Interaction of Gene, Environment and Timing in the Trans- Generational Transmission of Mood Disorders

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המרכז לבריאות הנפש גהה
GEHA MENTAL HEALTH CENTER

Gil Zalsman
Ethical Disclosure

No Conflict of interest for this study

Advisor for:

- JNJ RND
- Elminda ltd Israel
- Prophase LLC, NY
- PANSS institute NY

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1. AFSP young investigator grant-2005-2007 (Zalsman)
2. PHS grants MH62185 and MH48514 (J.J. Mann)
3. The National Institute for Psychobiology in Israel Grants 29/98, 9b/99 (Zalsman)

Organizations:

1. ECNP- Board Member and Chair of Education
2. EPA- Child Psychiatry Section Vice Chair
3. Israeli Society for Biological Psychiatry-president

Vulnerability to depression

Conclusions

Stressful exposures in pre-pubertal or adolescent phases in development may influence differently the structural integrity of specific brain regions and emotion regulation behaviors and this is moderated by the genetic vulnerability of the subject for depression and despair.

These findings indicate a possible GxExT interaction in mood dysregulation that is a core symptom in the development of depression and suicidal behavior in the young.

What do we know about pediatric depression?

1. **Depression runs in families** **(Ott, Brent, Mann)**
2. **Depression is clinically and epidemiologically different before and after puberty**

For review: Zalsman, Brent and Birmaher,
Child and Adlo Psychiatric clinics of North Am 2005

Depression in Children & Adolescents

Early Childhood:

- looks sad
- tearful
- slow movements or **irritability**
- monotone voice
- hopeless
- self in negative terms
- school problems
- **somatization!!**

Late childhood and adolescents:

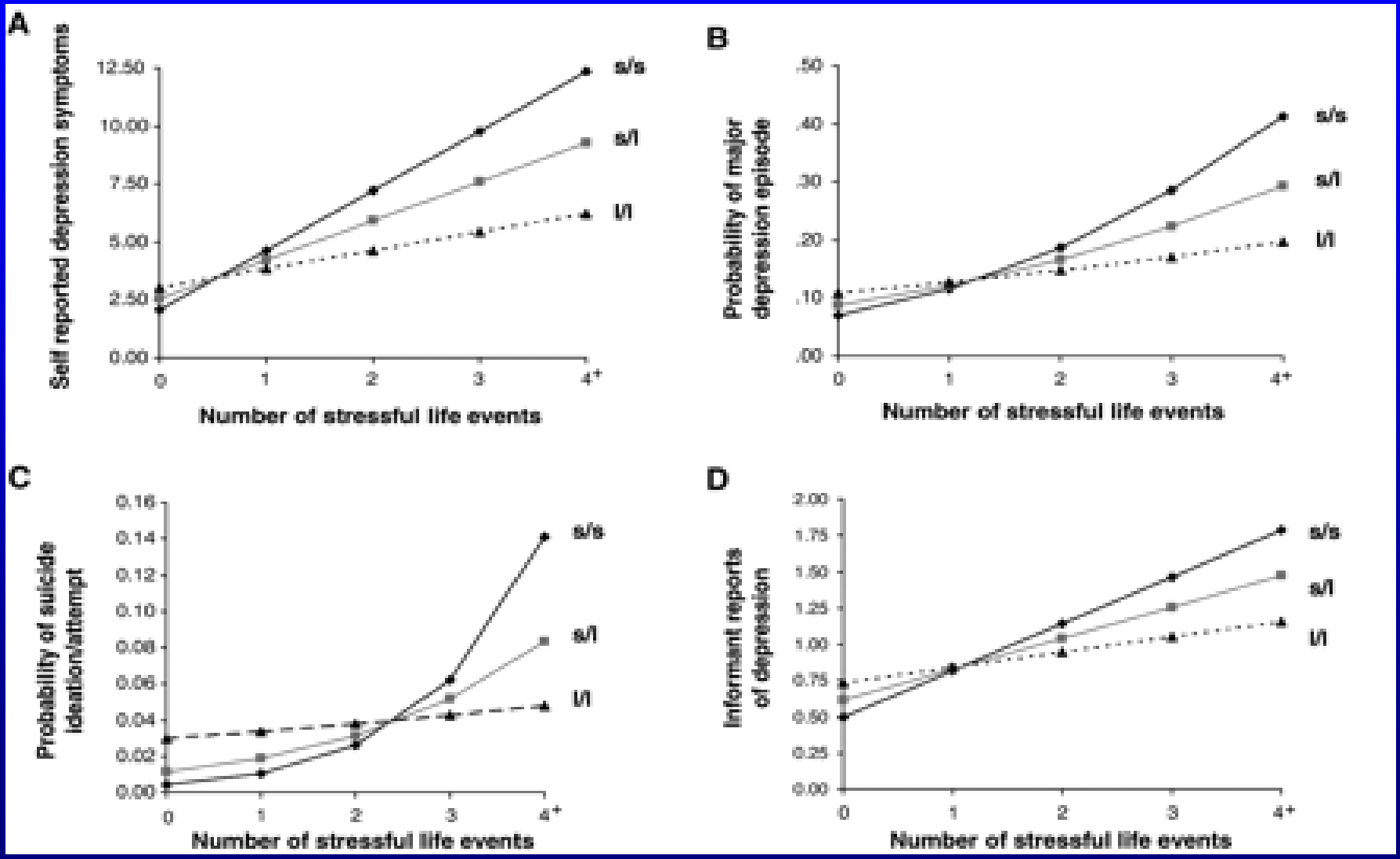
- low self esteem
- apathy
- **depressed mood**
- **anxiety**
- low concentration
- Risk taking behavior
- **suicide attempts**

GxE→ D

Childhood Adversity

5HTTLPR
Gene X Environment Interaction
Caspi et al. 2003

*counted SLE



Caspi et al. Science, 2003

5HTTLPR
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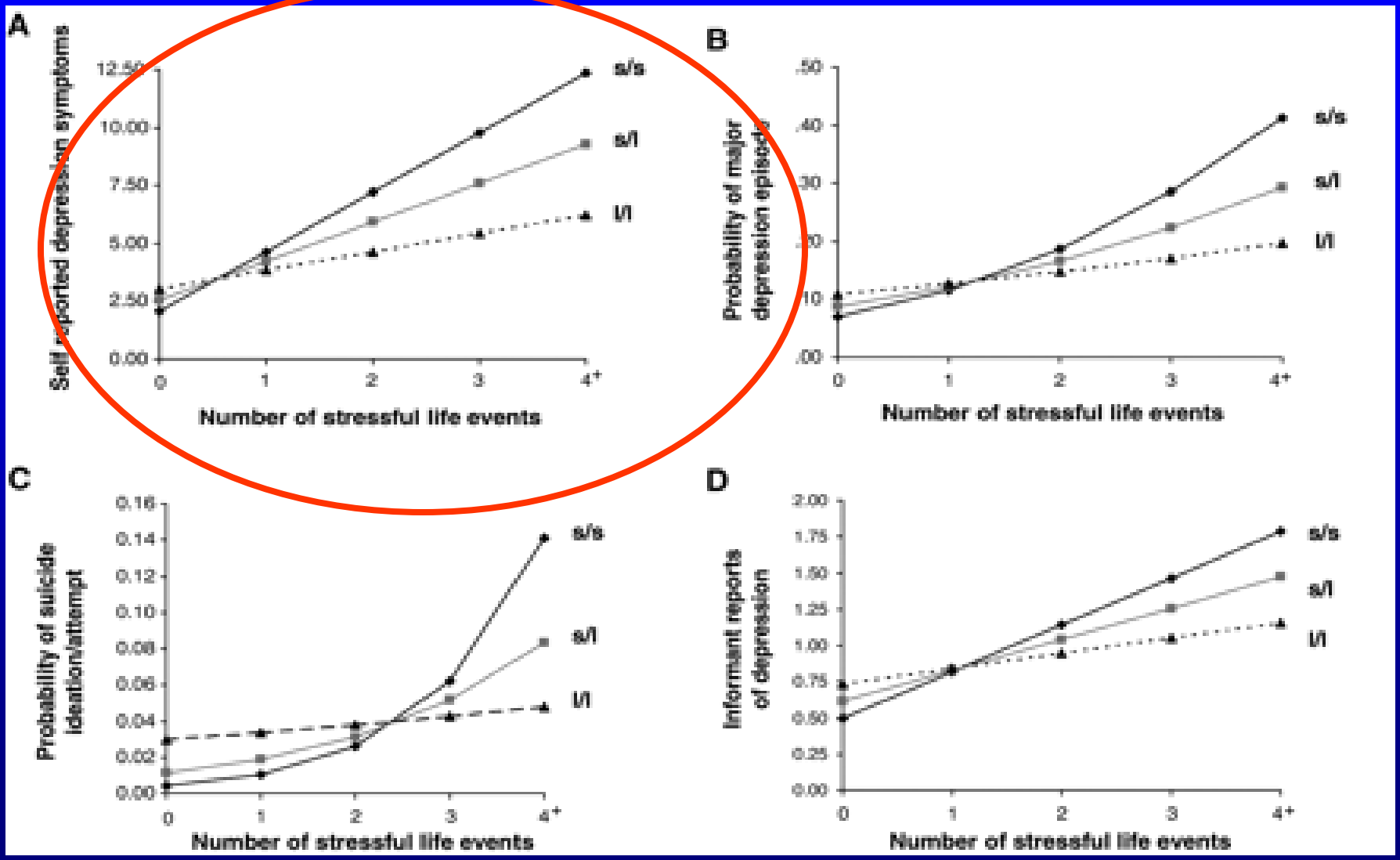


