1-12-2009

Identifying Schizophrenia: Paradigm Shift 'The UHR Research'

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If early intervention leads to better outcome can ‘earliest’ intervention prevent progress to frank psychosis or Delay it?

Clinical
Epidemiological
Neuropsychological
Neurophysiological
Neuroimaging
Animal Studies

Cognitive Neurosciences

Clinical studies of Early Psychosis initiative

‘At-Risk for Psychosis’ Challenges

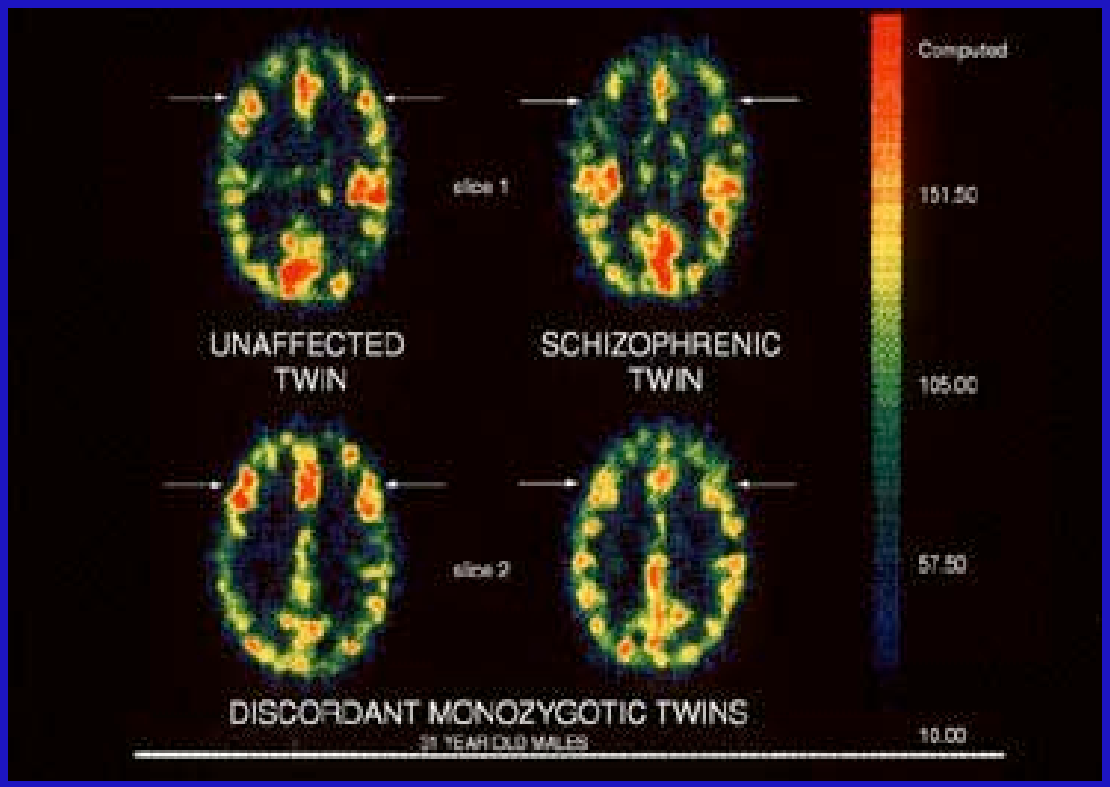
- Significant public health merit
- Unfolding brain development & maturation in SZ.
- specificity in Non-specific symptoms
- Consensus in Definitions & Measurements
- Predictive validity of symptoms & Risk factors
- Biomarkers & behavioral markers of regional brain dysfunction
- Argument for Intervention: when & how?

Opening up windows of opportunities for identification & treatment

- ‘ How operationally benign the process was….”(McGlashan)
- Need to refine identification in adolescents
- Refining the criteria's prevention
- Medication trial = Medication free challenge
- Ongoing functional decline
- Suicide
- Homicide or risk

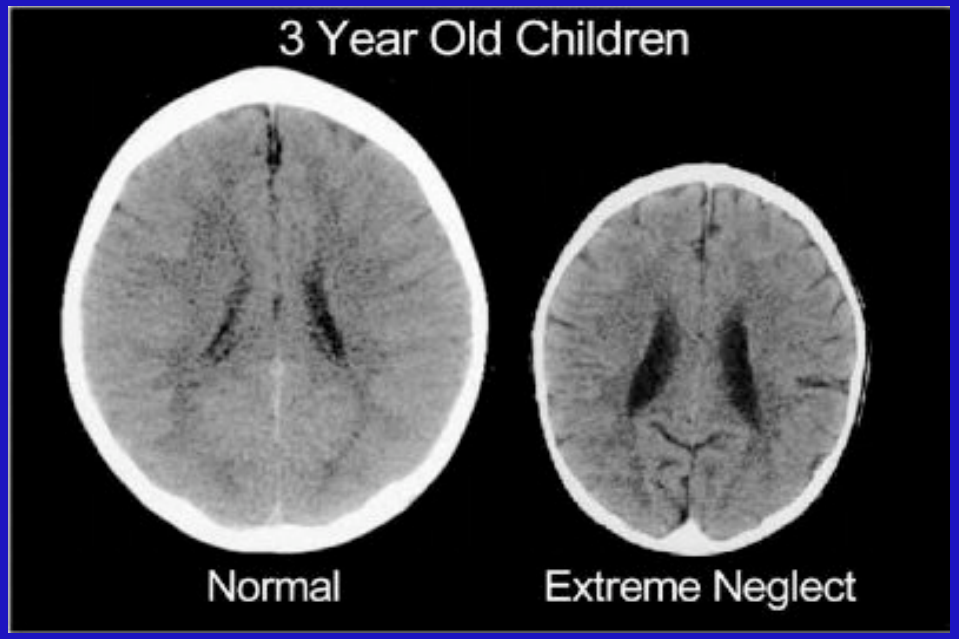
Genetics , familial,
Environmental Risk

Genetic High risk group (GHR)
Clinical High Risk Group (CHR)
Ultra High Risk group (UHR)

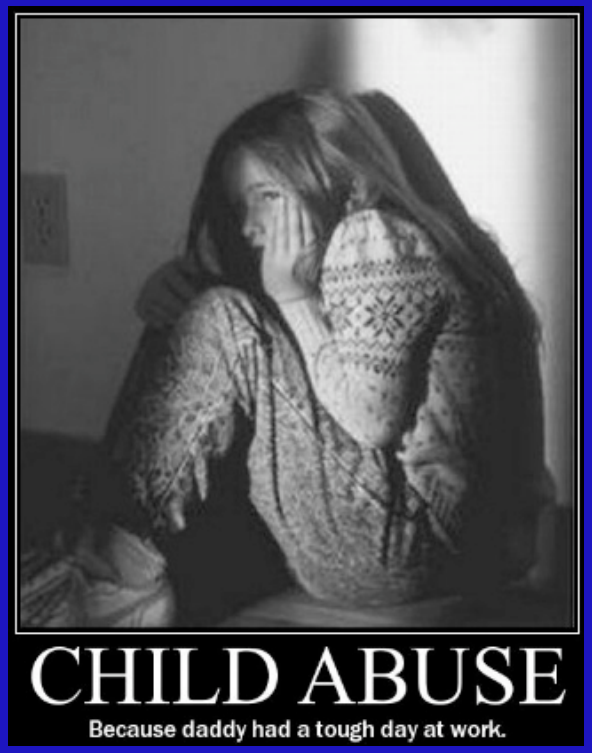


PET imaging showing areas of brain activity in twins - one schizophrenic, one not.
Image courtesy Dr. Karen Berman, Clinical Brain Disorders Branch, NIMH, NIH)

Childhood Experience and the Expression of Genetic Potential: What Childhood Neglect Tells Us About Nature and Nurture [1, 2]



Neuronal development & Child abuse



1.Chen TJ, Med Hypotheses. 2006;66(5):1043-4.
2.Anda RF,Eur Arch Psychiatry Clin Neurosci. 2006 Apr;256(3):174-86. 2005

Commonly described prodromal features of schizophrenia (modified from Yung, 2006)

