

Predictors and Mechanisms of Conversion to Psychosis in At Risk Youth: Toward a Prevention Strategy

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Presenter Disclosure

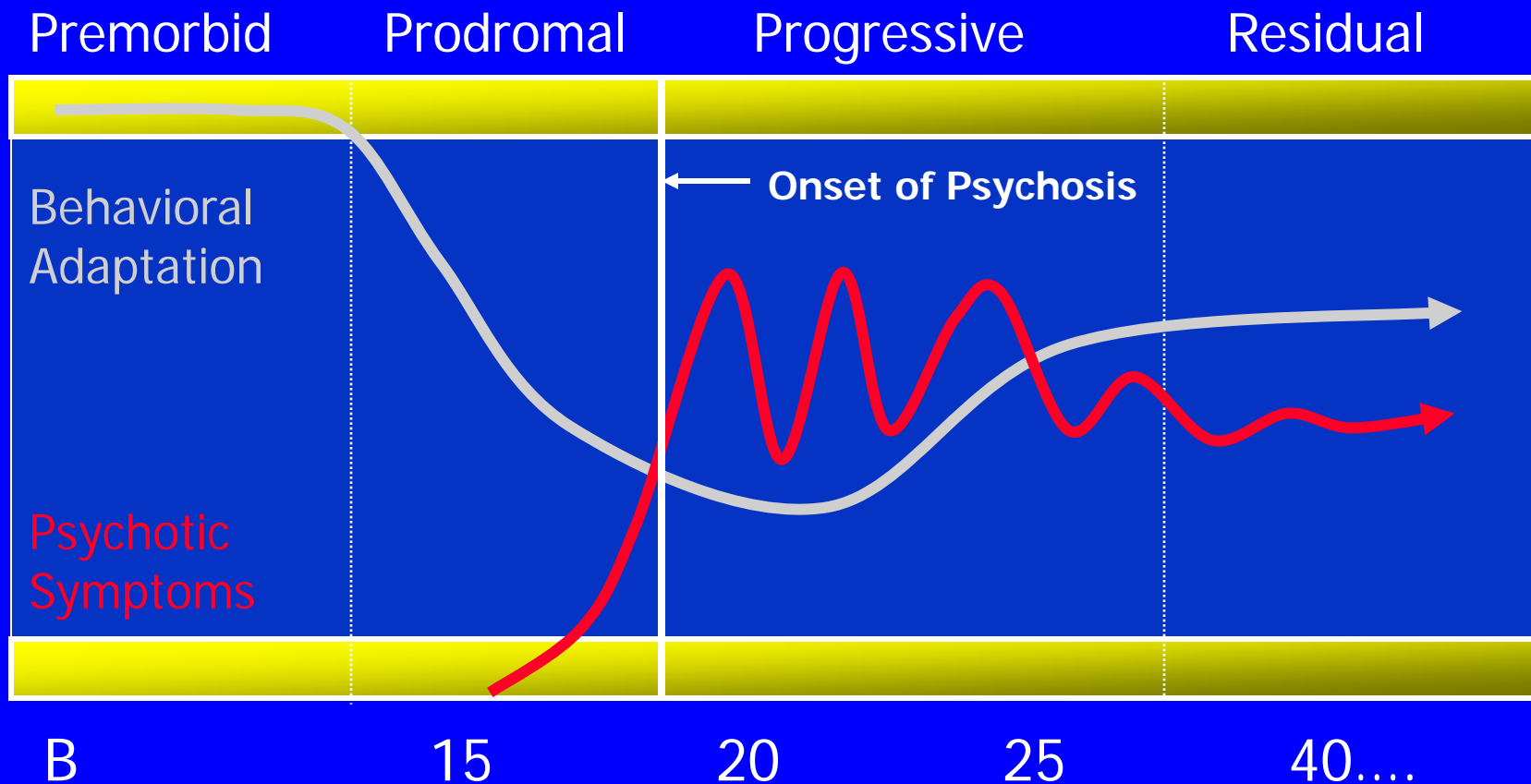
Tyrone D. Cannon has no personal financial relationships with commercial interests relevant to this presentation.

3 Parts to Today's Talk

- Prediction of Psychosis
 - How do we find people most at risk for imminent onset?
- Mechanisms of Onset of Psychosis
 - Is there neural deterioration before onset that could potentially be prevented
- Prevention of Psychosis
 - What approaches available now show promise for preventing onset and/or functional disability?

Prodromal Risk Approach to Psychosis

- SIPS/SOPS: Onset or worsening in past year of sub-psychotic intensity positive symptoms or genetic risk with recent functional decline
- Initial studies observed 50-60% conversions to psychosis within 1 year; most conversions are to schizophrenia and schizoaffective disorder, others to mood disorders with psychotic features



Example: Perceptual Abnormalities

P. 4. DESCRIPTION: PERCEPTUAL ABNORMALITIES/HALLUCINATIONS

- a. Unusual perceptual experiences. Heightened or dulled perceptions, vivid sensory experiences, distortions, illusions.
- b. Pseudo-hallucinations or hallucinations into which the subject has insight (i.e. is aware of their abnormal nature.)
- c. Occasional frank hallucinations that may minimally influence thinking or behavior.

Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

PERCEPTUAL ABNORMALITIES/HALLUCINATIONS Severity Scale (circle one)

0 Absent	1 Questionably Present	2 Mild	3 Moderate	4 Moderately Severe	5 Severe but Not Psychotic	6 Severe and Psychotic
	Minor, but noticeable perceptual sensitivity (e.g. heightened, dulled, distorted, etc.).	Unexpected, unformed perceptual experiences/ changes that are puzzling but are not considered to be significant.	Repeated, unformed, images (e.g., shadows, trails, sounds, etc.), illusions, or persistent perceptual distortions that may be worrisome or experienced as unusual.	Recurrent illusions or momentary hallucinations that are recognized as not real yet can be frightening or captivating, and may affect behavior slightly. Not sure of source of experiences.	Hallucinations that occasionally affect thinking or behavior, that are experienced as possibly external to self or possibly real. Skepticism can be induced.	Recurrent hallucinations perceived as real and distinct from the person's thoughts. Clearly influence thinking, feeling, and/or behavior. Skepticism cannot be induced.

North American Prodrome Longitudinal Study (NAPLS)

ORIGINAL ARTICLE

Prediction of Psychosis in Youth at High Clinical Risk

A Multisite Longitudinal Study in North America

Tyrone D. Cannon, PhD; Kristin Cadenhead, MD; Barbara Cornblatt, PhD; Scott W. Woods, MD; Jean Addington, PhD; Elaine Walker, PhD; Larry J. Seidman, PhD; Diana Perkins, MD; Ming Tsuang, MD; Thomas McGlashan, MD; Robert Heinssen, PhD

Context: Early detection and prospective evaluation of individuals who will develop schizophrenia or other psychotic disorders are critical to efforts to isolate mechanisms underlying psychosis onset and to the testing of preventive interventions, but existing risk prediction approaches have achieved only modest predictive accuracy.

Objectives: To determine the risk of conversion to psychosis and to evaluate a set of prediction algorithms maximizing positive predictive power in a clinical high-risk sample.

Design, Setting, and Participants: Longitudinal study with a 2½-year follow-up of 291 prospectively identified treatment-seeking patients meeting Structured Interview for Prodromal Syndromes criteria. The patients were recruited and underwent evaluation across 8 clinical research centers as part of the North American Prodrome Longitudinal Study.

Main Outcome Measure: Time to conversion to a fully psychotic form of mental illness.

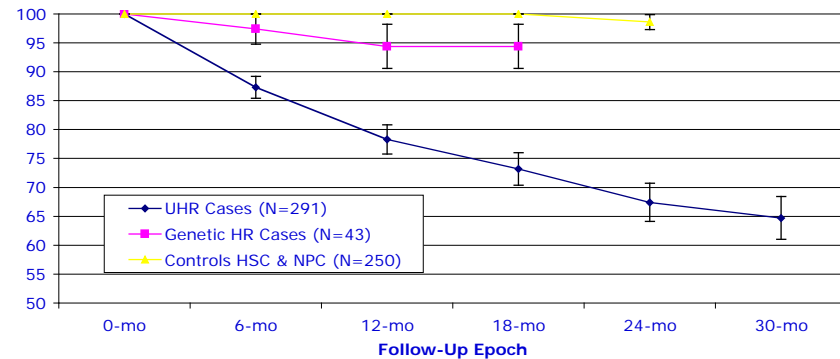
Results: The risk of conversion to psychosis was 35%, with a decelerating rate of transition during the 2½-year follow-up. Five features assessed at baseline contributed uniquely to the prediction of psychosis: a genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse. Prediction algorithms combining 2 or 3 of these variables resulted in dramatic increases in positive predictive power (ie, 68%-80%) compared with the prodromal criteria alone.

