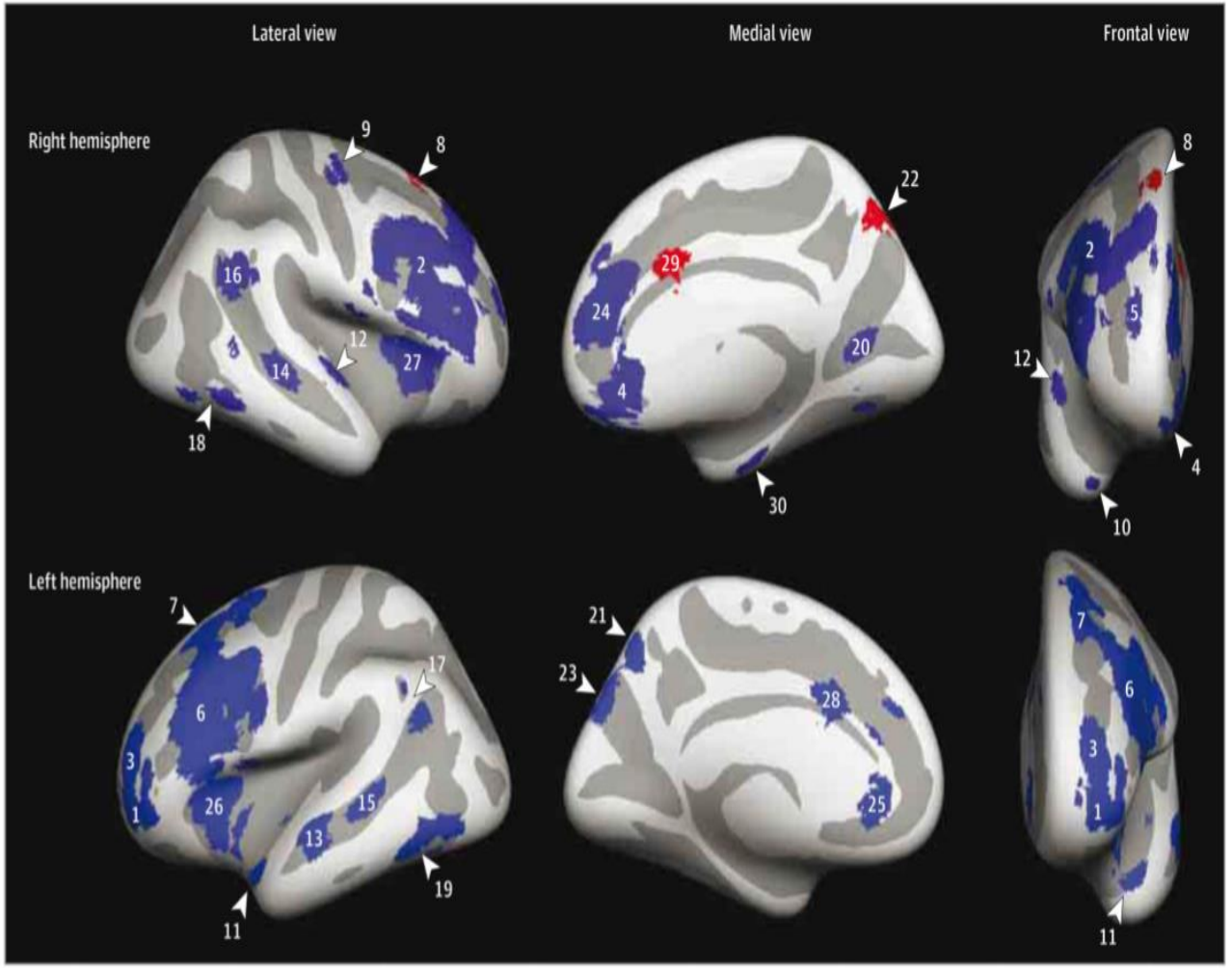
Prenatal stress and mood in young adulthood





