Predicting Psychosis: Promising Research in Early Identification, Intervention and Prevention

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I Have Nothing to Disclose

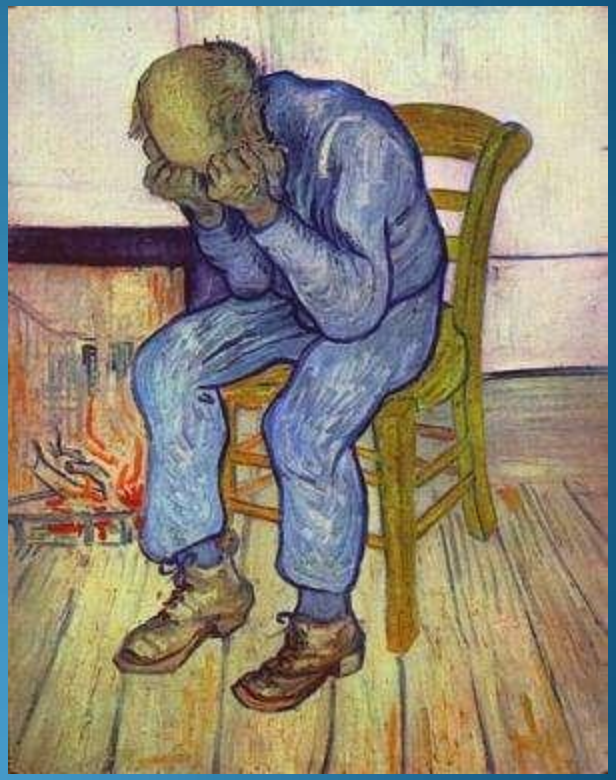
care

COGNITIVE ASSESSMENT AND RISK EVALUATION

Early Identification, Intervention and Prevention of Psychosis in Adolescents and Young Adults

What is Psychosis?

- Conditions that affect the mind, where there has been some loss of contact with reality.
- Thoughts and perceptions are disturbed and the individual may have difficulty understanding what is real and what is not.



Psychotic Symptomotology

Positive Symptoms

- Hallucinations
- Delusions

Cognitive Deficits

- Memory
- Attention
- Language
- Executive Function

Mood Symptoms

- Depression
- Dysphoria
- Suicidality
- Euphoria
- Irritability

Disorganized Symptoms

- Bizarre Behavior
- Thought Disorder

Negative Symptoms

- Apathy/Avolition
- Anhedonia
- Alogia
- Inattention
- Poor social function
- Poverty of thought
- Blunted affect

A series of paintings by Louis Wain from the early 1900's.

Differential Diagnosis of Psychosis

Primary Psychotic Disorders

- Schizophrenia
- Schizoaffective disorder
- Brief psychotic disorder
- Delusional disorder

Affective Disorders

- Bipolar I disorder, manic episode
- Major depression with psychotic features

Differential Diagnosis of Psychosis

Secondary Psychotic Disorders

- Substance induced psychotic disorder
- Psychosis secondary to a general medical condition
- Delirium
- Dementia

Leading Causes of Disability

Ages 15-44 in Developed Regions

Both Sexes	Males	Females
1. Major Depression	1. Alcohol use	1. Major depression
2. Alcohol Use	2. Traffic accidents	2. Schizophrenia
3. Traffic accidents	3. Major depression	3. Traffic accidents
4. Schizophrenia	4. Self-inflicted injuries	4. Bipolar disorder
5. Self-inflicted injuries	5. Schizophrenia	5. OCD
6. Bipolar Disorder	6. Drug use	6. Alcohol use
7. Drug use	7. Violence	7. Osteoarthritis

Murray and Lopez, 1996

Early Identification, Intervention and Prevention of Psychosis in Adolescents and Young Adults

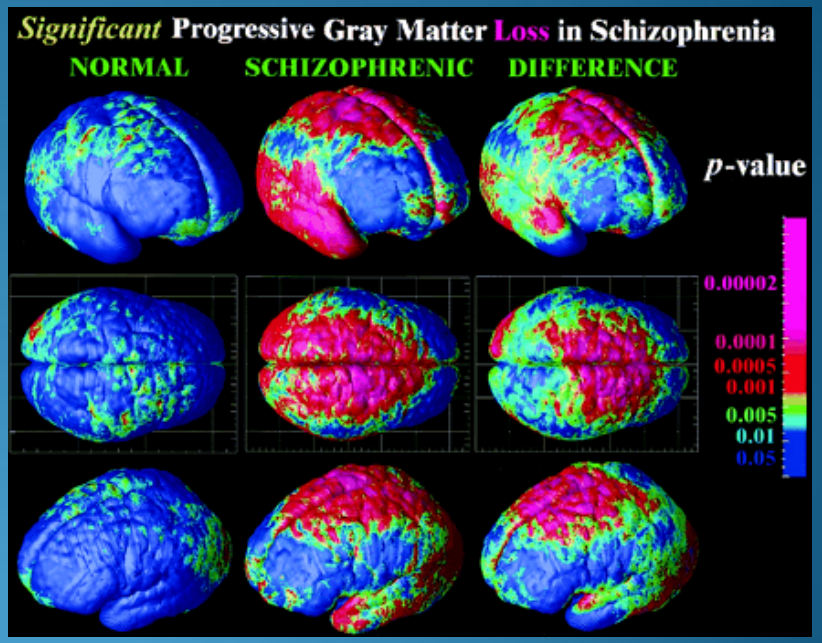
Problem

- Prevalence of Schizophrenia: 2.2 million US
- 100K new onset of psychosis per year in US
- Significant cause of lifetime disability in young people
- Duration of Untreated Psychosis 1-2 years in most studies

Solution

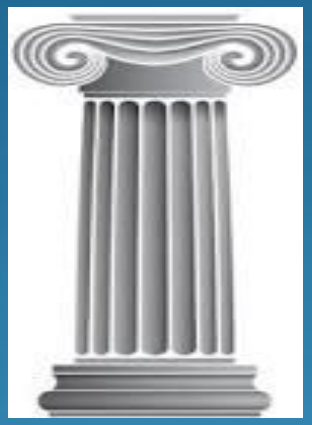
- Early identification and intervention can improve prognosis, reduce costs
- Identify neuropathological mechanisms at psychosis onset and develop precision pre-emptive treatment

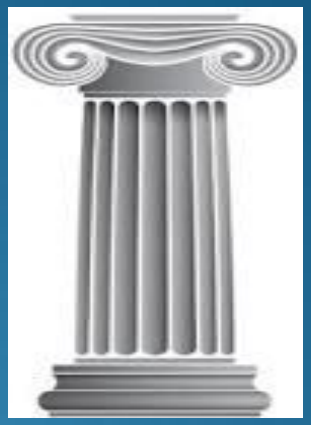
A Window of Opportunity: Intervene During Early Brain Development



Thompson et al 2001, Proc. Natl. Acad. Sci

Psychosis Prevention

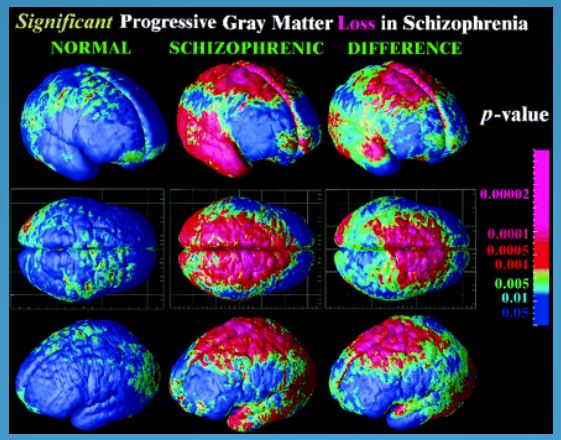




Early Identification Prediction

Identify Mechanisms of Disease Onset

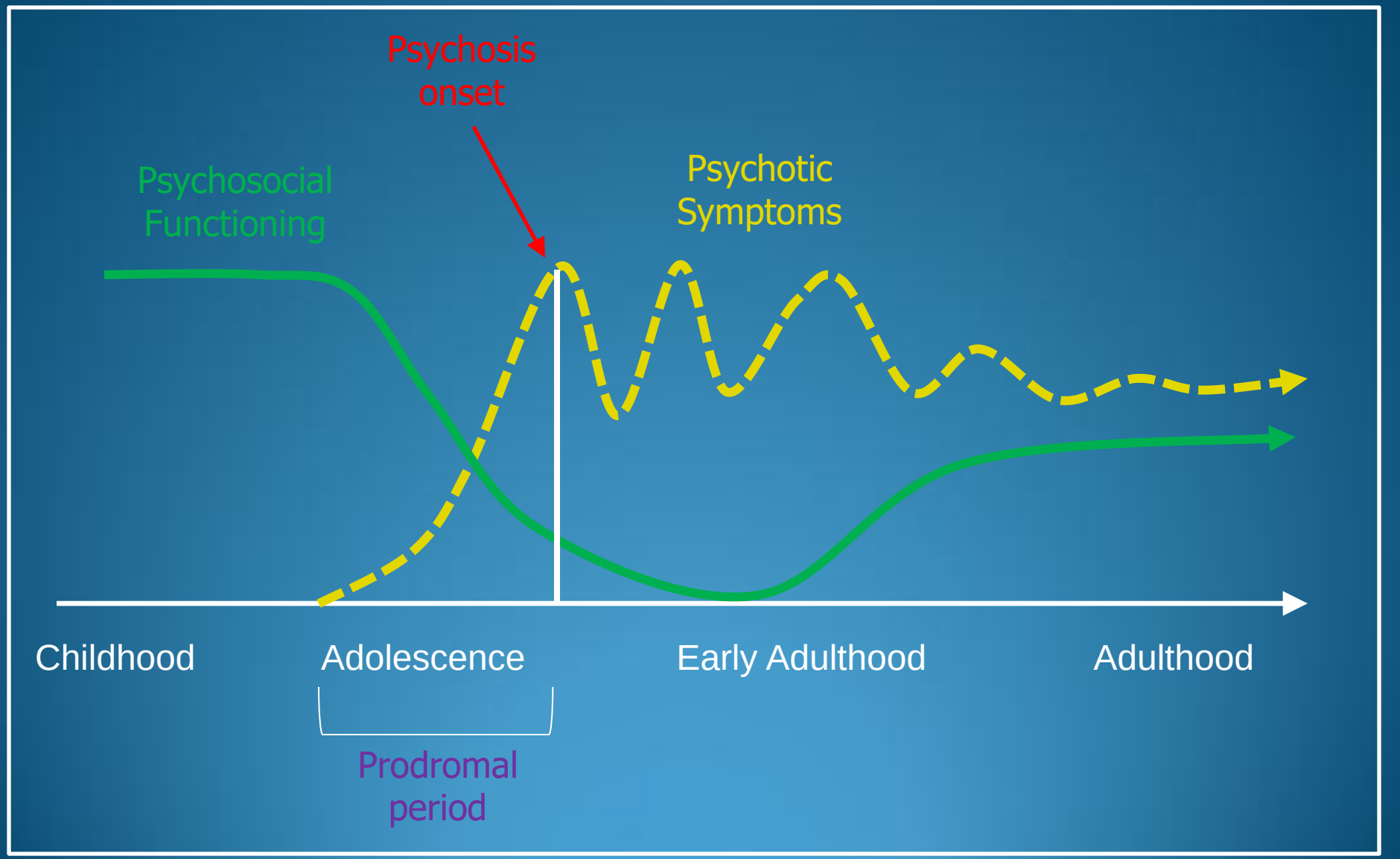
Targeted Intervention



Early Identification and Prevention of Illness

- Cancer
- Diabetes
- Osteoporosis
- Heart Disease

Moving from reactive to proactive with early detection



The Prodrome of Schizophrenia

- Period of altered functioning or symptomatology before the onset of frank or threshold psychosis.
- Prodromal symptoms and signs tend to be non-specific and, therefore, prospective detection is complicated by a high false-positive rate.
- The mental state thought to be a prodrome is best termed as “At-Risk”, “Clinical High Risk” or “Ultra High Risk”, a state that confers high, but not inevitable risk of development of a psychotic disorder in the near future.

*Yung AR, McGorry PD . The prodromal phase of first episode psychosis: past and current conceptualisations. Schizophrenia Bulletin 1996; : 353– 370.

Who Is at Risk?

- Young people between the ages of 12 and 30 who are experiencing the new onset of subsyndromal psychotic symptoms.
- Relatives of schizophrenia patients who are demonstrating a deterioration in functioning

DSM V Proposed Criteria for Psychosis Risk Syndrome

- At least one of the following symptoms is present in attenuated form, with relatively **intact reality testing**, and is of sufficient severity or frequency to warrant clinical attention:
  - Delusions.
  - Hallucinations.
  - Disorganized speech.
- Symptom(s) present at least 1X/week for the past month.
- Symptom(s) must have begun or worsened in the past year.
- Symptom(s) is distressing and disabling.
- Symptom(s) is not better explained by another mental disorder and is not attributable to the physiological effects of a substance.
- Criteria for any psychotic disorder have never been met

Community Outreach and Education

- Schools, Colleges, Universities
- Mental Health Practitioners
- Primary Care Providers
- Advocacy Groups – National Alliance for Mentally Ill
- Internet

UCIN

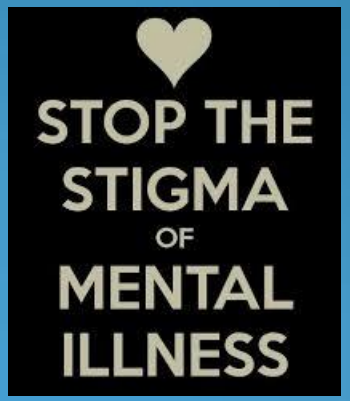

A mental illness is a disease, not a choice.
END THE STIGMA
mani


IMAGINE IF YOU GOT BLAMED FOR HAVING CANCER.
END THE STIGMA & DISCRIMINATION OF MENTAL ILLNESS @ bringchange2mind.org


Shatter the Stigma
Mend the Mind


STAND UP TO STIGMA
Let's talk about MENTAL HEALTH


EachMind MATTERS
California's Mental Health Movement


STOP THE STIGMA OF MENTAL ILLNESS


STOP THE JUDGMENT
START THE HEALING

Contents lists available at ScienceDirect

Schizophrenia Research

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

Psychosis risk screening with the Prodromal Questionnaire — Brief Version (PQ-B)

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[a] Department of Psychiatry, University of California at San Francisco, San Francisco, CA, United States
[b] San Francisco Department of Veteran's Affairs Medical Center, San Francisco, CA, United States
[c] Department Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles, CA, United States
[d] Department of Psychology, University of California at Los Angeles, Los Angeles, CA, United States

Please indicate whether you have had the following thoughts, feelings and experiences **in the past month** by checking "yes" or "no" for each item. **Do not include experiences that occur only while under the influence of alcohol, drugs or medications that were not prescribed to you.** If you answer "YES" to an item, also indicate how distressing that experience has been for you.