Neurotic symptoms

- Anxiety
- Restlessness
- Anger, irritability

Changes in volition

- Apathy, loss of drive
- Boredom, loss of interest
- Fatigue, reduced energy

Mood-related symptoms

- Depression
- Anhedonia
- Guilt
- Suicidal ideas
- Mood swings

Cognitive changes

- Disturbance of attention and
- concentration
- Preoccupation, daydreaming
- Thought blocking
- Reduced abstraction

Young AY& Mcgorry PD, Prediction of Psychosis: setting the stage, BJP 2007, 191 suppl 51

Symptoms suggesting high risk

Physical symptoms

Somatic complaints

Loss of weight

Poor appetite

Sleep disturbance

Attenuated or sub-threshold versions of psychotic symptoms [1, 2]

Perceptual abnormalities

Suspiciousness

Ideas of reference

Change in sense of self, others or the world

Other symptoms

Obsessive–compulsive phenomena

Dissociative phenomena

Increased interpersonal sensitivity

Behavioral changes

Deterioration in role functioning

Social withdrawal

Impulsivity

Odd behavior

Aggressive, disruptive behavior

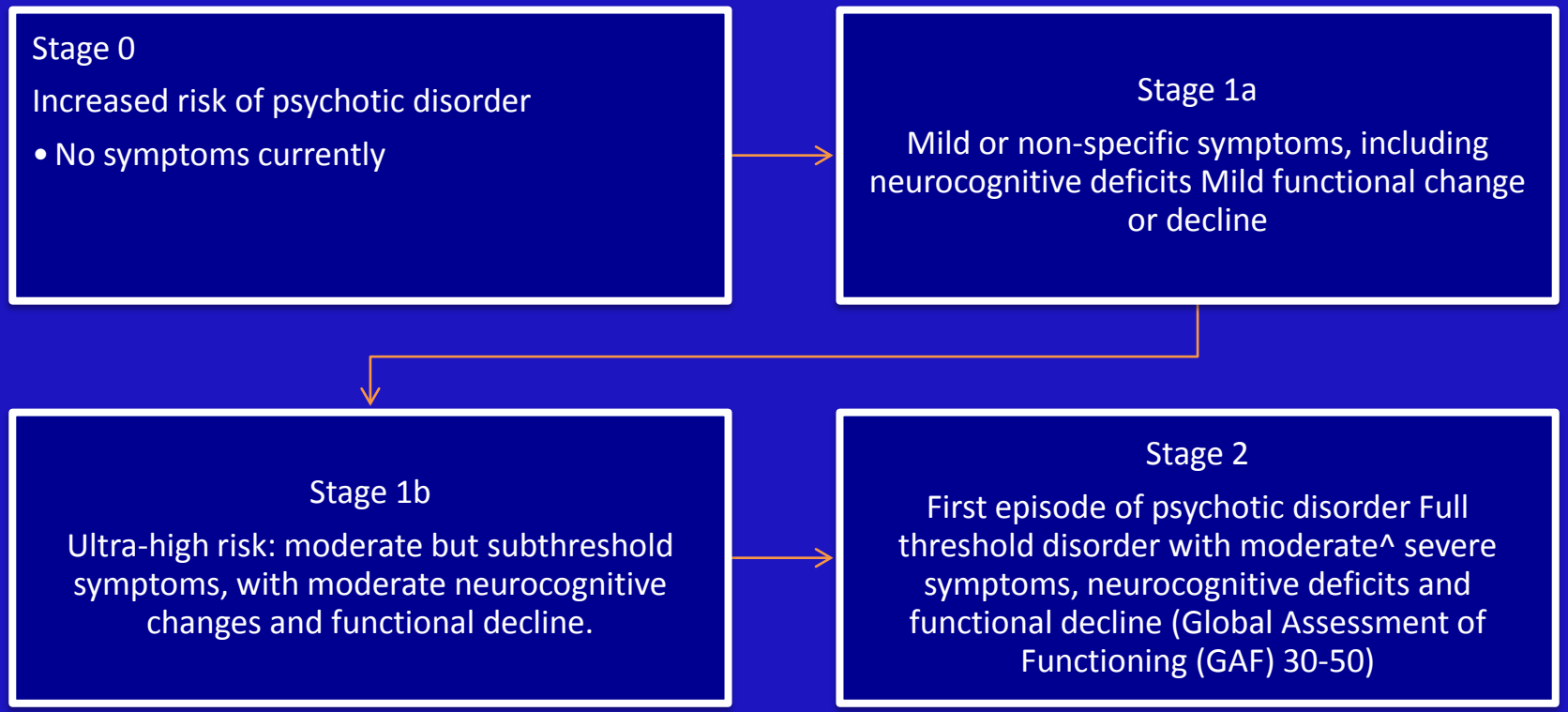
The prodrome concept runs into problem variability, lack of specificity [3]

1.Tien, A.Y. (1991) Distributions of hallucinations in the population. Social Psychiatry and Psychiatric Epidemiology, 26, 287-292.
2.van Os, J.,Hanssen,M., Bijl, R.V., et al (2001) Prevalence of psychotic disorder and community level of psychotic symptoms: An urban-rural comparison. Archives of General Psychiatry, 58, 663-668.
3.Young AY& Mcgorry PD, Prediction of Psychosis: setting the stage, BJP 2007, 191 sp 51

UTILITY OF A CLINICAL STAGING MODEL[1]

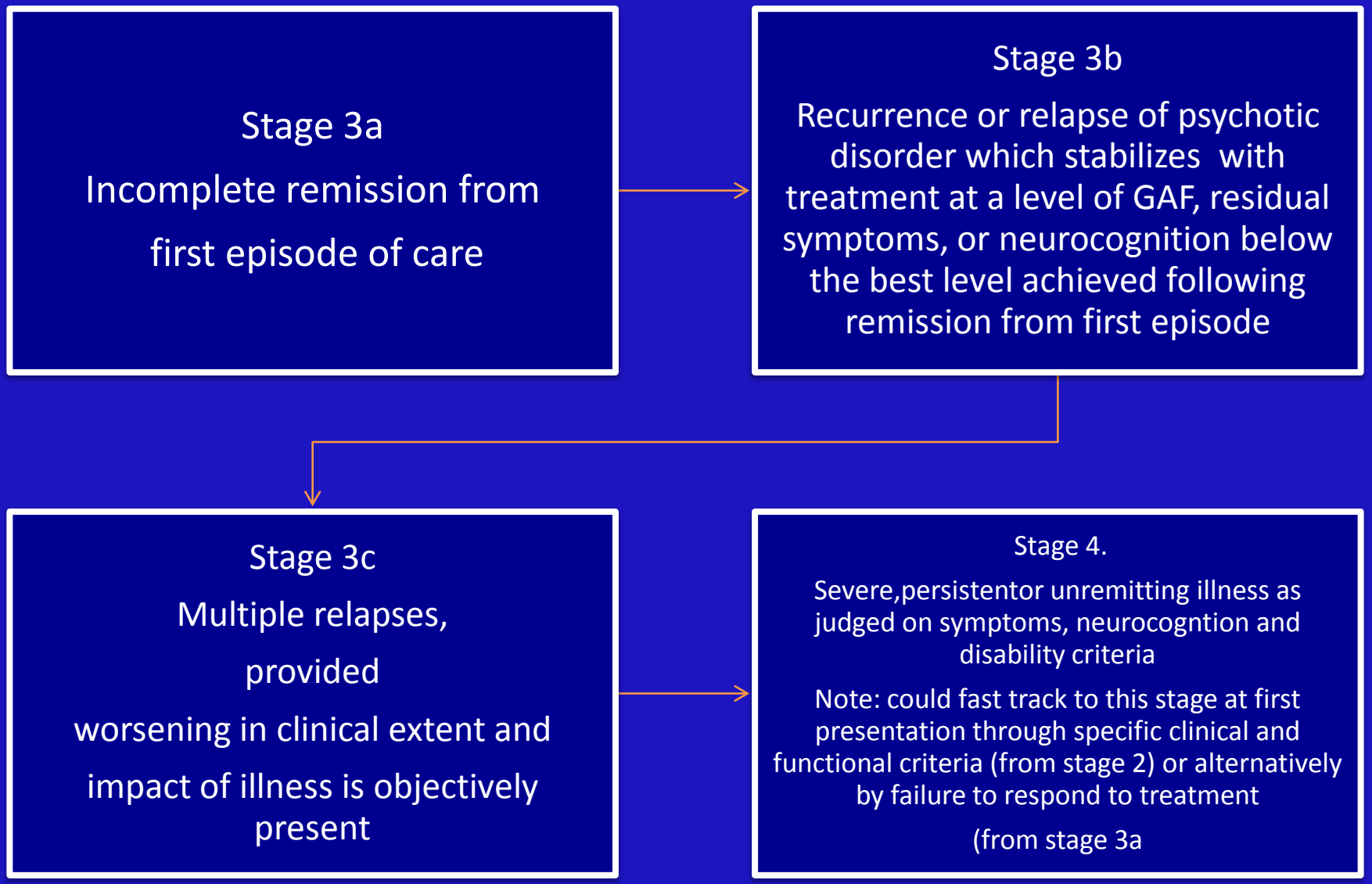
(e.g. malignancy) QOL & Survival depends upon earliest possible intervention

