First-episode psychosis in children and adolescents: research advances and opportunities for intervention

Carmen Moreno MD, PhD

Child and Adolescent Psychiatry Department

Hospital General Universitario Gregorio Marañón

School of Medicine Universidad Complutense

IiSGM, CIBER, Madrid (Spain)

Co-chair ECNP Child and Adolescent Psychopharmacology Network

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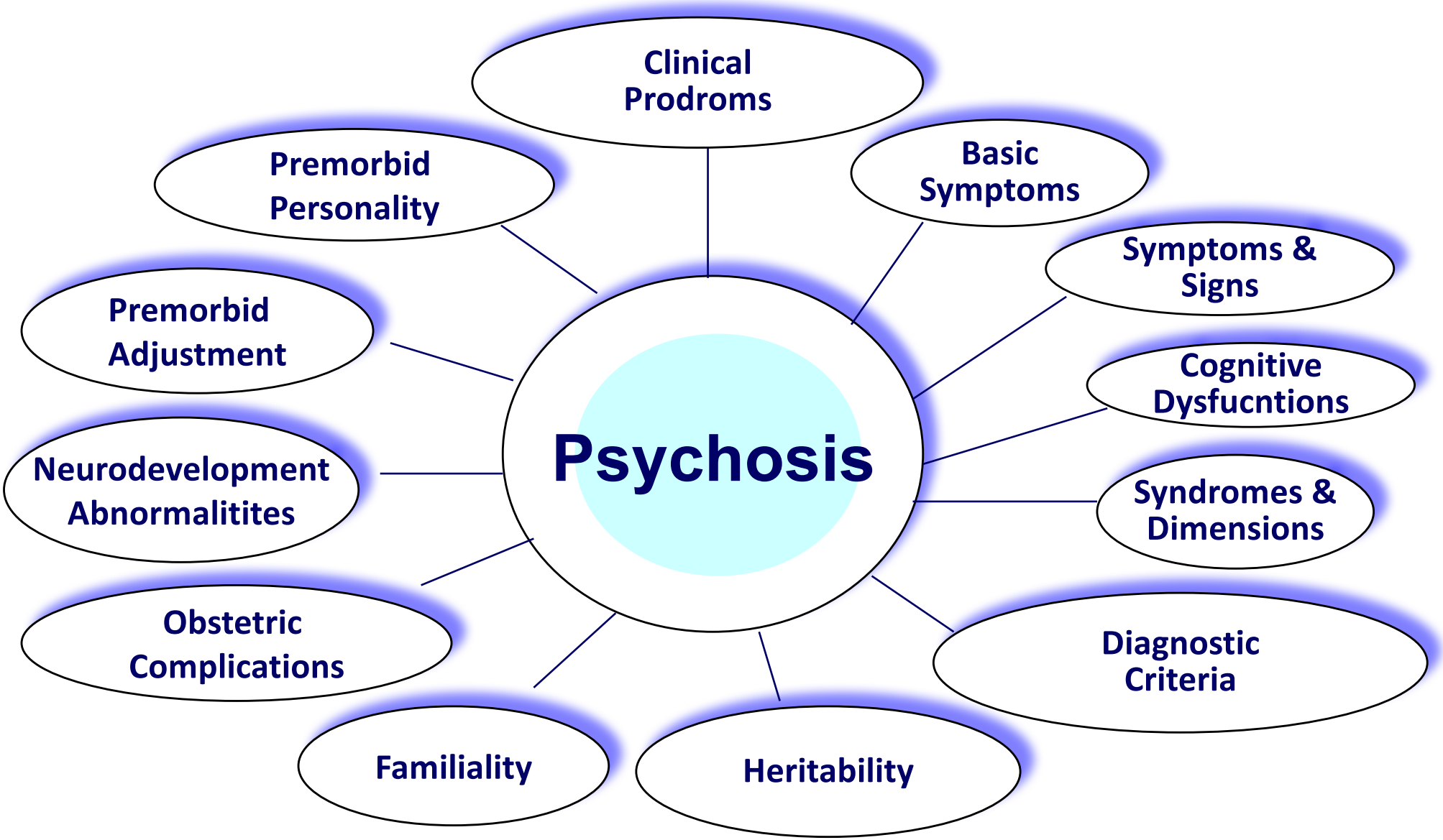
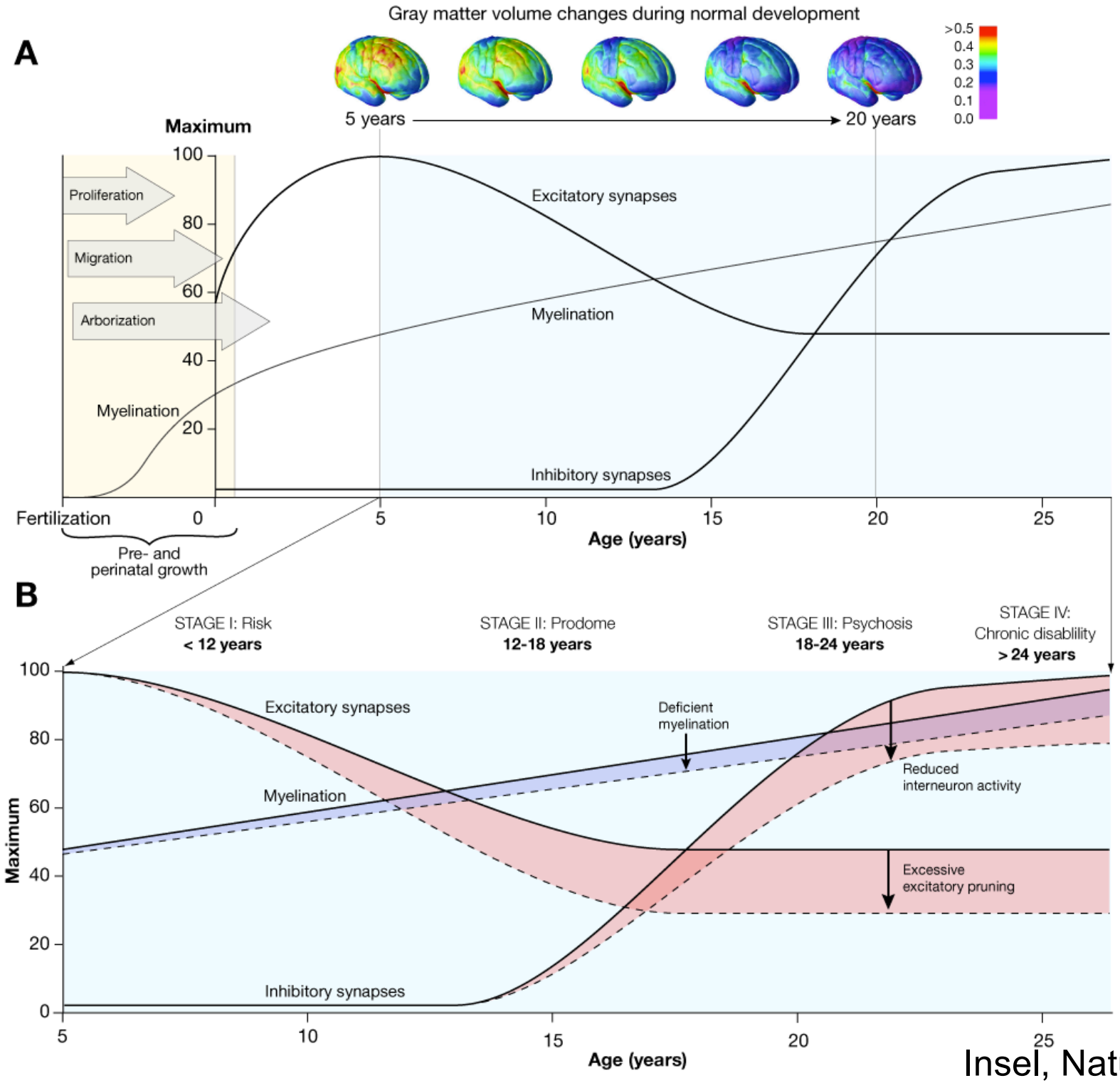
Otsuka	X	
Lundbeck	X	
Bristol-Myers Squibb	X	
Servier	X	

No share holdings in pharmaceutical companies

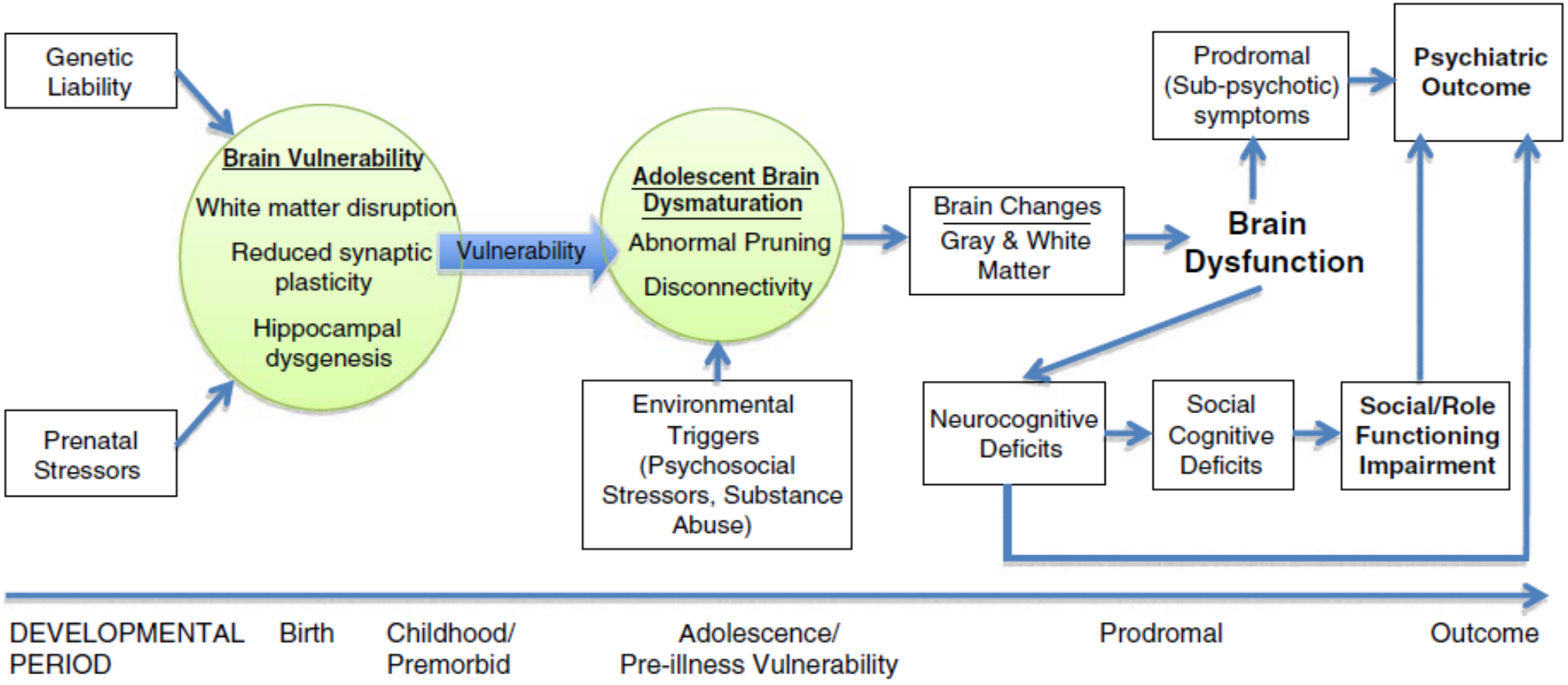
Phenotypic complexity in Psychosis





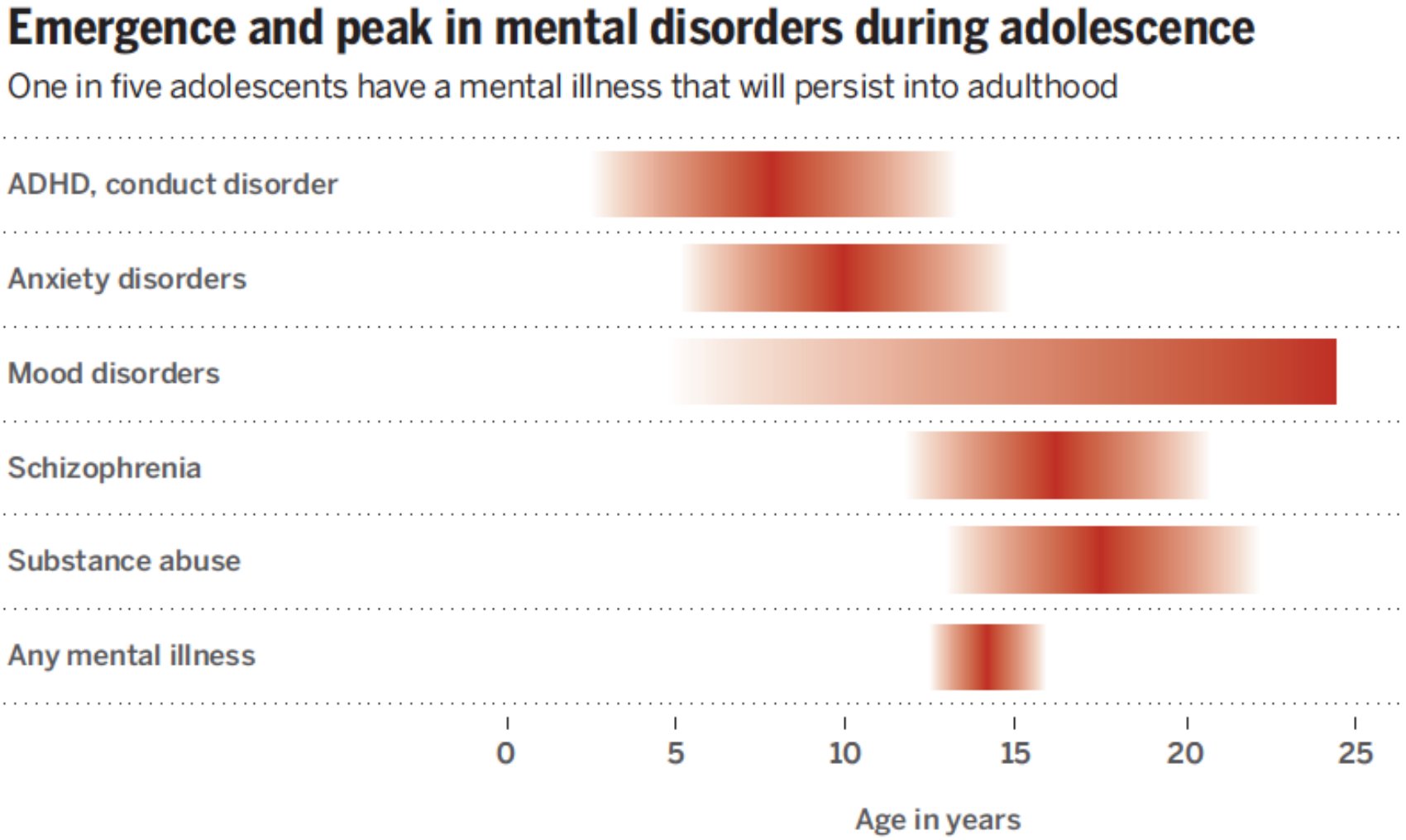
Insel, Nature 2010

Vulnerability-Stress Model



Niendam et al., 2009

Psychiatric (and psychotic) disorders emerge during childhood and adolescence



Lee, Heimer et al., SCIENCE sciencemag.org 31 OCTOBER 2014 • VOL 346 ISSUE 6209

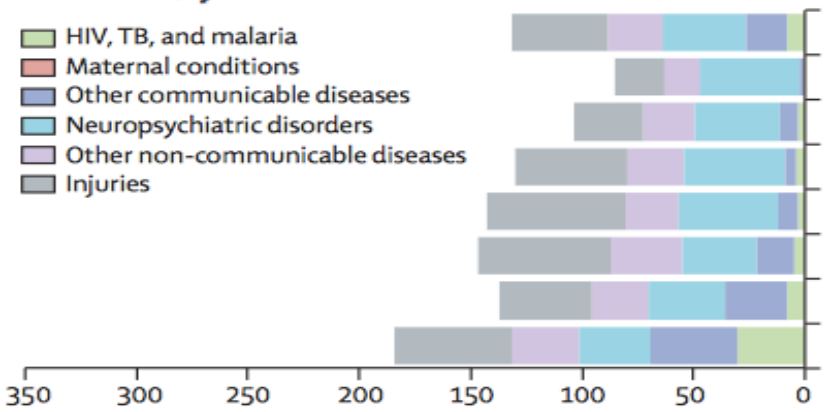
Global burden of disease in young people aged 10–24 years: a systematic analysis

Lancet 2011; 377: 2093–102

Fiona M Gore, Paul J N Bloem, George C Patton, Jane Ferguson, Véronique Joseph, Carolyn Coffey, Susan M Sawyer, Colin D Mathers

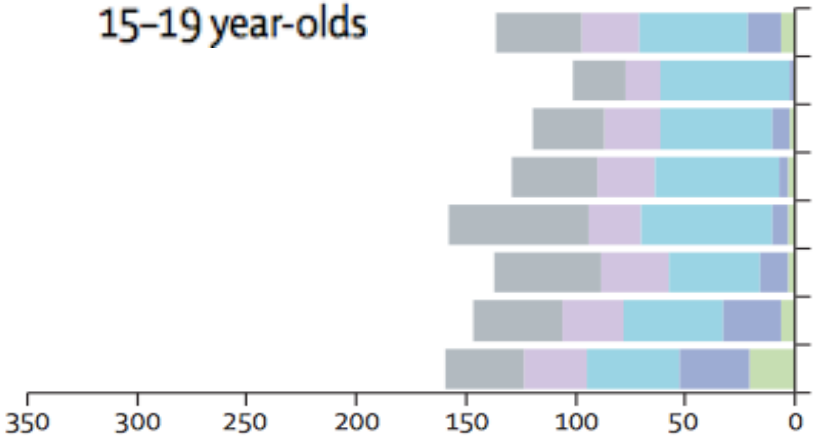
Major causes of disease burden in DALYs in adolescents per 1000 population

A 10–24-year-olds.



Unipolar depressive disorders	193 (8·2%)
Road traffic accidents	127 (5·4%)
Schizophrenia	96 (4·1%)
Bipolar disorder	88 (3·8%)
Violence	81 (3·5%)
Alcohol use	71 (3·0%)
HIV/AIDS	70 (3·0%)
Self-inflicted injuries	67 (2·8%)
Tuberculosis	60 (2·6%)
Lower respiratory infections	60 (2·6%)

C 15–19 year-olds



Unipolar depressive disorders	86 (9·9%)
Schizophrenia	46 (5·3%)
Road traffic accidents	46 (5·3%)
Bipolar disorder	44 (5·1%)
Alcohol use	34 (4·0%)
Violence	26 (3·0%)
Self-inflicted injuries	24 (2·8%)
Panic disorder	23 (2·7%)
Asthma	18 (2·0%)
HIV/AIDS	17 (2·0%)

Early-onset psychosis (EOP)

- Onset <18 years
- Insidious onset over a crucial developmental period
- Overlapping symptoms in different diagnoses
- Absence of diagnostic-specific categories
- Schizophrenia worst prognosis, likely due to association with premorbid functioning and negative symptoms.
  - Early-onset schizophrenia 25% partial remission, 50% chronic (Tolbert 1996)

Studies in EOP are difficult to perform (ethics, recruitment…), low sample sizes…

Ballageer et al. 2005; Volkmar, 1996; Menezes and Milovan, 2000McKenna et al.1994; McClellan et al. 2002; Nicolson et al, 2000

Prevalence of psychotic symptoms in childhood and adolescence

Metaanalyses of population-based studies

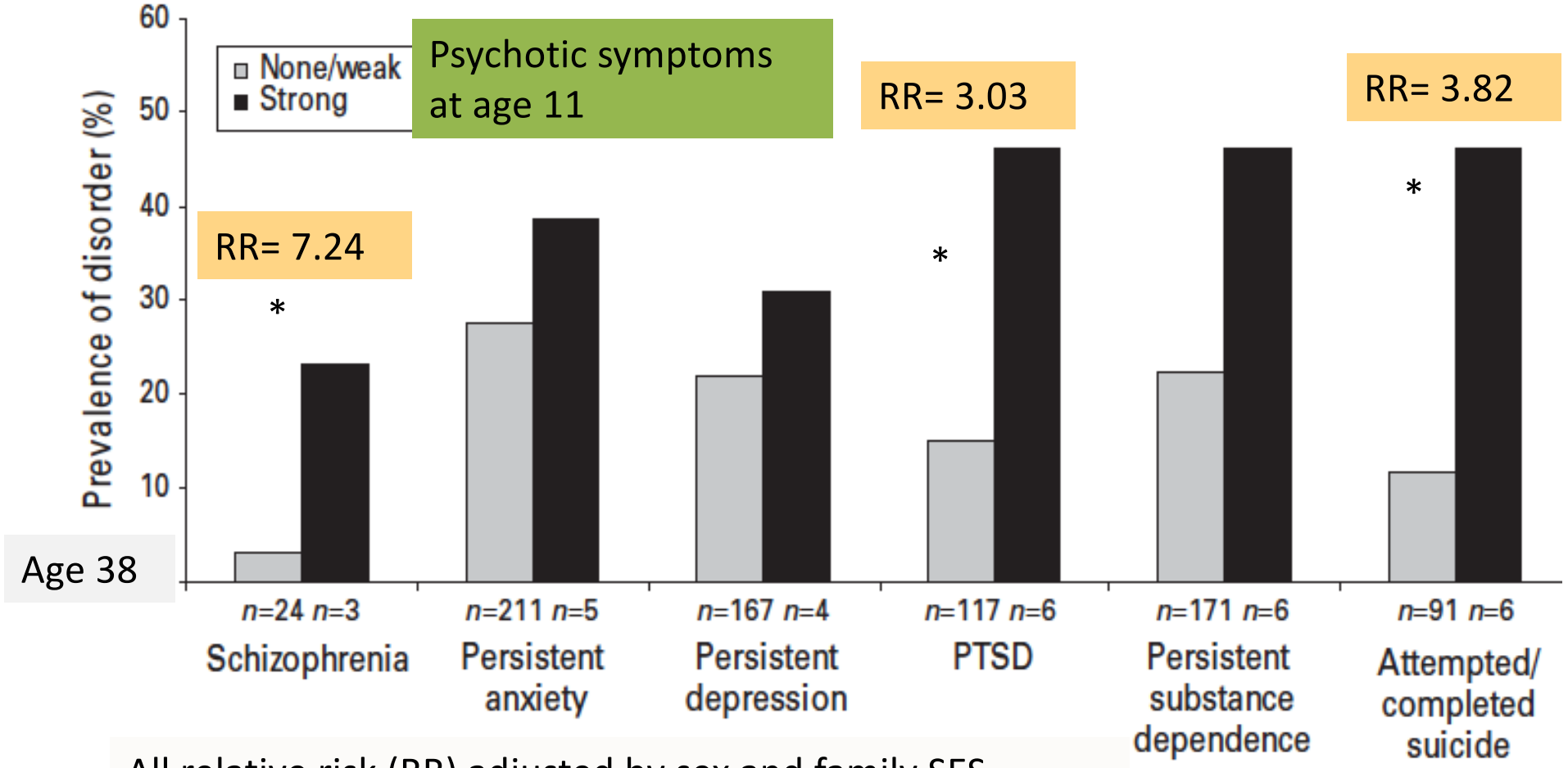
Median prevalence of psychotic symptoms:
-children 9-12: **17%**
-adolescents 13-18: **7.5%** Kelleher et al, Psychologial Medicine 2012

Cross-sample replication (n = 5422 and n = 2230)

Dimension	Prevalence Rate "Ever"	Prevalence Rate "Often"/"Almost Always"
Hallucinations	30.1	6.4
Delusions	66.5	11.2
Paranoia	89.7	26.4
Grandiosity	45.8	12.0
Paranormal beliefs	48.6	16.2
Any CAPE experience	94.8	43.3

Wigman et al, Schiz Bull 2011

Psychotic symptoms in childhood as a marker of general vulnerability

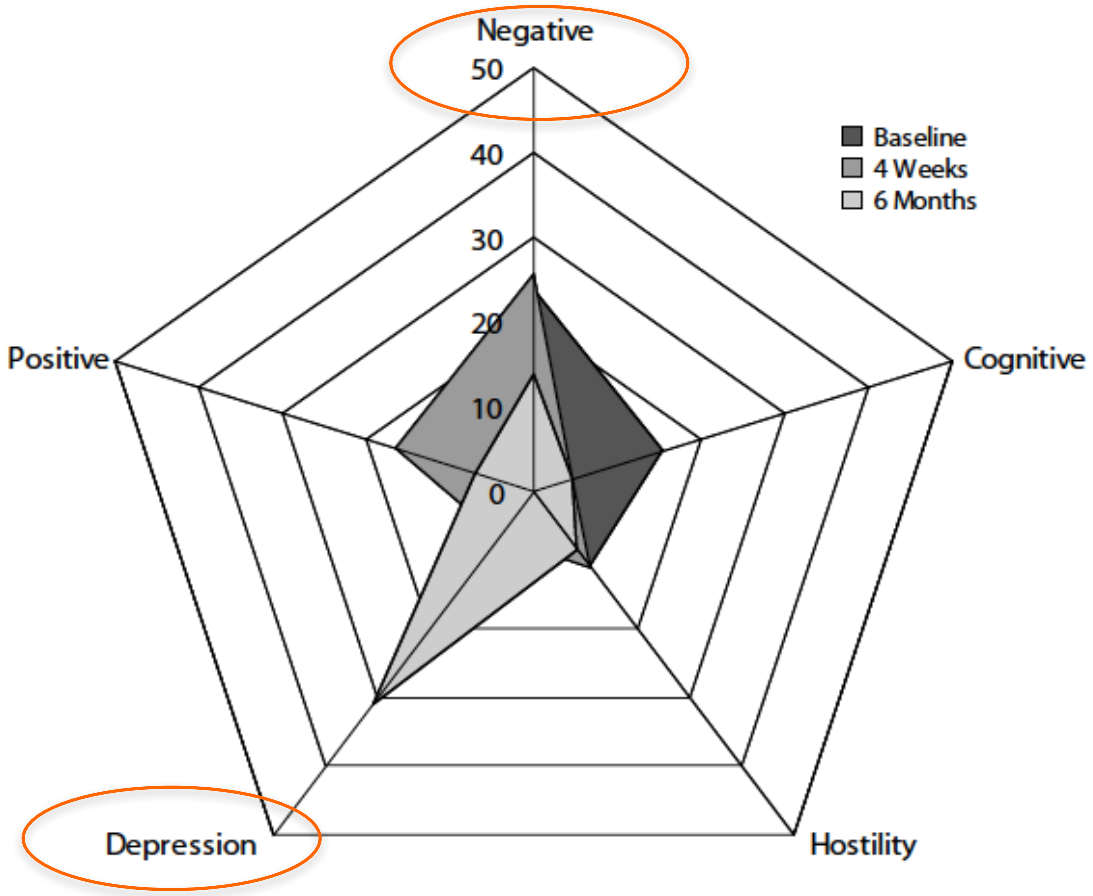


All relative risk (RR) adjusted by sex and family SES

H. L. Fisher et al.

Psychological Medicine (2013), **43**, 2077–2086.

Predominance of Symptoms Over Time in Early-Onset Psychosis



N=99 FEP

Dimensional structure remained stable over time

Rapado-Castro et al, 2010

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH
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Two-year diagnostic stability in early-onset first-episode psychosis

Josefina Castro-Fornieles, Immaculada Baeza, Elena de la Serna, Ana Gonzalez-Pinto, Mara Parellada, Montserrat Graell, Dolores Moreno, Soraya Otero, Celso Arango

First published: 20 July 2011 Full publication history

N= 83, ages 9-17

Bipolar disorder	***13***	***Bipolar disorder***	***12***	***92.31***	***p* = 1.00[b]**
		Psychotic disorder NOS	1		
Schizophrenia spectrum dis.	***40***	***Schizophrenia spectrum dis.***	***36***	***90.00***	***p* = 0.125[b]**
Schizophrenia	5	Schizophrenia	5	100	
Schizoaffective disorder	5	Schizoaffective disorder	5	100	
Schizophreniform disorder	30	Schizophreniform disorder	0	0	
		Schizophrenia	26	(86.66)[a]	
		Bipolar disorder	1		
		No present diagnosis	3		
Depressive disorder	***8***	***Depressive disorder***	***3***	***37.50***	***p* = 0.063[b]**
		Bipolar disorder	2	(25.00%)[a]	
		Schizophrenia	1		
		Psychotic disorder NOS	1		
		No present diagnosis	1		
Other psychosis	***22***	***Other psychotic disorder***	***3***	***13.64***	***p* < 0.001[b]**
Psychotic disorder NOS	17	Psychotic disorder NOS	2	11.76	
		Schizophrenia	7		
		Bipolar disorder	4		
		Schizoaffective disorder	2		
		Depressive disorder	1		
		No present diagnosis	1		
Brief psychotic disorder	5	Brief psychotic disorders	0	0	
		Schizophrenia	2		
		Psychotic disorder NOS	1		
		No present diagnosis	2		

Global consistency for all diagnoses 63.9%

Castro-Fornieles et al, 2011

VIEWPOINT

Mental Disorders in Childhood

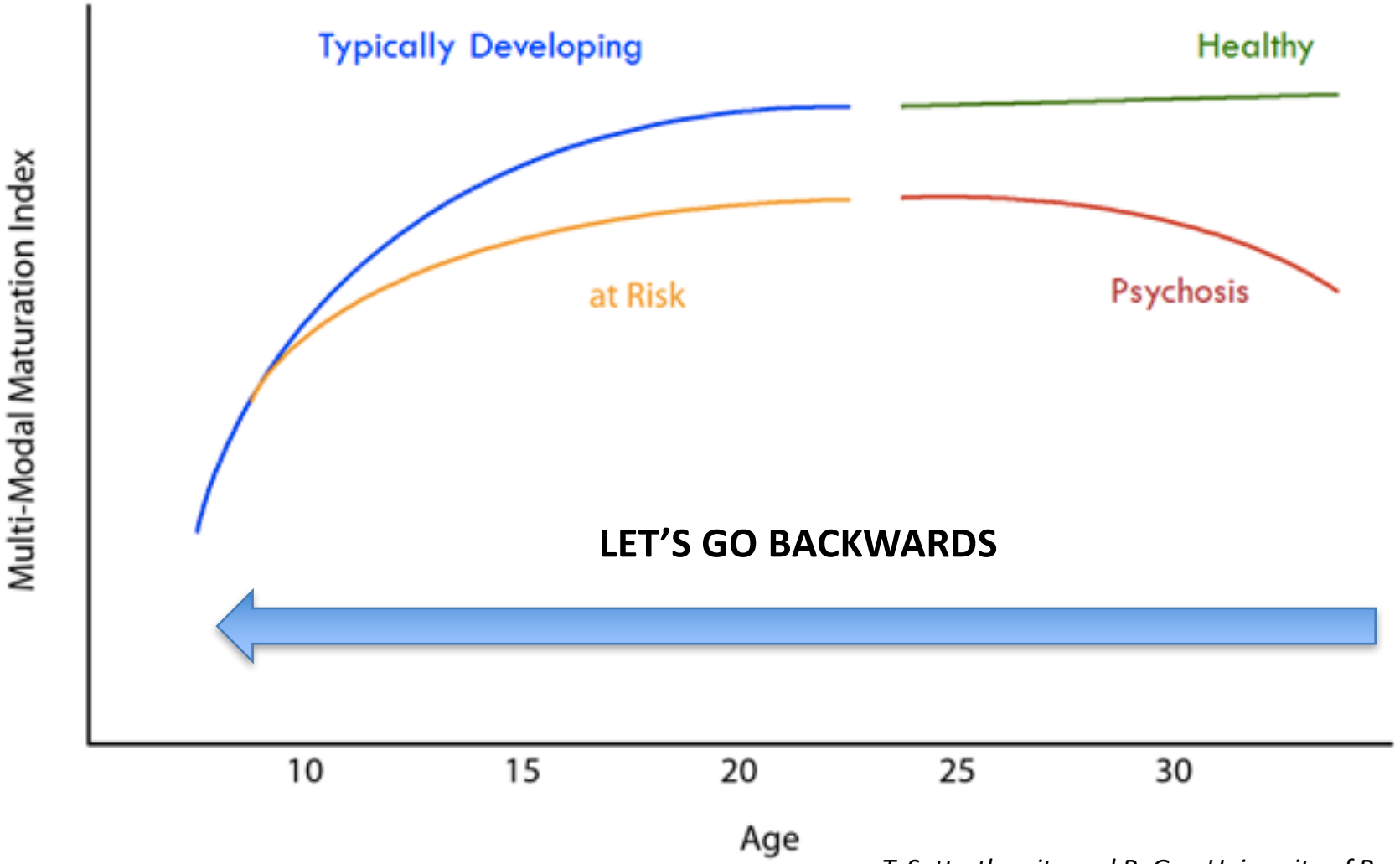
Shifting the Focus From Behavioral Symptoms to Neurodevelopmental Trajectories

Thomas R. Insel, MD
National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

Author Reading at jama.com

The recent Global Burden of Disease Study reported on morbidity and mortality for 291 disorders and injuries across 187 countries.[1] Expressed as "years lost to disability," mental and substance abuse disorders accounted for nearly 23% of global morbidity, more than any other group of disorders.[2] Although it may seem surprising that mental and substance abuse disorders would, by this measure, be more disabling than heart disease or cancer, at least part of the explanation velopment are extraordinary. In contrast to other organ systems, the brain develops, in part, through the exuberant overproduction of cells and connections, followed by a several-year sculpting of pathways by massive elimination of much of the neural architecture along with myelination of select fibers for rapid transmission of information. The human brain continues to develop into the third decade, with cortical maturation usually not completed until age 25.