1. **Do familiar surroundings sometimes seem strange, confusing, threatening or unreal to you?**
   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

2. **Have you heard unusual sounds like banging, clicking, hissing, clapping or ringing in your ears?**
   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

3. **Do things that you see appear different from the way they usually do (brighter or duller, larger or smaller, or changed in some other way)?**
   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

4. **Have you had experiences with telepathy, psychic forces, or fortune telling?**
   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

5. **Have you felt that you are not in control of your own ideas or thoughts?**
   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

Clinical High-Risk Paradigm

- Clinical high-risk criteria designed to capture population at risk of imminent onset
- Rates of conversion to full psychosis
  - 15% by 1 year
  - 30% by 2 years
- Diagnostic outcomes
  - ~80% schizophrenia spectrum
  - ~20% mood and atypical psychoses

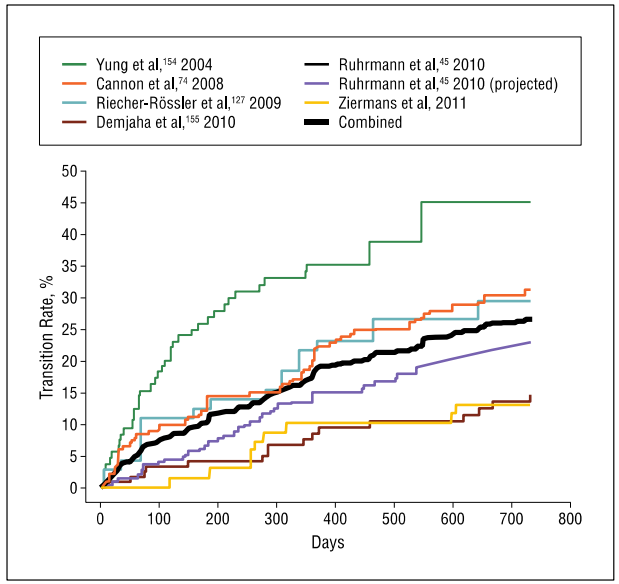


Figure 4. Meta-analysis of transition risk in studies reporting Kaplan-Meier estimates of psychosis transition over time in the high-risk state (n=984 individuals) (for details of the study, see Fusar-Poli et al[75]). These risks are based on treated cohorts with no standardized treatment, so transition rate estimates are not for natural course or untreated cases.

Fusar-Poli et al. *JAMA Psychiatry* 2013;70:107-1

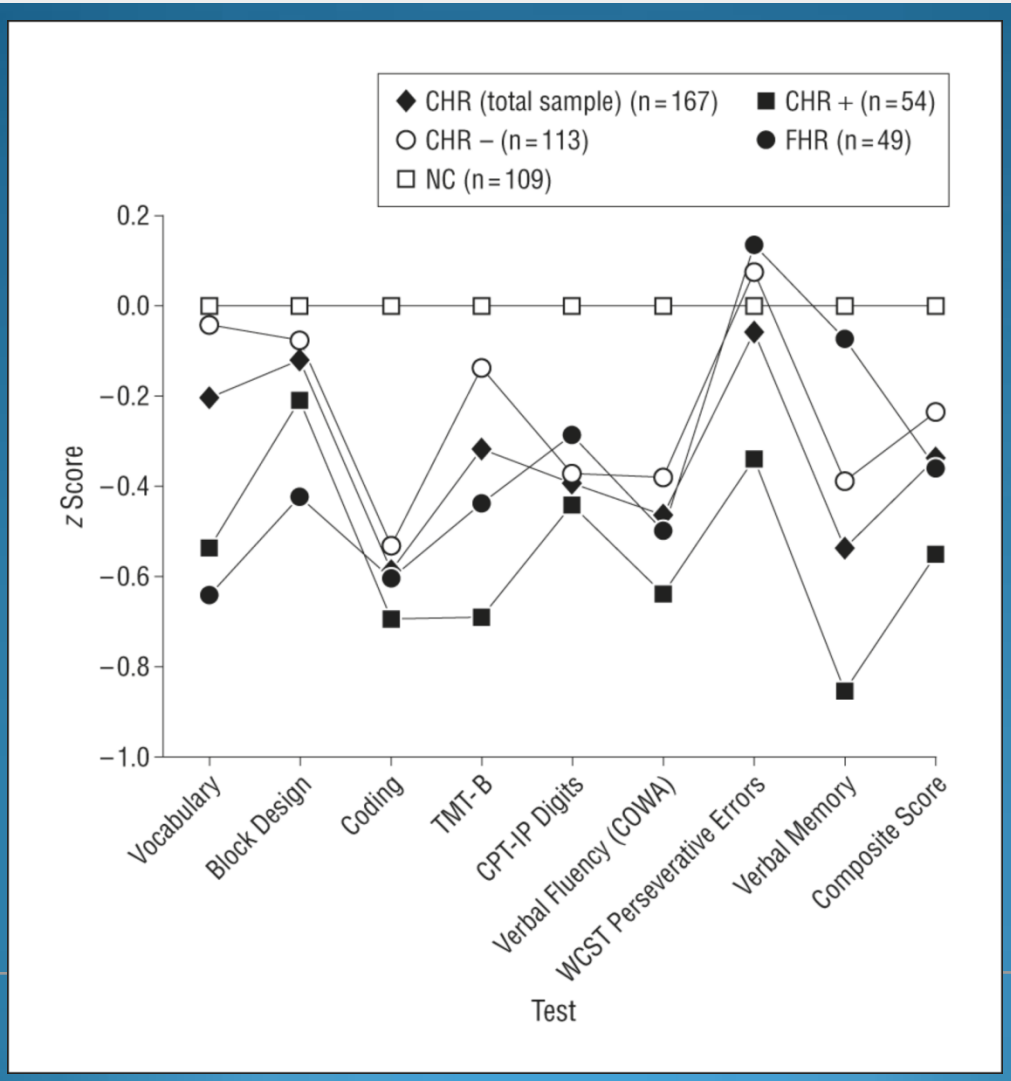
Risk Factors for Psychotic Conversion in the NAPLS1 Study

- Family history of psychosis plus a deterioration in functioning
- Suspiciousness/paranoia
- Unusual thought content
- Decline in social functioning
- Drug abuse

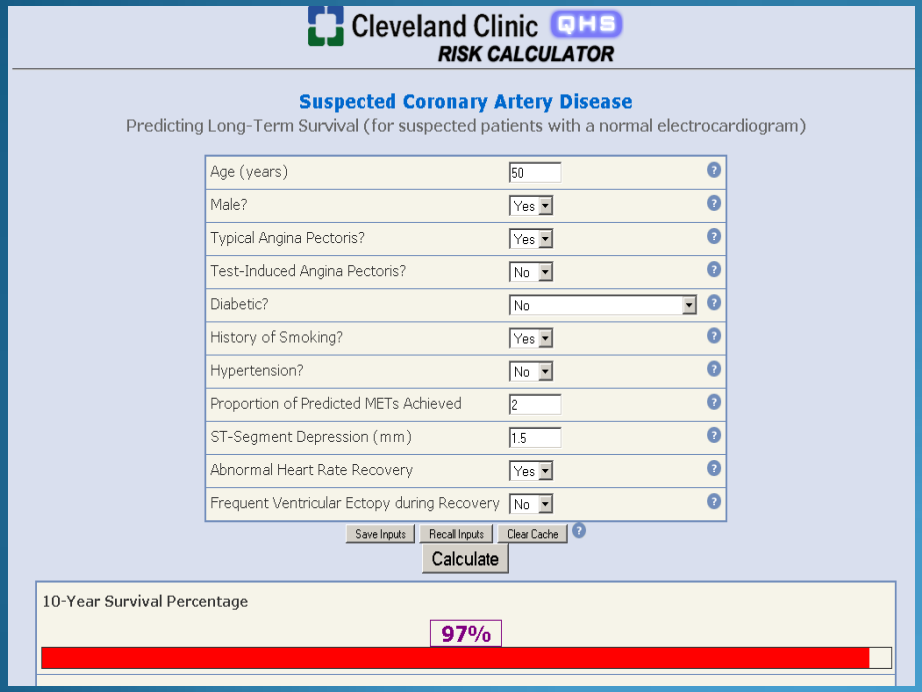
80% Conversion rate when 3 factors combined

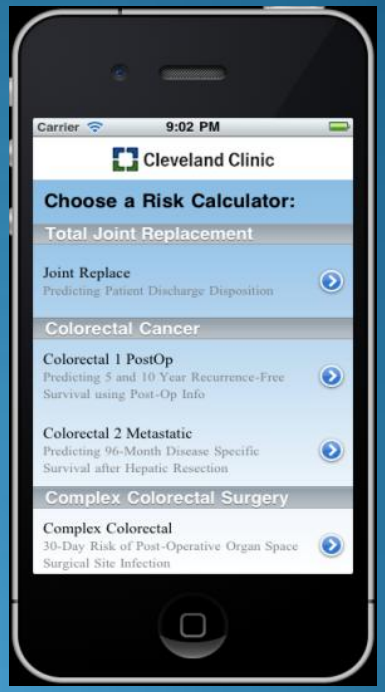
From: **Neuropsychology of the Prodrome to Psychosis in the NAPLS Consortium: Relationship to Family History and Conversion to Psychosis**

Arch Gen Psychiatry. 2010;67(6):578-588



The Development of a Psychosis Risk Calculator





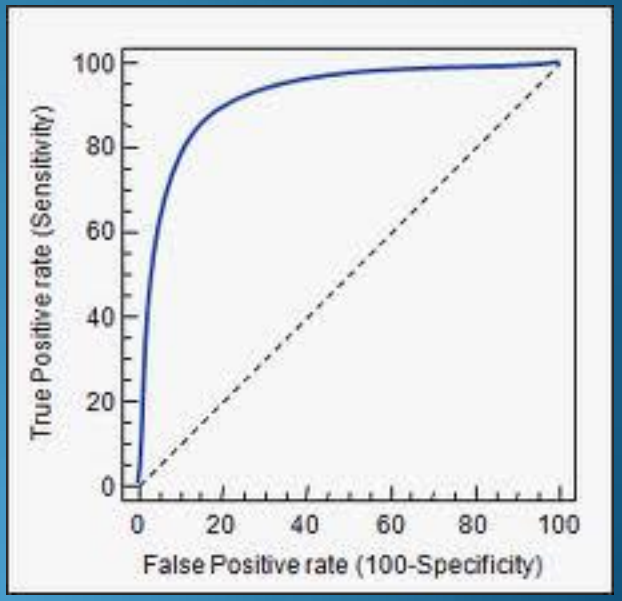
Nomogram Validation by Concordance Index (AUC)

