Childhood Abuse: A Neurobiological Perspective

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National Health Collaborative on Violence and Abuse

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DBRP - Current and Former Members

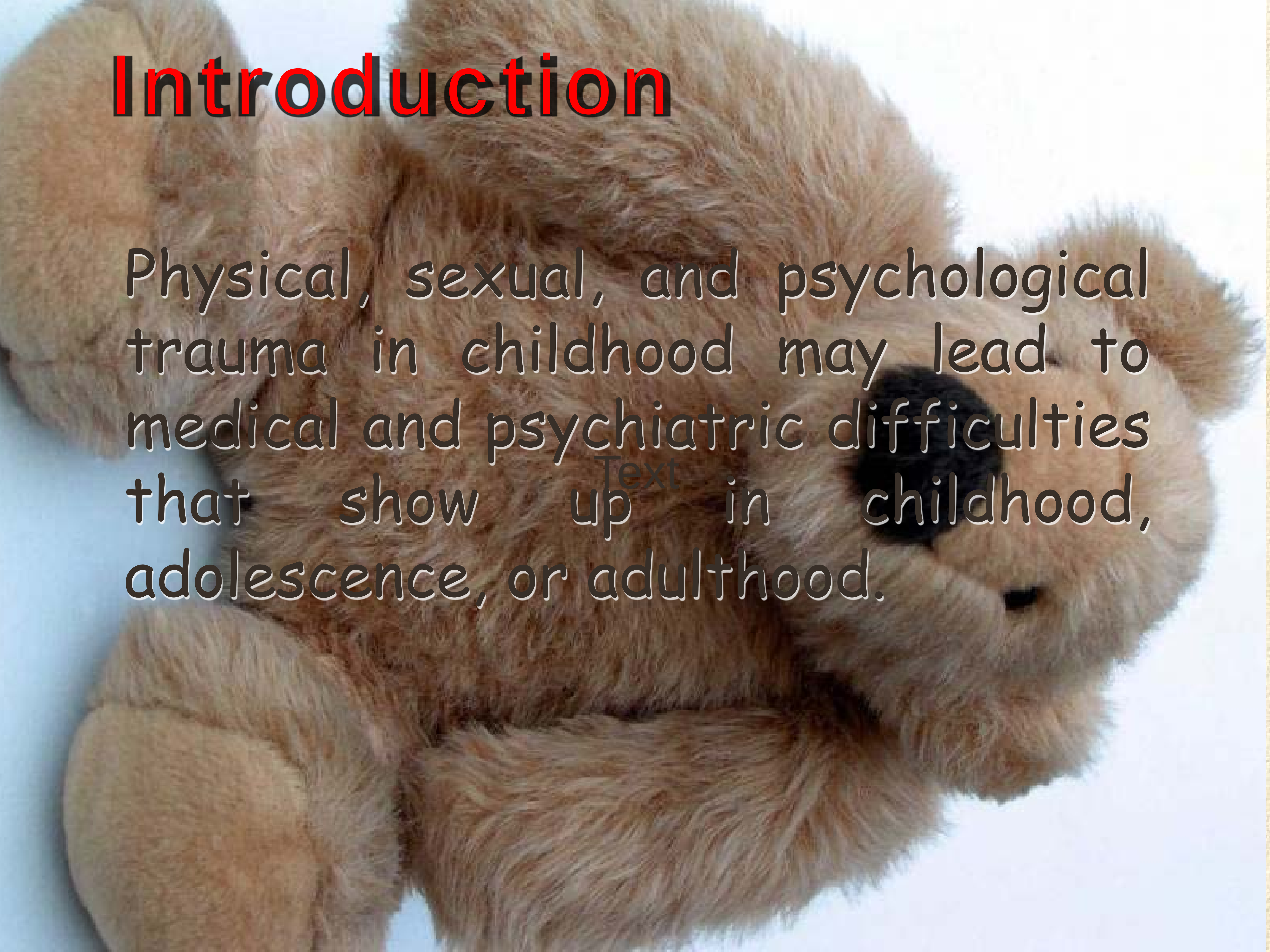
Support - Maltreatment and Trauma Studies

NIMH RO1 MH53636 (1997-2001)
RO1 MH66222 (2003-2008)
RO1 MH91391 (2010-2015)

NIDA RO1 DA16934 (2003-2007)
RO1 DA17846 (2004-2009)

NARSAD (2005-2007)

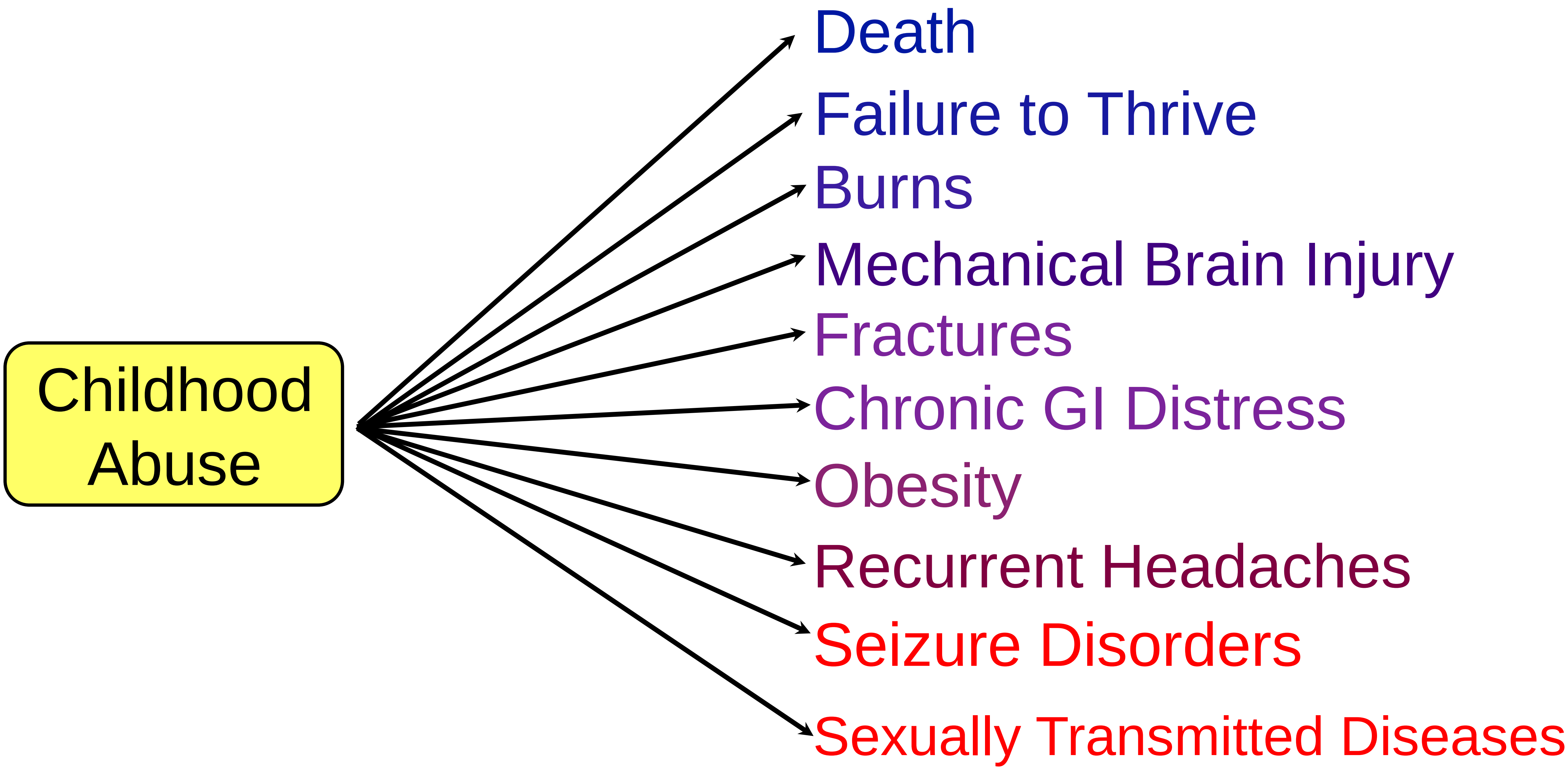
Simches Family



Introduction

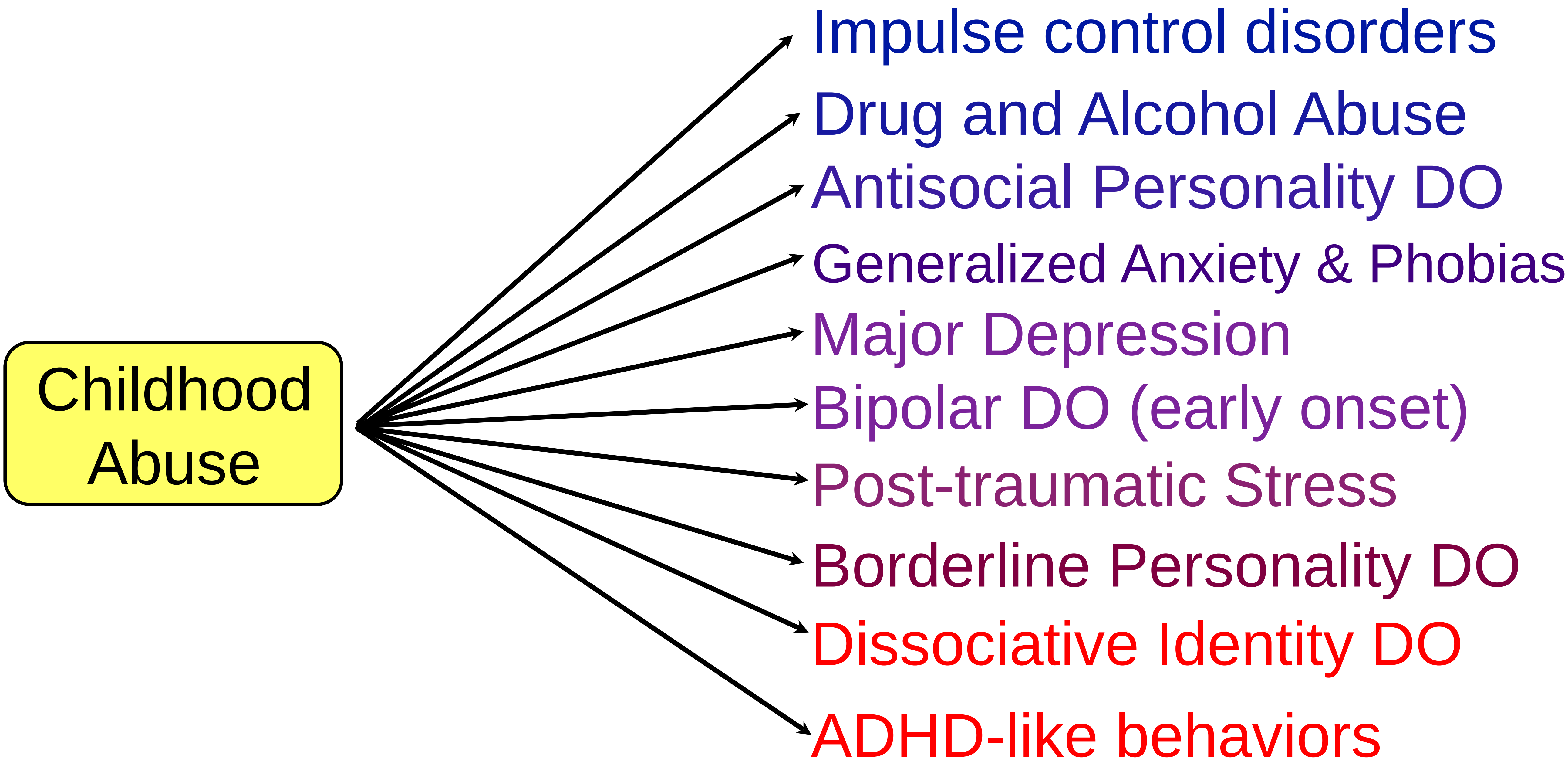
Physical, sexual, and psychological trauma in childhood may lead to medical and psychiatric difficulties that show up in childhood, adolescence, or adulthood.

Introduction



medical

Introduction



psychiatric

Question?

- What factor, or combination of factors, shape outcome?

Resilience

Vulnerability

Fixed

Malleable

Possibilities

- Genes
- Timing (developmental stage when abuse occurs)
- Type of abusive experience
- Protective factors

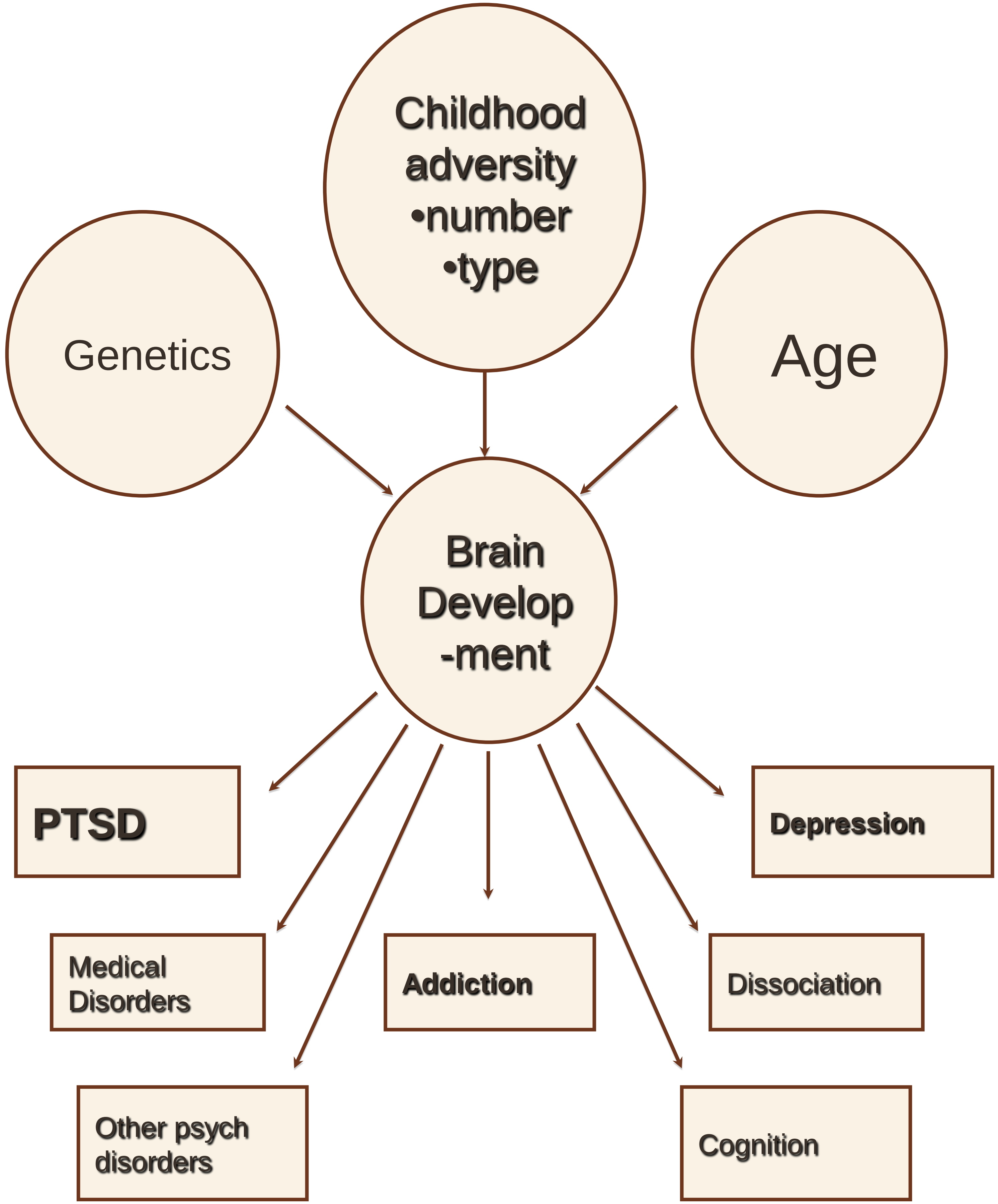
Possibilities

- Genes
- Timing (developmental stage when abuse occurs)
- Type of abusive experience
- Protective factors

Hypothesis

We have proposed that early childhood maltreatment acts as a severe stressor, that produces a cascade of physiological and neurohumoral responses which leads to enduring alterations in the patterns of brain development, and that alterations in brain function set the stage for the emergence of psychiatric disorders.

Introduction



How can stressful experience influence the developing brain?

How stressful early experience influences the developing brain.

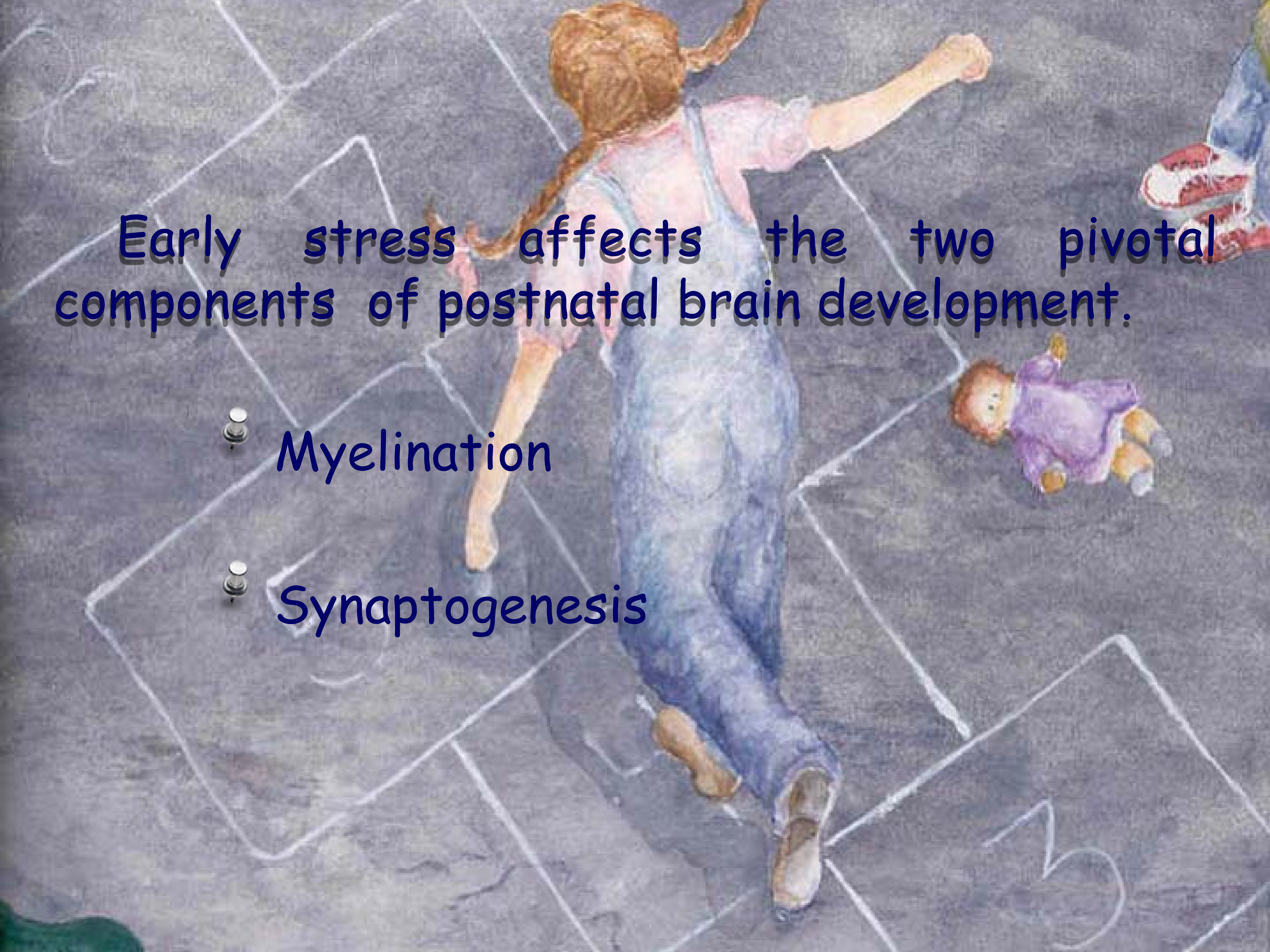
Step 1

Early stress programs our stress hormone systems to have a more exaggerated and prolonged response to subsequent stressors.

How stressful early experience influences the developing brain.

Step 2

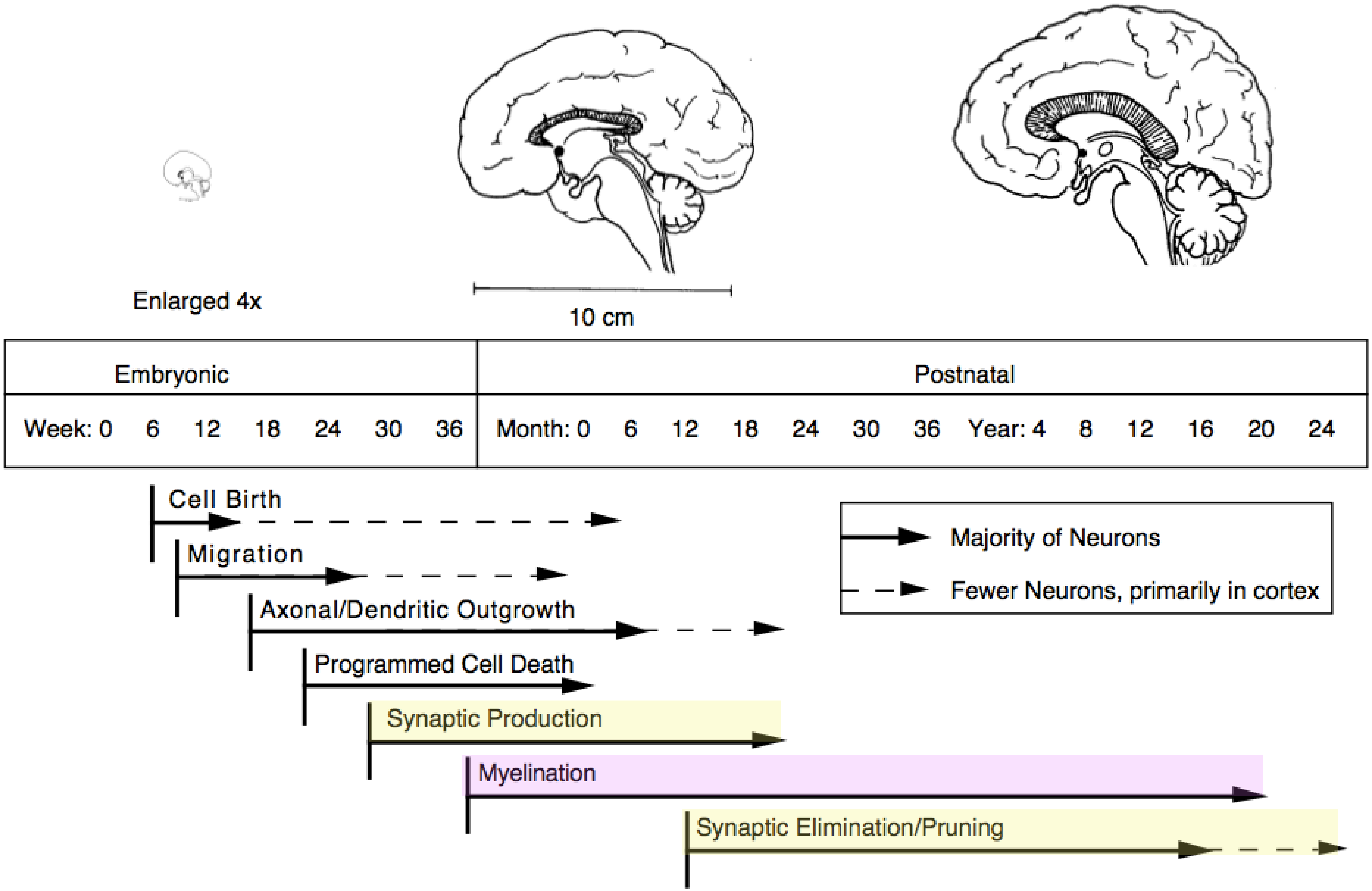
Exposure of the developing brain to stress hormones exerts consequences by affecting gene expression, myelination, neural morphology, neurogenesis and synaptogenesis.



Early stress affects the two pivotal components of postnatal brain development.

- Myelination
- Synaptogenesis

Human Brain Development

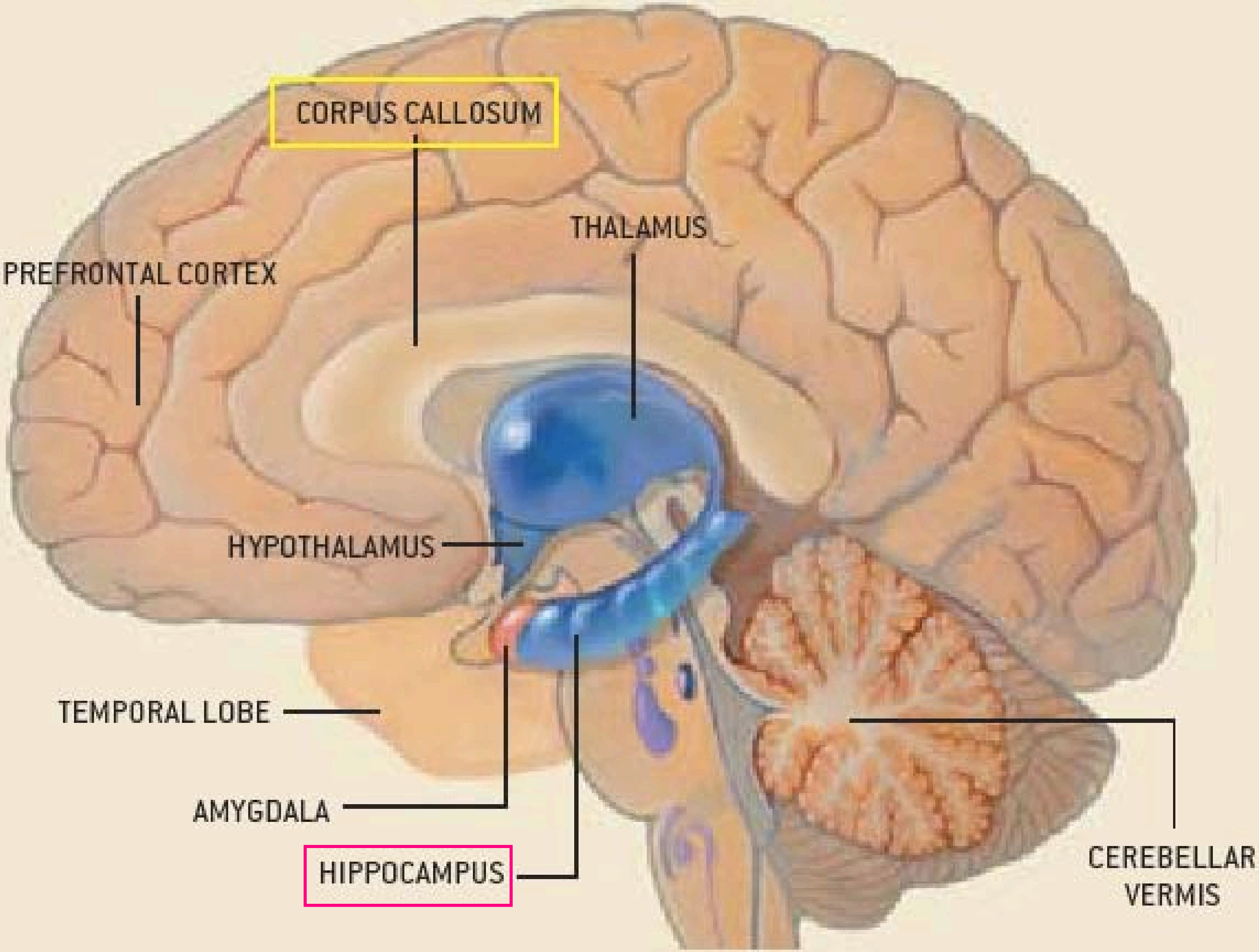


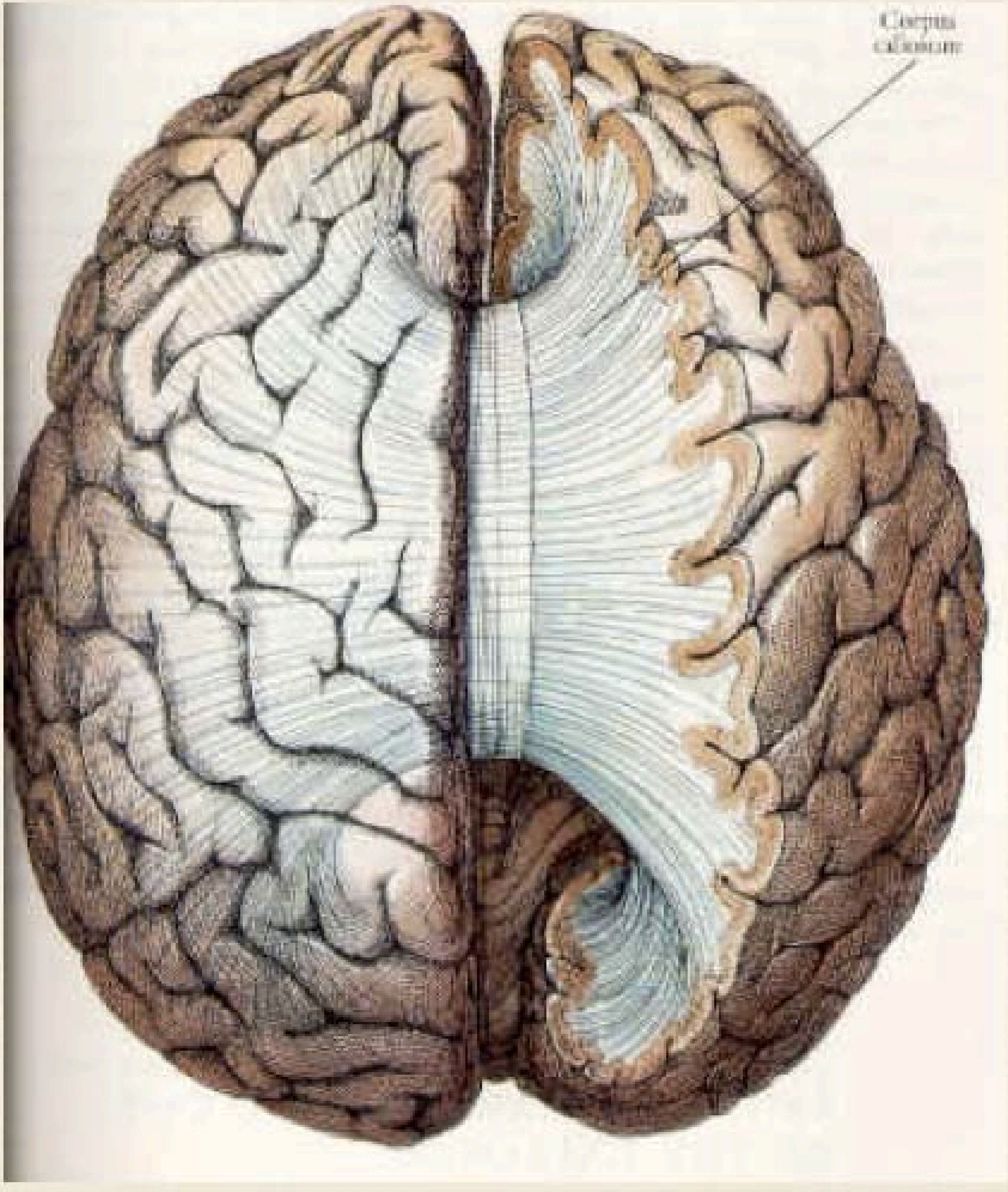
How stressful early experience influences the developing brain.