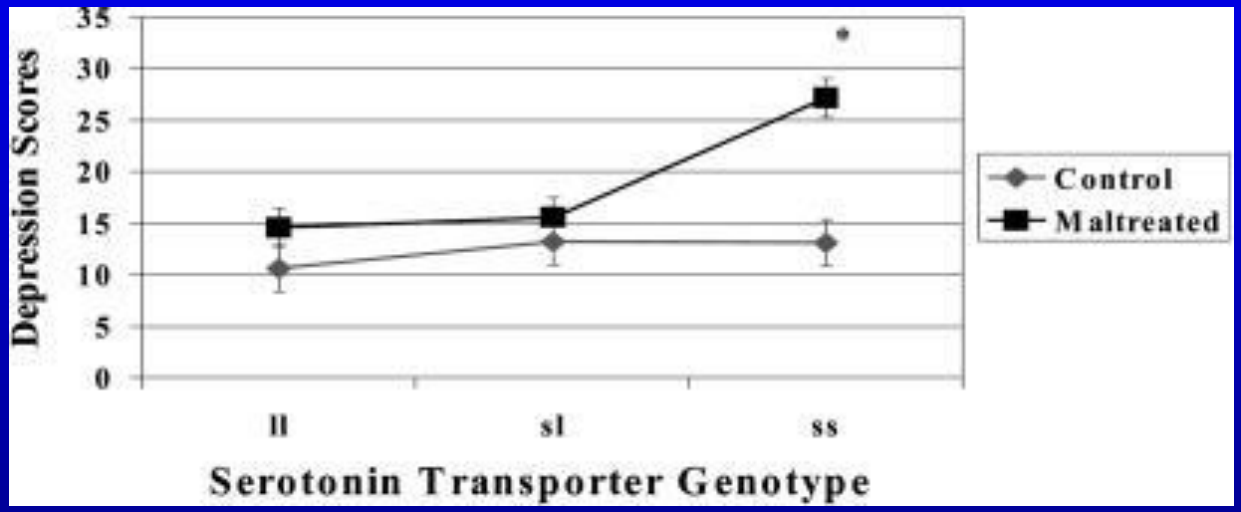
Caspi et al. Science, 2003

Social supports and serotonin transporter gene moderate depression in maltreated children.

Kaufman J et al.

Proc Natl Acad Sci USA 2004; 101:17316-17321

(N=101)



Maltreated children (57 age 10-15; were removed from their parents' care) with the s/s genotype and no positive supports had the highest depression ratings.

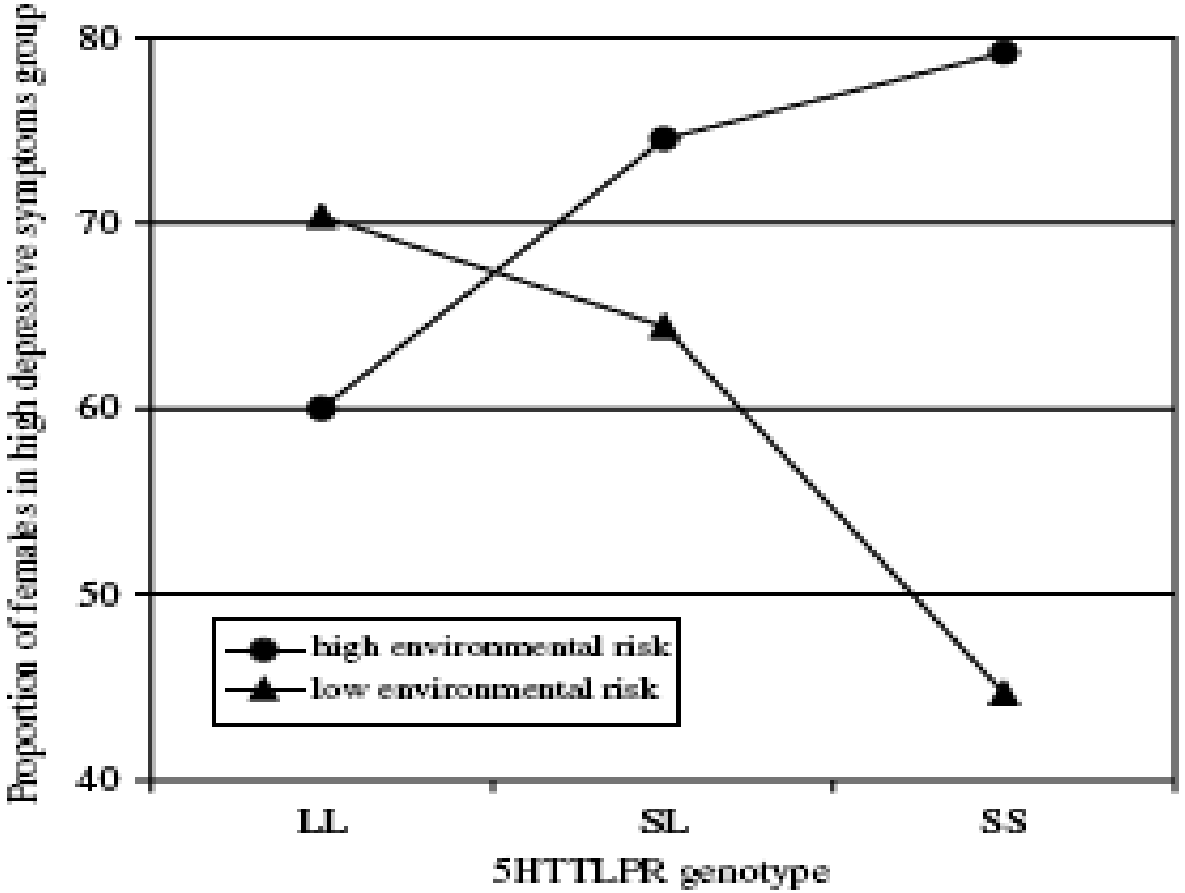


Figure 1 Proportion of female subjects with a high level of depression by environmental risk group and genotype.

♀

Eley et al., Mol Psychiatry 2004

N=1990, age 10-20

Article

Association of a Triallelic Serotonin Transporter Gene Promoter Region (5-HTTLPR) Polymorphism With Stressful Life Events and Severity of Depression

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Maria A. Oquendo, M.D.

Ainsley K. Burke, Ph.D.

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David A. Brent, M.D.

Steven P. Ellis, Ph.D.

David Goldman, M.D.

J. John Mann, M.D.

Objective: The lower expressing allele of the serotonin transporter gene 5′ promoter region (5-HTTLPR) polymorphism is reported to be associated with susceptibility to depression and suicidality in response to stressful life events. The authors examined the relationship of a triallelic 5-HTTLPR polymorphism to stressful life events, severity of major depression, and suicidality.

Method: Mood disorder subjects (N=191) and healthy volunteers (N=125), all Caucasian subjects of European origin, were genotyped for the triallelic 5-HTTLPR polymorphism (higher expressing allele: L_A; lower expressing alleles: L_G, S). All subjects underwent structured clinical interviews to determine DSM-IV diagnoses, ratings of psychopathology, stressful life events, developmental history, and suicidal behavior. CSF 5-HIAA was assayed in a subgroup of subjects.

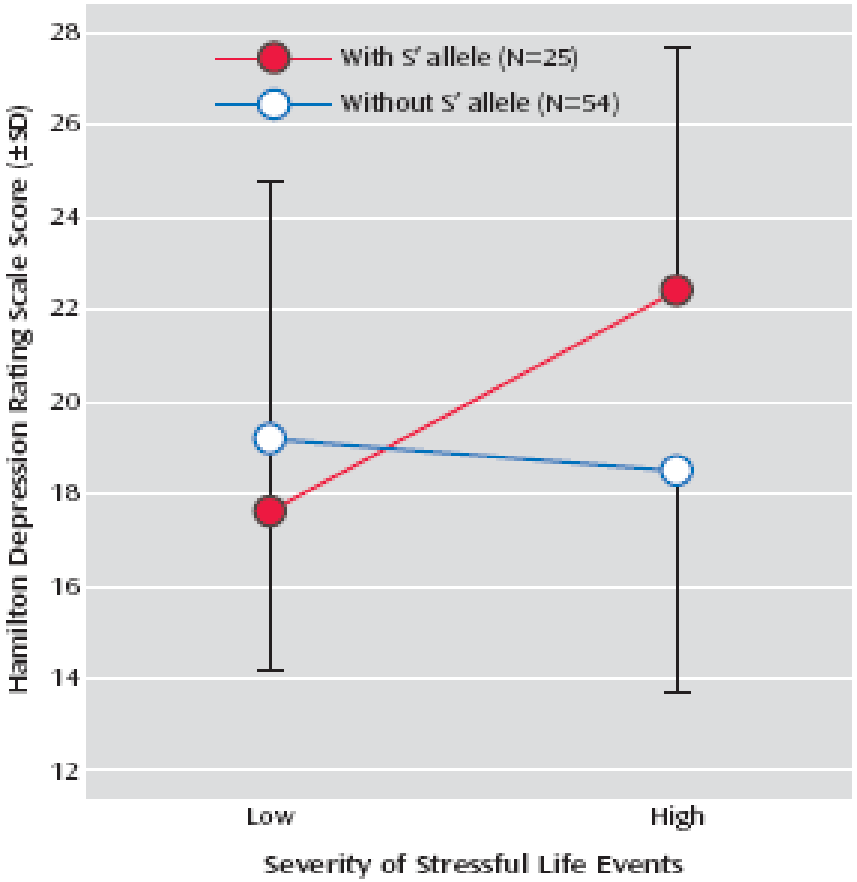
Results: Lower expressing alleles independently predicted greater depression severity and predicted greater severity of major depression with moderate to severe life events compared with the higher expressing L_A allele. No associations with suicidal behavior and CSF 5-HIAA were found.

Conclusions: Lower expressing transporter alleles, directly and by increasing the impact of stressful life events on severity, explain 31% of the variance in major depression severity. The biological phenotype responsible for these effects remains to be elucidated.