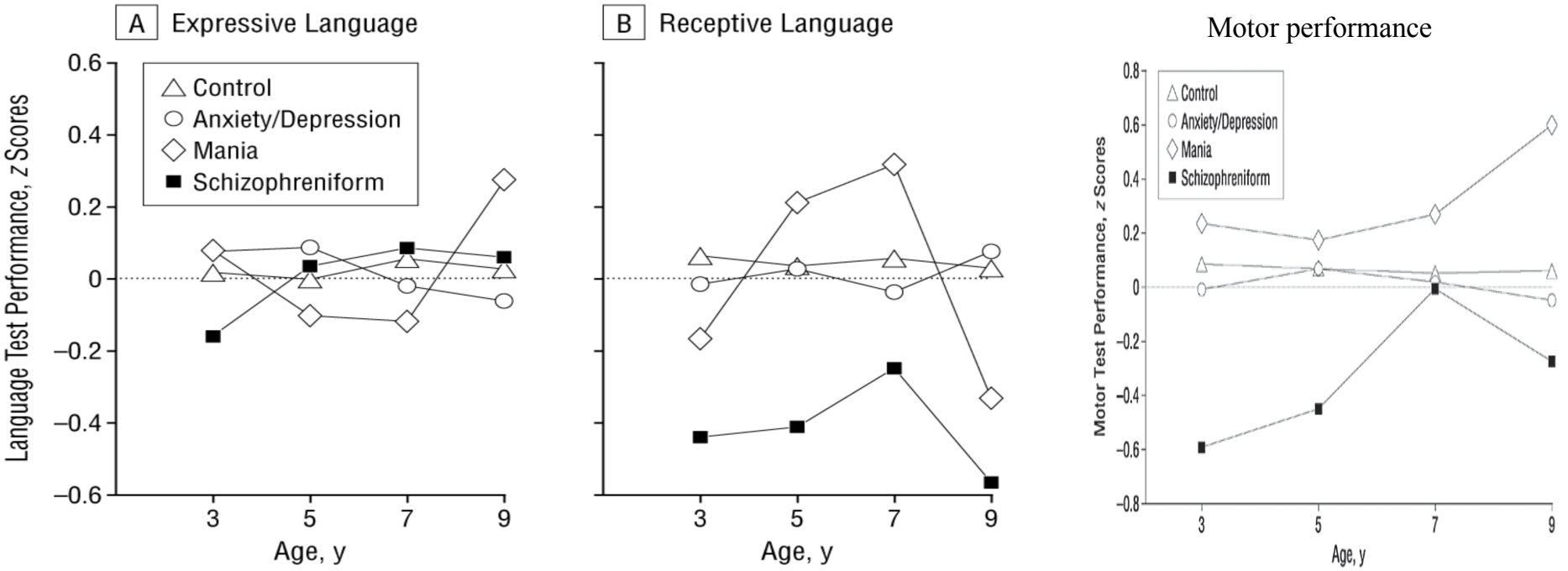
Developmental trajectories as vulnerability markers of psychosis



T. Satterthwaite and R. Gur, University of Pennsylvania

Abnormalities in language and motor development in psychosis

Dunedin Multidisciplinary Health and Development Study Total birth cohort born 1972/73 in Dunedin (N=1037), age 26



Cannon et al (2002) Arch Gen Psych

Schizophrenia Research

Premorbid impairments in early-onset psychosis: Differences between patients with schizophrenia and bipolar disorder

Sociodemographic characteristics, premorbid IQ, and developmental abnormalities in SZ and BP groups compared with healthy controls.

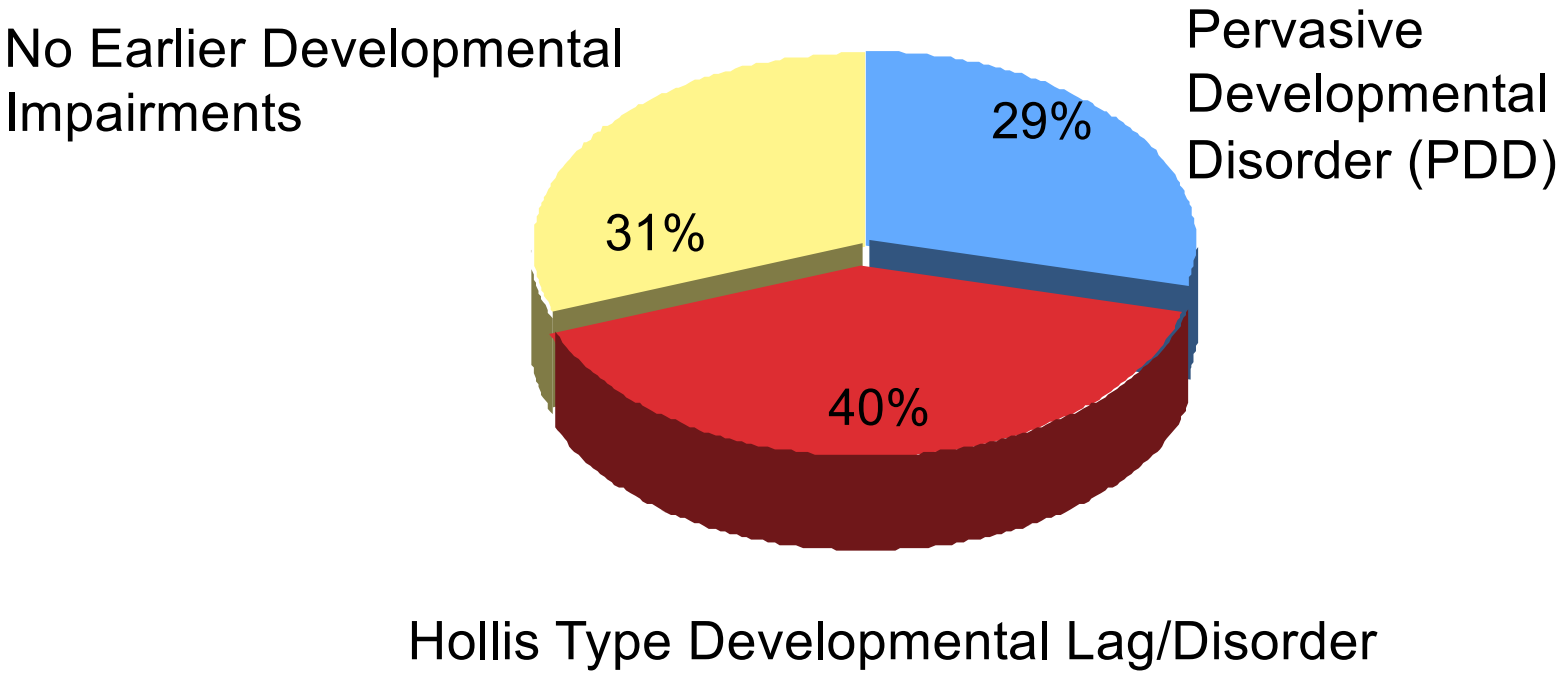
	Controls (N = 91)	SZ (N = 46)	BP (N = 23)	Statistic		Comparisons
	Mean (SD)	Mean (SD)	Mean (SD)	F[a]	p	
Age	15.1 (1.9)	15.42 (2.01)	16.04 (1.39)	2.113	0.124	
Subjects' years of education	8.8 (1.87)	8.2 (2.17)	8.96 (1.29)	2.229	0.111	
Parental years of education	14.91 (4.10)	11.69 (3.78)	10.87 (2.71)	16.463	**<0.001**	Controls[c] > SZ***; controls > BP***
Parental SES	3.29 (1.34)	2.73 (1.35)	2.43 (1.04)	5.249	**0.006**	Controls[c] > BP*
Premorbid IQ	103 (12.91)	86.33 (13.16)	87.17 (16.43)	25.837	**<0.001**	Controls[c] > SZ***; controls > BP***
	%	%	%	χ^{2b}	p	
Gender (% male)	61.5	73.3	69.6	2.017	0.365	
Developmental abnormalities	11.1	27.3	4.3	8.461	**0.015**	Controls[b] < SZ*

Childhood PAS scores in schizophrenia and bipolar disorder compared with healthy control group.

	SZ (N = 46)		BP (N = 23)		Controls (N = 91)		Statistic		Comparisons[a]
	χ	SD	χ	SD	χ	SD	F[b]	p	
Total PAS-C	0.36	0.21	0.28	0.16	0.12	0.10	**18.554**	**<0.001**	Controls < SZ***; Controls < BP***
PAS Acad-C	0.36	0.21	0.35	0.20	0.16	0.13	**5.784**	**0.004**	Controls < SZ**; Controls < BP*
PAS Social-C	0.36	0.28	0.21	0.21	0.08	0.13	**20.787**	**<0.001**	Controls < SZ***; controls < BP**
PAS1-C	2.24	1.93	1.13	1.52	0.53	0.87	**16.078**	**<0.001**	Controls < SZ***; BP < SZ*
PAS2-C	2.07	1.74	1.39	1.20	0.45	0.79	**20.280**	**<0.001**	Controls < SZ***; controls < BP***
PAS3-C	3.04	1.55	3.09	1.31	1.82	1.30	1.389	0.253	
PAS4-C	1.33	1.38	1.09	1.28	0.15	0.58	**11.003**	**<0.001**	Controls < SZ***; controls < BP**

Payá et al 2013

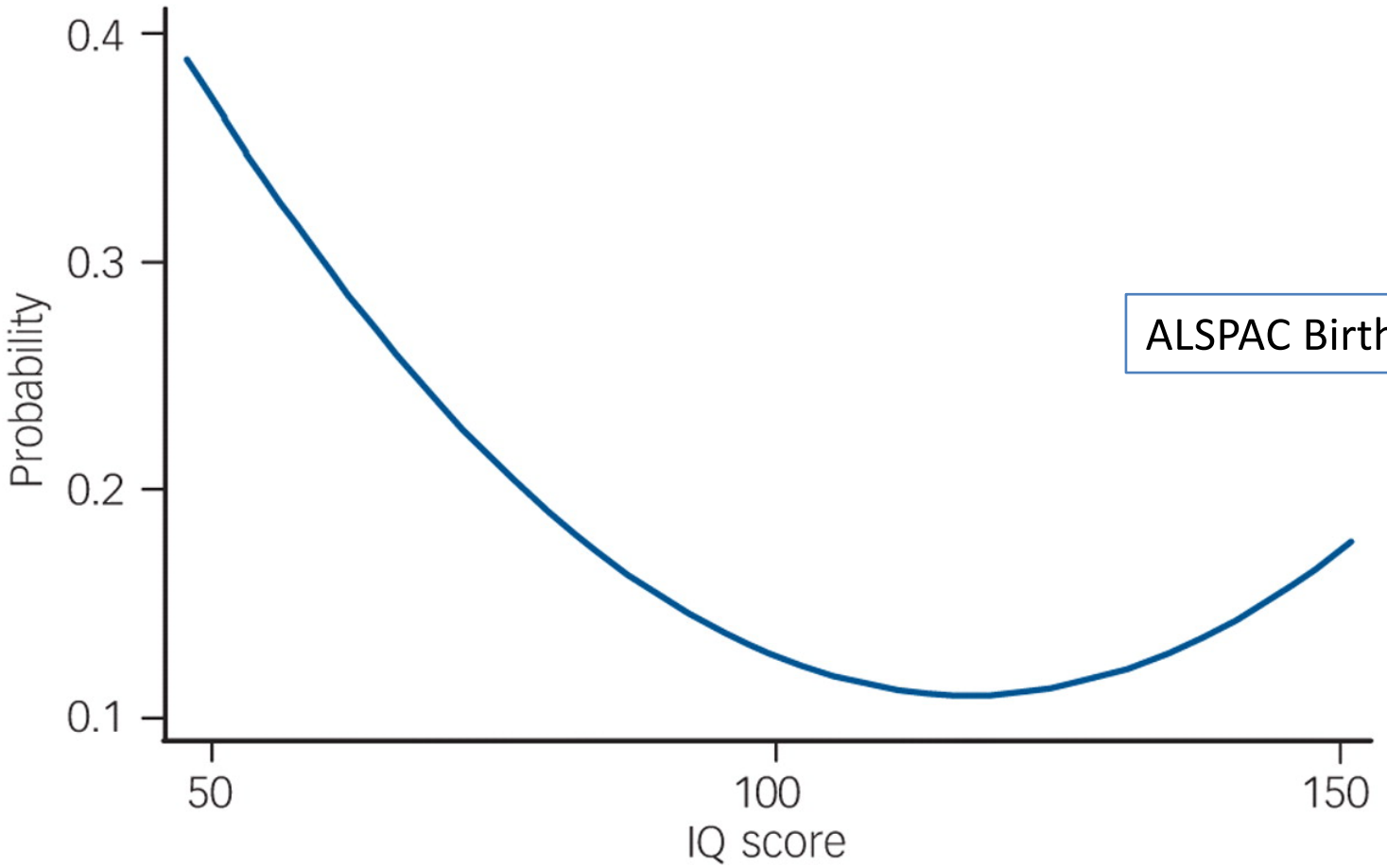
Developmental disorders in COS



Possible common early brain developmental pathway mediating copy number variant association with early onset disorder

Rapoport et al, 2009

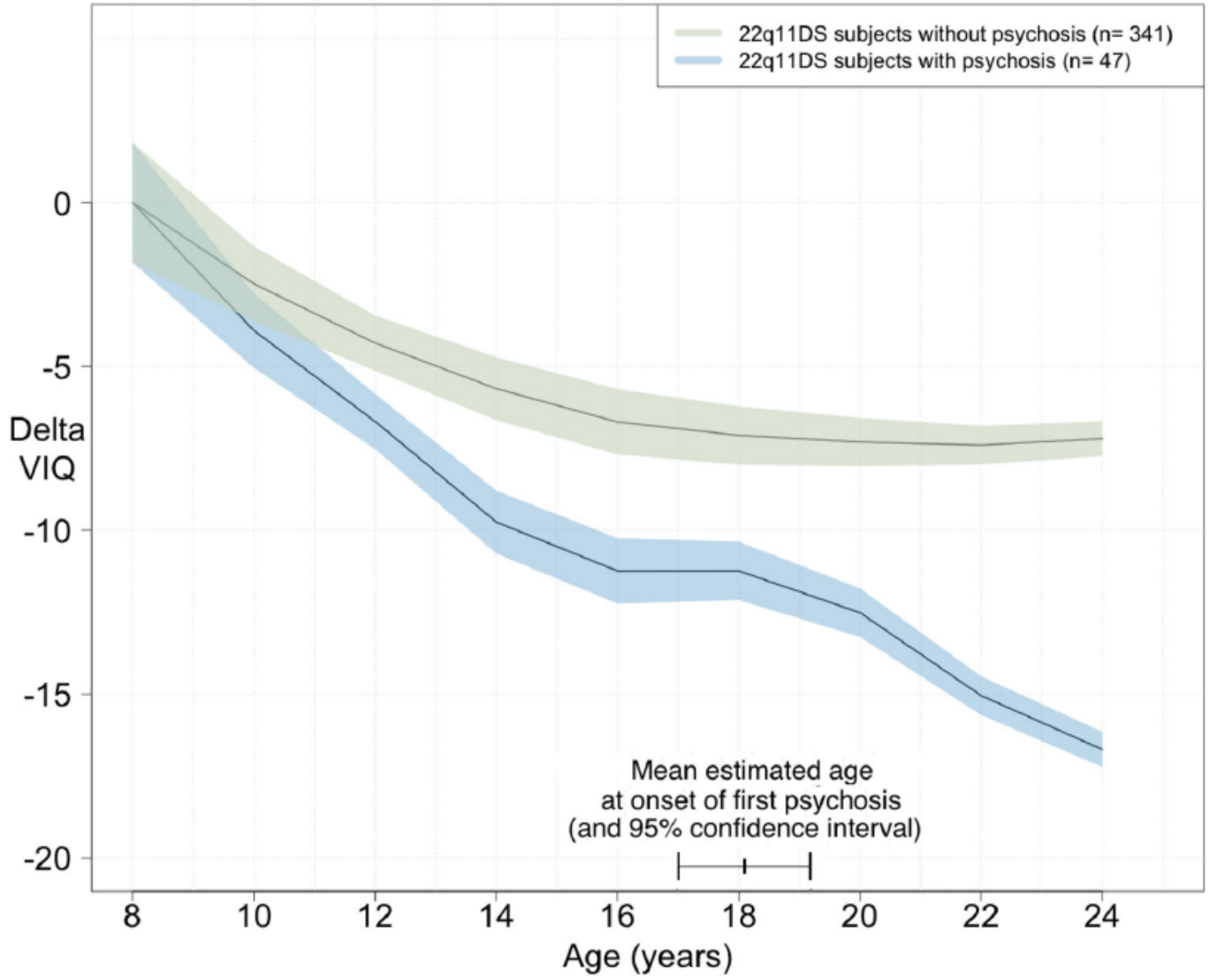
Childhood IQ as a risk factor for psychosis



ALSPAC Birth cohort

Predicted probability of psychosis-like symptoms according to IQ score
(Horwood, J. et al. Br J Psychiatry 2008)

Cognitive decline preceding psychosis in 22q11 deletion syndrome



Vorstman et al.

JAMA Psychiatry. 2015 April 1; 72(4): 377–385

Neurocognitive outcomes in EOP and controls

	BASELINE ASSESSMENT			2-YEAR ASSESSMENT		
	EOP (N=24)	Controls (N=29)	*Analysis*	EOP (N=22	Controls (N=29)	*Analysis*
Attention	-0.72±0.92	0.01±0.74	$p = 0.002$	-0.30±0.75	0.30±0.55	$p = 0.002$
Working memory	-1.30±0.98	0.03±0.85	$p \leq 0.001$	-1.10±0.82	0.28±0.99	$p \leq 0.001$
Executive function	-0.88±0.75	0±0.68	$p \leq 0.001$	-0.53±0.61	0.25±0.56	$p \leq 0.001$
Learning & memory	-1.80±1.47	0.01±0.79	$p \leq 0.001$	-1.03±1.39	0.16±0.91	$p \leq 0.001$
Global	-1.17±0.74	0.01±0.53	$p \leq 0.001$	-0.71±0.75	0.24±0.91	$p \leq 0.001$

-EOP showed lower scores than controls in overall cognitive functioning and in all specific domains assessed both at Baseline and at 2-year FU

-Significant differences between EOP subtypes only for Learning and memory ($p<0.04$), but significance disappeared after covarying with PANSS scores at 2-yr ($p=0.35$)

Mayoral et al. Neuropsychological functioning in adolescents with first episode psychosis. Eur Psychiatry 2008; 23(5):375-83

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH
Journal of Child Psychology and Psychiatry 53:3 (2012), pp 323–331 doi:10.1111/j.1469-7610.2011.02475.x

Longitudinal study of neurological soft signs in first-episode early-onset psychosis

	Longitudinal follow-up							
	Healthy controls			Patients			Time × Group interaction	After controlling for changes in the PANSS
	F	*df*	*p*-Value	*F*	*df*	*p*-Value	*p*-Value	*p*-Value
Sensory integration	6.00	(1, 79)	**.016**	9.21	(1, 70)	**.003**	.249[a]	**.033**
Motor coordination	0.19	(1, 79)	.658	6.44	(1, 70)	**.013**	**.032**[b]	**.038**
SCMA	2.39	(1, 79)	.126	8.51	(1, 70)	**.005**	**.027**[b]	.197
Others	1.70	(1, 79)	.195	35.65	(1, 68)	**< .001**	**< .001**[b]	**< .001**
Total	6.67	(1, 79)	**.012**	34.80	(1, 68)	**< .001**	**< .001**[b]	**< .001**

EOP showed more NSS than controls both at baseline ($p < .001$) and 2-year FU ($p < .001$)

No differences were found in the number of signs among diagnostic subgroups

Mayoral et al., 2012

Contents lists available at ScienceDirect

Psychiatry Research

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

The impact of neuropsychological functioning and coping style on perceived stress in individuals with first-episode psychosis and healthy controls

	Perceived stress			
	FEP		HC	
Coping style	*r**	*p*	*r**	*p*
Task-Focussed	−0.429	**0.014**	−0.066	0.747
Emotion-Focussed	0.433	**0.013**	0.507	**0.008**
Avoidance-Focussed	−0.250	0.167	−0.035	0.866
Neuropsychological Test/Domain	*r**	*p*	*r**	*p*
General intelligence				
Premorbid IQ	0.423	**0.018**	−0.592	**0.002**
Current IQ	0.273	0.125	−0.479	**0.013**
Immediate attention				
Digit Span forward	0.319	0.075	−0.167	0.416
Working memory				
Digit Span backward	0.306	0.088	−0.400	**0.043**
Letter-Number Sequencing	0.495	**0.004**	−0.519	**0.007**
Verbal learning and memory				

Allott et al., 2015

Contents lists available at ScienceDirect

Schizophrenia Research

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

Fraguas et al., 2015

Progressive brain changes in children and adolescents with early-onset psychosis: A meta-analysis of longitudinal MRI studies

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Sporn, 2003	-0,202	0,220	0,048	-0,633	0,228	-0,921	0,357
Reig, 2009	-0,480	0,277	0,077	-1,024	0,064	-1,730	0,084
Arango, 2012	-0,570	0,178	0,032	-0,918	-0,222	-3,208	0,001
	-0,435	0,124	0,015	-0,678	-0,193	-3,522	0,000

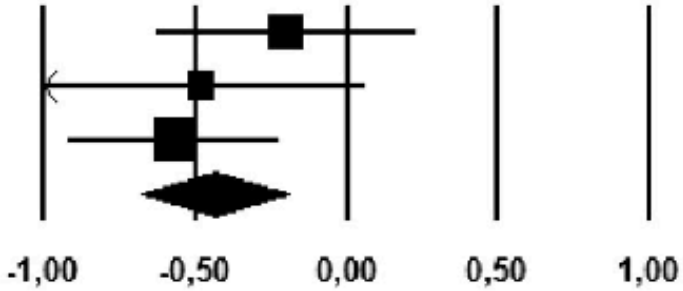


Fig. 2. Forest plot for the meta-analysis of the three studies assessing longitudinal changes in frontal gray matter volume.

Five original studies with 156 EOP
Mean duration of follow-up of 2.46 years (range 2.02–3.40)

EOP patients show greater progressive frontal GM loss over the first few years after illness onset.
Age at baseline MRI and diagnosis of schizophrenia moderate brain volume changes.

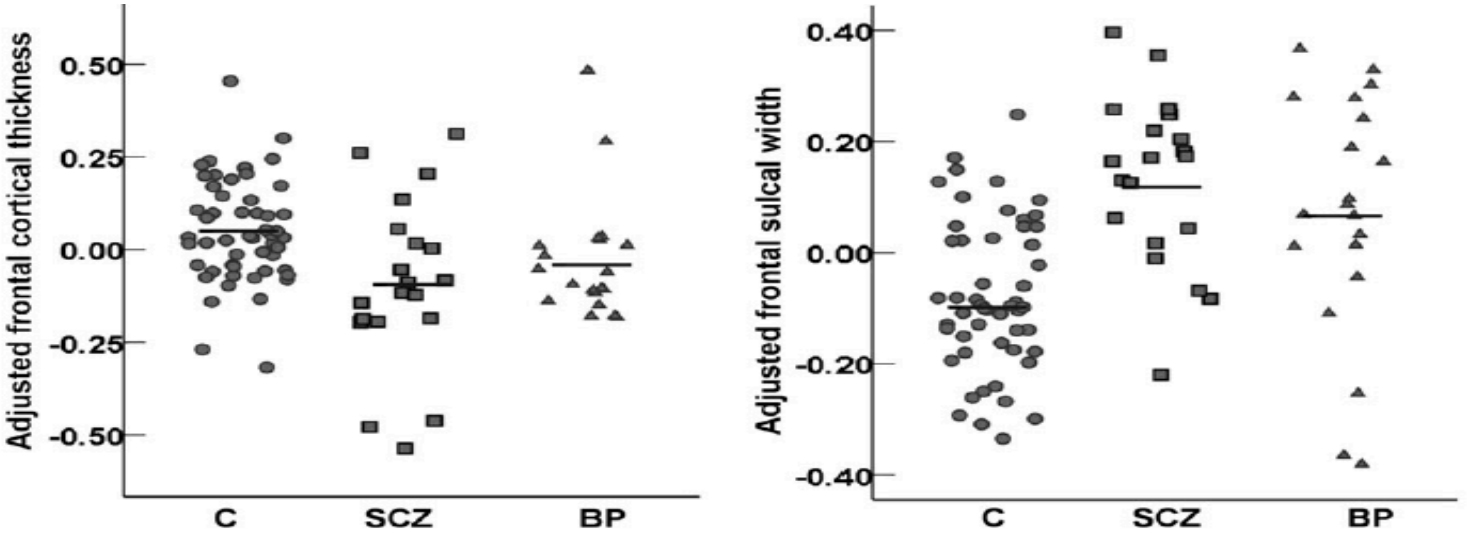
Contents lists available at ScienceDirect

Schizophrenia Research

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

Cortical morphology of adolescents with bipolar disorder and with schizophrenia

Joost Janssen [a,b,c,d,*,1], Yasser Alemán-Gómez [a,b,h,1], Hugo Schnack [d], Evan Balaban [e], Laura Pina-Camacho [a,b,j], Fidel Alfaro-Almagro [a], Josefina Castro-Fornieles [b,f,i], Soraya Otero [b,g], Inmaculada Baeza [b,f], Dolores Moreno [a,b,c], Nuria Bargalló [b,k,l], Mara Parellada [a,b,c], Celso Arango [a,b,c], Manuel Desco [a,b,h]



C: n = 52
SCZ: n=20
BP: n= 20

-Cortical thinning, decreased gyrification index and increased sulcal width of the frontal cortex are present at the time of the first psychotic episode.
-Decreased frontal GI is associated with the widening of the frontal sulci which may reduce sulcal surface area.
-These results suggest that abnormal growth of the frontal cortex represents a shared endophenotype for psychosis

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Progressive brain changes in children and adolescents with first-episode psychosis

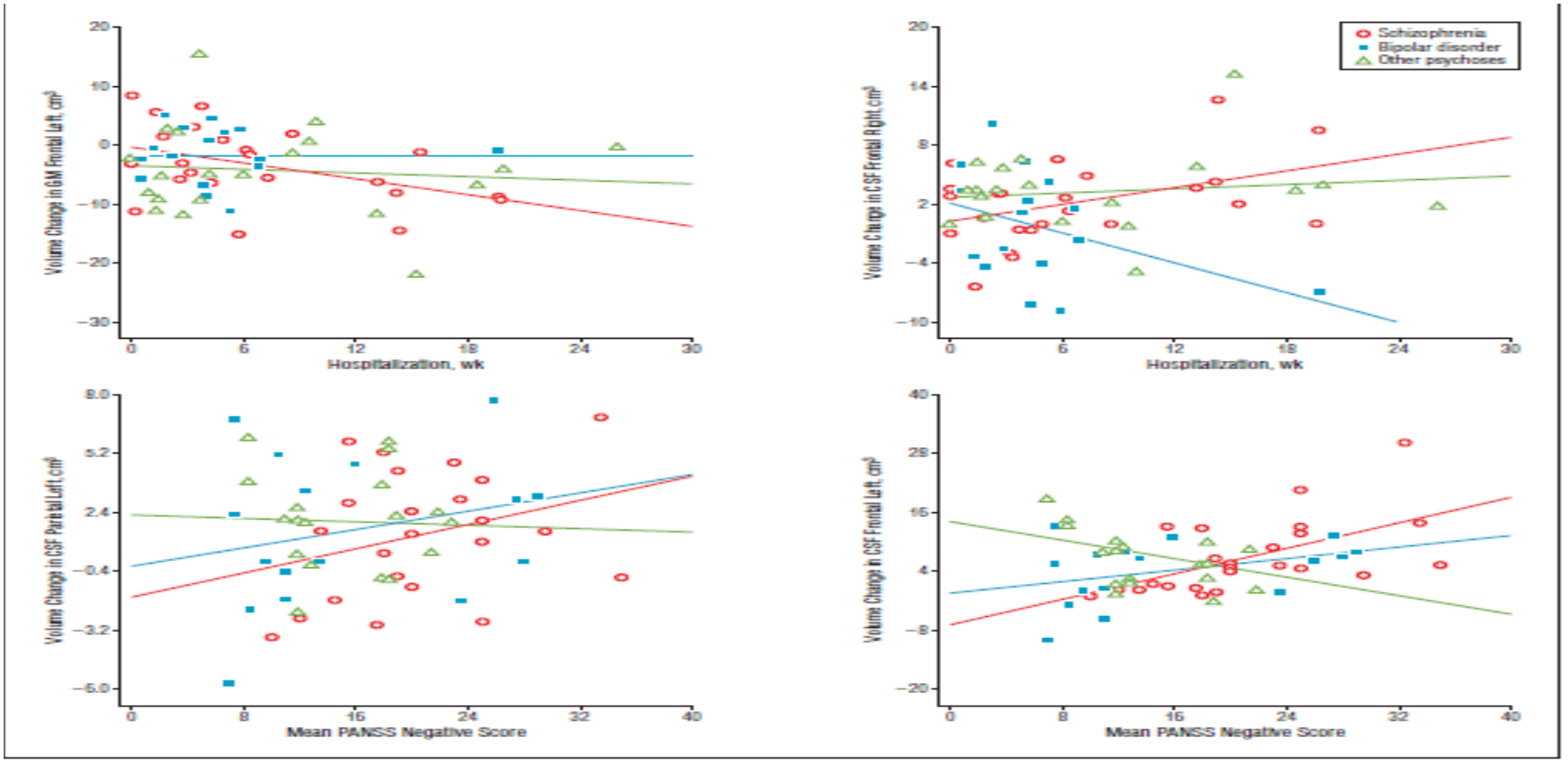


Figure. Relationship between the number of weeks hospitalized and the mean baseline and follow-up Positive and Negative Syndrome Scale (PANSS) score and gray matter (GM) and cerebrospinal fluid (CSF) volume changes within diagnostic subgroups.