Perfect Discrimination

Coin Toss

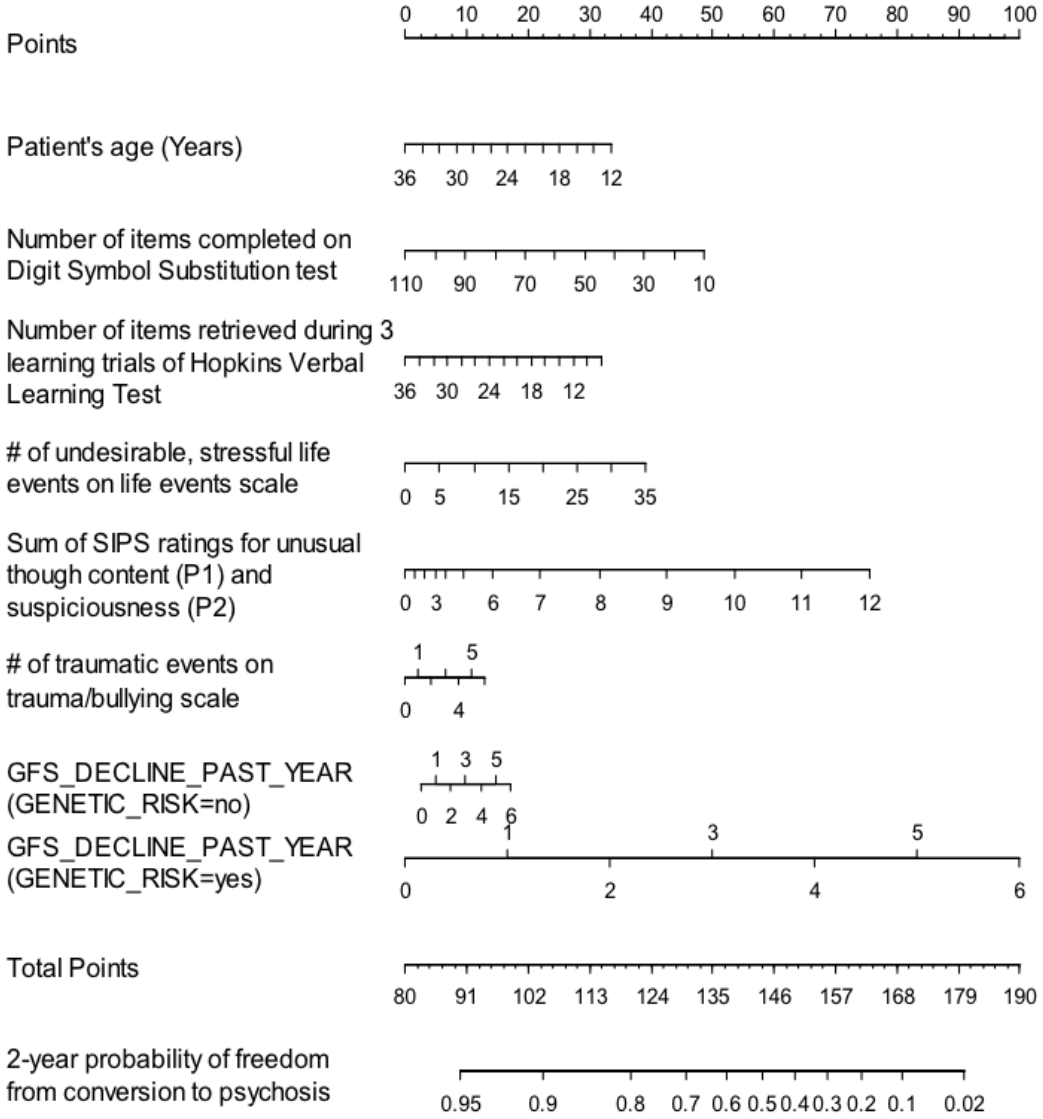
0.5 0.6 0.7 0.8 0 .9 1.0

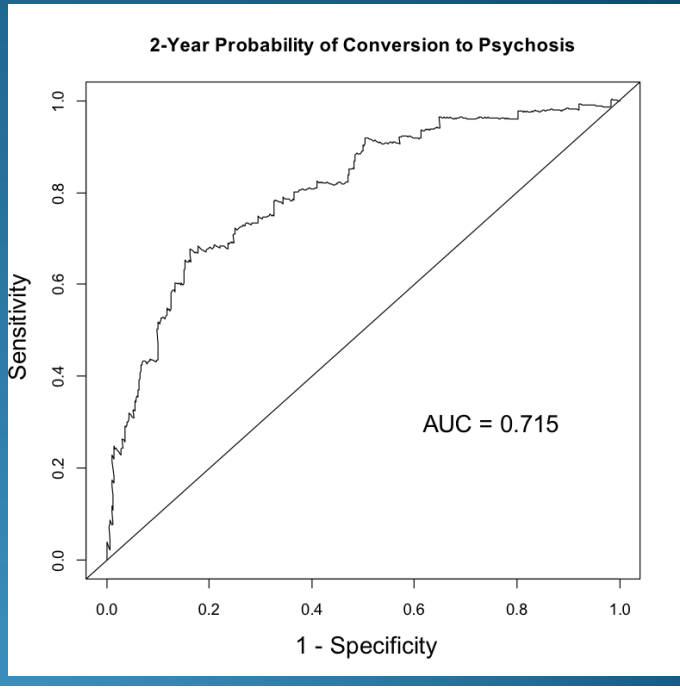
1. Randomly select 2 patients
   a. One of whom fails (reaches the event of interest)
   b. The other must “survive” longer
2. Concordance index is the proportion of these pairs in which patient who fails first also had worse nomogram prediction

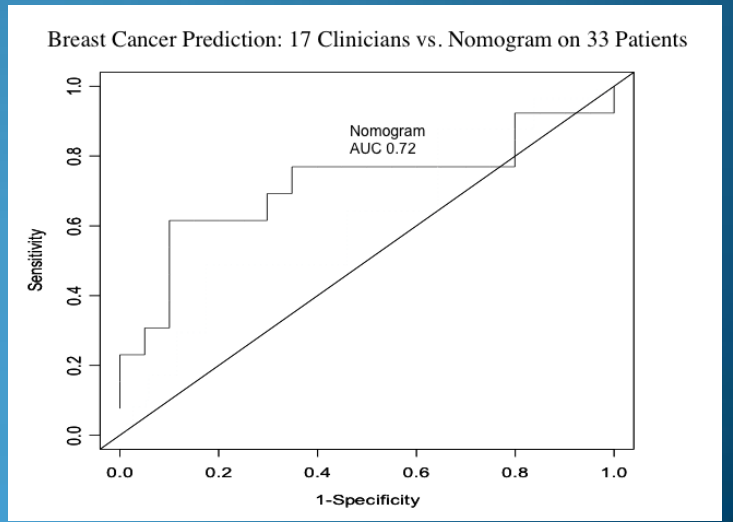


Graefen et al., *JCO*, 2002.

Nomogram for predicting 2-yr probability of freedom from conversion to psychosis

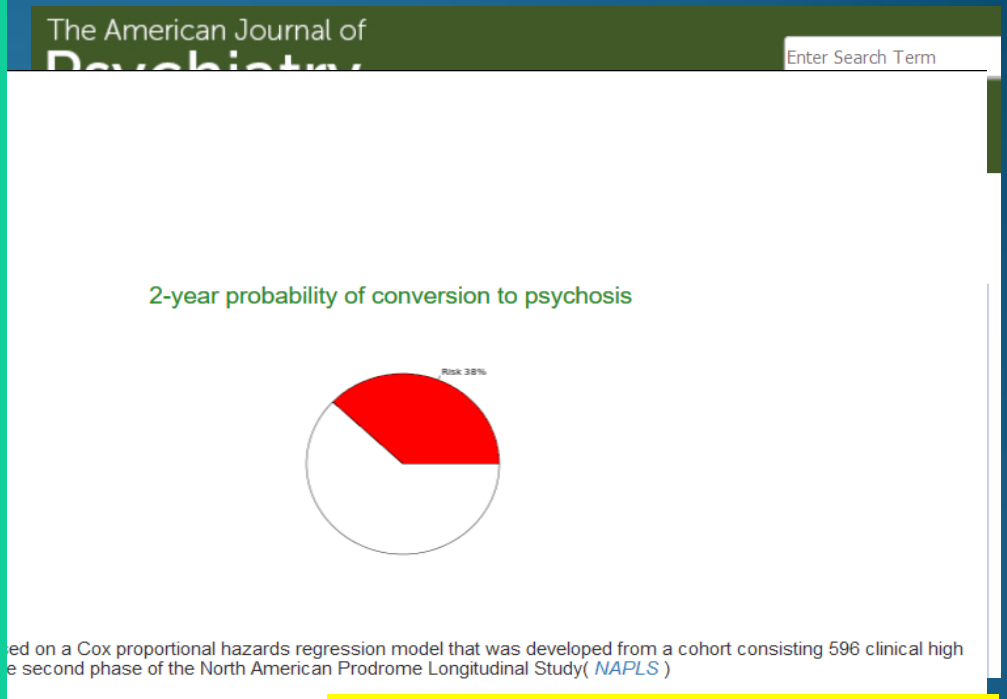






Early Identification: An Individualized Risk Calculator for Psychosis

- "Psychosis Risk Calculator", similar to those used in cardiovascular disease and cancer, identifies those individuals at greatest psychosis risk
- The risk calculator can be validly applied only for patients who screen positive on the Structured Clinical Interview for Psychosis Risk Syndromes, which requires training to administer.
- Important for use in studies of psychosis mechanism and clinical prevention trials



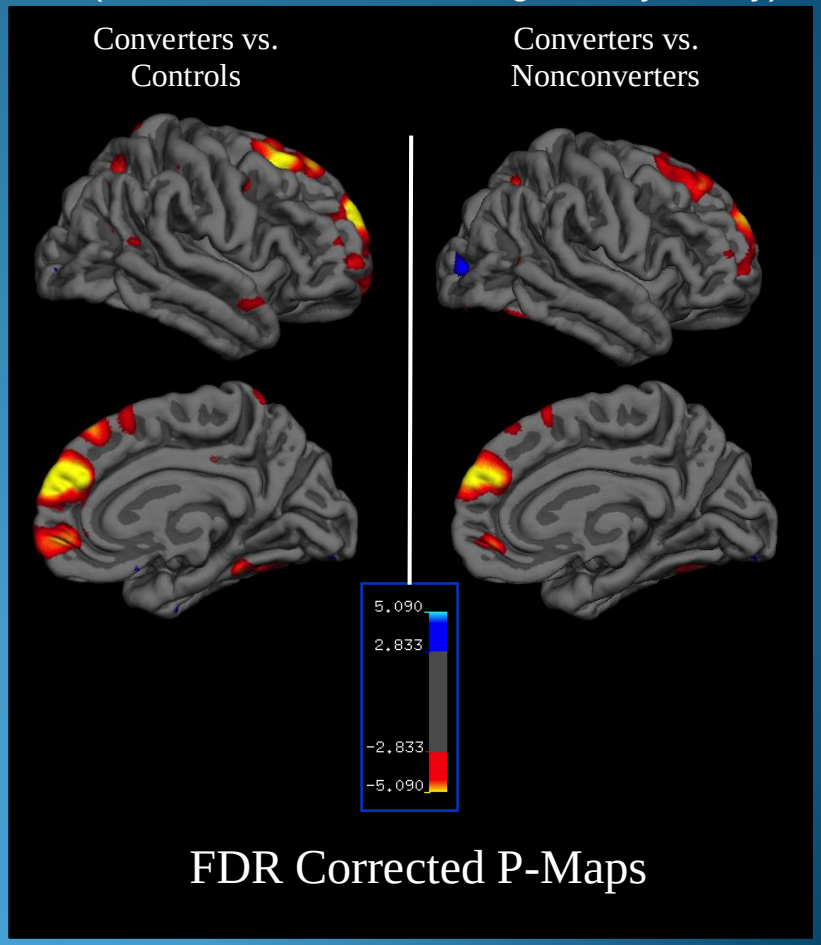
Key Predictors:
- Verbal Learning Deficits
- Slow Processing Speed
- Paranoia/Suspiciousness
- Unusual Thoughts
- Decline in Social Functioning
- Younger Age

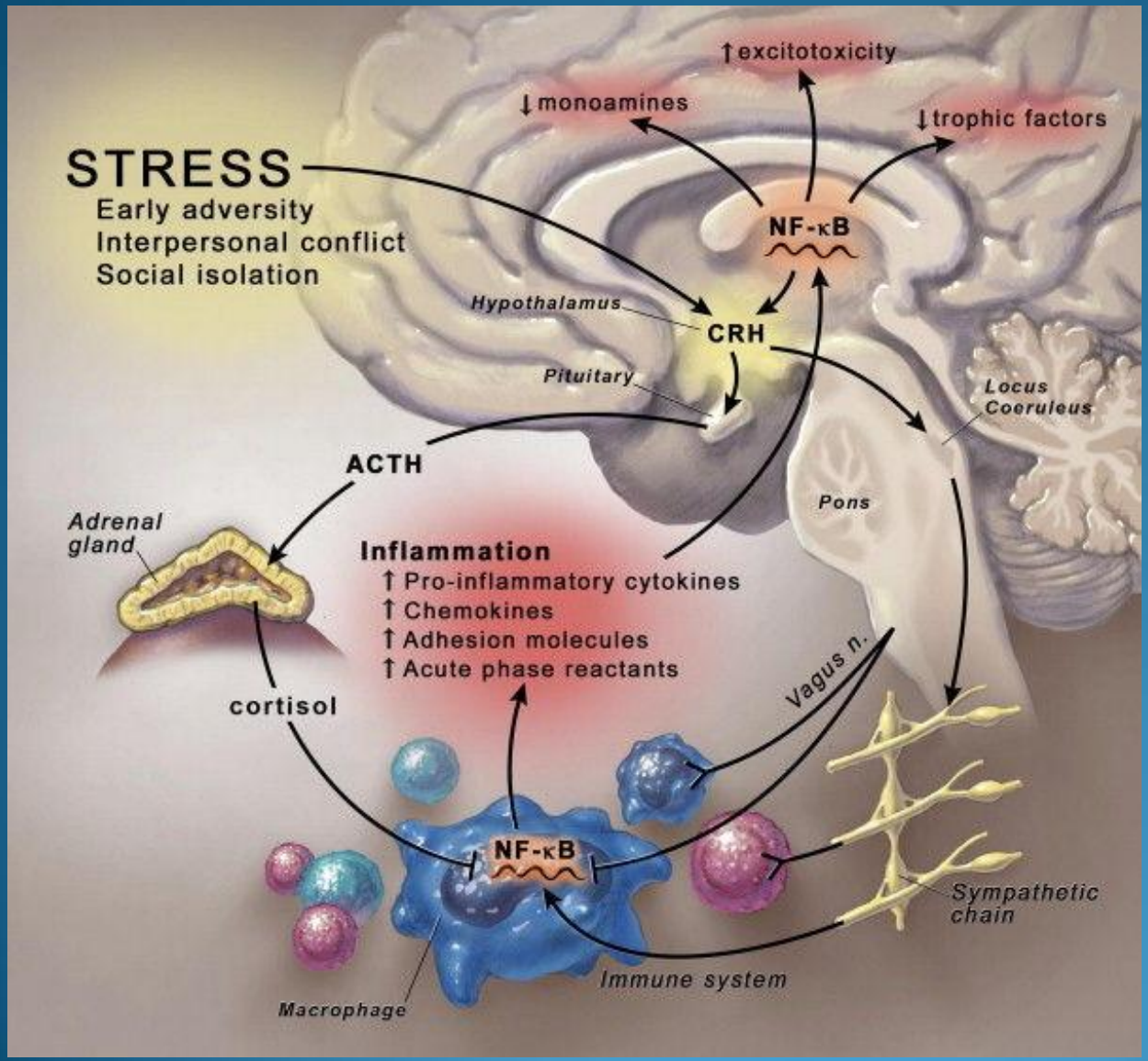
Early Psychosis Biomarkers – Prediction, Mechanism, Treatment Personalization