Step 3

Impact of early stress on the developing brain depends on timing, vulnerability of specific brain regions, and genetic factors.

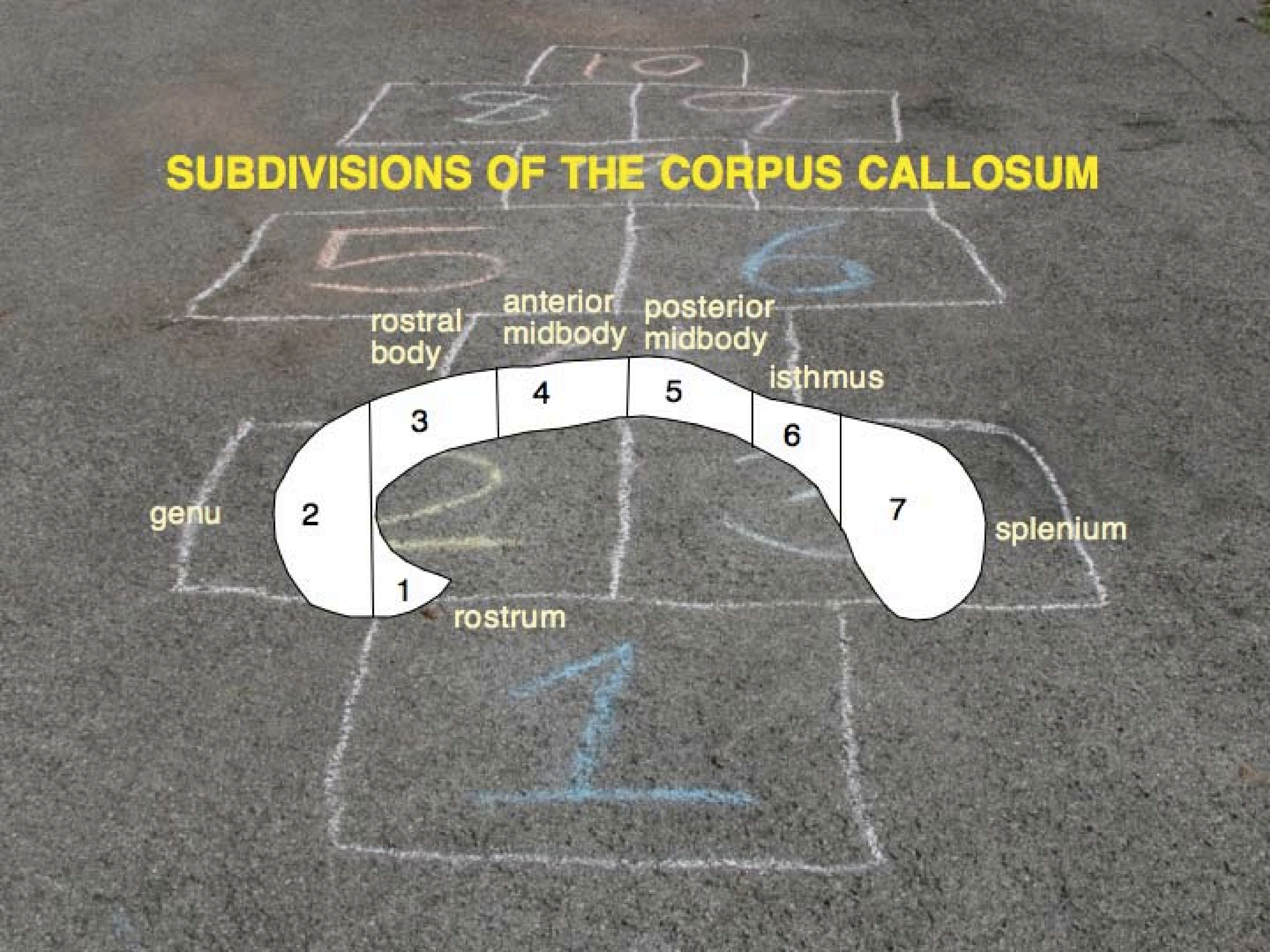
First Neuroimaging Findings




Corpus callosum

Childhood Abuse and the Regional Anatomy of the Corpus Callosum

Myelinated regions, such as the corpus callosum (CC) are potentially vulnerable to the impacts of early exposure to excessive levels of stress hormones, which suppress glial cell division critical for myelination.


SUBDIVISIONS OF THE CORPUS CALLOSUM
rostral body
anterior midbody
posterior midbody
isthmus
3
4
5
6
genu
2
7
splenium
1
rostrum

Comparison between abused/neglected boys, non-abused psychiatric control boys (contrast group), and healthy boys.

Region	Abused/neglected	Contrast	Healthy	Group diff.
1 (rostrum)	0.306	0.109	0.128	0.1000
2 (genu)	0.761	0.900	0.864	0.1300
3 (rostral body)	0.463	0.615	0.606	0.0020
4 (ant. midbody)	0.361	0.486	0.523	0.0001
5 (post. midbody)	0.331	0.416	0.429	0.0055
6 (isthmus)	0.889	1.100	1.152	0.0043
7 (splenium)	0.403	0.466	0.496	0.5450
(n)	13	13	61	

Overall differences between groups, MANCOVA, $p < 0.0001$

Association of Early Experience and Age on Regional Anatomy of Corpus Callosum in Boys, Based on Step-wise Regression.

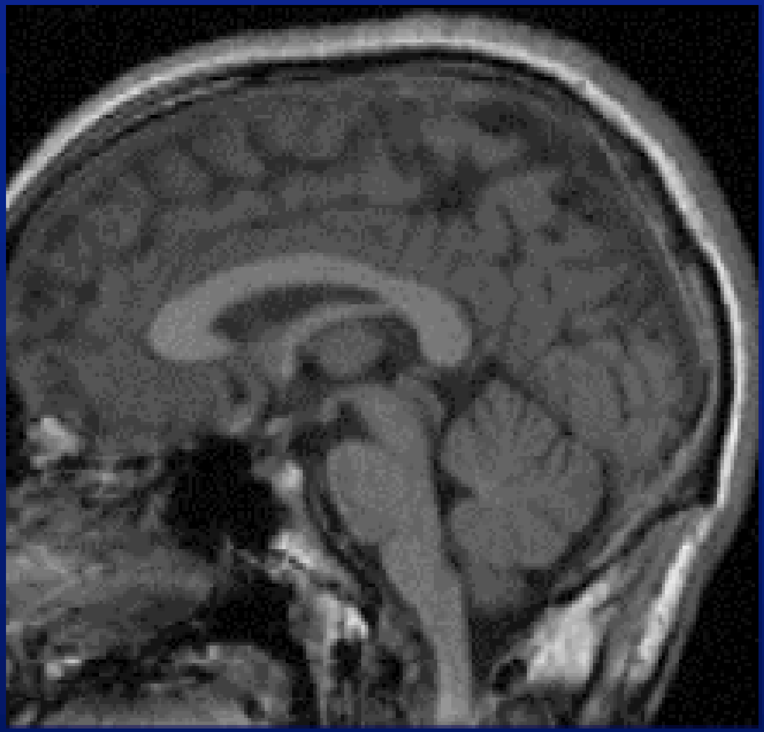
Region	Physical Abuse	Sexual Abuse*	Neglect*	Age**	PTSD*
1 (rostrum)	--	--	-41.7%†	7.4%ζ	--
2 (genu)	--	--	-29.2%¥	--	--
3 (rostral body)	--	--	-33.2%¥	--	--
4 (ant. midbody)	-9.6%†	--	-30.7%¥	--	--
5 (post. midbody)	--	--	-40.2%¥	1.5%†	--
6 (isthmus)	--	--	-45.7%¥	--	--
7 (splenium)	--	-18.3%†	-24.2% ξ	--	--

†p < 0.10, ζp < .05, ξp < .01, ¥p < .001

*Values are expressed as % change in volume associated with positive history

**Values are expressed as % change in volume per year of age.

Childhood abuse affects corpus callosum



Control

Neglect

The morphology of the corpus callosum is significantly affected by early neglect (as well as physical abuse and sexual abuse).

Teicher et al. (2004) Biological Psychiatry 56, 80-85

Association of Early Experience and Age on Regional Anatomy of the Corpus Callosum in Girls, Based on Step-wise Regression.

Region	Physical Abuse	Sexual Abuse*	Neglect*	Age**	PTSD
1 (rostrum)	--	--	--	--	--
2 (genu)	--	--	--	--	--
3 (rostral bod	--	-20.8%ζ	--	--	--
4 (ant. midbo	--	-29.7%¥	--	--	--
5 (post. midb	--	-17.7%ζ	--	--	--
6 (isthmus)	--	-23.7%ζ	+37.6ξ	--	--
7 (splenium)	--	--	-43.9%†	+5.2%ζ	--

†$p < 0.10$, ζ$p < .05$, ξ$p < .01$, ¥$p < .001$

*Values are expressed as % change in volume associated with positive history

**Values are expressed as % change in volume per year of age.

De Bellis MD et al., Developmental traumatology. Part II: Brain development. Biol Psychiatry 1999, 45: 1271-84.

44 maltreated children and adolescents with PTSD and 61 matched controls underwent comprehensive assessments and MRI.

Most significant finding was reduced midsagittal area of corpus callosum in PTSD subjects.

There was a greater corpus callosum area reduction in maltreated males than maltreated females with PTSD.

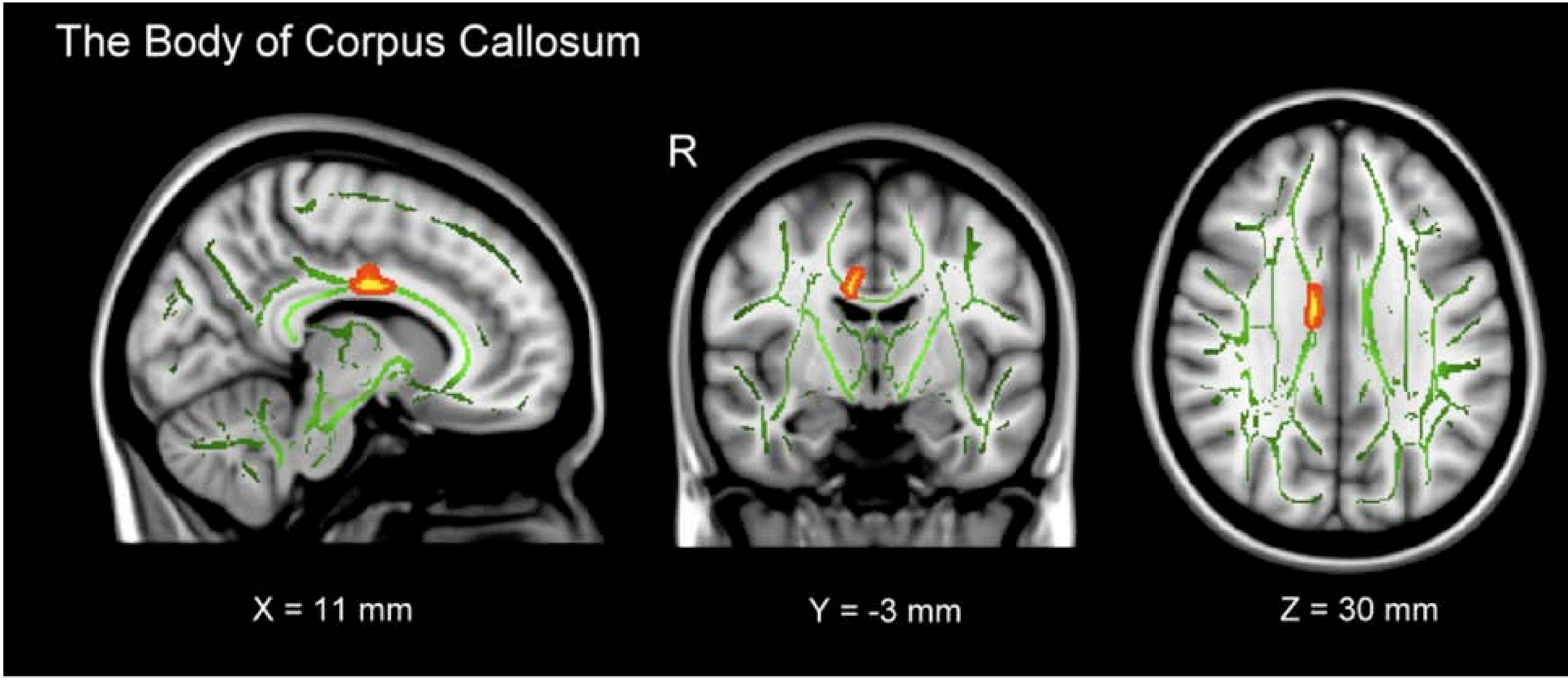
Sánchez et al. (1998). "Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys." Brain Research 812(1-2): 38-49.

Infant male monkeys raised individually in a nursery from 2 to 12 months were compared to age-matched infants raised in a semi-naturalistic social environment. Although overall brain volumes did not differ, the corpus callosum was significantly decreased in the nursery group.

Degree of cognitive impairment correlated with alterations in corpus callosum size.

Corpus Callosum

Reduced area or integrity of the corpus callosum is the most consistent neurobiological finding in children and adults with histories of exposure to childhood abuse.

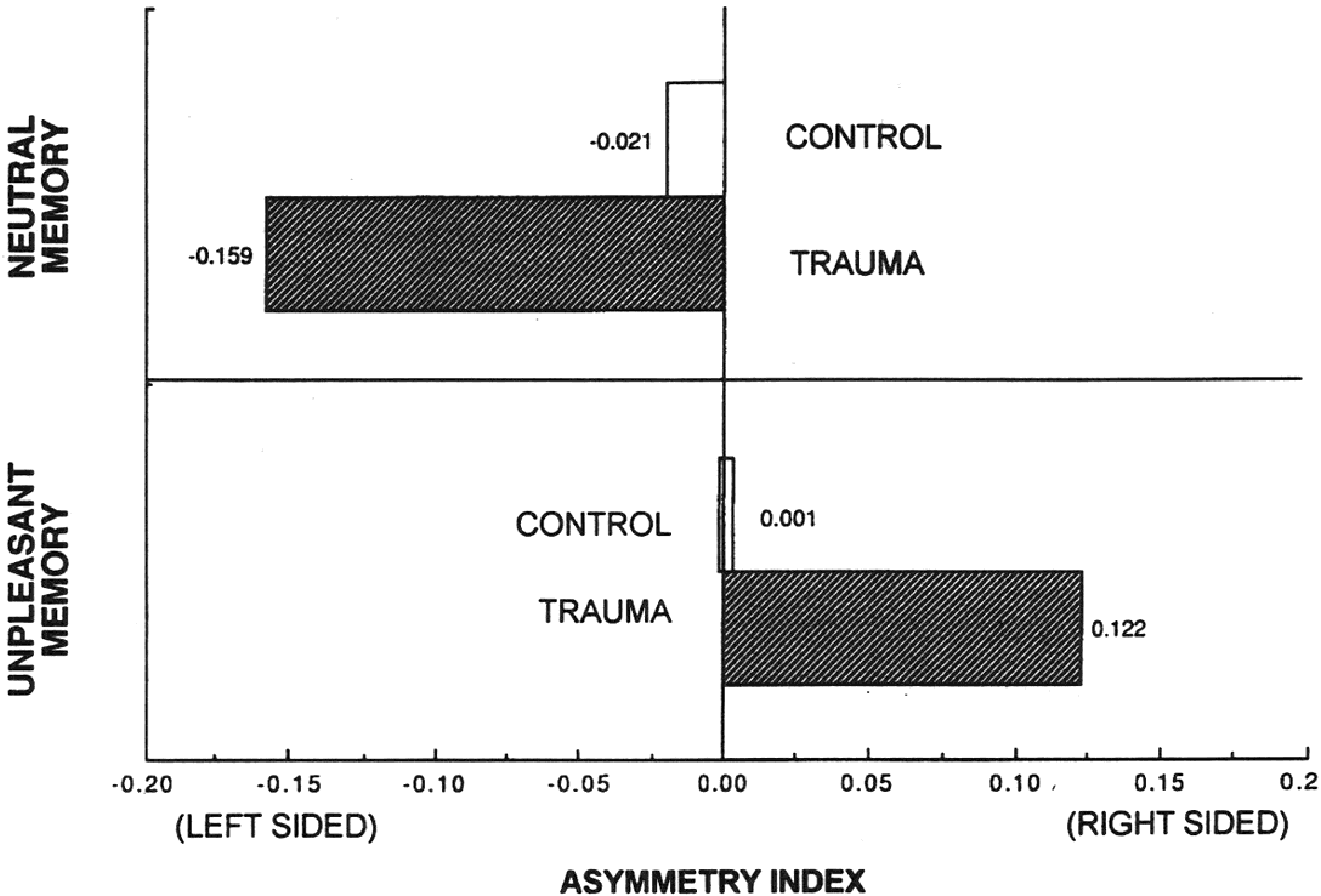


Using Diffusion Tensor Imaging we found that the integrity of the middle portion of the corpus callosum correlated inversely with degree of exposure (ACE score) to childhood abuse in young adults (n = 191).

Corpus Callosum and Hemispheric Laterality

- Hemispheric brain activity was measured in adult subjects under two conditions: first, during recall of a neutral memory, and then during recall of an unpleasant affectively-laden early experience.

Right-Left Evoked Response Asymmetry



Schiffer F, Teicher MH, Papanicolaou AC: Evoked potential evidence for right brain activity during the recall of traumatic memories. J Neuropsychiatry Clin Neurosci 1995; 7(2):169-75

Deficient Hemispheric Integration

Our discoveries that abused patients have diminished right-left hemisphere integration and a smaller corpus callosum suggest an intriguing model for the emergence of borderline splitting. With less integrated hemispheres, they may shift between logical and rational state to highly emotional state. Lack of integration between the hemispheres may also be a factor in the genesis of dissociation and multiple distinct identities.

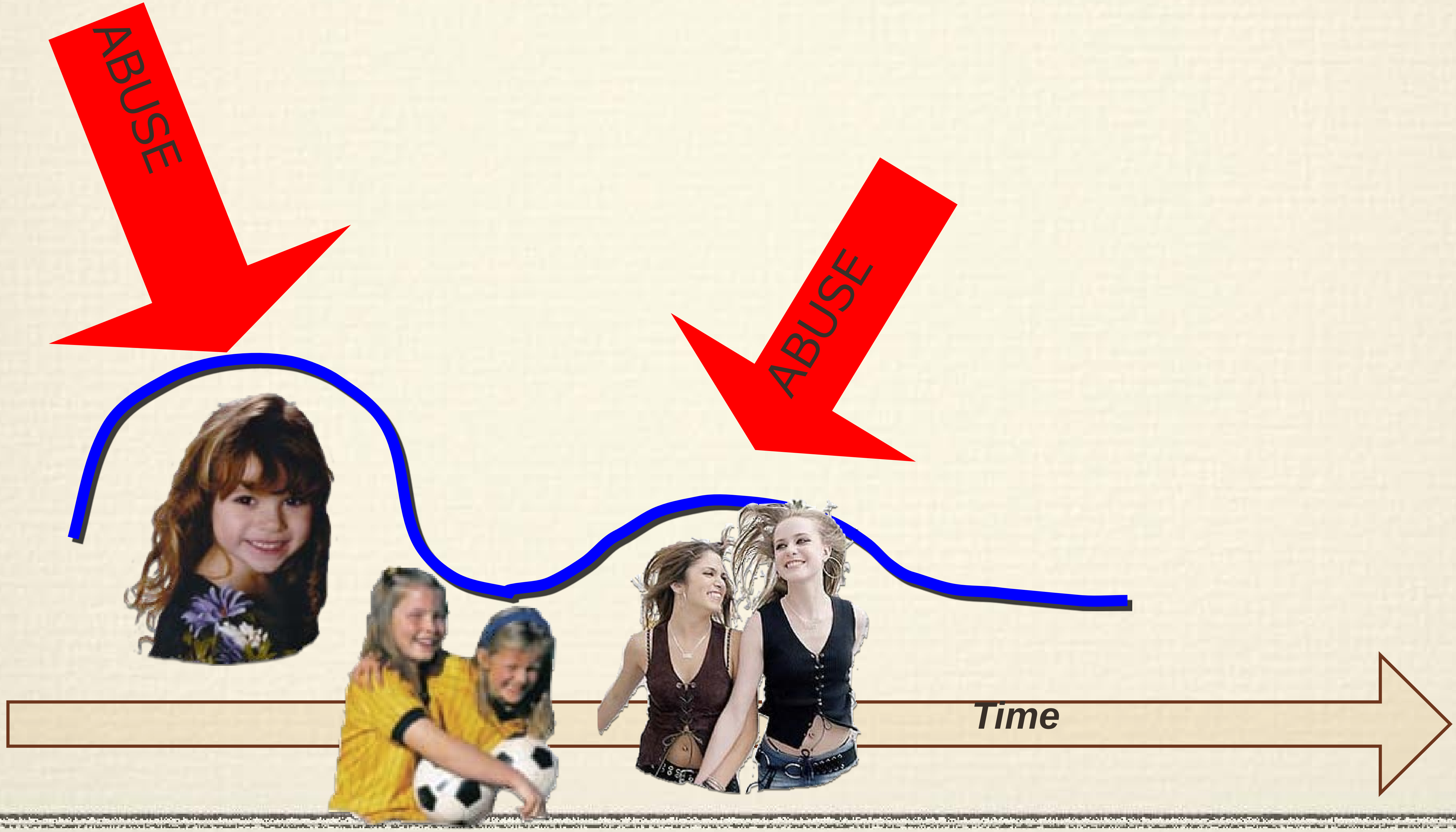

Sensitive Periods

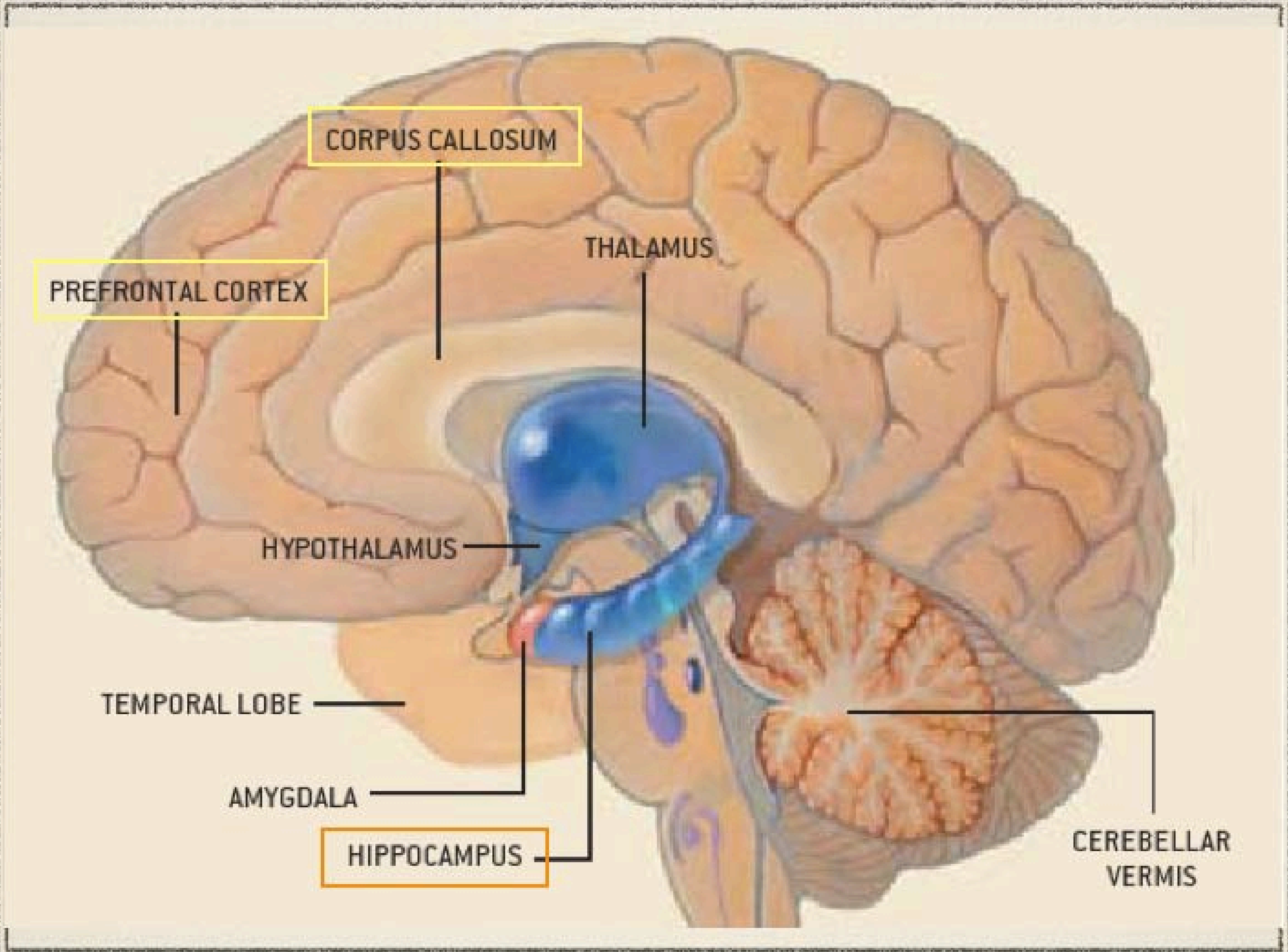
Sensitive Periods

The brain is molded by experiences, such as stress, that occur throughout the lifespan. However, there are particular stages of development when experience exerts either a maximal (sensitive period) or essential (critical period) effect.

Hubel and Wiesel won the Nobel Prize in Medicine and Physiology (1981) for this discovery.