Higher GM loss and LCR volume in frontal lobe after 2 years

Volume loss correlated with worst clinical prognosis

Arango et al., 2012

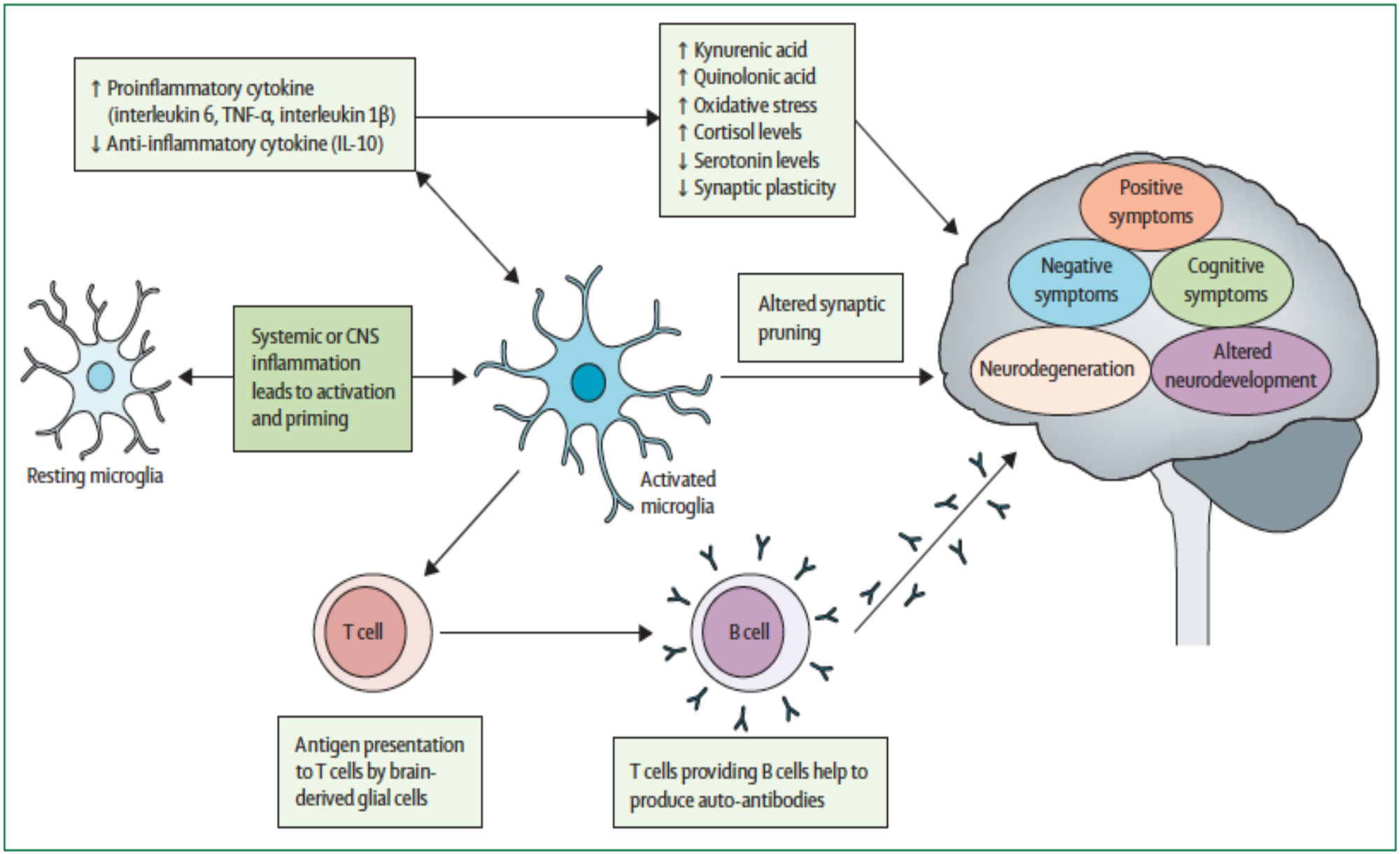


***Figure 2*: Possible mechanisms of immune-mediated causation of psychosis**

TNFα=tumour necrosis factor α. CNS=central nervous system.

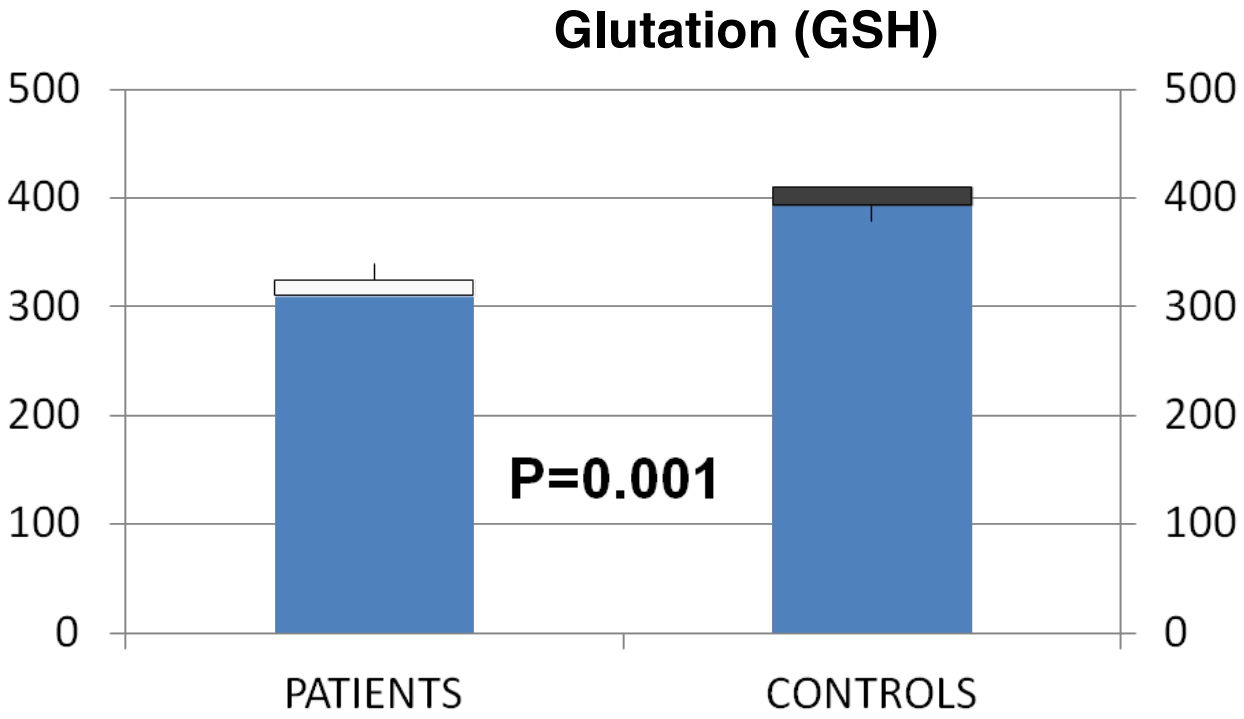
RESEARCH ARTICLE Open Access

Reduced antioxidant defense in early onset first-episode psychosis: a case-control study

Juan Antonio Micó[1], Maria Olga Rojas-Corrales[1], Juan Gibert-Rahola[1], Mara Parellada[2], Dolores Moreno[2], David Fraguas[3], Montserrat Graell[4], Javier Gil[5], Jon Irazusta[5], Josefina Castro-Fornieles[6], Cesar Soutullo[7], Celso Arango[2], Soraya Otero[8], Ana Navarro[9], Inmaculada Baeza[6], Mónica Martínez-Cengotitabengoa[9], Ana González-Pinto[10*]

102 children and adolescents with a first psychotic episode
98 healthy controls

-Decrease in antioxidant defense: decreased TAS and glutathione levels
-Higher lipid damage (LOOH) and glutathione peroxidase activity



Micó et al. BMC Psychiatry 2011, 11:26
http://www.biomedcentral.com/1471-244X/11/26

Antiinflammatory and oxidative/nitrosative stress markers in first-episode psychosis

N= 117 FEP

	B	SE	Wald	OR	CI 95%	P
PGE_2	0.005	0.002	3.721	1.005	1.000–1.009	.054
COX2	0.017	0.007	6.509	1.017	1.004–1.031	**.011**
$NO-_2$	0.369	0.163	5.137	1.447	1.051–1.991	**.023**
TBARS	0.182	0.162	1.269	1.200	0.874–1.649	.260
PPARγ act	–0.832	0.631	1.741	0.435	0.126–1.498	.187
15d-PGJ_2	–0.023	0.007	10.099	0.977	0.963–0.991	**.001**

Abbreviations: B, median; COX-2: cyclooxygenase 2; CI, confidence interval; NO-2, nitrites; OR, odds ratio; PGE2, prostaglandin E2; PPARg act, peroxisome proliferator activated receptors activity; SE, standard error; TBARS, thiobarbituric acid reactive substances; 15d-PGJ2, prostaglandin 15-deoxy-PGJ2.
Association between FEP and level of biomarker. All the biomarkers were analyzed together and adjusted for age, gender, body mass index, cannabis use per month, and cotinine level. The bold values in the table represent the values reaching statistical significance ($P < .05$).

Increase in intracellular components of a main pro-inflammatory pathway and decrease in the antiinflammatory

Psychosis may be biologically toxic

García Bueno et al, Schiz Bull, 2014

Differences on pro/anti-inflammatory markers between baseline and 6 months follow-up in FEP

Marker	Patients baseline (N=85)	Patients follow-up (N=85)	Statistics	p value
iNOS -WBc-	131.44 ± 51.43	**109.05 ± 52.89**	Z=-2.47	**0.013**
COX2 -WBc-	161.08 ± 164.82	**230.60 ± 169.86**	Z=-3.13	**0.002**
NFκB -act-	12.13 ± 23.75	5.52±2.75	Z=-0.20	0.845
PGE_2 -sol-	522.29 ± 770.33	**870.02 ± 741.96**	Z= -4.58	**<0.001**
NO^-_2 -sol-	14.94 ± 6.20	17.61 ± 7.34	Z=-1.88	0.060
TBARS -sol-	3.65 ± 3.81	**4.50 ± 1.75**	Z=-3.69	**<0.001**
IκBα -WBc-	86.36 ± 49.97	104.21 ± 82.09	Z=-0.73	0.468
15d-PGJ_2-sol-	571.25 ± 154.15	**408.89 ± 150.69**	Z=-5.72	**<0.001**
PPARγ -WBn-	79.45 ± 33.51	**55.94 ± 49.09**	Z=-2.35	**0.019**
PPARγ -act-	1.29 ± 0.93	1.09 ± 0.55	Z=-1.11	0.267

García-Bueno et al, Int J Neuropsychopharmacol, 2014

Oxidative stress variables in healthy controls (HC) and healthy controls with family history of psychosis (HC-FHP)

	Mean (SD)		U	z	p	OR
	HC	HC-FHP				
CAT (U/ml)	10988 (4386)	9072 (6720)	434.00	0.828	0.408	-
cGPx (mU/ml)	905 (459)	953 (1100)	381.500	1.423	0.155	-
GSH (mM)	383 (156)	433 (179)	412.00	−1.078	0.281	-
LOOH (μM)	5.97 (3.90)	7.50 (6.24)	362.00	−0.388	0.698	-
SOD (U/ml)	4038 (2936)	2618 (2653)	363.00	1.633	0.102	-
TAS (mM)	1.31 (0.47)	0.95 (0.40)	281.00	2.606	**0.009**	**2.937**

Results non affected by social and family environment factors
After adjusting for FES dimensions TAS diff remained:
OR= 10.86, 95% CI= 1.82−64.74, *p*= 0.009

Gonzalez-Pinto et al., BMC Psychiatry, 2012

FEP onset ≤18 vs ≥25: Baseline results

Marker Baseline	**Onset ≤18** **(mean, SD)** **(n=27)**	**Onset ≥25** **(mean, SD)** **(n=43)**	Intergroup analyses **(onset ≤18 vs onset ≥25)**	
			Statistic (F)	P-Value
NF*k*B-act	24.96 (37.90) (n=13)	8.53 (15.17) (n=21)	7.184	**0.012**
iNOS-WBc-	119.0 (49,03) (n=22)	143.34 (50.63)(n=30)	1.706	0.198
COX2-WBc-	174.90 (163.63)(N=21)	126.93 (47.62)(n=30)	1.324	0.256
NO^{-}_{2}-sol-	15.32 (7.81) (n=13)	15.40(5.22) (n=22)	0.189	0.667
PGE_2-sol-	554.37(501.38) (n=25)	431.67(439.79)(n=39)	1.919	0.171
TBARS -sol-	2.88(2.42) (n=22)	2.99 (3.08)(n=38)	0.217	0.643
I*k*Bα-wbC-	89.51(55.22) (n=22)	80.89(45.44)(n=30)	0.011	0.918
$15dPGJ_2$-sol-	558.35(136.68) (n=25)	608.25(193.59)(n=35)	0.818	0.370
PPAR-act-	1.38 (1.04)(n=15)	1.11(0.92)(n=29)	1.062	0.309

Non-parametric 1 factor ANCOVA. Independent variable: age-onset group; dependent variables: values of pro- and anti-inflammatory markers; covariates: days between first psychotic symptoms until baseline visit, age of onset of cannabis use, tobacco use, total dose of antipsychotics (chlorpromazine equivalents)

Moreno et al., submitted

FEP onset ≤18 vs ≥25: 6mo-FU results

Marker 6-months FU	**Onset ≤18** **(mean, SD)** **(n=27)**	**Onset ≥25** **(mean, SD)** **(n=43)**	Intergroup analyses **(onset ≤18 vs onset ≥25)**	
			Statistic (F)	P-Value
NF*k*B-act	6.01 (2.06)(n=20)	5.65 (3.24)(n=38)	3.898	**0.042**
iNOS-WBc	125.13 (49.30)(n=18)	105.14 (53.46)(n=37)	1.572	0.216
COX2-WBc	189.57(136.72)(n=18)	271.51(203.93)(n=37)	2.148	0.149
NO^-_2-sol-	16.28(7.06)(n=20)	19.31(7.00)(n=38)	1.782	0.188
PGE_2-sol	968.52(667.41)(n=20)	676.39(638.38)(n=38)	3.884	**0.070**
TBARS -sol	4.61(2.57)(n=20)	4.53(1.36)(n=38)	0.001	0.975
I*k*Bα-wbC	97.39(76.96)(n=18)	116.32(91.71)(n=37)	0.277	0.601
$15dPGJ_2$-sol	375.60(120.72)(n=20)	424.60(183.27)(n=38)	1.551	0.219
PPAR-act	1.19(0.42)(n=20)	1.138(0.64)(n=38)	2.529	0.118

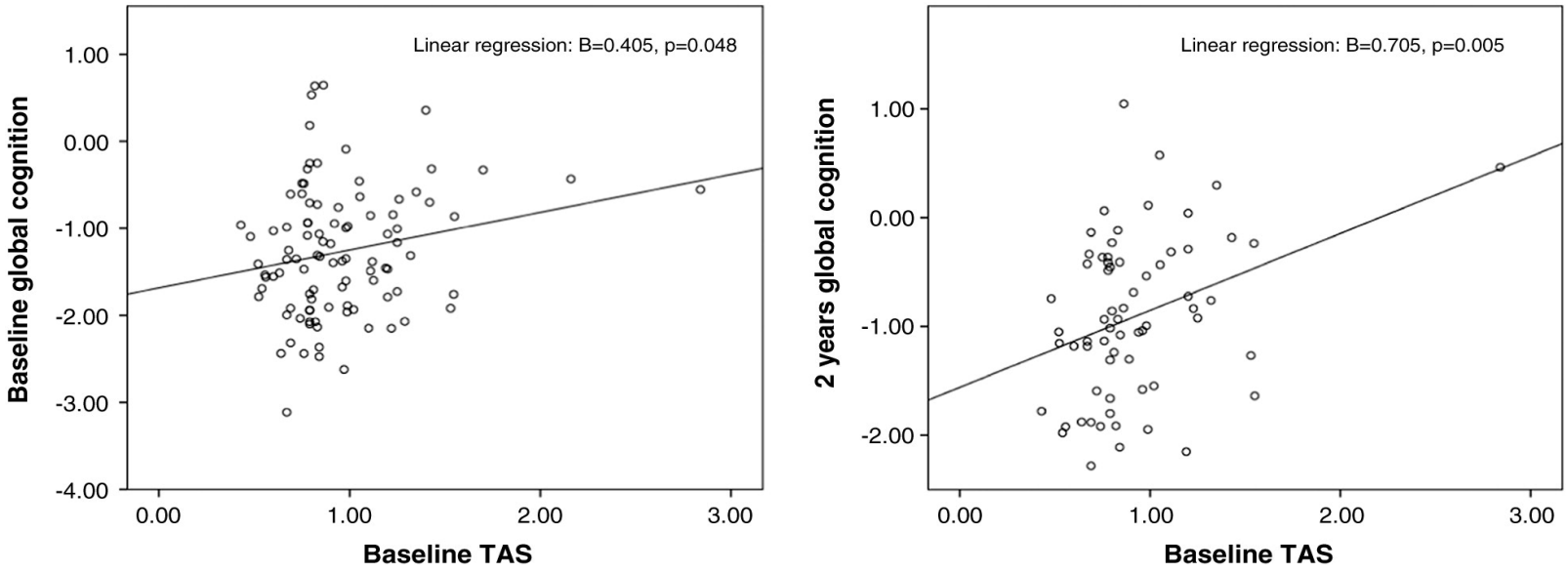
Non-parametric 1 factor ANCOVA. Independent variable: age-onset group; dependent variables: values of pro- and anti-inflammatory markers; covariates: days between first psychotic symptoms until baseline visit, age of onset of cannabis use, tobacco use, total dose of antipsychotics (chlorpromazine equivalents)

Moreno et al., submitted

Contents lists available at ScienceDirect
Schizophrenia Research
journal homepage: www.elsevier.com/locate/schres

Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study

105 early onset-first episode psychosis and 97 healthy controls
Age 9–17 years



-Oxidative imbalance in this population (lower baseline TAS) has been associated with worse cognitive outcomes at 2-year follow-up
-TAS was not associated with cognitive functioning in healthy controls

Martinez-Cengotitabengoa et al, 2014

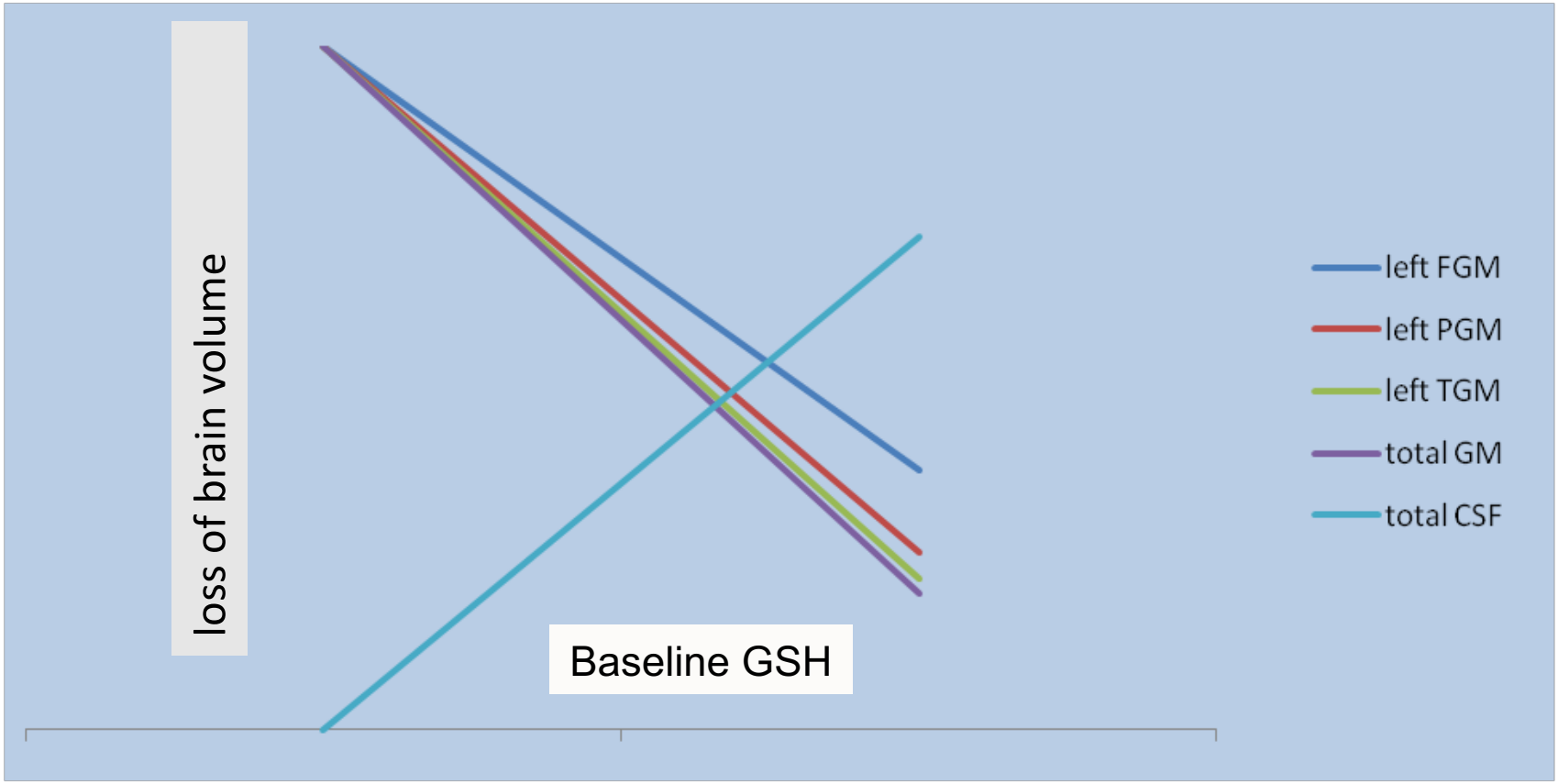
Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study

David Fraguas [a,b], Ana Gonzalez-Pinto [c], Juan Antonio Micó [d], Santiago Reig [a,e], Mara Parellada [a], Mónica Martínez-Cengotitabengoa [c], Josefina Castro-Fornieles [f], Marta Rapado-Castro [a], Immaculada Baeza [f], Joost Janssen [e], Manuel Desco [e,g], Juan Carlos Leza [h], Celso Arango [a,*]



Fraguas et al., Schizophrenia Research 2012

Schizophrenia Bulletin
doi:10.1093/schbul/sbt198

Differential Neurodevelopmental Trajectories in Patients With Early-onset Bipolar and Schizophrenia Disorders

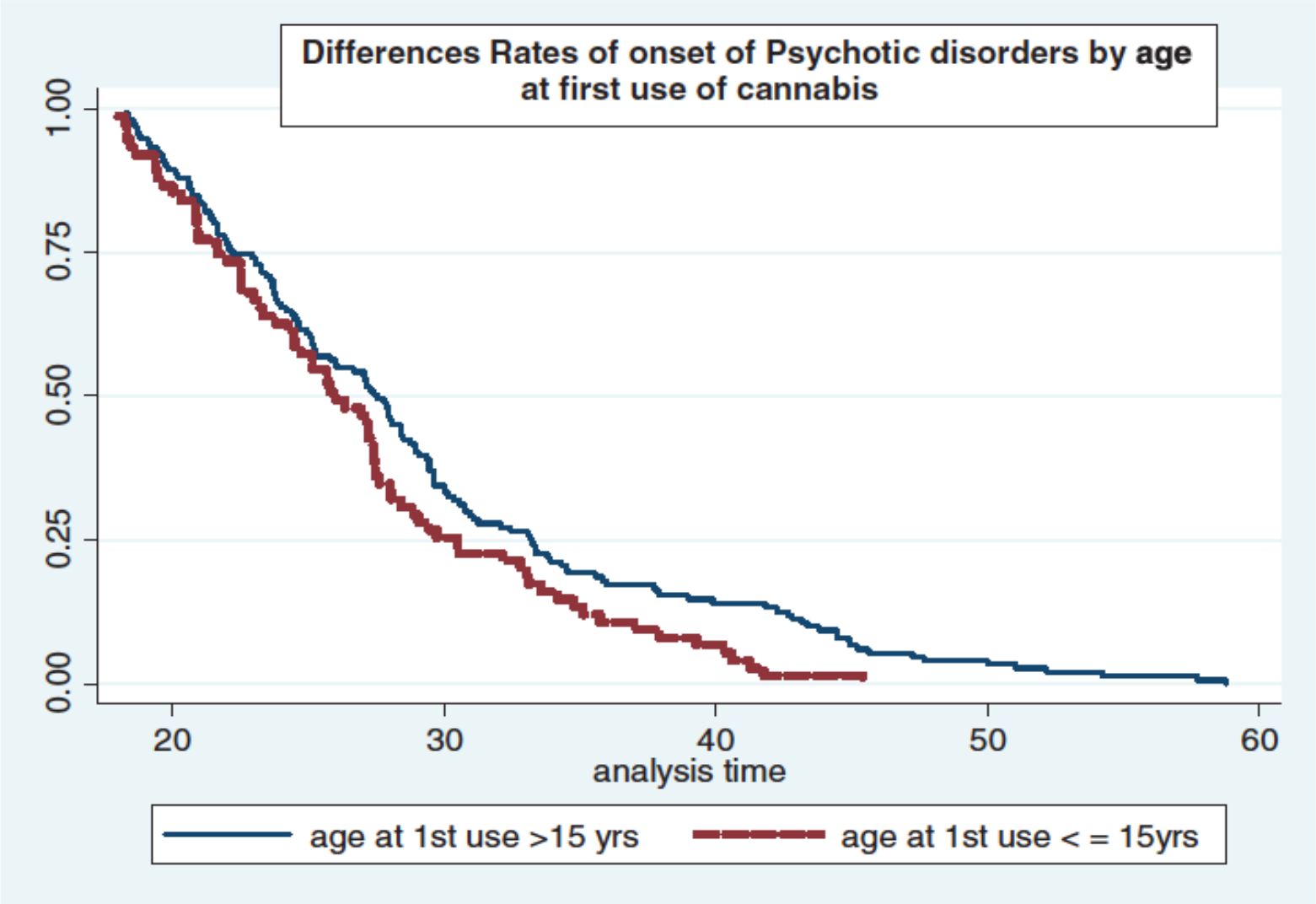
Early-onset psychotic bipolar patients have low intelligence quotient, more neurological signs, reduced frontal gray matter at the time of their first psychotic episode, and greater brain changes than healthy controls.

However, patients with early-onset schizophrenia seem to have more social impairment, developmental abnormalities (eg, language problems), and lower academic achievement in childhood than early-onset bipolar patients.

Some of these abnormal developmental trajectories are more related to early-onset psychotic symptoms of these 2 syndromes than to categorically defined DSM disorders.

Arango et al., 2013

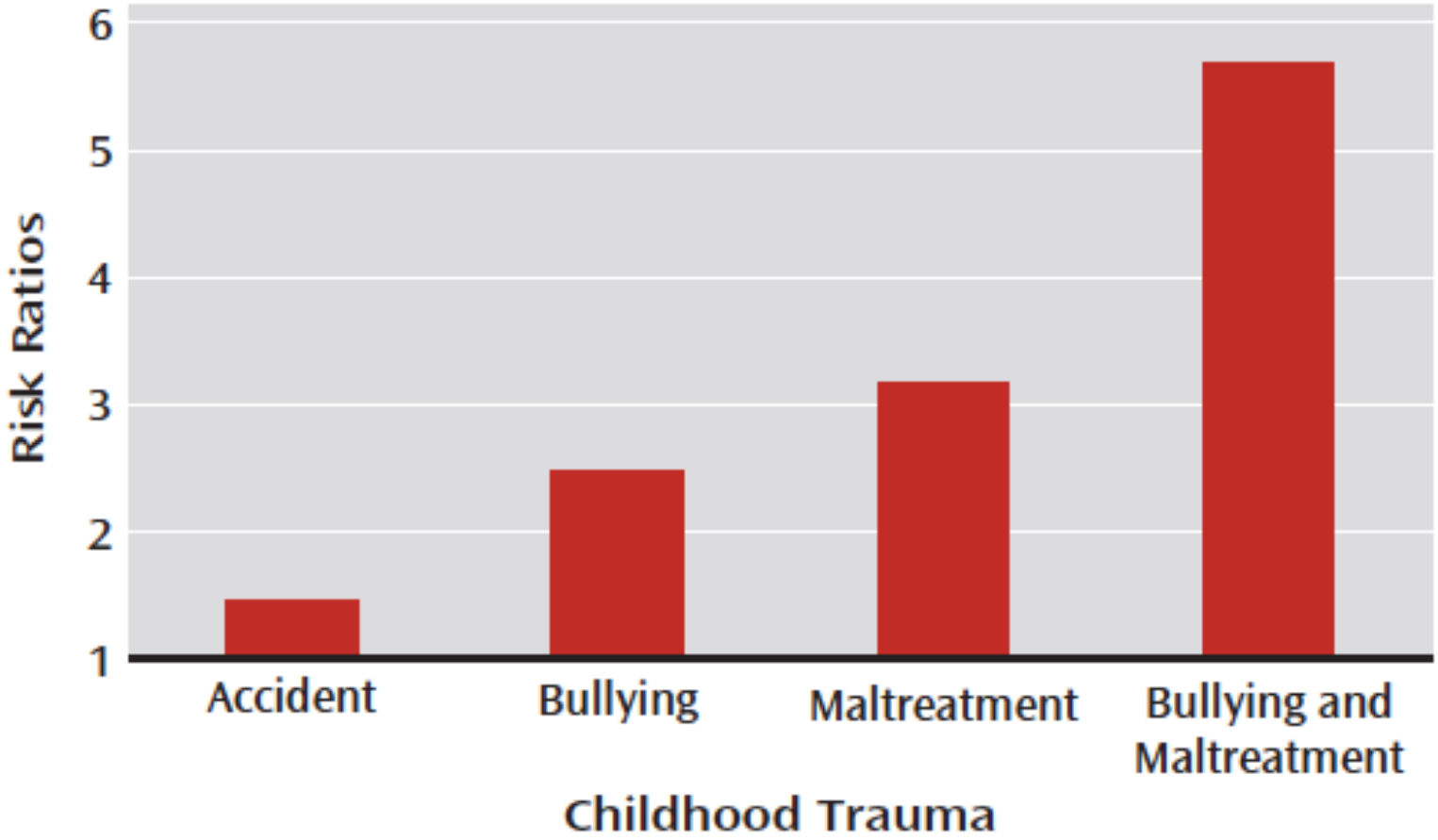
Earlier onset of cannabis use associated with earlier onset of psychosis



Di Forti et al., Schizophr Bull (2014) 40 (6): 1509-1517.