(Am J Psychiatry 2006; 163:1588–1593)

Zalsman et al. Am J Psychiatry 2006, 163:1588-1593

FIGURE 1. Relationship of Depression Severity and Stressful Life Events by 5-HTTLPR Genotype[a]



[a] Stressful life events score measured by St. Paul-Ramsey Scale (30, 31). High and low stressful life events were defined using a median split. The overall model was significant ($F=2.22$, $df=13, 78$, $p<0.02$), and independent effects were found for genotype ($F=4.71$, $df=2, 78$, $p<0.02$) and the interaction of genotype and St. Paul-Ramsey Scale score ($F=2.27$, $df=6, 78$, $p<0.05$).

- Third allele
- Subjective SLE

***Zalsman et al. Am J Psychiatry* 2006, 163:1588-1593**

OOPS!!!!

- Risch N et al. JAMA, 2009;302:492

Meta-analysis of 14 studies found no significant association (OR=1.05)

Karg et al. 2011: **Meta-analysis revisited**

META-ANALYSIS

ONLINE FIRST

The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited

Evidence of Genetic Moderation

Katja Karg, BSc; Margit Burmeister, PhD; Kerby Shedden, PhD; Srijan Sen, MD, PhD

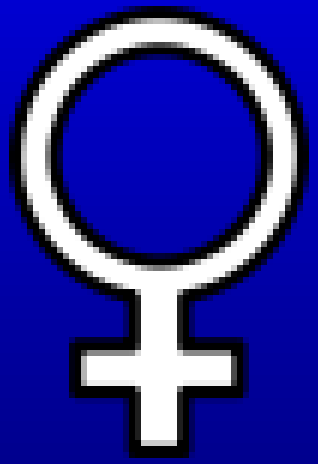
Arch Gen Psychiatry.
Published online January 3, 2011.

Data Synthesis: We included 54 studies and found strong evidence that 5-HTTLPR moderates the relationship between stress and depression, with the 5-HTTLPR *s* allele associated with an increased risk of developing depression under stress ($P = .00002$). When stratifying our analysis by the type of stressor studied, we found strong evidence for an association between the *s* allele and increased stress sensitivity in the childhood maltreatment ($P = .00007$) and the specific medical condition ($P = .0004$) groups of studies but only marginal evidence for an association in the stressful life events group ($P = .03$). When restricting our analysis to the studies included in the previous meta-analyses, we found no evidence of association (Munafò et al studies, $P = .16$; Risch et al studies, $P = .11$). This suggests that the difference in results between meta-analyses was due to the different set of included studies rather than the meta-analytic technique.

Suggested model

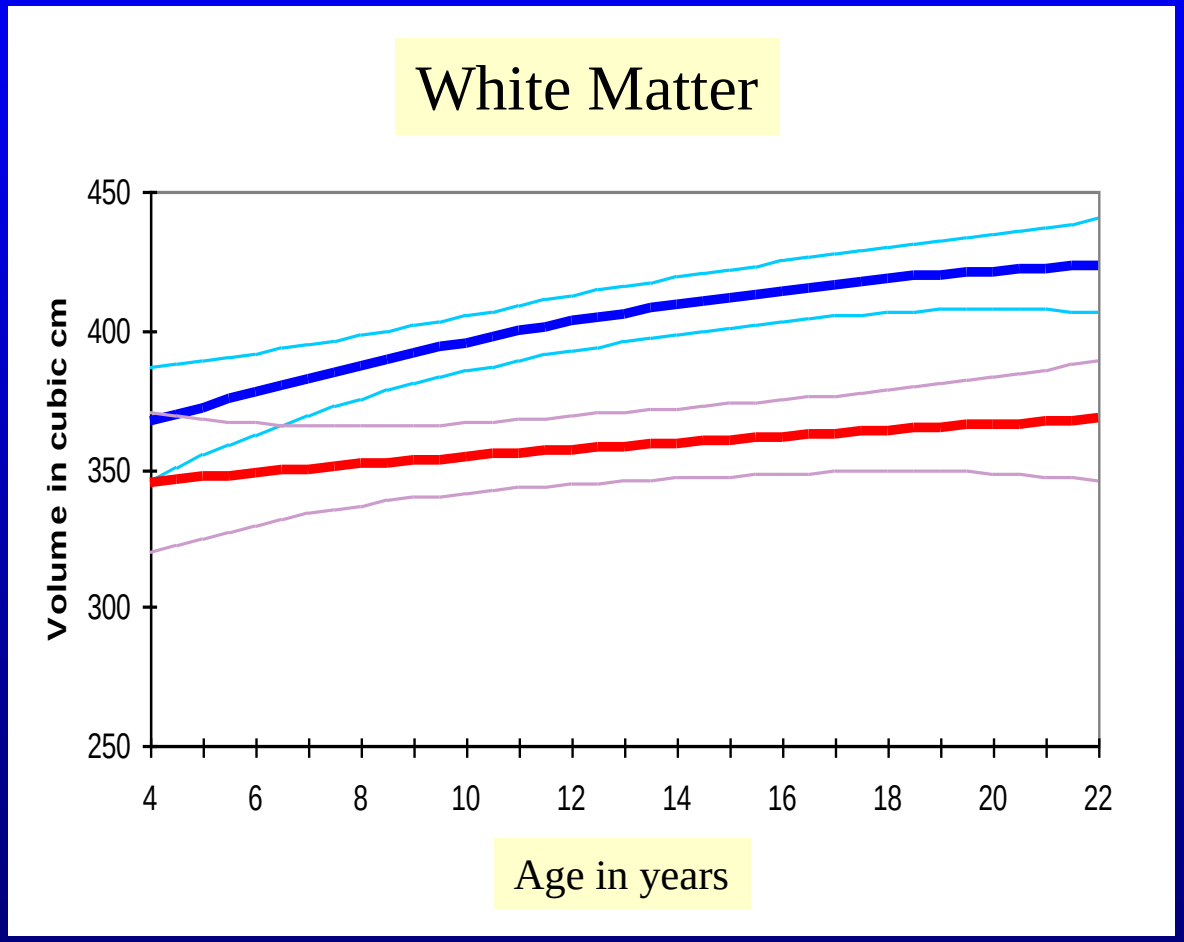
Zalsman G. Timing is critical. Eur Psychiatry. 2010;25(5):284-6

Do boys and girls have different brains?



Yes....

White Matter



Male (152 scans from 90 subjects)
Female (91 scans from 55 subjects)

95% Confidence Intervals

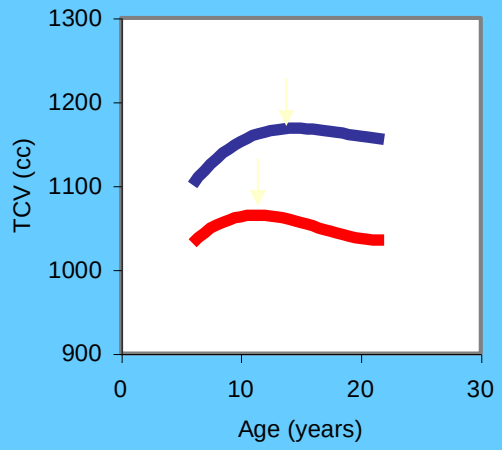
From Jay Giedd, NIMH with permission

Sex Differences in *Trajectories*

224 Females (375 scans) 287 Males (559 scans)

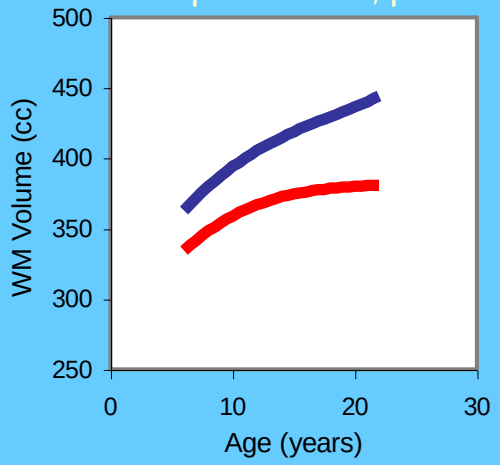
Total Cerebral Volume

Shape: F=9.26; p<.0001



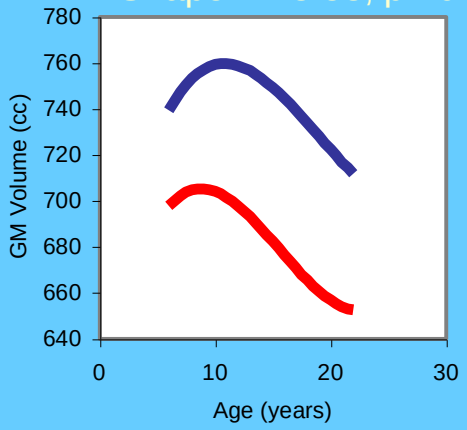
Total White Matter

Shape: F=9.75; p<.0001



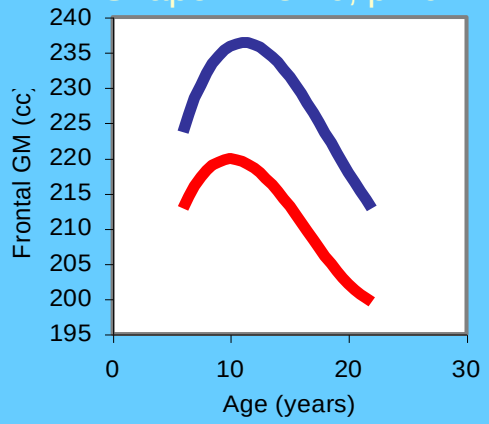
Total Gray Matter

Shape: F=3.58; p=.014



Frontal Gray Matter

Shape: F=3.16; p=.024



From Jay Giedd, NIMH with permission

Are brains of children and adolescents different?

Are brains of children and adolescents different?