Sensitive Periods




CORPUS CALLOSUM
PREFRONTAL CORTEX
THALAMUS
HYPOTHALAMUS
TEMPORAL LOBE
AMYGDALA
HIPPOCAMPUS
CEREBELLAR
VERMIS

Sensitive Periods

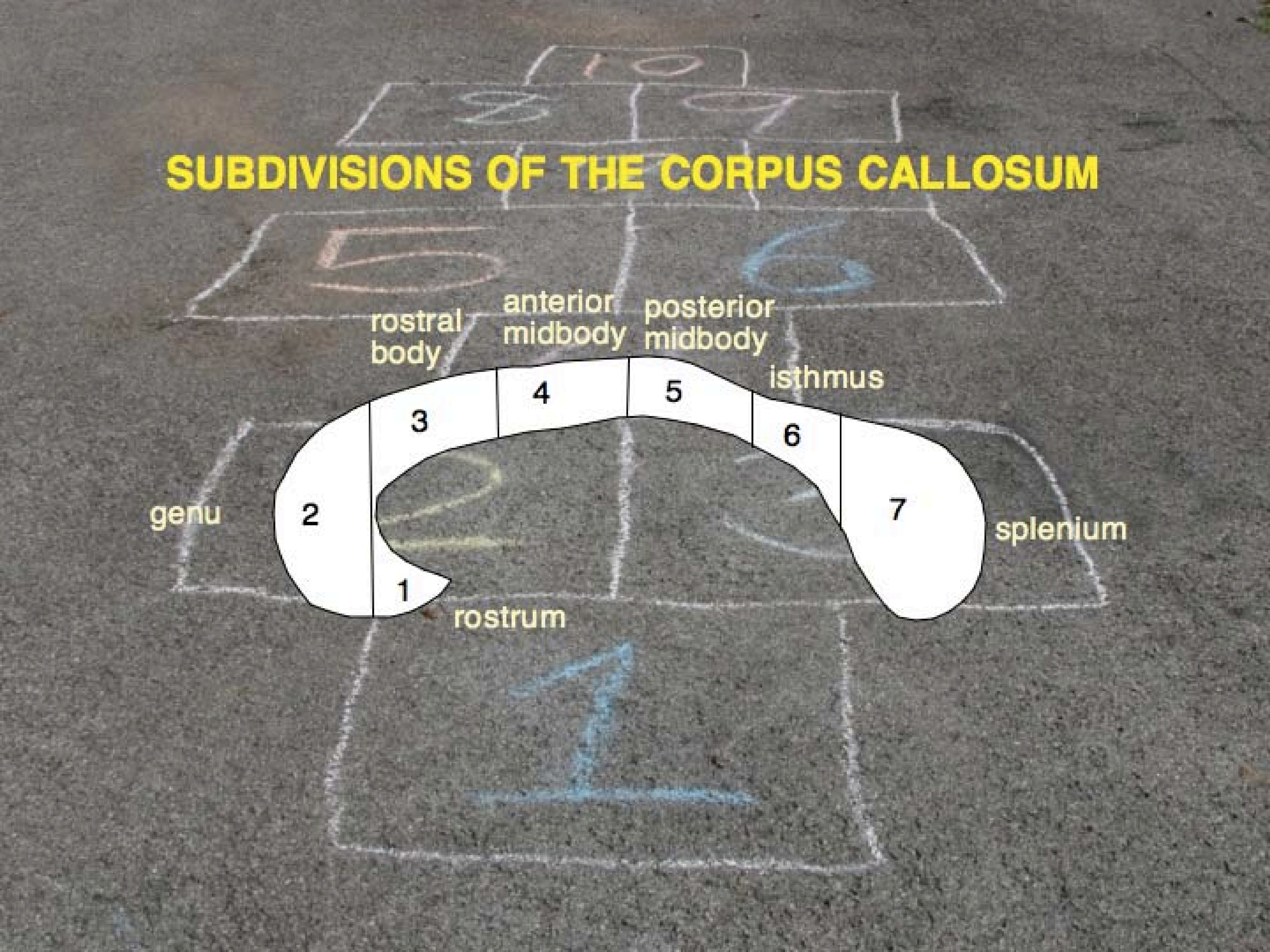
Study I

Subjects: 18-22 year olds with history of 3 or more episodes of forced sexual contact, by individuals outside the immediate family, accompanied by fear or terror and threats of harm to self or others (n=30).

Sensitive Periods

Subjects: Recruited from the community and were selected based on childhood history with no prerequisite for any degree or type of psychiatric difficulty.

564 screened / 30 abused, 30 controls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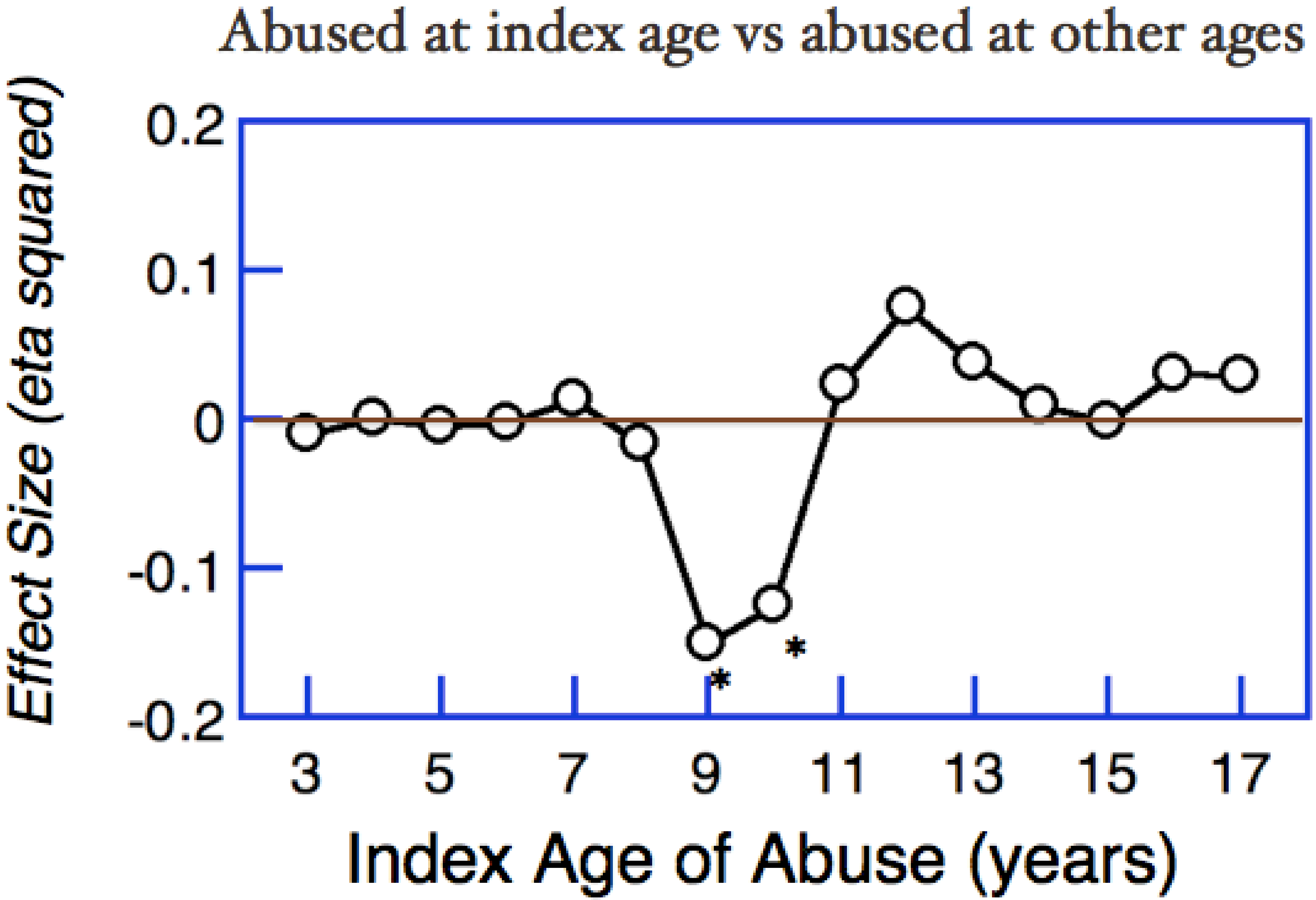
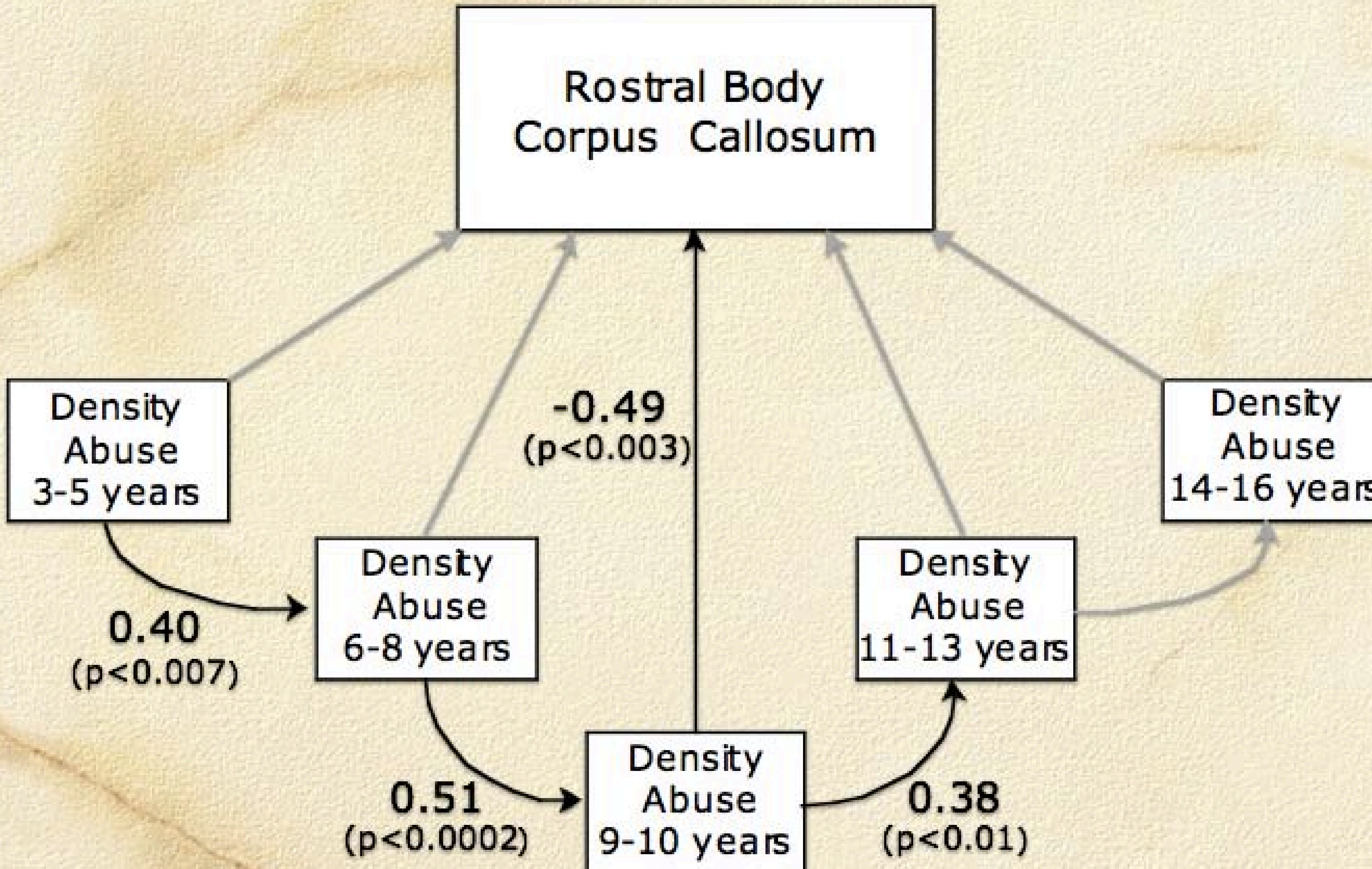
Corpus Callosum - Rostral Body

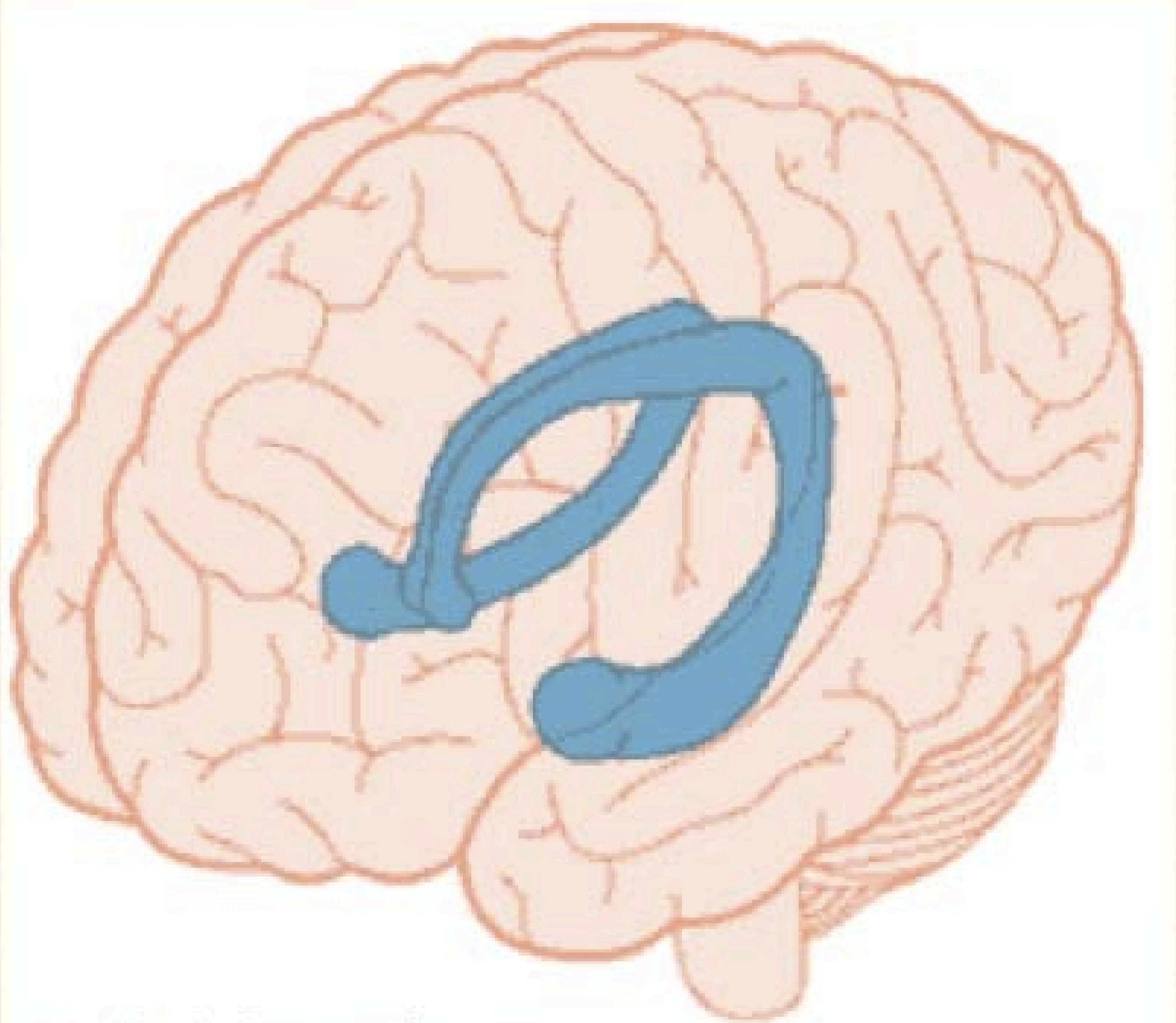


CC area reduced 22.4% in subjects who experienced abuse at age 10 (n=5).



Rostral Body
Corpus Callosum
Density
Abuse
3-5 years
Density
Abuse
6-8 years
Density
Abuse
9-10 years
Density
Abuse
11-13 years
Density
Abuse
14-16 years
-0.49
(p<0.003)
0.40
(p<0.007)
0.51
(p<0.0002)
0.38
(p<0.01)

Hippocampus

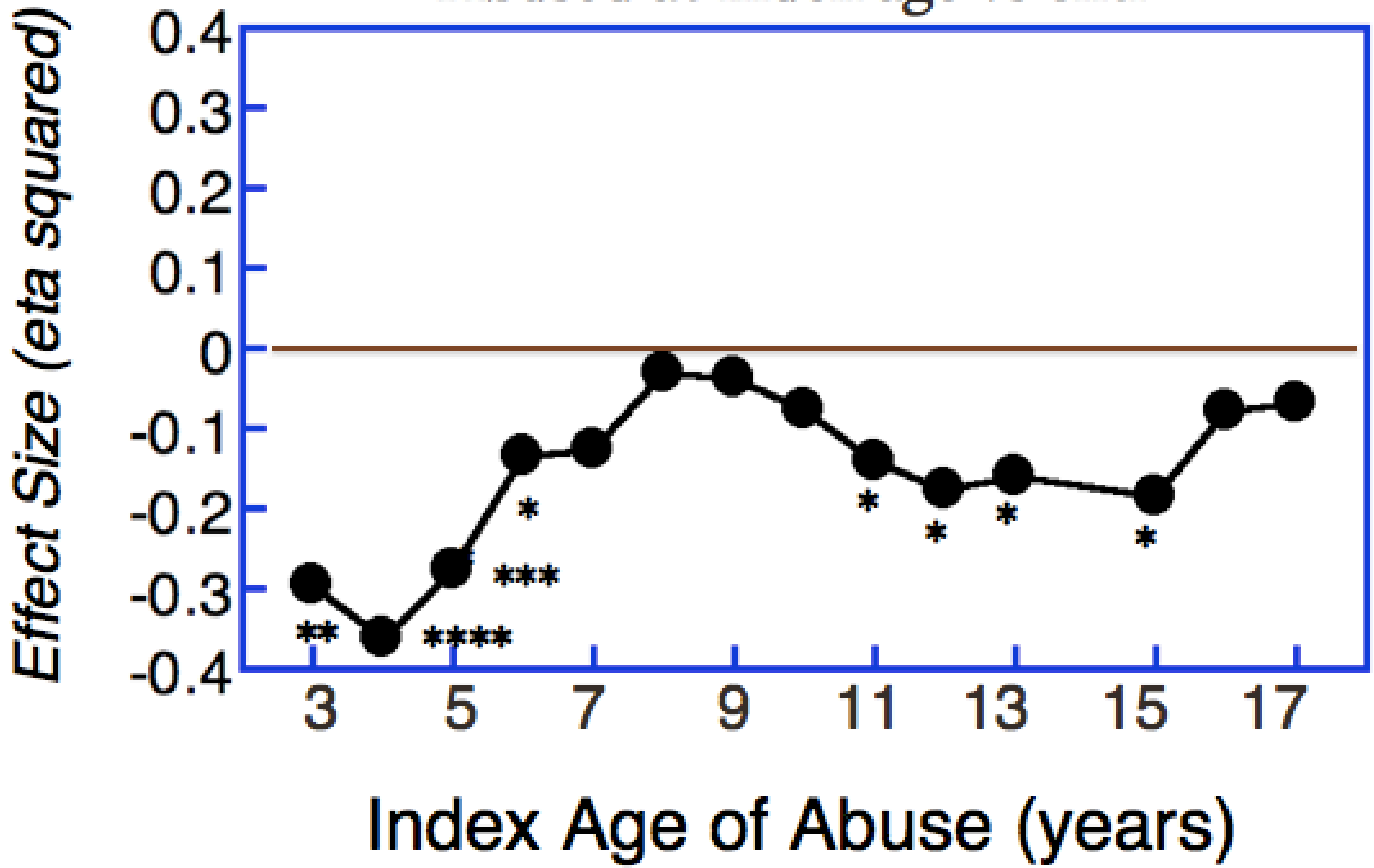


Hippocampus

Preclinical studies have demonstrated the marked vulnerability of the hippocampus to ravages of stress. This region has a protracted ontogeny, persistent postnatal neurogenesis, and a high density of stress hormone receptors. Exposure to stress can effect the development of synapses, the birth of new neurons, the dendritic branching of neurons and the survival of neurons in the hippocampus.

Hippocampus

Abused at index age vs cntl



Hippocampal volume reduced 13.2% in subjects who experienced abuse at age 4 (n=7).

Hippocampus

- Hippocampus plays a critical role in memory consolidation and retrieval.

- Hippocampus may also play a critical role in the development of depression. It appears that medications and interventions that treat depression restore or enhance hippocampal neurogenesis.

Frontal Lobes

Frontal Lobes

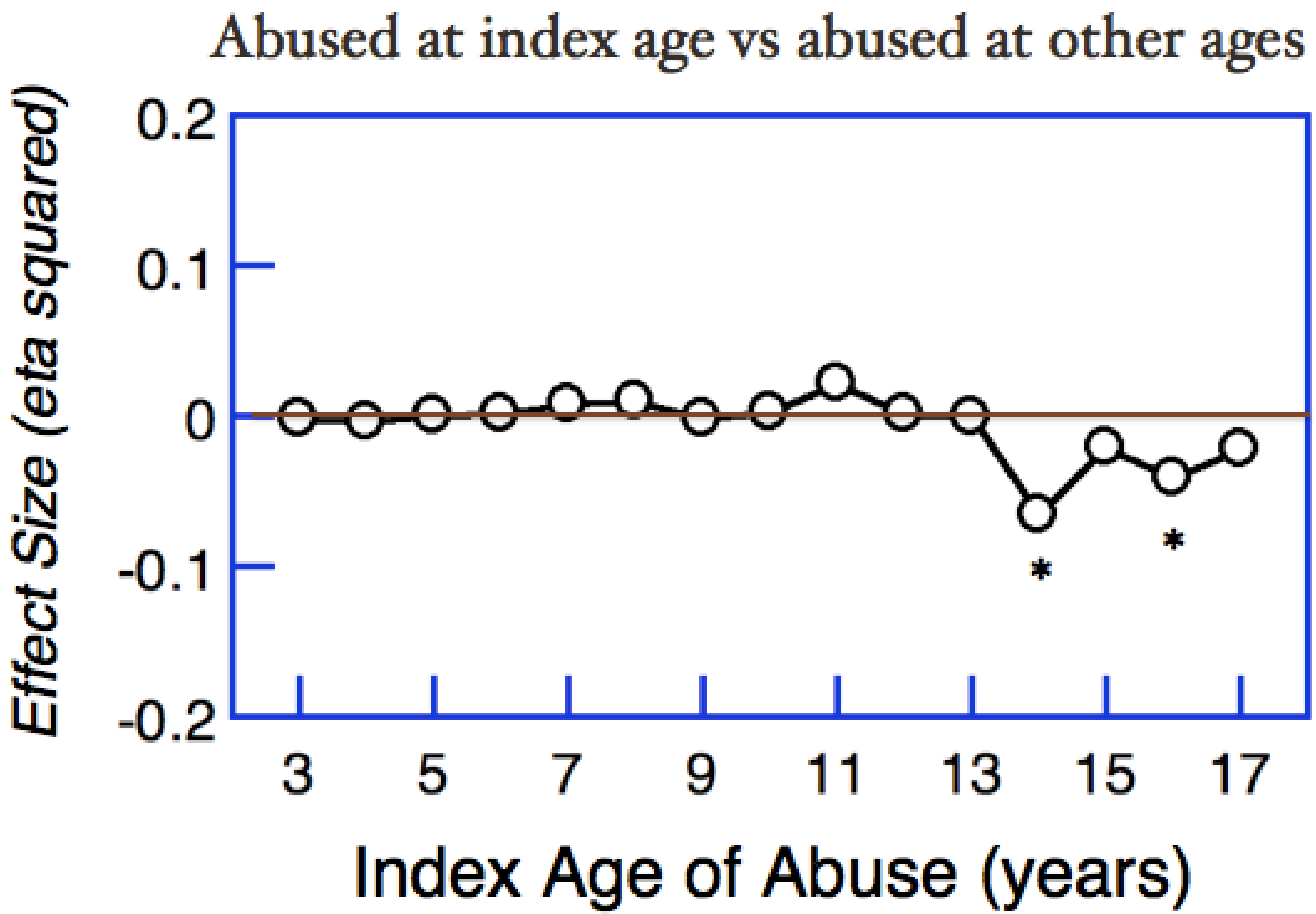
- The frontal lobes are important for attention, executive function, working memory, motivation, and behavioral inhibition

- Executive functions are cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands.

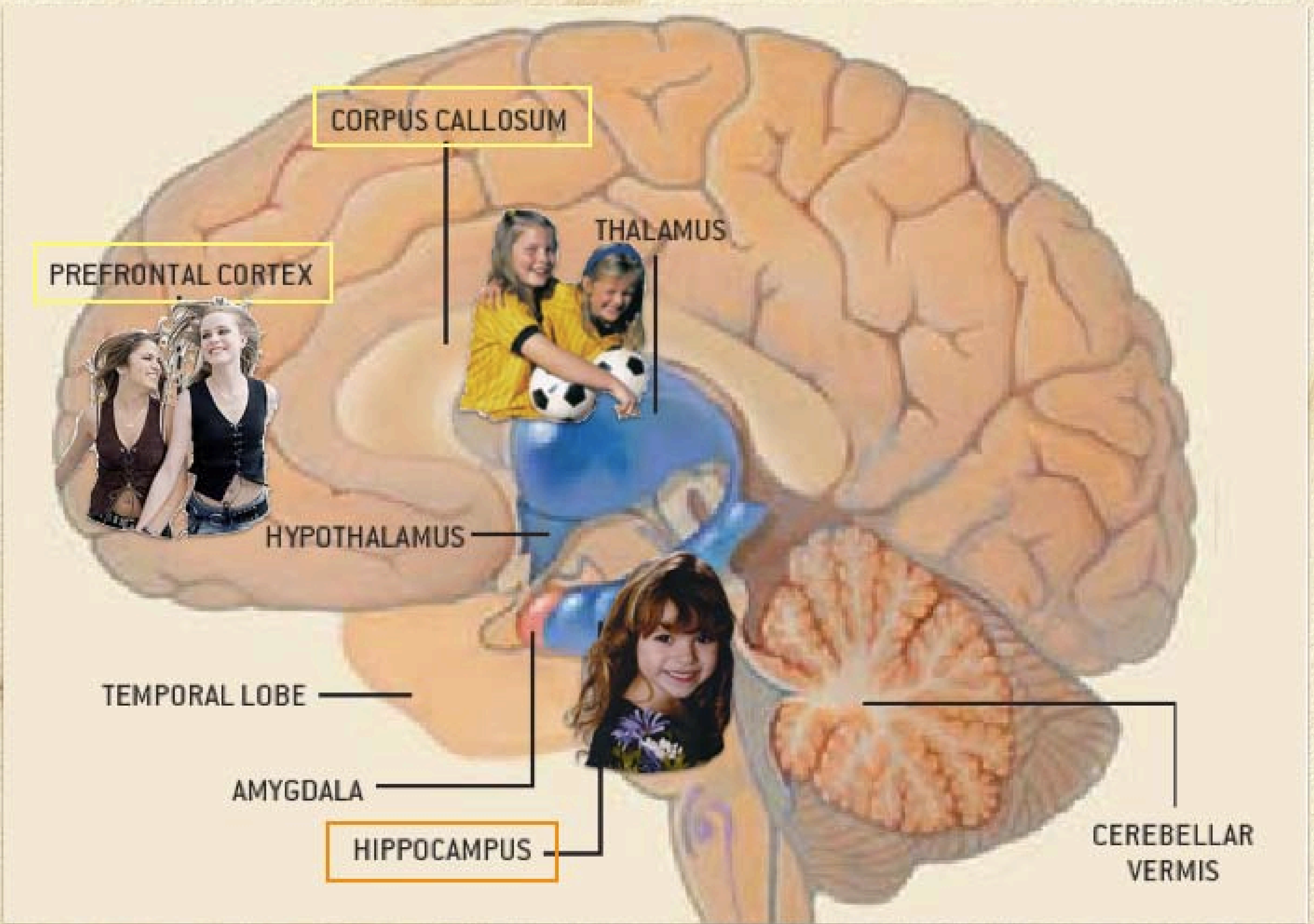
Frontal Lobes

- The frontal lobes are important in our ability to plan and anticipate outcomes (cognitive flexibility) and to direct attentional resources to meet the demands of non-routine events.
- The frontal lobes are important in self-monitoring and self-awareness - necessary for appropriateness of behavior and behavioral flexibility

Prefrontal Cortex



PFC GMV reduced 5.8% in subjects who experienced abuse at age 14 (n=4).


