7th JOINT MEETING
In pediatria e medicina dell'adolescenza
Sobre pediatría y medicina de la adolescencia

21-22-23-24 OTTOBRE 2015 CATANZARO ITALIA

CHILDHOOD ADVERSITIES IN ETÀ INFANTILE

&

RISCHIO PSICOTICO IN ETÀ ADULTA

Pasquale De Fazio
Antonella Bruni

U.O. Psichiatria Universitaria
Università "Magna Graecia"
Catanzaro

Key points

1. Concetto di Psicosi
2. Fattori di rischio
- ✓ prossimali e distali rispetto all'esordio
- ✓ genetici, biologici, ambientali.
3. La nostra ricerca
4. Prospettive future

Le Psicosi sono l'espressione di una grave alterazione dell'equilibrio psichico dell'individuo, con compromissione del cosiddetto esame di realtà.

Schizophrenia Research 146 (2013) 10–16

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Schizophrenia Research

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

Reimagining psychoses: An agnostic approach to diagnosis

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"***Translational mapping across domains***"
R-Doc = Criteri di domini di ricerca
Traslare un comportamento nei sistemi neurorasmettiroriali specifici coinvolti.

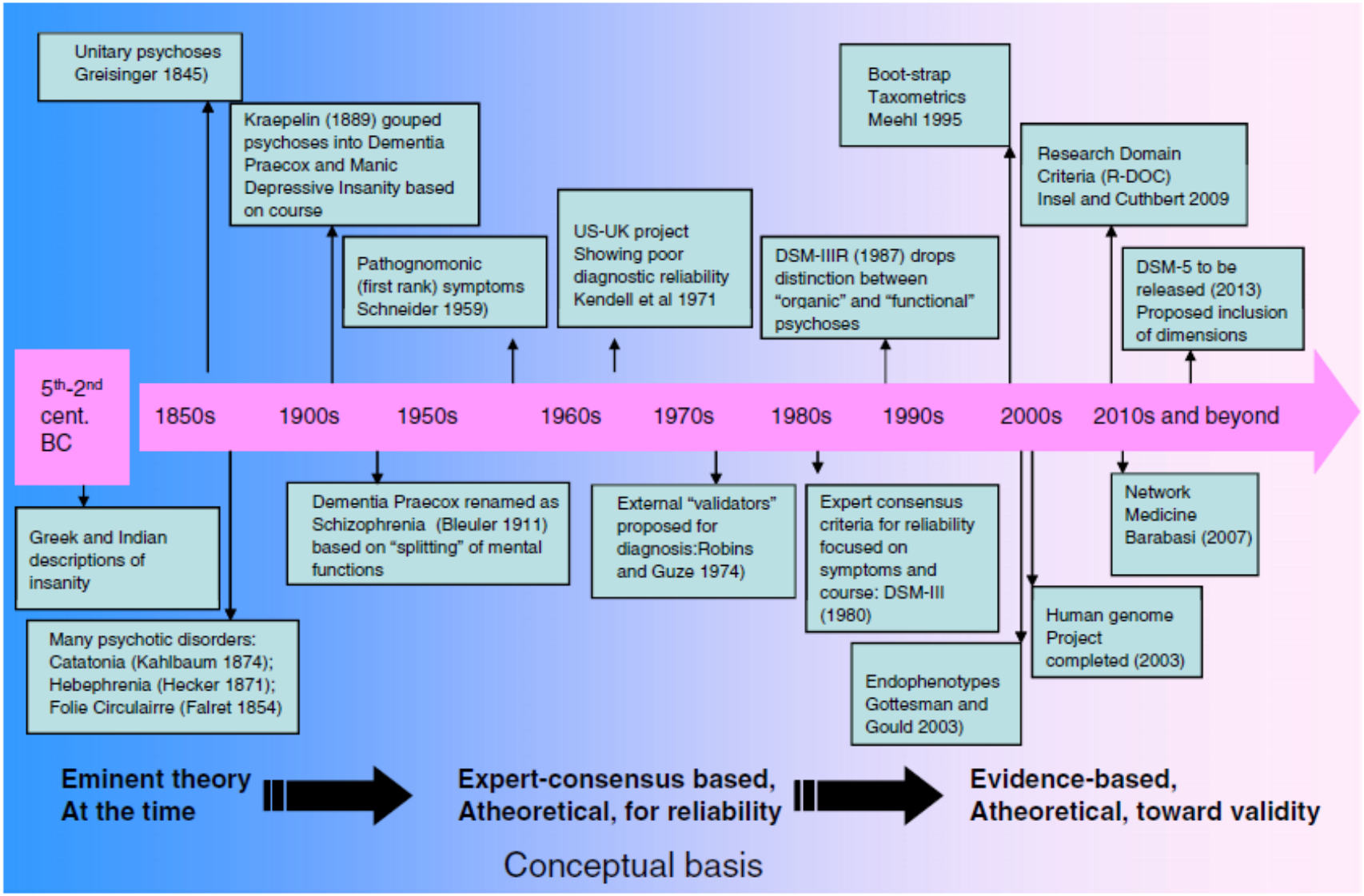


Fig. 1. The history of nosology of schizophrenia.