Gray Matter

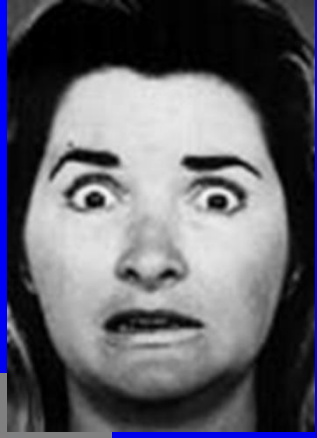
Brain Development in Healthy Children & Adolescents

Longitudinal and Cross-Sectional Data
(243 Scans from 145 Subjects)

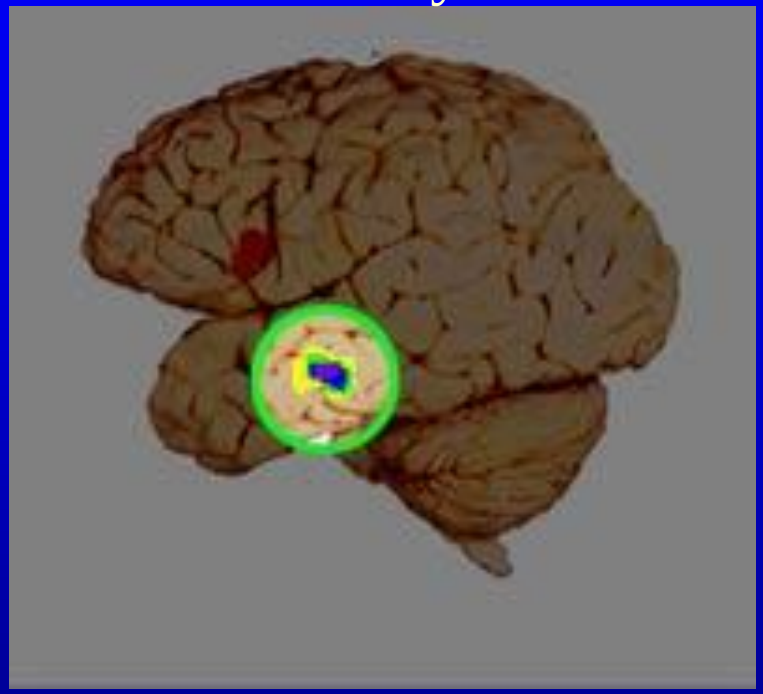
Frontal Gray Matter

From Jay Giedd, NIMH with permission

Reading Emotions Differently



12y

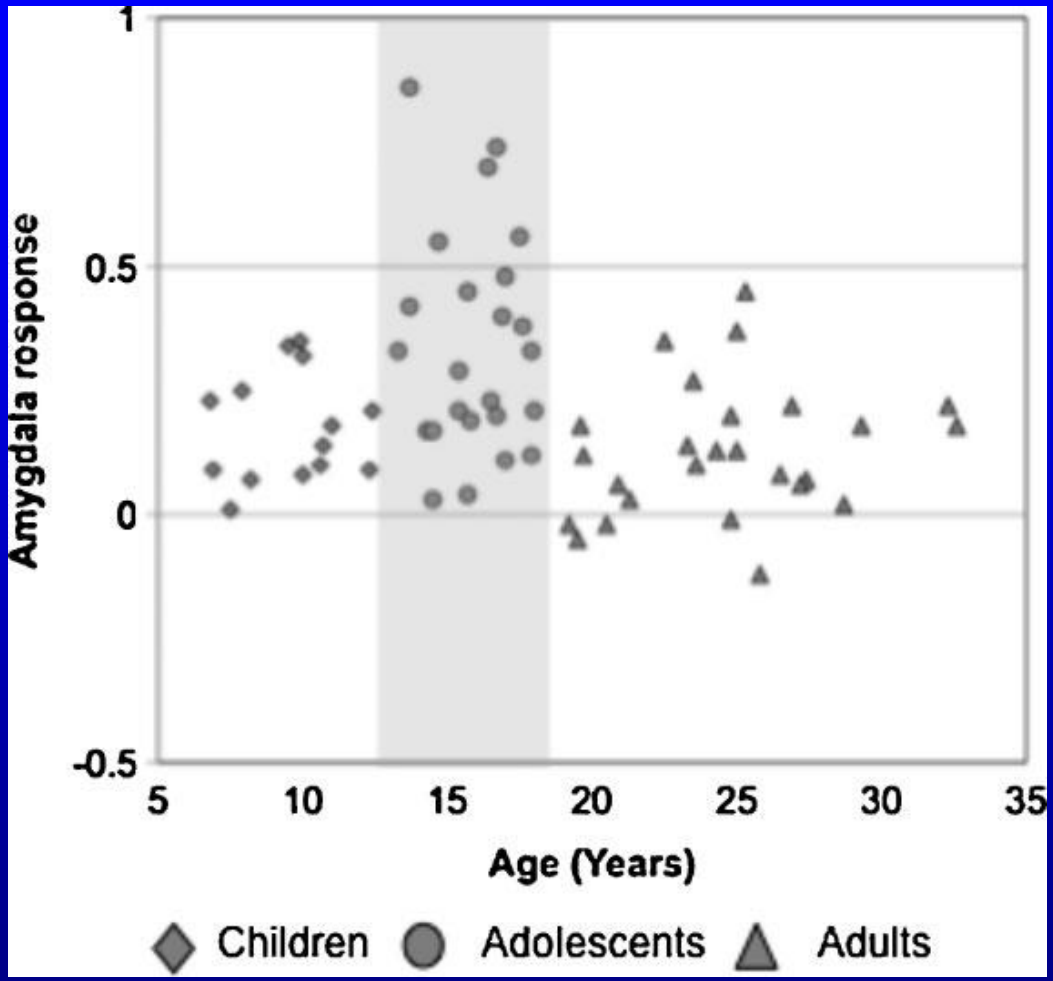


22y

When reading emotion, teens **(left)** rely more on the amygdala, while adults **(right)** rely more on the frontal cortex.

Deborah Yurgelon-Todd, 2000

Amygdala response to fearful faces as a function of age.



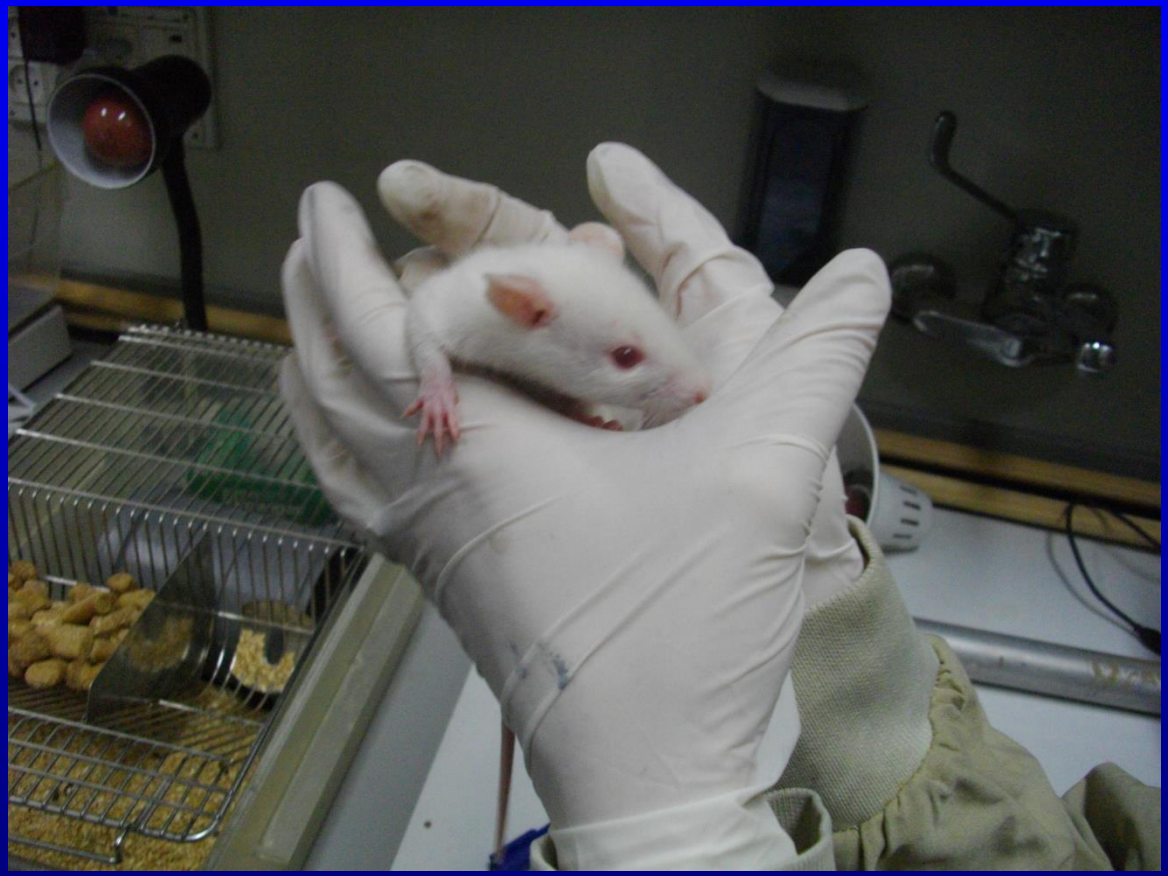
Casey et al., Dev Psychobiol 52: 225–235, 2010.

Hare et al., Biological Psychiatry 63:927-934, 2008.

Suggested model

Zalsman G. Timing is critical. Eur Psychiatry. 2010;25(5):284-6

WKY



WKY

The Wistar Kyoto (WKY) rat, is stress-reactive, and is considered as a "genetic animal model of depression" with anxiety-like behaviors

Depression-like symptoms under stress:

- **Reduced body weight**
- **Disturbed REM sleep**
- **Increased immobility duration in the swim test**
- **Greater "anhedonia" (reduced consumption of a sweet solution)**
- **Symptoms can be prevented by chronic antidepressant treatment**

(Lahmane et al., 1997).