CORPUS CALLOSUM
THALAMUS
PREFRONTAL CORTEX
HYPOTHALAMUS
TEMPORAL LOBE
AMYGDALA
HIPPOCAMPUS
CEREBELLAR
VERMIS

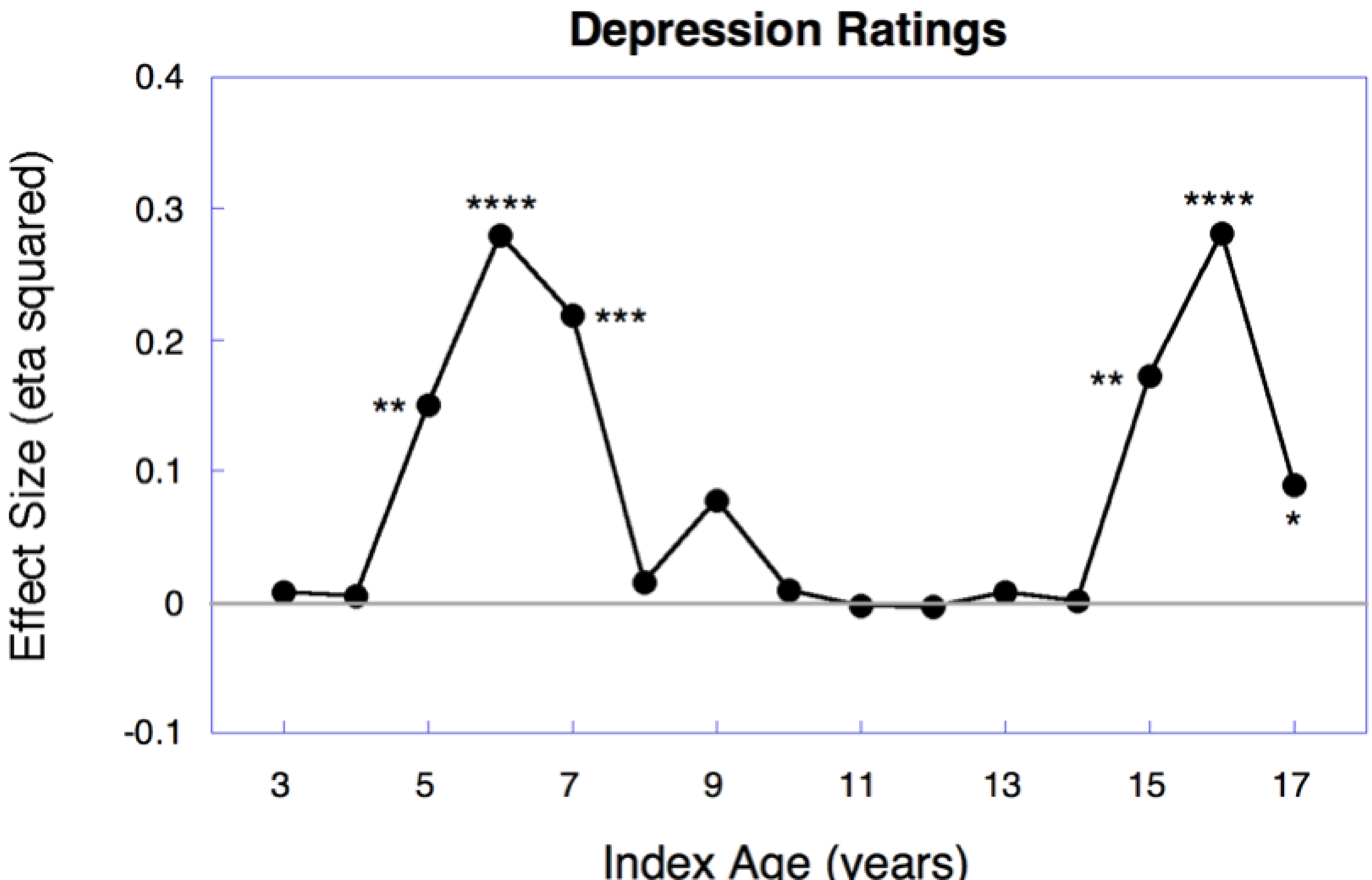
Depression Associated with Trauma/Loss

Depression

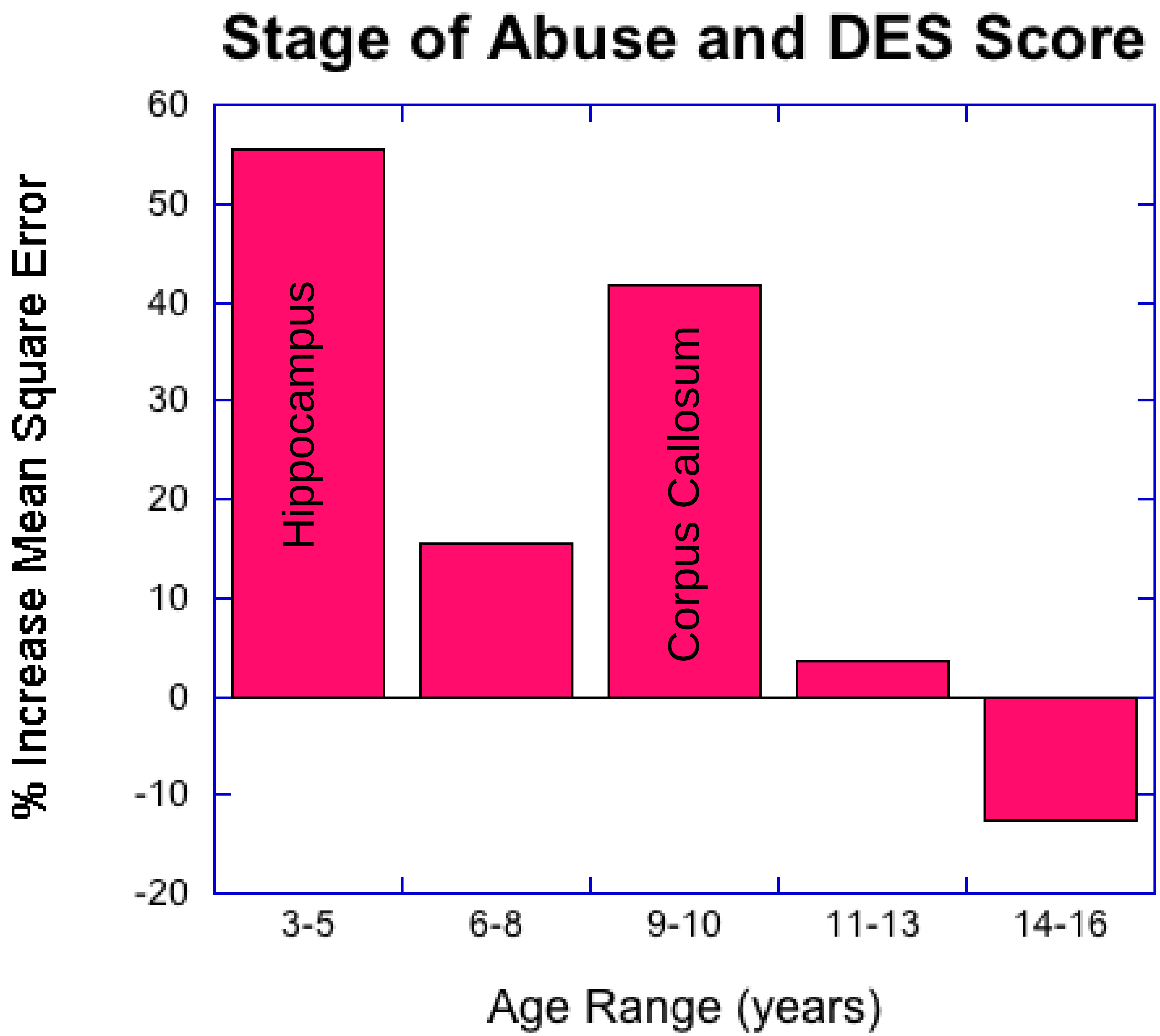
- Reduction in both prefrontal cortex and hippocampal volume have been reported in subjects with depression.

- Depression is the most common adult psychiatric consequence of exposure to childhood sexual abuse.

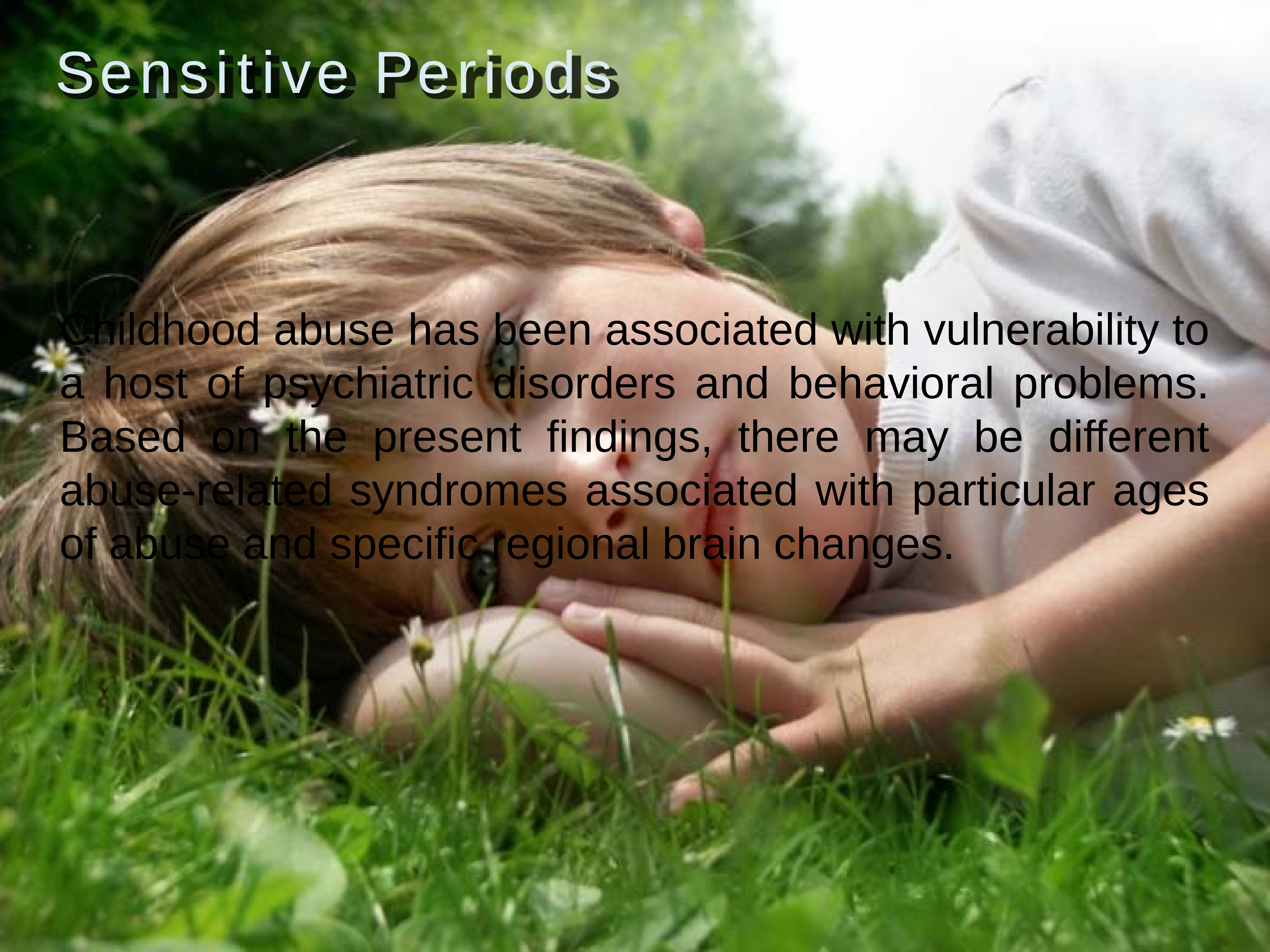
- Do young adults with exposure to CSA during hippocampal or prefrontal cortex sensitive periods have higher ratings of depression?


Depression Ratings
Effect Size (eta squared)
0.4
0.3
0.2
0.1
0
-0.1
3
5
7
9
11
13
15
17
Index Age (years)
****
***
**
****
**
*

Dissociation and Sexual Abuse



Sensitive Periods

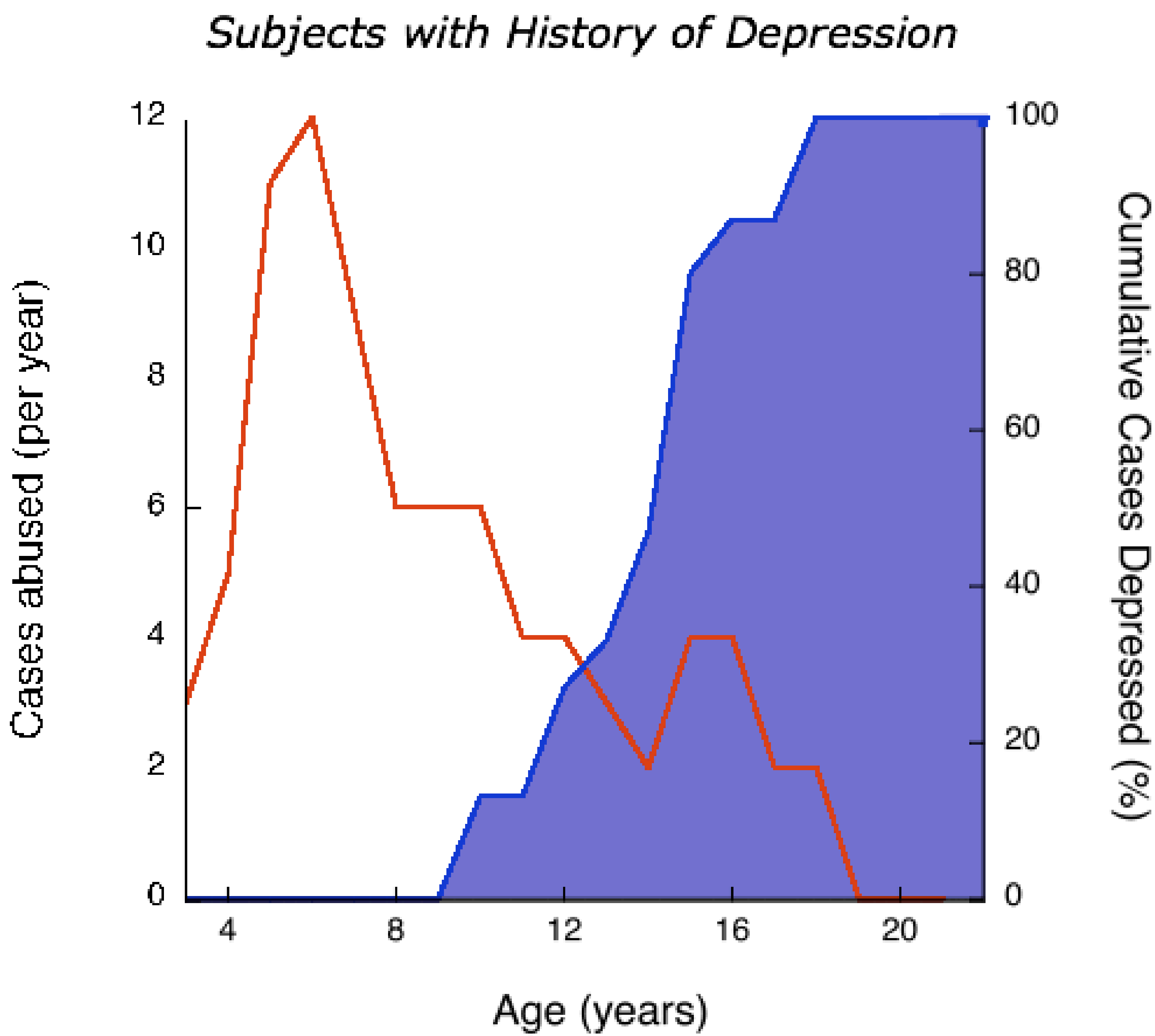


Childhood abuse has been associated with vulnerability to a host of psychiatric disorders and behavioral problems. Based on the present findings, there may be different abuse-related syndromes associated with particular ages of abuse and specific regional brain changes.

Windows of Opportunity

Identifying sensitive periods may also provide insight into key ages at which stimulation or environmental enrichment may optimally benefit development of specific brain regions.

Delayed Effects of Early Abuse



Teicher, M.H., Samson, J.A., Polcari, A., and Andersen, S.L. (2009) Length of time between onset of childhood sexual abuse and emergence of depression in a young adult sample: a retrospective clinical report. J Clin Psychiatry 70, 684-691

Delayed Effects of Early Stress

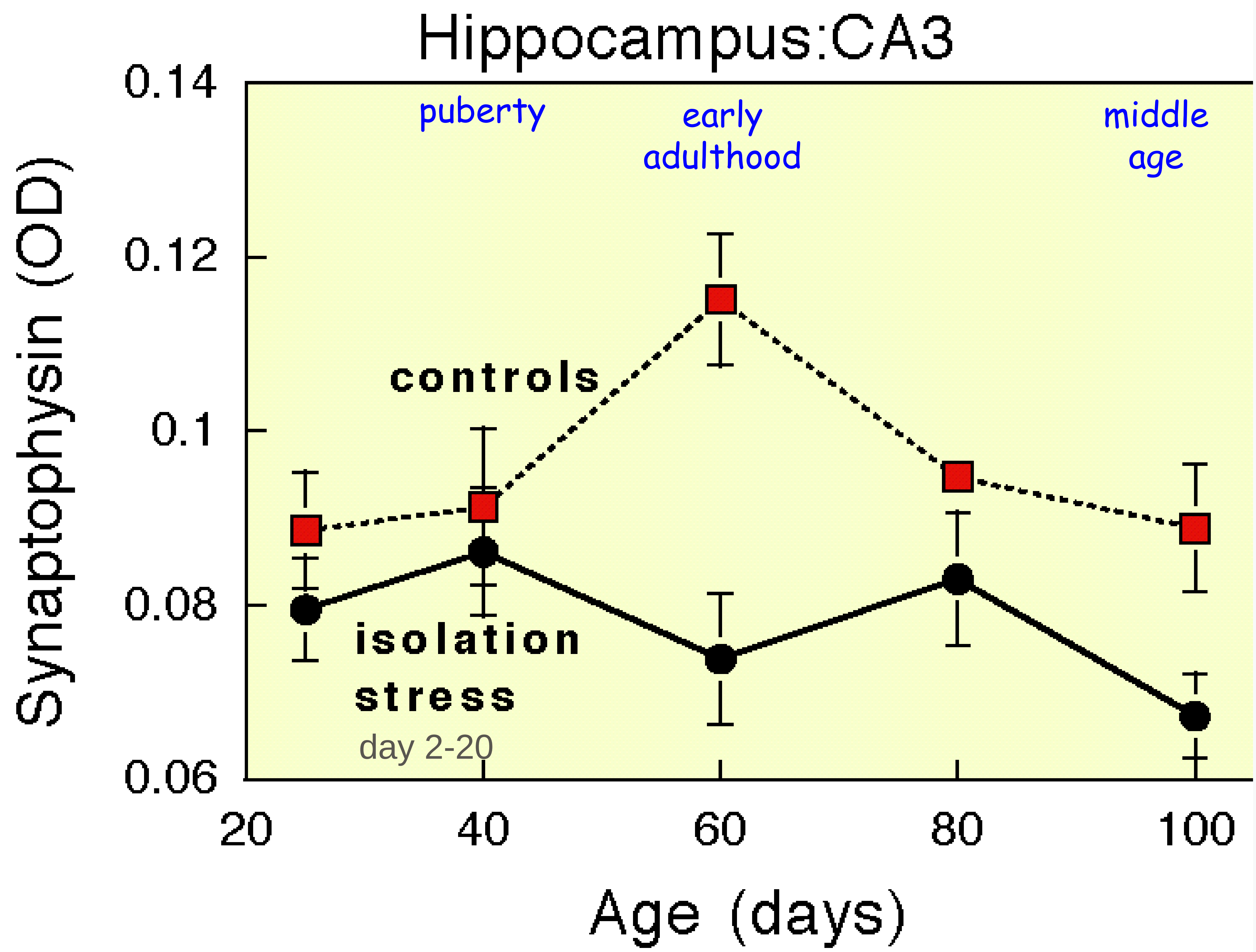
Overall, these findings are most compatible with the hypothesis that childhood exposure to sexual abuse sensitizes the individual to later emergence of depression during adolescence, and that it shifts the peak period of risk from mid-adolescence to early adolescence.

Childhood abuse leading to PTSD, Dissociative Identity Disorder, Borderline Personality Disorder, or Major Depression has been associated with reduced hippocampal size in adulthood.

Study	Groups (n)	Reduction / Side
Bremner et al 1997	PTSD (17), NL (17)	-12% L
Stein 1997	PTSD/DID (21) NL (21)	-5% L
Dreissen et al 2000	Borderline (21), NL(21)	-16% L,R
Vythilingam et al, 2002	Depressed (21), NL (14)	-15% L
Vermetten et al, 2006	DID (15), NL (23)	19.2% L,R
Andersen et al, 2008	Abused (26), NL (17)	6.8% L,R

Childhood abuse leading to PTSD has not been associated with reduced hippocampal size in childhood.

Study	Groups (n)	Result
De Bellis et al 1999	PTSD (44), NL (61)	NS
Carrion et al 2001	PTSD Sx (24), Hx NL (24)	NS
De Bellis et al 2002	PTSD (28), NL (66)	NS



Andersen, S.L., and Teicher, M.H. (2004) Delayed effects of early stress on hippocampal development. Neuropsychopharmacology 29, 1988-1993

Does the nature of the maltreatment matter?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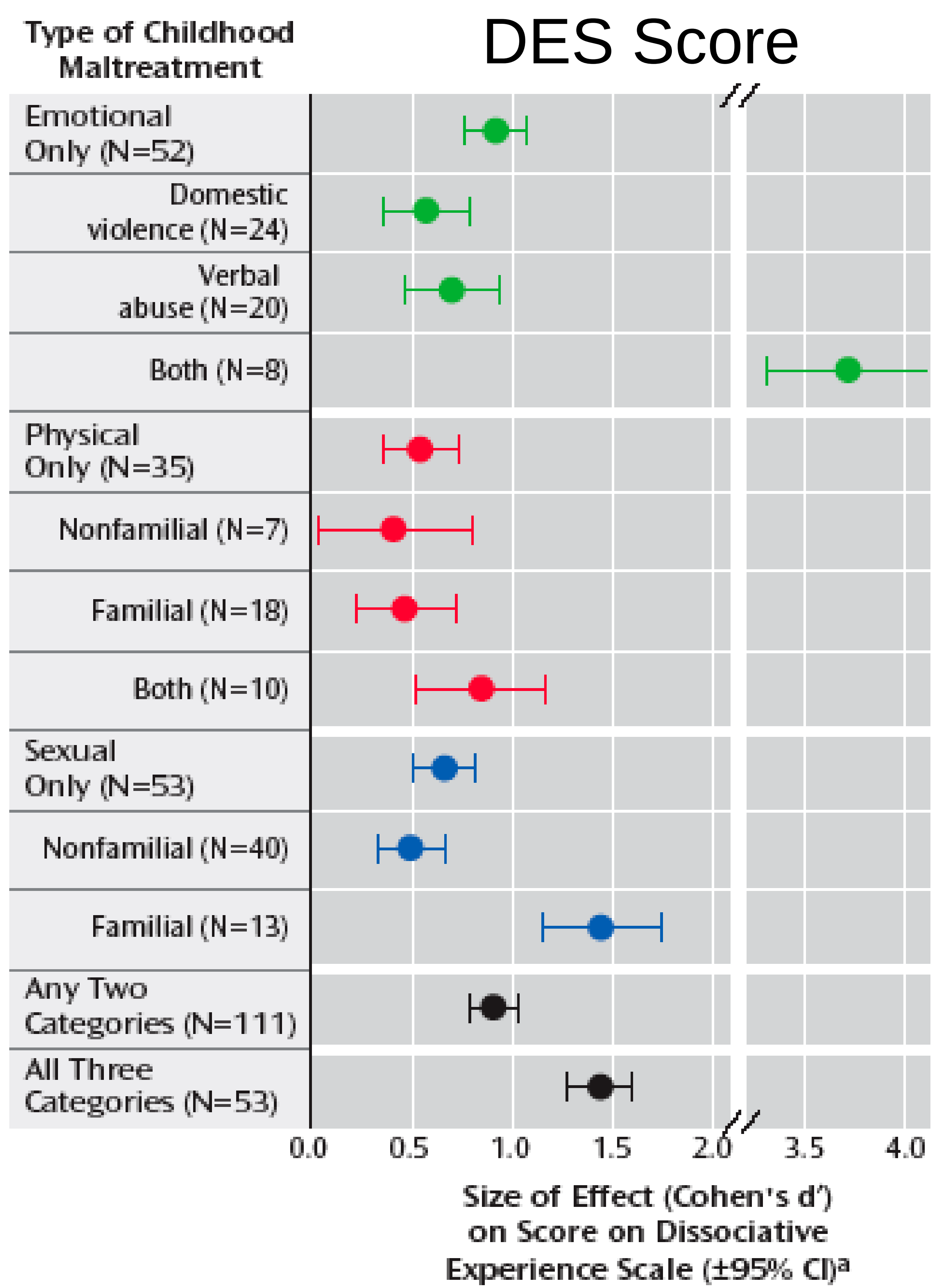
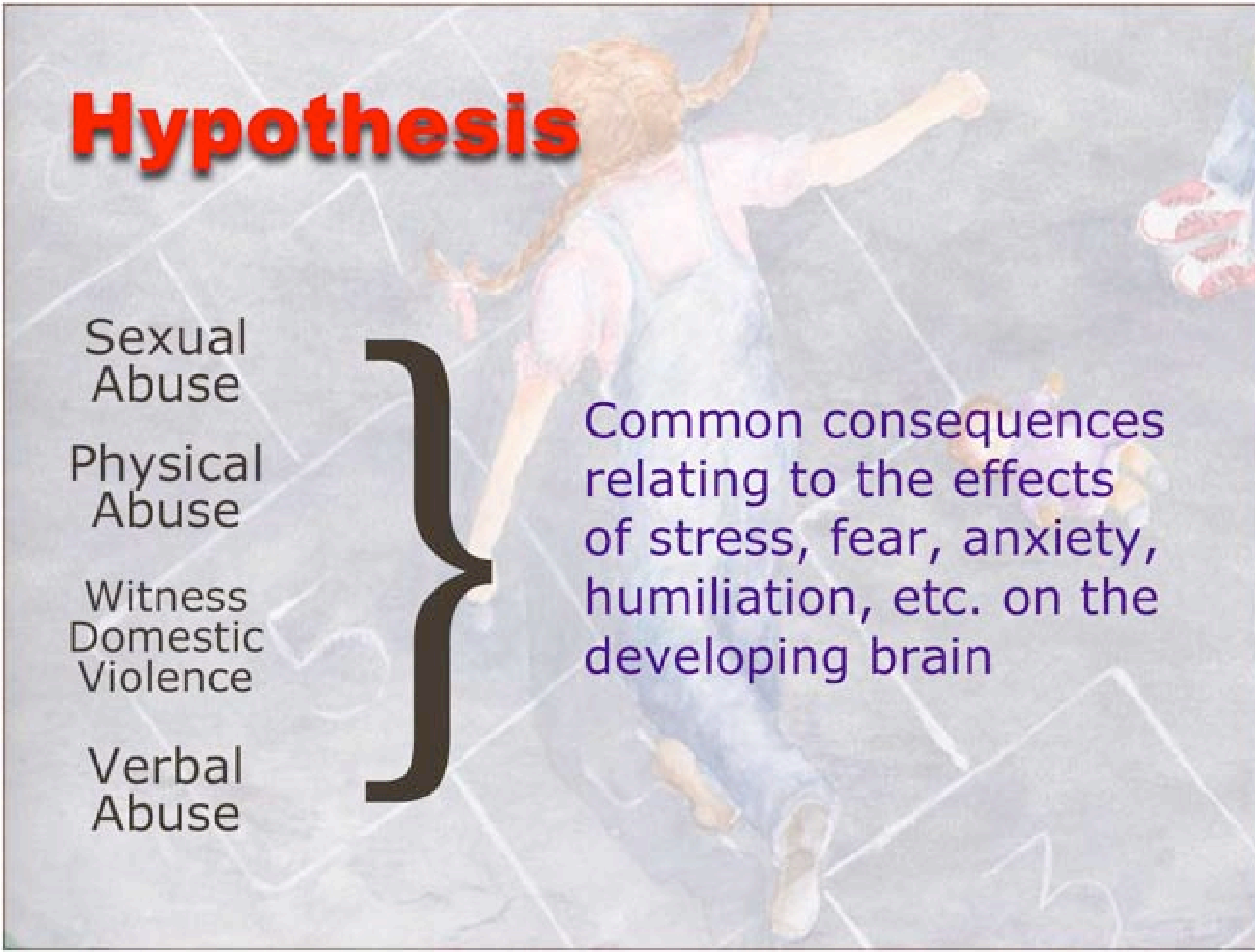
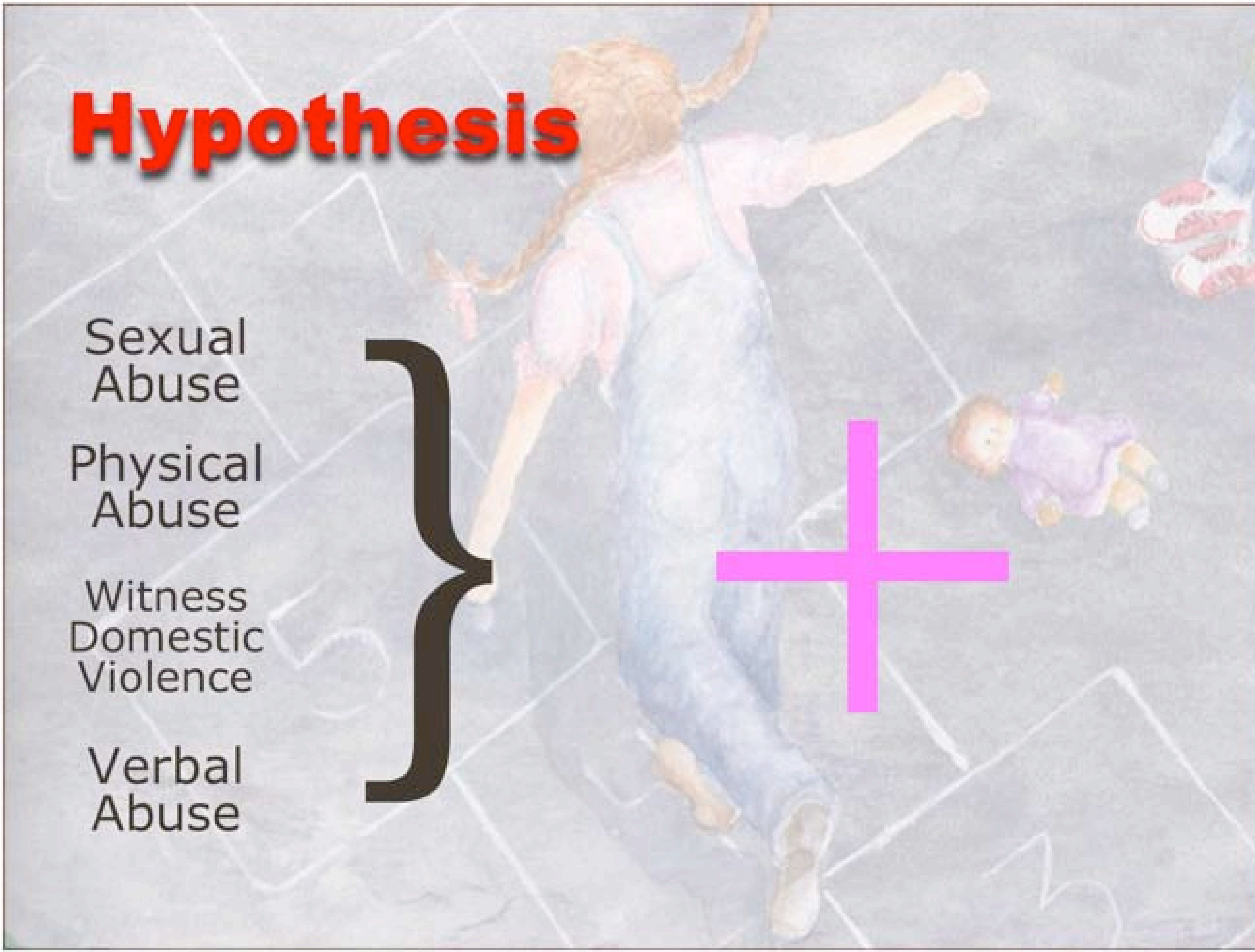
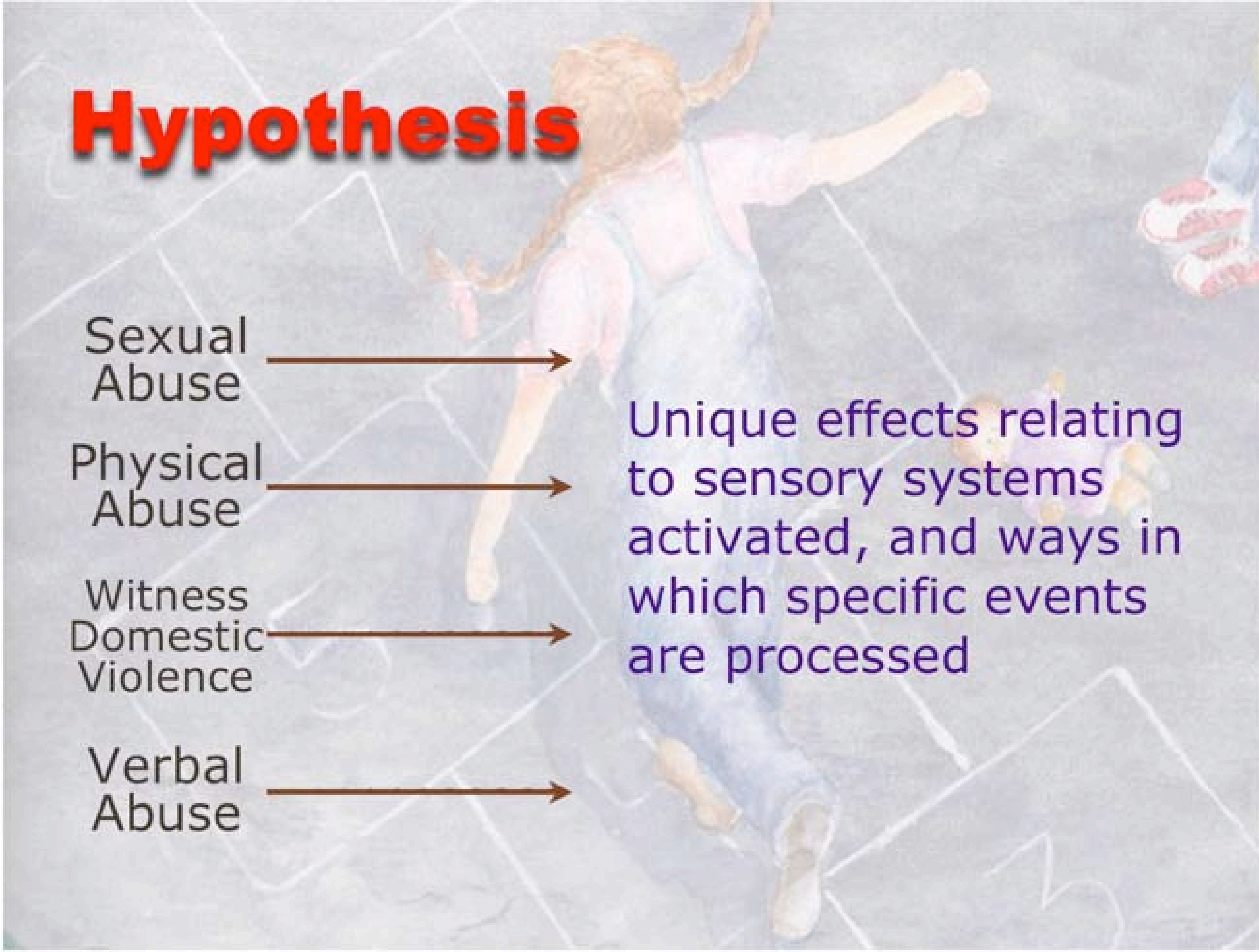
AMERICAN PSYCHIATRIC ASSOCIATION
ajp.psychiatryonline.org