- Neuroimaging
- Electrophysiology
- Neuroendocrine
- Inflammation/Oxidative Stress
- Neurocognition
- Genetic

Biomarker research examines
- Mechanisms that underlie gray matter thinning and
- Interventions that target these processes

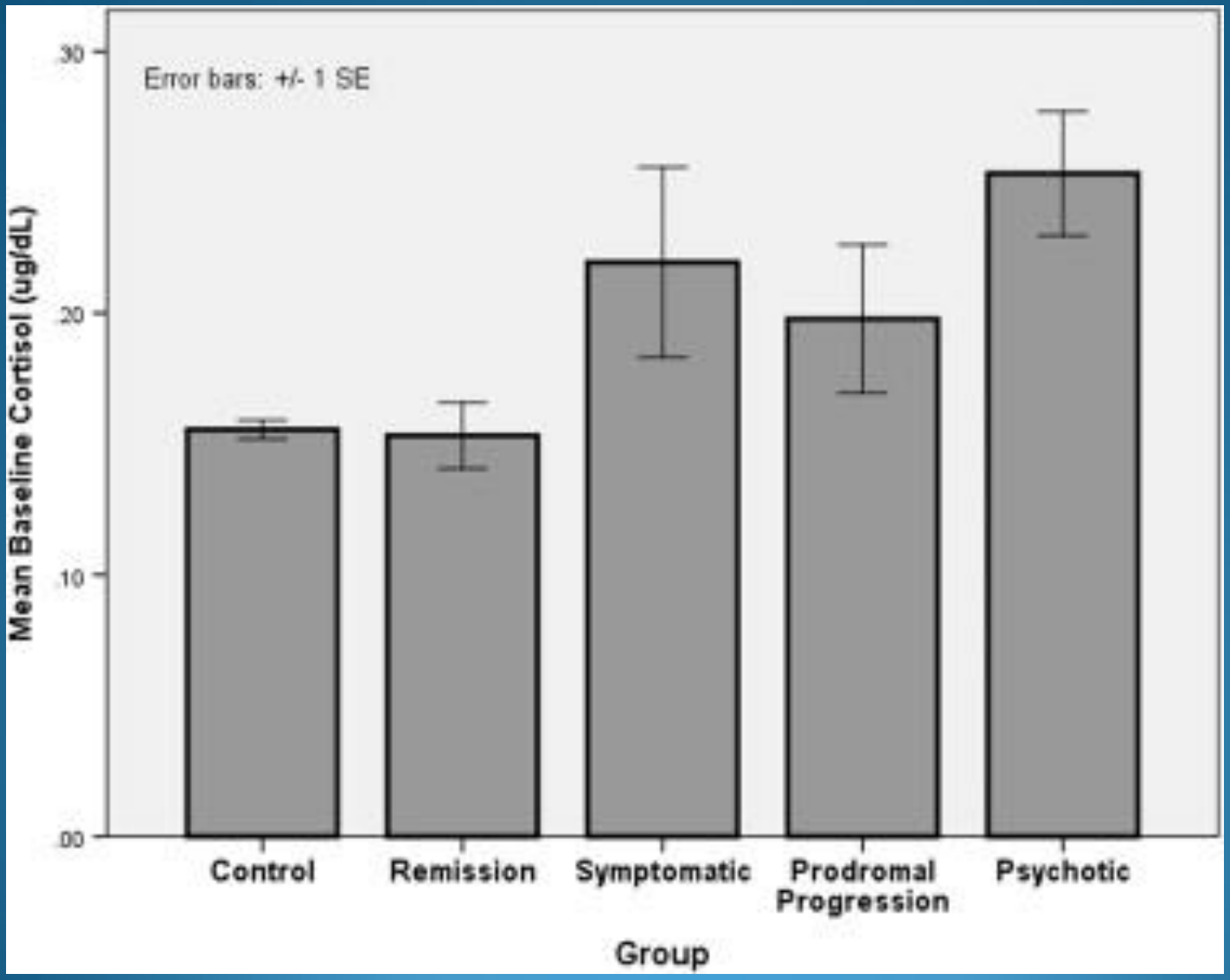
Young people who later convert to psychosis show a steeper rate of cortical thinning in superior and medial prefrontal cortex (Cannon et al 2015, Biological Psychiatry)





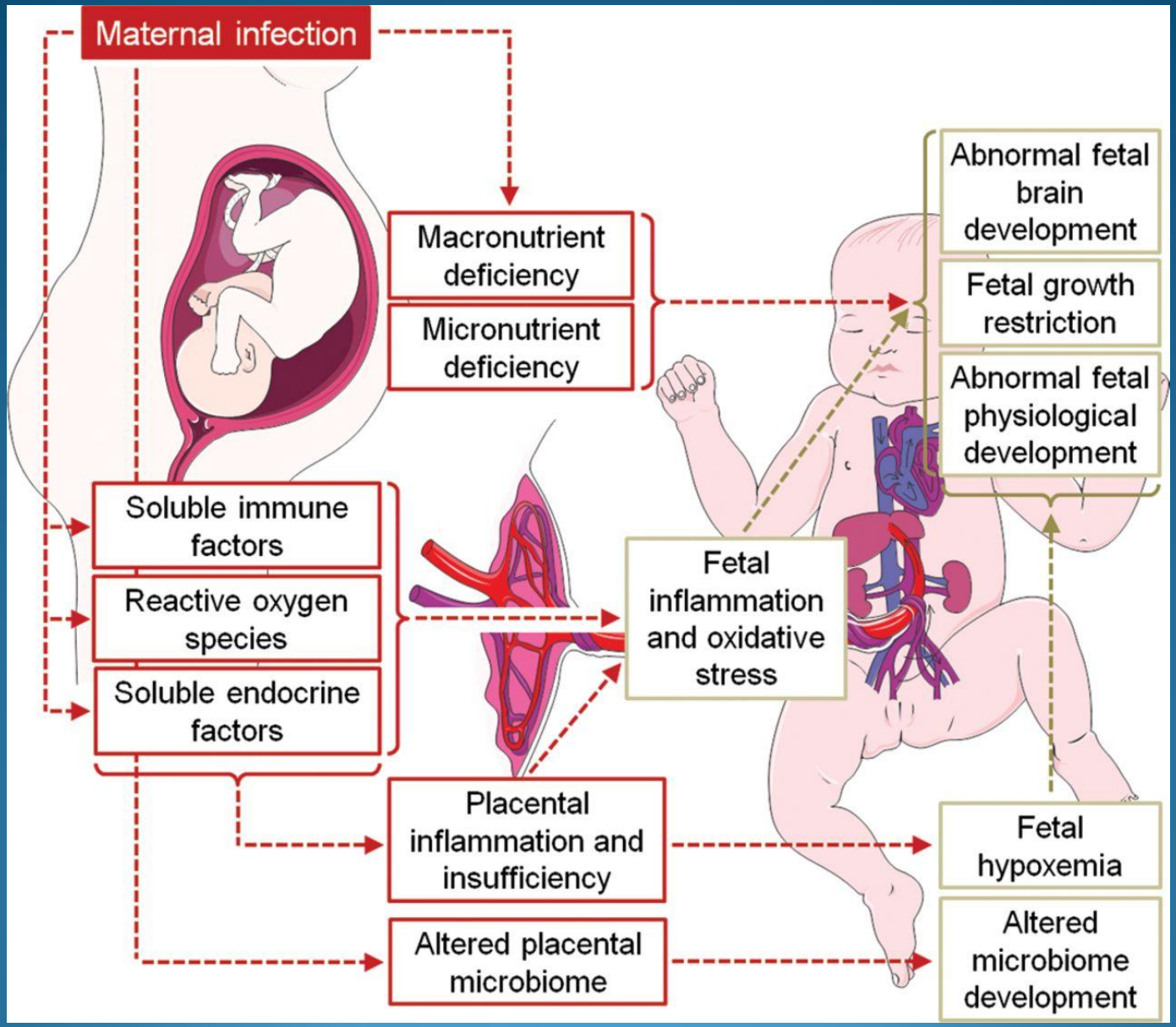
- Stress contributes to the release of Corticotropin Releasing Hormone (CRH) and an inflammatory response via NF-KB
- Nuclear Factor - kappaB (NF-kB) pathways contribute to both central and peripheral inflammation and oxidative stress

Salivary Cortisol and Clinical Outcome



Walker et al Biological Psychiatry 2013


Psychosocial stress
Early life stress
Leaky gut
Diet
T cell dysfunction
Chronic inflammation
Obesity
Schizophrenia
Diabetes
Cardiovascular disease
Depression
Cancer



Labouesse et al, **Long-term pathological consequences of prenatal infection: beyond brain disorders.** American Journal of Physiology 2015

Schizophrenia Bulletin vol. 41 no. 2 pp. 419–428, 2015
doi:10.1093/schbul/sbu099
Advance Access publication August 6, 2014

Towards a Psychosis Risk Blood Diagnostic for Persons Experiencing High-Risk Symptoms: Preliminary Results From the NAPLS Project

Diana O. Perkins[*,1,14], Clark D. Jeffries[2,14], Jean Addington[3], Carrie E. Bearden[4], Kristin S. Cadenhead[5], Tyrone D. Cannon[6,7], Barbara A. Cornblatt[8], Daniel H. Mathalon[9], Thomas H. McGlashan[7], Larry J. Seidman[10], Ming T. Tsuang[11], Elaine F. Walker[12], Scott W. Woods[7], and Robert Heinssen[13]

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[14]These authors contributed equally to the article.

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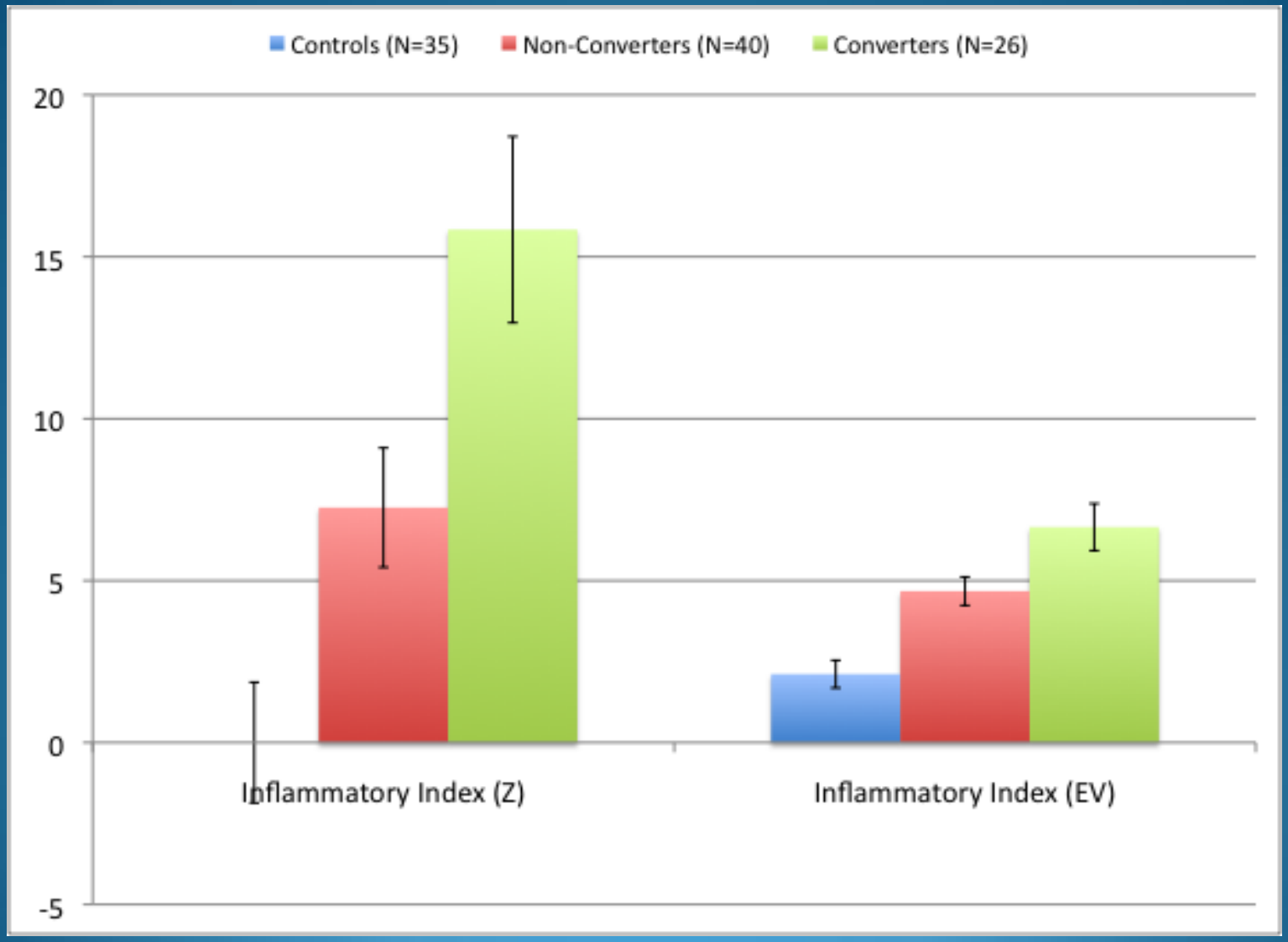
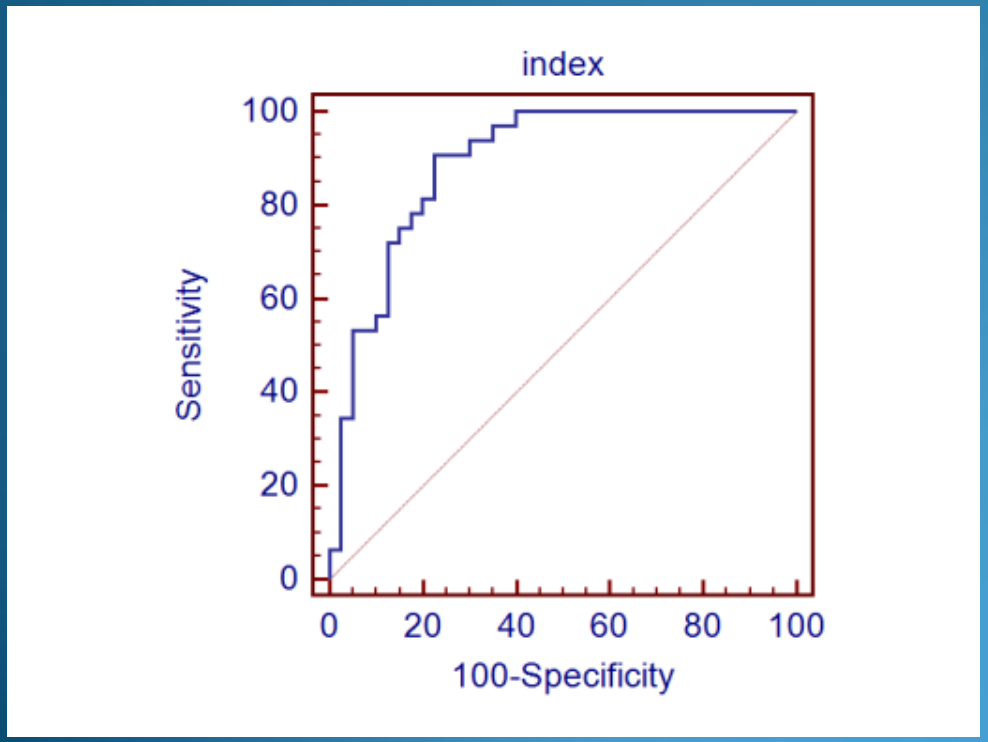
Plasma Analytes of Inflammation/Oxidative Stress: NAPLS II