- ✓ **fundamental assumptions**
- ✓ early stages better response
- ✓ treatments offered likely benign & effective.[2]



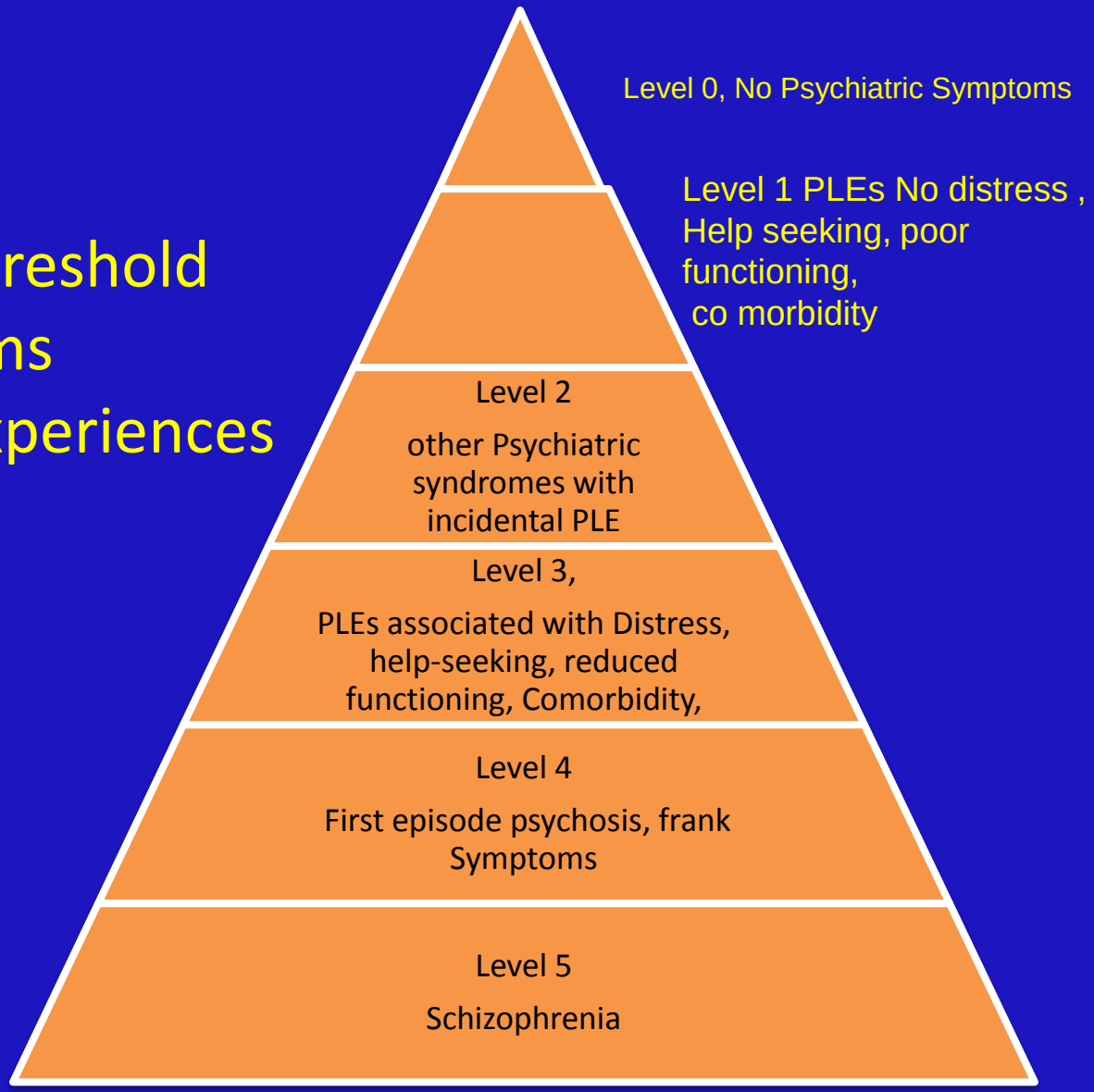
1.Young AY& McGorry PD, Prediction of Psychosis: setting the stage, BJP 2007, 191 sp 51

2.McGorry, P.D.,Hickie, I. B.,Yung, A. R., et al (2006) Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Australia and New Zealand Journal of Psychiatry, 40, 616^622.



Young AY& Mcgorry PD, Prediction of Psychosis: setting the stage, BJP 2007, 191 sp 51

Detect sub threshold symptoms Psychotic-like-experiences (PLE)



Substance use

Cannabis : contrasting results,
'role of cannabis as a risk for onset of psychosis'.

- Prospective studies : '.SU contribute to the onset' [1]
- 'irrespective' of identified risk
- Cannabis use increases likelihood of psychotic relapse [2]
- Increased psychotic experiences –in non-clinical general population [3]
- Neither use nor dependence (1 year prior) -- associated with higher risk in F/U 1 Y
- High levels use → less motivated to seek Tx. [4]
- Edinburgh study,: 'more likely to have psychotic-like symptoms at baseline' [5]
- No longitudinal data for transition to psychosis

1.Hornicroft, 1990, 2.Linszen et al, 1994), 3.Johns et al, 2004 (PACE cohort) 4.Phillips et al, 2002a, 5.Miller et al, 2001

Stress
Adverse Life Events (ALE)

- Precede onset [1]
- Cause Relapses in established disorders [2]
- Hypothesis: ALE may actually precipitate onset in vulnerable individuals.
- Minor life events or day-to-day hassles: are more stressful than major events [3]
- Subjective experiences of stress,
- More intense negative affect to subjective appraisals [4]
- Difference in tolerance
  - psychotic like symptoms
  - lifetime experience of major stressors in prodromal & UHR, [5]
  - significant association: 'impaired tolerance of normal stress' and psychosis onset in UHR [6.]

1.Bebbington et al, 1993, 2.Hirsch et al, 1996
3.Malla & Norman, 1992 , 4.Myin-Germeys et al (2001) 5. Miller et al, 2001), 6. Yung et al, 2005

Social Functioning

- • Clinical High Risk subjects consistently
- demonstrate deficits equivalent to those
- seen in FE subjects in
- – current social functioning
- – premorbid social functioning
- – social cognition
- • facial affect recognition
- • social judgments
- Addington et al. 2008 Brit J Psych;
- Addington et al. 2008 Schiz Res

- Addington et al. 2008 Brit J Psych;
- Addington et al. 2008 Schiz Res

Social Functioning, social cognition [1,2]

- Both UHR & GHR show impairment,
- UHR > GHR
- Duration of prodromal symptoms UHR– related - impaired
- PS & NS - not significant
- Both a trait and state marker of risk schizophrenia / psychotic disorders,
- Mediating vulnerability
- Early indicator,
- Prodromal stage- modest impairment
- Prefrontal dysfunction

1.Shim G Social functioning deficits in young people at risk for schizophrenia.
, Aust N Z J Psychiatry. 2008 Aug;42(8):678-85

2.Chung YS, Deficit of theory of mind in individuals at ultra-high-risk for schizophrenia
. Schizophr Res. 2008 Feb;99(1-3):111-8.