Conclusions: These findings demonstrate that prospective ascertainment of individuals at risk for psychosis is feasible, with a level of predictive accuracy to that in other areas of preventive medicine provide a benchmark for the rate and shape of risk function against which standardize intervention programs can be compared.

Arch Gen Psychiatry. 2008;65(1):28-37

NAPLS SIPS+ Sample	General Population	Relative Risk
35.3%	0.08%	405

Survival Distribution Function in NAPLS Consortium



Risk Variable	N	p	PPP	Sens.	Spec.
Meets SIPS criteria for Prodrome	291		35		
Meets SIPS criteria AND					
Any drug abuse	270	.003	43	29	83
Social impairment (Mod-Severe)	290	.03	46	80	43
Suspicion (Mod-Severe)	291	.006	43	79	37
Unusual thought content (Mod-Severe)	291	.002	48	56	62
Genetic Risk + Sign. Functional Decline	291	.001	52	66	59
SOC + UTC + GR/SFD	290	.0001	81	30	90

European Prediction of Psychosis (EPOS) Study

ORIGINAL ARTICLE

Prediction of Psychosis in Adolescents and Young Adults at High Risk

Results From the Prospective European Prediction of Psychosis Study

Stephan Ruhrmann, MD; Frauke Schultze-Lutter, PhD; Rabno K. R. Salokangas, MD, PhD, MSc; Markus Heinimaa, MD; Don Linszen, MD; Peter Dingemans, PhD; Max Birchwood, PhD; Paul Patterson, PhD; Georg Juckel, MD; Andreas Heinz, MD; Anthony Morrison, PhD; Shôn Lewis, MD; Heinrich Graf von Reventlow, DiplPsych; Joachim Klosterkötter, MD

Context: Indicated prevention is currently regarded as the most promising strategy to attenuate, delay, or even avert psychosis. Existing criteria need improvement in terms of specificity and individual risk assessment to allow for better targeted and earlier interventions.

Objective: To develop a differential predictive clinical model of transition to first-episode psychosis.

Design: Prospective multicenter, naturalistic field study with a total follow-up time of 18 months.

Setting: Six early-detection outpatient centers in Germany, Finland, the Netherlands, and England.

Participants: Two hundred forty-five help-seeking patients in a putatively prodromal state of psychosis according to either ultra-high-risk (UHR) criteria or the basic symptom-based criterion cognitive disturbances (COGDIS).

Main Outcome Measure: Incidence of transition to psychosis.

Results: At 18-month follow-up, the incidence rate for

transition to psychosis was 19%. Combining UHR and COGDIS yielded the best sensitivity. A prediction model was developed and included positive symptoms, bizarre thinking, sleep disturbances, a schizotypal disorder, level of functioning in the past year, and years of education. With a positive likelihood ratio of 19.9, an area under the curve of 80.8%, and a positive predictive value of 83.3%, diagnostic accuracy was excellent. A 4-level prognostic index further classifying the general risk of the whole sample predicted instantaneous incidence rates of up to 85% and allowed for an estimation of time to transition.

Conclusions: The prediction model identified an increased risk of psychosis with appropriate prognostic accuracy in our sample. A 2-step risk assessment is proposed, with UHR and cognitive disturbance criteria serving as first-step criteria for general risk and the prognostic index as a second-step tool for further risk classification of each patient. This strategy will allow clinicians to target preventive measures and will support efforts to unveil the biological and environmental mechanisms underlying progression to psychosis.

Arch Gen Psychiatry. 2010;67(3):241-251

Table 3. Cox Proportional Hazard Model

Predictor Variable	β	SE	Wald	HR (95% CI)	P Value
SIPS Positive subscale score >16	1.571	0.428	13.46	4.81 (2.078-11.134)	<.001
Bizarre thinking score >2 on SIPS	0.865	0.387	4.99	2.38 (1.112-5.074)	.03
Sleep disturbances score >2 on SIPS	0.793	0.387	4.19	2.21 (1.034-4.717)	.04
Schizotypal personality disorder according to SIPS	1.037	0.423	6.01	2.82 (1.231-6.464)	.01
GAF-M score, highest in the past year ^a	0.033	0.015	5.02	1.03 (1.004-1.064)	.03
Years of education, including university ^a	0.250	0.086	8.25	1.28 (1.084-1.521)	.004

Table 4. Classification of Predefined Risk

Characteristic	Risk Class of the Prognostic Index			
	I	II	III	IV
Prognostic score ^a	<-0.50	-0.50 to 0.81	0.82 to 2.12	>2.12
No. of patients (%) ^b	32 (13.5)	99 (41.6)	72 (30.3)	35 (14.7)
Estimated time to transition, mean (SEM), d	537.1 (10.7) ^c	521.1 (10.3) ^d	514.6 (11.4) ^e	366.4 (35.3) ^f
IIR of transition to psychosis, %				
At month 9	3.5	4.3	7.8	48.0
At month 12	3.5	8.0	9.6	59.5
At month 18 ^g	3.5	8.0	18.4	85.1
Distribution of inclusion criteria, %				
COGDIS	18.8	14.1	5.6	2.9
UHR	25.0	31.3	37.5	14.3
Both	56.3	54.5	56.9	82.9

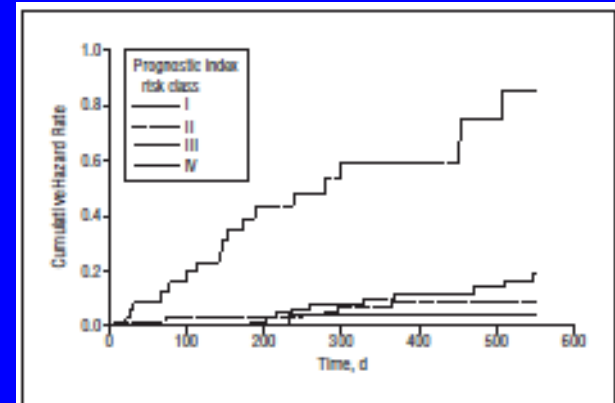


Figure 3. Kaplan-Meier survival analysis for risk classes of prognostic Index (n=245).