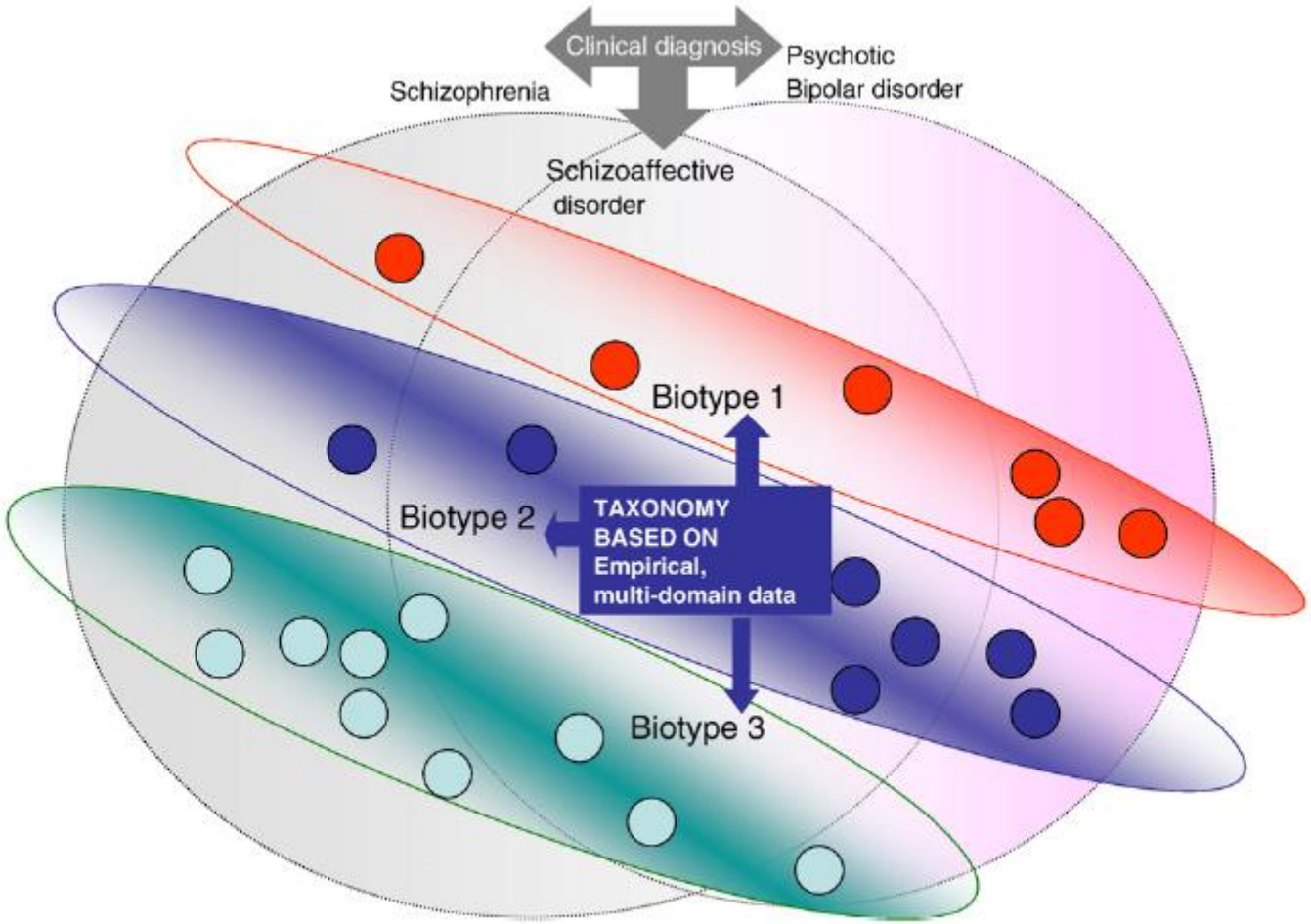
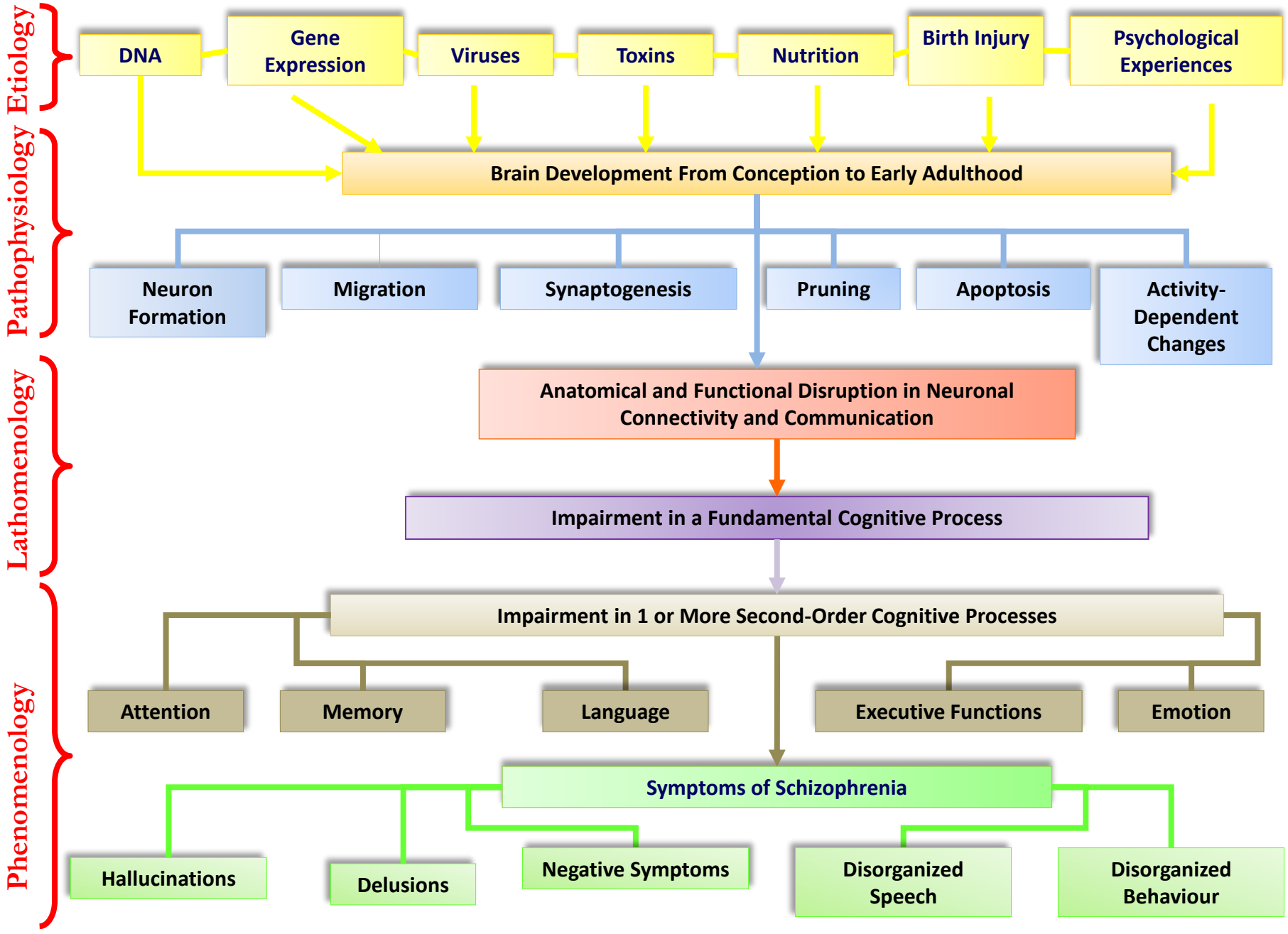
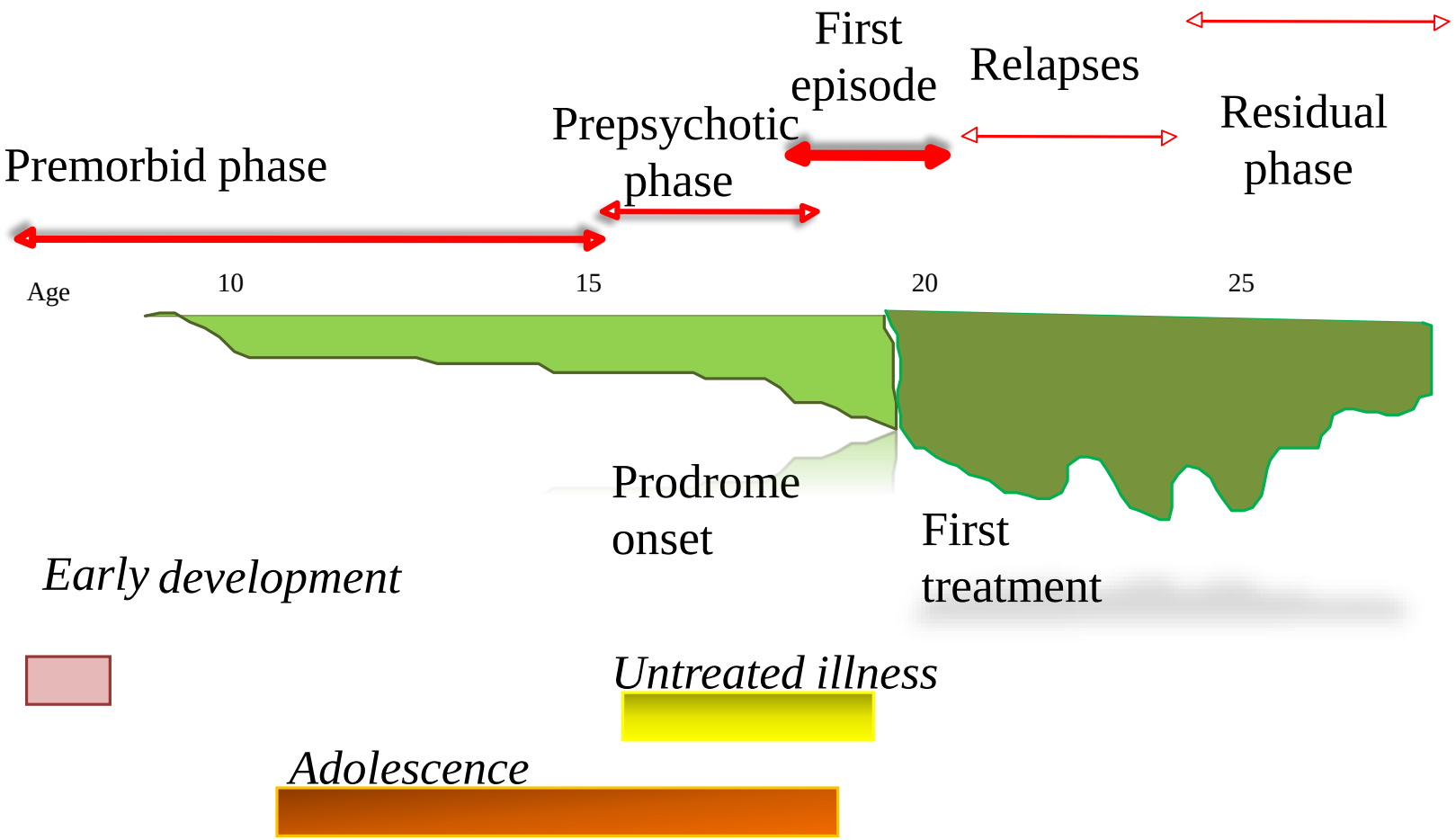