DES Score
Type of Childhood Maltreatment
Emotional Only (N=52)
Domestic violence (N=24)
Verbal abuse (N=20)
Both (N=8)
Physical Only (N=35)
Nonfamilial (N=7)
Familial (N=18)
Both (N=10)
Sexual Only (N=53)
Nonfamilial (N=40)
Familial (N=13)
Any Two Categories (N=111)
All Three Categories (N=53)
0.0
0.5
1.0
1.5
2.0
3.5
4.0
Size of Effect (Cohen's d') on Score on Dissociative Experience Scale (±95% CI)a


Hypothesis
Sexual Abuse
Physical Abuse
Witness Domestic Violence
Verbal Abuse
Common consequences relating to the effects of stress, fear, anxiety, humiliation, etc. on the developing brain


Hypothesis
Sexual Abuse
Physical Abuse
Witness Domestic Violence
Verbal Abuse
+


Hypothesis
Sexual Abuse
Physical Abuse
Witness Domestic Violence
Verbal Abuse
Unique effects relating to sensory systems activated, and ways in which specific events are processed

Study Design

Goal: Recruit ideal groups of subjects to test hypotheses regarding the relationship between early adverse experience and brain development.

Study Design

Ideal: As free as possible from confounding factors that can affect brain development.

No head trauma, neurological disorders, perinatal problems, maternal substance abuse, or exposure to any other form of trauma (MVA, natural disasters, near drownings, animal attacks, etc.)

Study Design

RO1 1 (1999-2004)

Childhood Sexual Abuse

RO1 2-4 (2003-09)

Verbal Abuse
Witnessing Domestic Violence
Harsh Corporal Punishment
Trauma (PA/SA)

Study Design

Advertise Aggressively

RO1 1 (1999-2004)	RO1 2-4 (2003-09)
"Psychiatric Research"	"Memories of Childhood"
18-22 years	18-25 years
right handed	right handed
unmedicated	unmedicated

Study Design

Collect Extensive Information

RO1 1 (1999-2004)	RO1 2-4 (2003-09)
Mailed booklets 350 items	Online enrollment 2342 items
n = 564	n = 1663

Study Design

Prescreen, Invite & Interview

RO1 1 (1999-2004)

SCID Axis I
DIB
SCID-D
TAI

RO1 2-4 (2003-09)

SCID Axis I
SCID Axis II
TAI

Study Design

Neuroimaging

RO1 1 (1999-2004)
GE 1.5T Scanner
T1 volumetric morph
T2-relaxometry
Dynamic Susceptibility Contrast

(n=60)

RO1 2-4 (2003-09)
Siemens 3T Trio
T1 volumetric morph
T2-relaxometry
Diffusion Tensor Imaging
Functional Connectivity
Spectroscopy
MPH-challenge

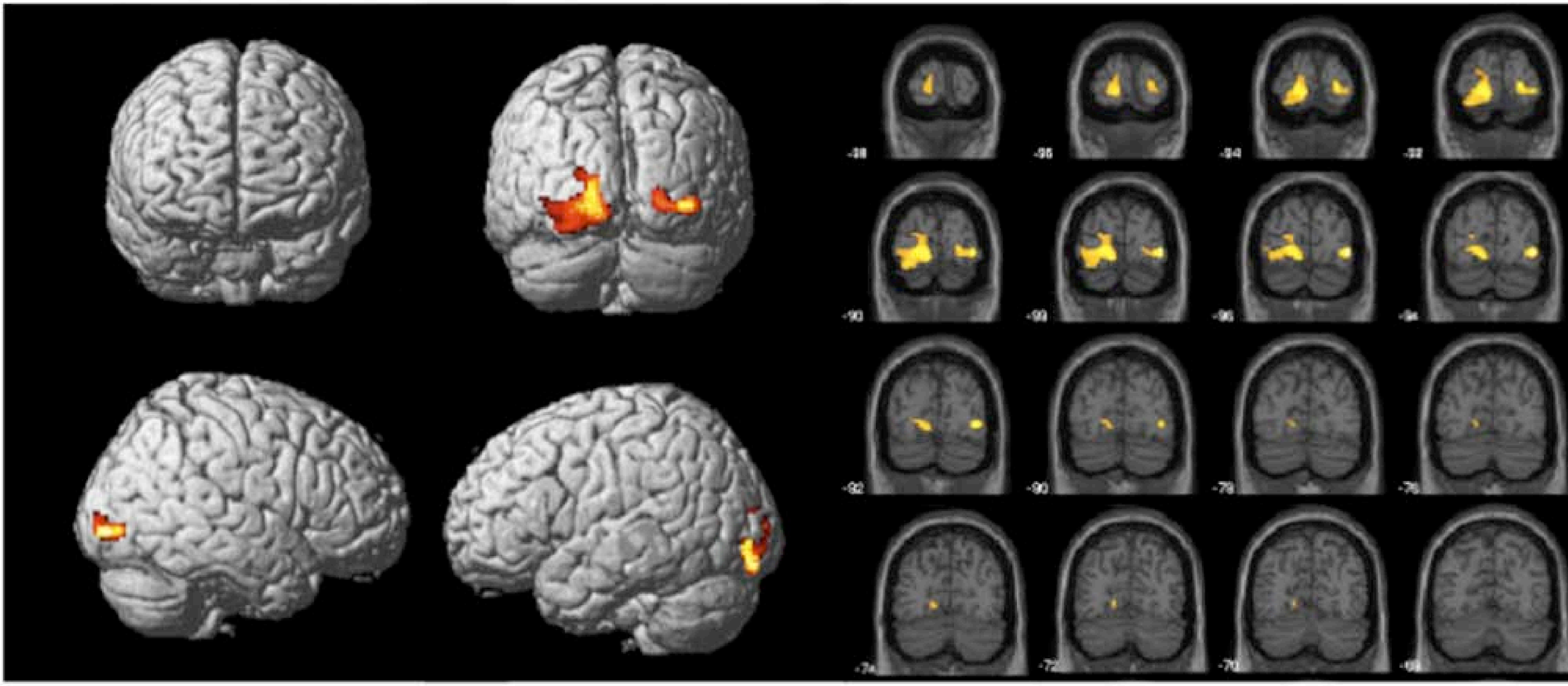
(n=193)

Childhood Sexual Abuse

Voxel-Based Morphometry

VBM is a fully automated whole-brain morphometric technique that detects regional structural differences in gray matter volume between groups on a voxel-by-voxel basis.

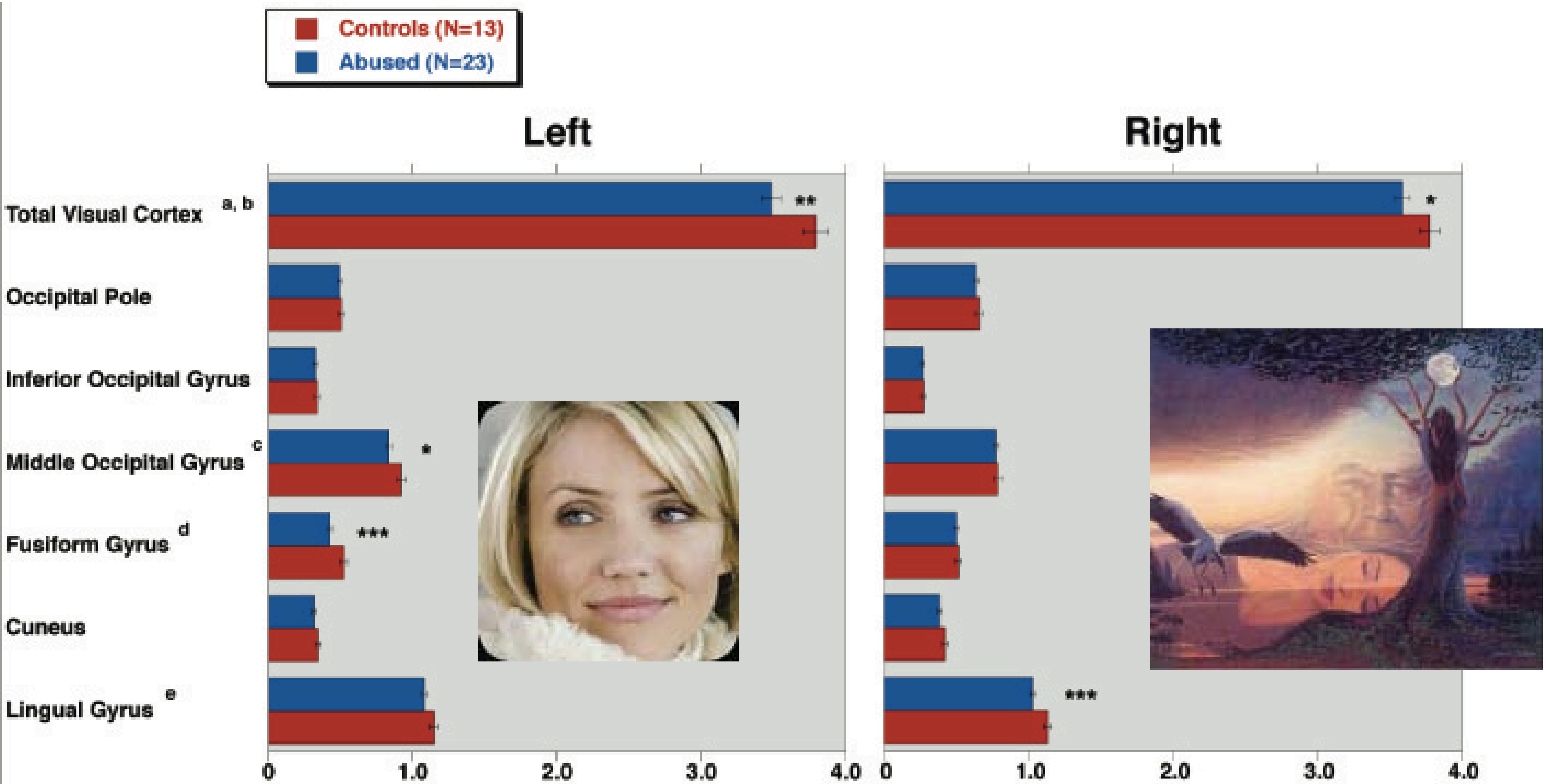
Repeated Exposure to Childhood Sexual Abuse



Reduces gray matter volume 14.1% in left primary and secondary visual cortex.

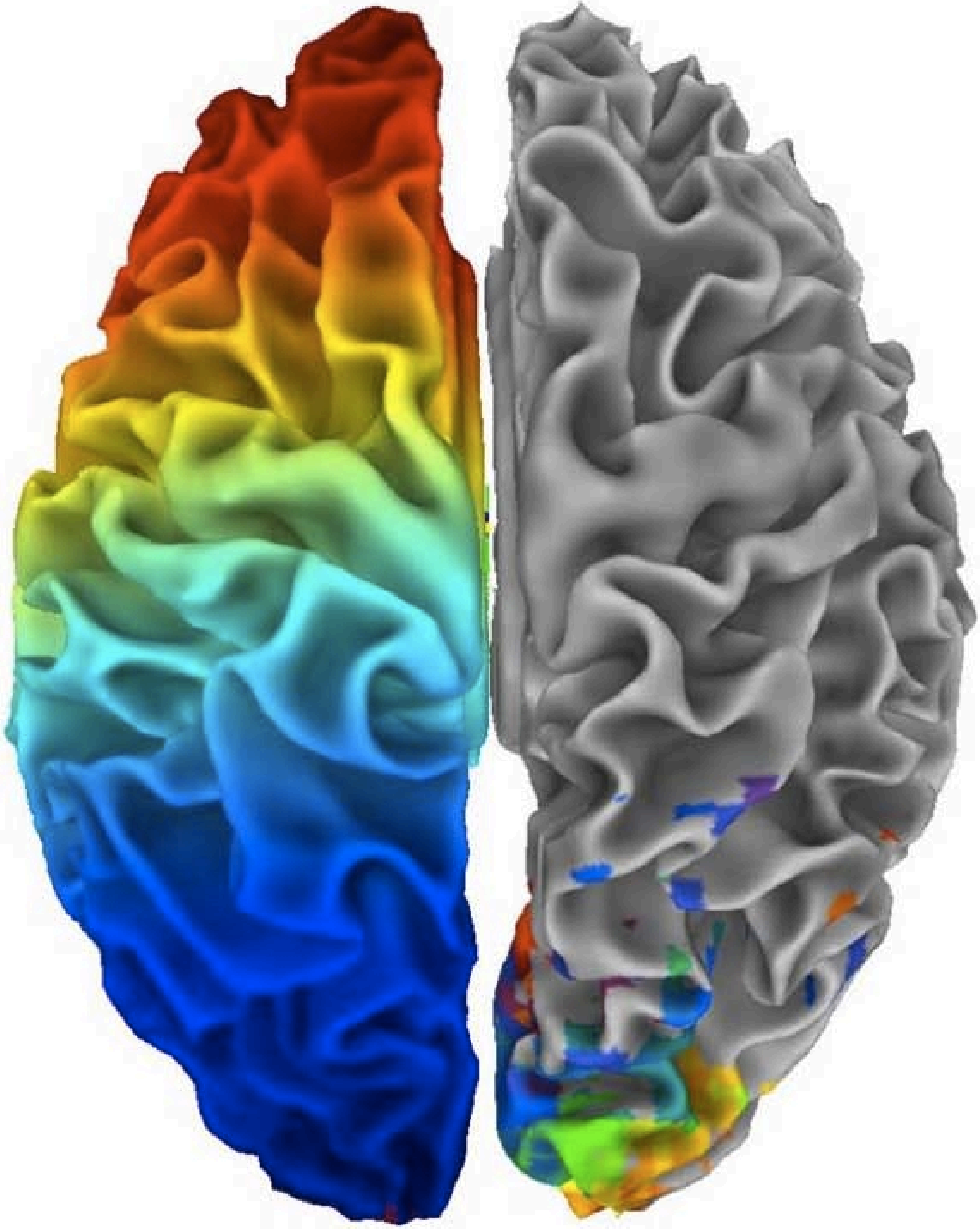
Tomoda, A., Navalta, C.P., Polcari, A., Sadato, N., and Teicher, M.H. (2009) Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. Biol Psychiatry 66, 642-648

Cortical Surface-Based Analysis



FreeSurfer

Cortical Surface Analysis



Cortical Thickness

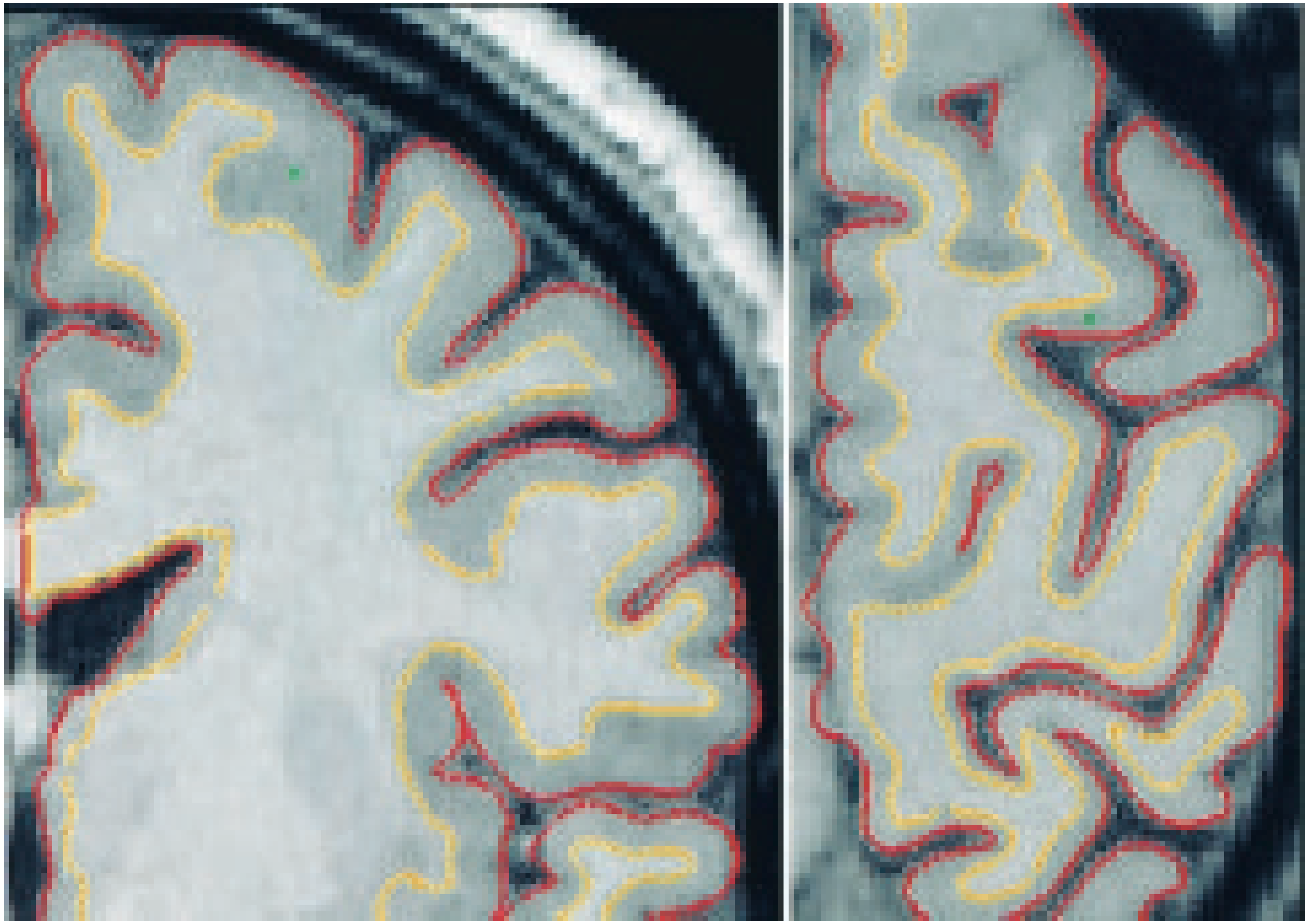


Fig. 1. Coronal (Left) and horizontal (Right) slices of the left hemisphere with gray/white (yellow) and pial (red) surfaces overlaid. The green crosses indicate a point at which using the coronal view only would result in a dramatic overestimation of the thickness of the cortex.

Orbital Frontal Cortex

- The orbitofrontal cortex (OFC) is a region of association cortex of the human brain involved in cognitive processes such as decision making.
- In particular, the human OFC is thought to regulate planning behavior associated with sensitivity to reward and punishment.

Bechara, A.; Damasio, A. R.; Damasio H. & Anderson, S.W. (1994) "Insensitivity to future consequences following damage to human prefrontal cortex". *Cognition* **50**: 7-15

Precuneus

- The interconnected medial prefrontal regions and the posteromedial parietal cortex have been proposed to represent a network through which personal identity and past personal experiences are interlinked with one another, with the net interactions permitting us to move between representation and awareness of self.

Andrea E. Cavanna and Michael R. Trimble (2006). The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129: 564-583.

Precuneus

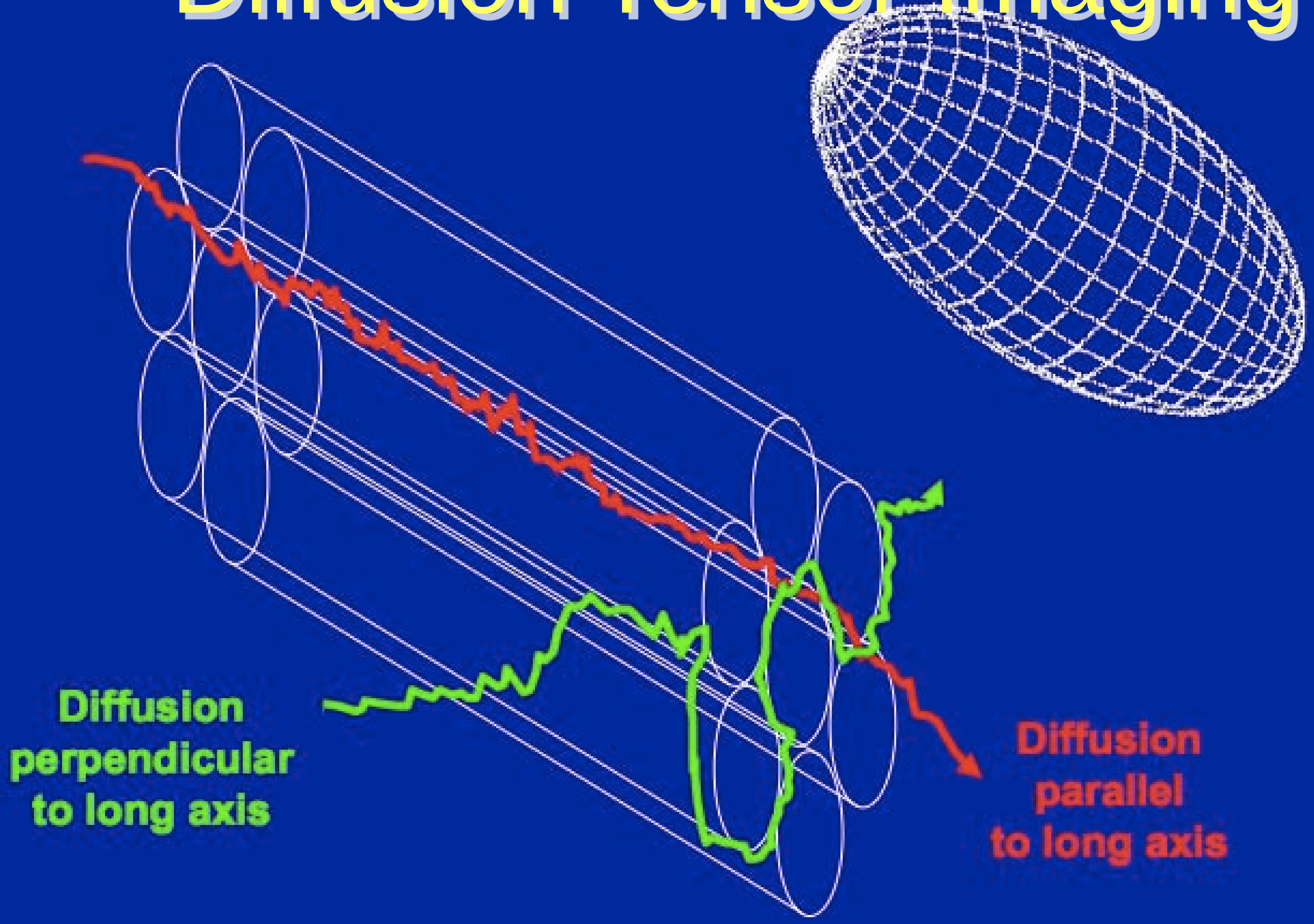
- Autobiographical memory
- Self versus non-self representation
- Self-referential judgements
- First- versus third-person perspective
- Perceived agency
- Mind reading/social cognition.