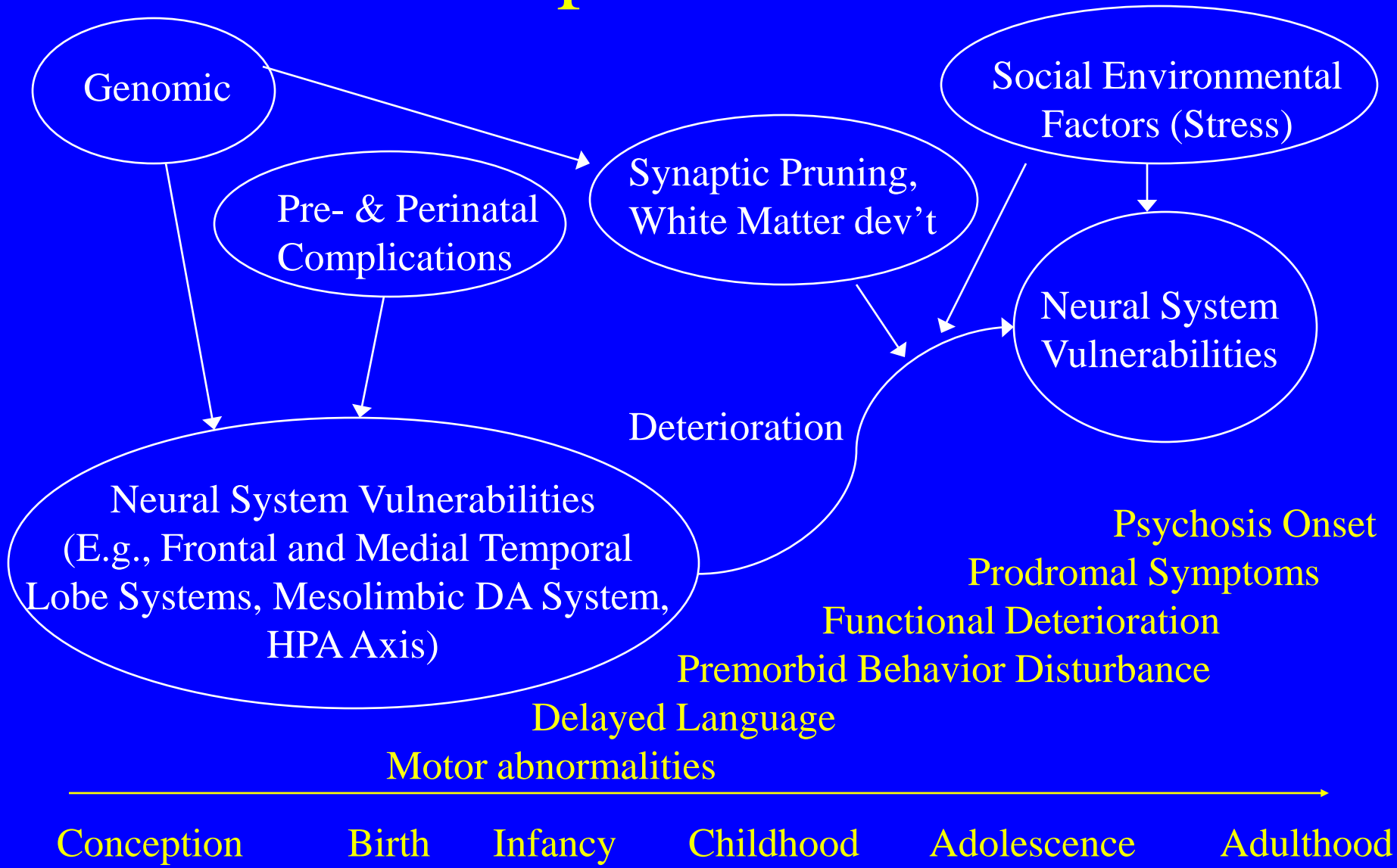
Implications

- Clinical and psychosocial measures easily implemented in community sites can achieve 80% positive prediction for psychosis
 - Enable more selective recruitment into prevention studies, avoiding exposure of false positives to potential adverse effects
 - Sensitivity can still be improved (perhaps w/ biological measures)
- Prodrome represents a critical period for studying changes in brain function associated with onset of psychosis
 - Fewer confounding influences than in first-episode patients
 - Can lead to elucidation of predictive biomarkers

Part II

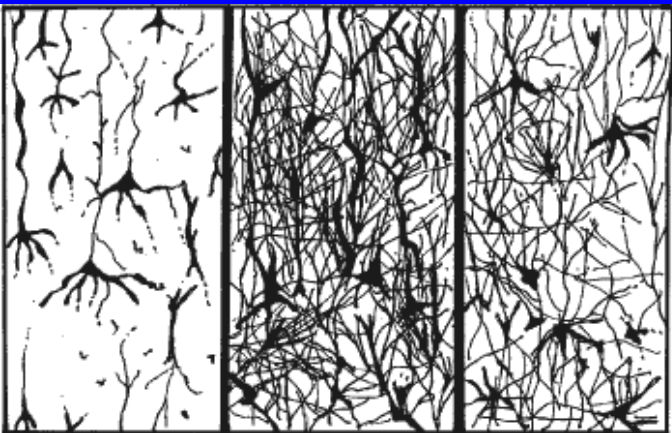
Mechanisms of Conversion to Psychosis

Developmental Model

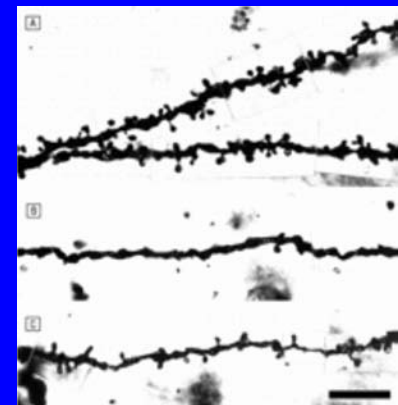
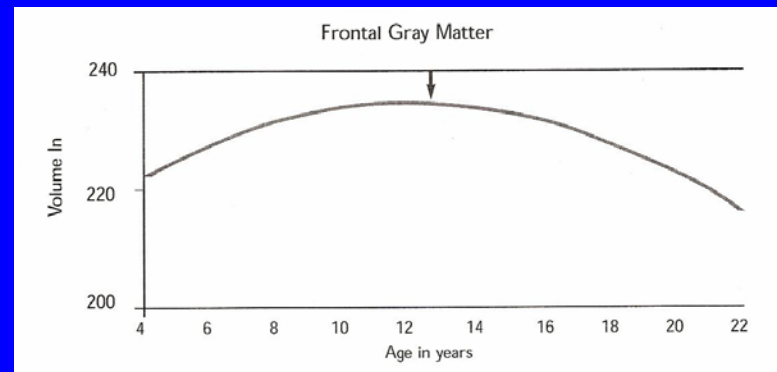


Adolescent Neurodevelopment: Gray Matter

- Typical Development
 - Synapses are overproduced early in development
 - During adolescence and early adulthood, normal pruning process occurs eliminating 40% of cortical synapses in frontal lobe (Huttenlocher, 1979)
 - Pruning results in fine tuning/increased efficiency of cortical networks
- Patients with schizophrenia have a ↓ dendritic spine density (Glantz & Lewis, 2000) but intact number of neurons (Selemon, 1995) potentially resulting from a disrupted pruning process

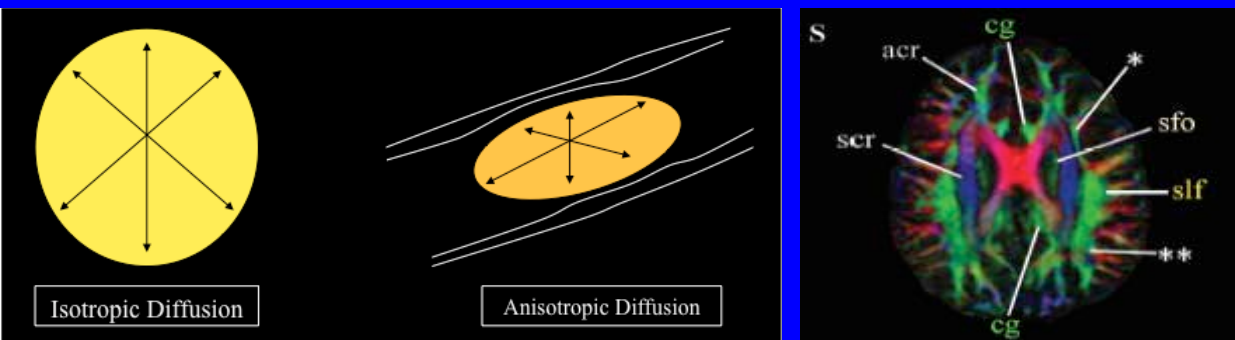
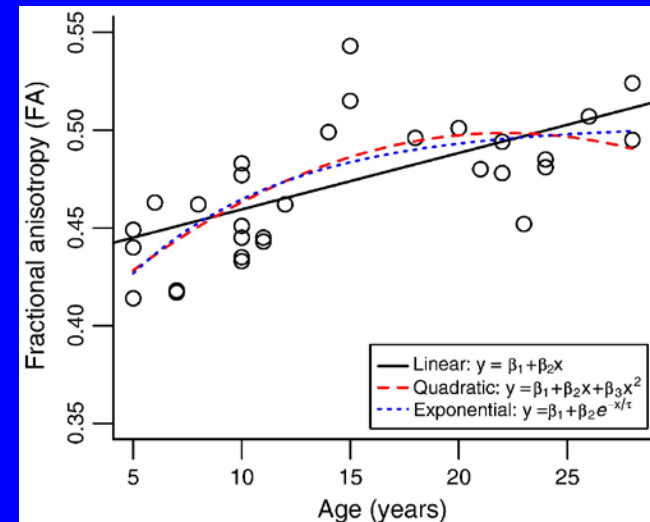
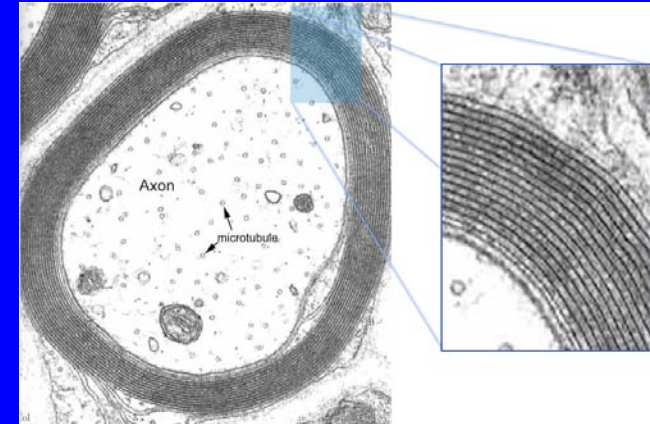