Fig. 2. A proposed approach to disease identification using biomarkers agnostic to conventional diagnostic categories.


Etiology
Pathophysiology
Lathomenology
Phenomenology
DNA
Gene Expression
Viruses
Toxins
Nutrition
Birth Injury
Psychological Experiences
Brain Development From Conception to Early Adulthood
Neuron Formation
Migration
Synaptogenesis
Pruning
Apoptosis
Activity-Dependent Changes
Anatomical and Functional Disruption in Neuronal Connectivity and Communication
Impairment in a Fundamental Cognitive Process
Impairment in 1 or More Second-Order Cognitive Processes
Attention
Memory
Language
Executive Functions
Emotion
Symptoms of Schizophrenia
Hallucinations
Delusions
Negative Symptoms
Disorganized Speech
Disorganized Behaviour

Clinical Course



Keshavan

State of the art

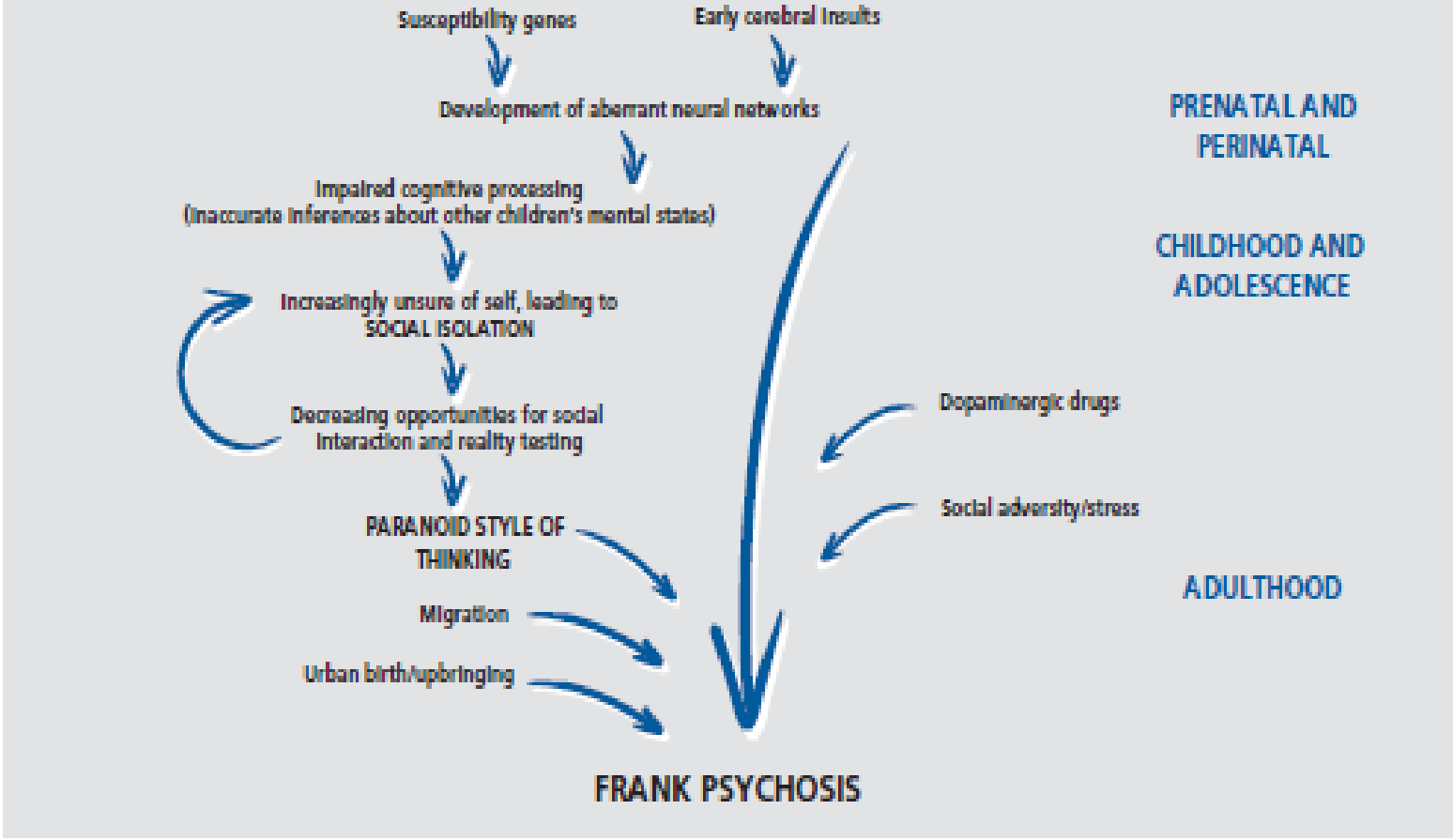


Figure 2. The cascade of increasingly abnormal function that culminates in the onset of full-blown psychosis, including the main risk factors for psychosis over life.[30]

frontiers in
PSYCHIATRY

HYPOTHESIS AND THEORY ARTICLE
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doi: 10.3389/fpsyt.2011.00046

Hodological resonance, hodological variance, psychosis, and schizophrenia: a hypothetical model

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Schizophrenia is a disorder with a large number of clinical, neurobiological, and cognitive manifestations, none of which is invariably present. However it appears to be a single nosological entity. This article considers the likely characteristics of a pathology capable of such diverse consequences. It is argued that both deficit and psychotic symptoms can be manifestations of a single pathology. A general model of psychosis is proposed in which the informational sensitivity or responsivity of a network ("hodological resonance") becomes so high that it activates spontaneously, to produce a hallucination, if it is in sensory cortex, or another psychotic symptom if it is elsewhere. It is argued that this can come about because of high levels of modulation such as those assumed present in affective psychosis, or because of high levels of baseline resonance, such as those expected in deafferentation syndromes associated with hallucinations, for example, Charles Bonnet. It is further proposed that schizophrenia results from a process (probably neurodevelopmental) causing widespread increases of variance in baseline resonance; consequently some networks possess high baseline resonance and become susceptible to spontaneous activation. Deficit symptoms might result from the presence of networks with increased activation thresholds. This hodological variance model is explored in terms of schizo-affective disorder, transient psychotic symptoms, diathesis-stress models, mechanisms of antipsychotic pharmacotherapy and persistence of genes predisposing to schizophrenia. Predictions and implications of the model are discussed. In particular it suggests a need for more research into psychotic states and for more single case-based studies in schizophrenia.