Verbal Abuse
*!#$^&@

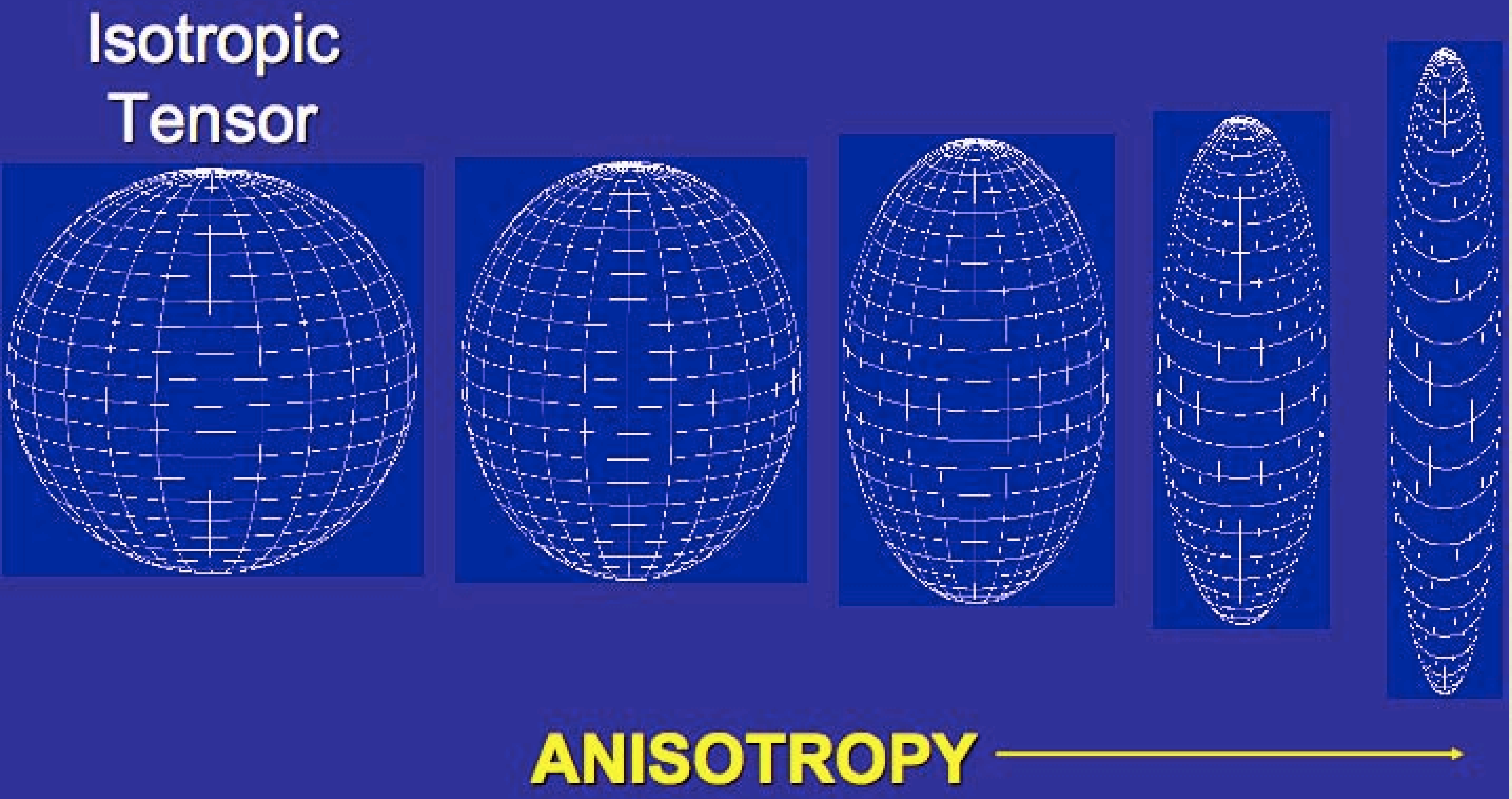
Verbal Abuse

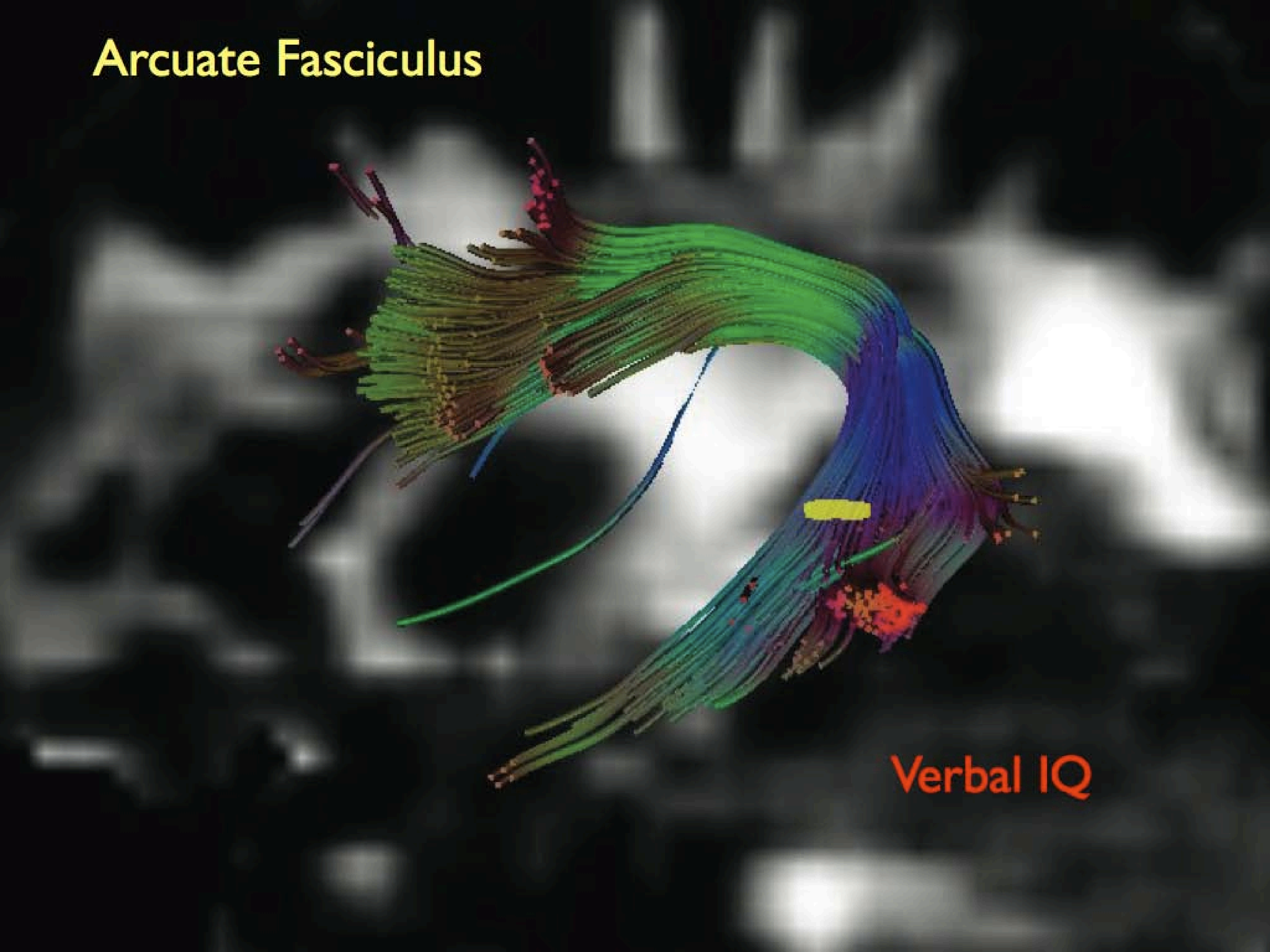
*!#$^&@

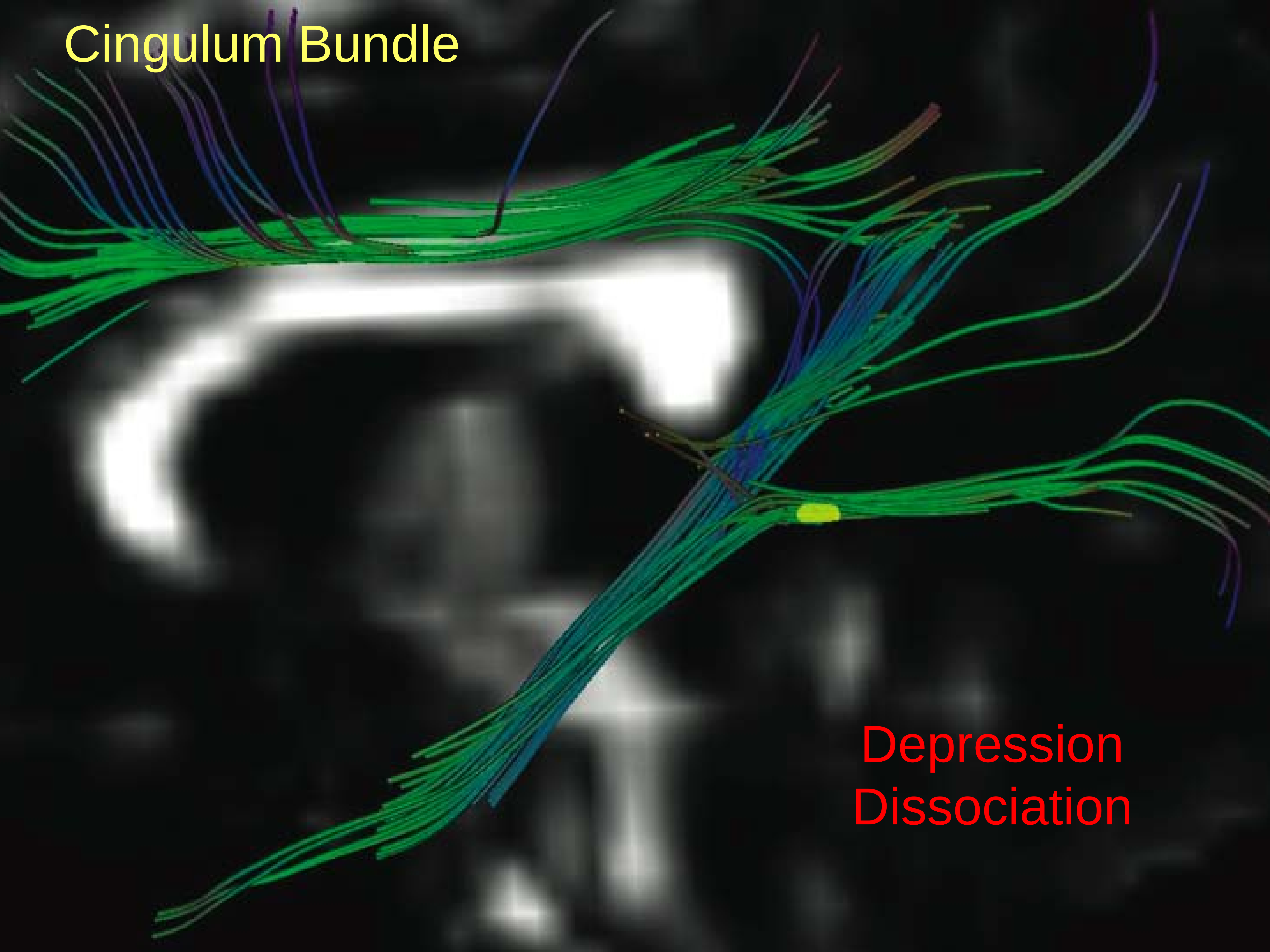
Diffusion Tensor Imaging

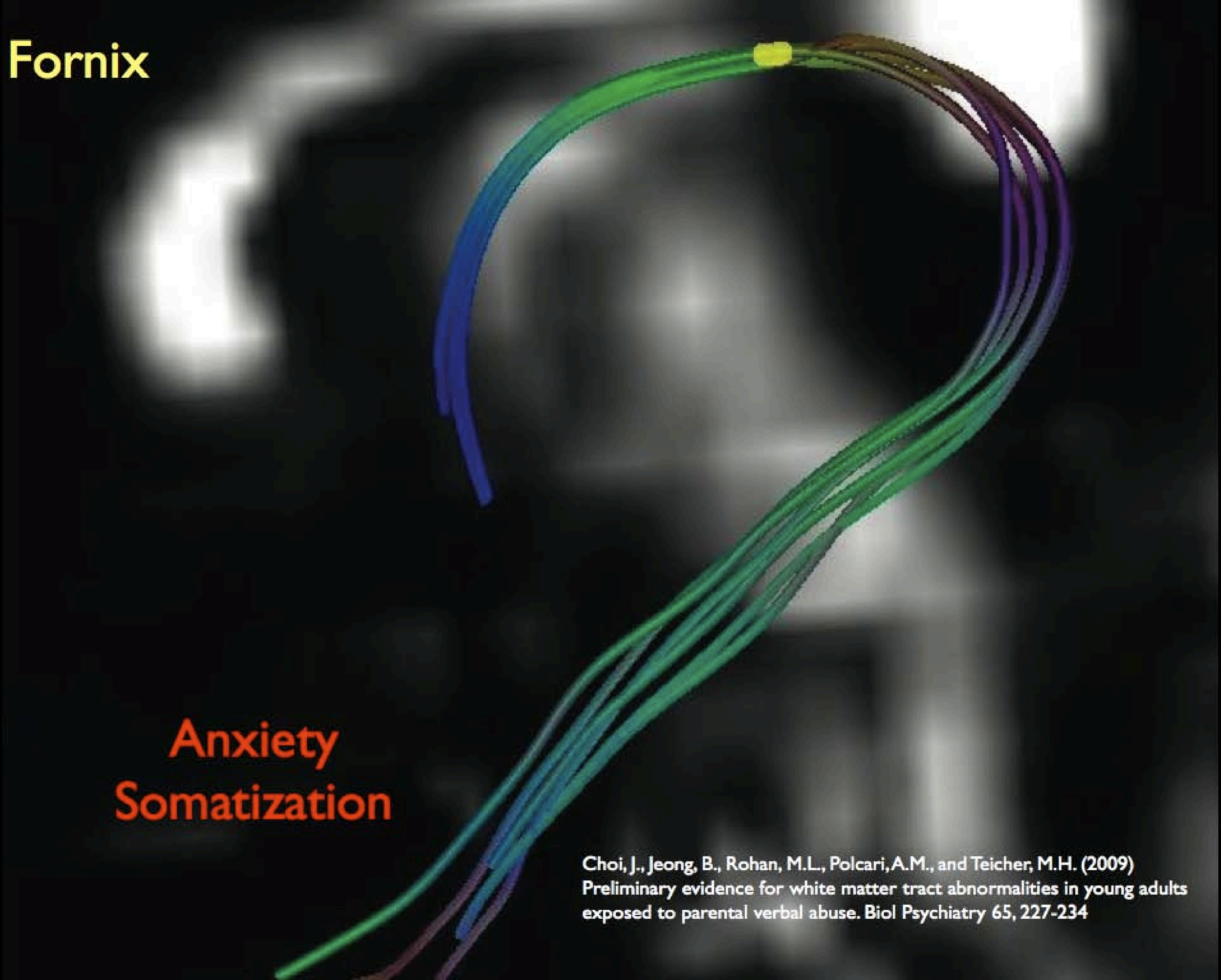


Diffusion Tensor Imaging

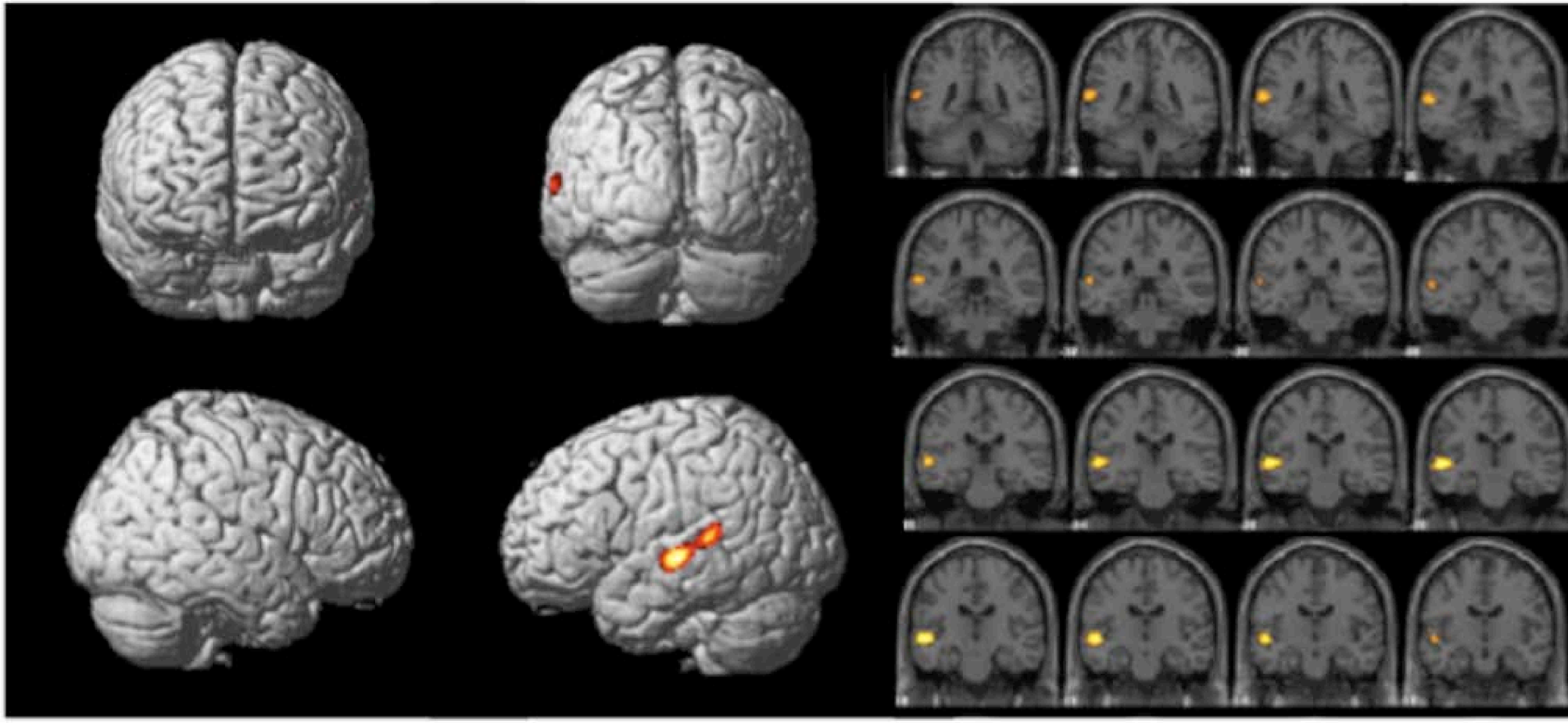



Arcuate Fasciculus
Verbal IQ


Cingulum Bundle
Depression
Dissociation


Fornix
Anxiety
Somatization
Choi, J., Jeong, B., Rohan, M.L., Polcari, A.M., and Teicher, M.H. (2009)
Preliminary evidence for white matter tract abnormalities in young adults
exposed to parental verbal abuse. Biol Psychiatry 65, 227-234

Verbal Abuse: Voxel-based morphometry

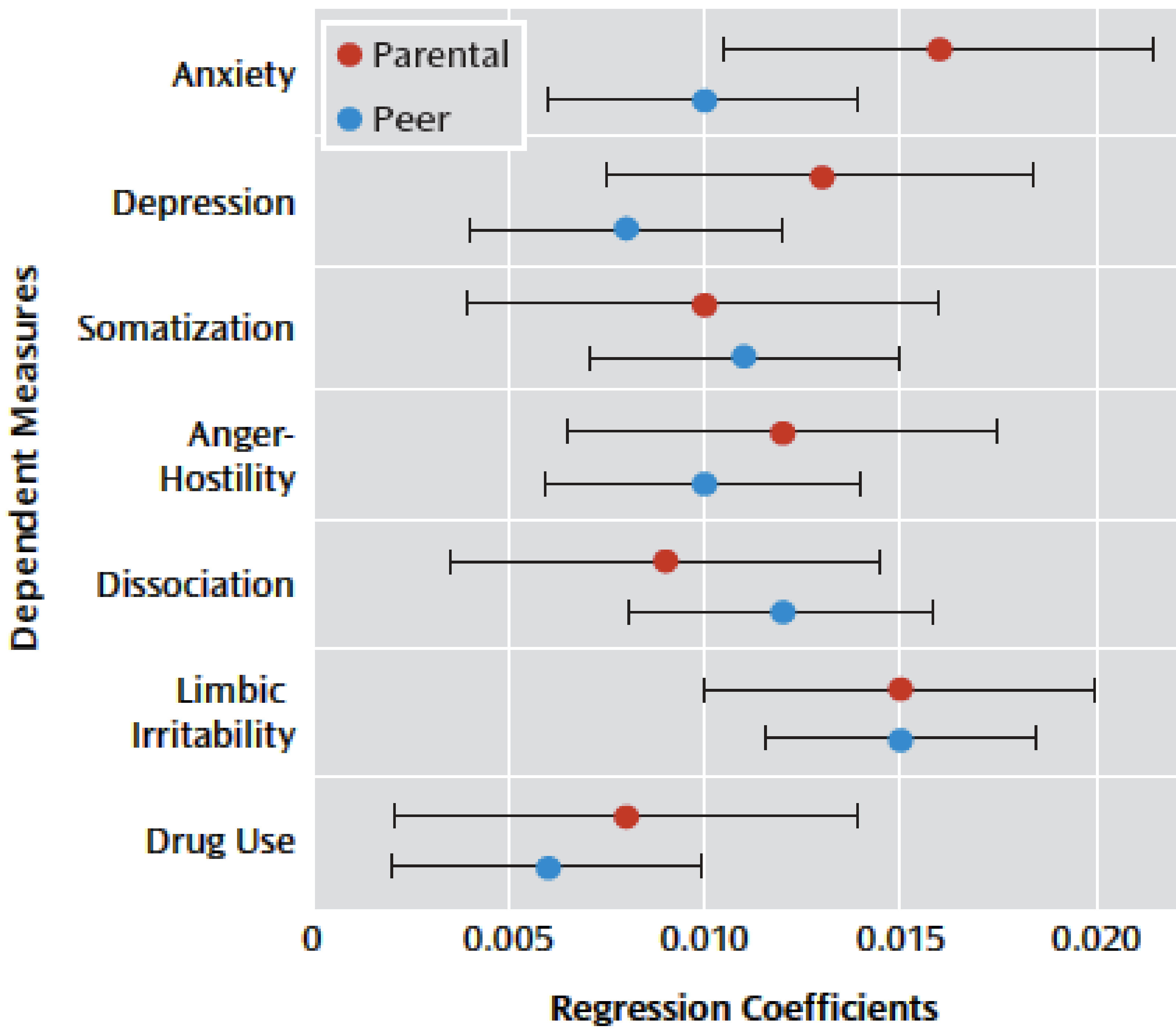


Increased gray matter volume
left superior temporal gyrus

Peer Verbal Abuse

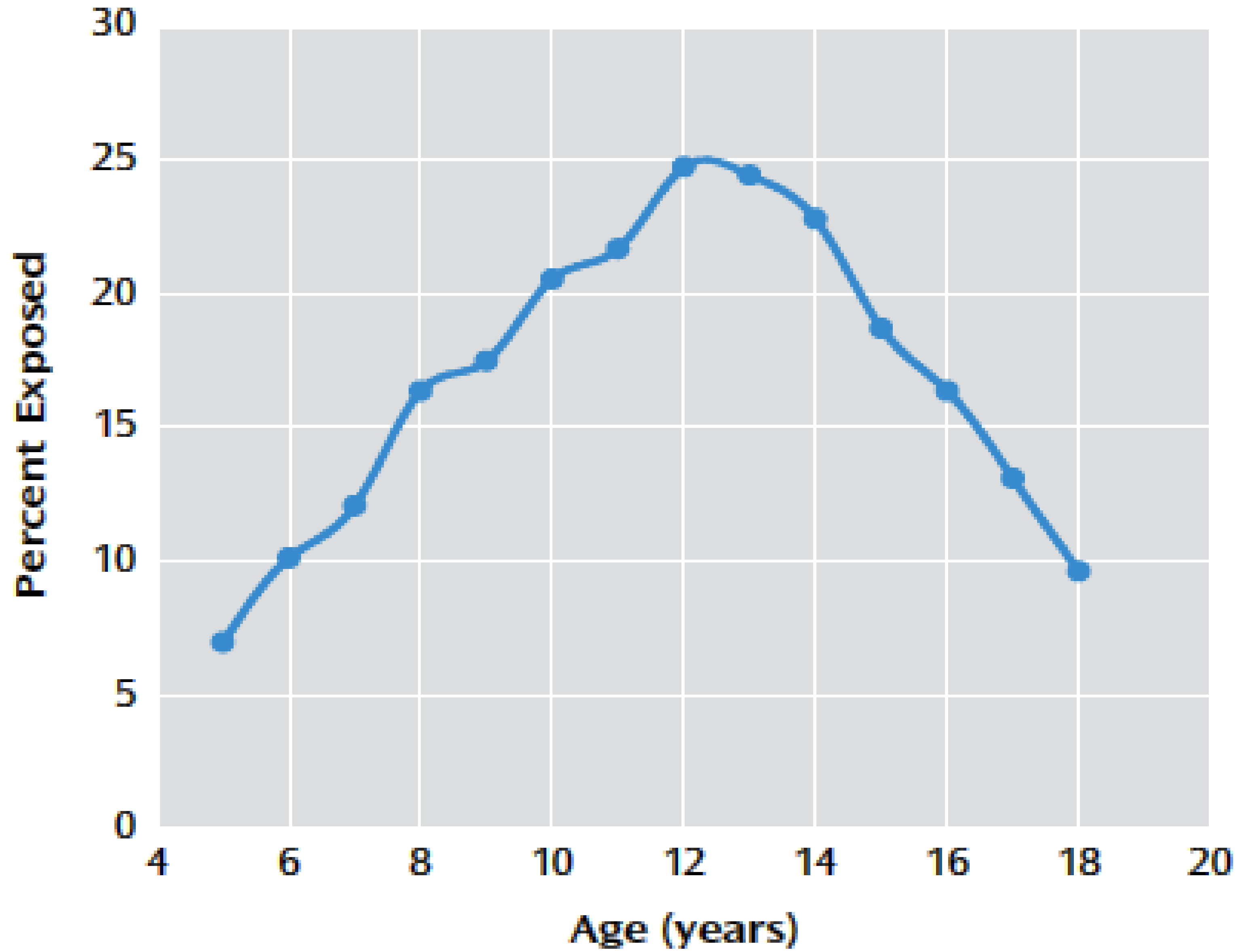
Peer Verbal Abuse

FIGURE 3. Effect of Exposure to Parental Verbal Abuse and Peer Verbal Abuse on Symptom Ratings and Drug Use in 848 Young Adults[a]

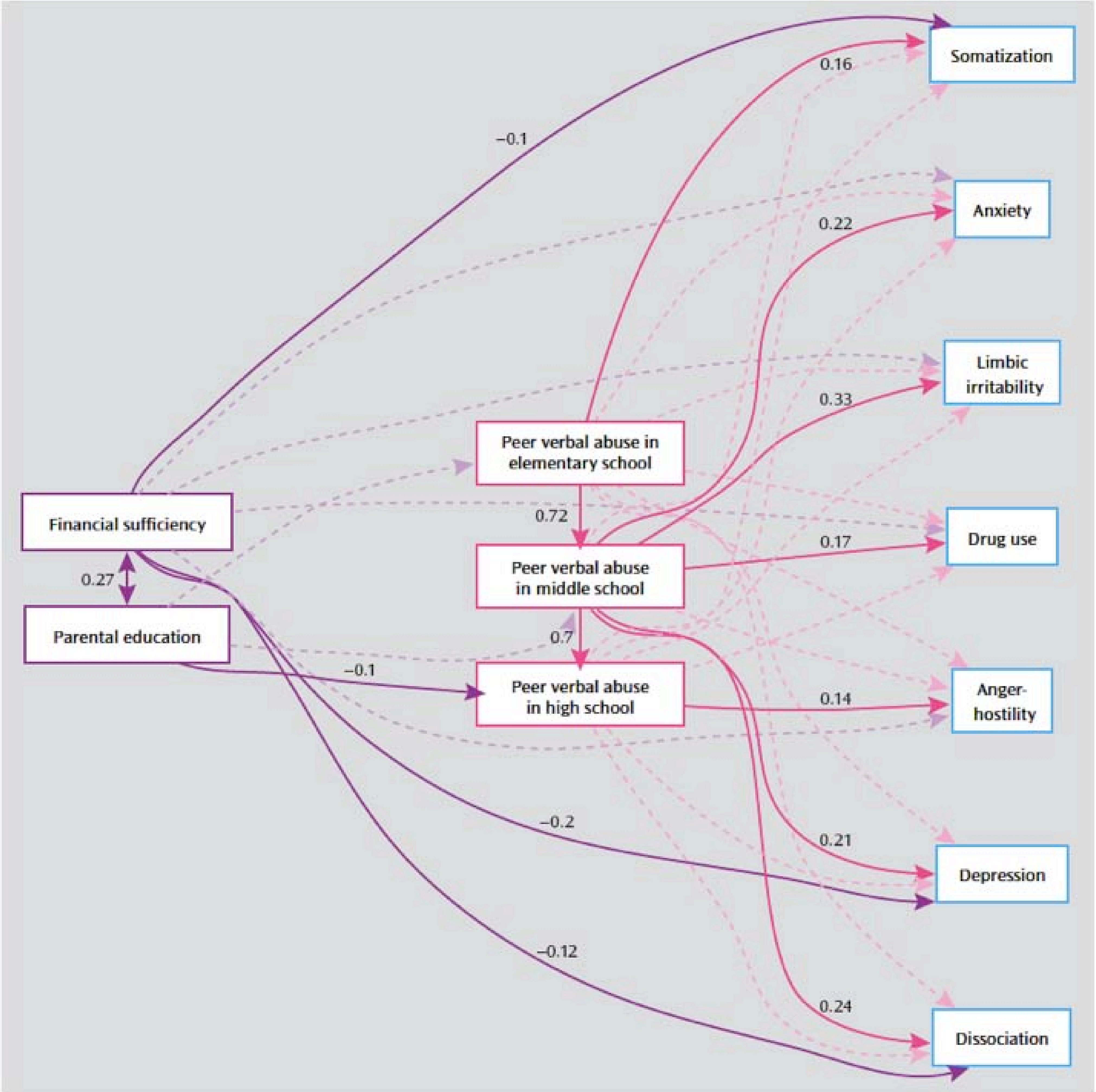


Peer Verbal Abuse

FIGURE 4. Percentage of 1,662 Young Adults in a Community Sample Reporting Exposure to Significant Peer Verbal Abuse Between Ages 5 and 18[a]



[a] Significant peer verbal abuse was defined as maximal peer Verbal Abuse Questionnaire scores ≥30). Note that exposure peaks at ages 12–13.