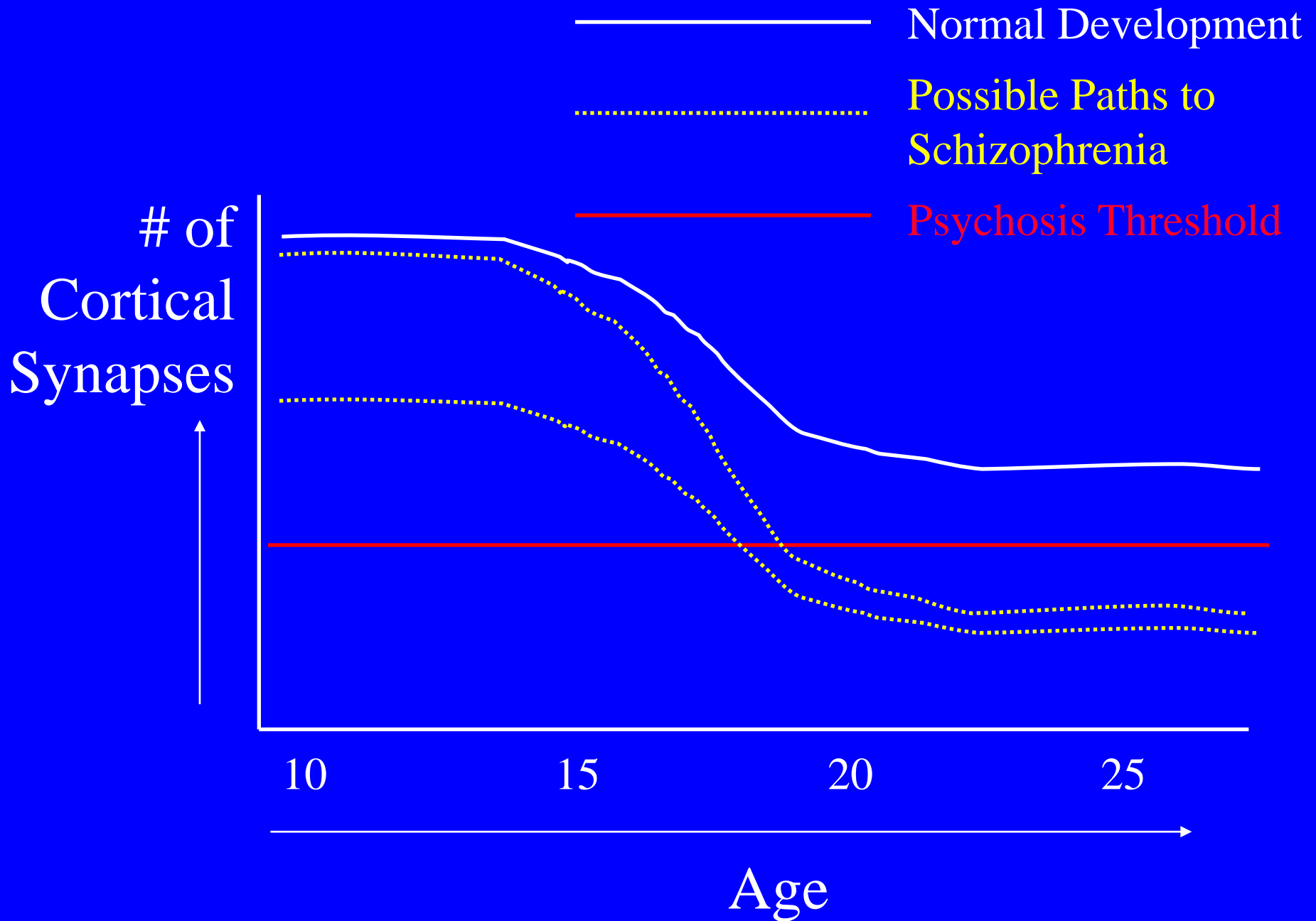
at a child's birth at 7 years of age at 15 years of age



Adolescent Neurodevelopment: White Matter

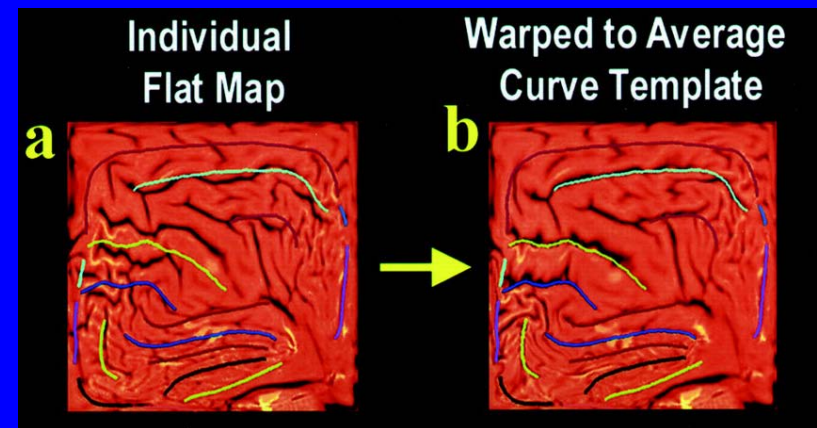
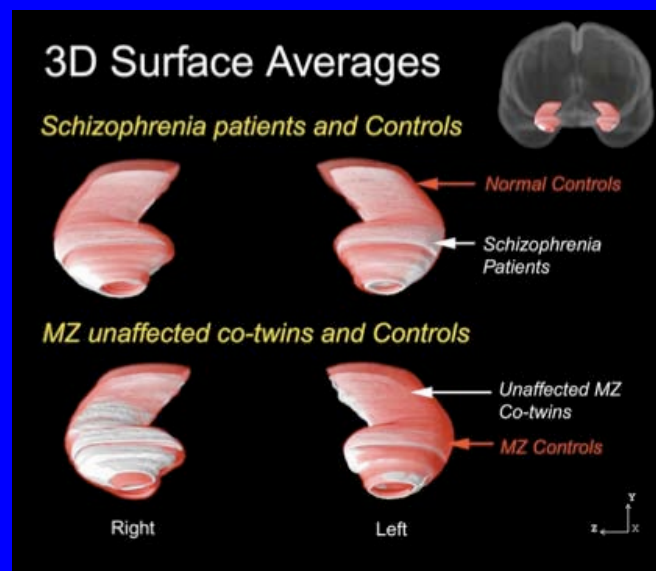
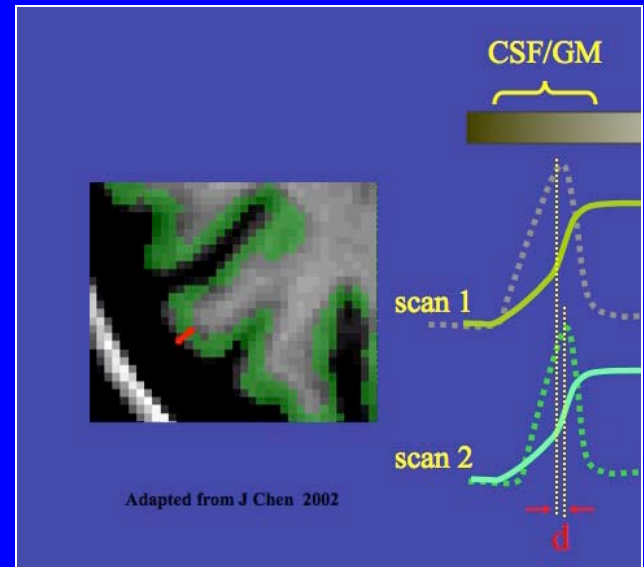
- Typical Development
 - Oligodendrocyte (myelin sheath) surrounds axon, increasing conduction velocity
 - Hippocampus and frontal lobe undergo majority of myelination in adolescence and into early adulthood
 - DTI indices of myelination and axonal organization (e.g., fractional anisotropy) increase during this period
- Patients with schizophrenia show reductions in white matter volume and lower FA in key tracts





Anatomical Imaging Using Surface Based Algorithms

- Comparison of voxel intensities between scans at brain's (or structure's) edges
- Adjust cortical folding pattern using deformation-based approaches