Modello “a Clessidra” dei fattori di Rischio

Un modello secondo il quale una serie di fattori eziologici confluisce nella parte superiore combinandosi e convergendo in una patologia comune. Successivamente si diversificano in manifestazioni fenotipiche distinte.

ETEROGENEITA’ TRA FATTORI COINVOLTI NELLA SUSCETTIBILITA’ VS FATTORI COINVOLTI NELLE MANIFESTAZIONI CLINICHE DEL DISTURBO

Schizophrenia Bulletin vol. 31 no. 3 pp. 672–696, 2005
doi:10.1093/schbul/sbi034
Advance Access publication on July 14, 2005

Structural Brain Imaging Evidence for Multiple Pathological Processes at Different Stages of Brain Development in Schizophrenia

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Key words: schizophrenia/longitudinal/neurodevelopment/neurodegeneration/brain changes/psychosis/prodrome/cognition/neuroimaging/stress/HPA axis

Introduction

It is now generally accepted that schizophrenia is associated with structural brain abnormalities, with the most consistent findings being enlarged lateral ventricles and reduced medial temporal and prefrontal lobe volumes.[1–3] While such abnormalities are likely to be subtle,[4] the nature, timing, and course of the associated neurobiological changes have proven difficult to elucidate.[5–6] The dominant "neurodevelopmental" paradigm, positing that these structural brain changes are caused by early prenatal or perinatal nonprogressive insults,[7–11] has been supported by longitudinal magnetic resonance imaging (MRI) studies that have found no progressive structural brain changes in advanced stages of illness (see below and table 1). This model has however come under increased scrutiny in light of more recent longitudinal MRI studies that have found progressive structural brain changes occurring from the earliest phases of the illness.[12–18] The

Modificazioni precoci
(alterazioni del neurosviluppo)

✓ riduzione di volume delle strutture del lobo temporale,
✓ dilatazione ventricolare,
✓ riduzione delle circonvoluzioni corticali,
✓perdita della asimmetria fisiologica,in assenza di effetti correlati all'età e di elementi neuropatologici degenerativi (ad esempio inclusioni citoplasmatiche, perdita neuronale, gliosi).

Studi di neuroimaging al primo episodio:

Numerosi studi suggeriscono che le anomalie strutturali precedono la comparsa dei primi sintomi e consistono nelle alterazioni a carico delle strutture temporali e frontali e delle loro connessioni con le strutture limbiche; le stesse che si osservano in forma più grave nei pazienti con forme croniche di malattia.

Studi di neuroimaging in pazienti ad alto rischio: (High Risk)

riduzione del volume del complesso amigdala-ippocampo in soggetti a rischio rispetto ai controlli sani e vs soggetti già al primo episodio di Schizofrenia. Soggetti ad alto rischio= con almeno 2 membri della famiglia con patologia psicotica accertata.

ORIGINAL ARTICLE

Regionally Specific Disturbance of Dorsolateral Prefrontal–Hippocampal Functional Connectivity in Schizophrenia

Andreas S. Meyer-Lindenberg, MD, PhD; Rosanna K. Olsen; Philip D. Kohn; Timothy Brown; Michael F. Egan, MD; Daniel R. Weinberger, MD; Karen Faith Berman, MD

Background: Two brain regions often implicated in schizophrenia are the dorsolateral prefrontal cortex (DLPFC) and the hippocampal formation (HF). It has been hypothesized that the pathophysiology of the disorder might involve an alteration of functional interactions between medial temporal and prefrontal areas.

Methods: We used neuroimaging data acquired during a working memory challenge and a sensorimotor control task in 22 medication-free schizophrenic patients and 22 performance-, age-, and sex-matched healthy subjects to investigate "functional connectivity" between HF and DLPFC in schizophrenia. The HF blood flow, measured with positron emission tomography, was assessed within a probabilistic template. Brain areas whose activity was positively or negatively coupled to HF were identified using voxelwise analysis of covariance throughout the entire brain and analyzed using a random effects model.

Results: During working memory, patients showed reduced activation of the right DLPFC and left cerebellum. In both groups, inverse correlations were observed between the HF and the contralateral DLPFC and inferior parietal lobule. While these did not differ between diagnostic groups during the control task, the working memory challenge revealed a specific abnormality in DLPFC-HF functional connectivity—while the right DLPFC was significantly coupled to the left HF in both groups during the control task, this correlation was not seen in healthy subjects during working memory but persisted undiminished in patients, resulting in a significant task-by-group interaction.

Conclusions: Our results suggest a regionally specific alteration of HF-DLPFC functional connectivity in schizophrenia that manifests as an unmodulated persistence of an HF-DLPFC linkage during working memory activation. Thus, a mechanism by which HF dysfunction may manifest in schizophrenia is by inappropriate reciprocal modulatory interaction with the DLPFC.

Arch Gen Psychiatry. 2005;62:379-386

Table 1. Demographics, Performance, and Symptoms*

	Male/ Female, No.	Age, y	Education, y	Right-Handed, No. (%)	Accuracy, %†		PANSS		
					0-Back Task	2-Back Task	Positive Rating	Negative Rating	Total
Controls (n = 22)	16/6	31.8 ± 7.8	16.5 ± 2.5	21 (95)	98.3 ± 3.9	68.8 ± 10.9	...	...	...
Patients (n = 22)	16/6	30.6 ± 6.5	13.5 ± 2.7	21 (95)	95.3 ± 12.3	67.8 ± 15.8	16.35 ± 6.3	17.3 ± 6.3	65.2 ± 15.8
t Test	...	*P* = .60	*P* < .001	*P* > .99	*P* = .30	*P* = .85	...	...	...

Abbreviation: PANSS, Positive and Negative Syndrome Scale.
*Unless otherwise indicated, values are mean ± SD.
†Chance = 25%.

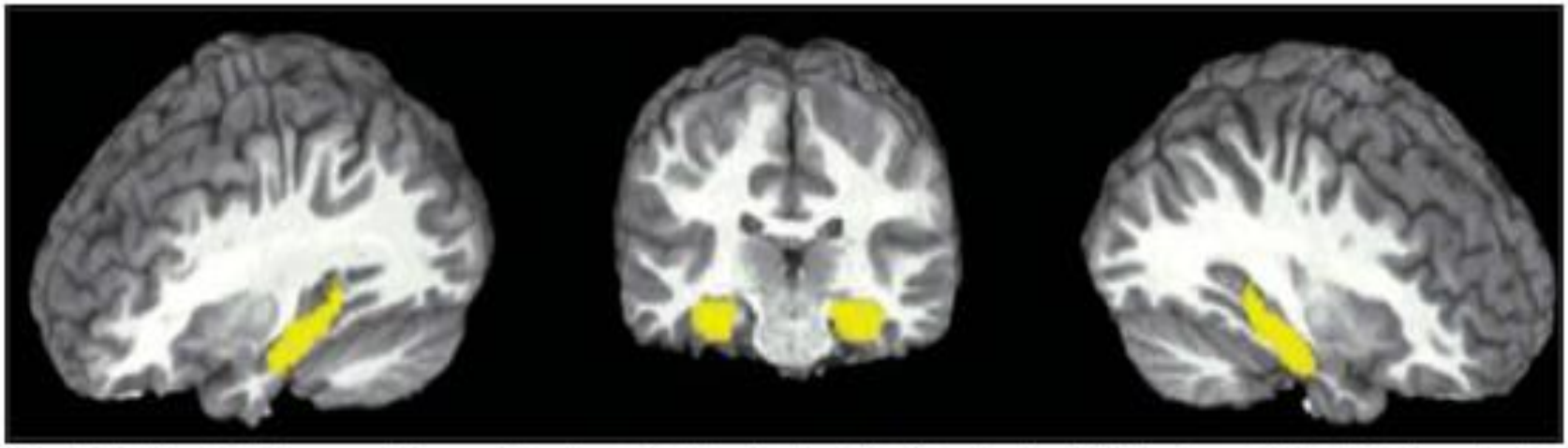

Figure 1. The left and right hippocampal volumes of interest, as derived from the International Consortium for Brain Mapping probabilistic brain atlas, rendered on 3-dimensional reconstructions of a representative brain.