The theory of social defeat explains affective appraisal & response for environmental factors enhancing risk for schizophrenia

Marginalization, Social exclusion, Physical & Sex Abuse, Migration, Ethnicity increase prevailing risk level

Social defeat, Environment & Enhanced Risk of SZ

- Previously, - proposed theory: Long-term experience of social defeat, defined as a subordinate position or as outsider status, may well be the common denominator for these findings [1]
- This interpretation is compatible with the
  - High levels of competition in urban areas,
  - Fewer career opportunities for people with low IQ,
  - Social exclusion experienced by immigrants and people with hearing impairments and
  - The humiliation of being abused

- Not Purely-Genetic risk factors:
- urban environment, migration,
- low IQ,
- hearing impairment [2]
- use of illicit drugs.
- Physical & sexual abuse [3]

1.Selten & Cantor-Graae, 2005. 2.Thewissen et al, 2005 3.Read et al, 2005

Search for Bio-markers

- Abnormal body movements, correlated with prodromal symptoms (dopamine effect)
- Tendency to interpret nonsensical babbling as words and phases
- ‘ tendency to read meaning into meaningless sensory information may produce ‘ matrix of unreality’ that prompts initial psychotic phase.

Reduction in Mismatch negativity amplitude MMN & Heschl's gyrus reduction

- Seen in chronic state
- Not seen in FES (Umbricht et al 2006)
- Reduced by NMDA
- Involvement of auditory cortex in pathogenesis (Salisbury et al 2007) schizophrenia
- Pathological changes are not confined to specific brain regions, PFC

Prodromal Syndrome assessment tools

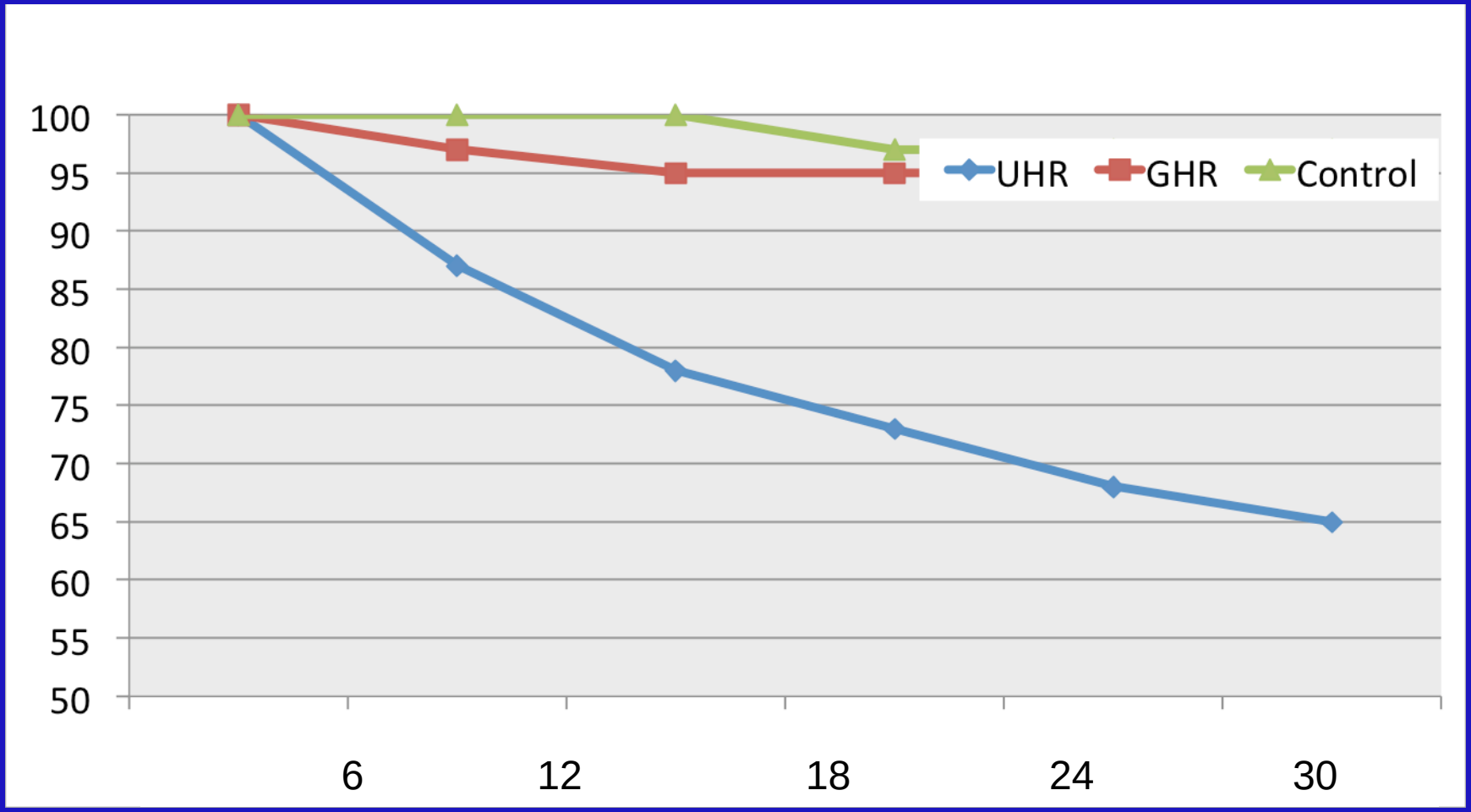
- Identification by a structures interview
  - Structured interview for prodromal syndrome (SIPS)
  - Comprehensive Assessment of At Risk mental state (CAARMS)
  - Bonn scale for assessment of basic symptoms (BSABS
- Syndromes
  - Attenuated positive symptom syndrome
  - Brief intermittent psychotic syndrome
  - Genetic risk + deterioration syndrome

Variable Transition Rates

Study	N	Rate (%)	Follow-up (months
Current average		33%	
PACE (Aus)	104	35	12
PRIME (Yale)	13	54	12
PRIME (NA)	60	35	12
RAP (NY)	34	27	6
EDIE (UK)	23	22	12
CARE (SD)	50	15	12
Toronto	50	20	12
PAS, Newcastle, AUS		50	12
TOPP, Norway		43	12
Manchester (UK)		22	12
PACE (Aus), 2006		9.2	6

- Declining TR @ 0.8 times at PACE(1995-2000)
- Explained by:
- a- reduction in duration of symptom prior to help,
- b-more false positive

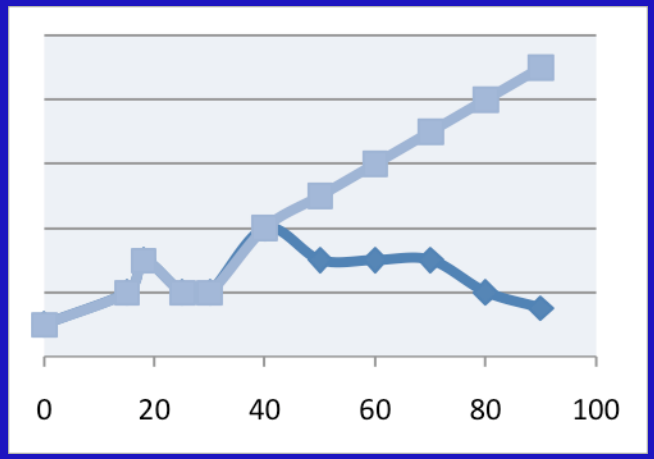
Survival distribution function in North American study



Cannon et al. Arch Gen Psychiatry 2008;65:28-37

Transition Rate or Conversion to Psychosis depends upon the vulnerability of selected group

- Status Natural untreated transition in heterogeneous risk group
- Status of Preventable transition by a treatment (Non-drug or drug therapy)
- Selection is criteria dependent which leads to variability in transition rate.