(Exposure to stress) at different developmental windows

G x E x Gender x T

T1 (27)

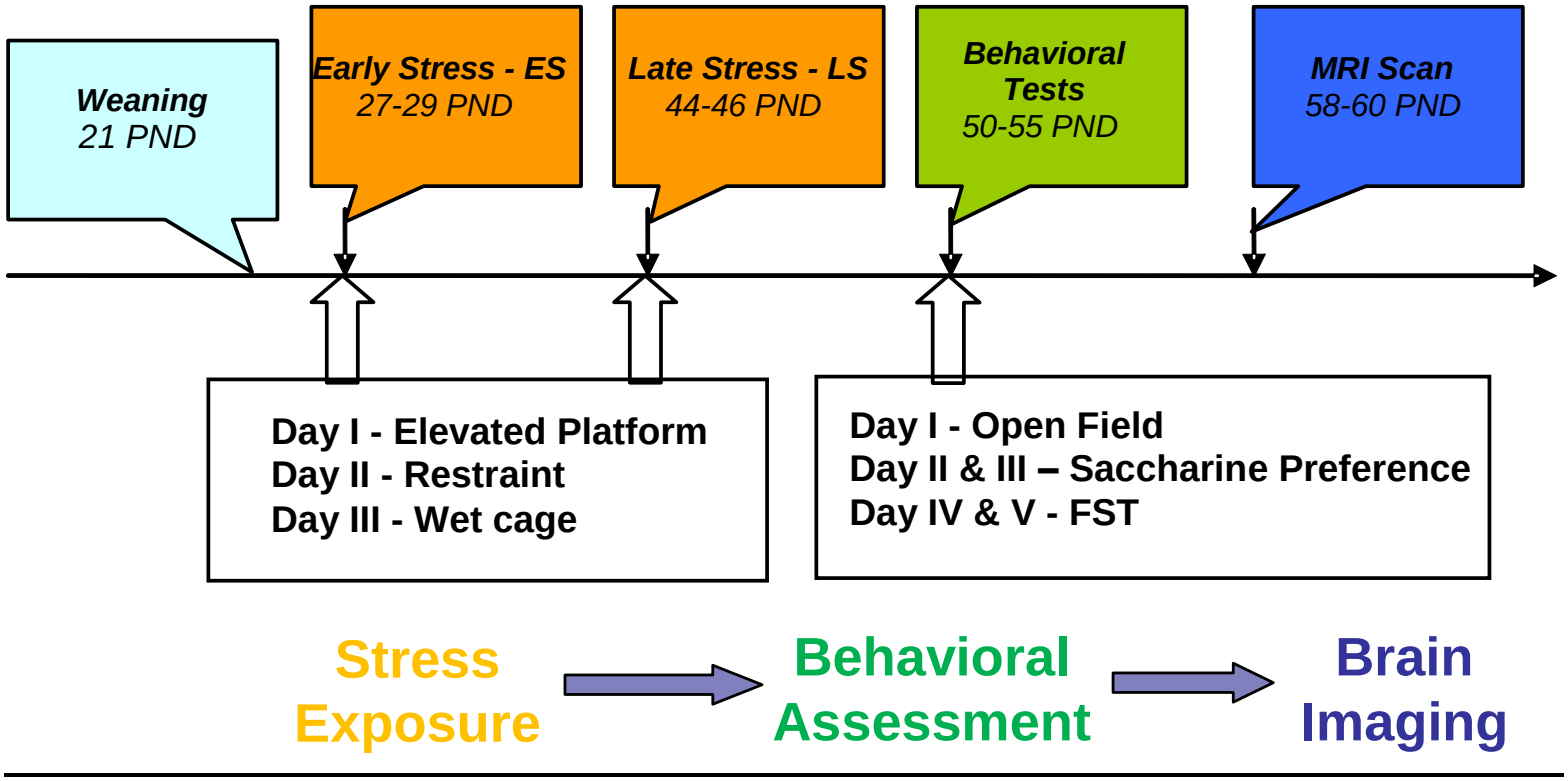
T2 (44)

T3 (58)