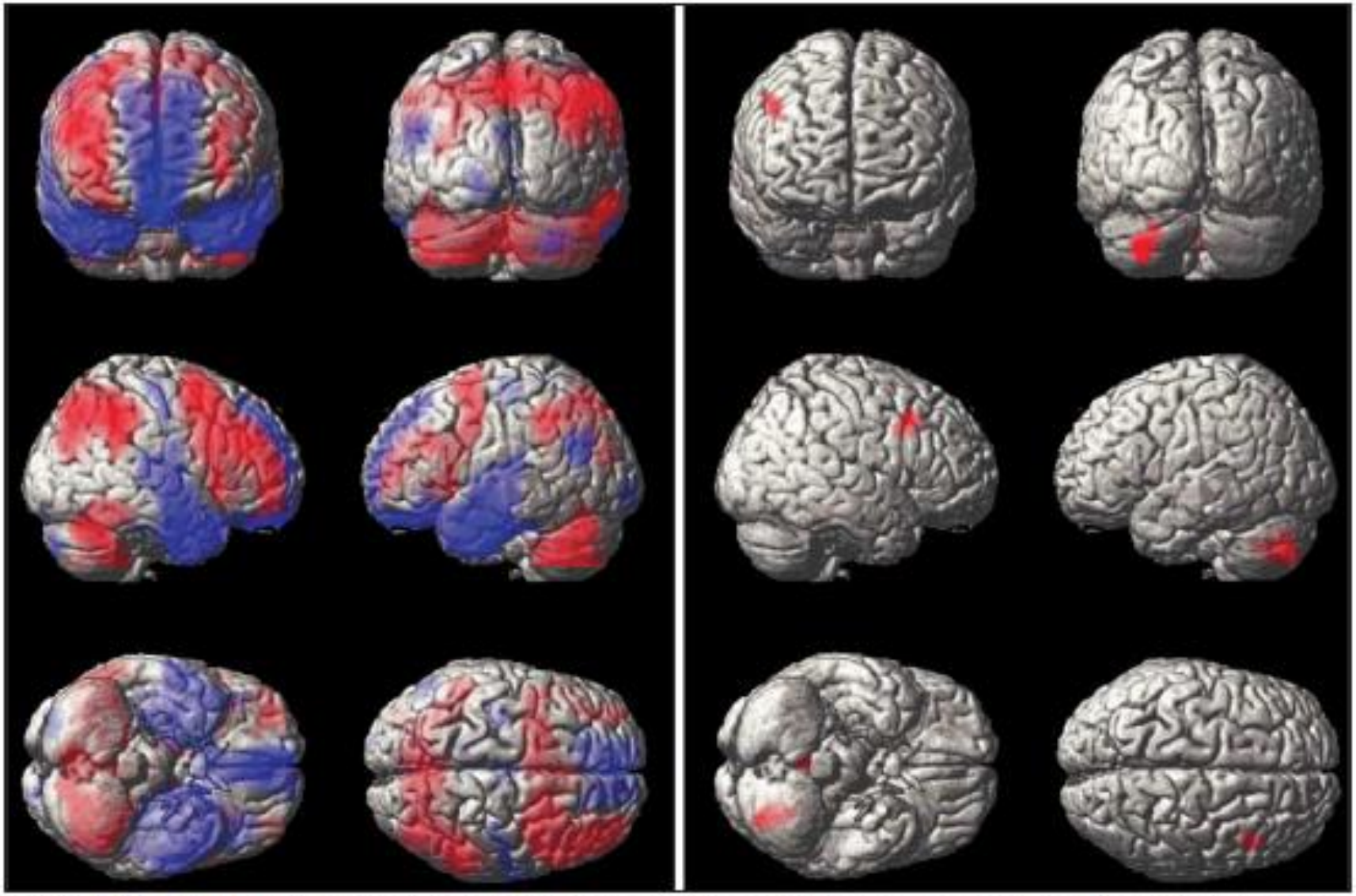

Figure 2. Left, Main effect of task-significant activations (red) and deactivations (blue), comparing the working memory condition (2-back) with its sensorimotor control (0-back). Right, Task × group interaction analysis of regional cerebral blood flow data, showing regions where healthy subjects activate significantly more (red) or less (blue) than patients. Highlighted voxels are significant at $P \leq .01$ ($P \leq .05$ corrected for multiple comparisons).