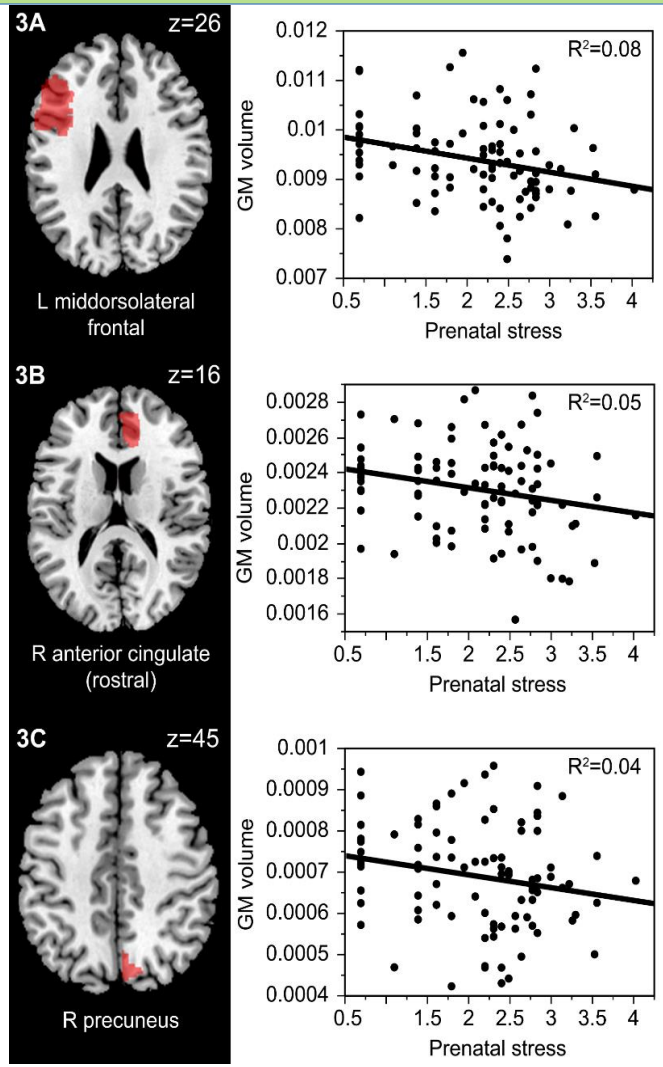


Metaanalysis of hypometabolic ROIs in depressed patients vs. healthy controls



Jensen et al., 2015

Prenatal stress and GM volume in young adulthood



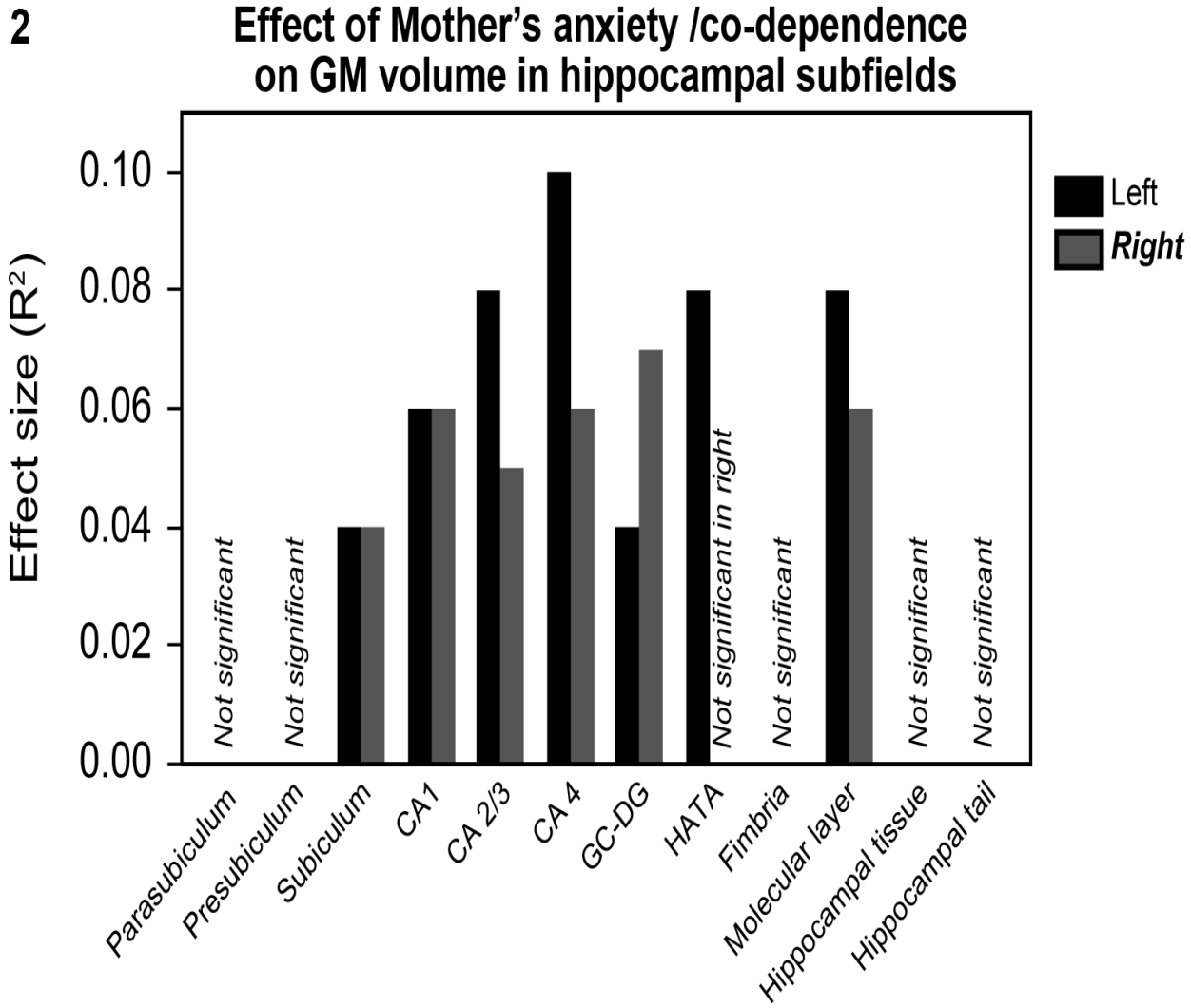
Mareckova et al, Cerebral Cortex, 2018

Perinatal stress and human hippocampal volume: Findings from typically developing young adults

Measure of prenatal stress	Left hippocampus	Right hippocampus
Birth weight	$t_{(125)} = -1.32$, $p = 0.19$	$t_{(125)} = -0.38$, $p = 0.71$
Stressful life events during first half of pregnancy	$t_{(92)} = -1.07$, $p = 0.29$	$t_{(92)} = -0.82$, $p = 0.41$
Stressful life events during second half of pregnancy	$t_{(121)} = -0.80$, $p = 0.42$	$t_{(121)} = -0.93$, $p = 0.35$
Measure of early postnatal stress	**Left hippocampus**	**Right hippocampus**
Stressful life events during first six months after birth	$t_{(123)} = -0.08$, $p = 0.94$	$t_{(123)} = -0.89$, $p = 0.37$
Stressful life events during 6 to 18 months after birth	$t_{(116)} = 0.03$, $p = 0.97$	$t_{(116)} = -0.01$, $p = 0.99$
Anxiety and co-dependence during first weeks after birth	**$t_{(121)} = -2.90$, $p = 0.004$, $R^2 = 0.07$**	**$t_{(121)} = -2.61$, $p=0.01$, $R^2=0.05$**
Dysregulated mood and wellbeing during first weeks after birth	$t_{(119)} = -0.48$, $p = 0.63$	$t_{(119)} = -0.85$, $p = 0.40$
Dysregulated mood and wellbeing at six months after birth	$t_{(123)} = -1.29$, $p = 0.20$	$t_{(123)} = -0.79$, $p = 0.43$