Child abuse and risk for psychosis

FIGURE 1. Risk of Psychotic Symptoms at Age 12 Associated With Cumulative Childhood Trauma



ARSENEAULT, CANNON, FISHER, ET AL.

Am J Psychiatry 168:1, January 2011

Prognostic factors depend on outcomes

- **Clinical** (diagnosis, symptom type and severity, course-relapse/remission/readmission, treatment, insight, suicidality)
- **Functional** (global, social, educational/occupational, disability/dependency, quality of life
- **Cognitive** (attention, working memory, executive function, global cognition, IQ)
- **Neuroimaging** (volume change)
- ***Treatment -related***

Diaz-Caneja et al., 2015

npj | Schizophrenia

www.nature.com/npjschz

REVIEW ARTICLE OPEN

Predictors of outcome in early-onset psychosis: a systematic review

The most replicated predictors of worse clinical, functional, cognitive, and/or biological outcomes in EOP

- Premorbid difficulties (developmental delays and poor premorbid adjustment)
- Symptom severity (especially of negative symptoms) at baseline
- Longer duration of untreated psychosis (DUP)

Diaz-Caneja et al., 2015

Long-term outcome of early-onset schizophrenia vs other early-onset psychosis

21 studies, N= 716, mean age ≤18 years

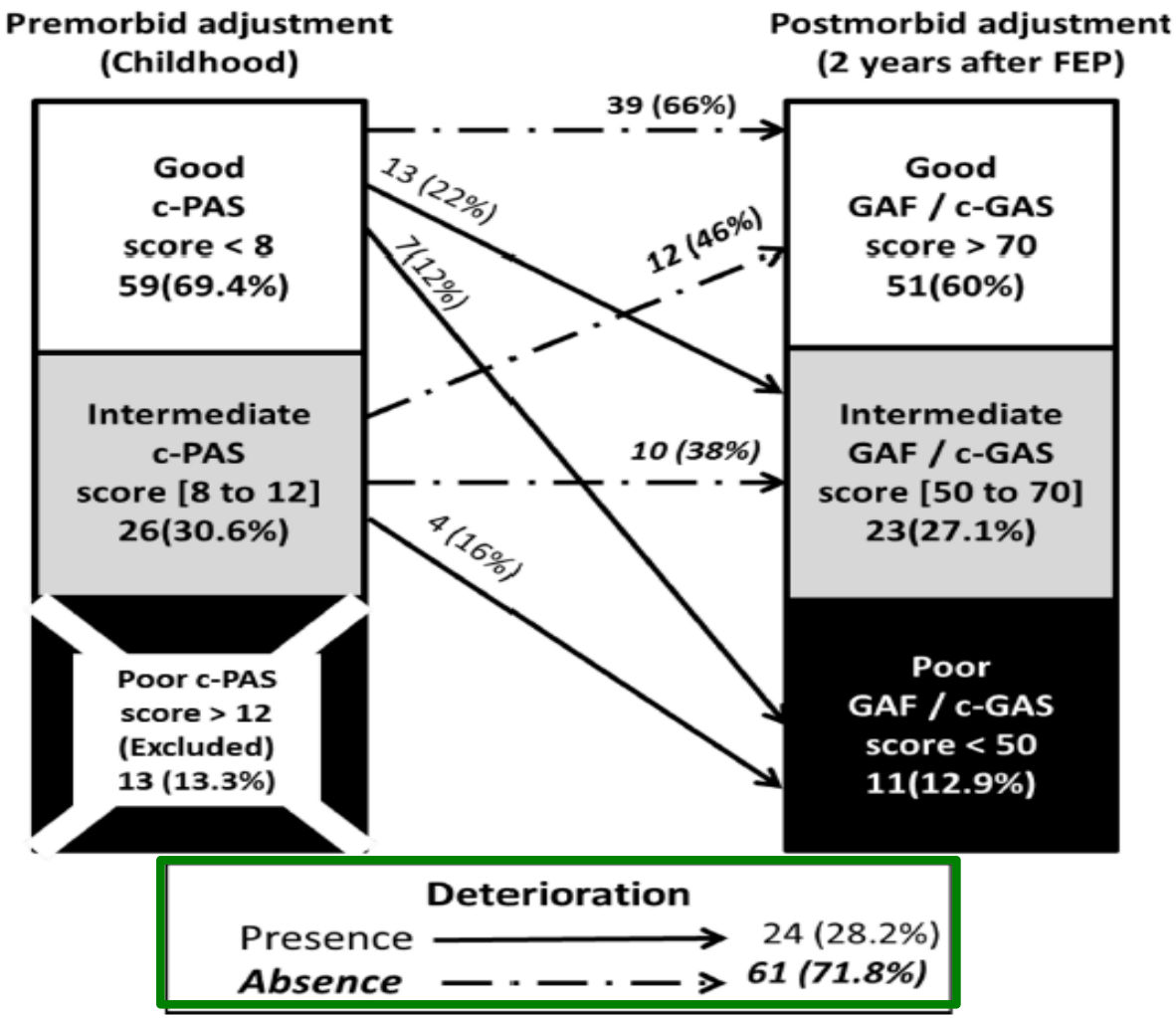
Percentages of subjects by diagnosis														
Outcome variable	EOS				Mixed						Analysis			
	Mean	SD	Range	Median	Mean Rank	Mean	SD	Range	Median	Mean Rank	U	z	p	rho
	N = 422				N = 294									
Good	15.4	7.7	0-28	15.8	300.05	19.6	9.1	0-29	21.0	442.40	37368	-9.08	<.001	0.34
Moderate	24.5	14.6	0-60	23.7	299.75	33.6	12.9	18-52	37.0	442.83	37241	-9.13	<.001	0.34
Poor	60.1	18.9	27-100	60.5	410.59	46.8	17.8	24-79	47.0	283.73	40051	-8.09	<.001	0.30

Clemmensen et al., 2012

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-015-0693-5

ORIGINAL CONTRIBUTION

Functional deterioration from the premorbid period to 2 years after the first episode of psychosis in early-onset psychosis



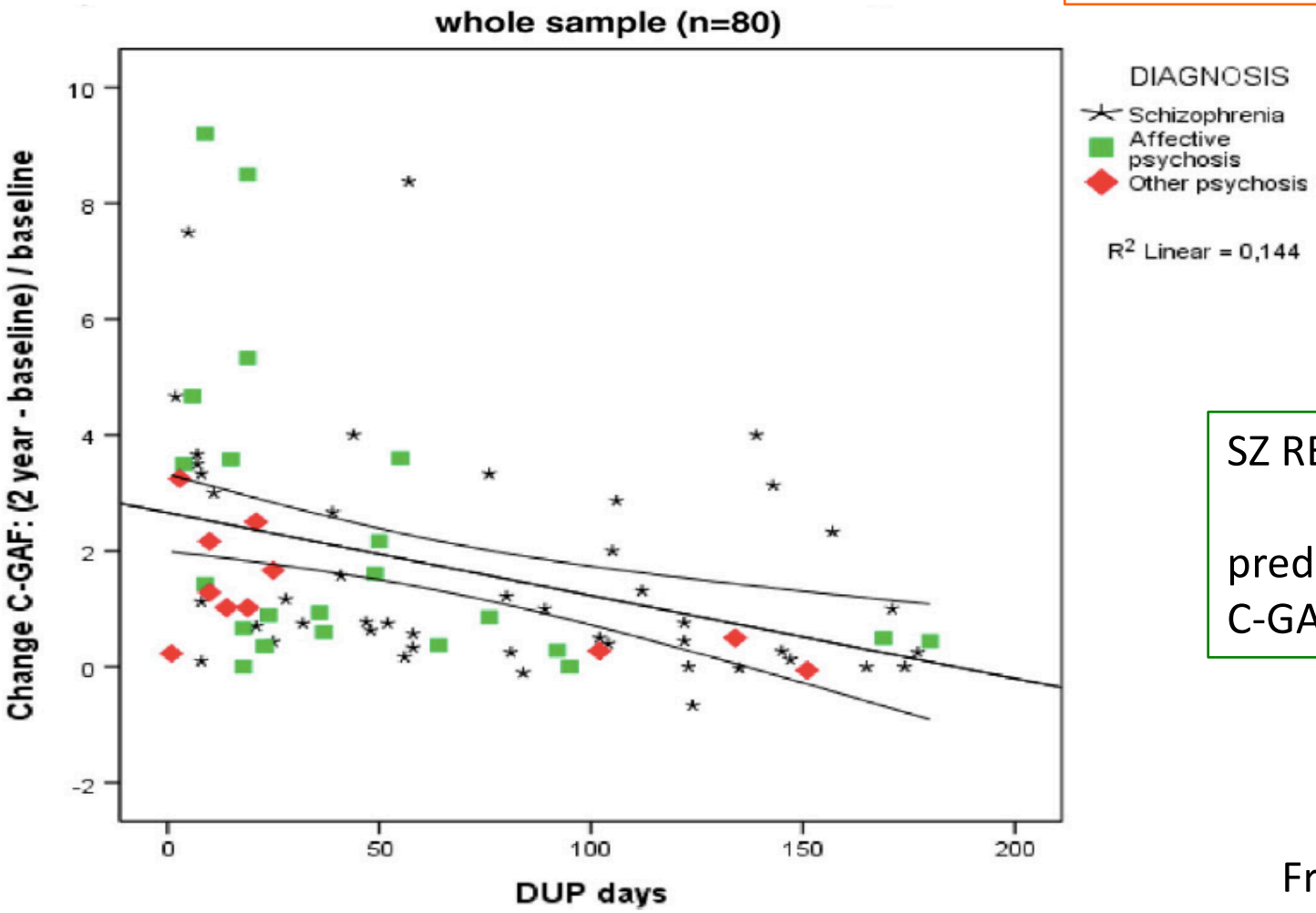
DUP and CGI
73.7 % variance explained

SS and affective psychosis
had comparable deterioration

Del Rey Mejías et al., 2015

Duration of untreated psychosis predicts functional and clinical outcome in children and adolescents with first-episode psychosis

DUP < 6 months



SZ REMISSION

predicted by
C-GAF and DUP

Fraguas et al., 2014

Contents lists available at ScienceDirect

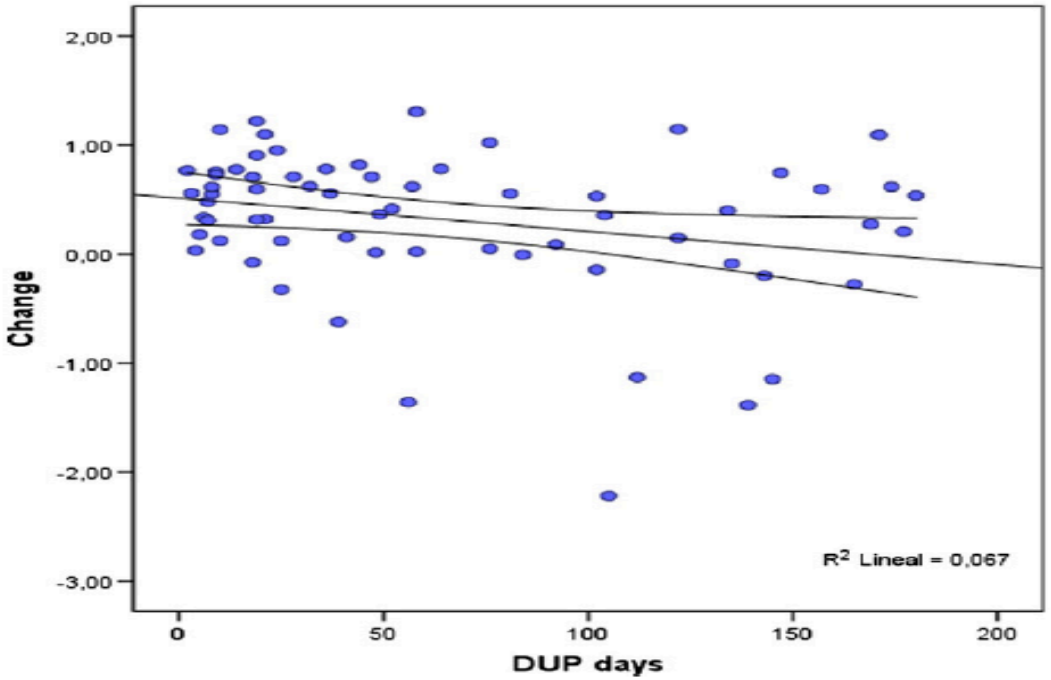
Schizophrenia Research

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

A longitudinal study on the relationship between duration of untreated psychosis and executive function in early-onset first-episode psychosis

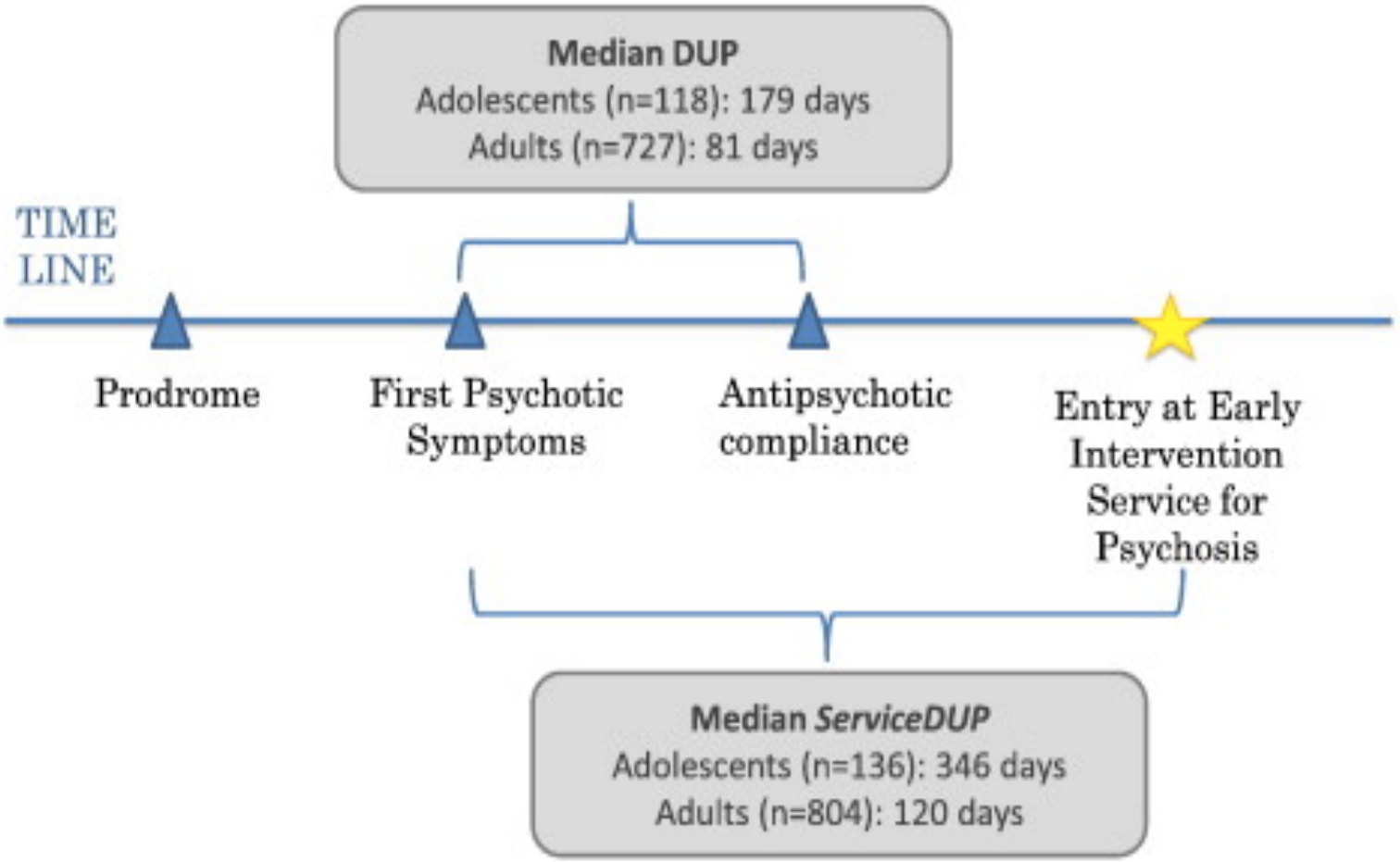
David Fraguas [a,*], Jessica Merchán-Naranjo [a], Ángel del Rey-Mejías [a], Josefina Castro-Fornieles [b], Ana González-Pinto [c], Marta Rapado-Castro [a,d,e], Laura Pina-Camacho [a,f], Covadonga M. Díaz-Caneja [a], Montserrat Graell [g], Soraya Otero [h], Inmaculada Baeza [b], Carmen Moreno [a], Mónica Martínez-Cengotitabengoa [c,i], Elisa Rodríguez-Toscano [a], Celso Arango [a], Mara Parellada [a]

Change in executive functioning through the 2-year follow-up.

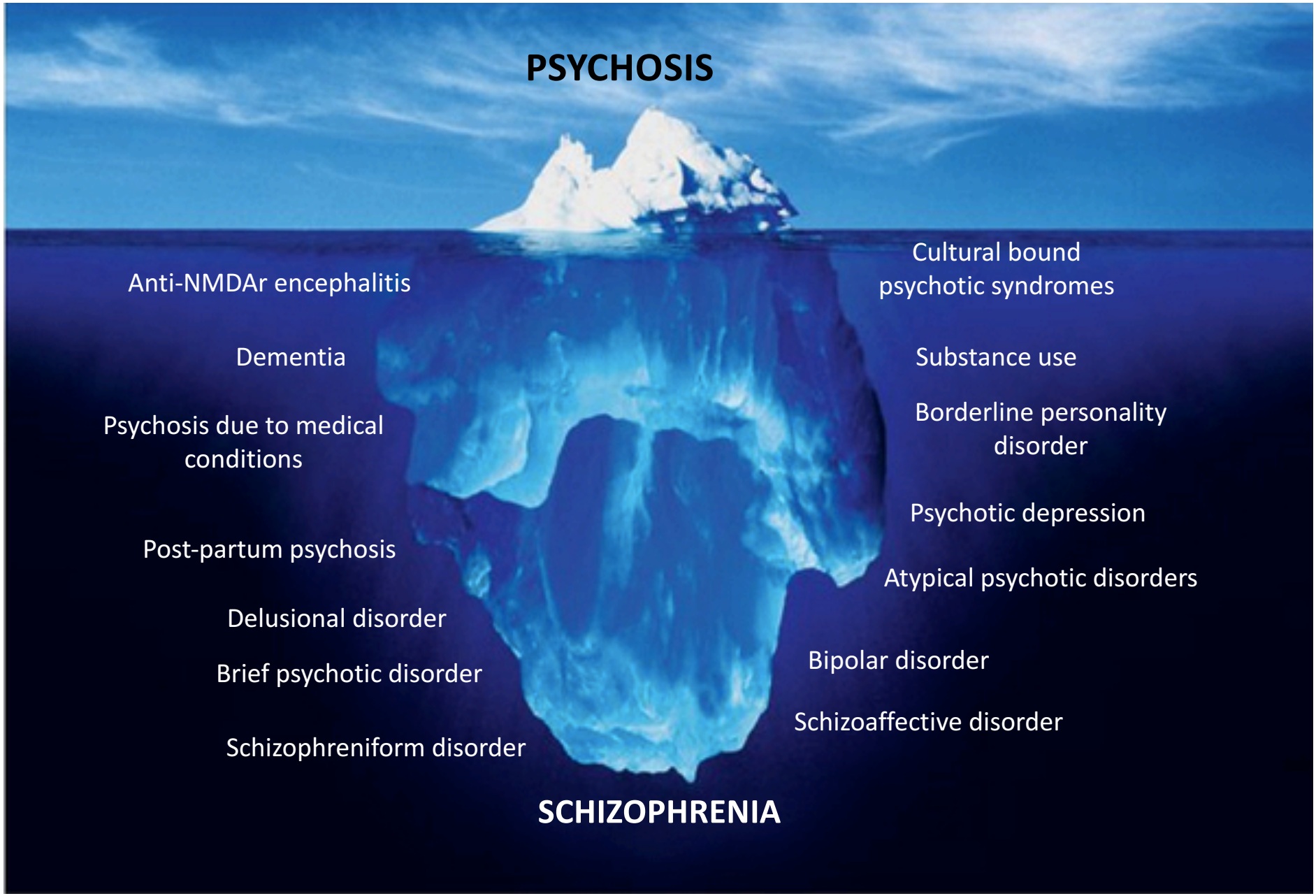


Shorter DUP (e.v. 8.7%, p= 0.013) and greater severity of baseline negative symptoms (e.v. 10.0%, p= 0.008) were significantly associated with greater improvement in EF.

DUP for adolescent- vs adult-onset psychosis

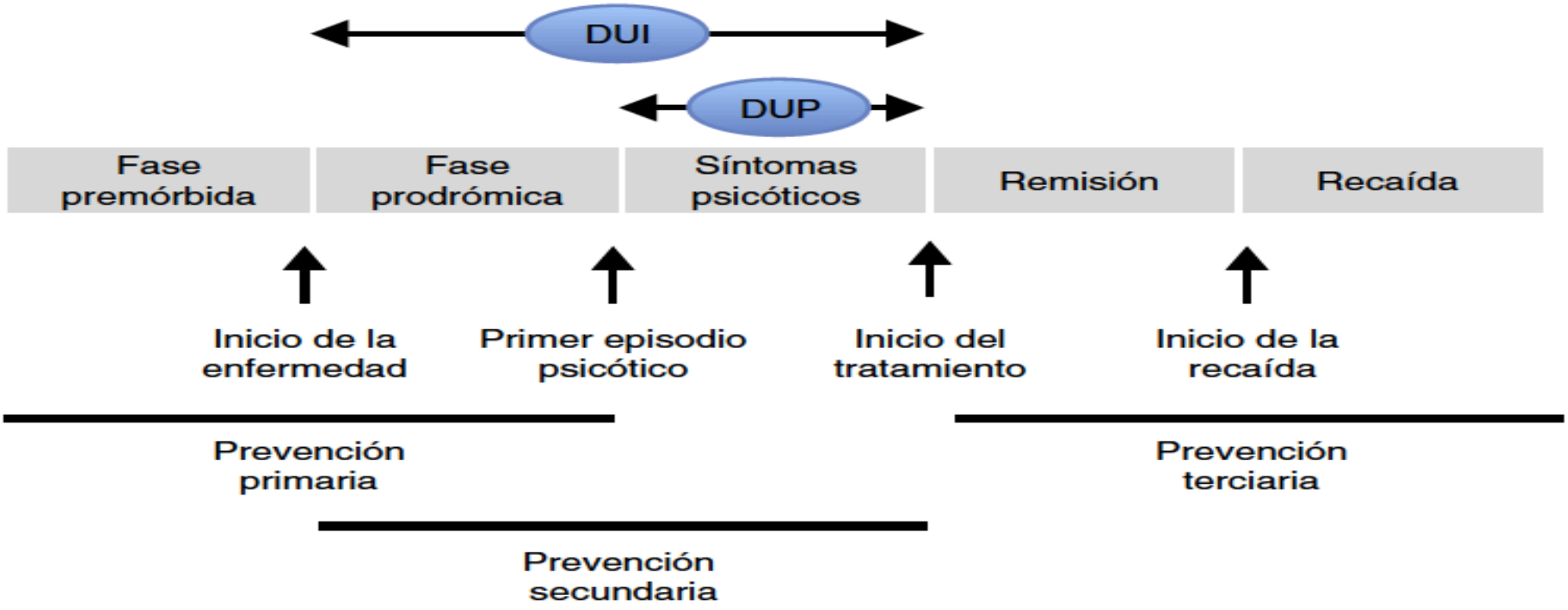


Dominguez et al. 2013

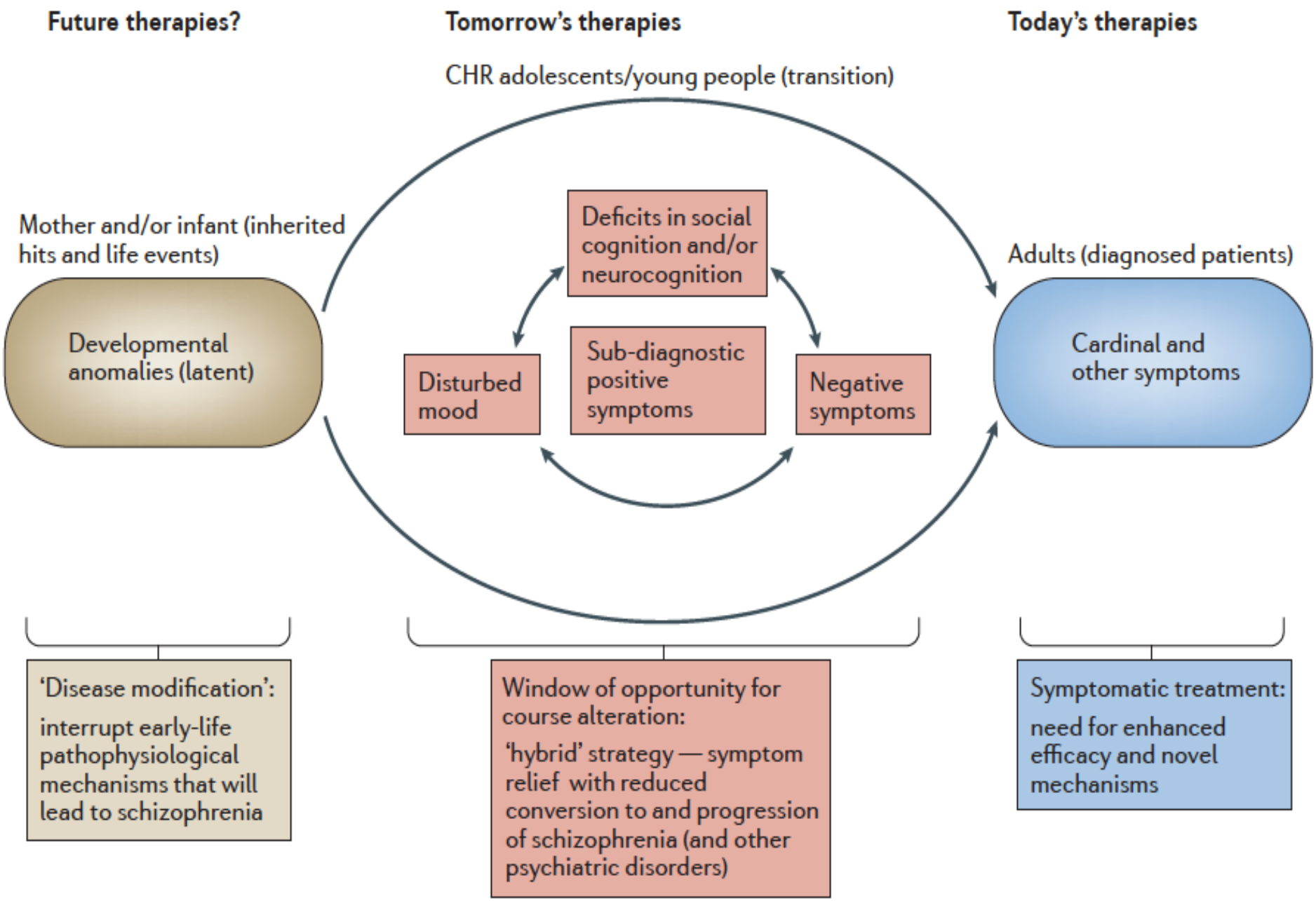

PSYCHOSIS
Anti-NMDAr encephalitis
Dementia
Psychosis due to medical conditions
Post-partum psychosis
Delusional disorder
Brief psychotic disorder
Schizophreniform disorder
Cultural bound psychotic syndromes
Substance use
Borderline personality disorder
Psychotic depression
Atypical psychotic disorders
Bipolar disorder
Schizoaffective disorder
SCHIZOPHRENIA