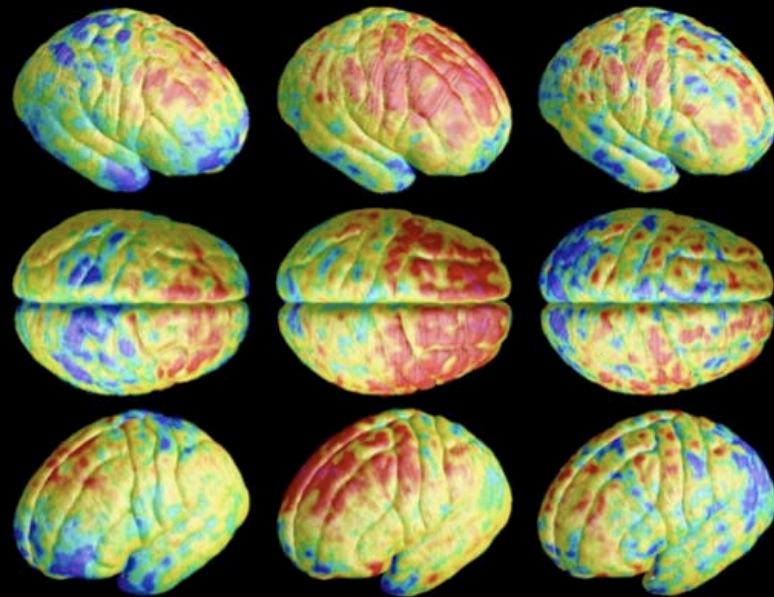


Thompson et al, J Neurosci 2003

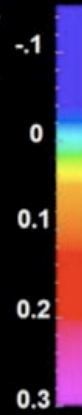
Steeper rate of surface contraction in prefrontal cortex in youth with first-episode schizophrenia compared with healthy controls

Average Brain Surface Contraction

CTRL FESZ DIFFERENCE

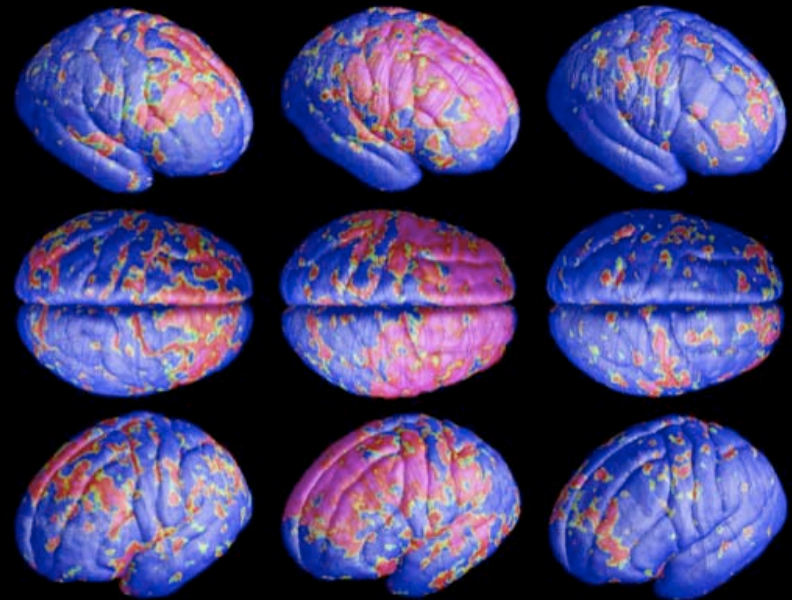


Surface Contraction Rate (mm/yr)



Significant Brain Surface Contraction

CTRL FESZ DIFFERENCE

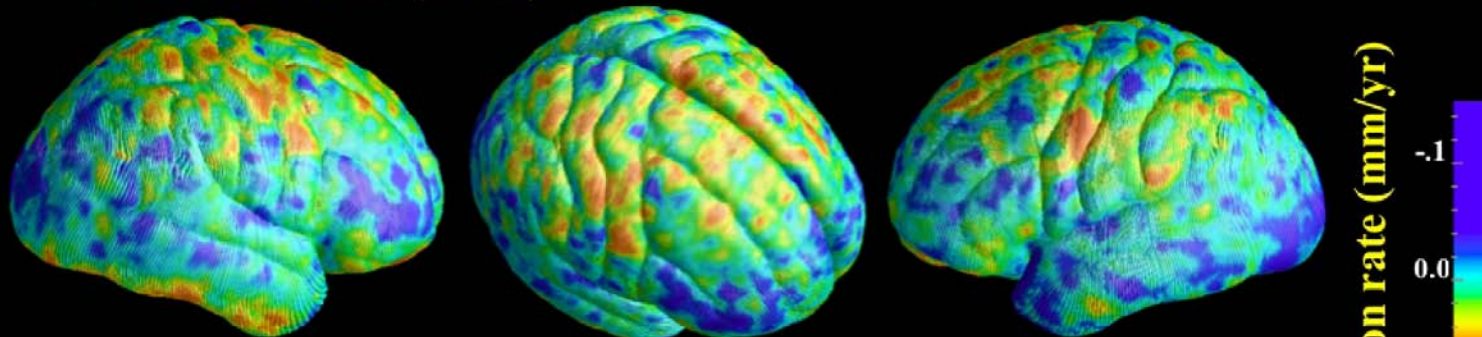


P-value

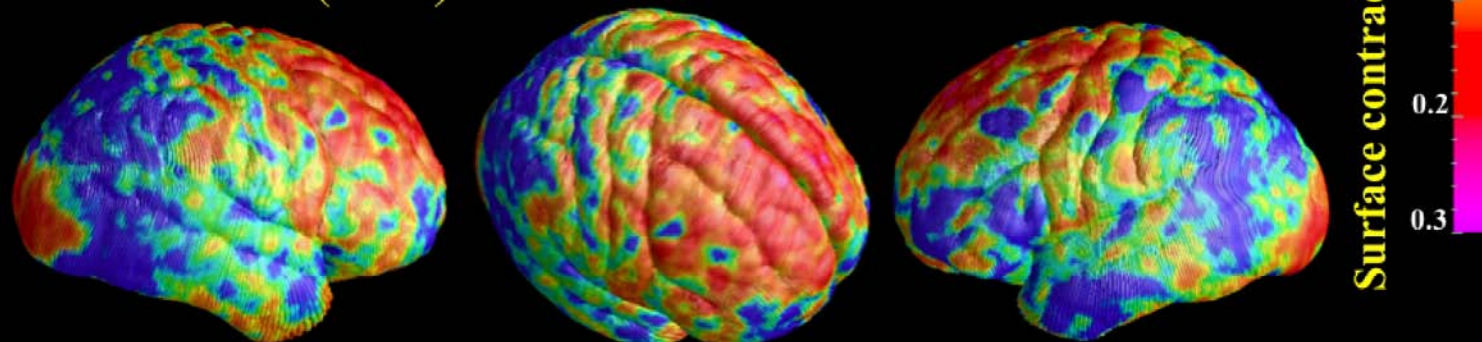


Steeper rate of surface contraction in prefrontal cortex in prodromal youth who convert to psychosis compared with those who do not

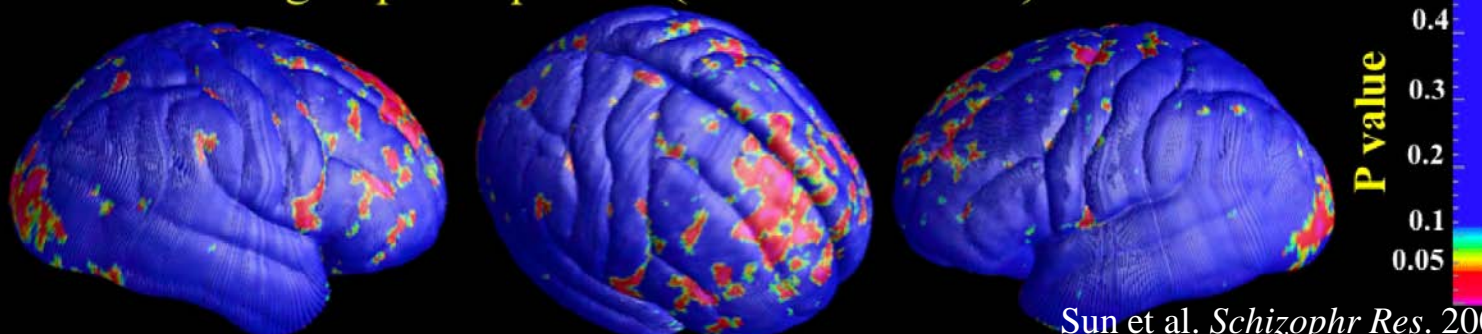
Non-converters (n=23)