♂

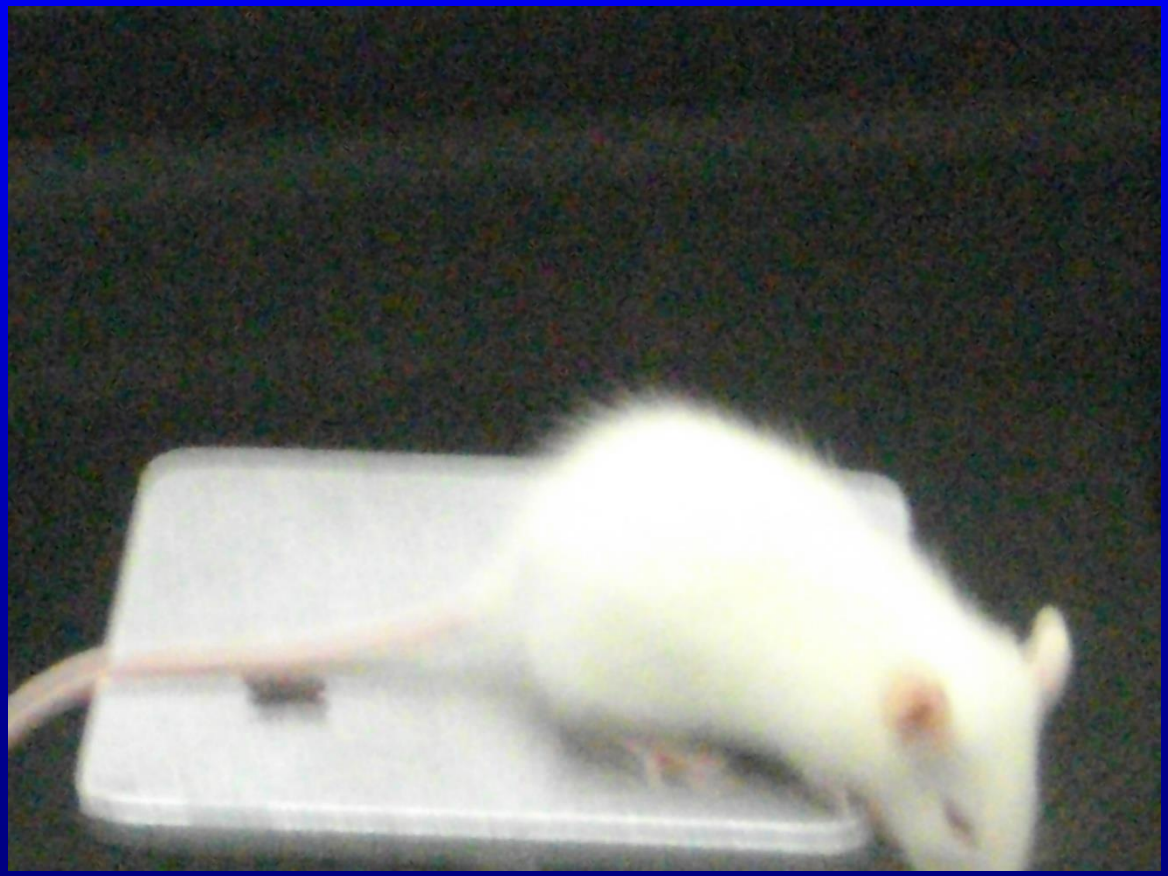
WKY

Study design

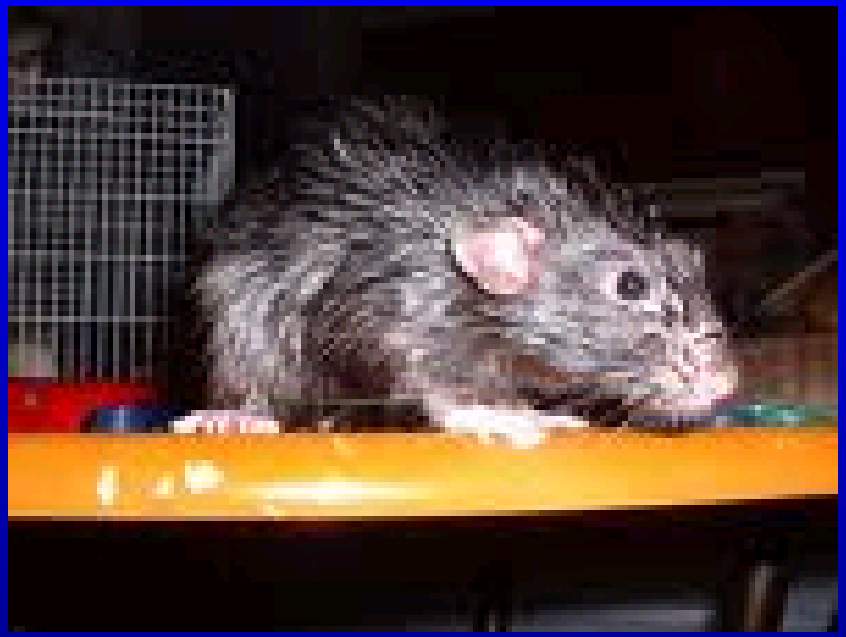


Acute Stress

Acute Stress



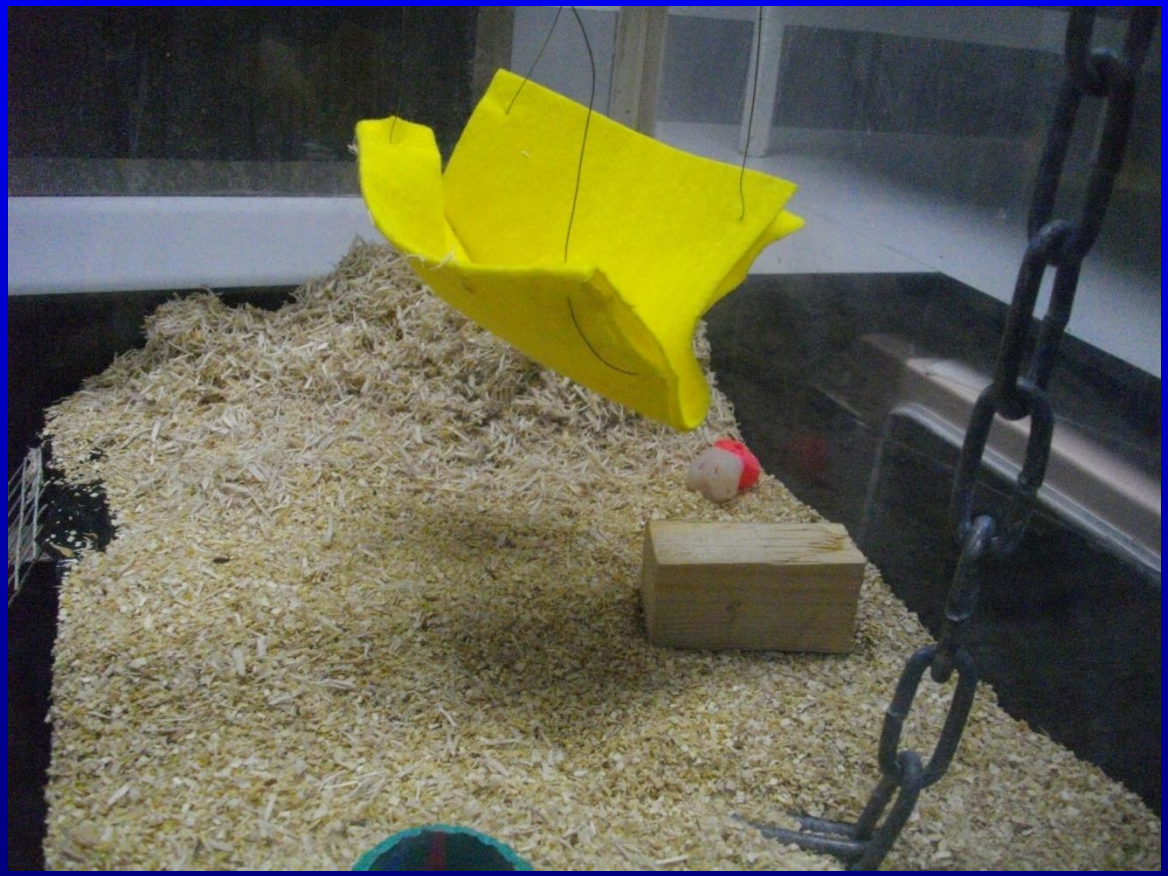
Wet cage



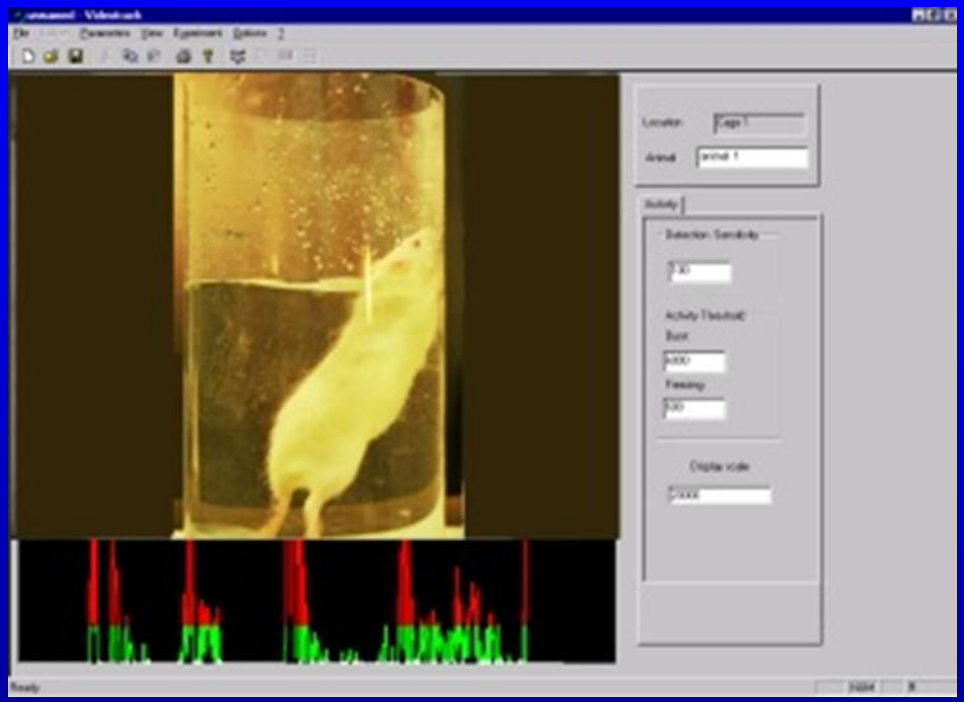
Enrichment (psychotherapy)

Enriched Environment

Enriched Environment



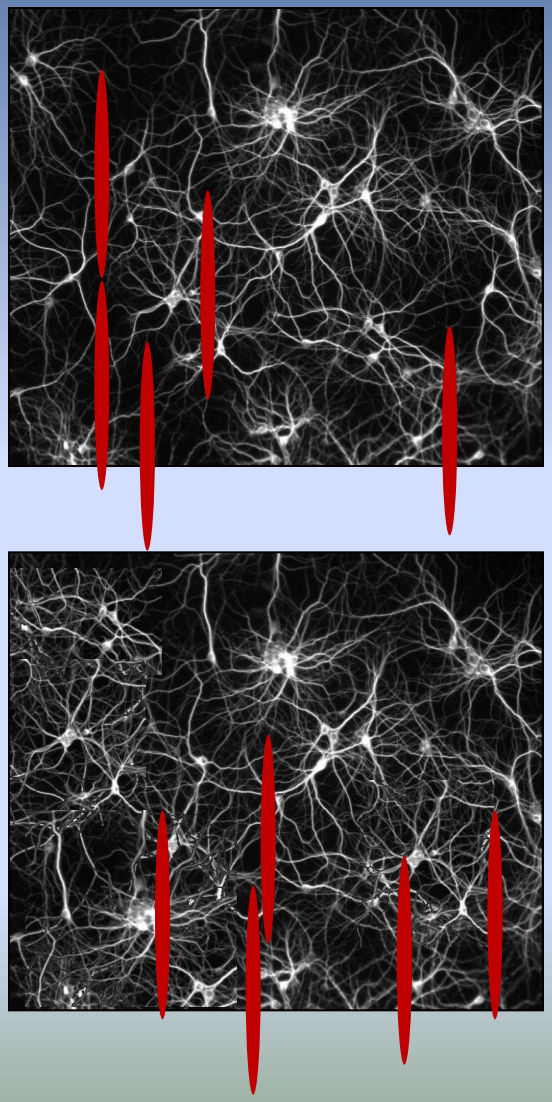
Saccharin test for anhedonia
Swim test for dispare