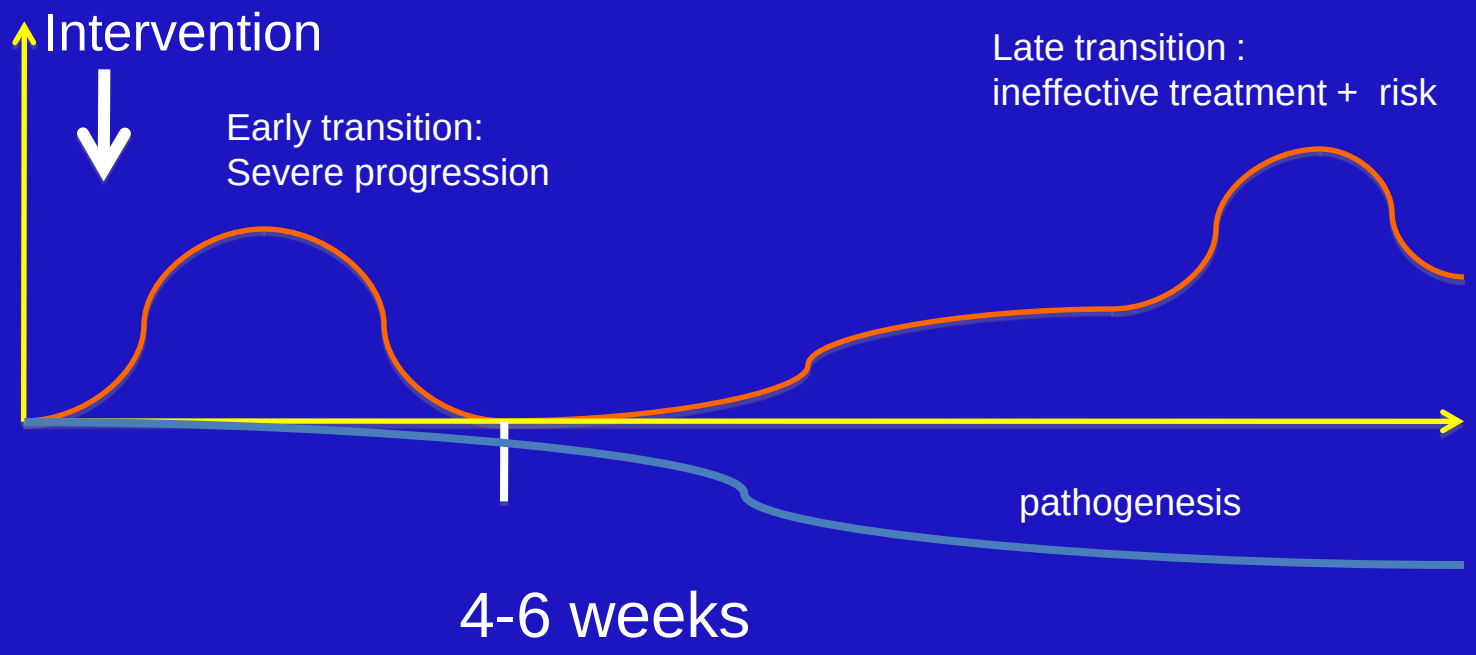
NAPLS

"… prospective ascertainment of .. At risk for psychosis is feasible, with a level of predictive accuracy comparable to that in other areas of medicine".. Tyrone Cannon

- N=291, F/U 30 months, 8 centers, tallied 77 individual predictors variables at base.
- Variables covered 10 domains
- 5 additional criteria over SIPS increased chances of prediction by 80%
- 35% TR, RR 405 in general population.

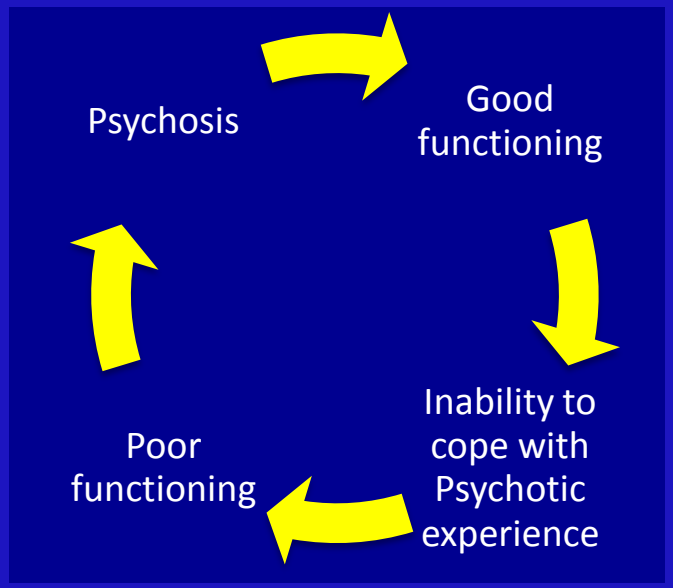
UHR Status (CAARMS)

- Sensitive (92%)predictor (TR 12/13)
- Specificity was 62% Low functioning – as a predictor



Measurement of social and role functioning for assessment of UHR is challenging

- Cornblatt et al : two scales
- 1. Global Scale of functioning: Social
- 2.Global Scale of functioning: Role
- Excellent interrater reliability
- Functional decline as a risk
- Functional improvement – a prognostic indicator in UHR



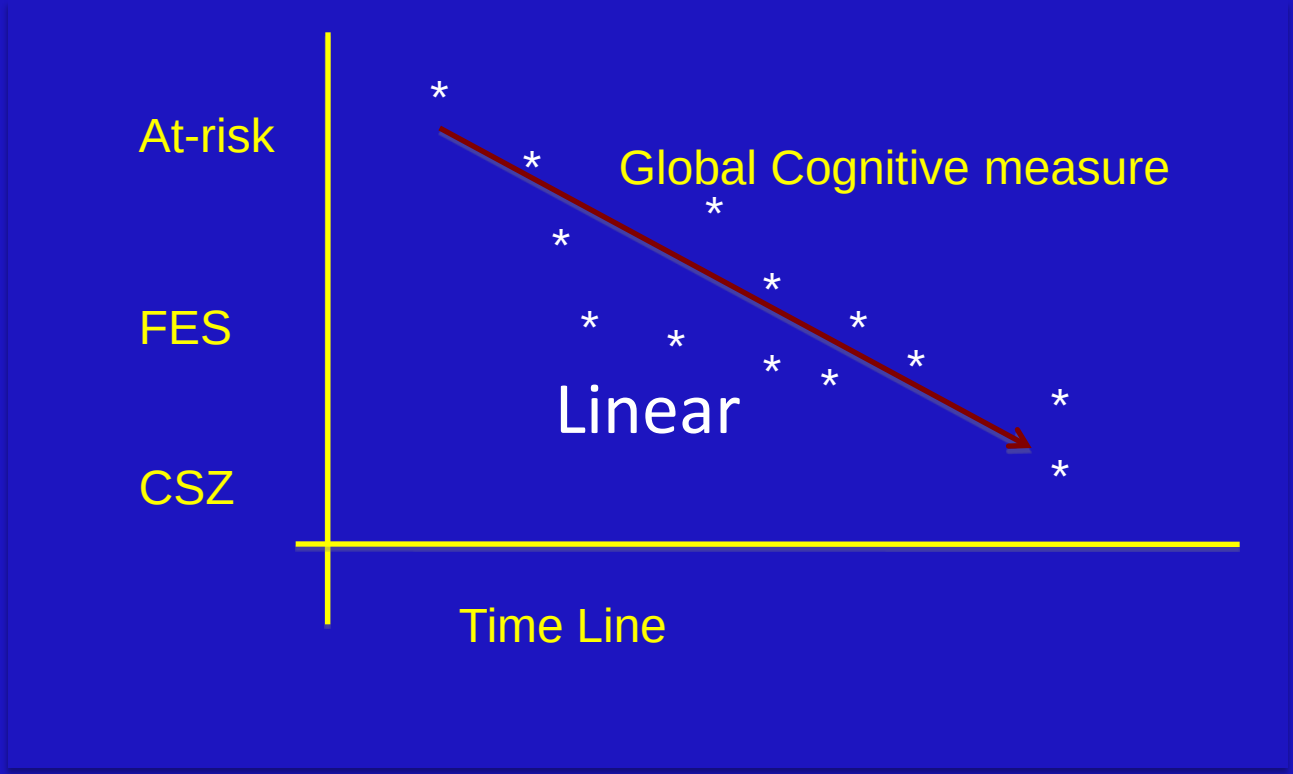
Community initiative & experience

'highlight the need for comprehensive universal public mental health interventions'.

- Educational campaign for destigmatization in a comparative study, Oslo, Norway:
- Drop in suicidal behavior
- Age at first contact- reduced , younger with milder symptoms
- Shorter DUP

Do Cognitive Deficits Progress During the Course of Schizophrenia? Yes, on all parameters

Cognition declines as psychosis progresses



Cognitive Deficits

Cognitive performance profiles

intermediate to normal control and first

episode psychosis cohorts across domains

of attention, memory and executive ability.

Degree of deficit at base does not predict psychosocial outcome.