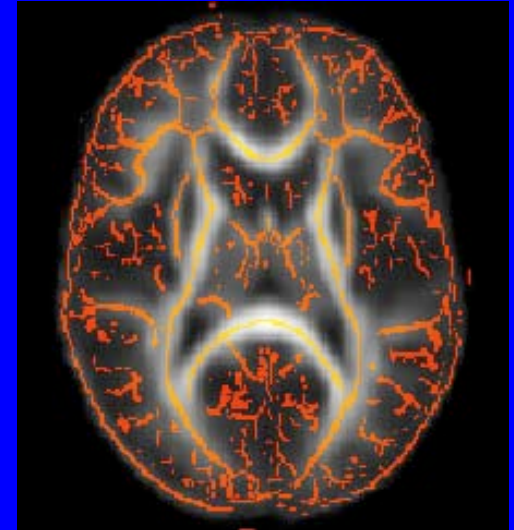
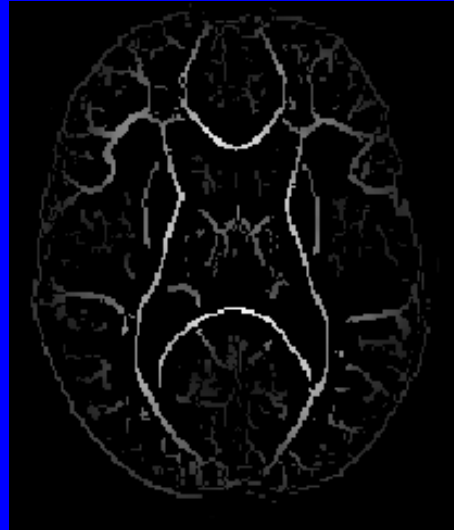
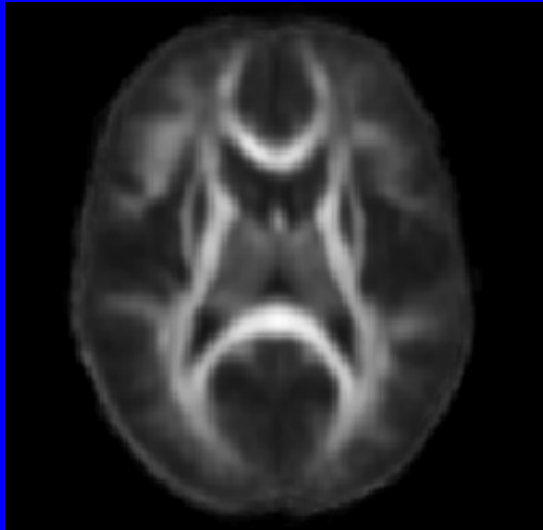
Converters (n=12)



Between-group Comparison (two-tailed t-tests)



Diffusion Imaging Using Tract Based Spatial Statistics



Creates Mean FA
(from all subjects)

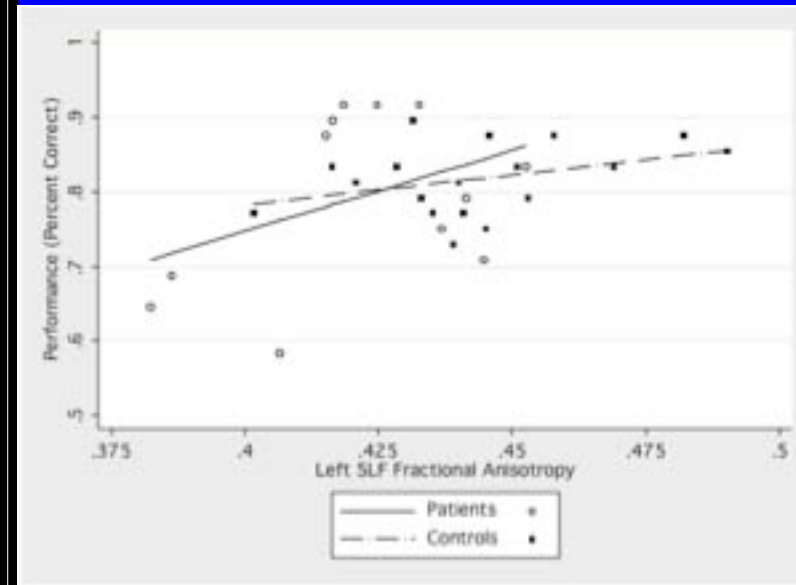
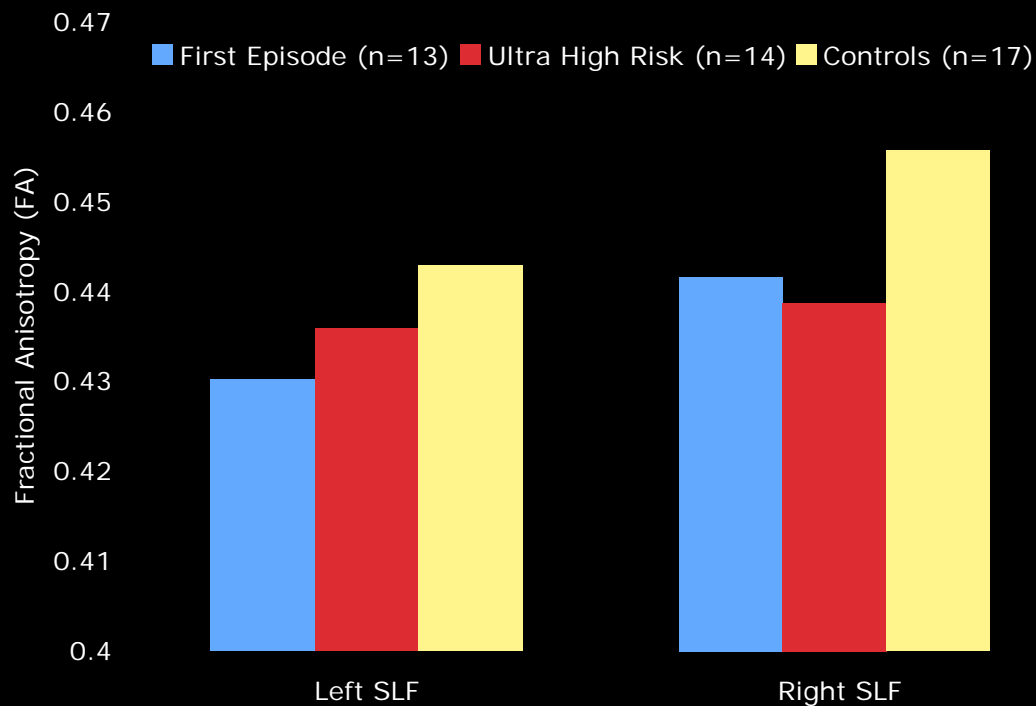
Creates skeleton based on regions of
white matter shared between all subjects
(center of tracts)

Overlays skeleton with
each subject's FA map



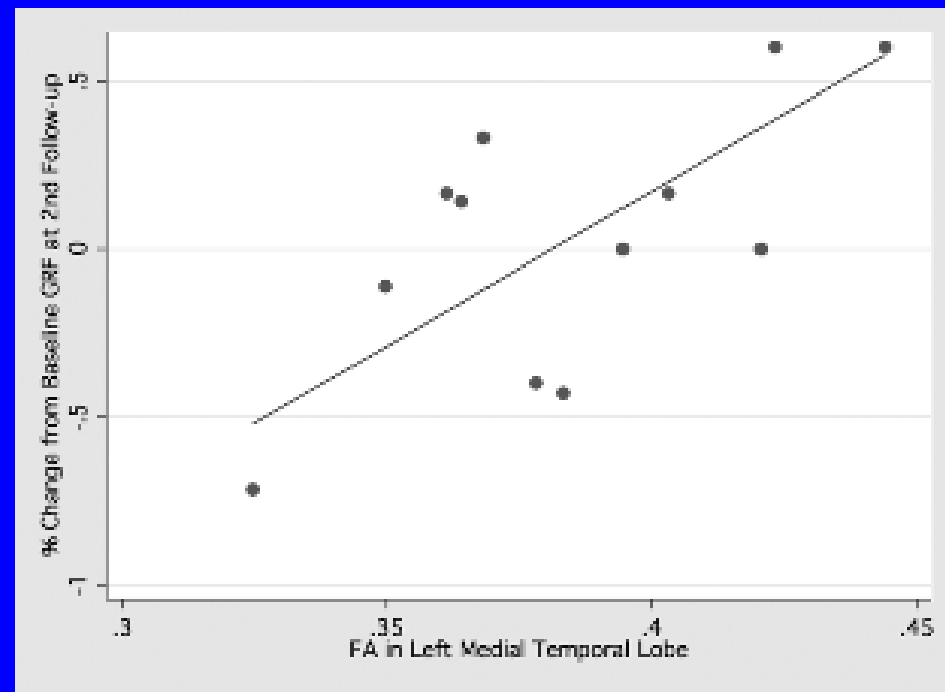
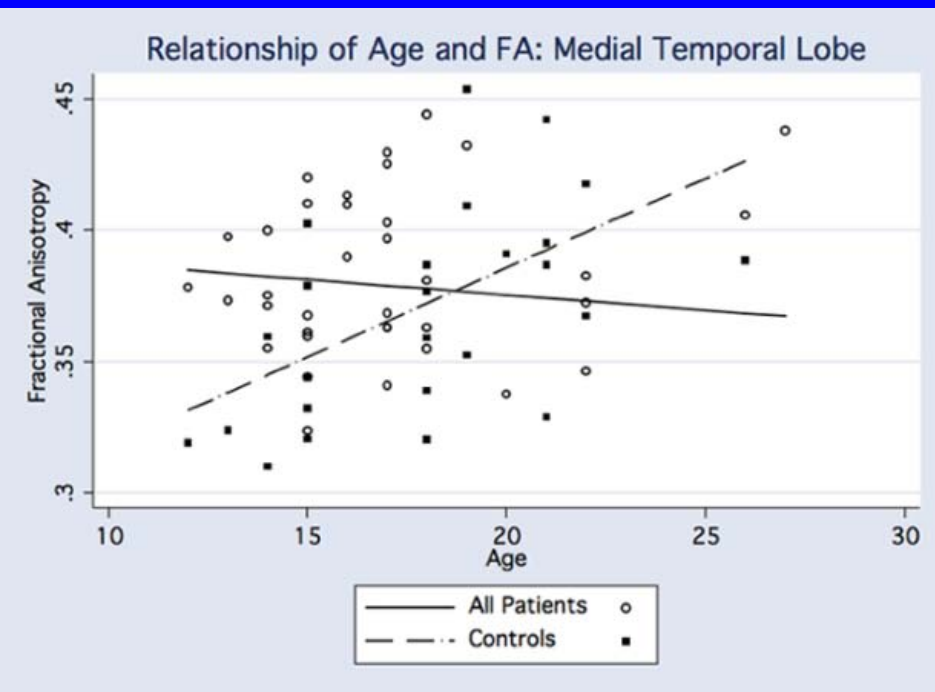
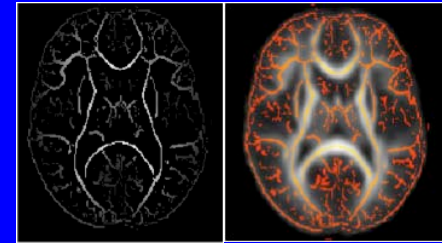
selects voxels at center
of the tracts (brightest
voxels) and assigns that
value to skeleton so that
data is in same space but
represents each subjects
own center of the tract