Slide courtesy of Diana Perkins, UNC

Prediction with 16-analyte “blood test” CHR-NP vs CHR-P

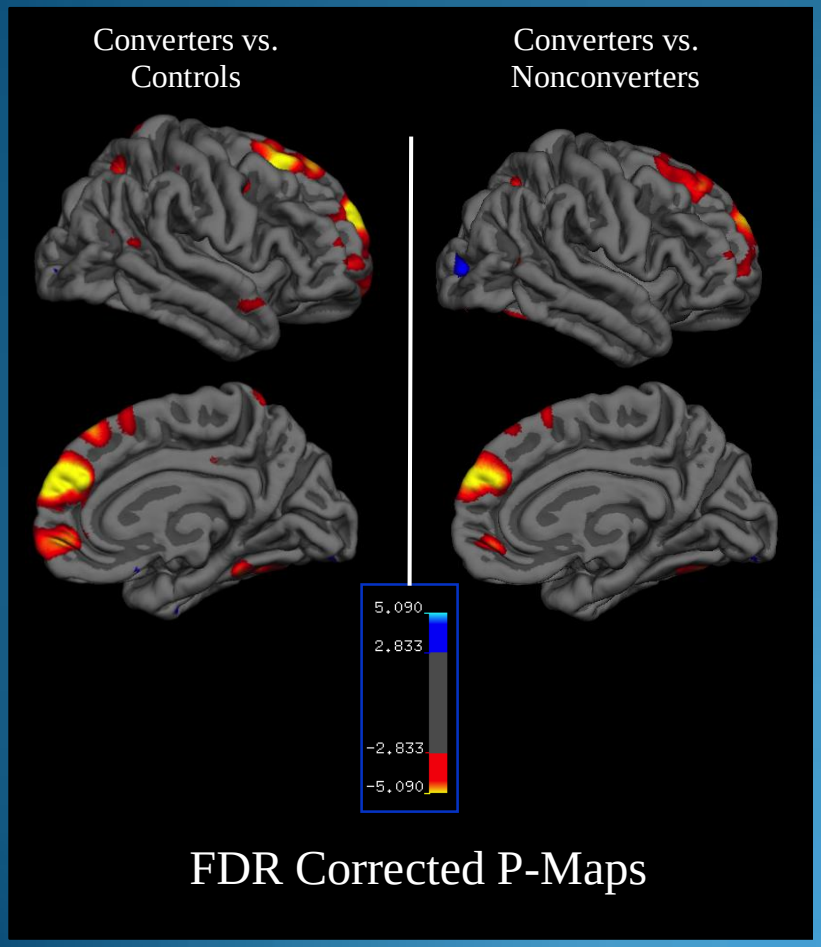
Area under the ROC curve (AUC)	0.89
Standard Error[a]	0.04
95% Confidence interval[b]	0.79 to 0.95
z statistic	10.3
Significance level P (Area=0.5)	<0.0001

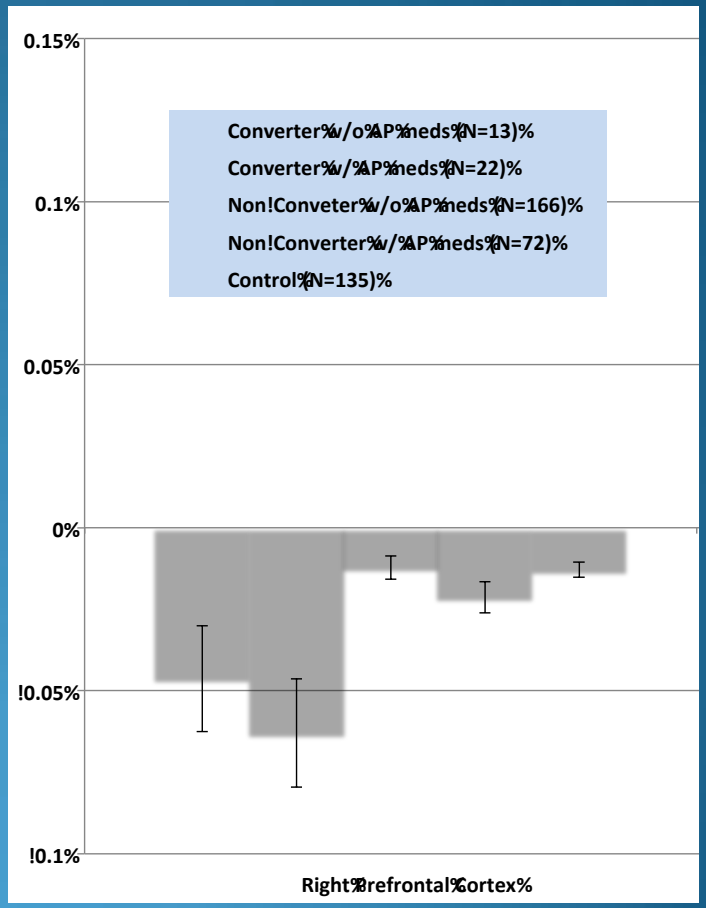


Optimized Index Threshold: 5.11
Sensitivity: .91
Specificity: .78

Towards a Psychosis Risk Blood Diagnostic for Persons Experiencing High-Risk Symptoms: Preliminary Results From the NAPLS Project
Perkins et al: Schizophr Bull. 2015 Mar; 41(2): 419–428

Young people who later convert to psychosis show a steeper rate of cortical thinning in superior and medial PFC (Cannon et al 2015, Biological Psychiatry)





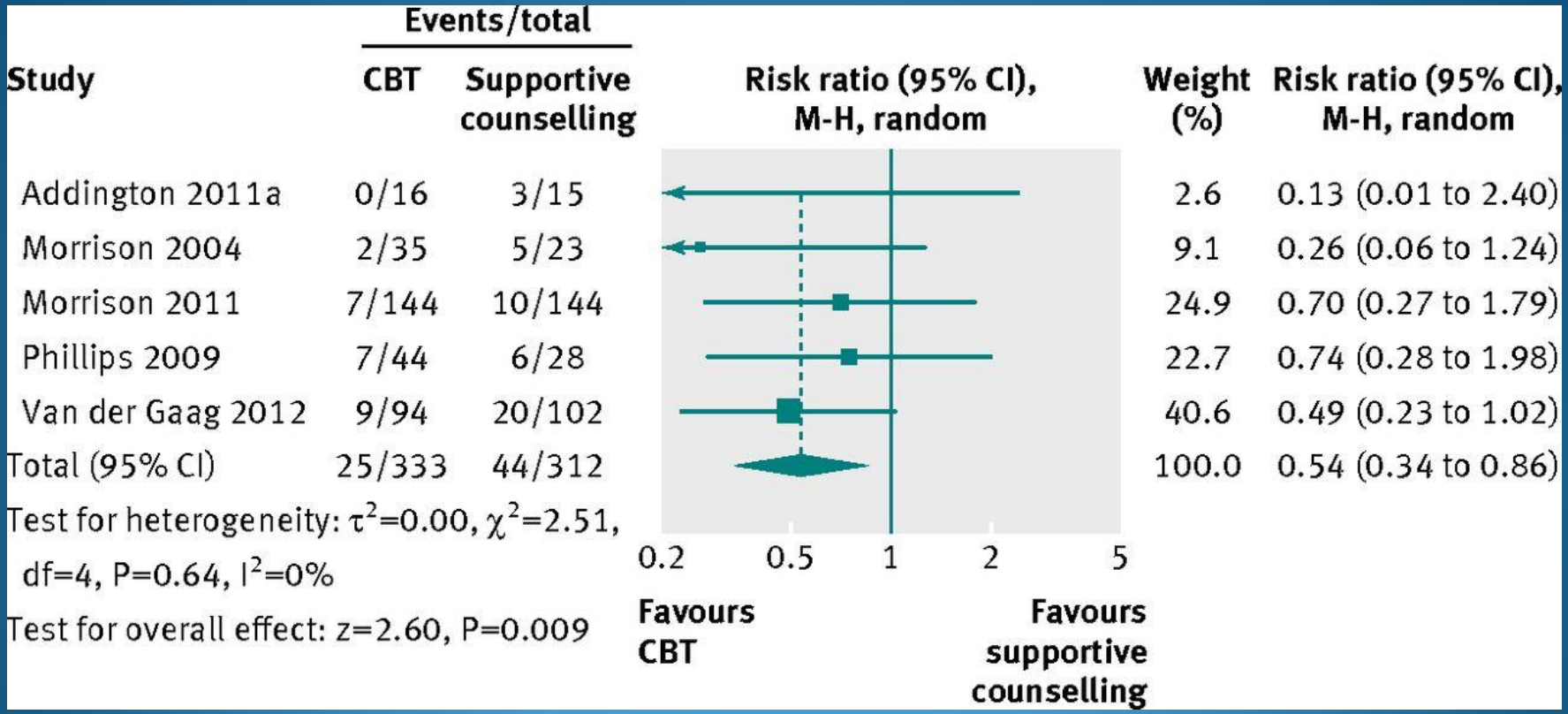
Cannon et al. *Biological Psychiatry* 2015;77:147-157

Intervention

Clinical High Risk Trials

- Cognitive Behavioral Therapy
- Antipsychotics
- Omega 3 Fatty Acids

Cognitive Behavioral Therapy versus Supportive Therapy and Prevention of Psychosis



Early interventions to prevent psychosis: systematic review and meta-analysis
Stafford MR et al *BMJ 2013; 346*

CBT or CBSM studies showing reduction in Cortisol

Study	Design & Subjects	Results
Lok et al. (2011).	187 MDD-patients	CT at study-entry enhanced cortisol declines over the day throughout the two-year follow-up
Brand et al (2011)	46 recruits with phobias	CBT reduced salivary cortisol.
Urizar et al (2011)	57 Low income mothers with infants	CBSM group had lower cortisol levels than women in the UC group at 18 months postpartum
Antoni et al. (2009)	85 participants with breast cancer	CBSM intervention showed better psychosocial adaptation (lower anxiety symptoms) and physiological adaptation (lower cortisol, greater Th1 cytokine [interleukin-2 and interferon-gamma] production and IL-2:IL-4 ratio)
Hammerfaldet al. (2006)	83 healthy subjects psychosocial stress test.	Subjects in the CBSM group showed significantly reduced cortisol stress responses..
Antoni et al (2005).	25 HIV-infected men	Greater reductions in cortisol.depressed mood during CBSM

Antipsychotic Trials in CHR

Study	Modality	Result
McGlashan AJP 2006	Olanzapine vs Placebo (N=60, Double Blind)	No difference in rate of psychotic conversion (16% vs 38%). Significant weight gain
McGorry ACP 2002	Risperidone + CBT vs Needs Based Treatment (N=59)	Reduced psychotic conversion rate at 6 months (10% vs 36%) but not at 12 months (19% vs 26%)
McGorry JCP 2012	Risperidone + CBT vs Placebo + CBT vs Placebo + Supportive Therapy (N=115, Double Blind)	No difference in psychotic conversion rate (10.7% vs 9.6% vs 21.8%) but improvement in symptoms and functioning

Not reported or ongoing:
Amisulpride vs supportive care (Ruhrmann) N=124
Ziprasidone vs placebo (Woods) N=51+
Aripiprizole vs placbo vs CBT (Bechdolf) N=156+

ORIGINAL ARTICLE

Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

A Randomized, Placebo-Controlled Trial

G. Paul Amminger, MD; Miriam R. Schäfer, MD; Konstantinos Papageorgiou, MD; Claudia M. Klier, MD; Sue M. Cotton, PhD; Susan M. Harrigan, MSc; Andrew Mackinnon, PhD; Patrick D. McGorry, MD, PhD; Gregor E. Berger, MD

Replication Attempts:

NAPLS
Neuropro

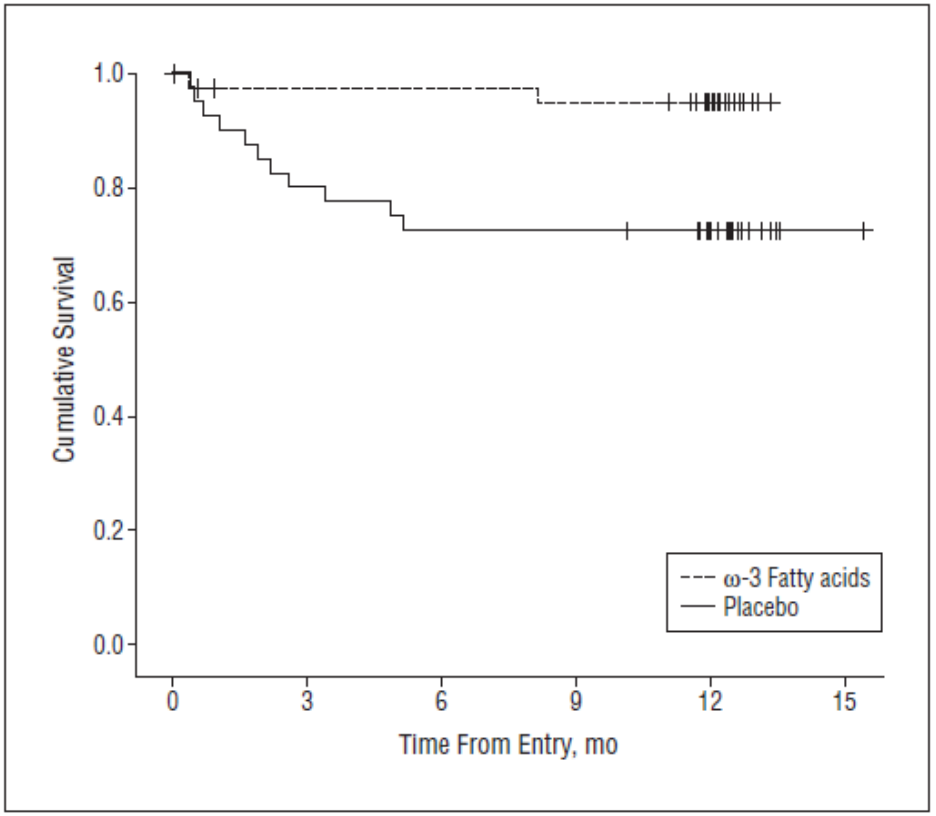
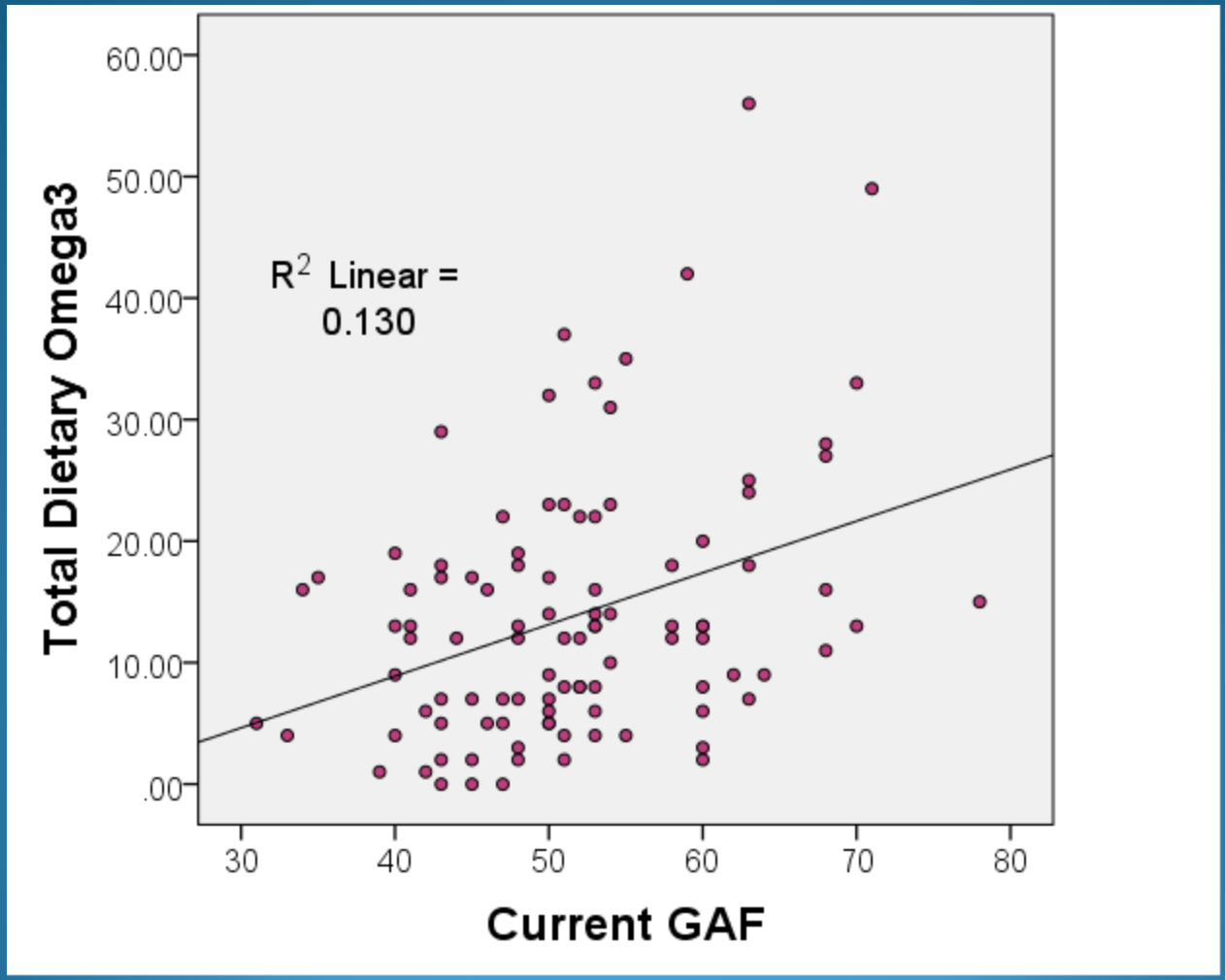


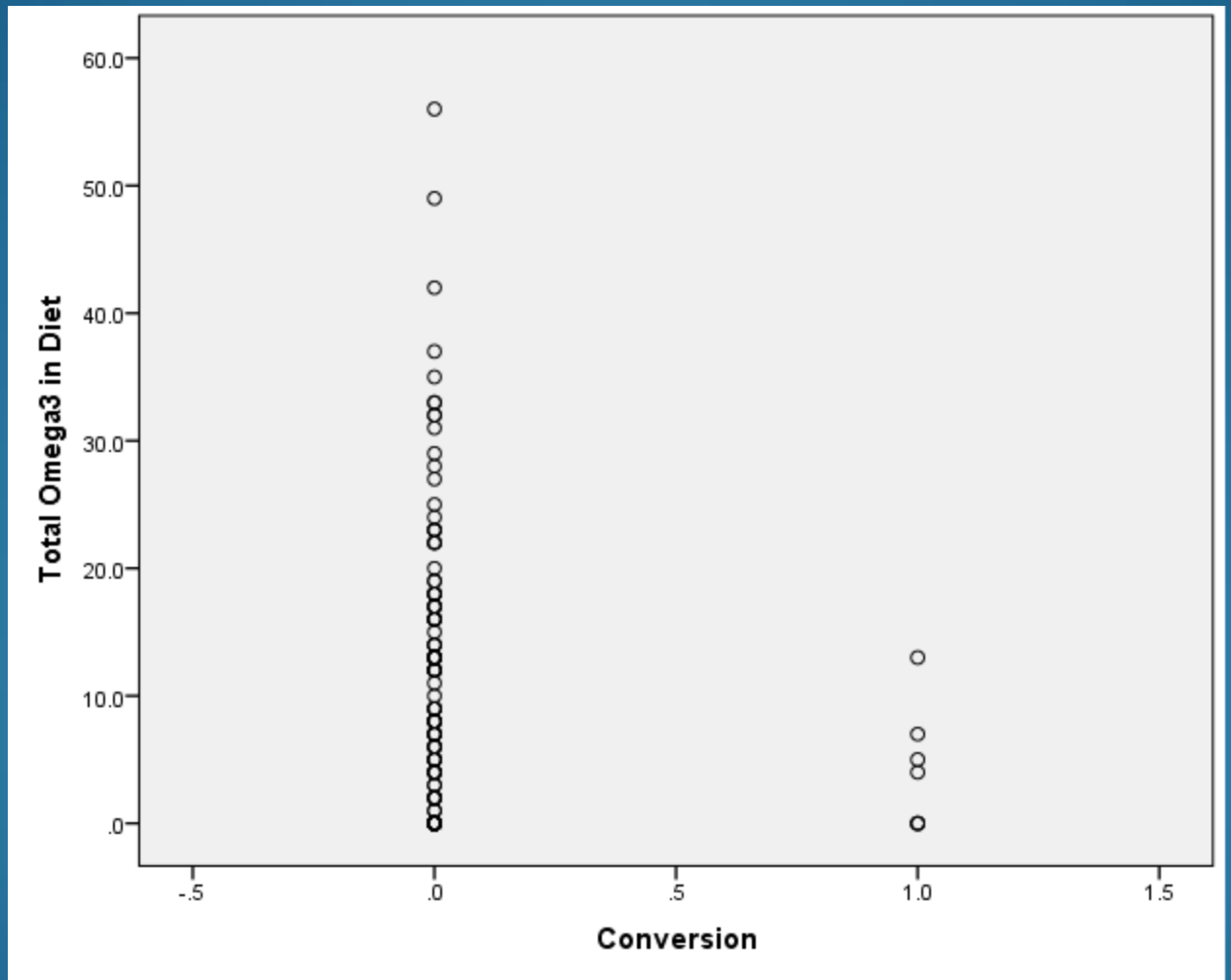
Figure 2. Kaplan-Meier estimates of the risk of transition from the at-risk state to psychotic disorder in patients assigned to ω-3 fatty acids or placebo (*P*=.007 by log-rank test).

Arch Gen Psychiatry. 2010;67(2):146-154

Dietary Omega 3 is Associated with Global Functioning



Dietary Omega 3 and Later Conversion to Psychosis

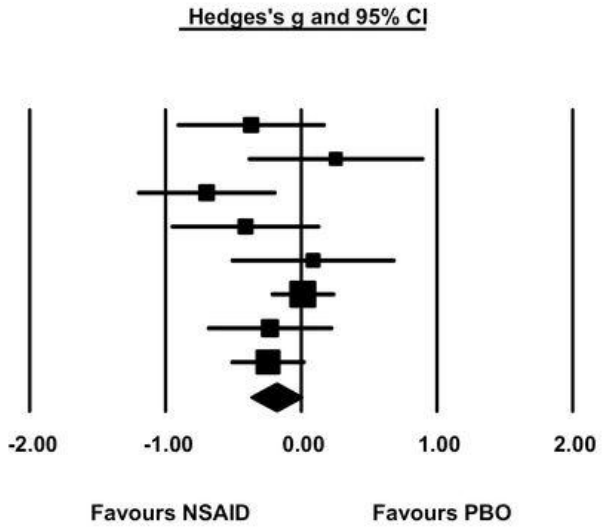


Omega 3

- Essential for normal brain function and development
- Abnormal phospholipid and FA metabolism in schizophrenia
- Omega-3FAs effect genes related to modulation of glutamate
- Protective agent against neurotoxicity
- Efficacy in RA, Crohn's, asthma, dyslipidemia, dementia, BPD, MDD, ADD
- Potential Benefits:
  - Symptomatic Improvement
  - Lower dose of Antipsychotics
  - Improved Metabolic Profile
  - Neurocognition
  - Neuroprotection
  - Anti-inflammatory

Efficacy of adjunctive nonsteroidal anti-inflammatory drug (NSAID) use for schizophrenia assessed by Positive and Negative Syndrome Scale (PANSS) positive score.