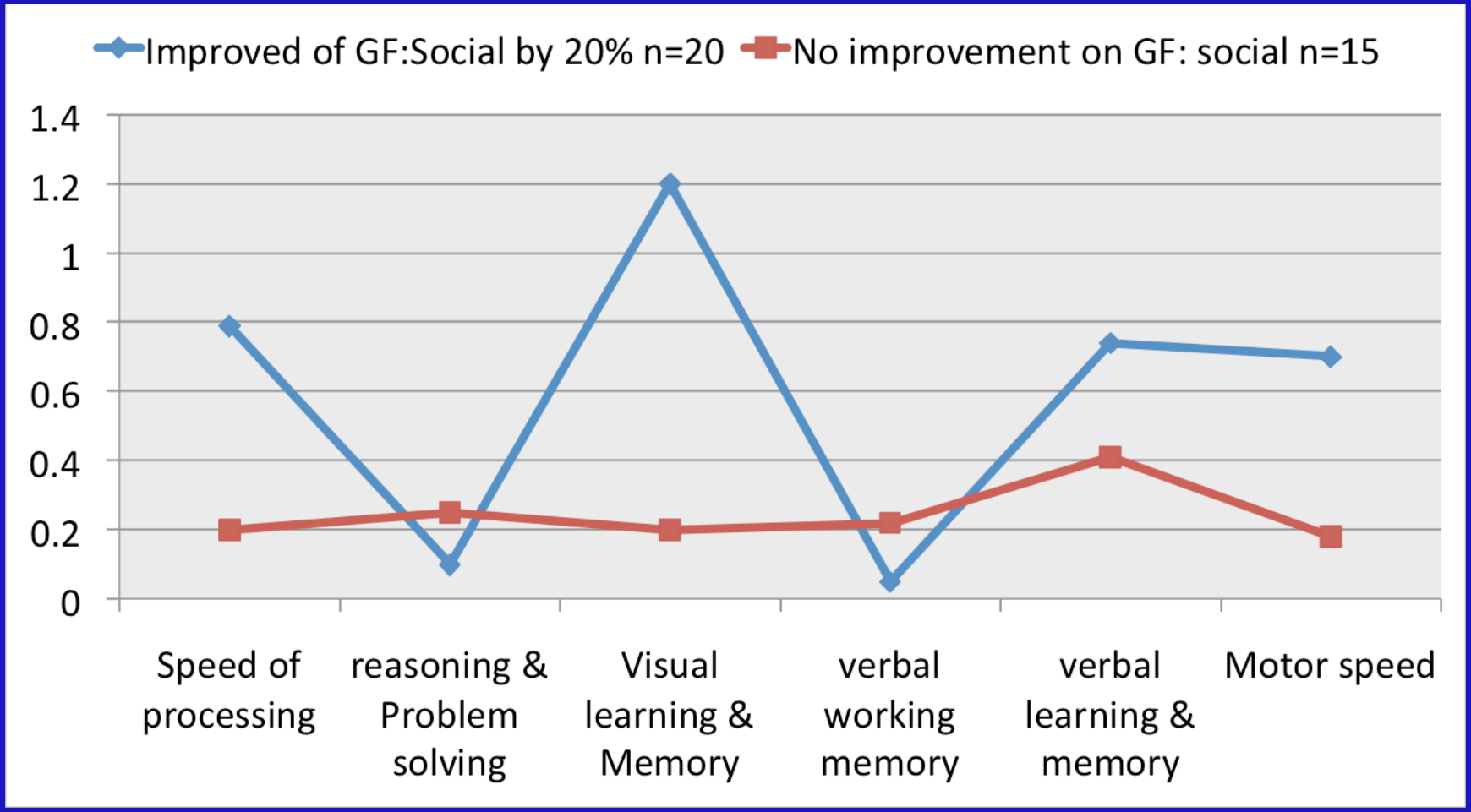
The course of change in follow up does does differentiate good & poor functional outcome

Neurocognitive impairment in UHR
1.Working memory, 2.Executive Functioning

- Represent neurocognitive trait as markers for SZ.
- Working memory, - consistently impaired throughout the course [1]
- Working memory - impaired prior to the onset of psychotic illness [2]
- Immediate verbal recall deficits - prior to illness onset, indicate compromised prefrontal functioning.
- Olfactory identification deficits - occur prior to psychosis onset [3].
- despite this, --- predictive value of neurocognitive variables has proved to be disappointingly poor.

1. Goldman-Rakic, 1994, 2. Brewer et al, 2005, 3.(Brewer et al, 2001).

Profile of Change in Mean Cognition



Whether cognitive function declined over the transition to psychosis?

- The origin of CI- unclear.
- some deficits are apparent prior to the onset
- if subjects with CI progress. unknown
- there may be a specific decline in visual memory and
  - attentional set-shifting, reflecting impairments in efficient organization of visual stimuli.
- This may be caused by either the illness itself or treatment with antipsychotic medication.

Wood SJ, Cognitive decline following psychosis onset: data from the PACE clinic
Br J Psychiatry Suppl. 2007 Dec;51:s52-7 .

Neurobiological- HPA
dysfunction may play a role

- Higher cortisol levels
- Abnormal circadian cortisol rhythms Kaneko et al, 1992).
- N=12 UHR participants
- Combined dexamethasone corticotrophin releasing hormone (DEX/CRH) test (Thompson et al, 2007).
- Over a 2-year, 3 of the 12 participants developed psychosis.

- participants who did not make the transition
  - → higher cortisol levels,
  - Greater severity of depression- anxiety symptoms.
- Dysregulated HPA-axis in UHR may represent ' *comorbid depression' rather than factors for process of emerging psychosis*

Neuroplasticity provides foundation for possibility ‘re-generating’ neurons

Hypertrophy of brain Regions using cognitive functions

Navigation expertise and the human hippocampus: A structural brain imaging analysis
Eleanor A. Maguire: the experiment of London Taxi Drivers

Intensive Computer based cognitive mediation as therapeutic intervention: NIHM Study

Impaired Neuroplasticity in Schizophrenia and the Neuro-regenerative

- FES : progressive loss of cortical and subcortical gray matter [1-6]
- childhood-onset SZ, cortical volume loss: 1%-3% per year during the first 5 years.[7]
- High risk for SZ: brain tissue loss during the transition.[8]
- Assumed –it was due to
  - brain atrophy,
  - neurotoxicity, or
  - neurodegeneration that involved
  - loss of neurons in the gray matter.
- However, it has become apparent brain volume loss was due to:
  - shrinkage of the neuropil surrounding the neurons, [9]
  - reduction in dendrite length by a half
  - decrease in number and size of dendritic extensions.[10,11]

Furthermore,

- decline in neurotropin 3 (NT-3), [12]

suggesting that

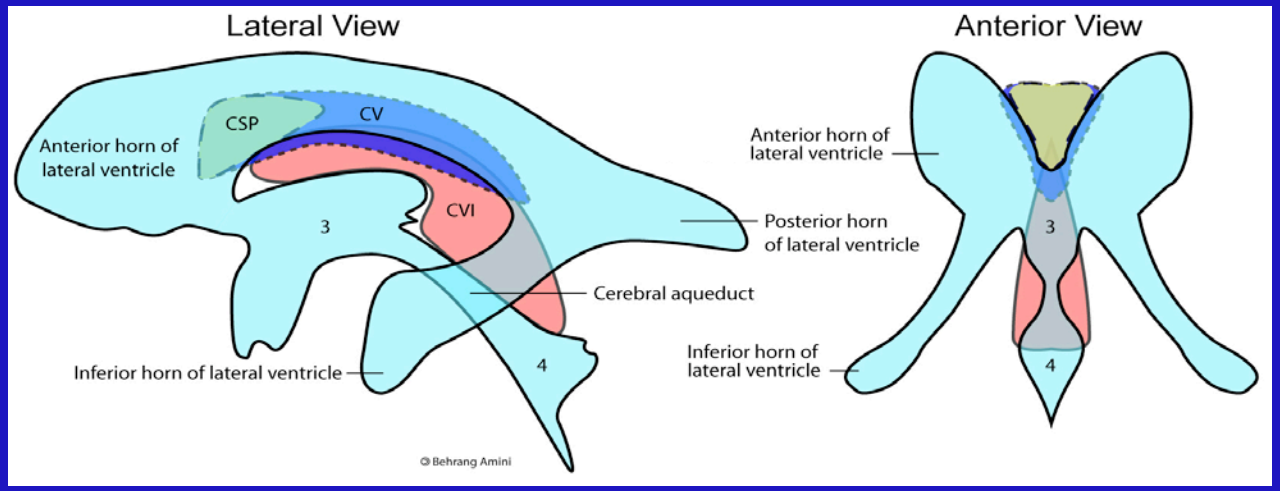
- brain tissue loss during psychosis may be caused by a decline in growth factors that are critical in brain development, neuroplasticity, and
- synaptic connectivity.