DTI of Superior Longitudinal Fasciculus and Verbal Working Memory



FA predicted working memory performance
First Episode Patients: $F(1,11)=6.28$ $p=.029$
Controls: $F(1,16)=8.55$, $p=.010$

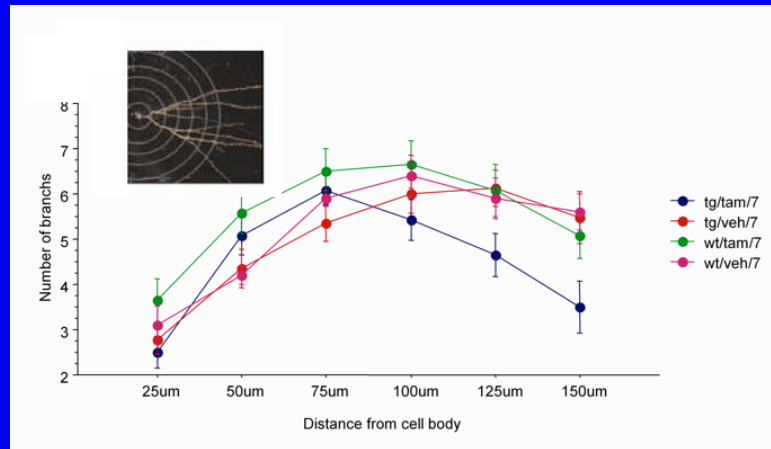
DTI-Based Assay of Medial Temporal Lobe White Matter Fails to Show Normal Increase with Age and Associates with Poorer Functional Outcome in UCLA Prodromal Patients



Potential Genomic Contributors

- Gray Matter

- Sequence variations in DISC1, RGS4, AKT1

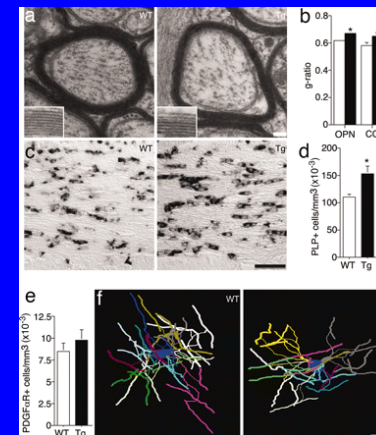


Li et al.
PNAS 2007

- Altered expression of these genes + BDNF etc.

- White Matter

- Sequence variations in Neuregulin 1 and its receptors (erbB)



Roy et al.
PNAS 2007

- Altered expression of oligodendrocyte genes

NAPLS II Aims

1. Replicate clinical risk prediction algorithm in a new prospective sample and extend it by incorporating information on neurocognitive functioning
 - 720 prodromal patients, 240 demographically matched controls
 - Focus is on maximizing prediction (PPP and sensitivity) using measures easily implemented in community settings
2. Investigate a model of disrupted adolescent brain development resulting in dysconnectivity as the proximal mechanism underlying conversion to psychosis
 - Gray matter density, white matter integrity (FA), functional connectivity/coherence

NAPLS II Enrollment (close to study midpoint)

Site	Prodromal	Controls	Total
UCLA	46	21	67
Emory	35	19	54
Harvard	15	25	40
Hillside	31	16	47
UNC	47	14	61
UCSD	33	25	58
Calgary	52	30	82
Yale	36	13	49
TOTALS	295	163	458
Targeted, overall*	305	103	408
Targeted, by site*	38	13	51

*Targeted enrollment from Feb 1, 2009, through Aug 30, 2010

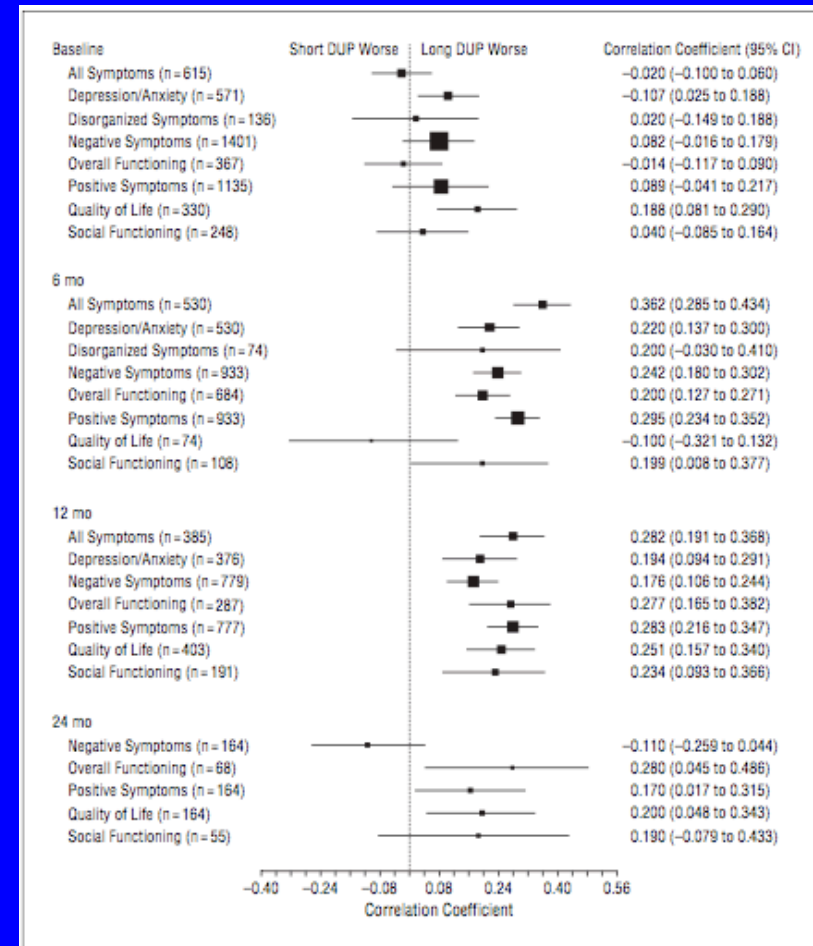
Part III

Prevention of Psychosis

Drug Treatment of Schizophrenia

Factors Associated with Response

- Antipsychotic drugs produce (at least partial) relief of positive symptoms in most patients, but response is variable, and negative symptoms and cognitive and role functioning deficits largely refractory
- A longer duration of untreated psychosis (i.e., time between onset of symptoms and the initiation of treatment) is associated with:
 - Poorer drug response
 - Increased likelihood of relapse
 - Poorer long-term outcome



Randomized Controlled Prevention Trials in Patients at Clinical High-Risk for Psychosis