Study name	NSAID	Statistics for each study			
		Hedges's g	Lower limit	Upper limit	p-Value
Mueller et al. 2002	celecoxib, 400mg/day	-0.367	-0.918	0.183	0.191
Rapaport et al. 2005	celecoxib, 400mg/day	0.256	-0.394	0.907	0.440
Akhondzadeh et al. 2007	celecoxib, 400mg/day	-0.696	-1.210	-0.181	0.008
Mueller et al. 2010	celecoxib, 400mg/day	-0.409	-0.961	0.142	0.146
Mueller et al. 2004b/unpublished	celecoxib, 400mg/day	0.089	-0.519	0.696	0.775
Rappard and Mueller 2004/unpublished	celecoxib, 400mg/day	0.013	-0.225	0.251	0.913
Laan et al. 2010	aspirin, 1000mg/day	-0.229	-0.695	0.237	0.335
Weiser et al. 2012/unpublished	aspirin, 1000mg/day	-0.243	-0.520	0.035	0.086
		-0.189	-0.373	-0.005	0.044

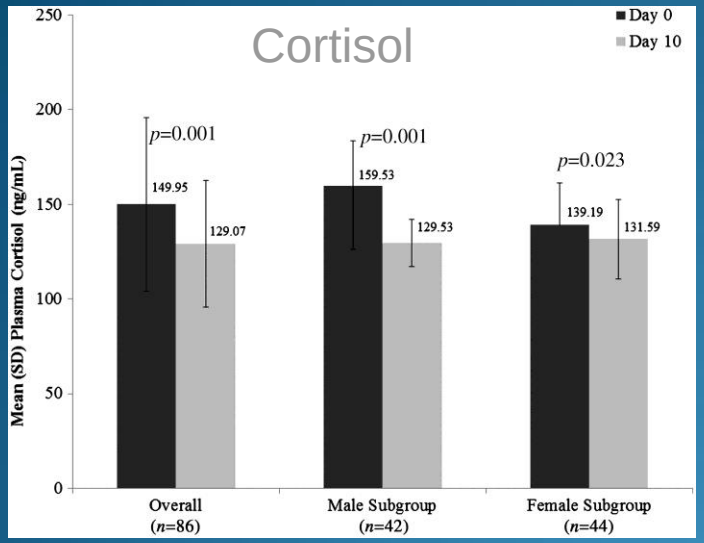


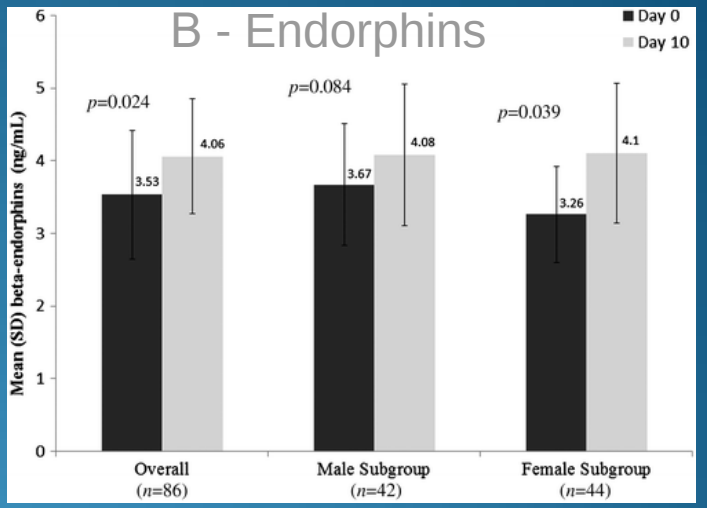
"In post hoc subgroup analyses, however, suggestive effects were observed in studies on aspirin (effect size = −0.29), studies conducted in inpatients (effect size = −0.44), and studies of or samples enriched with first-episode patients (effect size = −0.39)."

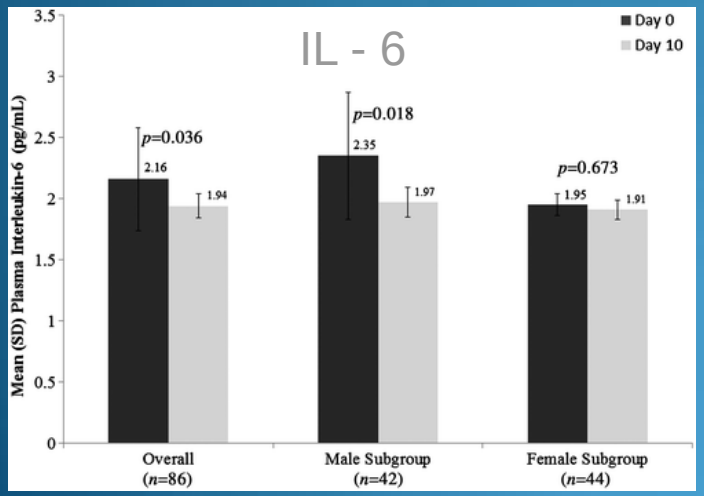
Masahiro Nitta et al. Schizophr Bull 2013;39:1230-1241

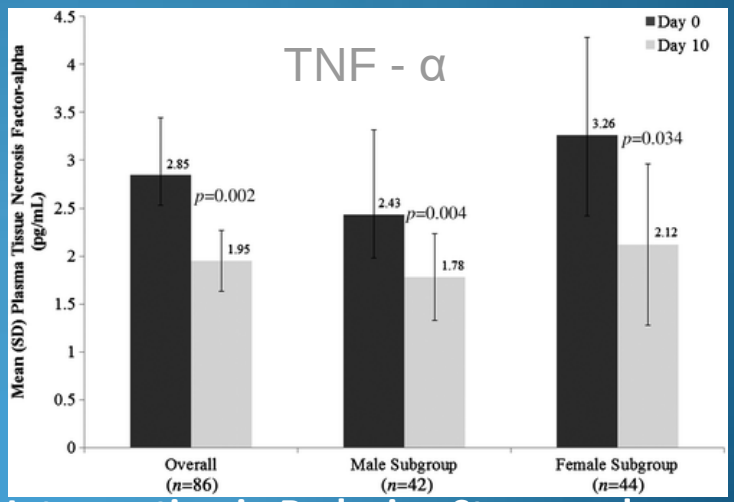
Schizophrenia Bulletin

YOGA



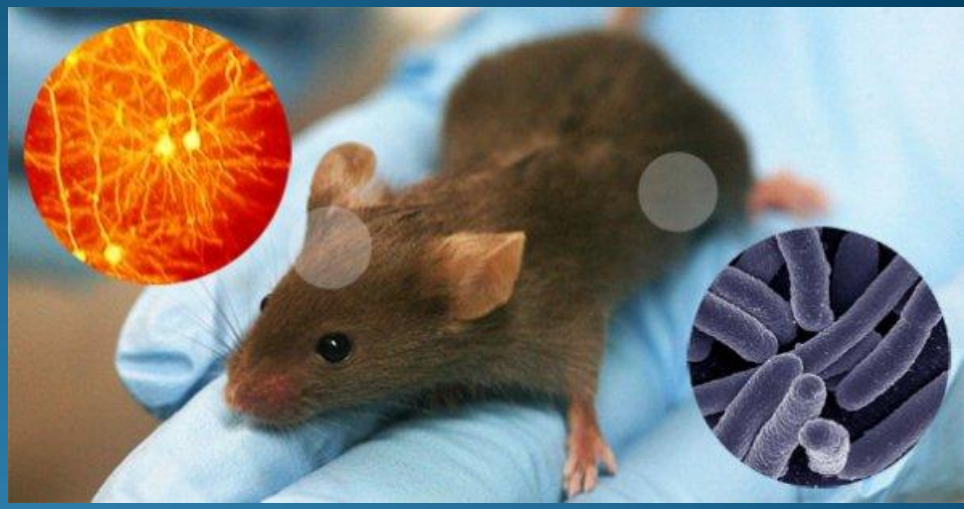






Yadav et al, Efficacy of a Short-Term Yoga-Based Lifestyle Intervention in Reducing Stress and Inflammation: Preliminary Results *The J of Alternative and Complementary Medicine*. 2012.

The Microbiome Affects Behavior and Brain Function



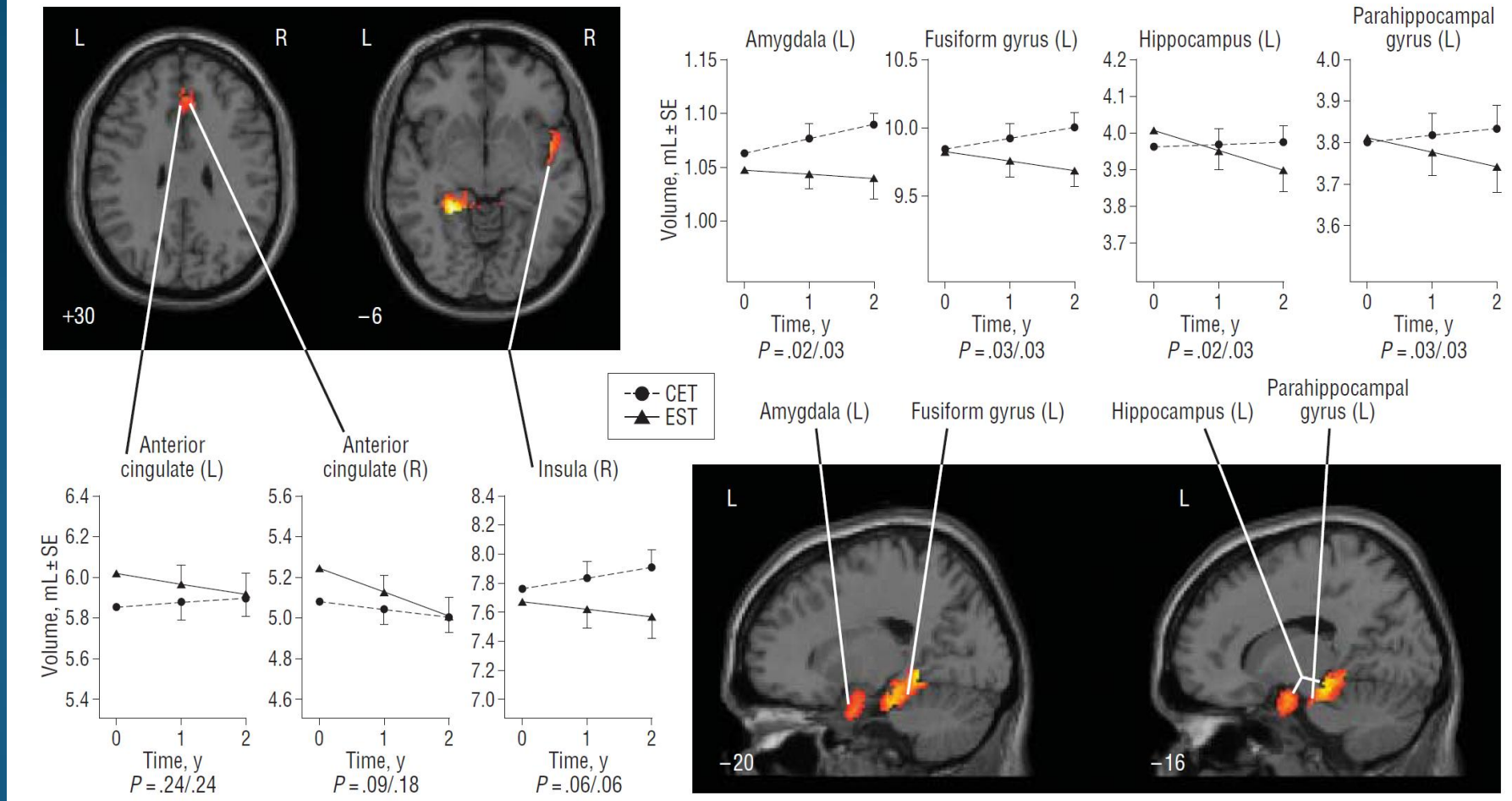
- Germ-free mice, without any microbiome, are more active, less anxious and less risk-averse than normal mice.
- Their brains differ in the gene expression.
- Microbiome transplants lead to normal behavior and gene expression if performed early,

Diaz-Heijtz et al Proc Natl Acad Sci U S A. 2011 Feb 15;108(7):3047-52.

- The behavior of normal adult mice changed after being fed a probiotic bacterium , *Lactobacillus rhamnosus* found in yogurts and dairy products.
- The levels of signalling chemicals (GABA receptor mRNA expression) in the brain changed
- Behaviors associated with stress, anxiety and depression were reduced.

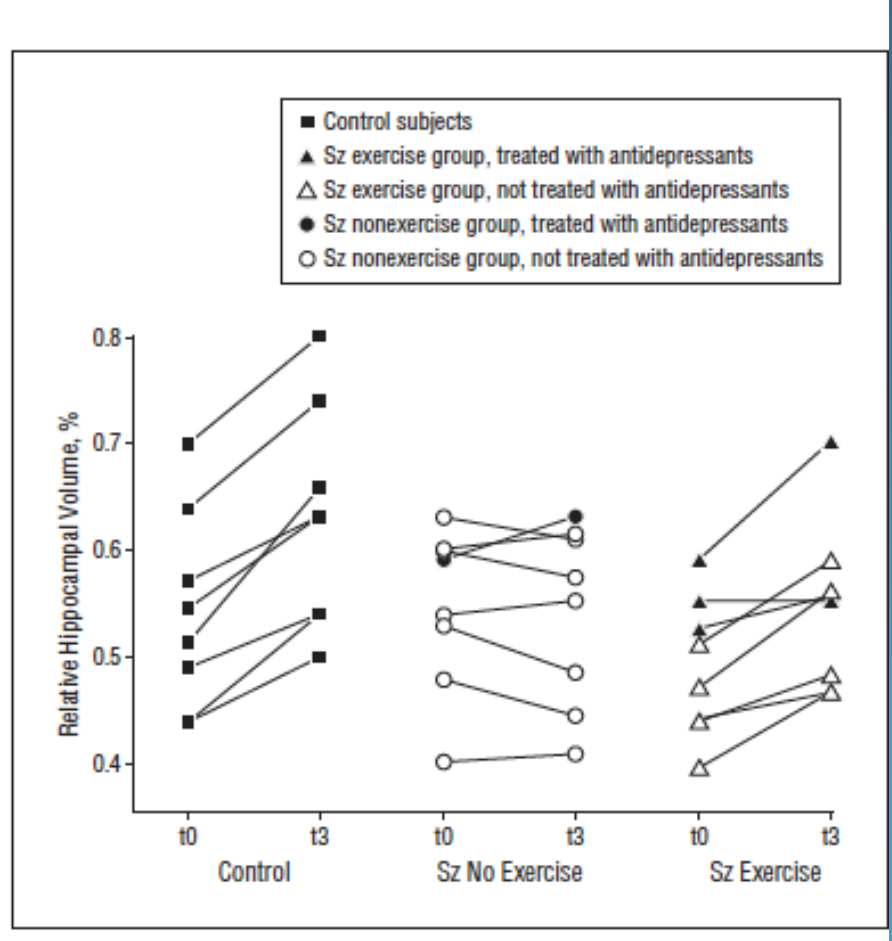
Bravo et al Proc Natl Acad Sci U S A. 2011 Sep 20;108(38):16050-5.