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental

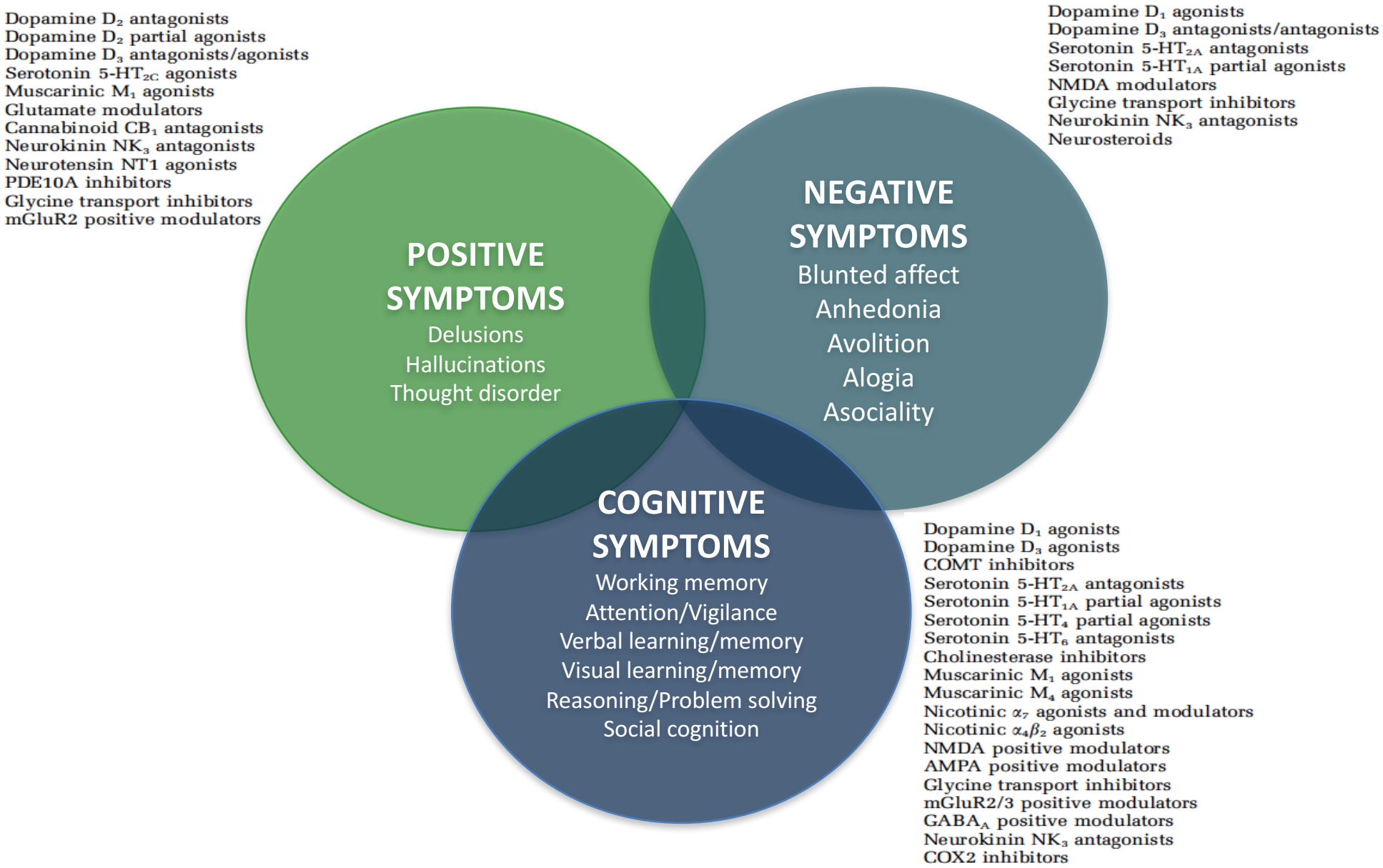


Arango et al., 2017



Millan et al., 2016

Possible pharmacological targets in schizophrenia

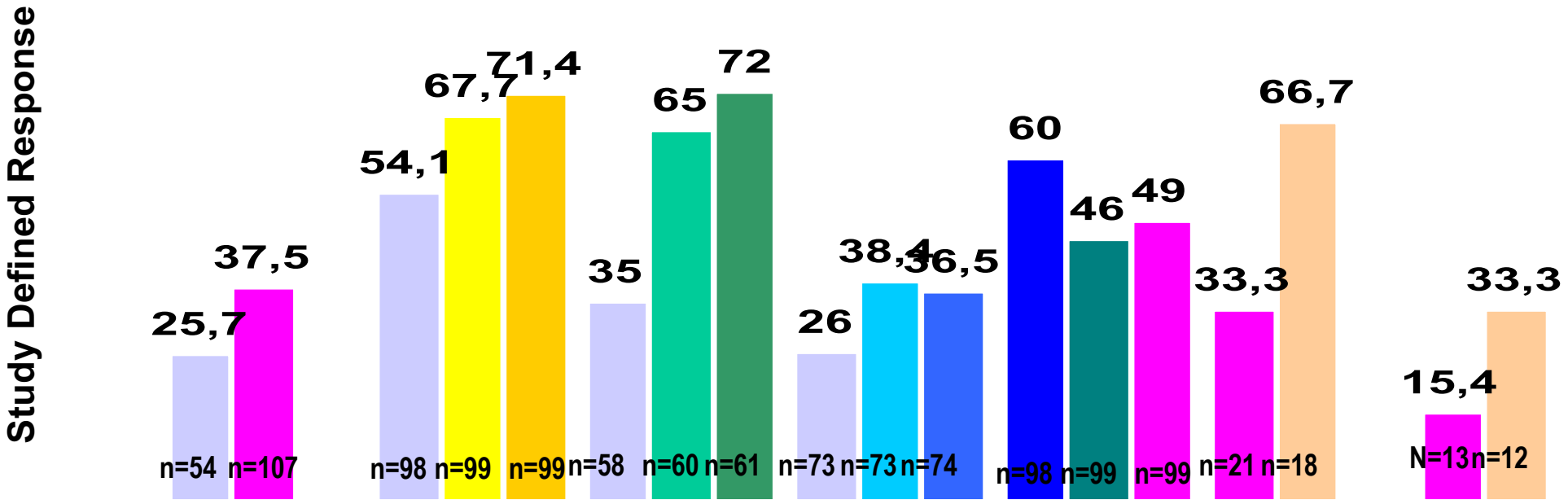


The drug discovery pipeline in schizophrenia
JA Gray and BL Roth

Molecular Psychiatry (2007) 12, 904–922

"Response" Rates in Schizophrenia: NNTs[1-4]= 5-10

1. ≥30% BPRS ↓ and CGI-S ≤3 after ≥4 wks p=ns
2. ≥30% PANSS ↓ p=ns
3. ≥20% PANSS ↓ p<0.001
4. ≥30% PANSS ↓ p<0.001
5. "Response": ≥20% BPRS ↓ and CGI-I ≤ 2 p=ns
6. Rx refractory ≥30% BPRS ↓ and CGI-I ≤ 2 p=0.038
7. Rx refractory: "Partial Response" ≥20% BPRS ↓ p=ns

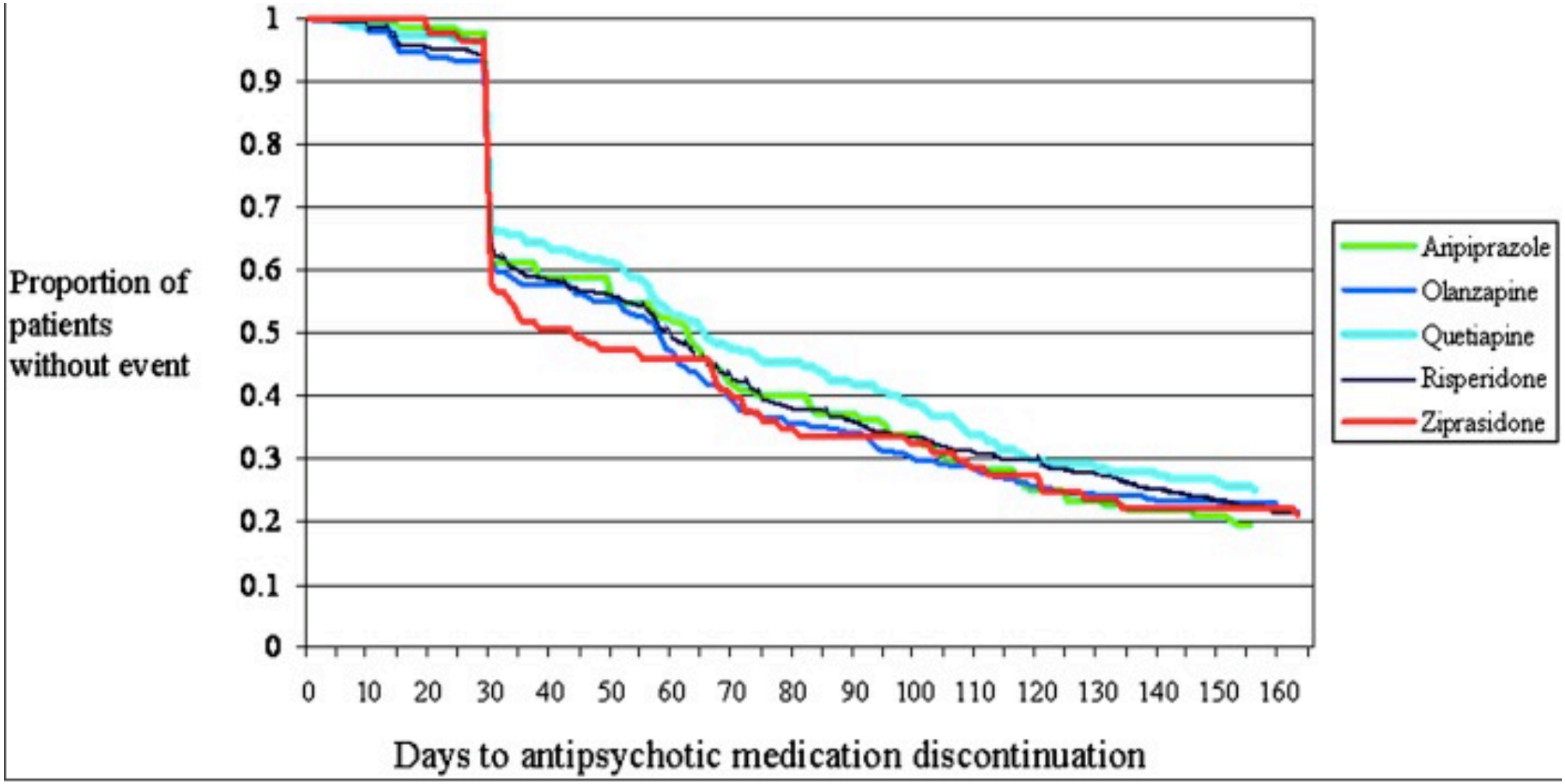


#"Strict" response: ≥20% BPRS ↓ and CGI-S < 3 PLUS persistence until week 8: Mol: 50%, RIS: 46%, OLA: 34%

* "Full" response: ≥20% BPRS ↓ and CGI-S < 3 or BPRS ≤35: OLA: 7.7%, CLO: 0%

1. Kryzhanovskaya et al. J Am Acad Child Adolesc Psychiatry. 2009 Jan;48(1):60-70; 2. Findling RL et al. Am J Psychiatry. 2008 Nov;165(11):1432-41; 3. Haas M et al. Poster at 160th meeting of American Psychiatric Assoc. 2007; 4. Findling RL et a Poster at AACAP Meeting 2008; 5. Sikich L et al. Am J Psychiatry 2008;165:1420-31; 6. Kumra S et al. Biol Psychiatry 2008 7. Shaw P et al. Arch Gen Psychiatry 2006

Comparative Effectiveness of Second-Generation Antipsychotic Medications in Early-Onset Schizophrenia



Olfson et al., 2012

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www.elsevier.com/locate/euroneuro

REVIEW

Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: Comprehensive review of prospective head-to-head and placebo-controlled comparisons

David Fraguas [a,b], Christoph U. Correll [c], Jessica Merchán-Naranjo [b], Marta Rapado-Castro [b], Mara Parellada [b], Carmen Moreno [b], Celso Arango [b,*]

- 34 studies (2719 children and adolescents)
- Head to head and placebo-controlled
- Clozapine better on refractory schizophrenia
- No other differences in efficacy between SGA

BJPsych | The British Journal of Psychiatry (2010) 196, 434–439. doi: 10.1192/bjp.bp.109.066217

Review article

Efficacy of atypical *v.* typical antipsychotics in the treatment of early psychosis: meta-analysis

Nicolas A. Crossley, Miguel Constante, Philip McGuire and Paddy Power

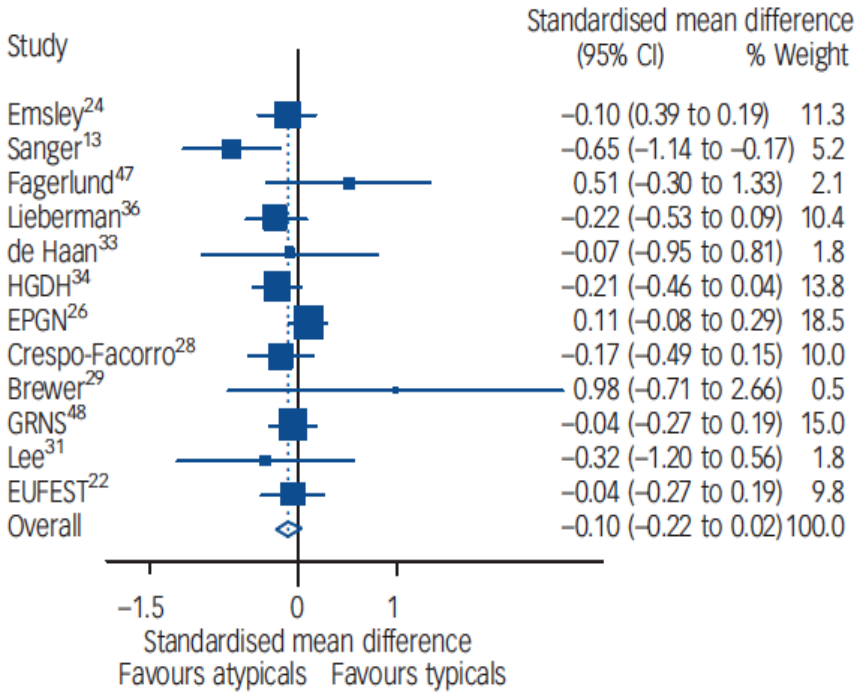


Fig. 3 Comparisons of symptoms scales at short term (around 3 months) between the two groups.

Effect sizes were standardised using Hedges' *g* and pooled using a random-effects model. Non-significant difference favouring atypicals shown ($P=0.12$). Heterogeneity $\chi^2=15.3$ (d.f. =11) $P=0.17$, $I^2=28\%$. EPGN, Early Psychosis Global Network; GRNS, German Research Network on Schizophrenia; EUFEST, European First-Episode Schizophrenia Trial.

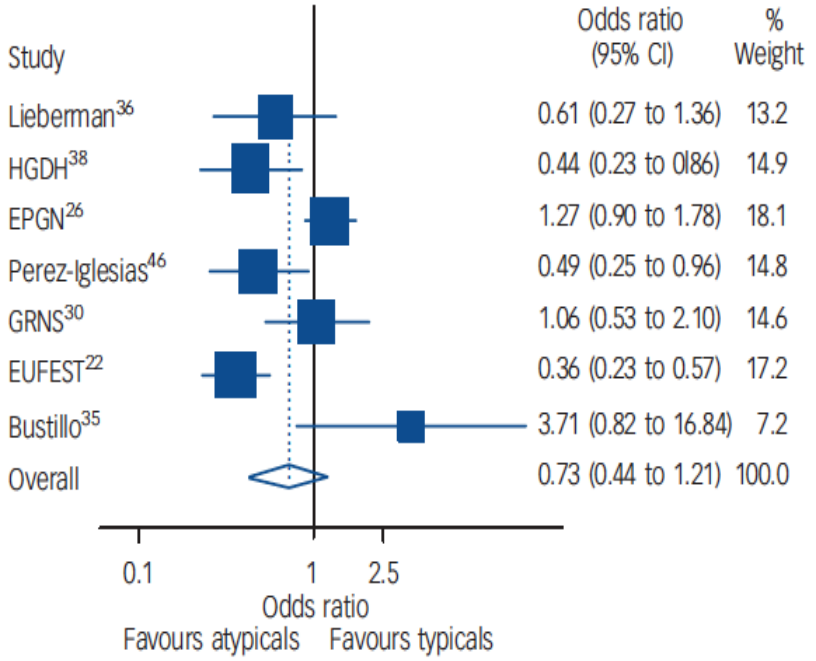
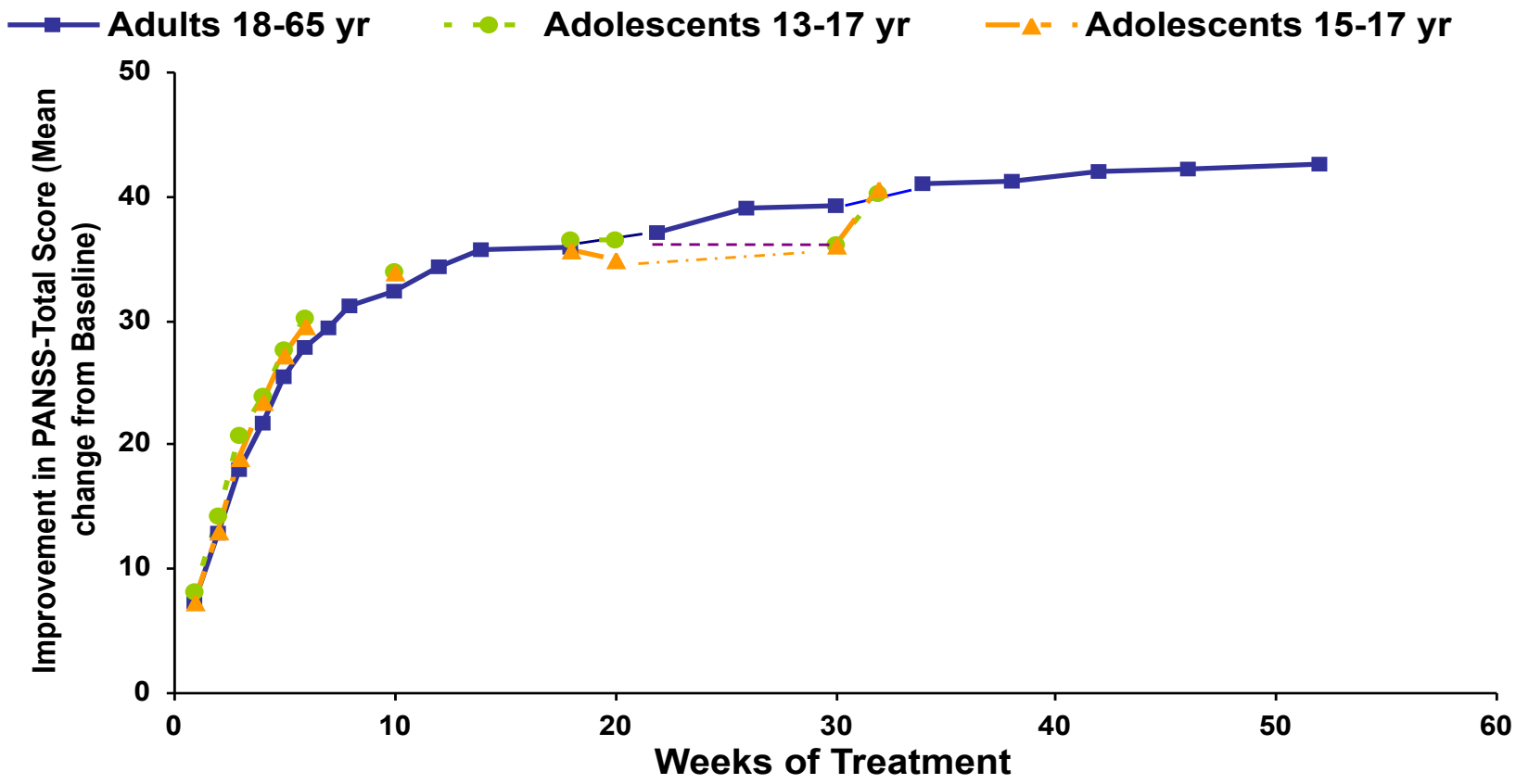


Fig. 2 Comparison of discontinuation rates among participants receiving first- *v.* second-generation antipsychotics.

$P=0.22$. Heterogeneity $\chi^2=28.55$ (d.f. =6) $P<0.001$, $I^2=79.0\%$. EPGN, Early Psychosis Global Network; GRNS, German Research Network on Schizophrenia; EUFEST, European First-Episode Schizophrenia Trial.
For clarity purposes, the first author of the first published paper is used in Table DS1 in cases where more than one article reporting outcomes of the study has been included.

Long-Term Symptom Improvement is Similar in Adolescents and Adults (OC)



	Adolescents 13-17 yr	Adolescents 15-17 yr	Adults 18-65 yr
Baseline scores	94.3 (n=196)*	93.4 (n=147)*	95.1 (n=853)*
At endpoint	(n=118)	(n=91)	(n=334)

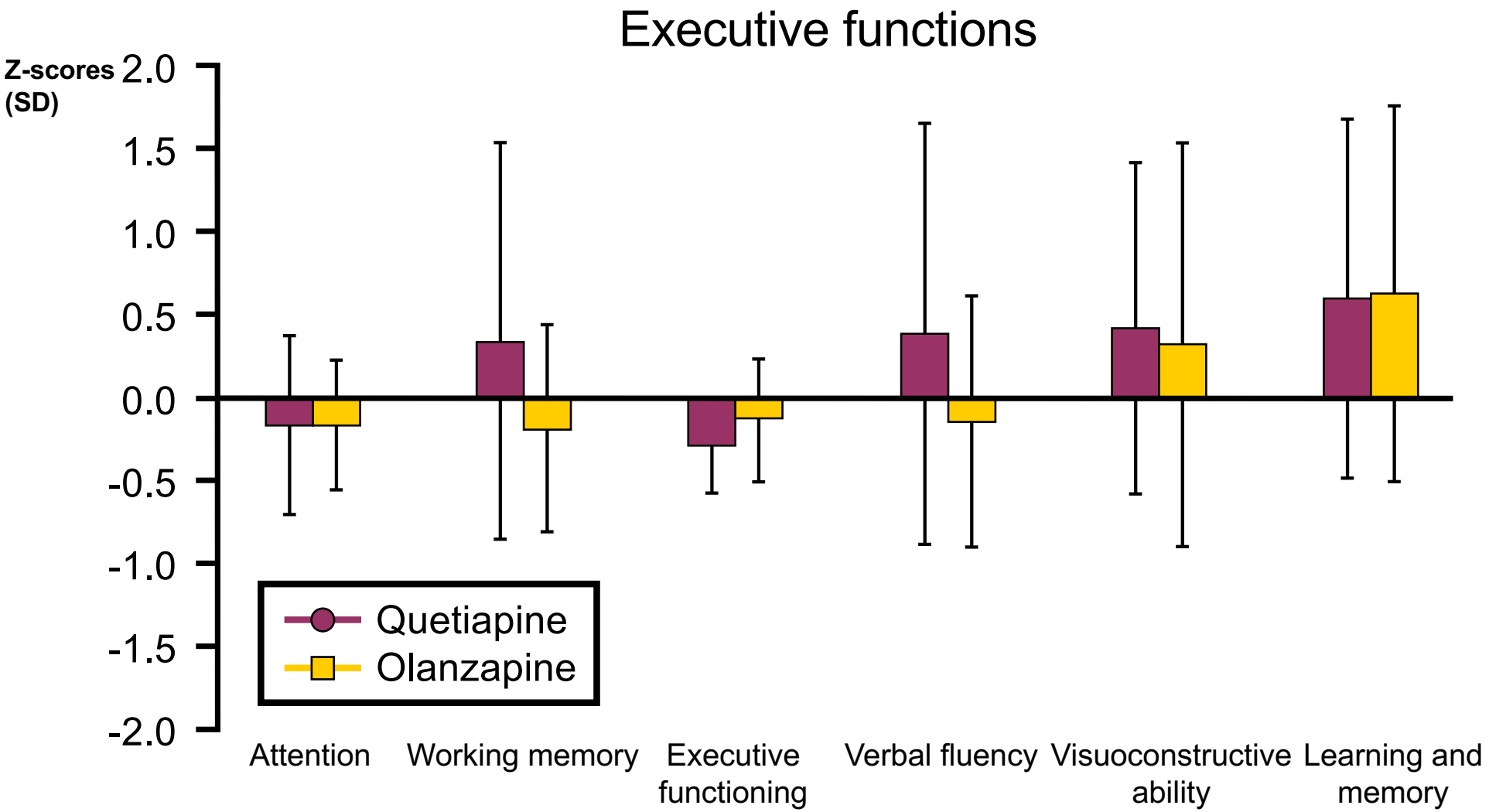
* Including only patients who received aripiprazole and had both a baseline and at least one post-baseline PANSS Total Score evaluation

Antecedents of Treatment Response Over Time in Early-Episode Psychosis

		Wk 4				Month 6			
Trajectory		OR	95.0% CI (Range)		*P*	OR	95.0% C.I (Range)		*P*
Good response	Being male	1.34	0.78–2.28		.29	0.72	0.42–1.25		.24
	Age at onset	1.14	0.90–1.45		.28	1.12	0.86–1.46		.39
	Good premorbid functioning	1.24	0.76–2.03		.38	2.01	1.18–3.43		.01
	Not having schizophrenia	2.04	1.26–3.30		.00	2.11	1.24–3.60		.01
	Cognitive functioning	1.42	1.01–1.98		.04	0.79	0.55–1.12		.18
	Constant	0.00			.00	0.00			.00
		R^2	Sensitivity	Specificity	Accuracy	R^2	Sensitivity	Specificity	Accuracy
	Model fit indices	0.09	0.81	0.33	80.68	0.22	0.84	0.48	82.70
		OR	95.0% CI (Range)		*P*	OR	95.0% CI (Range)		*P*
Poor response	Being male	0.56	0.28–1.13		0.11	1.19	0.57–2.47		0.65
	Age at onset	0.70	0.50–0.98		0.04	0.70	0.49–1.00		0.05
	Good premorbid functioning	0.89	0.45–1.73		0.72	0.69	0.35–1.36		0.28
	Not having schizophrenia	0.58	0.29–1.16		0.12	1.31	0.66–2.58		0.44
	Cognitive functioning	0.53	0.34–0.82		0.00	0.80	0.52–1.22		0.30
	Constant	0.00			0.00	0.00			0.00
		R^2	Sensitivity	Specificity	Accuracy	R^2	Sensitivity	Specificity	Accuracy
	Model fit indices	0.62	0.91	0.77	89.00	0.47	0.90	0.60	87.32

Levine and Rabinowitz, 2010

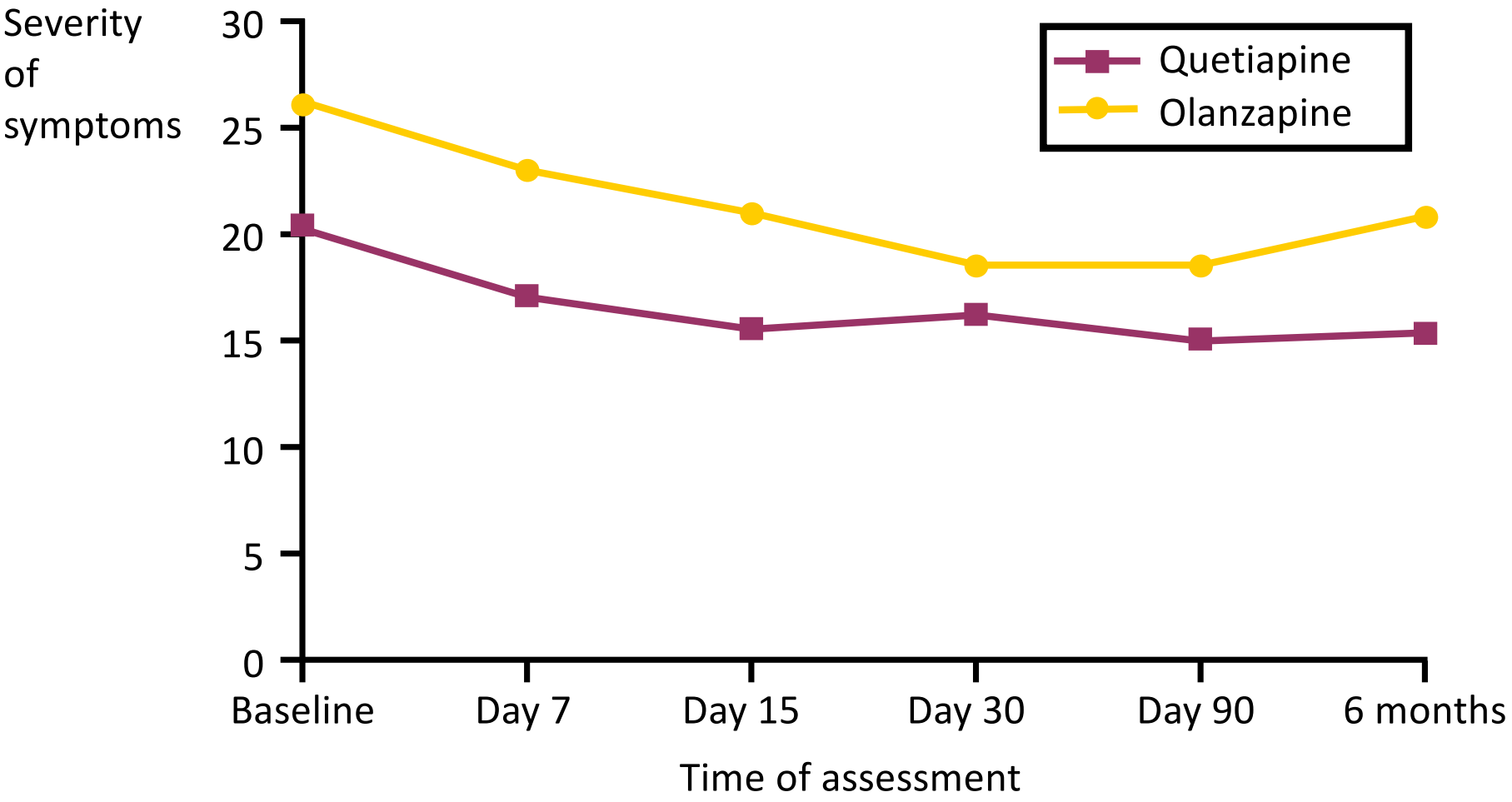
Cognition: Tasks grouped in cognitive domains



- No cognitive improvement was observed in any of the groups
- No differences between groups

Robles et al 2011

Negative symptom reduction with SGA



- Significant symptom reduction from baseline to end of treatment only for the quetiapine group: olanzapine 16.5% (W=-2.533, p=0.833); quetiapine 25.6% (W=-2.533, p=0.011)

Arango et al 2009

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 53 NUMBER 11 NOVEMBER 2014

NEW RESEARCH

Second-Generation Antipsychotic Use in Children and Adolescents: A Six-Month Prospective Cohort Study in Drug-Naïve Patients

Celso Arango, MD, PhD, Miriam Giráldez, PharmD, PhD, Jessica Merchán-Naranjo, MSc, Inmaculada Baeza, MD, PhD, Josefina Castro-Fornieles, MD, PhD, Jose-Angel Alda, MD, Carmen Martínez-Cantarero, MD, PhD, Carmen Moreno, MD, PhD, Pilar de Andrés, MSc, Cristina Cuerda, MD, PhD, Elena de la Serna, PhD, Christoph U. Correll, MD, David Fraguas, MD, PhD, Mara Parellada, MD, PhD

CG Clinical Guidance

- Olanzapine, quetiapine, and risperidone significantly increase body weight in the first 6 months after initiation of treatment in children and adolescents.
- After the first 3 months, patients on olanzapine and risperidone continue to gain weight through month 6.
- No relationship was detected between administered olanzapine dose and increase in BMI z score. This is in contrast to the relationship between higher risperidone doses and greater BMI increase.
- At 6 months of treatment, olanzapine significantly increases almost all lipid parameters.
- Patients under 12 years of age on risperidone may be at higher risk for glucose intolerance than older patients.
- Close screening and monitoring is necessary when prescribing risperidone, quetiapine, and olanzapine, as many of the side effects continue to develop during the first 6 months of treatment.