Rats MRI

Tel Aviv University MRI

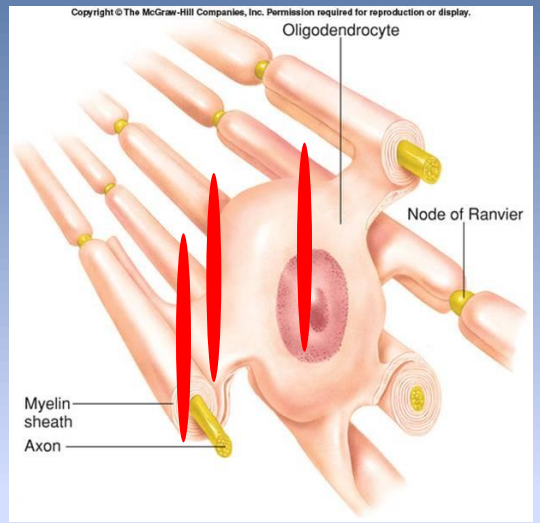
DTI – microstructure in gray matter



Sparse cells -
higher diffusion
higher ADC

Dense cells –
Lower diffusion
Lower ADC

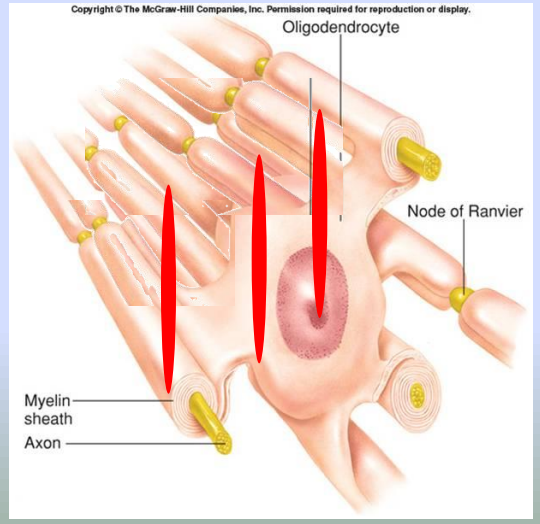
DTI – microstructure in white matter



Sparse axons -

higher diffusion – **higher ADC**

lower anisotropy - **lower FA**



Dense axons –

lower diffusion – lower ADC

higher anisotropy - higher FA

Results

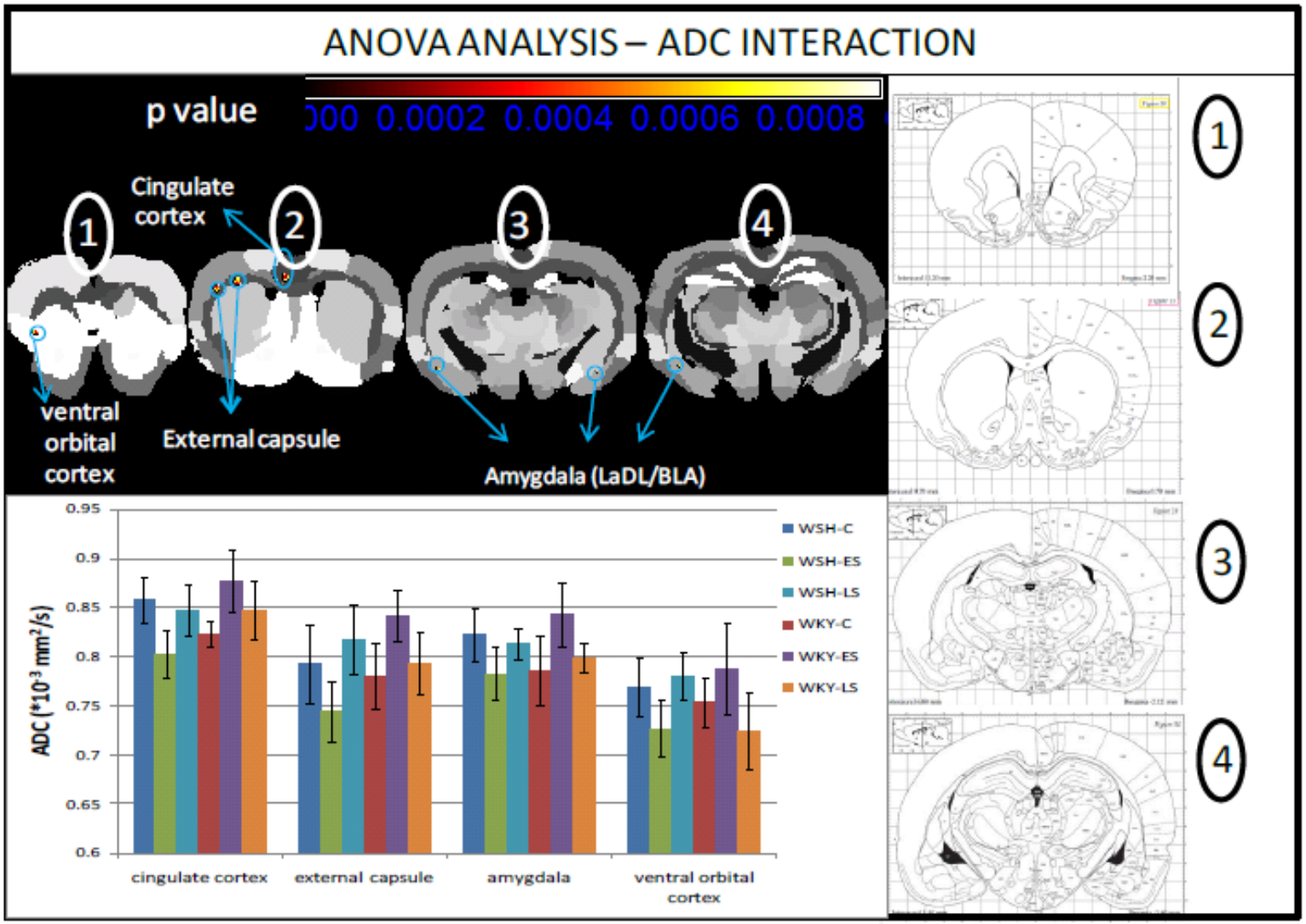
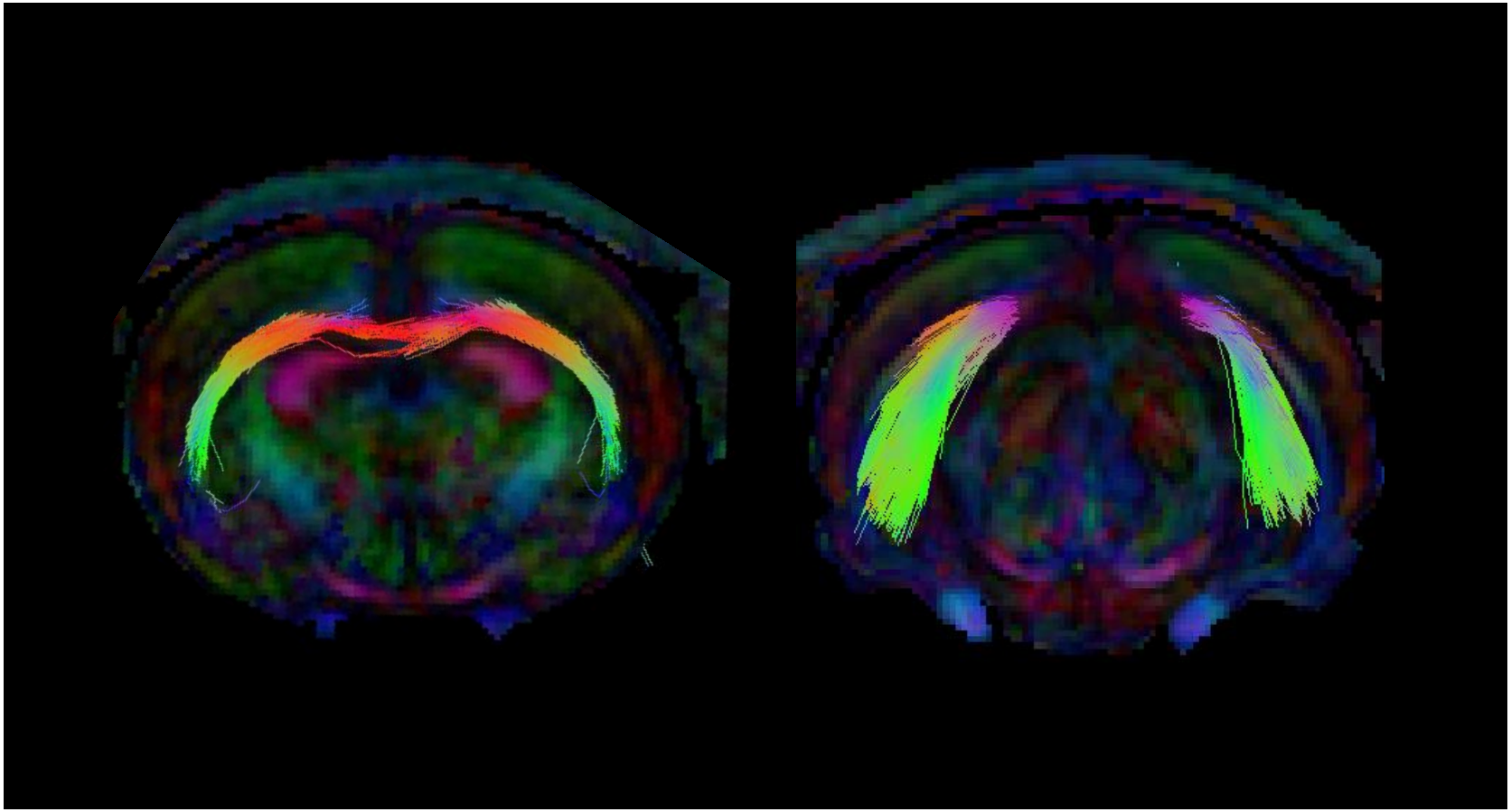


Figure 2: ADC interaction. The graph presents the 6 groups: wistar control- WSH-C (blue); wistar early stress – WSH-ES (green); wistar late stress – WSH-LS (cyan); WKY control – WKY-C (red); WKY early stress – WKY-ES (purple); WKY late stress – WKY-LS (orange). The significant clusters with the interaction marked on the atlas slices regions corresponding to paxinos & watson atlas.

DTI Results for GXEXT

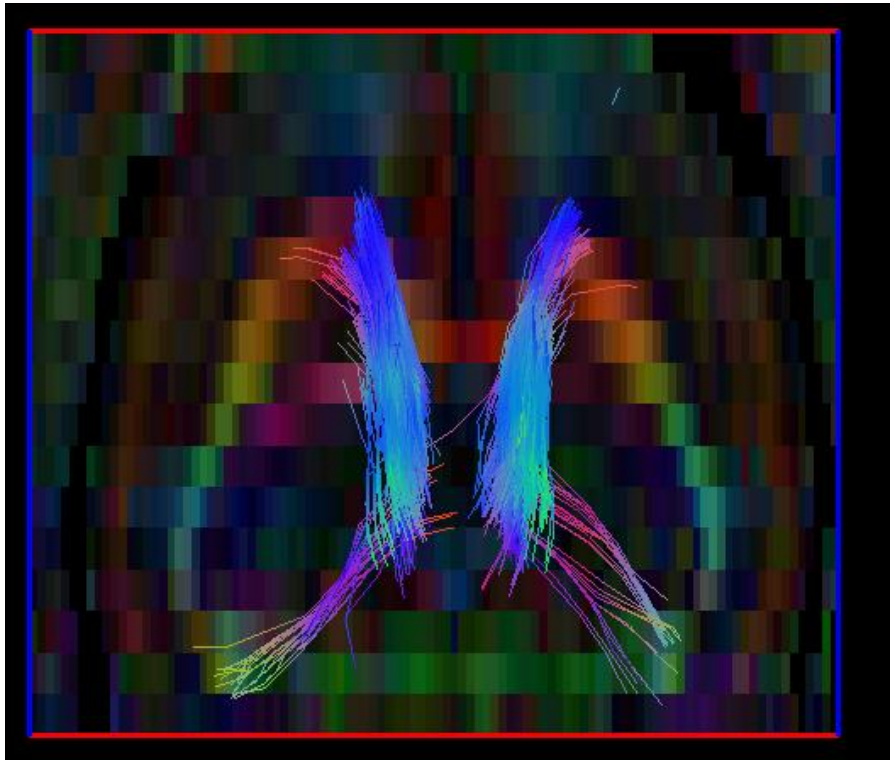
Significant interactions were found in the following regions: ventral orbital cortex (VO), cingulate cortex (Cg1 and Cg2), external capsule and the amygdala (lateral amygdaloid nucleus, dorsolateral part – LaDL; basolateralamygdaloid nucleus, anterior part – BLA).