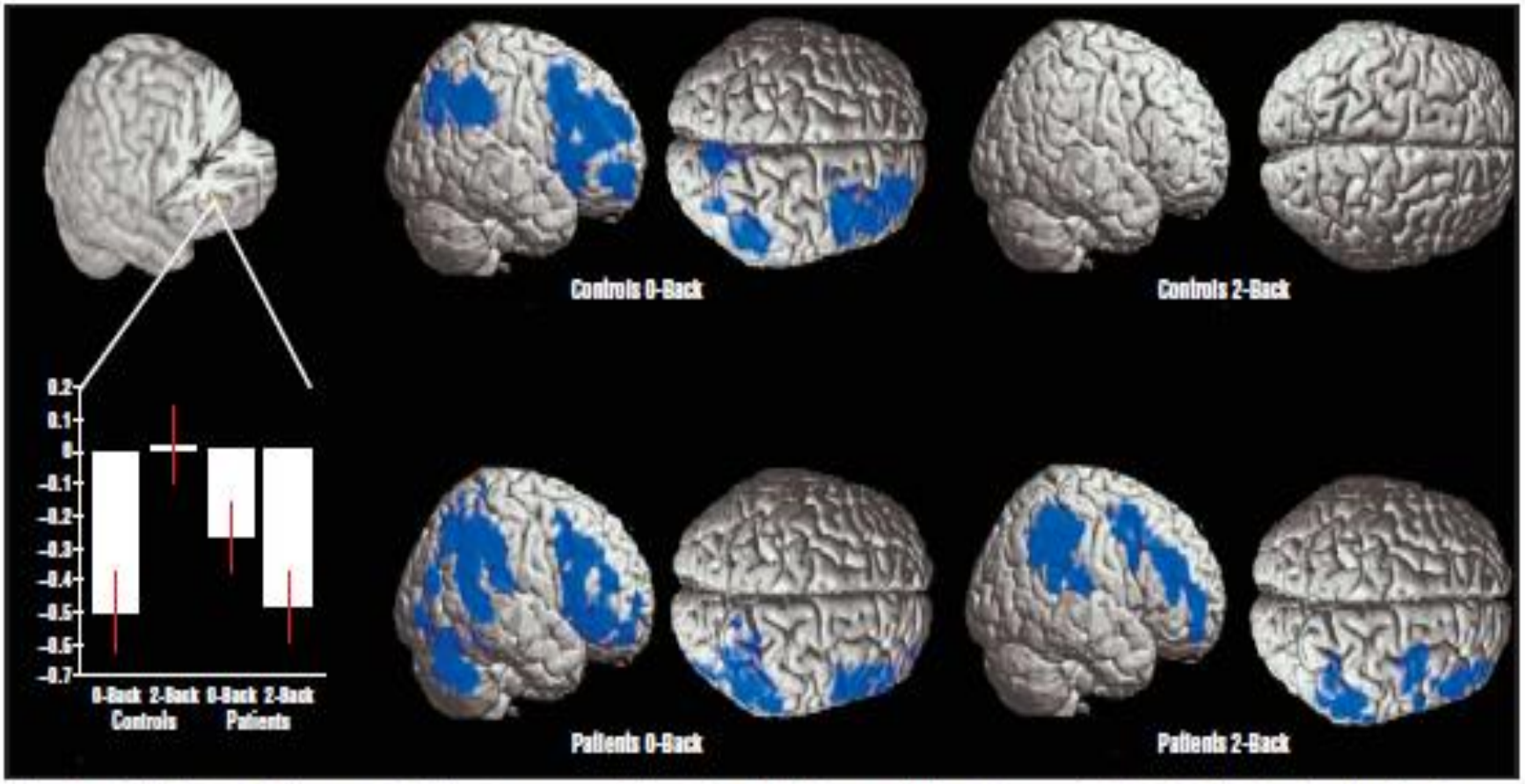

Figure 3. Top left, Cutout showing area of significant group × task interaction of left hippocampal formation connectivity in the right dorsolateral prefrontal cortex. Bottom left, Mean values for covariation with left hippocampal formation in the region of interaction, showing significant coupling during both the 2-back and 0-back tasks in patients but only during the 0-back task in controls. Error bars indicate standard errors. Center and right, Analysis of covariance maps showing areas that were significantly negatively correlated with left hippocampal formation regional cerebral blood flow. Highlighted voxels are significant at $P \leq .01$ ($P \leq .05$ corrected for multiple comparisons).

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Brain-Derived Neurotrophic Factor (BDNF) Val^{66}Met Polymorphism Differentially Predicts Hippocampal Function in Medication-Free Patients with Schizophrenia

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Section on Integrative Neuroimaging (DPE, SMW, AMI, PDK, KFB), Clinical Brain Disorders Branch, Genes, Cognition and Psychosis Program (DPE, AMI, SMW, PDK, BK, JA, KFB), National Institute of Mental Health, NIH, DHHS, Bethesda MD 20892; and the Lieber Institute for Brain Development (DRW), Johns Hopkins Medical Campus, Baltimore Maryland 21205

Abstract

A Val^{66}Met single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene impairs activity-dependent BDNF release in cultured hippocampal neurons and predicts impaired memory and exaggerated basal hippocampal activity in healthy humans. Several clinical genetic association studies, along with multi-modal evidence for hippocampal dysfunction in schizophrenia indirectly suggest a relationship between schizophrenia and genetically-determined BDNF function in the hippocampus. To directly test this hypothesized relationship, we studied 47 medication-free patients with schizophrenia or schizoaffective disorder and 74 healthy comparison individuals with genotyping for the Val^{66}Met SNP and [^{15}O]H_2O positron emission tomography (PET) to measure resting and working memory-related hippocampal regional cerebral blood flow (rCBF). In patients, harboring a *Met* allele was associated with significantly less hippocampal rCBF. This finding was opposite to the genotype effect seen in healthy participants, resulting in a significant diagnosis-by-genotype interaction. Exploratory analyses of interregional resting rCBF covariation revealed a specific and significant diagnosis-by-genotype interaction effect on hippocampal-prefrontal coupling. A diagnosis-by-genotype interaction was also found for working-memory related hippocampal rCBF change, which was uniquely attenuated in *Met* allele-carrying patients. Thus, both task-independent and task-dependent hippocampal neurophysiology accommodates a *Met* allelic background differently in patients with schizophrenia than in control subjects. Potentially consistent with the hypothesis that cellular sequelae of the *BDNF* Val^{66}Met SNP interface with aspects of schizophrenic hippocampal and frontotemporal dysfunction, these results warrant future investigation to understand the contributions of unique patient trait or state variables to these robust interactions.

Human Molecular Genetics, 2013, Vol. 22, No. 10 **2055–2066**
doi:10.1093/hmg/ddt056
Advance Access published on February 7, 2013