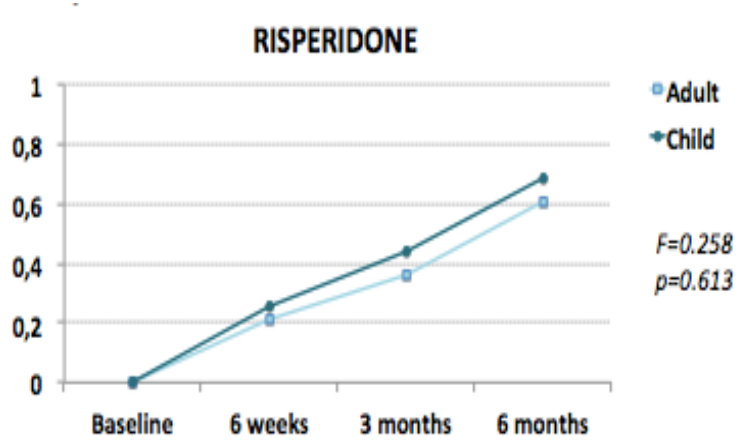
Weight and metabolic changes after 3-m treatment with SGA

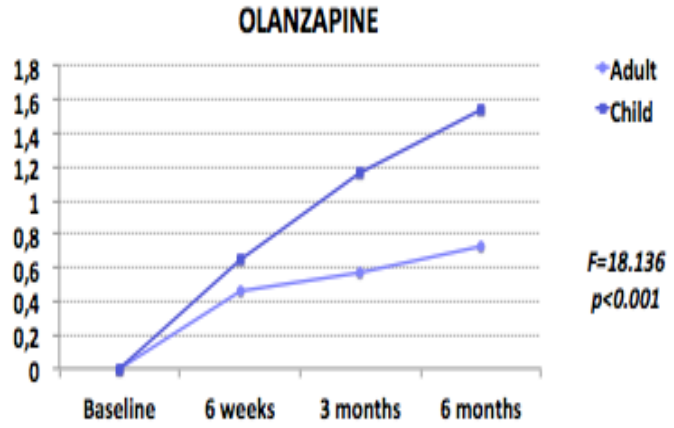
	Bipolar Disorder (N=31)	Psychotic Disorder (N=29)	Non-psychotic Disorders (N=30)
	% change	% change	% change
Weight kg	6.6 (5.8)	5.9 (4.3)	4.1 (4.0)
BMI	2.3 (2.1)	0.5 (6.8)	-0.2 (6.4)
BMI z-score	0.6 (0.6)	0.5 (0.4)	0.6 (0.7)
SPB mm Hg	-3.1 (20.3)	-2.0 (20.1)	3.4 (16.7)
DPB mm Hg	-0.4 (12.6)	3.9 (23.3)	-0.4 (14.1)
Glucose mg/dl	2.80 (16.0)	2.30 (26.2)	3.4 (10.2)
Total-chol mg/dl	10.1 (22.5)	9.7 (19.4)	2.12 (22.3)
HDL-chol mg/dl	-0.5 (8.6)	3.04 (11.8)	1.01 (8.2)
LDL-cholmg/dl	9.1 (17.8)	4.5 (15.8)	2.4 (24.6)
TG mg/dl	5.8 (40.9)	12.1 (41.2)	-0.9 (47.9)
TSH mU/L	1.63 (11.4)	0.1 (2.6)	0.1 (1.5)
Free T4 ng/d	-0.6 (1.6)	-0.5 (1.1)	-0.2 (0.4)

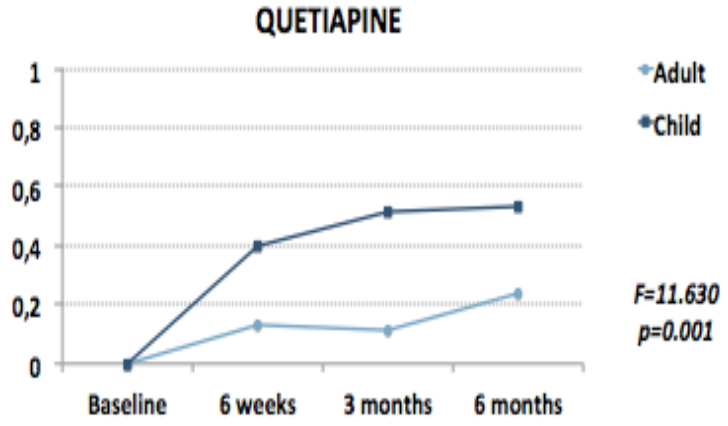
Non-significant differences between groups

Moreno et al, 2010

Increase in BMI z-scores: differences between paediatric and adult patients







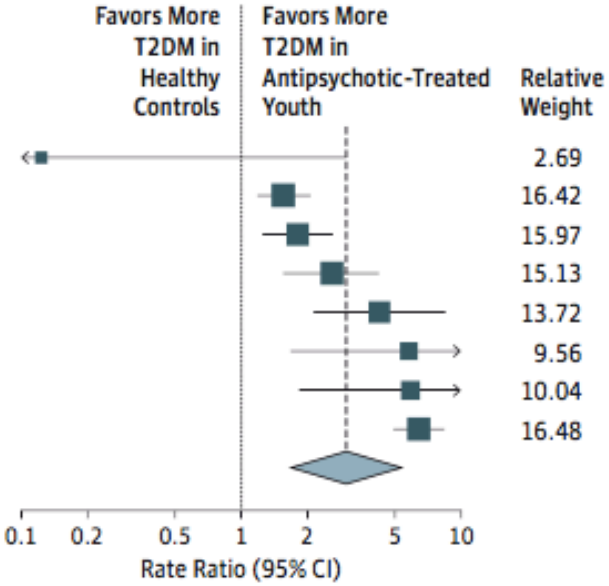
Diaz-Caneja et al., in preparation

Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics
A Systematic Review and Meta-analysis

Britta Galling, MD; Alexandra Roldán, MD; René E. Nielsen, MD, PhD; Jimmi Nielsen, MD, PhD; Tobias Gerhard, PhD; Maren Carbon, MD; Brendon Stubbs, PhD; Davy Vancampfort, PhD; Marc De Hert, MD, PhD; Mark Olfson, MD, MPH; Kai G. Kahl, MD; Andres Martin, MD; Jeff J. Guo, MD; Hsien-Yuan Lane, MD, PhD; Fung-Chang Sung, PhD, MPH; Chun-Hui Liao, MD; Celso Arango, MD; Christoph U. Correll, MD

Figure 2. Forest Plot of Incidence Rate Ratio for T2DM per Patient-Years in Antipsychotic-Exposed Youth vs Healthy Controls

Source	Statistics for Each Study: Rate Ratio (95% CI)	Z-Value	*P* Value	No. With Diabetes/Total No.: Antipsychotic-Exposed Youth	Healthy Controls
Arango et al,[46] 2014	0.123 (0.005-3.030)	-1.281	.200	1/136	0/6
McIntyre and Jerrell,[48] 2008	1.560 (1.185-2.055)	3.165	.002	125/36473	85/38700
Morrato et al,[50] 2010	1.812 (1.260-2.605)	3.207	.001	48/2648	74/7397
Sohn et al,[55] 2015	2.574 (1.568-4.228)	3.736	<.001	27/8161	37/28792
Andrade et al,[34] 2011	4.249 (2.144-8.421)	4.145	<.001	12/3710	26/34156
Liao et al,[52] 2011 (SGA)	5.774 (1.690-19.725)	2.797	.005	4/1755	7/17734
Liao et al,[52] 2011 (FGA)	5.889 (1.847-18.775)	2.997	.003	4/2835	10/41735
Enger et al,[47] 2013	6.412 (4.934-8.331)	13.904	<.001	71/12309	265/294564
Total	3.019 (1.703-5.351)	3.783	<.001		



FGA indicates first-generation antipsychotic; SGA, second-generation antipsychotic; and T2DM, type 2 diabetes mellitus.

Extrapiramidal effects at baseline and after 1-year of antipsychotic treatment

	All patients (N=265)								
	Baseline (N=265)		3- month (N=210)		6- month (N=160)		1-year (N=110)		Baseline-Follow-upa
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p
Total Dyskinesia Score	3	4.5	4.4	5.0	4.8	5.0	4.3	5.1 a	<.001
Total Parkinsonism Score	2.0	3.4	4.0	5.1	3.5	4.6	3.1	4.4 a	<.001
Total Cognition Score	3.9	3.1	3.4	2.9	3.3	3.0	3.3	3.0 a	<.001
Total Akathysia Score	.7	2.7	.5	2.0	.4	1.4	.5	1.5	.6
	Naïve patients (N= 134)								
	Baseline (N=134)		3- month (N=126)		6- month (N=101)		1-year (N=75)		Baseline-Follow-upa
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p
Total Dyskinesia Score	2.7	3.4	4.6	5.8	4.8	5.1	5.5	5.1	<.001
Total Parkinsonism Score	1.6	2.9	3.7	4.8	4.0	4.6	3.2	3.9	<.001
Total Cognition Score	4	3.2	3.8	3.1	3.4	3.0	2.7	2.7	<.001
Total Akathysia Score	.7	2.4	.7	2.2	.7	1.9	.5	1.4	.4

Tardive Dyskinesia

- ✓ 5.8%
- ✓ less frequent in older subjects
- ✓ Increased risk with psychotic symptoms and longer exposure to antipsychotics

Garcia-Amador et al, 2016

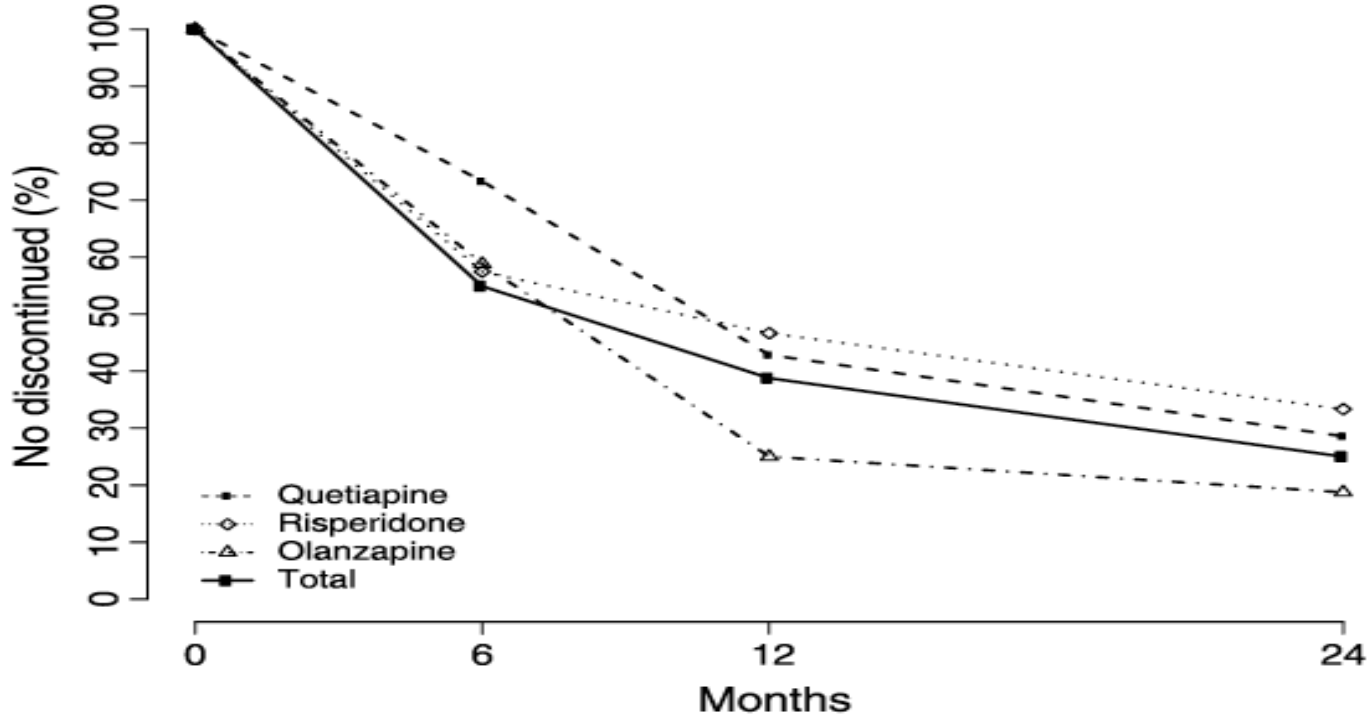
ORIGINAL CONTRIBUTION

Journal of Clinical Psychopharmacology • Volume 33, Number 4, August 2013

Twenty-Four Months of Antipsychotic Treatment in Children and Adolescents With First Psychotic Episode

Discontinuation and Tolerability

Ana Noguera, MD,†‡§ Patricia Ballesta, PhD,*†‡§ Immaculada Baeza, MD, PhD,*†‡§ Celso Arango, MD,§// Elena de la Serna, PhD,// Ana González-Pinto, MD, PhD,§¶** Mara Parellada, MD, PhD,§// Montserrat Graell, MD,†† Carmen Moreno, MD, PhD,§// Soraya Otero, MD, PhD,§‡‡‡ and Josefina Castro-Fornieles, MD, PhD*†‡§*



Dscontinuation rates:

44.5% at 6 months

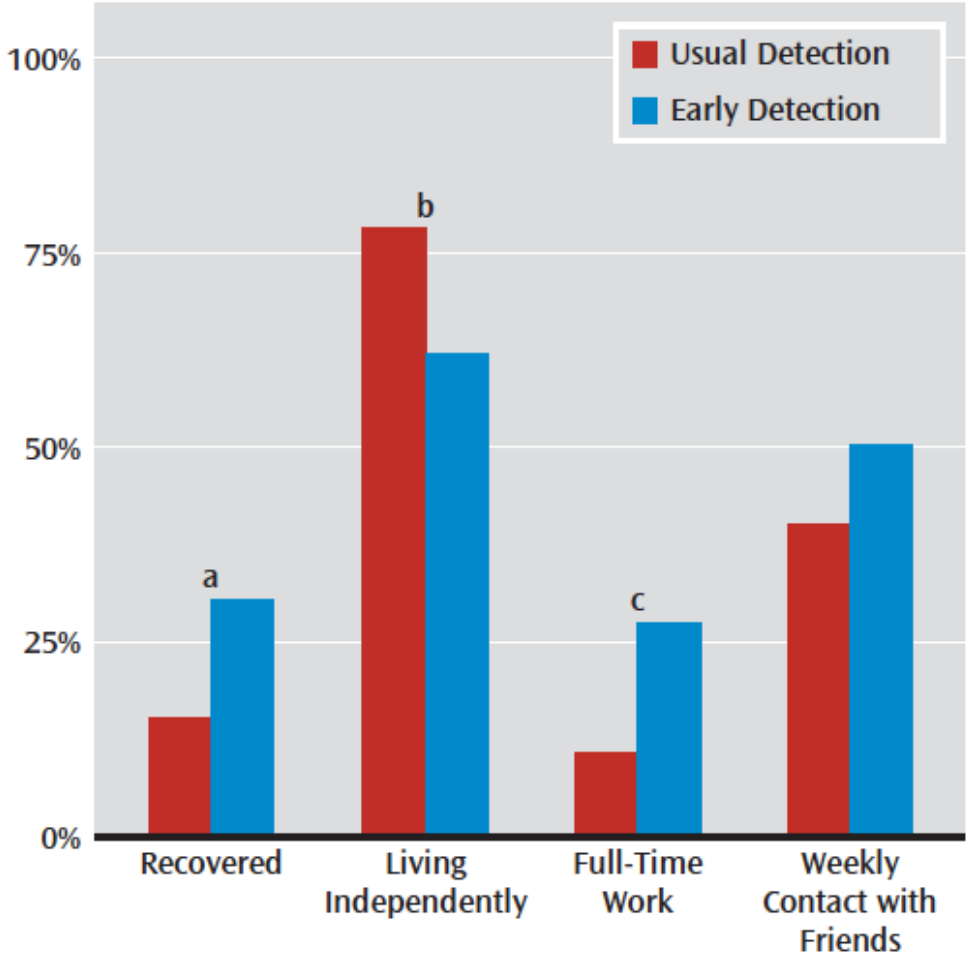
59.1% at 12 months

70.9% at 24 months.

Discontinuation rates similar between antipsychotics.
High maintenance rates in the clozapine group.

Fostering mental health literacy and help-seeking at the onset of the disorder

Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome.

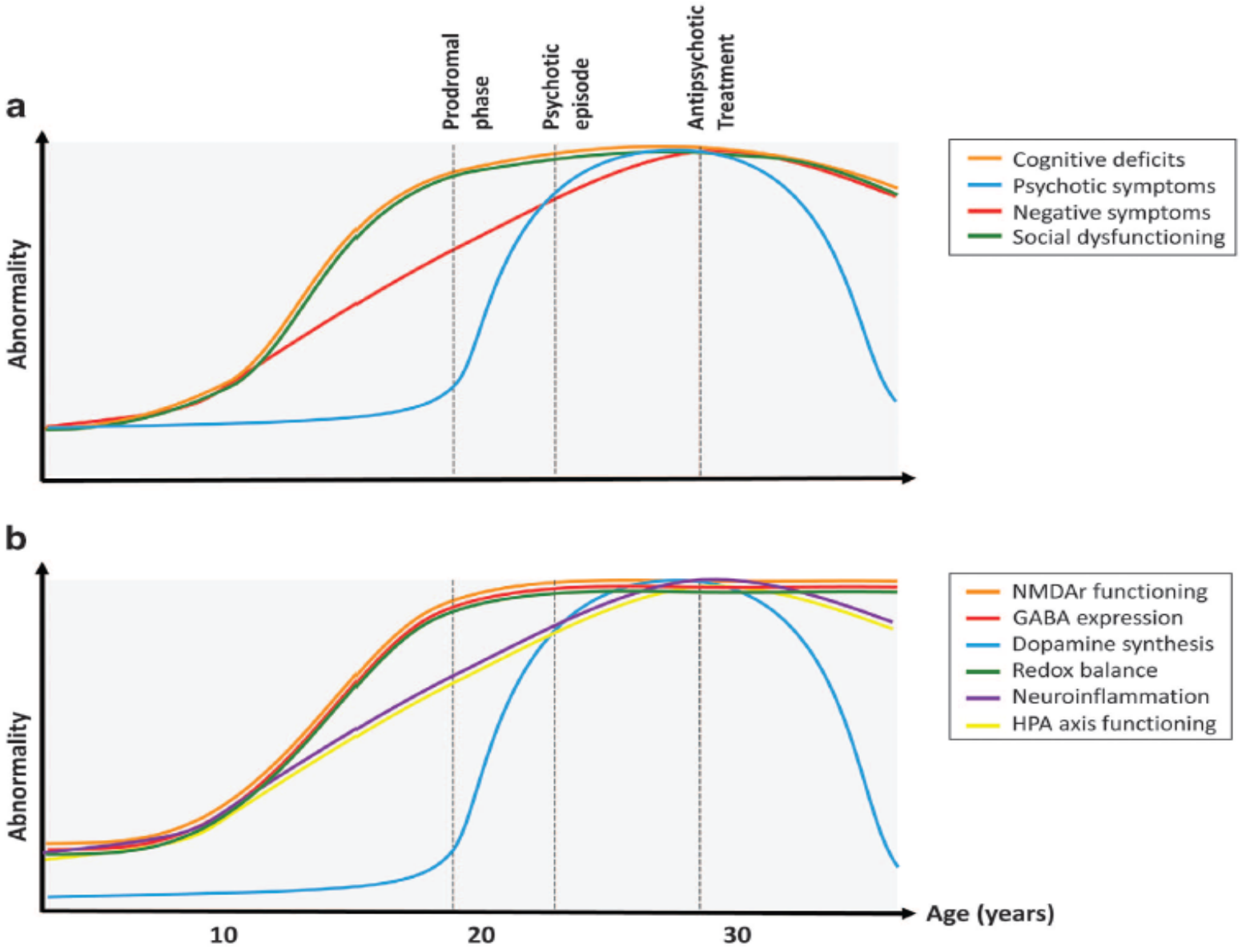


HEGELSTAD, LARSEN, AUESTAD, ET AL. *Am J Psychiatry 169:4, April 2012*

Steps to overcome barriers for pharma development in psychosis

- Development of non-dopaminergic strategies targeting symptomatic dimensions other than positive symptoms.
- Targeting of other mechanisms involved in the pathophysiology of schizophrenia (e.g. inflammation, immunity)
- Repurposing of strategies available for other conditions.
- Study of more homogeneous subgroups
- Translational approaches
- Strategies aimed at modifying neurodevelopmental trajectories and primary and secondary preventative strategies

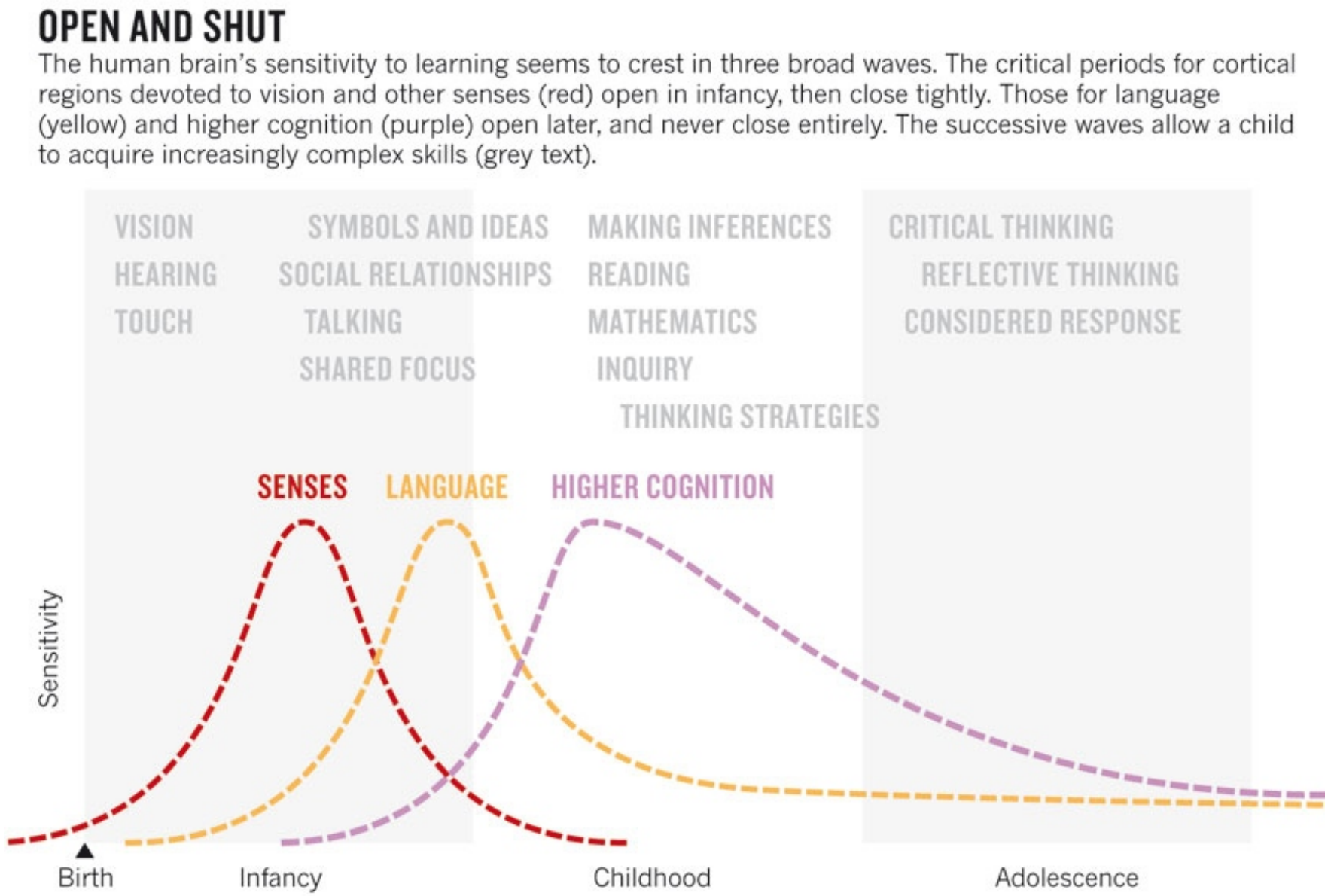
Neurodevelopmental basis of drug development



IE Sommer *et al*

npj Schizophrenia (2016) 16003

Critical periods for intervention



Bardin, Nature 2012.

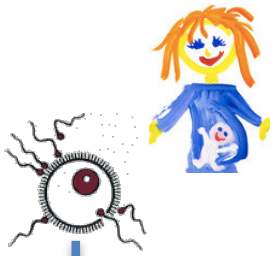
Developmentally sensitive interventions

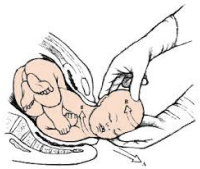
Clinical risk symptoms

Good prenatal care to improve nutrition, reduce maternal infection, substance misuse, stress, obstetric complications

- Screening for cognitive, social and motor deficits
- Prevention of trauma and bullying
- Participation in sports, art, music

- CBT, family therapy
- Medication
- Supported employment for clinical conditions







CONCEPTION | **BIRTH** | **PRE-SCHOOL** | **PRIMARY SCHOOL** | **PUBERTY ADOLESCENCE** | **LATE TEENS AND 20s**

Good perinatal support, good supportive parental care, early mothe r-child interaction support

- Support school function
- Support relationships
- Fami
- ly psychoeducation
- Cognitive enhancement

- Prevention of substance use
- Management of risk taking
- Prosocial activities
- Forming identity

Familial risk for psychosis

Adapted from Seidman and Nortendoft. Schiz Bulletin, 2015

The other effects of antipsychotics

International Journal of Neuropsychopharmacology (2013), **16**, 121–135. © CINP 2011
doi:10.1017/S1461145711001775

Risperidone normalizes increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation

Karina S. MacDowell[1,2,3], Borja García-Bueno[1,2,3], José L. M. Madrigal[1,2,3], Mara Parellada[2,4], Celso Arango[2,4], Juan A. Micó[2,5] and Juan C. Leza[1,2,3]

[1] *Department of Pharmacology, Faculty of Medicine, Complutense University, Madrid, Spain*
[2] *Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)*
[3] *Instituto de Investigación Sanitaria Hospital 12 de Octubre (I+12), Madrid, Spain*
[4] *Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón and Department of Psychiatry, Faculty of Medicine, Complutense University, Madrid, Spain*
[5] *Department of Pharmacology, Faculty of Medicine, University of Cádiz, Spain*

Preventive interventions on adolescent oxidative stress

Juvenile Antioxidant Treatment Prevents Adult Deficits in a Developmental Model of Schizophrenia

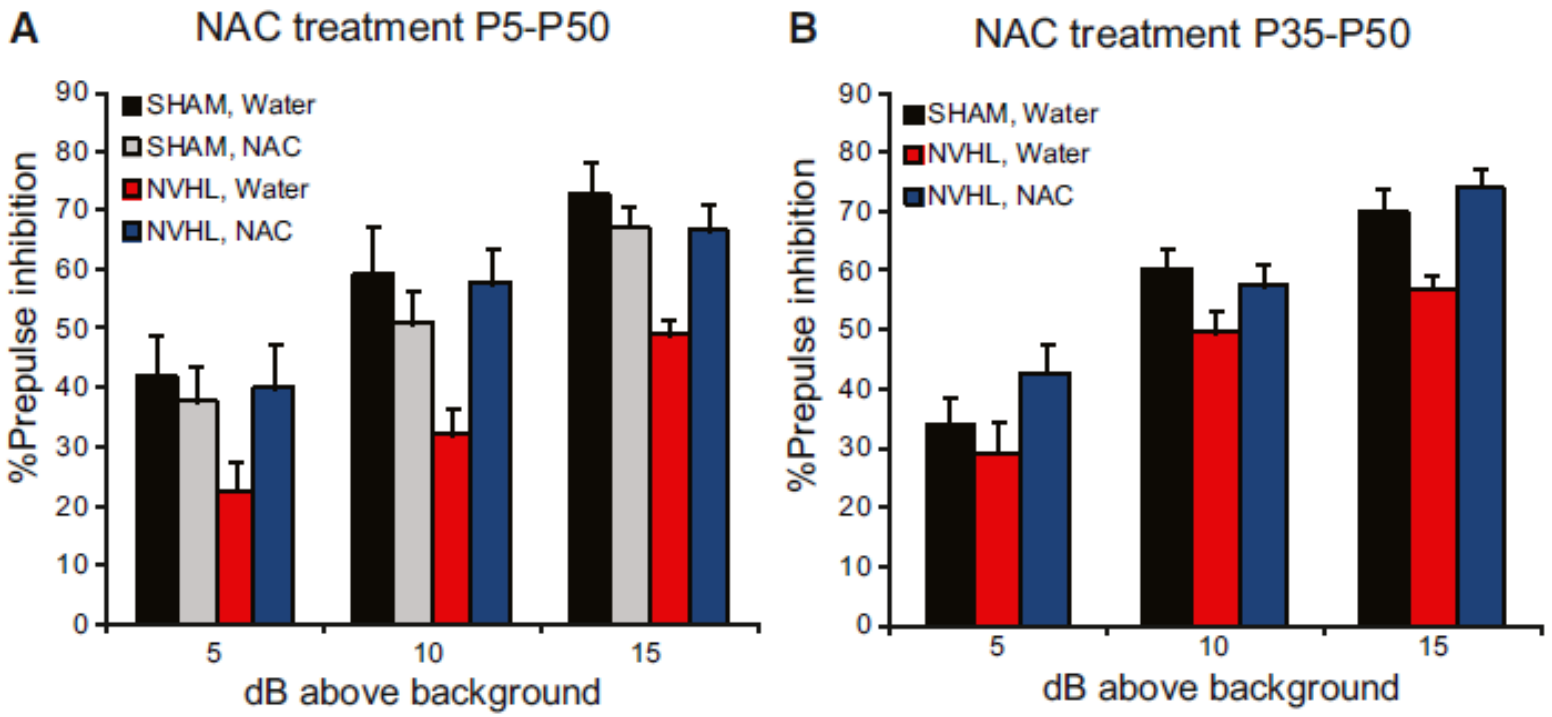
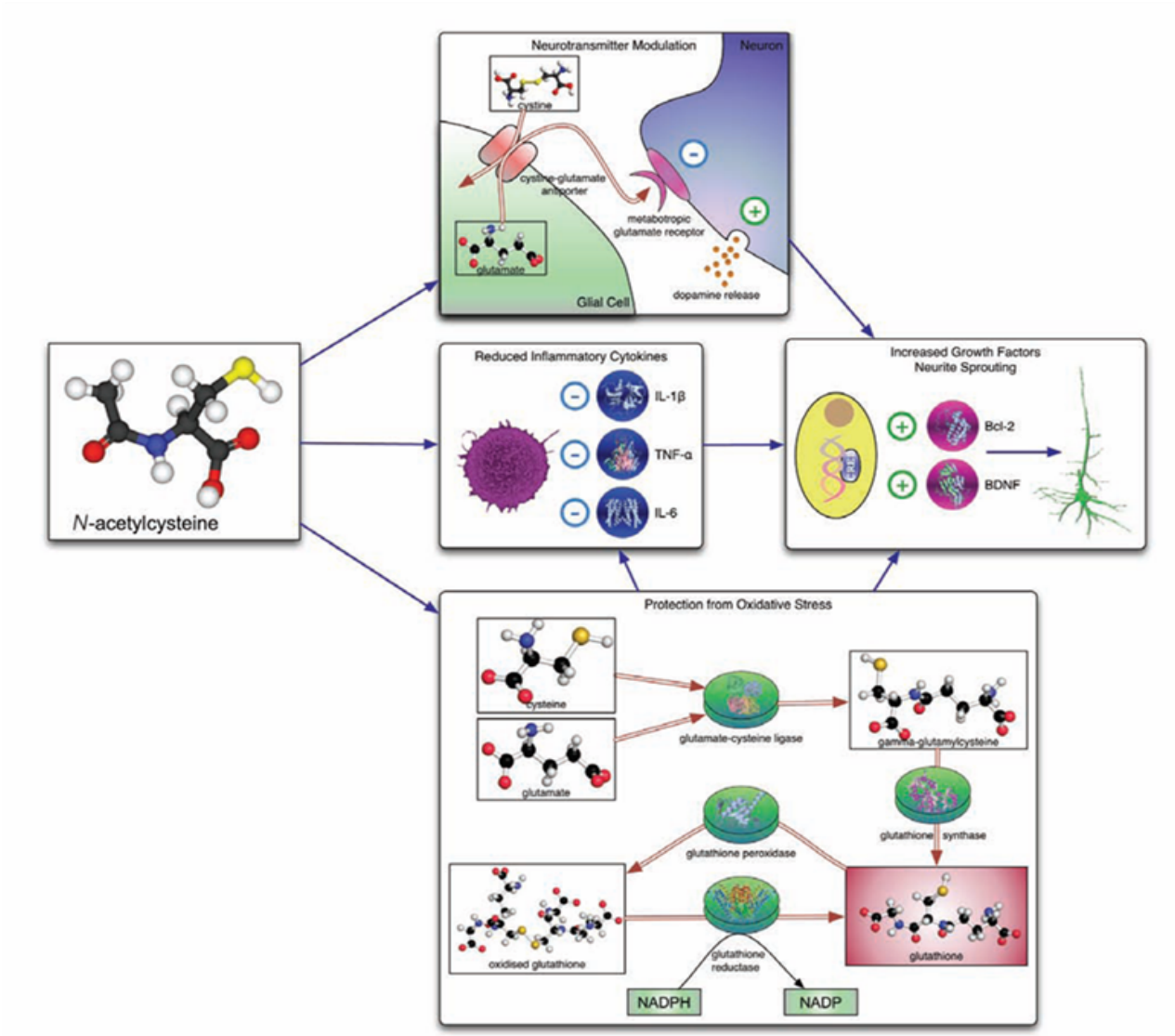


Figure 8. Prepulse Inhibition Deficits Were Rescued with Antioxidant Treatment

Cabungcal et al.,

Neuron *83*, 1073–1084, September 3, 2014

Mechanisms of action of N – Acetylcysteine (NAC)



- Substrate for GSH synthesis
- Scavenge oxidants directly
- Anti-inflammatory properties
- Modulate neurotransmitter pathways (DA and glutamate)

Dean et al; J. Psychiatry Neurosci 2011; 36(2): 78-86

Effect of 48-week N – Acetylcysteine treatment on grey matter loss and oxidative metabolism in early onset first episode psychosis: a randomized, double-blind, placebo-controlled clinical trial

Aim: To evaluate the effect of 48-week of NAC treatment on grey matter change (MRI at baseline and after a year)

Secondary Objectives:

1. Markers of oxidative status (TAOS, NOx, GSH/GSSG, antioxidants).
2. Psychopathology (PANSS, HAM-D, YMRS) and psychosocial functioning (C-GAS, WHO-DAS).
3. Effect on antipsychotic dosage and side effects.