Somatization
Anxiety
Limbic irritability
Drug use
Anger-hostility
Depression
Dissociation
Financial sufficiency
Parental education
Peer verbal abuse in elementary school
Peer verbal abuse in middle school
Peer verbal abuse in high school
−0.1
0.16
0.22
0.33
0.72
0.17
0.27
0.7
−0.1
0.14
−0.2
0.21
−0.12
0.24

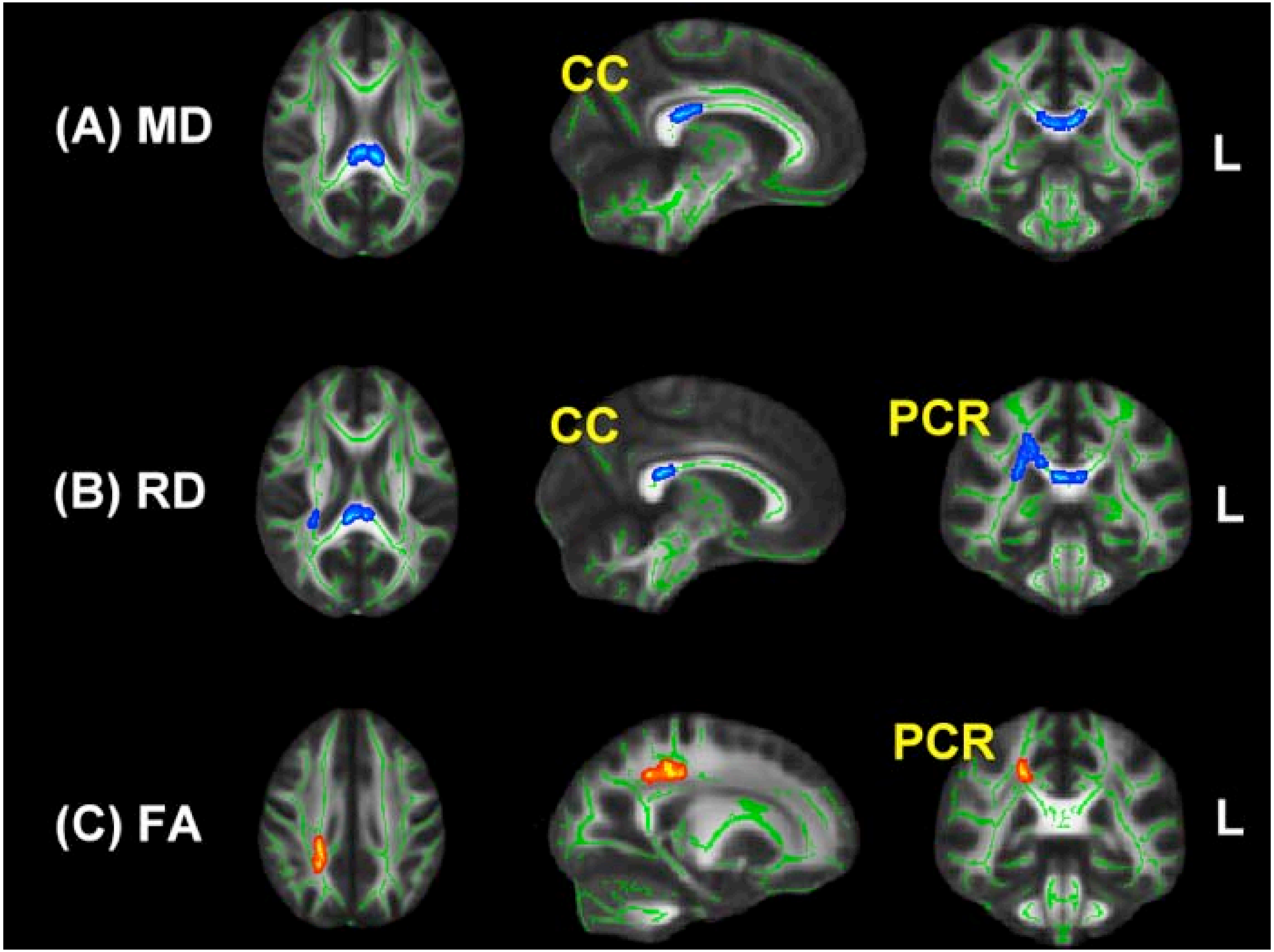


Figure 5. Regions identified by TBSS in the corpus callosum (CC) and posterior corona radiata (PCR) in which there were correlations between degree of exposure to peer verbal abuse and mean diffusivity (MD), radial diffusivity (RD) and fractional anisotropy (FA) (n = 63).

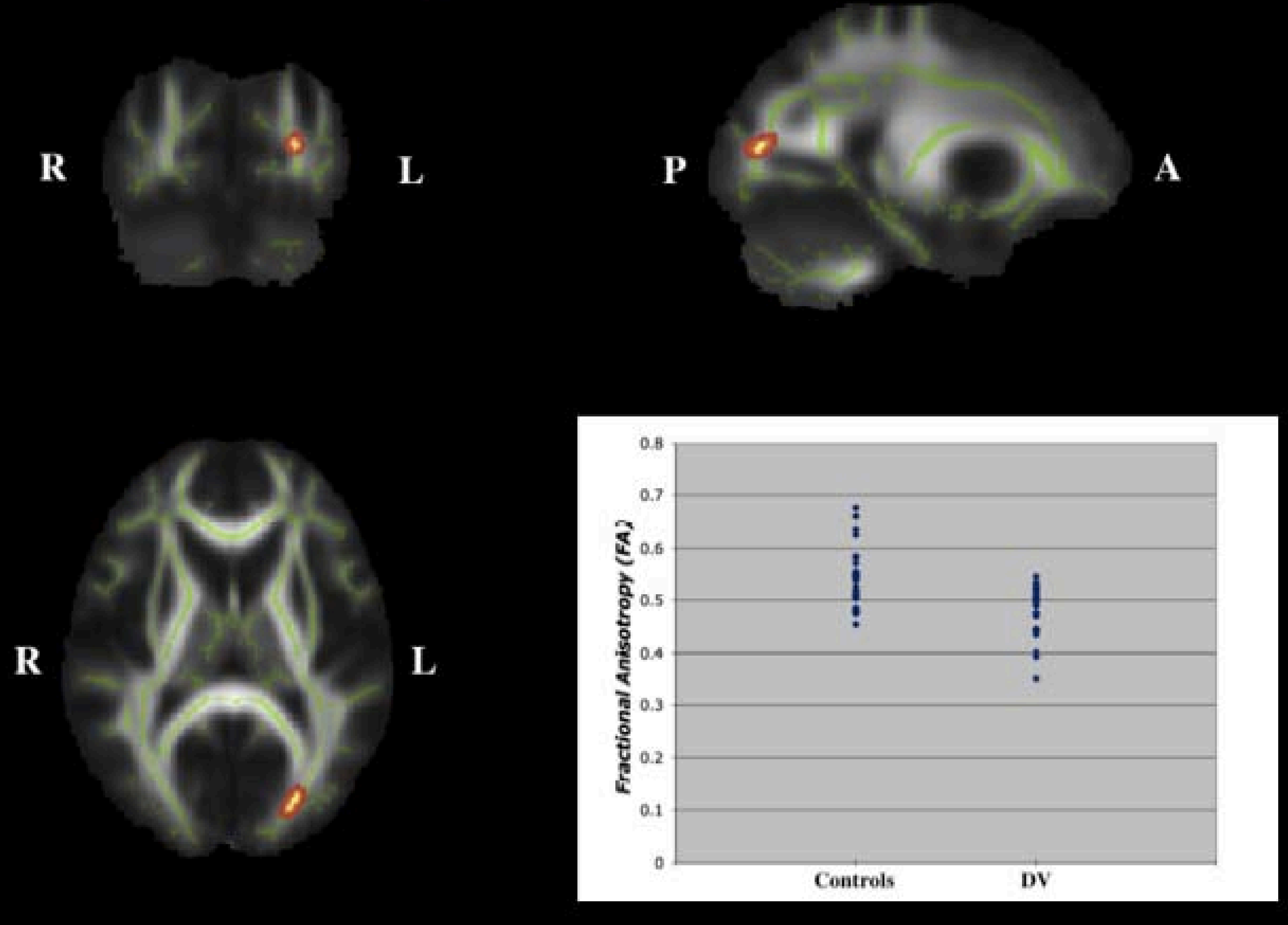
Witnessing Domestic Violence

Witnessing Domestic Violence

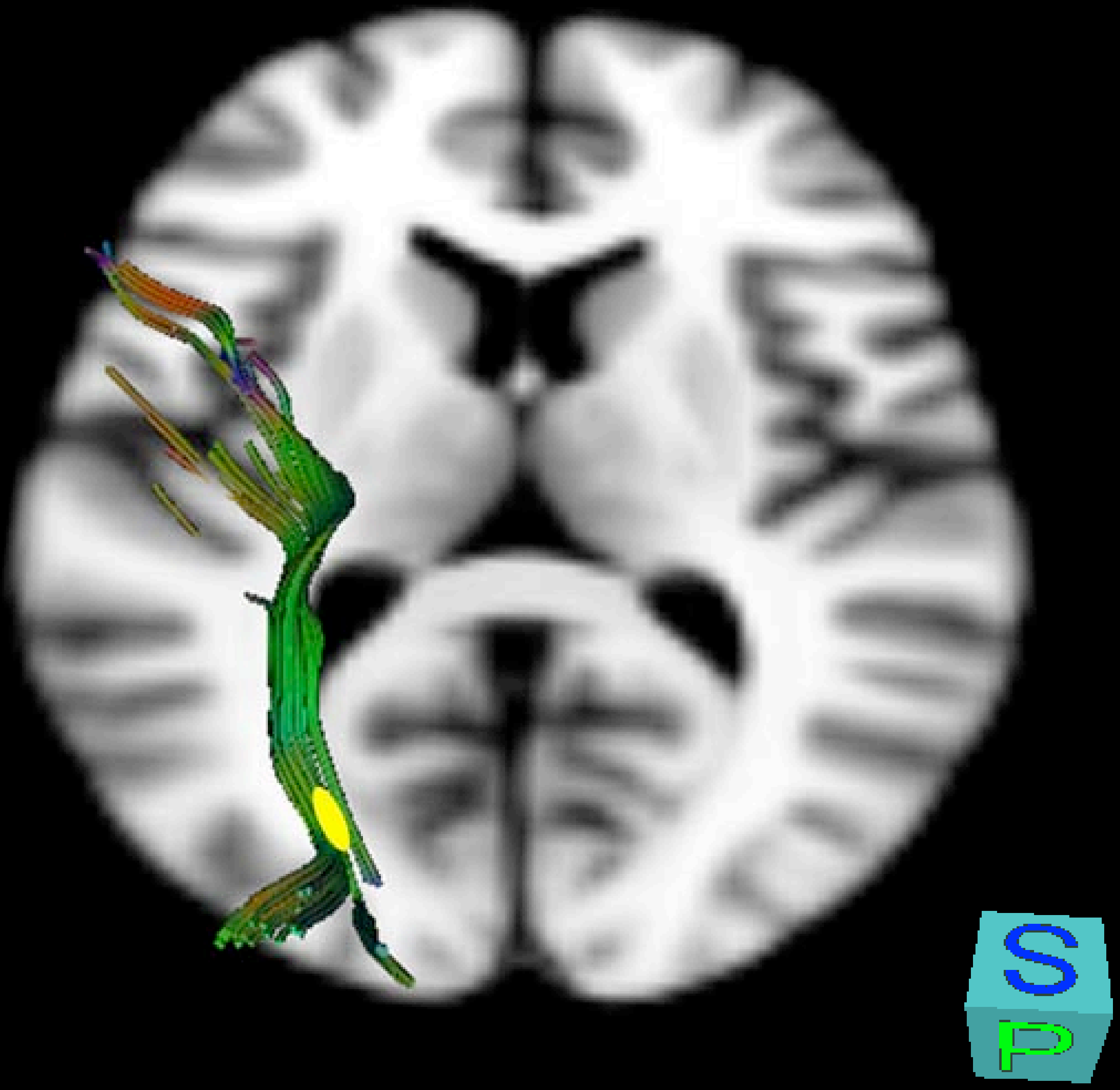
Witnessing Domestic Violence

- 1402 volunteers screened
- (16F/4M, 22.4±2.48 yrs) who witness domestic violence but were exposed to no other forms of trauma
- (19F/8M, 21.9±1.97 yrs) healthy controls

Witnessing Domestic Violence



Inferior Longitudinal Fasciculus

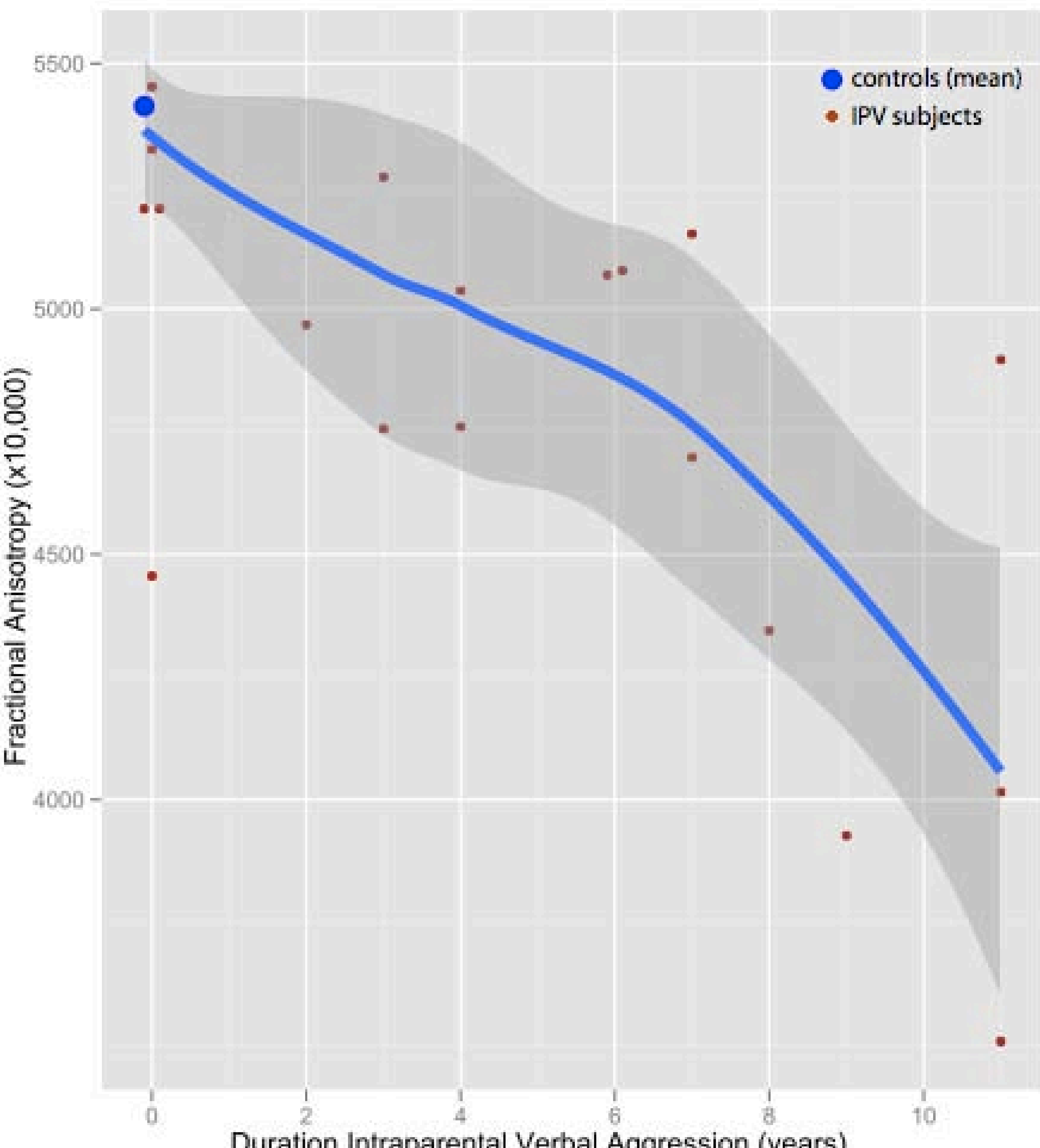


Witnessing Domestic Violence

- FA values in this region were significantly associated with ratings of depression, anxiety, somatization, and dissociation ($r=-0.502$, $p<0.001$; $r=-0.421$, $p=0.003$; $r=-0.377$, $p=0.01$; $r=-0.365$, $p=0.012$).

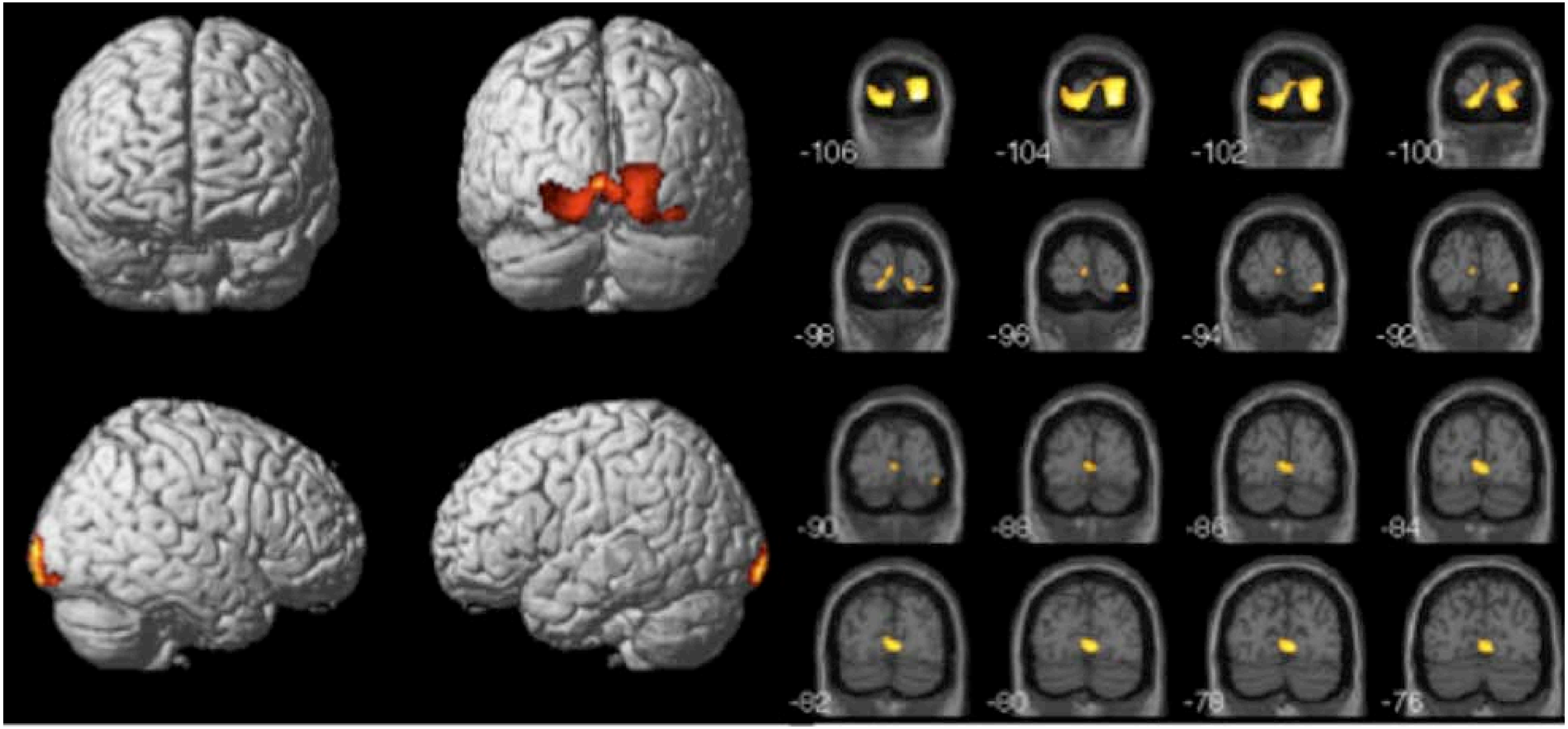
Witnessing Domestic Violence

- The inferior longitudinal fasciculus connects occipital and temporal cortex, and is the main component of the visual-limbic pathway that subserves emotional, learning and memory functions that are modality specific to vision.



controls (mean)
IPV subjects
5500
5000
4500
4000
Fractional Anisotropy (x10,000)
0
2
4
6
8
10
Duration Intraparental Verbal Aggression (years)

Witnessing Domestic Violence



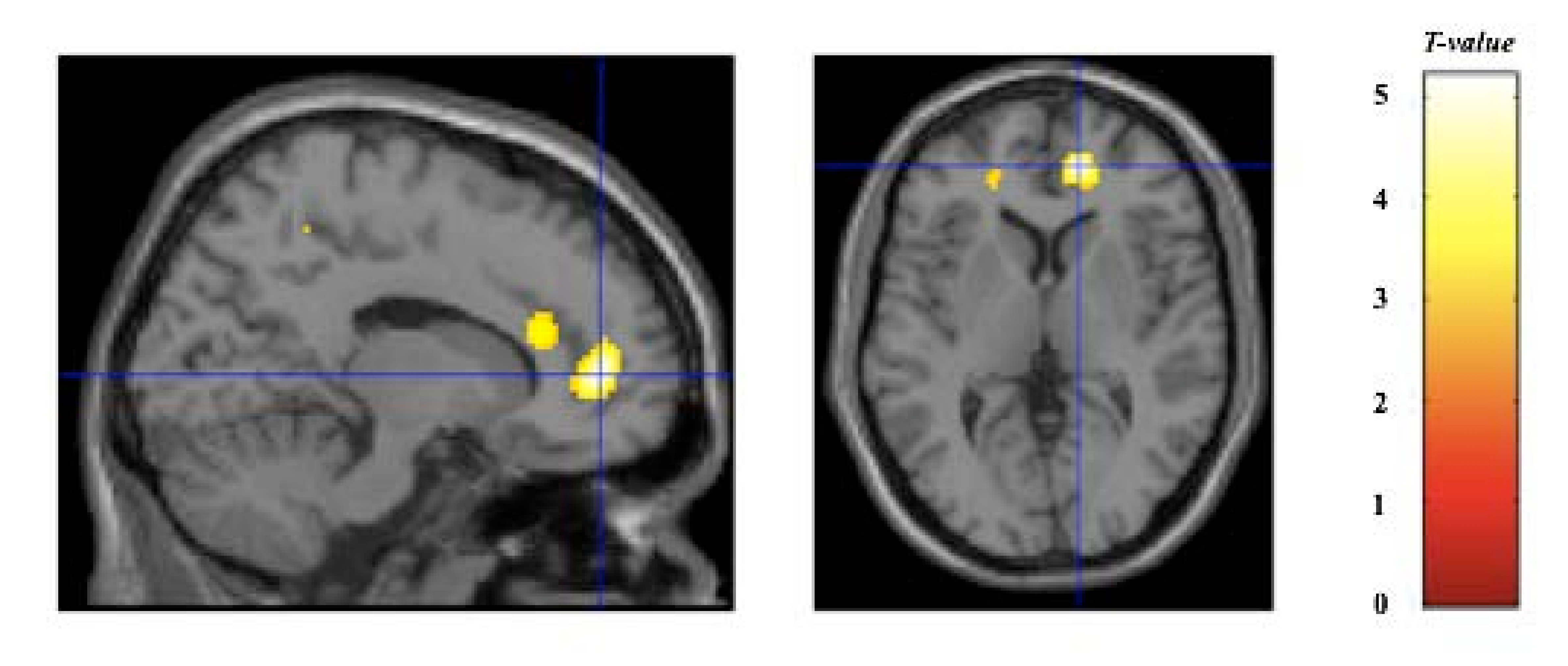
WDV subjects had a 20.5% GMV reduction in right Lingual Gyrus, (BA17), 6.8% reduction in right BA18, and 16.4% reduction in left BA17.

FreeSurfer

Cortical Surface Analysis

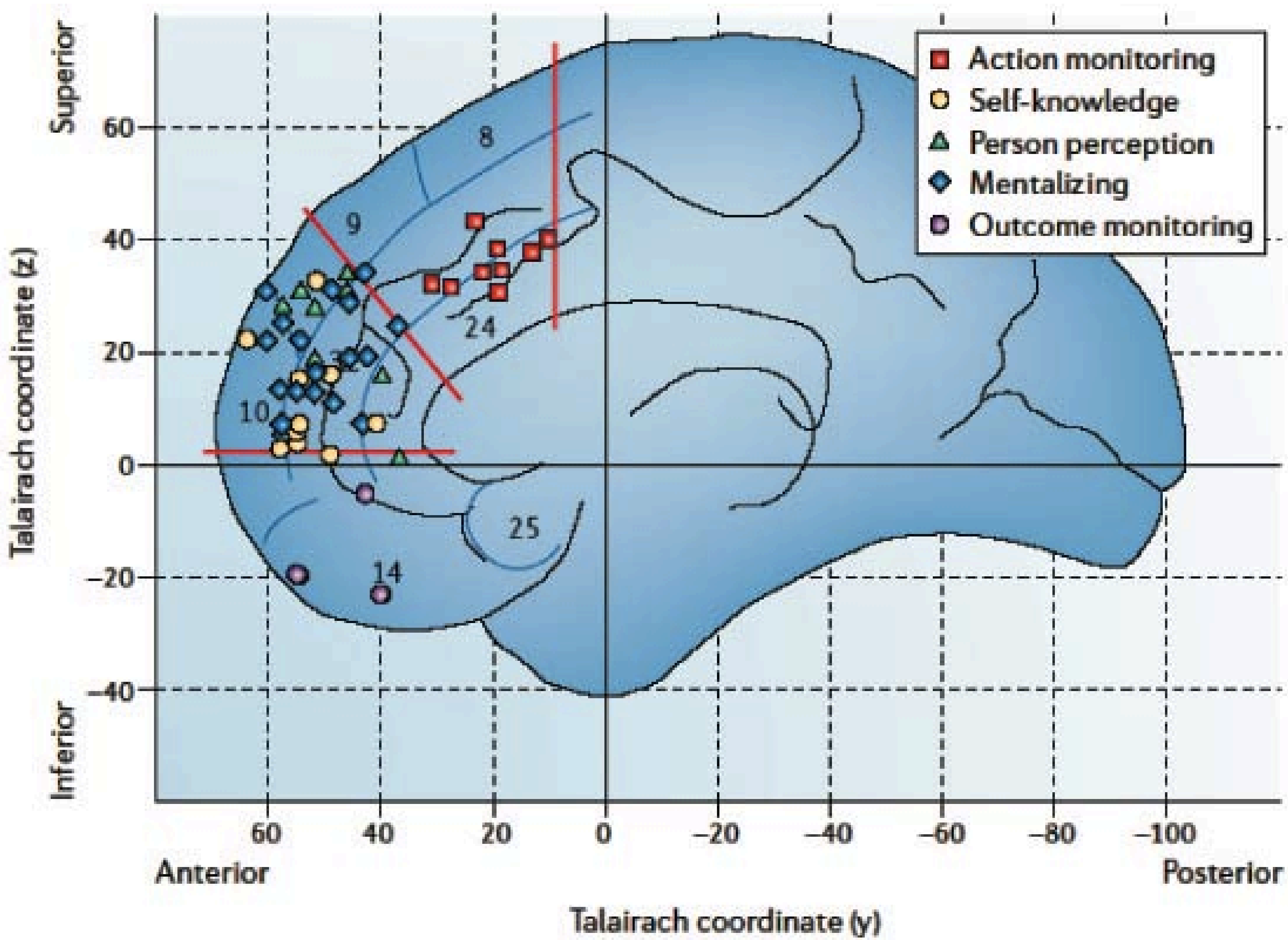
Corporal Punishment

Corporal Punishment



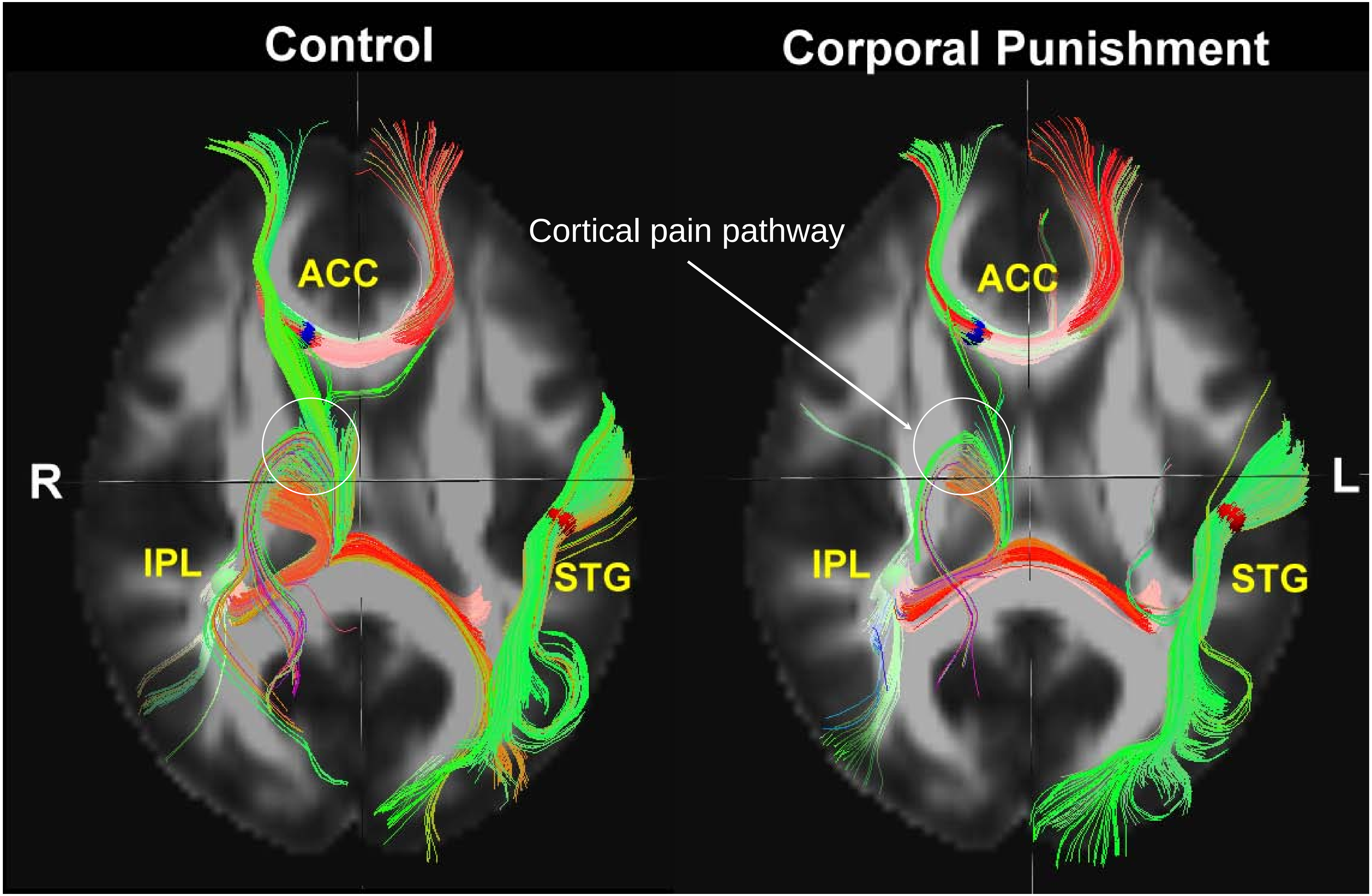
Right Medial Medial Prefrontal Cortex (BA10)
Left medial frontal gyrus (DLPFC) (BA9)
Right anterior cingulate gyrus (BA24)