Imaging

- Findings generally demonstrate structural
- and functional changes post conversion
- but no differences to aid prediction
- Longitudinal increase in lateral ventricles, decrease in brain volume
- White matter & grey matter changes
- Histropathological correlation?

Cavum septum pellucidum (CSP) in High risk subjects

- Abnormal (CSP) [is a space between the two leaflets of the septum pellucidum],
- no significant correlations with symptoms.[1]
- Reduced neurotransmitter function in CSP [2]
- NT activity is reduced in UHR (N-acetylaspartateThe NAA concentrations of the UHR cases and FES -- correlated with the severity of negative symptoms). [2]



1. Choi JS et al. Cavum septum pellucidum in subjects at ultra-high risk for psychosis: compared with first-degree relatives of patients with schizophrenia and healthy volunteers. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Jul 1;32(5):1326-30

2.Aydin K, Altered metabolic integrity of corpus callosum among individuals at ultra high risk of schizophrenia and first-episode patients. Biol Psychiatry. 2008 Nov 1;64(9):750-7

Schizophrenia Bulletin vol. 34 no. 2 pp. 330–340, 2008
doi:10.1093/schbul/sbm158
Advance Access publication on January 27, 2008

Brain Structure and Function Changes During the Development of Schizophrenia: The Evidence From Studies of Subjects at Increased Genetic Risk

Proton Magnetic Resonance Spectroscopy in First Episode Psychosis and Ultra High-Risk Individuals

by Stephen J. Wood, Gregor Berger, Dennis Velakoulis, Lisa J. Phillips, Patrick D. McGorry, Alison R. Yung, Patricia Desmond, and Christos Pantelis

Article	Sample Size	Measure	Findings
Cross-sectional studies			
Phillips et al[19]	UHR-P = 20 UHR-NP = 40 CTRL = 139	Volume of hippocampus and whole brain	UHR vs UHR-P
Pantelis et al[35]	UHR-P = 23 UHR-NP = 52	VBM of GM	UHR-P media inferio
Wood et al[23]	UHR-P = 6	^{1}H MRS in left medial temporal and left prefrontal (NAA/Cr and TMA/Cr)	UHR vs in pre
	UHR-NP = 24 CTRL = 21		UHR-P
Yücel et al[41]	UHR-P = 21	Presence or absence of the PCS	UHR vs hemis
	UHR-NP = 42 CTRL = 75	Interruptions of the CS	UHR-P
Walterfang et al[55]	UHR-P = 23 UHR-NP = 52	VBM of WM	UHR-P superi premo fascicu
Garner et al[66]	UHR-P = 31 UHR-NP = 63 CTRL = 49	Pituitary volume	UHR vs UHR-P
Jessen et al[24]	UHR-P = 3	^{1}H MRS in left frontal, left STG, and bilateral ACC	UHR vs ACC
	UHR-NP = 16 CTRL = 24		UHR-P ACC
Velakoulis et al[20]	UHR-P = 39 UHR-NP = 96 CTRL = 87	Volume of hippocampus, amygdala and whole brain	UHR vs UHR-P
Borgwardt et al[27]	UHR-P = 12	VBM of GM	UHR vs parah occipi inferic nucleu supra
	UHR-NP = 23 CTRL = 22		UHR-P insula
Berger et al[53]	UHR-P = 39 UHR-NP = 96 CTRL = 87	Lateral ventricular volume	UHR vs UHR-P
Fornito et al (unpublished data)	UHR-P = 35 UHR-NP = 35 CTRL = 33	ACC volume, thickness, and surface area	UHR vs UHR-P bilate
Longitudinal studies			
Pantelis et al[35]	UHR-P = 10	VBM of GM	UHR-P media region
	UHR-NP = 11		UHR-N No signi
Walterfang et al[55]	UHR-P = 10	VBM of WM	UHR-P fronto subad cerebe
	UHR-NP = 11		UHR-N subadjacent to right inferior parietal lobule

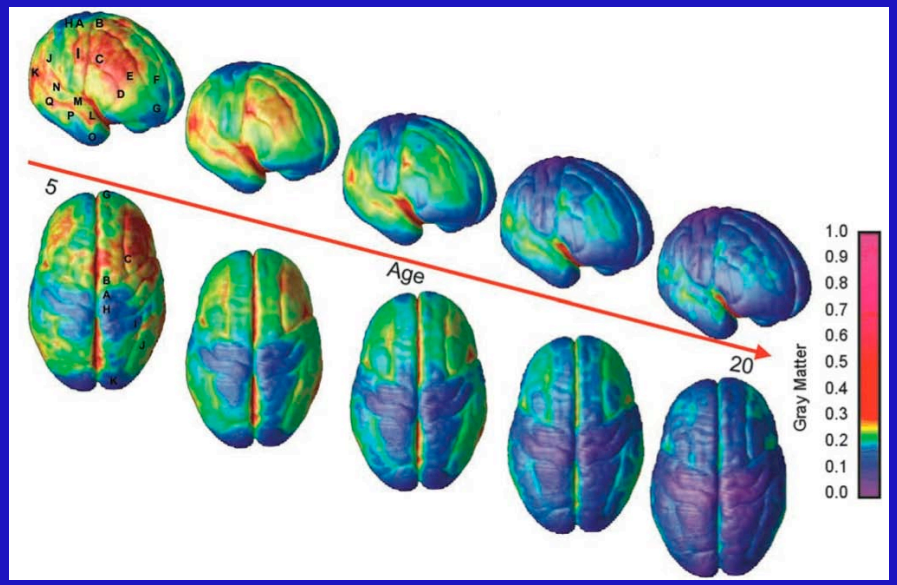
Consensus findings

1. Dysfunction maturational processes
2. loss of grey matter in DPFC
3. Aberrant mechanisms for brain maturation,
4. Subtle regionally and temporally specific changes through the course of psychosis,

(1) Early (pre- and perinatal) anomalies,

(2) *around the time of transition*

(3) Late (post-pubertal) changes soon after the onset of psychosis,



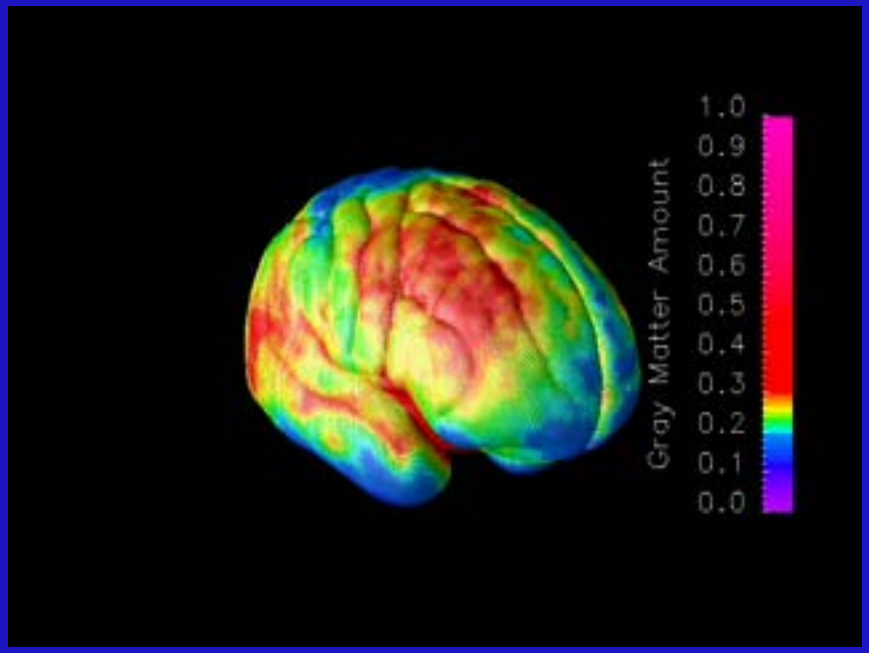
- The relative failure of neuroimaging measures to predict transition to psychosis suggests that standard volumetric techniques are incapable of capturing the subtle differences UHR with different outcomes

- As yet there are no convincing, replicated, reports of neuroimaging measures that predict the subsequent onset of psychosis.