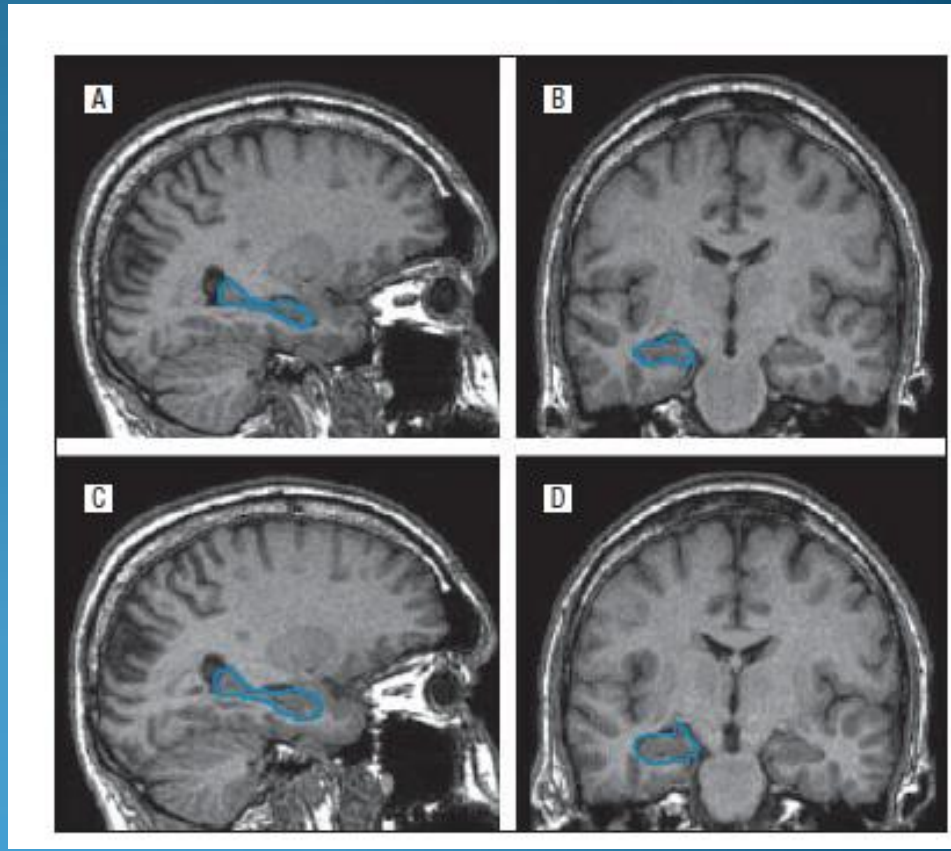
Gray matter change and improvement in social cognition with Cognitive Enhancement Training



Eack et al Arch Gen Psychiatry 2010

Exercise increases hippocampal volume and improves verbal learning in patients with schizophrenia





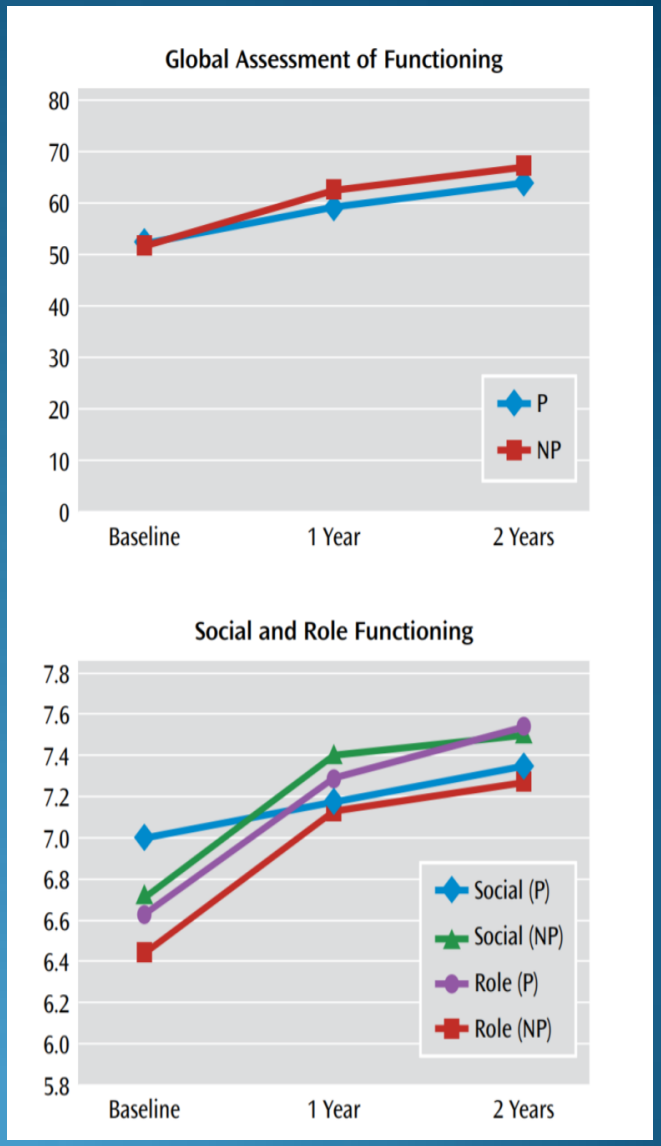
Pajonk et al Arch Gen Psych 2010

At Clinical High Risk for Psychosis: Outcome for Nonconverters

Jean Addington, Ph.D., Barbara A. Cornblatt, Ph.D., Kristin S. Cadenhead, M.D., Tyrone D. Cannon, Ph.D., Thomas H. McGlashan, M.D., Diana O. Perkins, M.D., Larry J. Seidman, Ph.D., Ming T. Tsuang, M.D., Ph.D., Elaine F. Walker, Ph.D., Scott W. Woods, M.D., and Robert Heinssen, Ph.D.

Am J Psychiatry. 2011 Aug; 168(8): 800–805.

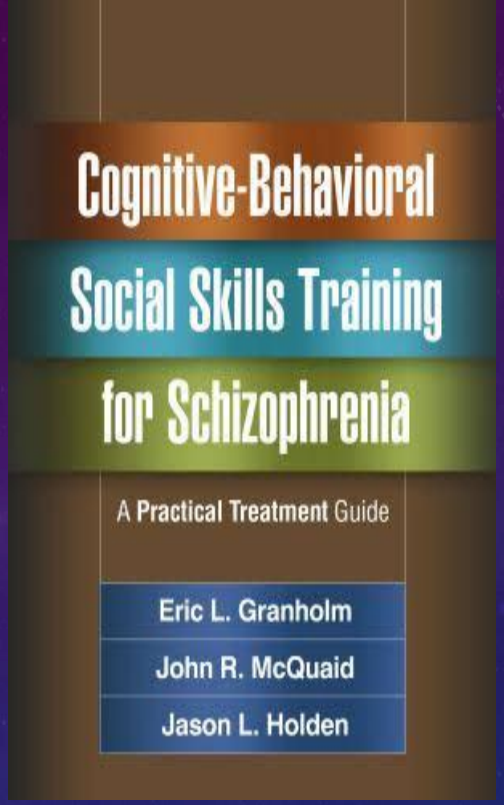
After 1 year of follow-up, CHR subjects who do not convert to psychosis continue to have significant functional deficits compared to healthy comparison subjects



CARE Funded Research

- “NAPLS3” - Predictors and Mechanisms of Conversion to Psychosis (NIMH U01)
- “ReGroup” - Cognitive Behavioral Social Skills Training for Youth at Risk of Psychosis (NIMH R01)
- “Progresar” Compensatory Cognitive Training in Clinical High Risk Latino Youth (NIMH R34)
- Disease Recovery Evaluation and Modification (DREaM) Study (Janssen)
- Anew (Lundbeck)

CBT+SST=CBSST WHY ADD CBT TO SST?



Sometimes people have the skills but don't use them.

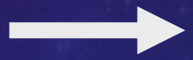
This is often because a thought is in the way.

Eric Granholm, Ph.D.
CBSST.org

RATIONALE FOR CBT FOR FUNCTIONING

Multiple Failure Experiences (Caused by illness; stigma; neurocognitive impairment; etc)

Defeatist Performance Beliefs ("I'm damaged;" "I'll just fail again")



Impaired Functioning (Work, school, leisure, etc)

Challenge Defeatist Beliefs → Improve Functioning

Compensatory Cognitive Training (CCT)

Elizabeth Twamley, PhD

- Purely compensatory intervention, no drills or computers
- Theoretical bases for CCT
  - Cognitive compensation
    - "Working around" deficits by reducing cognitive demands or handling them differently
  - Habit learning (Bayley et al., 2005; Knowlton et al., 1996; Keri et al., 2005; Clare et al., 1993)
    - Habits are particularly resistant to forgetting
    - Clients are trained to develop new cognitive habits (e.g., using a calendar)

Why use the compensatory approach?

- It can work around cognitive impairments and has the potential to induce brain plasticity
- The etiology of the cognitive impairments is not important
- It is recovery-oriented in its focus on linking strategy use to goals and roles in the community
- Evidence of improvement in cognition as well as generalization to functional outcomes

care

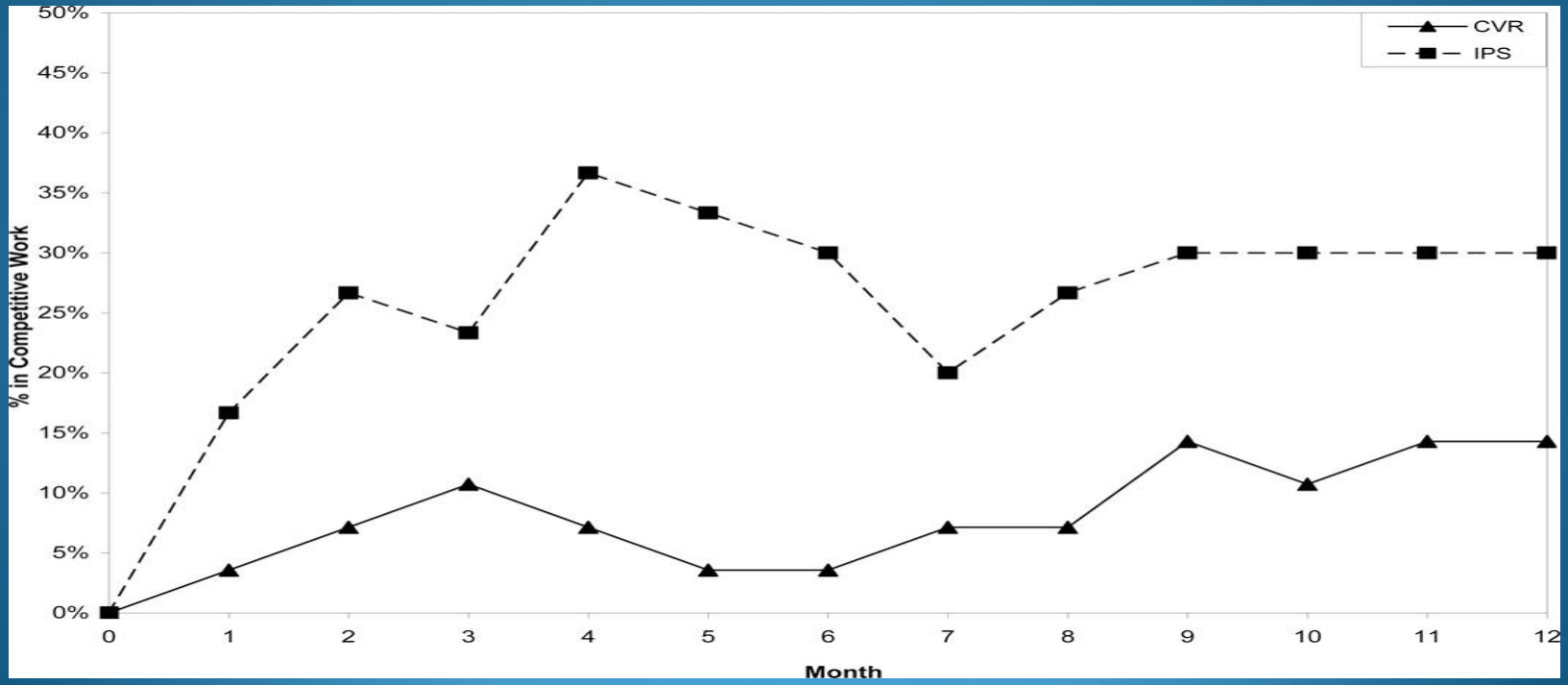
Cognitive Assessment and Recovery Enhancement Early Psychosis Treatment Program


Pharmacologic
Assessment
Diagnostic/Consultation
Neuropsychological
Neuroimaging/Metabolic
Psychotherapy
Individual/Group/
Family
Supported
Employment
Education
Client
Case Management
IOP
CBSST
Mindfulness
Psychoeducation
Psychoeducation
Cognitive
Remediation
Research
Mindfulness

Supported Employment/Education

Randomized controlled trial of supported employment compared to conventional vocational rehabilitation in older people with psychosis: rates of competitive work were double in supported employment (57% vs. 29%) and comparable to results in younger samples

(Twamley, Vella, Burton, Becker, Bell, & Jeste, *Schiz Res*, 2012)



Acknowledgements

- NAPLS Consortium
  - Jean Addington (Calgary)
  - Carrie Bearden (UCLA)
  - Ty Cannon (Yale)
  - Barbara Cornblatt (Hillside)
  - Dan Mathalon (UCSF)
  - Tom McGlashan (Yale)
  - Diana Perkins (UNC)
  - Larry Seidman (Harvard)
  - Elaine Walker (Emory)
  - Matcheri Keshavan (Harvard)
  - Bill Stone (Harvard)
- UCSD
  - Ming Tsuang
  - Elizabeth Twamley
  - Eric Granholm
  - Cris Achim
  - Anders Dale
  - Heline Mirzakhanian
  - Skylar Kelsven
- Other Collaborators
  - Camilo de la Fuente (Mexico INNN)

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COGNITIVE ASSESSMENT AND RISK EVALUATION

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