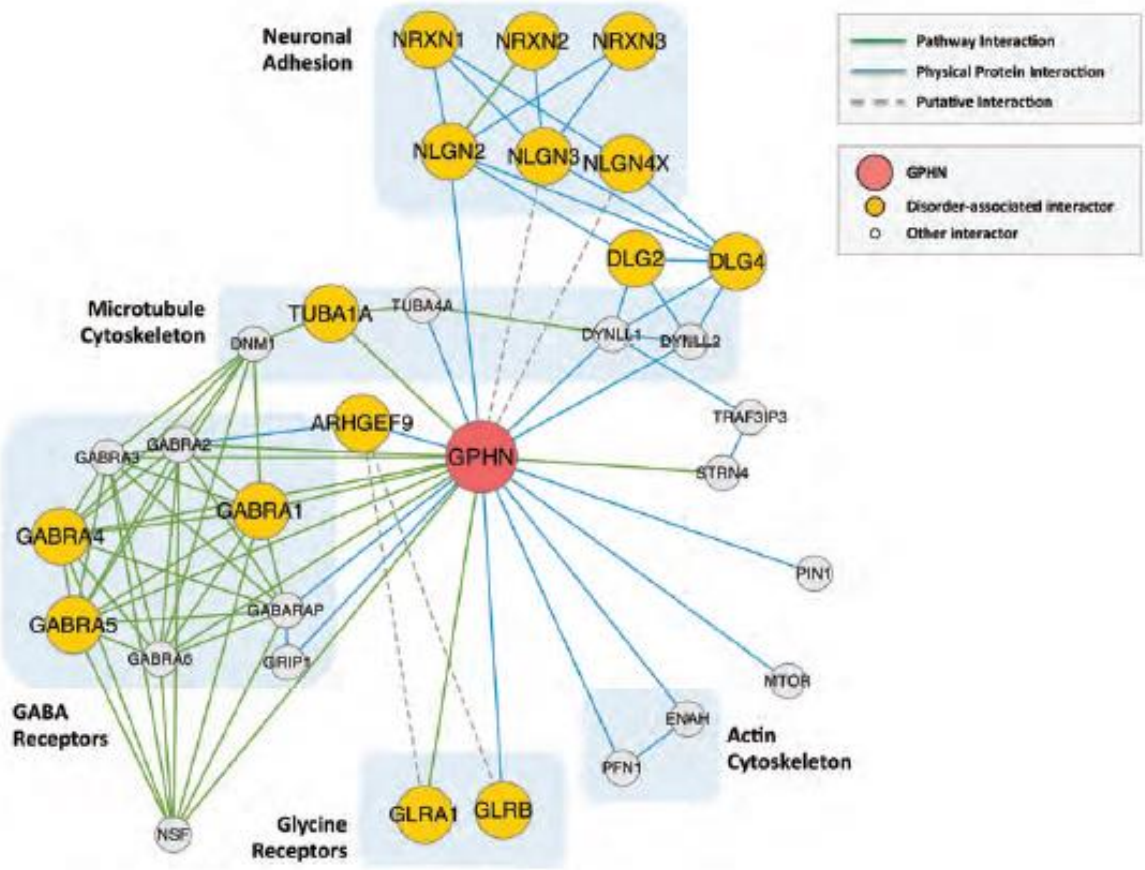
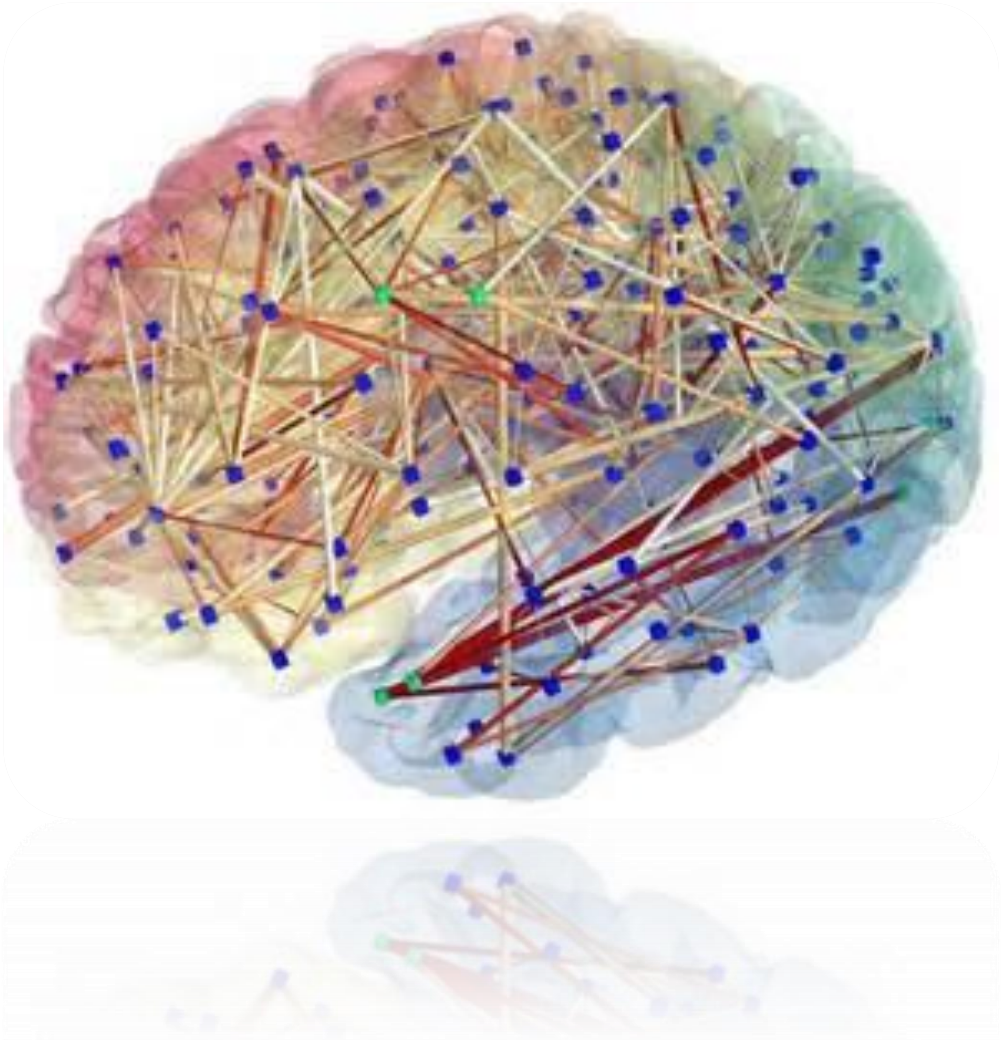


Figure 1. Functional interaction network of Gephyrin. The top 50 interactors of GPHN according to the STRING and GeneMANIA databases were manually filtered and integrated to define the bona-fide GPHN interaction network; the majority of direct interactors were retained. Gephyrin's interactions with other proteins have been reviewed by Tretter *et al.* (1) and Fritschy *et al.* (2). For full names of gene symbols in the figure, see Supplementary Material, Table S1.

Da Kraepelin al Connettoma



Schizophrenia Bulletin vol. 35 no. 5 pp. 847–850, 2009
doi:10.1093/schbul/sbp078
Advance Access publication on July 24, 2009

Who Is at Risk for a Psychotic Disorder?

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The Timeline of a Psychotic Disorder

Let us assume that we have the ability to accurately record all signs and symptoms of psychosis throughout the life of

Table 1. Risk Factors for Psychotic Disorders

Time of Assessment	Risk Factor	Examples
At any time	Genes	DISC1
	Family history	50% concordance for MZ twins
	Gender	Bimodal risk profile in females
	Culture	Immigrant status
	Living environment	Urbanicity
Distal to illness onset	Abnormal fetal development	Maternal malnutrition
	Abnormal cognitive development	Low IQ
	Early drug use	MJ before age 13
Proximal to illness onset	Mental status changes	Attenuated psychotic symptoms, basic symptoms
	Biomarker	Decrease of cortical gray matter, elevated DA release

Note: This list of risk factors is not exhaustive but is meant to illustrate 3 different types of risk factors. MZ, monozygotic; MJ, marijuana; DA, dopamine.

BMC Psychiatry

BioMed Central

Research article

Open Access

Stress load during childhood affects psychopathology in psychiatric patients

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Tzvetan Pop
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Address: [1]Department

Abstract

Background: Childhood stress and trauma have been related to adult psychopathology in different psychiatric disorders. The present study aimed at verifying this relationship for stressful experiences during developmental periods by screening stress load across life in adult psychiatric inpatients with different diagnoses compared to healthy subjects. In addition, a relationship between the amount of adverse experiences and the severity of pathology, which has been described as a 'building block' effect in posttraumatic stress disorder (PTSD), was explored for non-traumatic events in psychiatric disorders other than PTSD.

Methods: 96 patients with diagnoses of Major Depressive Disorder (MDD), schizophrenia, drug addiction, or personality disorders (PD) and 31 subjects without psychiatric diagnosis were screened for adverse experiences in childhood (before the age of six years), before onset of puberty, and in adulthood using the Early Trauma Inventory and the Posttraumatic Stress Diagnostic Scale. Effects of stress load on psychopathology were examined for affective symptoms, PTSD, and severity of illness by regression analyses and comparison of subgroups with high and low stress load.

Results: High stress load in childhood and before puberty, but not in adulthood, was related to negative affect in all participants. In patients, high stress load was related to depressive and posttraumatic symptoms, severity of disorder, and the diagnoses of MDD and PD.

Conclusion: Results support the hypothesis of stress-sensitive periods during development, which may interact with genetic and other vulnerability factors in their influence on the progress of psychiatric disorders. A 'dose' effect of stress load on the severity of psychopathology is not restricted to the relationship between traumata and PTSD.

Table 4: Stress Scores for the Diagnostic Subgroups and Periods of Life

Diagnostic Subgroup	
Major Depressive Dis. (N = 3	
Schizophrenia (N = 32)	
Drug Abuse (N = 15)	
Personality Disorder (N = 10)	
Subgroup differences: F(3,91) =	

Table 2: Stress Scores for the Different Groups and Periods of Life

	ELS[a] Events Stress load	PPS[b] Events Stress load	AS[c] Events Stress load
Patients (N = 96)	5.89 ± 5.8 46.4 ± 70.4	11.01 ± 7.1 172.2 ± 176.7	5.03 ± 3.6 135.7 ± 155.8
Comparison Ss (N = 31)	1.77 ± 2.2 10.7 ± 17.5	4.39 ± 3.58 45.1 ± 66.0	4.94 ± 3.1 45.7 ± 49.3
Group differences: F(1,125) =	14.84, p < .01 8.15, p < .01	24.62, p < .001 15.29, p < .001	F < 1. n.s. 9.99, p < .01

Note: See note in Table 2: Data represent the cumulated number of experienced events (top rows) and the stress load calculated accordingly to the ETI guidelines (bottom row). ELS: Early life stress before the age of 6 years. PPS: Prepubertal stress before the individual onset of puberty. AS: Adulthood stress between puberty and the current age. PDS: number of traumatic experiences across life. PSQ: Prenatal Stress Questionnaire; see note in Table 2. Results are presented in the format M ± SD. Statistical significance: *: p < .05, **: p < .01, ***: p < .001.