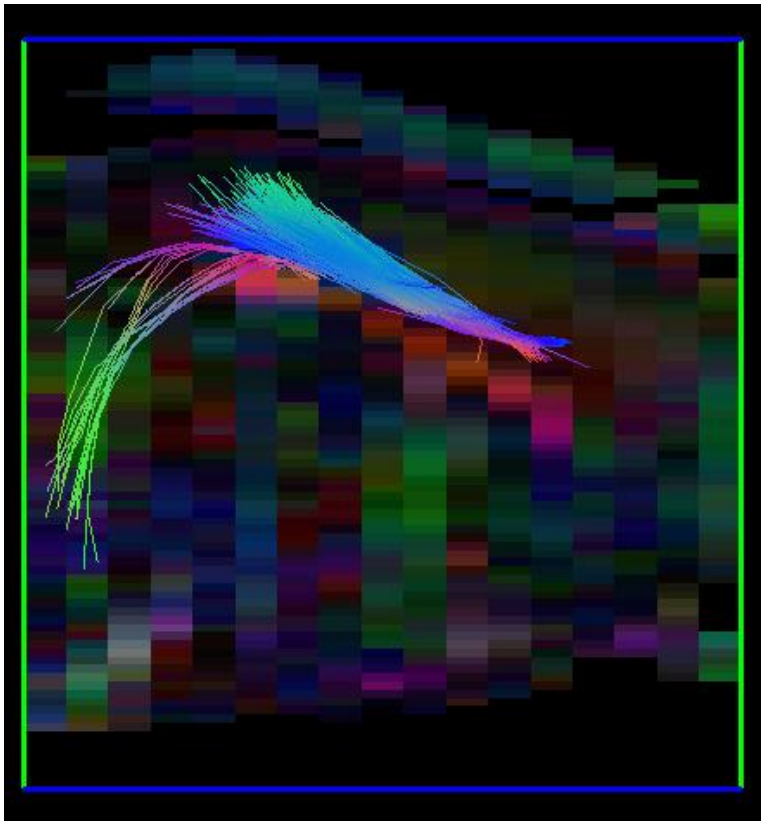
Fiber tracking



Corpus Callosum (CC)

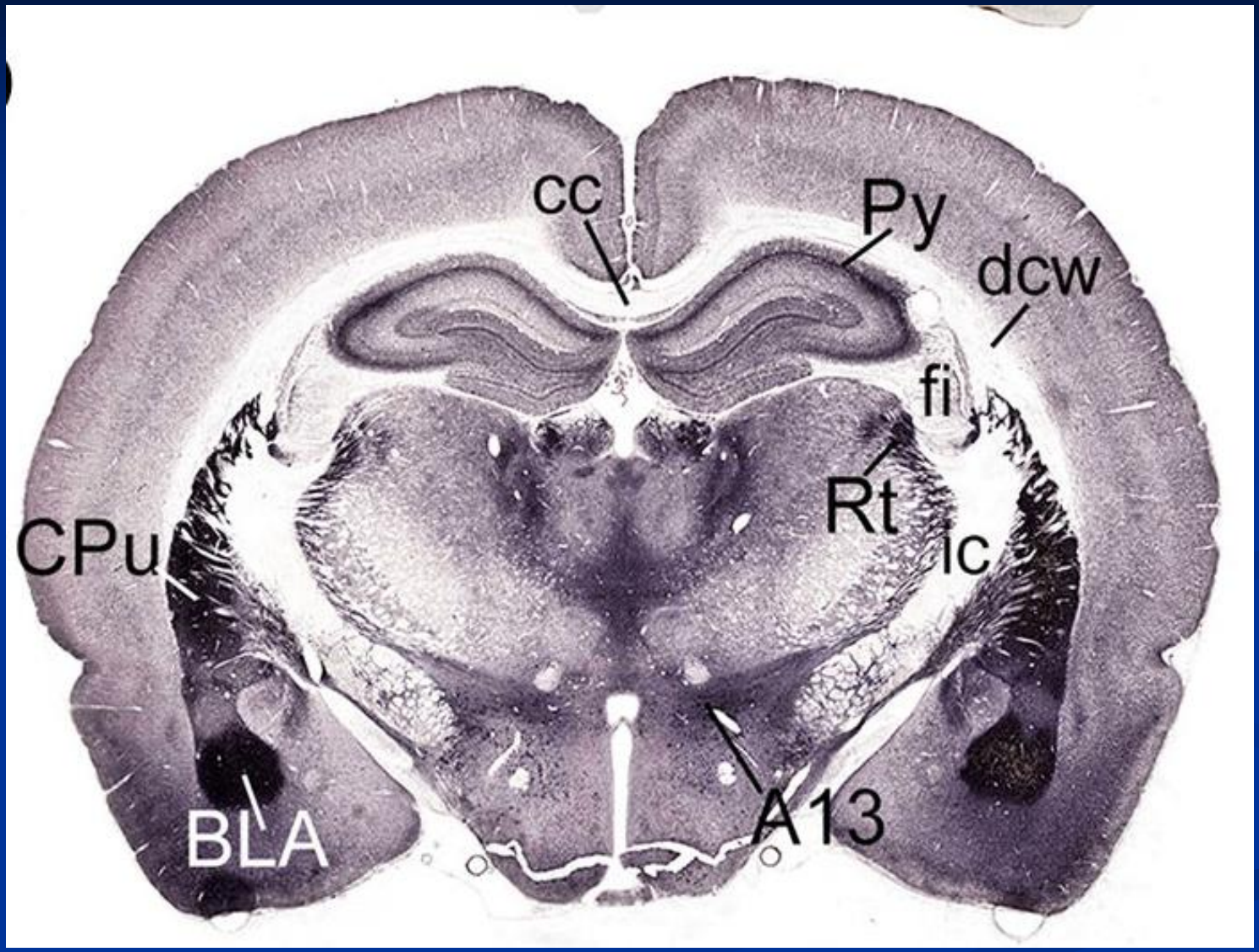
Cingulum





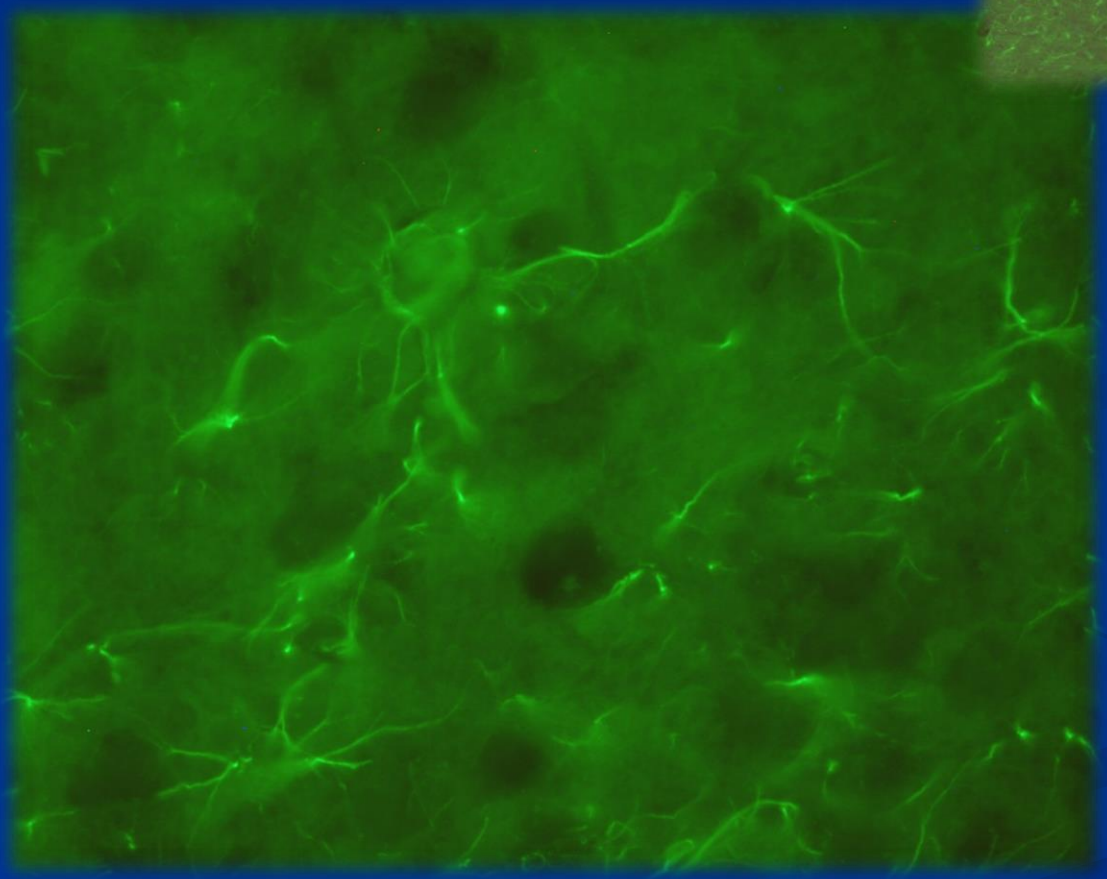
Results of Fiber Tracking: Decreased connectivity in the "depressed" brain

- **The WKY rat model exhibit overall decreased connectivity, as demonstrated by DTI parameters.**
- **Compared to control rats, WKY model exhibited decreased fractional anisotropy (FA) in the corpus callosum (P=0.035), the left cingulum (P=0.021) and right and left anterior commissure (P=0.012 and P=0.022, respectively).**
- **Low FA= less cells**
- **These results are consistent with findings in human depressed patients.**



Taken from gyangesi et al., 2014, brain struct funct.

Astrocyts



Limitations

Conclusions

Stressful exposures in pre-pubertal or adolescent phases in development may influence differently the structural integrity of specific brain regions and emotion regulation behaviors and this is moderated by the genetic vulnerability of the subject to depression and despair.

These findings indicate a possible GxExT interaction in mood dysregulation that is a core symptom in the development of depression and suicidal behavior in the young.

Our Team

Lab personnel

- Aron Weller
- Liat Shbiro
- Avihai Gutman
- Ruth Rosnan

Columbia University

- J John Mann

Tel Aviv University

- Abraham Weizman
- Alan Apter

Karolinska Institute

- Danuta Wasserman

AFSP young investigator grant-2005-2007 (Zalsman)
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The National Institute for Psychobiology in Israel Grants 29/98, 9b/99 (Zalsman)

My presentation can be downloaded from

www.zalsman.org