Dysregulated mood and wellbeing at 18 months after birth	$t_{(116)} = -0.70$, $p = 0.49$	$t_{(116)} = -0.72$, $p = 0.47$

Mareckova et al, Scientific Reports, 2018

Perinatal stress and human hippocampal volume: Findings from typically developing young adults



Mareckova et al, Scientific Reports, 2018

Better Treatment through Better Diagnostics

- Diagnosis limited to symptoms
  (but symptoms are late manifestations of brain disorders)
- Etiology unknown
  (treatments for symptoms not cures)
- Detection late; for most disorders, prevention not well developed

- Mental disorders are disorders of brain circuits, focus on **brain-based biomarkers,** whole **biosignatures**
- **Understand the etiology** through large population-based studies, understand the **mechanisms**
- Focus on **early detection** and prevention (not extreme comparisons of patients vs. controls, study both clinical and pre-clinical populations to identify early biomarkers, use **standardized methods for replication**)
- Move towards **personalized medicine and sex-dependent therapeutics** (take into account one's sex, genes etc.)

Thank you!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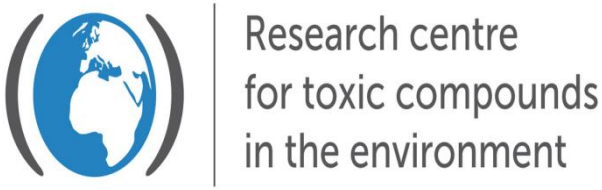
SEVENTH FRAMEWORK
PROGRAMME


Research centre
for toxic compounds
in the environment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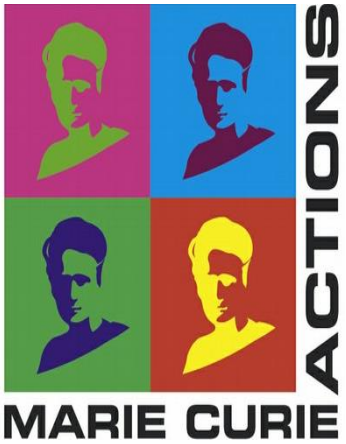
ACTIONS
MARIE CURIE