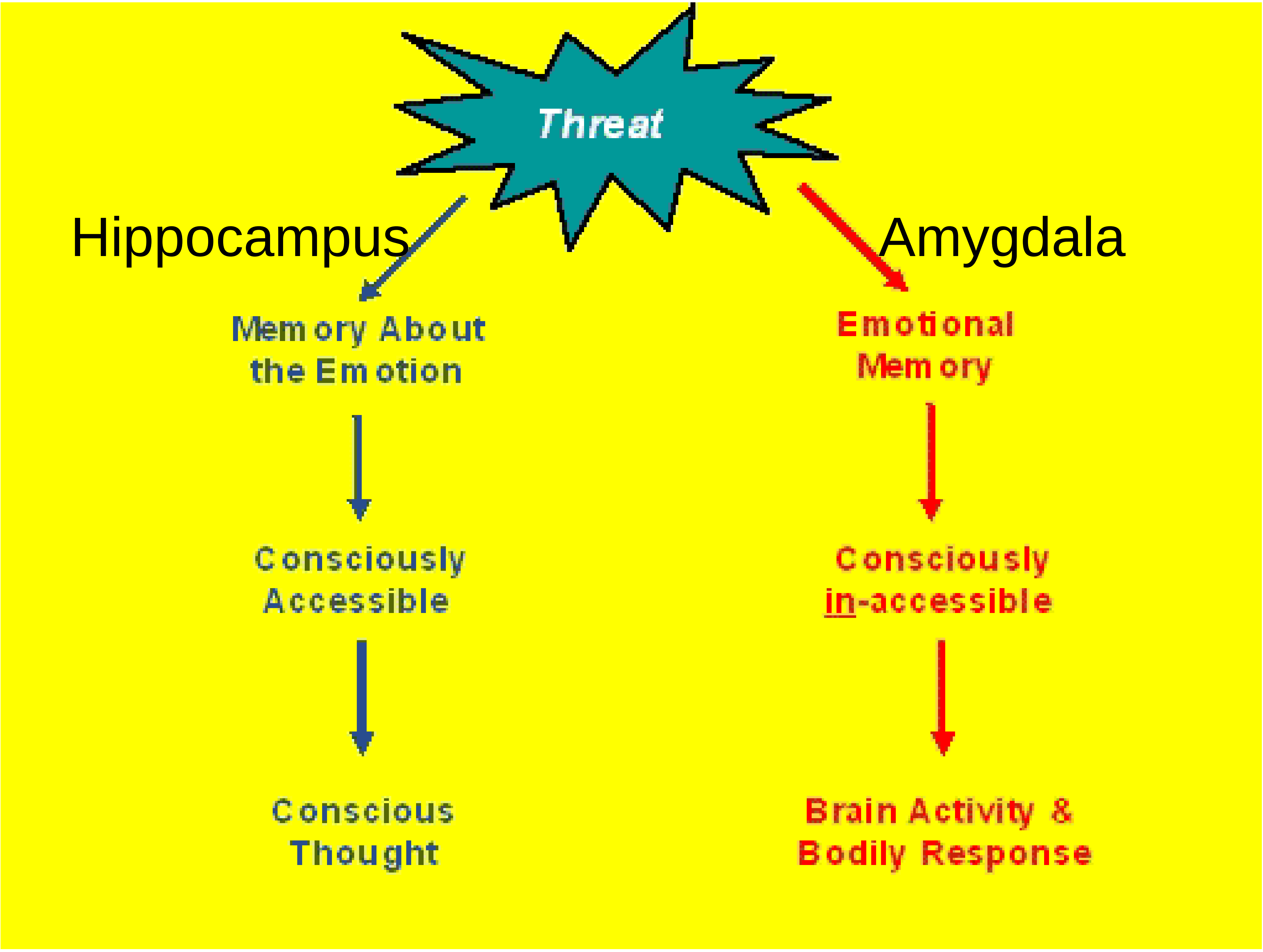
Tomoda, A., Suzuki, H., Rabi, K., Sheu, Y.S., Polcari, A., and Teicher, M.H. (2009) Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. Neuroimage 47 Suppl 2, T66-71



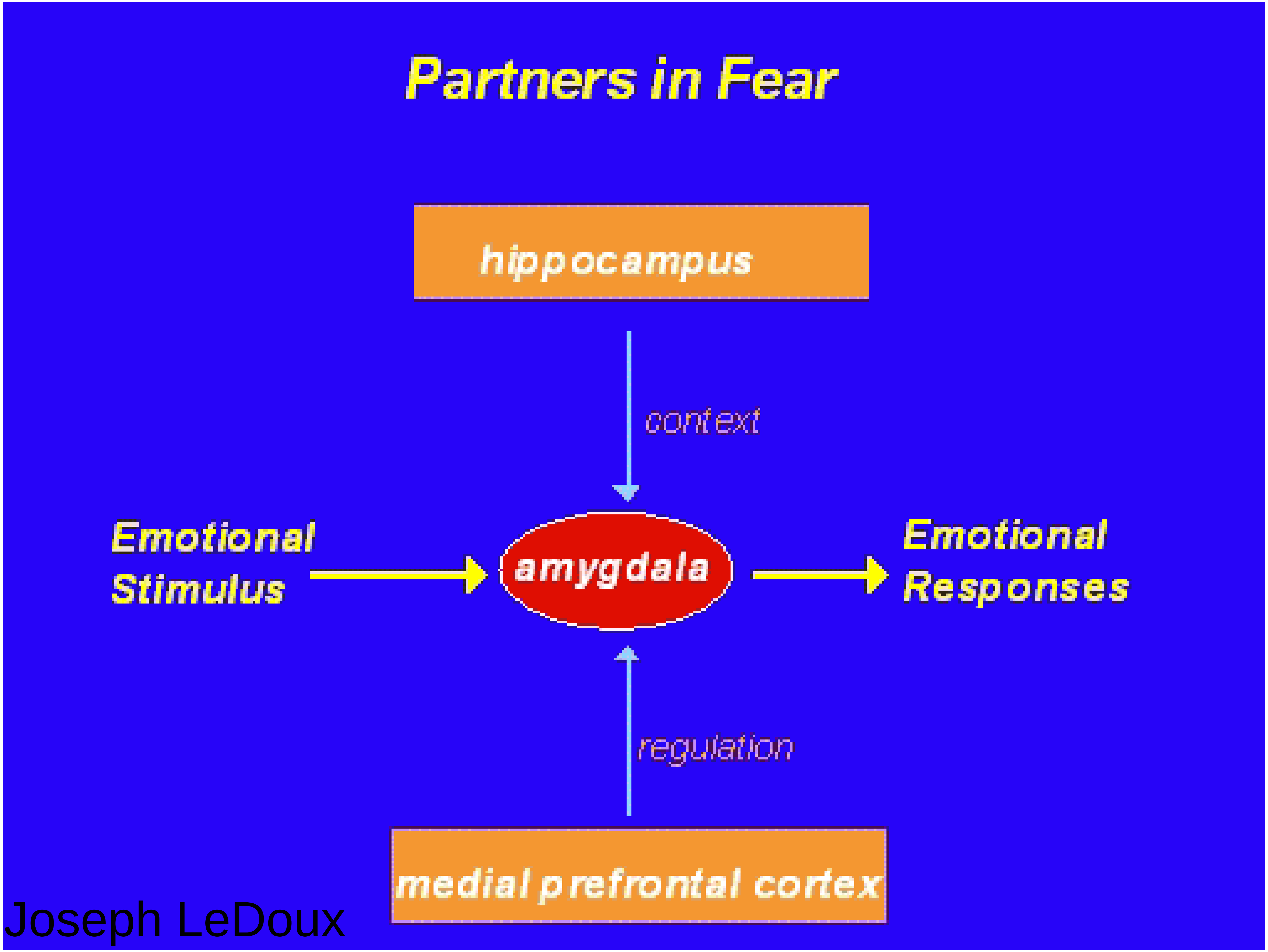
David M. Amodio and Chris D. Frith. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci. 2006, 7(4): 268-277.

Harsh Corporal Punishment

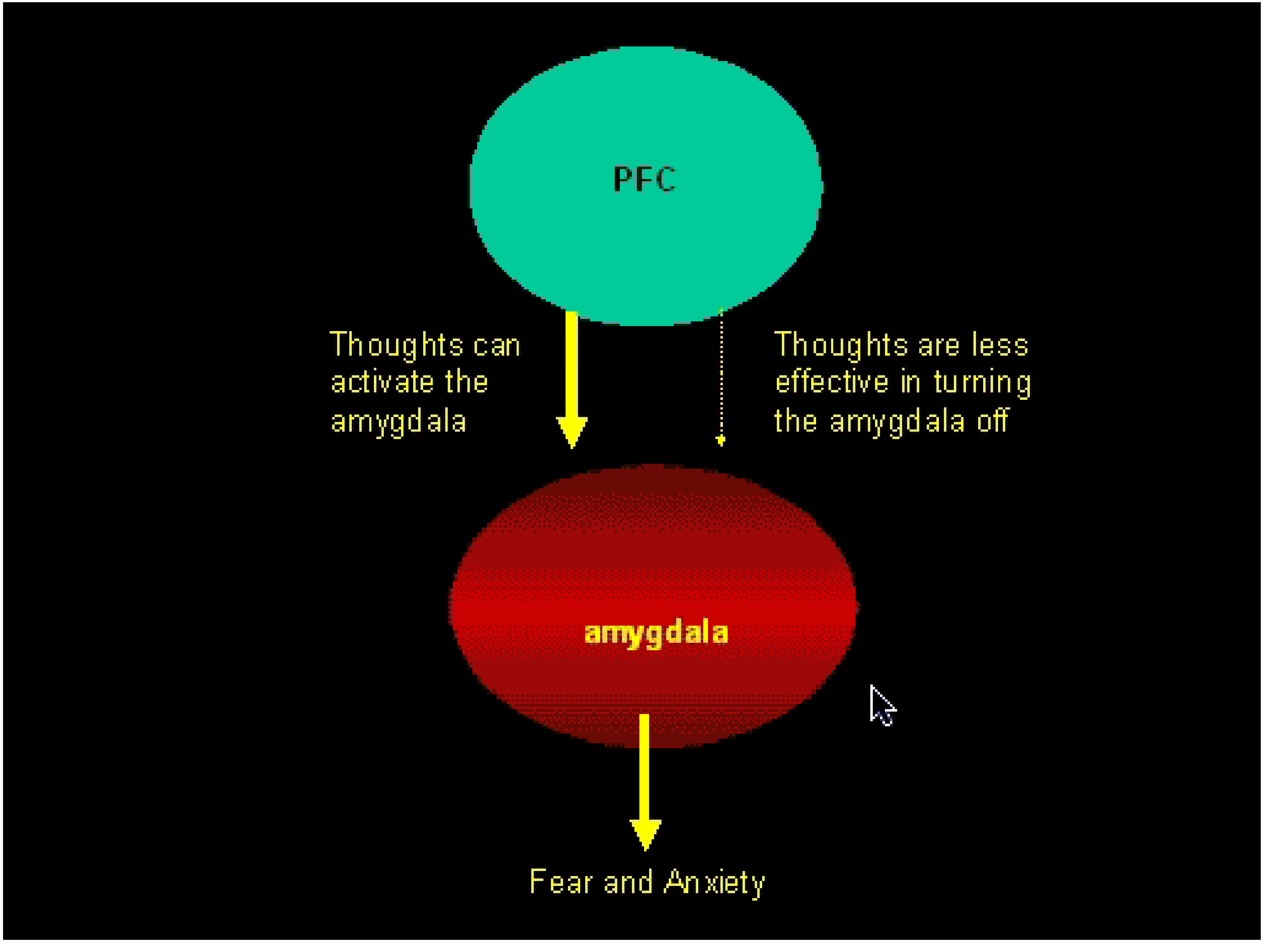




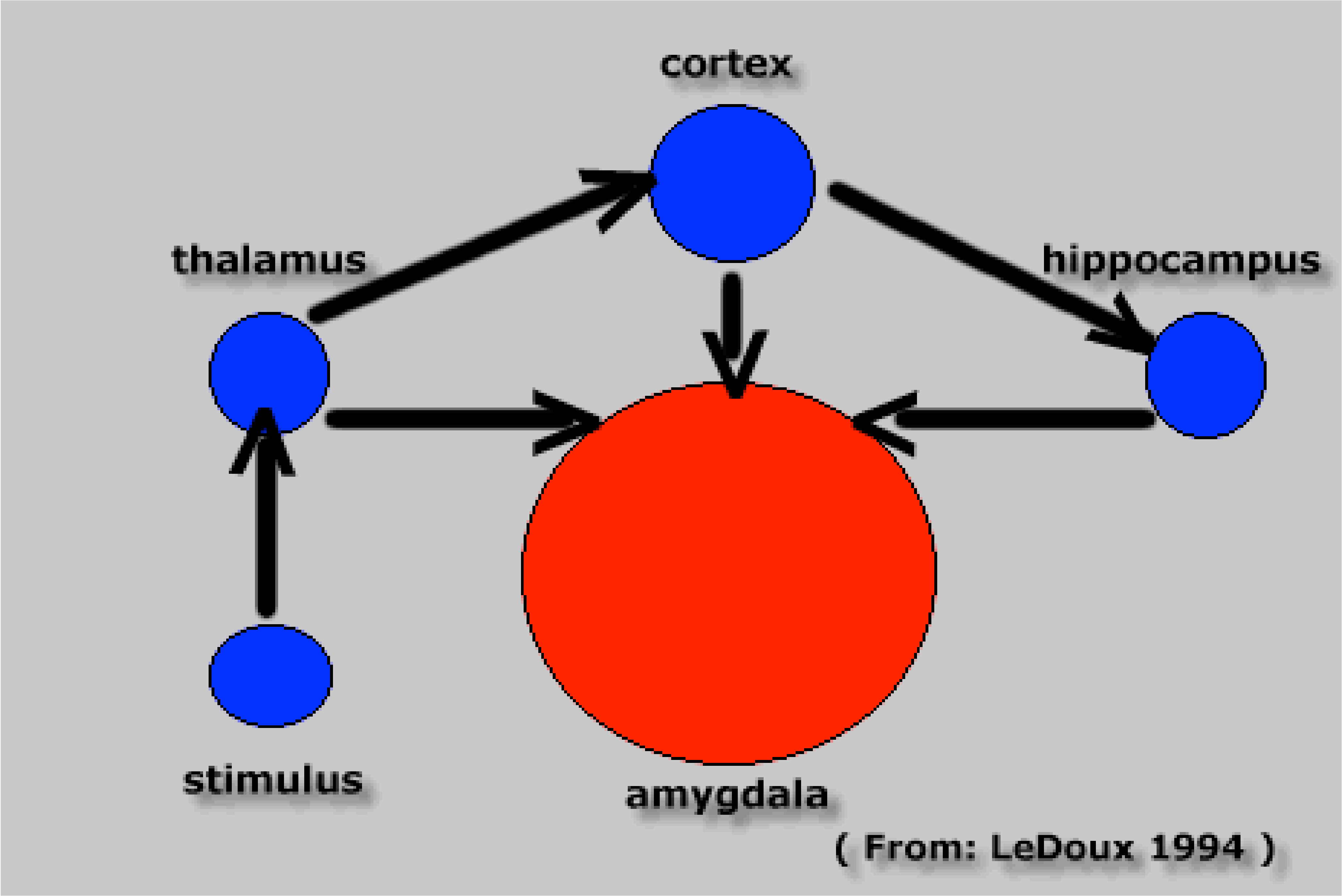
Joseph LeDoux



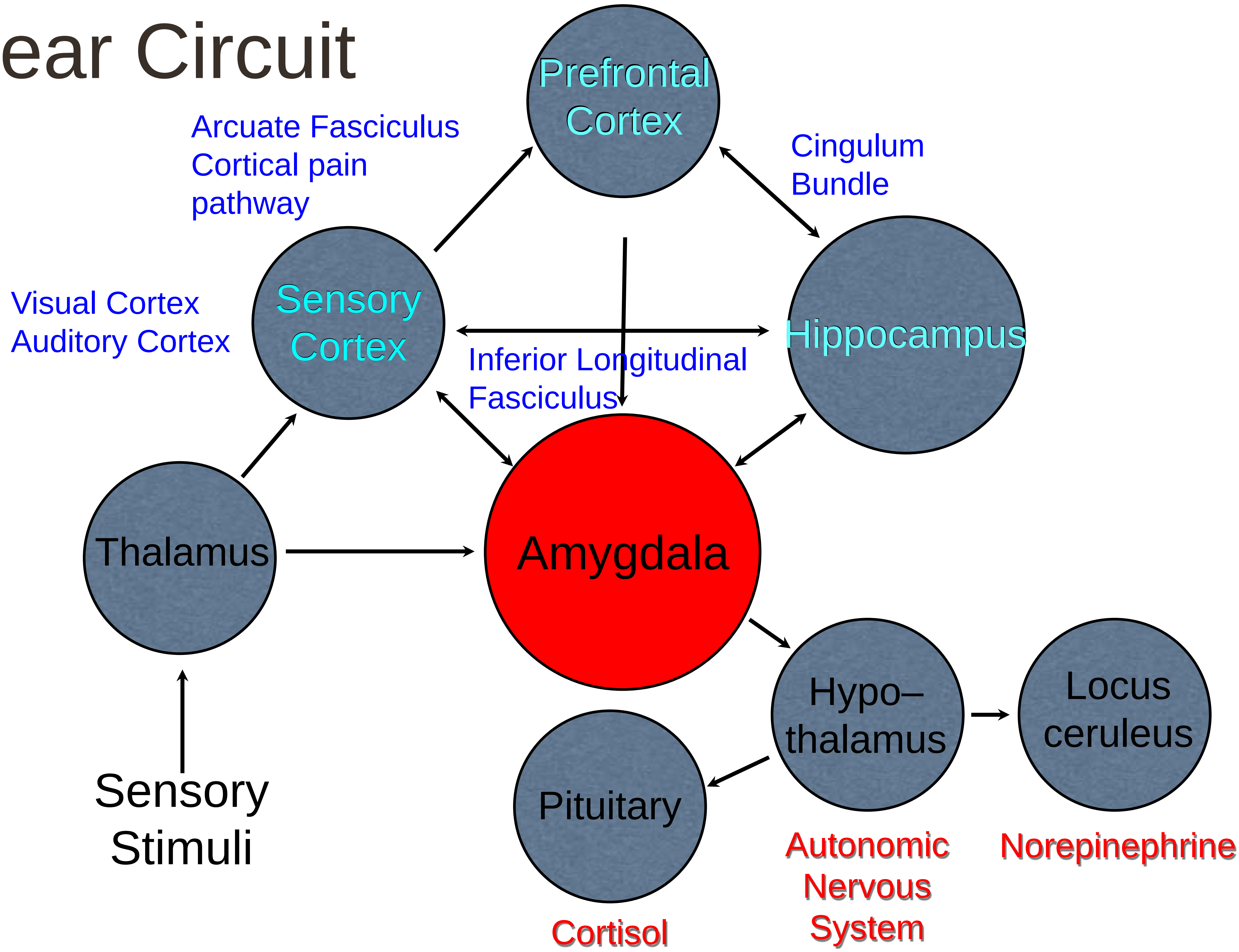
Joseph LeDoux



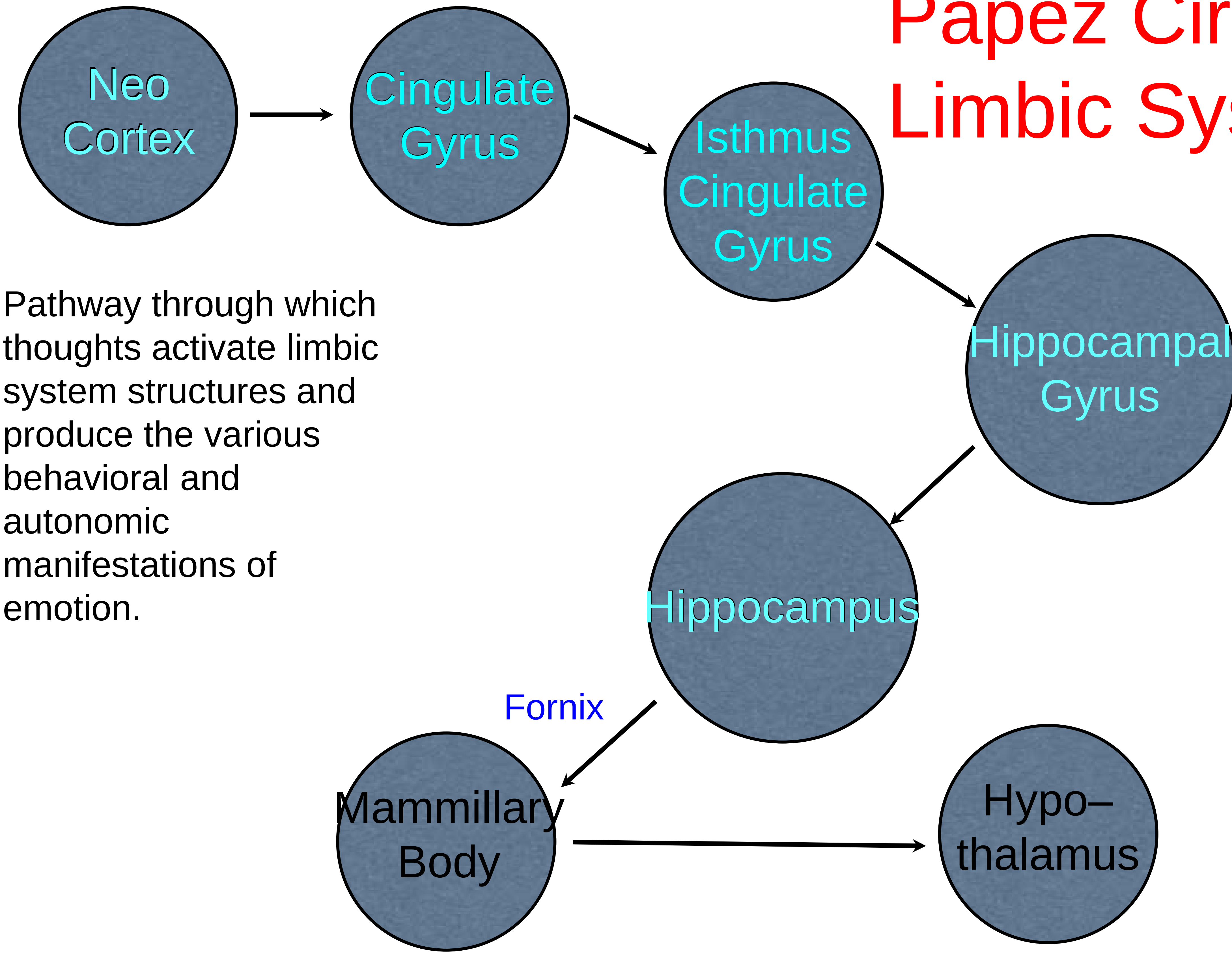
Joseph LeDoux


cortex
thalamus
hippocampus
stimulus
amygdala
(From: LeDoux 1994)

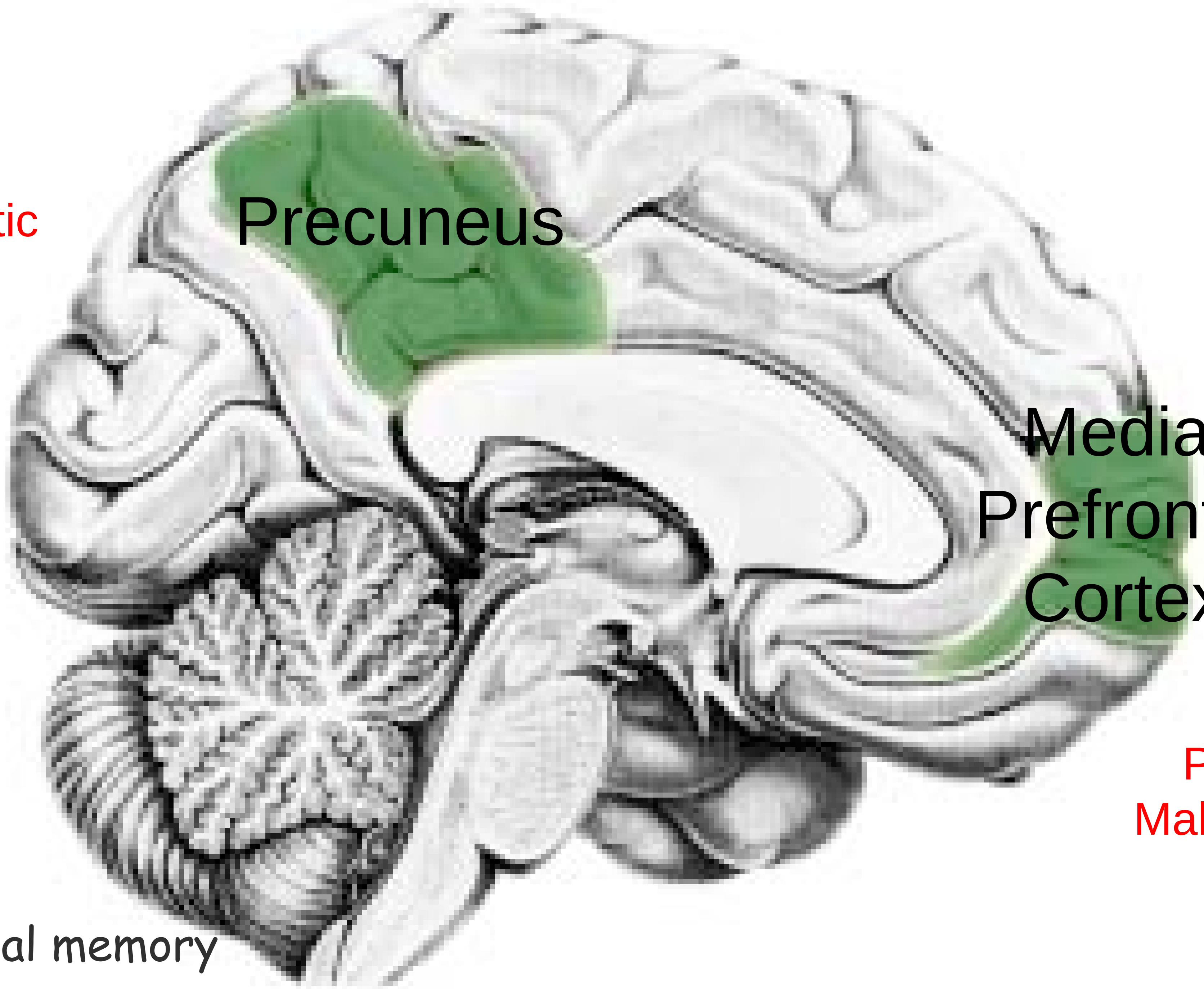
Fear Circuit



Papez Circuit - Limbic System



Pathway through which thoughts activate limbic system structures and produce the various behavioral and autonomic manifestations of emotion.



- Autobiographical memory
- Self versus non-self representation
- Self-referential judgements
- First- versus third-person perspective
- Perceived agency
- Mind reading/social cognition.

The mammalian brain has evolved to be sculpted by early experience, and adverse stressful early experience has been a routine part of our ancestry.

Is it plausible that the developing brain never evolved to cope with exposure to stress or maltreatment and is damaged in a non-adaptive manner?

The counterintuitive but logical alternative is that exposure to early stress produces a cascade of molecular and neurobiological effects that alters neural development in an adaptive way that prepares the adult brain to survive and reproduce in what it predicts will be a malevolent world.

Psychosocial acceleration, other adaptations?

In contrast, we hypothesis that adequate nurturing and absence of intense early stress permits our brains to develop in a manner that is less aggressive, more emotionally stable, social, empathic, and hemispherically-integrated. We believes that this enhances the ability of social animals to build more elaborate social structures and enables humans to better realize their creative potentials.

This may be more the exception than the rule.