Parameter	McGorry	McGlashan	Amminger	Morrison	Addington
Active tx vs control condition	Risperidone + CBT vs Placebo + Support	Olanzapine vs Placebo	Omega 3 Fatty Acids vs Placebo, CBT for both	CBT vs Monitoring	CBT vs Supportive Therapy
N's	31/28	31/29	41/40	35/23	27/24
Positive symptoms	↓	↓	↓	↓	No diff.
Conversion to psychosis	↓ at end of tx; no diff. at f/u	↓ at end of tx; no diff. at f/u	↓	↓ at end of tx; no diff. at f/u	No diff.
Negative symptoms	No diff.	No diff.	↓	No diff.	No diff.
Functioning	Not assessed	Not assessed	↓	Not assessed	No diff.
Side effects	Significant weight gain	Significant weight gain	None	None	None

Original Article

Psychoeducational multi-family group treatment with adolescents at high risk for developing psychosis

Mary P. O'Brien,¹ Jamie L. Zinberg,² Carrie E. Bearden,¹ Melita Daley,¹ Tara A. Niendam,² Alex Kopelowicz¹ and Tyrone D. Cannon^{1,2}

Abstract

Aim: In this study, we investigate the feasibility and acceptability of a 9-month psychoeducational multi-family group (PMFG) intervention for adolescents who are at ultra-high-risk (UHR) for developing psychosis.

Methods: The treatment programme was adapted from those previously shown to be effective in patients with established psychotic illness, but emphasizes content relevant to adolescence and to a pre-onset phase of illness.

Results: Participants report that psychoeducational presentations are

highly useful, they attend the PMFG group sessions regularly and report feeling comfortable in meetings and benefiting from them, and adolescents demonstrate improvement in symptoms and functional outcome.

Conclusions: This study was not a randomized controlled trial and multiple interventions were introduced simultaneously; thus, changes in outcome cannot be attributed to the PMFG intervention per se. Nonetheless, these results establish the acceptability of PMFG to adolescents and families, and encourage further research into the potential positive impact of PMFG with this at-risk population.

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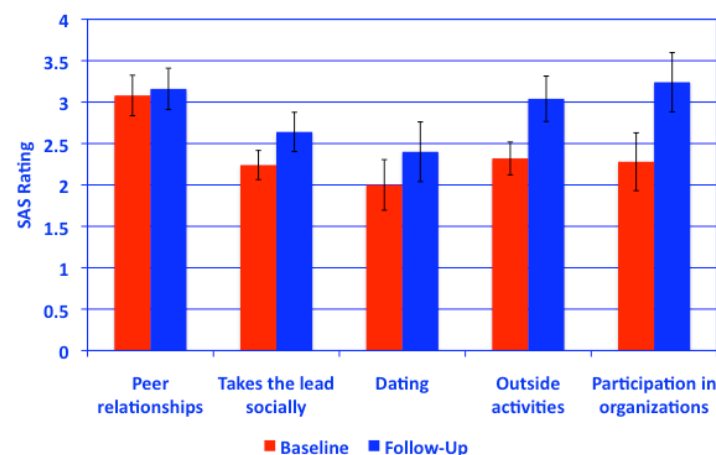
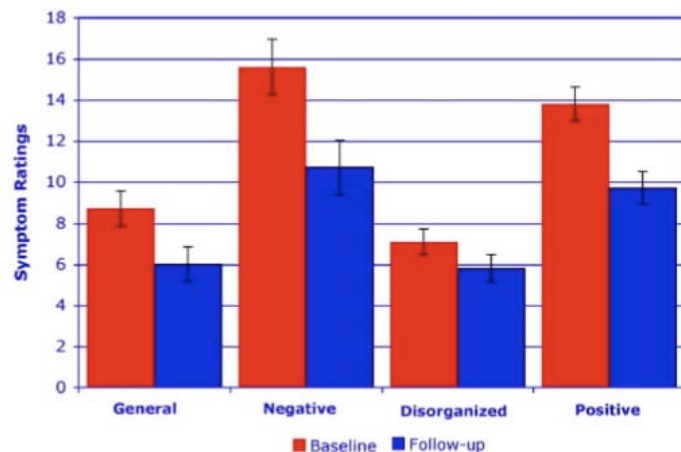


TABLE 1. Frequently raised topics for problem-solving discussions

Youth:

How can I manage my weight because it seems out of control since I started some new medications?

How can I remember to take my medication?

How can I increase my tolerance for social situations?

How do people find good friends? How do people initiate friendships?

How can I improve my grades at school?

How can I find sources of inspiration because I feel so unmotivated?

How can I get on with my schoolwork despite feeling unmotivated?

I wish I cared more about getting things done.

How can I manage when I feel overwhelmed and over-stimulated at school?

I would like to feel less 'lost' in school.

I would like to be on a team.

I would like to get a job.

How can I spend less time on the computer?

How can I convince my parents to say 'yes'? How can young people deal with hearing parents say 'no'?

I would like to have a better relationship with my father.

I want to feel less sad.

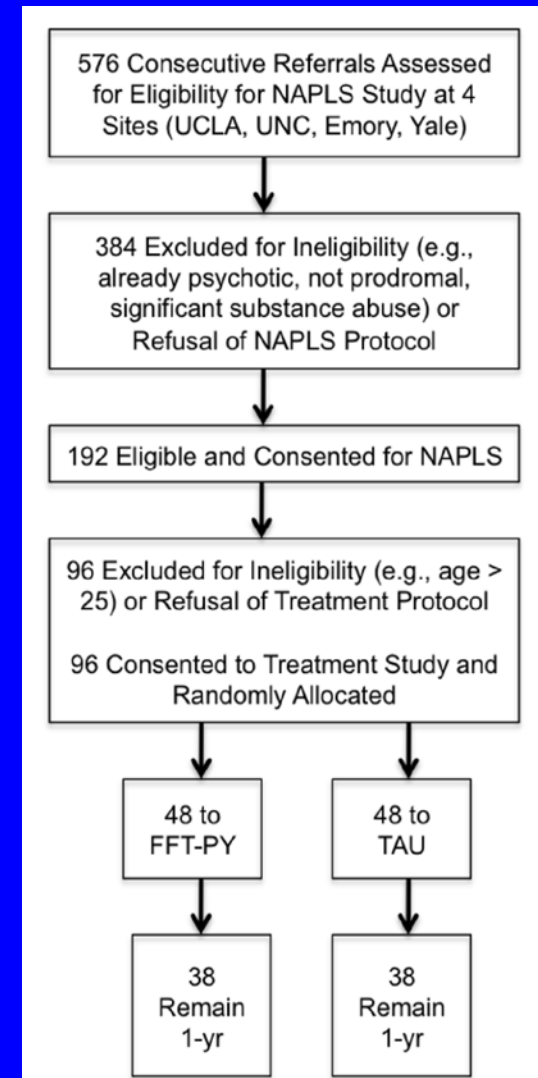
How can I deal with emotional distress without hurting myself?

How can I cope with having a caregiver in my space because my mom won't leave me home alone?

How can I stay on track when there is a lot of complexity at home?

A Prevention Trial of Family-Focused Treatment (FFT) in Youth at Risk for Psychosis

- Random assignment to 18 sessions of manualized FFT provided over a 6-month period versus Enhanced Care (EC), consisting of 5 sessions of psychoeducation and diagnostic feedback for families
 - Best-practice pharmacotherapy and crisis management as needed in both arms
- Primary, secondary, and tertiary hypotheses, respectively, are that at-risk youth will respond better to FFT than EC at 6- and 12-month follow-ups in terms of:
 - school and social functioning, family functioning, and parental distress,
 - symptom trajectories (SIPS scores)
 - time to first onset of full psychosis



Conclusions

- Profile of clinical risk indicators and family history has 80% positive predictive power for conversion to psychosis
 - Working toward objective assays of biomarkers
- Altered profiles of adolescent brain development may participate in onset
 - Steeper than normal rate of gray matter loss (pruning) and absence of normal increase in white matter (myelination)
 - Risk genes may influence gray & white matter changes
- Prevention may be possible
 - Omega 3 fatty acids appear promising across all endpoints
 - Antipsychotics reduce symptom severity but do not appear preventive
 - Psychosocial interventions may better impact functioning/disability
 - Working toward novel molecular targets for intervention that may restore normal development & prevent onset

Acknowledgements

- National Institute of Mental Health
- Garen, Shari, Brandon & Shannon Staglin & Music Festival for Mental Health
- International Mental Health Research Organization (IMHRO) and NARSAD
- Numerous collaborators at UCLA, other NAPLS sites, and institutions worldwide (especially Univ of Melbourne, Karolinska Institute, Konsanterveylaitos)
- Patients and families who have participated in our studies