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

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Centro de Investigación Biomédica En Red de Salud Mental

Potential role of minocycline

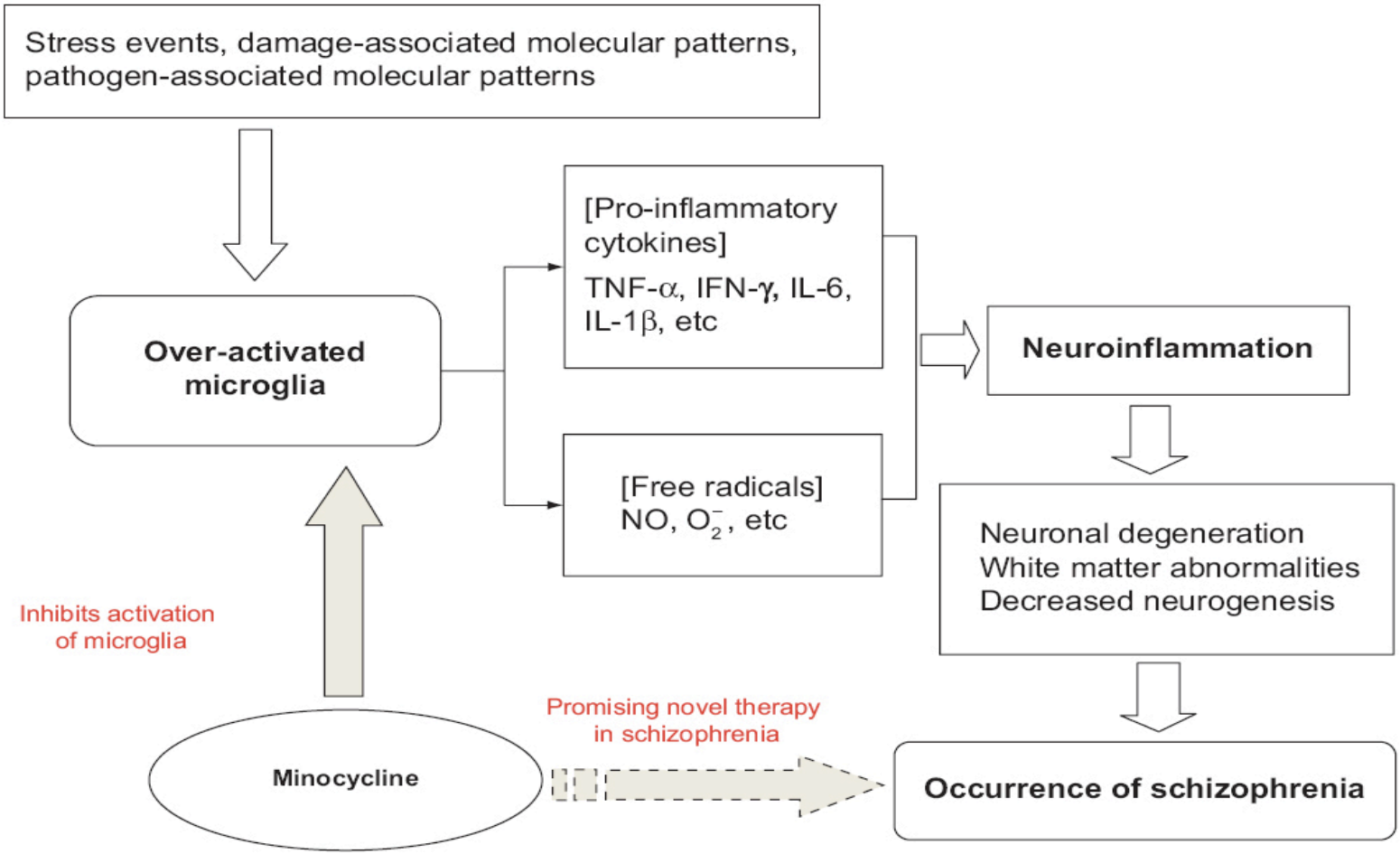


Figure 1 Microglia hypothesis of schizophrenia.
Notes: Stress events, damage-associated molecular patterns and pathogen-associated molecular patterns activate microglia in the central nervous system. Over-activated microglia release pro-inflammatory cytokines and free radicals. These mediators cause neuronal degeneration, white matter abnormalities and decreased neurogenesis, which eventually lead to the occurrence of schizophrenia. The appropriate control of microglial activation may thus be a promising therapeutic target for schizophrenia. Minocycline is a potent inhibitor of microglial activation and has a neuroprotective capacity. These properties of minocycline may be useful for the treatment in schizophrenia.
Abbreviations: IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; NO, nitric oxide; O_2^-, superoxide.

Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

FM Leweke[1,2], D Piomelli[3,4], F Pahlisch[1,3], D Muhl[2,3], CW Gerth[2], C Hoyer[1,2], J Klosterkötter[2], M Hellmich[5] and D Koethe[1,2]

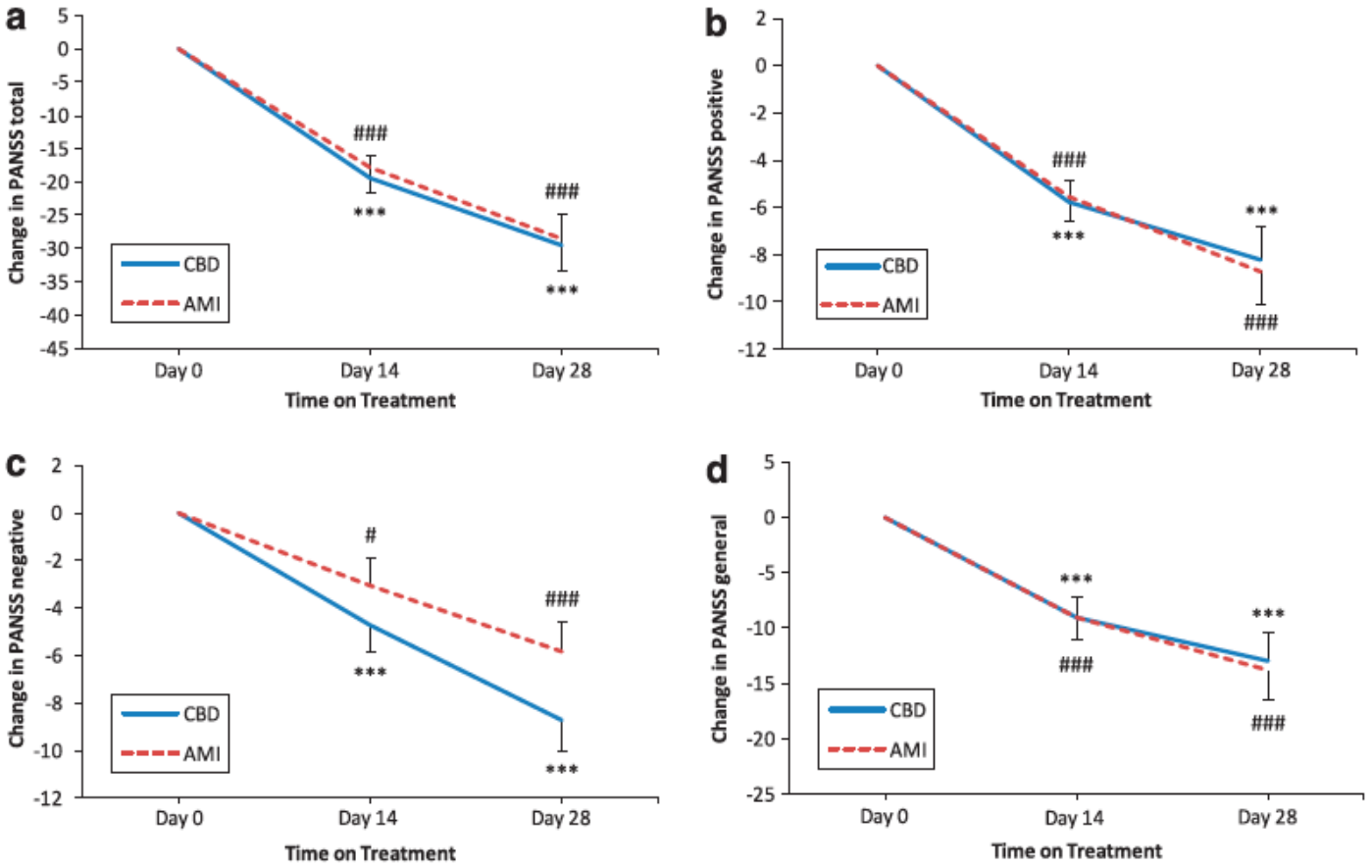
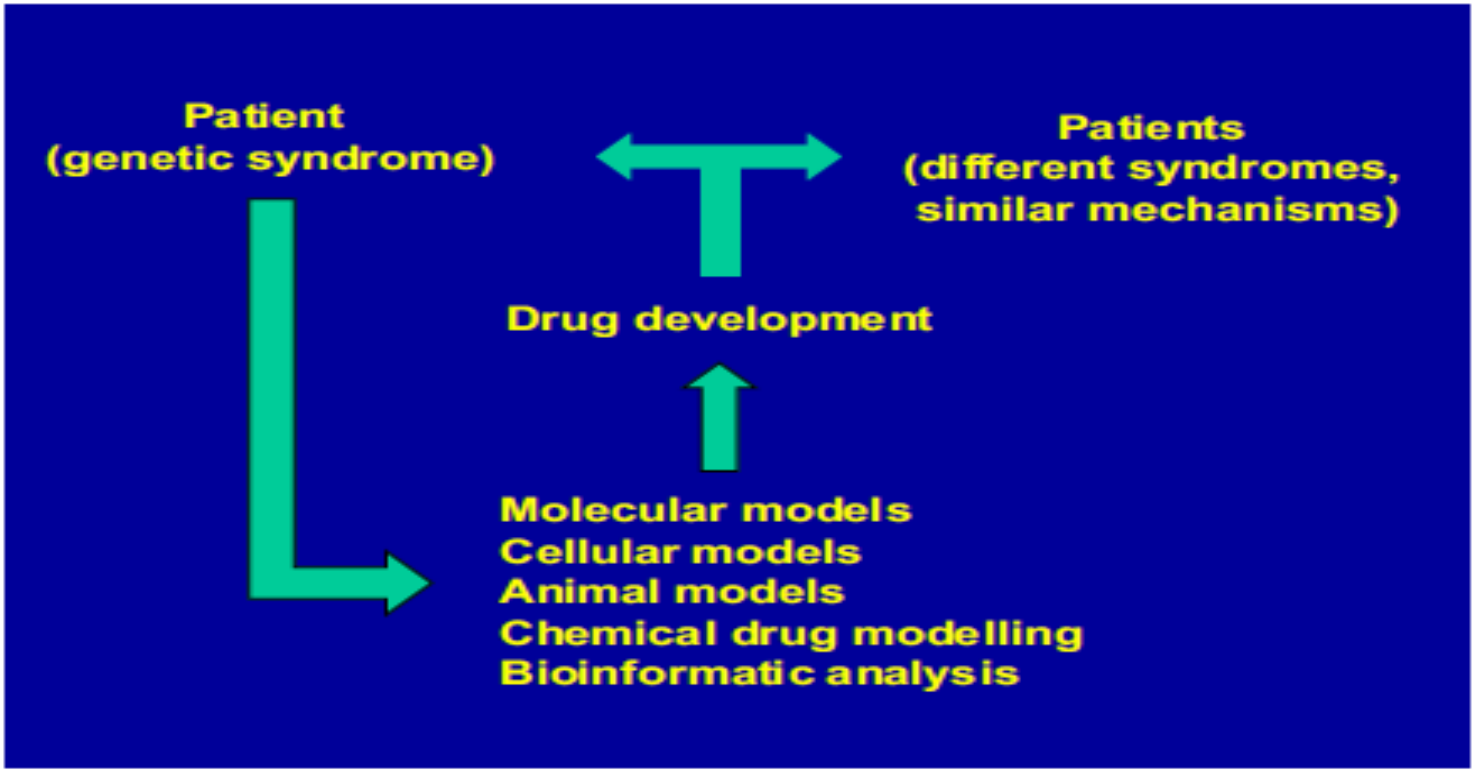


Figure 2 Changes from baseline in Positive and Negative Symptoms Scale (PANSS) scores determined using mixed effects repeated measures model analysis (adjusted for baseline). (**a**) PANSS total score. (**b**) PANSS-positive score. (**c**) PANSS-negative score. (**d**) PANSS general score. Data show predicted means and s.e. at each weak. Statistical significance is calculated between groups ($^{\dagger}P \leqslant 0.05$, $^{\dagger\dagger}P \leqslant 0.01$ and $^{\dagger\dagger\dagger}P \leqslant 0.001$) and vs baseline (that is, 0; *CBD, $^{\#}$AMI; $^{***/\#\#\#}P \leqslant 0.05$, $^{**/\#\#}P \leqslant 0.01$, $^{*/\#}P \leqslant 0.001$).

REVIEW

Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives

Defining more homogeneous subgroups: Study of patients with genetic syndromes



Persico, Arango, et al., European Neuropsychopharmacology (2015)

Psychological Medicine, Page 1 of 5.
doi:10.1017/S0033291716001355

EDITORIAL

Mental disorders of known aetiology and precision medicine in psychiatry: a promising but neglected alliance

D. Fraguas[1]*, C. M. Díaz-Caneja[1], M. W. State[2], M. C. O'Donovan[3], R. E. Gur[4] and C. Arango[1]

- Schizophrenia in genetic syndromes such as 22q11DS might constitute a relatively homogeneous subgroup based on shared aetiological factors.

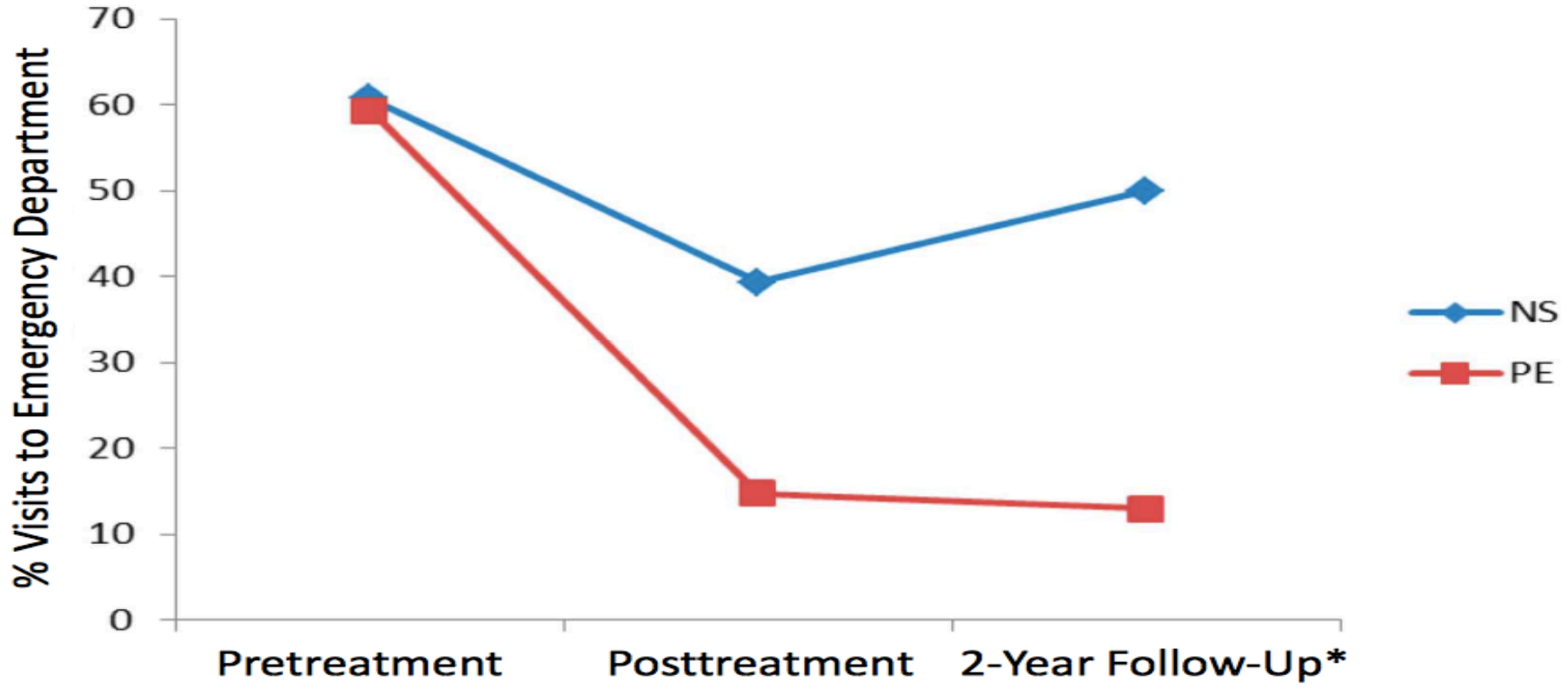
- Prevalence of 22q11DS in patients with schizophrenia is only 0.3%. Although models based on 22q11DS might have a limited direct effect on the whole population of subjects with schizophrenia, they still provide an appropriate scenario for testing specific treatment options and identifying novel therapeutic targets.

Intervention for Adolescents With Early-Onset Psychosis and Their Families: A Randomized Controlled Trial

Ana Calvo, PhD, Miguel Moreno, MD, PhD, Ana Ruiz-Sancho, MD, Marta Rapado-Castro, PhD, Carmen Moreno, MD, PhD, Teresa Sánchez-Gutiérrez, MSc, Celso Arango, MD, PhD, María Mayoral, PhD

	Pretreatment		Posttreatment			
	Mean	SD	Mean	SD	*p* Value	Difference Between PE and NS (*p* Value)
PANSS Positive						.163[b]
PE	14.77	8.22	10.72	14.33	**.022**[a,*]	
NS	16.92	9.10	11.77	3.93	**.006**[a,*]	
PANSS Negative						**.039**[b,*]
PE	16.55	7.27	12.84	7.87	**.013**[a,*]	
NS	17.03	7.42	15.81	6.37	.254[a]	
PANSS Total						.264[b]
PE	61.85	23.37	50.29	19.28	**.026**[a,*]	
NS	69.00	27.71	55.35	17.39	**.009**[a,*,***]	
GAF						.163[b]
PE	64.37	18.79	73.92	14.33	**.039**[a,*]	
NS	58.46	19.02	66.31	15.23	**.034**[a,*]	

Psychoeducational Group Intervention for Adolescents With Psychosis and Their Families: A Two-Year Follow-Up



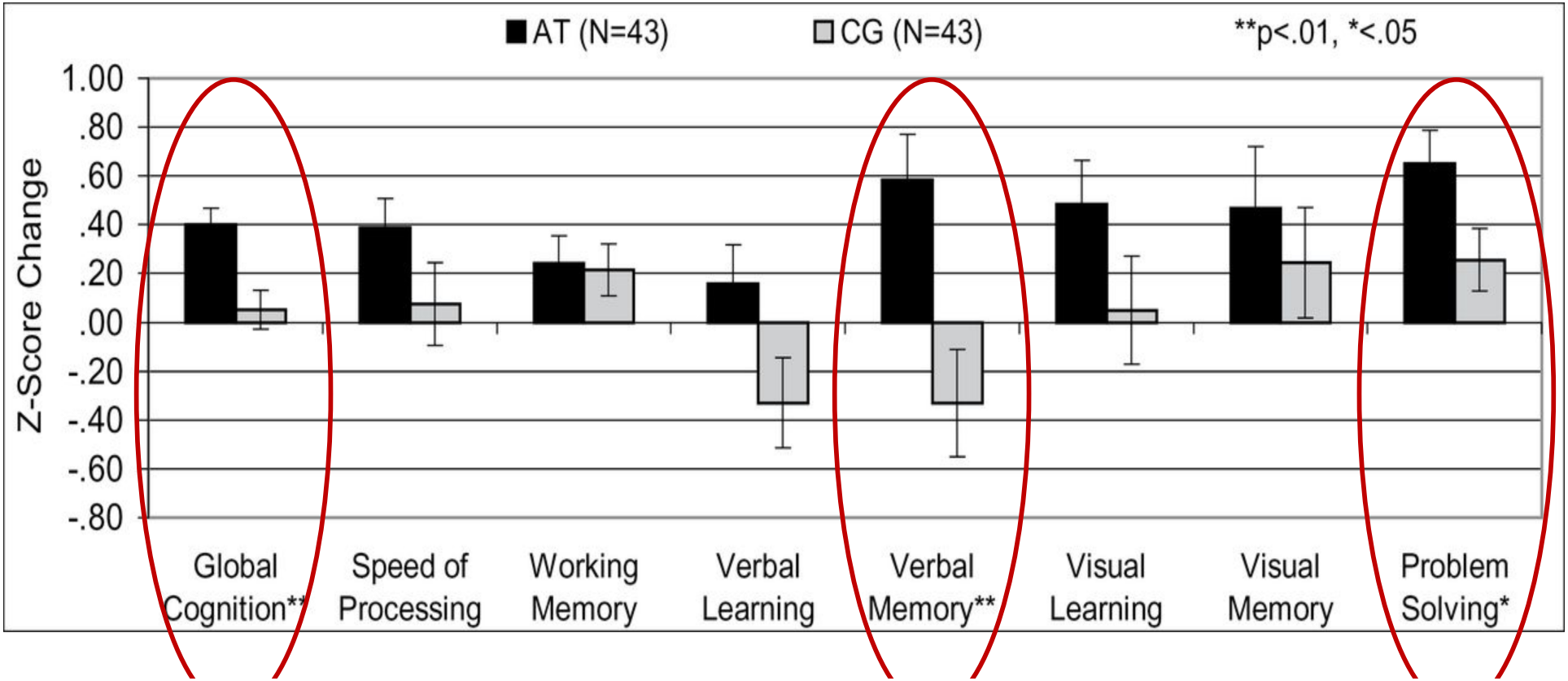
Calvo et al, JAACAP, 2016

Schizophrenia Bulletin vol. 41 no. 1 pp. 250–258, 2015
doi:10.1093/schbul/sbt232
Advance Access publication January 20, 2014

Neuroplasticity-Based Auditory Training Via Laptop Computer Improves Cognition in Young Individuals With Recent Onset Schizophrenia

Melissa Fisher[1,2], Rachel Loewy[1], Cameron Carter[3], Ashley Lee[1], J. Daniel Ragland[3], Tara Niendam[3], Danielle Schlosser[1], Lien Pham[3], Tara Miskovich[3], and Sophia Vinogradov*[,1,2]

86 subjects with recent onset schizophrenia (mean age of 21 years).
40 hours of training or 40 hours of commercial computer games over 8 weeks.

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European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)
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Enpr-EMA NETWORK
The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children.
Enpr-EMA's main objective is to facilitate studies in order to increase availability of medicinal products authorised for use in the paediatric population, by:
fostering high-quality, ethical research on the quality, safety and efficacy of medicines for use in children;
helping with the recruitment of patients for clinical trials;
enabling collaboration between networks and stakeholders;
avoiding unnecessary duplication of studies;
building up scientific and administrative competence at a European level;
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For the science and treatment of disorders of the brain
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RESEARCH & INNOVATION
JUNIOR SCIENTISTS
NEWS
ABOUT
MY ECNP
Search
ECNP / Research & Innovation / ECNP Networks / List of ECNP Networks /
Child and Adolescent Neuropsychopharmacology / ECAPN
ADHD
Anxiety Disorders
Bipolar Disorders
Child and Adolescent Neuropsychopharmacology >
Members
Roadmap
Output
European Child and Adolescent Clinical Psychopharmacology Network (ECAPN)
The European Child & Adolescent Psychopharmacology Network (ECAPN) is a well-established network of clinical Centres of Child and Adolescent Psychiatry (currently 12), based on several EU countries, all of whom are experts in paediatric psychopharmacology.
The ECAPN has been developed as an initiative of the European Child & Adolescent Psychopharmacology Network; its' aims include the identification of unmet needs in child and adolescent psychopharmacology, conducting collaborative scientific studies and clinical trials, and the development of strategies to improve state-of-the-art prescribing of medication to children and adolescents with psychiatric disorders in clinical practice.
The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children, supported by the European Medicine Agency. Enpr-EMA's main objective is to facilitate studies in order to increase availability of

Conclusions

- Psychotic disorders often start previous to adulthood
- Development shapes clinical presentation and biological correlates as well as interventions
- Therapeutic windows
- Detection and early-intervention are key to improve prognosis

cmoreno@hggm.es

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Cognitive reserve as a predictor of two year neuropsychological performance in early onset first-episode schizophrenia

Introduction: The concept of cognitive reserve (CR) has been defined as individual differences in the efficient utilization of brain networks which allow some people to cope better than others with brain pathology. CR has been developed mainly in the field of aging and dementia after it was observed that there appears to be no direct relationship between the degree of brain pathology and the severity of clinical manifestations of this damage. The present study applies the concept of CR to a sample of children and adolescents with a first episode of schizophrenia, aiming to assess the possible influence of CR on neuropsychological performance after two year follow-up, controlling for the influence of clinical psychopathology.

Methods: 35 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder (SSD) and 98 healthy controls (HC) matched for age and gender were included. CR was assessed at baseline, taking into account premorbid IQ, educational–occupational level and leisure activities. Clinical and neuropsychological assessments were completed by all patients at two year follow-up.

Results: The CR proxy was able to predict working memory and attention at two year follow-up. Verbal memory and cognitive flexibility were not predicted by any of the variables included in the regression model. The SSD group obtained lower scores than HC on CR. CR measures correctly classified 79.8% of the sample as being SSD or HC.