- Instead the most promising finding have been in Neuro-psych. domain, with strong evidence for impairments in prefrontal cortex.

The brain developing in normal healthy youth

COMT regulates DA turnover NMDA Delays Brain Maturation

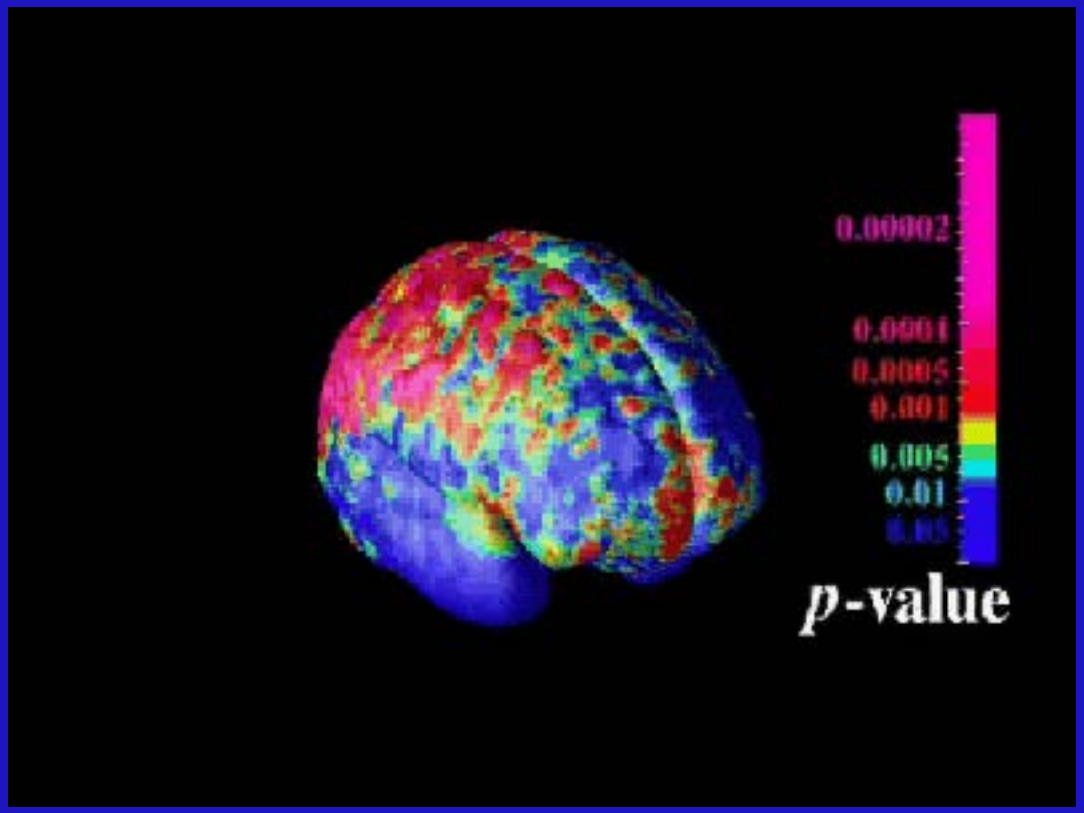


Time-lapse "movie" compresses 15 years of normal brain development (ages 5-20) into just a few seconds. Red indicates more gray matter, blue less gray matter. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned. Areas performing more basic functions mature earlier; areas for higher order functions mature later. The prefrontal cortex, which handles reasoning and other "executive" functions, emerged late in evolution and is among the last to mature.

Source: Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A. 2004 May 25;101(21):8174-9. Epub 2004 May 17. PMID: 15148381

The brain developing in childhood onset schizophrenia

Time-Lapse MRI movie shows the brain developing in 12 teens with childhood onset schizophrenia. Areas of gray matter loss - red and yellow — spread from back-to-front over 5 years. These teens lost gray matter in the prefrontal cortex at 4 times the rate of normal health teens



Source: Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Toga AW, Rapoport JL. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci U S A. 2001 Sep 25;98(20):11650-5. PMID: 11573002

Five Key Predictors

'Poorer the social function & the more severe the unusual thought content & suspiciousness, closer was the person to onset of psychosis"

- Genetic risk with recent deterioration in function.
- Higher levels of unusual thoughts
- Higher level of suspicion or paranoia.
- Greater social impairment
- History of substance abuse

Intervention

Should Antipsychotics be used in Prodromal phase or at-risk SZ

McGorry et al., 2002, AGP Melbourne	**Morrison et al., 2004, BJP Manchester**	**McGlashan et al., 2006, AJP North America**
6 month FU 12 month FU 12 month FU N=59	12 months F/U N=58	12 months F/U N=60
10% -Risperidone & CBT 36% -needs based	9%-CBT 22-30% monitoring	16% - Olanzapine 35% - Placebo
42% stopped risperidone	Dropout 13% for CBT, 14% for monitoring	Dropout – 55% for Olanzapine, 355 for Placebo

Three published studies : may be able to delay or even prevent onset of psychosis.

Preventive Family intervention; Expressed Emotion (EE)

- Predictive of psychotic relapse (Bebbington & Kuipers,1994)
- 'Not an artefact of patient morbidity' (Leff and Vaughn,1995)
- 'Family intervention is recommended to reduce relapse risk' (NICE, 2003)

1.Specific therapy V. need-based therapy (McGorry)

2. CONCLUSIONS: Without a specific treatment, 30-60% of persons with UHR develop frank psychosis,
3.Low-dose antipsychotic treatment seems to be effective
4. in Prevention or
5. delay of psychosis.

McGorry PD, Yung AR Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms, Arch Gen Psychiatry. 2002 Oct;59(10):921-8

BRITISH JOURNAL OF PSYCHIATRY (2004), 185, 291–297

Cognitive therapy for the prevention of psychosis in people at ultra-high risk

Randomised controlled trial

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Cognitive therapy Vs. monitoring :

- only conducted by the Early Detection and Intervention (EDIE) group Manchester showed a significant effect of the treatment.

Treatment Group	Follow-up Rate N (%)	PANNS Transition N (%)	Antipsychotic Medication N (%)	DSM-IV Psychotic Diagnosis N (%)
Cognitive Therapy (N = 35)	17 (49%)	7 (20%)	5 (14%)	7 (20%)
Monitoring (N = 23)	10 (43%)	5 (22%)	8 (35%)	7 (30%)

Morrison et al, 2004

Second-Generation Antipsychotics

- In contrast to haloperidol, several SGAs were reported to stimulate
- Neurogenesis in the adult rat, except for clozapine, which according to 2 reports has no effect.
- Studies with olanzapine have shown:
- Increased neurogenesis in the hippocampus
- Increased hippocampal neurogenesis after 28 days
- No change in the hippocampus but an increased proliferation in the prefrontal cortex,
- This result indicate: *A delay in the onset of psychosis*
-

Article

Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis

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Objective: This study asses
cacy of olanzapine in delayin
ing conversion to psychosis

sion to psychosis, a nearly significant dif-

'olanzapine versus supportive therapy and monitoring

- showed a trend
- *in effectively preventing*
- *or delaying psychosis (McGlashan et al, 2006).*
- Tx Gr.- lower levels of 'Prodromal' Symptomatology
- the clinical benefit, terms of transition rates, was more equivocal.

- In all, results of these first treatment trials suggest that both antipsychotic medication and psychological interventions might have a role in treating the difficulties and problems young people at ultra-high risk experience as well as delaying or preventing the onset of psychosis.

(Am J Psychiatry 2006; 163:790–799)

Conclusion

- Identification & prediction involve using different combinations of genetic, age range and symptomatic risk factors.
- However, even using these multiple-gate screening models, the majority of those selected still do not develop the disorder.
- This aids our detection of individuals in whom indicated preventive intervention may be justified.
- Arriving at a PPV of 100% would be a clear indication for pharmacological treatment in the identified group.