Conclusions: Lower scores on CR were observed in SSD than in HC and the CR measure correctly classified a high percentage of the sample into the two groups. CR may predict SSD performance on working memory and attention tasks.

de la Serna et al, 2012

European Neuropsychopharmacology (2011) 21, 621–645

www.elsevier.com/locate/euroneuro

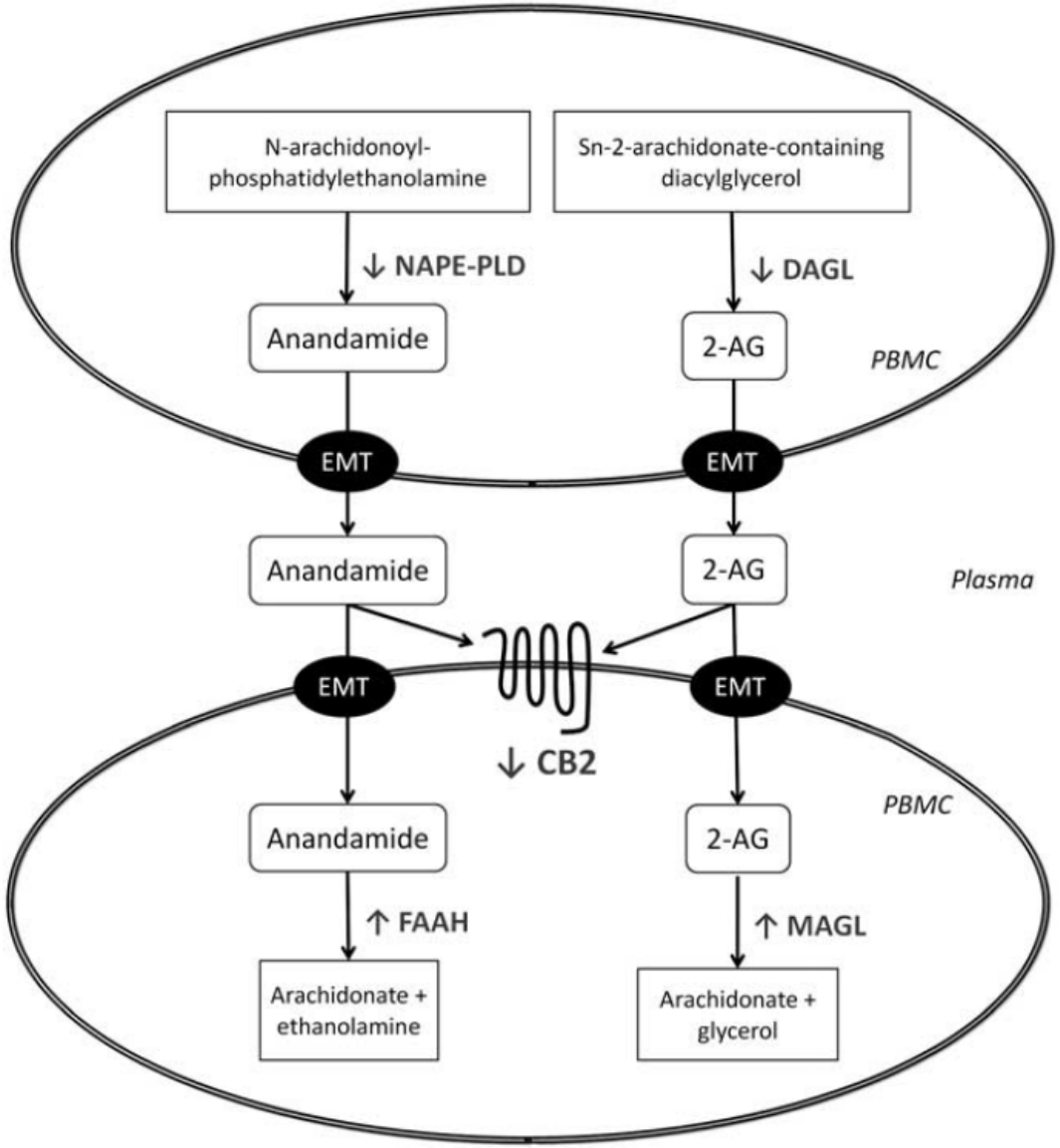
REVIEW

Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: Comprehensive review of prospective head-to-head and placebo-controlled comparisons

Fraguas et al., 2010

Aumento de peso (número de estudios)				
Fármacos	Total estudios	Más aumento con el 1º	No diferencias significativas	Más aumento con el 2º
CLZ vs OLZ	4	0	2	2
OLZ vs RIS	13	7	6	0
OLZ vs QTP	5	4	1	0
OLZ vs ARP	1	1	0	0
RIS vs ARP	1	0	1	0
RIS vs QTP	5	0	5	0
RIS vs CLZ	3	0	3	0
QTP vs ARP	1	0	1	0

Peripheral Endocannabinoid System Dysregulation in First-Episode Psychosis



↑ Higher expression in FEP than in healthy controls

↓ Lower expression in FEP than in healthy controls

M Bioque *et al*

Neuropsychopharmacology (2013) **38,** 2568–2577

Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

FM Leweke[1,2], D Piomelli[3,4], F Pahlisch[1,3], D Muhl[2,3], CW Gerth[2], C Hoyer[1,2], J Klosterkötter[2], M Hellmich[5] and D Koethe[1,2]

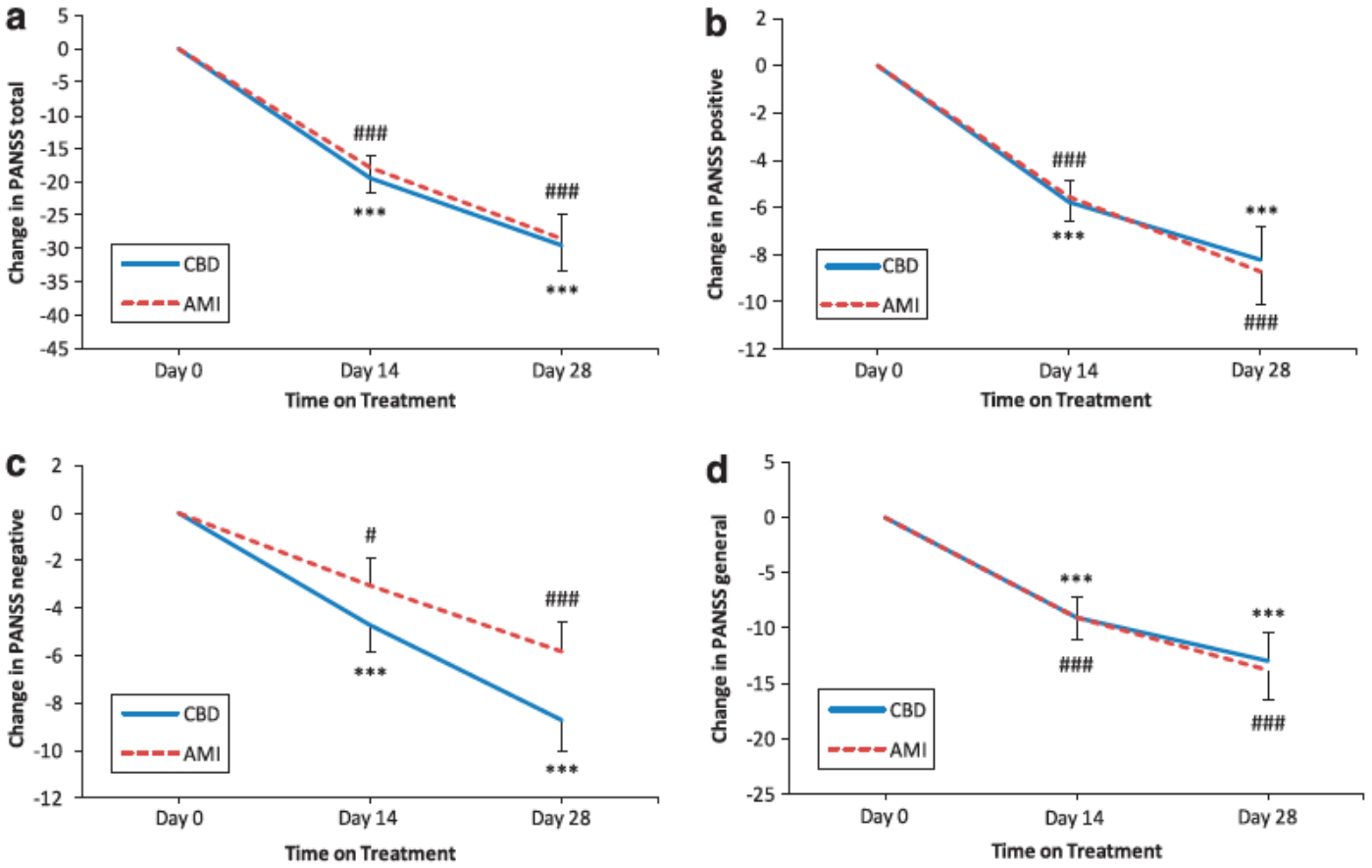


Figure 2 Changes from baseline in Positive and Negative Symptoms Scale (PANSS) scores determined using mixed effects repeated measures model analysis (adjusted for baseline). (**a**) PANSS total score. (**b**) PANSS-positive score. (**c**) PANSS-negative score. (**d**) PANSS general score. Data show predicted means and s.e. at each weak. Statistical significance is calculated between groups ($^{\dagger}P \leqslant 0.05$, $^{\dagger\dagger}P \leqslant 0.01$ and $^{\dagger\dagger\dagger}P \leqslant 0.001$) and vs baseline (that is, 0; *CBD, $^{\#}$AMI; $^{***/\#\#\#}P \leqslant 0.05$, $^{**/\#\#}P \leqslant 0.01$, $^{*/\#}P \leqslant 0.001$).

Psychological Interventions for Psychosis: A Meta-Analysis of Comparative Outcome Studies

TABLE 3. Effect Sizes for Psychological Interventions Compared With Other Interventions Pooled[a] (*continued*)

Comparison	N	Hedges' g	95% CI	Z-Score	Q	I^2 (%)
Social skills training vs. all other therapies						
All symptoms						
All eligible studies	16	0.06	–0.17, 0.28	0.49	45.33*	66.91
Excluding high risk of bias (≥3)	10	0.19*	0.02, 0.36	2.15	8.72	0.00
Excluding low risk of bias (≥2)	4	0.34	–0.02, 0.70	1.87	5.47	45.13
Positive symptoms						
All eligible studies	7	0.09	–0.23, 0.41	0.56	16.44*	63.51
Excluding high risk of bias (≥3)	6	0.09	–0.26, 0.45	0.50	16.41*	69.53
Negative symptoms						
All eligible studies	9	0.27*	0.01, 0.53	2.01	17.33*	53.83
Excluding high risk of bias (≥3)	7	0.32*	0.07, 0.56	2.55	10.25	41.47
Excluding low risk of bias (≥2)	4	0.56*	0.31, 0.82	4.29	1.99	0.00

Acta Psychiatrica Scandinavica

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A controlled randomized treatment study: the effects of a cognitive remediation program on adolescents with early onset psychosis

T. Ueland, B. R. Rund

First published: 10 December 2003 Full publication history

DOI: 10.1046/j.0001-690X.2003.00239.x View/save citation

Objective: To examine if a cognitive remediation program could be a positive supplement to a psychoeducational treatment program for adolescents with early onset psychosis.

Method: Twenty-six subjects, randomly assigned to cognitive remediation (n = 14) or control group (n = 12), were assessed on cognitive, clinical, psychosocial and behavioural measures.

Results: No significant between-group differences in pre- and post-treatment scores were found. This may be due to low statistical power. Exploratory within-group analyses showed that the training group improved on five of the 10 cognitive, and three of the five functioning outcome measures, while the control group improved on three of the cognitive, and one functioning outcome variable.

Conclusion: Based on these results we cannot conclude that the addition of this cognitive remediation program, yields better results than psychoeducation alone. However, within-group analyses indicate that on specific cognitive functions, as well as on some functioning outcome measures, the remediation program may have a positive effect.

ORIGINAL ARTICLE

Role for neonatal D-serine signaling: prevention of physiological and behavioral deficits in adult *Pick1* knockout mice

J Nomura[1,7], H Jaaro-Peled[1], E Lewis[2], P Nuñez-Abades[2,8], F Huppe-Gourgues[2], T Cash-Padgett[1], F Emiliani[1], MA Kondo[1], A Furuya[3], MA Landek-Salgado[1], Y Ayhan[1], A Kamiya[1], T Takumi[3,4], R Huganir[5], M Pletnikov[1,5], P O'Donnell[2,6,9] and A Sawa[1,5]

NMDA glutamate receptors have key roles in brain development, function and dysfunction. Regulatory roles of D-serine in NMDA receptor-mediated synaptic plasticity have been reported. Nonetheless, it is unclear whether and how neonatal deficits in NMDA-receptor-mediated neurotransmission affect adult brain functions and behavior. Likewise, the role of D-serine during development remains elusive. Here we report behavioral and electrophysiological deficits associated with the frontal cortex in *Pick1* knockout mice, which show D-serine deficits in a neonatal- and forebrain-specific manner. The pathological manifestations observed in adult *Pick1* mice are rescued by transient neonatal supplementation of D-serine, but not by a similar treatment in adulthood. These results indicate a role for D-serine in neurodevelopment and provide novel insights on how we interpret data of psychiatric genetics, indicating the involvement of genes associated with D-serine synthesis and degradation, as well as how we consider animal models with neonatal application of NMDA receptor antagonists.

Molecular Psychiatry advance online publication, 26 May 2015; doi:10.1038/mp.2015.61

Antioxidants and antiinflammatory agents in schizophrenia

Aspirin augmentation

Study name	Hedges's g	p-Value	Sample size: aspirin	Sample size: placebo	duration of treatment
Laan et al. 2010	0.37	0.13	33	37	12
Weiser et al. 2012	0.27	0.05	100	100	16
	0.30	0.01			

ES: 0.3, n = 270, 95% CI: 0.06–0.537

NAC augmentation

Study name	Hedges's g	p-Value	Sample size: placebo	Sample size: NAC	duration of treatment
Berk et al. 2008	0.445	0.009	71	69	24
	0.445	0.009			

ES: 0.45, n = 140, 95% CI: 0.112– 0.779

Sommer et al., Schiz Bulletin 2014

Altering the course of schizophrenia: progress and perspectives

Mark J. Millan[1], Annie Andrieux[2], George Bartzokis[3], Kristin Cadenhead[4], Paola Dazzan[5], Paolo Fusar-Poli[5], Jürgen Gallinat[6], Jay Giedd[7], Dennis R. Grayson[8], Markus Heinrichs[9], René Kahn[10], Marie-Odile Krebs[11], Marion Leboyer[12], David Lewis[13], Oscar Marin[14], Philippe Marin[15], Andreas Meyer-Lindenberg[16], Patrick McGorry[17], Philip McGuire[18], Michael J. Owen[19], Paul Patterson[20], Akira Sawa[21], Michael Spedding[22], Peter Uhlhaas[20], Flora Vaccarino[23], Claes Wahlestedt[24] and Daniel Weinberger[25]

Abstract | Despite a lack of recent progress in the treatment of schizophrenia, our understanding of its genetic and environmental causes has considerably improved, and their relationship to aberrant patterns of neurodevelopment has become clearer. This raises the possibility that 'disease-modifying' strategies could alter the course to — and of — this debilitating disorder, rather than simply alleviating symptoms. A promising window for course-altering intervention is around the time of the first episode of psychosis, especially in young people at risk of transition to schizophrenia. Indeed, studies performed in both individuals at risk of developing schizophrenia and rodent models for schizophrenia suggest that pre-diagnostic pharmacotherapy and psychosocial or cognitive-behavioural interventions can delay or moderate the emergence of psychosis. Of particular interest are 'hybrid' strategies that both relieve presenting symptoms and reduce the risk of transition to schizophrenia or another psychiatric disorder. This Review aims to provide a broad-based consideration of the challenges and opportunities inherent in efforts to alter the course of schizophrenia.

NATURE REVIEWS | DRUG DISCOVERY

Nature Reviews Drug Discovery 15, 485-515 (July 2016)

Perinatal Choline Effects on Neonatal Pathophysiology Related to Later Schizophrenia Risk

Randal G. Ross, M.D.

Sharon K. Hunter, Ph.D.

Lizbeth McCarthy, M.D.

Julie Beuler, B.S.

Amanda K. Hutchison, M.D.

Brandie D. Wagner, Ph.D.

Sherry Leonard, Ph.D.

Karen E. Stevens, Ph.D.

Robert Freedman, M.D.

Objective: Deficient cerebral inhibition is a pathophysiological brain deficit related to poor sensory gating and attention in schizophrenia and other disorders. Cerebral inhibition develops perinatally, influenced by genetic and in utero factors. Amniotic choline activates fetal α7-nicotinic acetylcholine receptors and facilitates development of cerebral inhibition. Increasing this activation may protect infants from future illness by promoting normal brain development. The authors investigated the effects of perinatal choline supplementation on the development of cerebral inhibition in human infants.

Method: A randomized placebo-controlled clinical trial of dietary phosphatidylcholine supplementation was conducted with 100 healthy pregnant women, starting in the second trimester. Supplementation to twice normal dietary levels for mother or newborn continued through the third postnatal month. All women received dietary advice regardless of treatment. Infants' electrophysiological recordings of inhibition of the P50 component of the cerebral evoked response to paired sounds were analyzed. The criterion for inhibition was suppression of the amplitude of the second P50 response by at least half, compared with the first response.

Results: No adverse effects of choline were observed in maternal health and delivery, birth, or infant development. At the fifth postnatal week, the P50 response was suppressed in more choline-treated infants (76%) compared with placebo-treated infants (43%) (effect size=0.7). There was no difference at the 13th week. A *CHRNA7* genotype associated with schizophrenia was correlated with diminished P50 inhibition in the placebo-treated infants, but not in the choline-treated infants.

Conclusions: Neonatal developmental delay in inhibition is associated with attentional problems as the child matures. Perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it.

(Am J Psychiatry 2013; 170:290–298)

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Schizophrenia Research 67 (2004) 237–245
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study

John McGrath[a,b,*], Kaisa Saari[c,d], Helinä Hakko[c,d], Jari Jokelainen[c,e,f], Peter Jones[g], Marjo-Riitta Järvelin[e,h], David Chant[a], Matti Isohanni[c]

Table 2
Male cohort members only (n=4616)

		Time at risk (years)	Incidence per 100000 years at risk	RR (95% CI)	Adjusted RR (95% CI)*
Schizophrenia					
Frequency of vitamin D supplements					
None	1	411	243	1 (reference)	1 (reference)
Irregularly	4	17,034	23	0.10 (0.01–0.82)	0.08 (0.01–0.95)
Regularly	46	123,686	38	0.15 (0.02–1.02)	0.12 (0.02–0.90)
Dose of vitamin D					
Less than 2000 IU/day	2	1474	136	1 (reference)	1 (reference)
At least 2000 IU/day	49	139,657	35	0.26 (0.06–1.02)	0.23 (0.06–0.95)

ORIGINAL ARTICLE

Preventive effects of minocycline in a neurodevelopmental two-hit model with relevance to schizophrenia

S Giovanoli[1,2,7], H Engler[3,7], A Engler[3], J Richetto[4,5,6], J Feldon[2], MA Riva[4,5], M Schedlowski[3] and U Meyer[1,2,6]

Maternal immune activation can increase the vulnerability of the offspring to develop neuroimmune and behavioral abnormalities in response to stress in puberty. In offspring of immune-challenged mothers, stress-induced inflammatory processes precede the adult onset of multiple behavioral dysfunctions. Here, we explored whether an early anti-inflammatory intervention during peripubertal stress exposure might prevent the subsequent emergence of adult behavioral pathology. We used an environmental two-hit model in mice, in which prenatal maternal administration of the viral mimetic poly(I:C) served as the first hit, and exposure to sub-chronic unpredictable stress during peripubertal maturation as the second hit. Using this model, we examined the effectiveness of the tetracycline antibiotic minocycline (MINO) given during stress exposure to block stress-induced inflammatory responses and to prevent subsequent behavioral abnormalities. We found that combined exposure to prenatal immune activation and peripubertal stress caused significant deficits in prepulse inhibition and increased sensitivity to the psychotomimetic drugs amphetamine and dizocilpine in adulthood. MINO treatment during stress exposure prevented the emergence of these behavioral dysfunctions. In addition, the pharmacological intervention blocked hippocampal and prefrontal microglia activation and interleukin-1β expression in offspring exposed to prenatal infection and peripubertal stress. Together, these findings demonstrate that presymptomatic MINO treatment can prevent the subsequent emergence of multiple behavioral abnormalities relevant to human neuropsychiatric disorders with onset in early adulthood, including schizophrenia. Our epidemiologically informed two-hit model may thus encourage attempts to explore the use of anti-inflammatory agents in the early course of brain disorders that are characterized by signs of central nervous system inflammation during development.

Translational Psychiatry (2016) **6,** e772; doi:10.1038/tp.2016.38; published online 5 April 2016

Arango et al, Schiz Bull 2015

we now have

evidence of certain things we knew in the past:

-premorbid adjustment is one of the best predictors of prognosis,

-the more subtle and insidious the onset the worse the prognosis

-schizophrenia is a síndrome with very heterogeneous course and outcome after a first psychotic episode

-lack of adherence to antipsychotic medication is the best predictor of relapse after a first psychotic episode.

However, we now know, and did not know then, that

-duration of untreated psychosis is very important for predicting long-term outcome

IQ is one of the best resilience factors

most of the (limited) progressive brain changes revealed by imaging studies take place within 2–5 years after the first psychotic episode (with potential implications for this therapeutic window

-the observed progressive changes may be different at the level of brain developmental trajectories that result in a very similar final brain structure.

-investing in early intervention programs using assertive and integrated treatments is not only beneficial for patients, but also cost-effective. It has been calculated that for each dollar invested in early intervention in psychosis, the economic pay-off is almost 18 dollars.1

-More importantly, we also know that intervening at the time of the first episode may already be too late.

-Five decades of research have also not been able to come up with biomarkers for prognosis and, in fact, the best predictors are still clinical and premorbid markers of development.

Research advances and opportunities for intervention

- Prevalence, age of onset of psychosis, cost of psychosis
- FEP structure and evolution.
- Prognosis based on: DUP, cognition, negative sxs,
- Neurodevelopment
- Neuroimaging
- Inflammation

Delays on implementing treatments for early-onset psychiatric disorders

Epidemiology and Psychiatric Sciences (2012), **21**, 47–57.
doi:10.1017/S2045796011000746

SPECIAL ARTICLE

Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles

G. de Girolamo[1*], J. Dagani[1], R. Purcell[2], A. Cocchi[3] and P. D. McGorry[2]

[1] *IRCCS Fatebenefratelli, Via Pilastroni 4, 25125 Brescia, Italy*
[2] *Department of Psychiatry, Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Australia*
[3] *A.O. Ospedale Niguarda Ca' Granda, Programma 2000, Via Livigno, 3, 20128 Milan, Italy*

Purpose of review. In this review, we provide an update of recent studies on the age of onset (AOO) of the major mental disorders, with a special focus on the availability and use of services providing prevention and early intervention.

Recent findings. The studies reviewed here confirm previous reports on the AOO of the major mental disorders. Although the behaviour disorders and specific anxiety disorders emerge during childhood, most of the high-prevalence disorders (mood, anxiety and substance use) emerge during adolescence and early adulthood, as do the psychotic disorders. Early AOO has been shown to be associated with a longer duration of untreated illness, and poorer clinical and functional outcomes.

Summary. Although the onset of most mental disorders usually occurs during the first three decades of life, effective treatment is typically not initiated until a number of years later. There is increasing evidence that intervention during the early stages of disorder may help reduce the severity and/or the persistence of the initial or primary disorder, and prevent secondary disorders. However, additional research is needed on effective interventions in early-stage cases, as well as on the long-term effects of early intervention, and for an appropriate service design for those with emerging mental disorders. This will mean not only the strengthening and re-engineering of existing systems, but is also crucial the construction of new streams of care for young people in transition to adulthood.

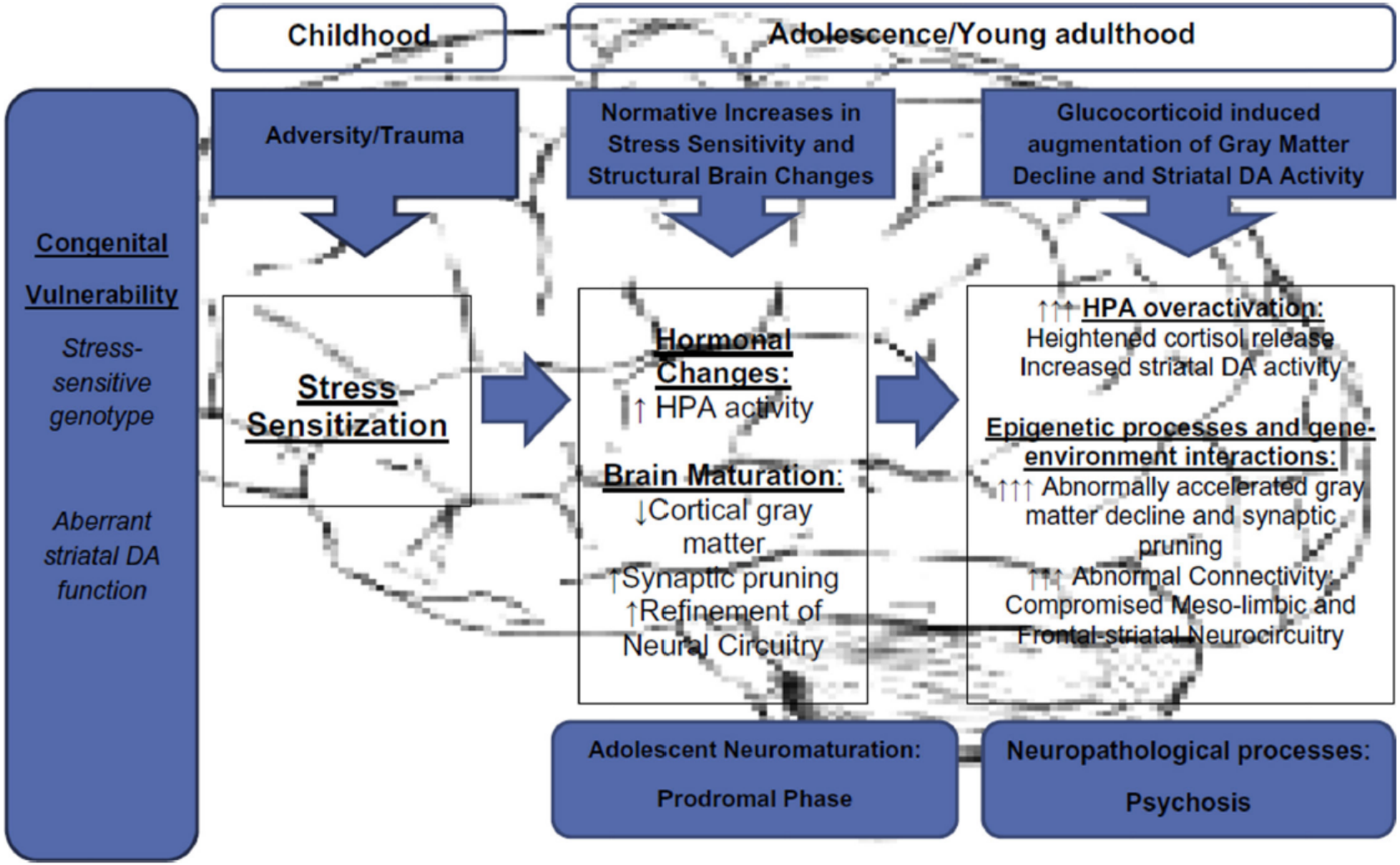
Received 1 July 2011; Revised 4 October 2011; Accepted 28 October 2011

Key words: Age of onset (AOO), early intervention, prevention, DUP, treatment delay.

Initial challenge: diagnosis
Potential psychotic disorders

- Schizophrenia
- Schizophreniform disorder
- Schizoaffective disorder
- Bipolar disorder
- Psychotic depression
- Brief psychotic disorder
- Psychotic disorder due to general medical condition
- Substance-induced psychotic disorder
- Post-psychotic depressive disorder of schizophrenia
- Shared psychotic disorder
- Culture-bound psychotic syndromes
- Atypical psychotic disorders

Childhood and adolescence as phases of major changes



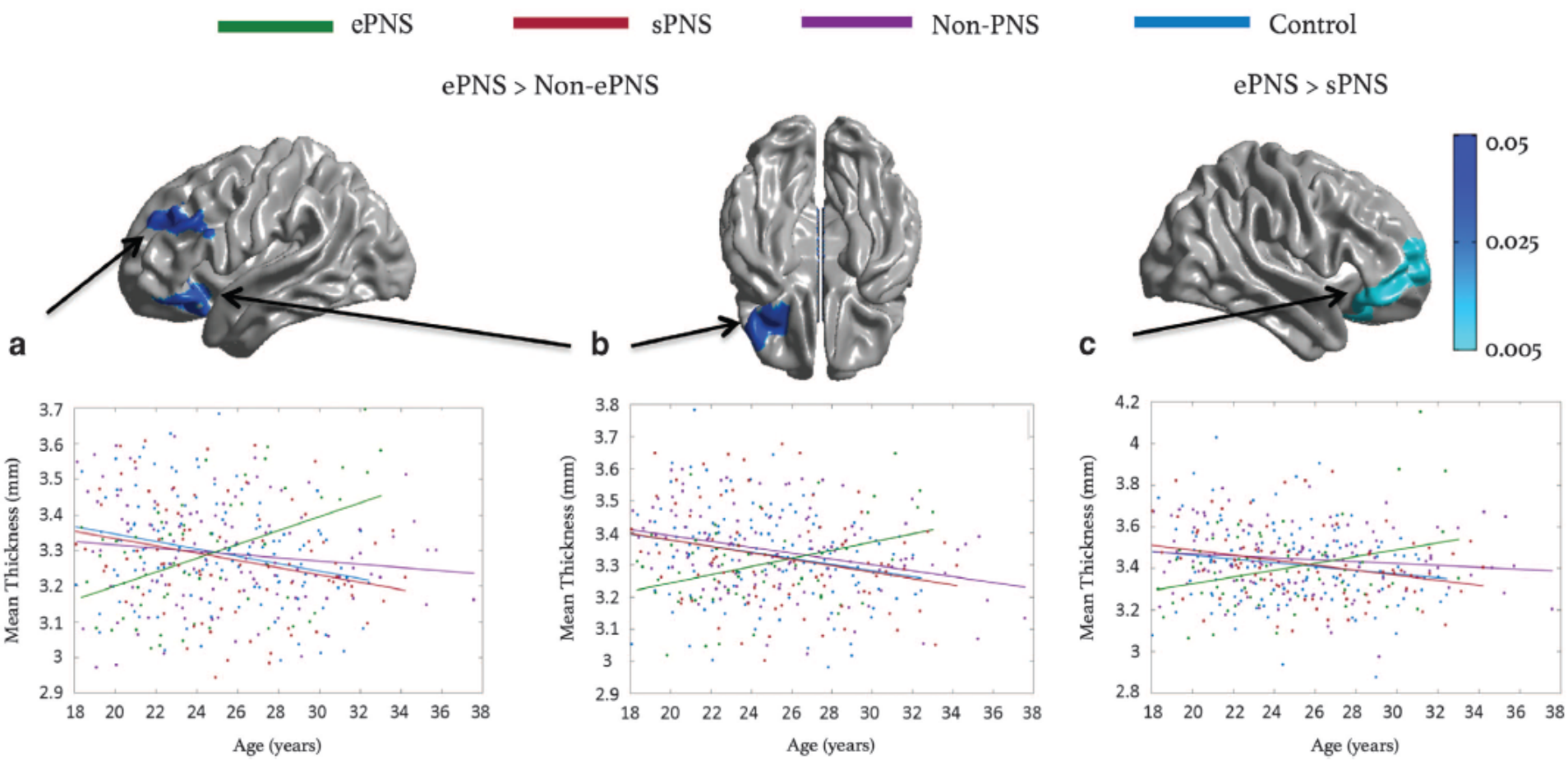
Holtzman et al.

Neuroscience. 2013 September 26; 249: 172–191.

ARTICLE OPEN

Age-related cortical thickness trajectories in first episode psychosis patients presenting with early persistent negative symptoms

Carolina Makowski[1,2,3], Michael Bodnar[2,4], Ashok K Malla[2,4], Ridha Joober[2,4] and Martin Lepage[1,2,4]



Early developmental signs in schizophrenia patients

	Newborn- 3 months	Infancy 3-12 months	Toddler- Pre-schooler 1- 4 years	Elementary school 5-12 years
Neuromotor and Minor Physical Anomalies		Sitting, walking, and standing delays	Potty training delays	Poor coordination and clumsiness, unusual movements
Speech/Language/ Hearing			Delays in speech and in receptive language, hearing impairments	Poor abnormal speech acquisition and quality; abnormal language including echolalia, meaningless laughter
Socioemotional Behavior			Preference for solitary play; fewer joy, more negative affect	More internalizing and externalizing disorders, psychotic symptoms at age 11-14
Cognition			Poorer IQ scores	Poorer IQ scores, declines in IQ scores from 4 to 7 years, poorer performance in other cognitive tasks

Adapted from Liu et al. Schizophrenia Bulletin, 2015.