ELSE: carico di stress prima dei 6 anni
PPS: carico di stress in epoca prepuberale
ASS: periodo di stress tra la pubertà e l'età corrente.

4 domini di stress:
- traumi, abbandono emozionale, abuso fisico, punizioni fisiche

Fattori di rischio distali ed avversità infantili nella Schizofrenia vs Disturbo Depressivo Maggiore: obiettivi della ricerca

- L'obiettivo **primario** della ricerca è quello di rilevare una specifica relazione tra ***fattori di rischio distali*** e ***avversità infantili*** nello sviluppo della Schizofrenia comparata al Disturbo Depressivo Maggiore.

- Uno degli obiettivi **secondari** intende esplorare la correlazione tra le suddette variabili epidemiologiche e la sintomatologia dei due Disturbi.

Partecipanti

Il campione è costituito da pazienti tra i 18-65 anni con diagnosi di Schizofrenia secondo DSM 5 (N=63), Controlli Sani (N=41) e di DDM (N=50), afferenti alla nostra U.O. nel periodo compreso tra Novembre 2011 e Maggio 2014.

Metodi

- **Intervista semistruttura**

- **Scheda relativa ai dati della Gravidanza, Parto e Peripartum** (Fattori di rischio Distali);

- "**Childhood Experiences of Care and Abuse**" (EUGEI);

- **PANSS** (Positive and Negative Syndrome Scale for Schizophrenia) *(Kay, 1987)*
- **HAM- D** (Hamilton Depression Rating Scale*) (Hamilton M., 1967)*

Statistical design

Forward Stepwise Linear Regression Analyses either considering **PANSS-positive, negative, general and total** as dependent variables, and as independent variables:

- "**distal risk factors**" corrected by age and gender were considered as independent predictors: first degree relatives with psychosis; stressful events during pregnancy; inadequate weight gain during pregnancy; nutritional deficiency during pregnancy; infections during pregnancy; Rh incompatibility; vaginal bleeding during pregnancy; gestational diabetes; preeclampsia; traumatic birth; postpartum hemorrhage; birth weight <2500 gr; head circumference at birth <32 cm; malformations; asphyxia at birth (all variables: yes=1, no=0); father's and mother's age at delivery (continuous).

- **early adverse childhood life events:** history of cannabis, cocaine, LSD, heroin or alcohol abuse; adoption; father's or mother's death; estrangement from father or mother; multiple changes of school; expulsion from school; home escape; foster care; economic difficulties; neglect of major needs; family tension; psychological, physical abuse or sexual abuse; lack of an adult figure of support; lack of peer figure of support; sense of loneliness (all variables: yes=1; no=0).

Alpha level for variables entering the logistic regression model was set at 0.04 and for removal 0.2; Odds Ratio (OR) and 95% confidence interval (CI) were calculated.

Table : Distal risk factors in MDD e Schizophrenia

	Schizophrenia	MDD	Controls	Comparison Schizophrenia vs Controls			Comparison MDD vs Controls			Comparison Schizophrenia vs MDD		
	%	%	%	χ^2	O.R.	p	χ^2	O.R.	p	χ^2	O.R.	p
First degree relatives with psychosis	23.5	9.8	2.0	10.667	**15.38**	**.001**	2.687		.101	3.001		.083
Stressful events during pregnancy	15.7	7.3	3.9	3.991	**4.56**	**.046**	0.510		.475	1.512		.219
Insufficient weight gain	29.4	2.4	2.0	14.529	**20.83**	**<.001**	0.024		.876	11.510	**16.67**	**.001**
Nutritional deficiency	15.7	2.4	0.0	7.221	**18.79**	**.007**	1.258		.262	4.519	**7.44**	**.034**
Infections	9.8	0.0	0.0	3.89	**10.98**	**.05**	-		-	2.98		**.084**
Rh factor incompatibility	2.0	0.0	0.0	1.01		.315	-		-	0.813		.367
Blood loss	11.8	0.0	2.0	3.835	**6.67**	**.05**	0.813		.367	3.85	**10.8**	**.05**
Gestational Diabetes	2.0	2.4	0.0	1.010		.315	1.258		.912	0.024		.876
Preeclampsia	2.0	0.0	0.0	1.010		.315	-		-	0.813		.367
Traumatic birth	35.3	7.3	15.7	5.16	**2.93**	**.023**	3.867		.145	10.10	**6.91**	**.002**
Postpartum hemorrhage	3.9	2.4	0.0	2.040		.153	1.258		.262	0.158		.691
Weight <2500 g	3.9	14.6	7.8	0.708		.400	1.082		.298	3.285		.07
Malformations	2.0	0.0	0.0	1.010		.315	-		-	0.813		.367
Birth asphyxia	7.8	2.4	2.0	1.893		.169	0.024		.876	1.292		.256

Schizophrenia Bulletin vol. 34 no. 6 pp. 1054–1063, 2008
doi:10.1093/schbul/sbn096
Advance Access publication on August 4, 2008

Prenatal Nutritional Deficiency and Risk of Adult Schizophrenia

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Converging evidence suggests that a neurodevelopmental disruption plays a role in the vulnerability to schizophrenia. The authors review evidence supporting in utero exposure to nutritional deficiency as a determinant of schizophrenia. We first describe studies demonstrating that early gestational exposure to the Dutch Hunger Winter of 1944–1945 and to a severe famine in China are each associated with an increased risk of schizophrenia in offspring

a vulnerability to schizophrenia in adolescence or adulthood. Accumulating data have implicated the in utero environment in the etiology of this disorder.[1] In this article, we review and discuss the sources of evidence for testing hypotheses about the relation of prenatal nutritional deficiency to offspring risk of schizophrenia. The long interval between an exposure in the prenatal period and the risk of schizophrenia in adulthood and the difficulty of obtaining precise data on prenatal nutritional intake are among the considerable challenges faced by researchers in this field. Nonetheless, successful studies have been built around historic events, a design sometimes referred to as a "natural experiment."

We first describe studies linking prenatal exposure to

Folate

The coincidence of the peak in risk of schizophrenia and schizoid personality disorder with congenital neural

Retinoids

Retinol (vitamin A) and other retinoids are essential nutrients that are required by the early embryo and fetus for gene expression, cell differentiation, proliferation, and migration.[36–39] Vitamin A deficiency in animals results in gross CNS malformations, including hydrocephalus, anencephaly, spina bifida,[40–42] and an underdeveloped posterior hindbrain,[43,44] including loss of the

Essential Fatty Acids

Essential fatty acids (EFAs) play critical roles in brain development. Humans do not have the ability to synthesize these fatty acids de novo and thus are largely dependent upon dietary sources.[30] Docosohexaenoic acid (DHA), an omega-3 fatty acid, is the primary structural fatty acid in the brain, comprising 25%–30% of the structural fatty acids in the gray matter.[30,31] Maternal supple-

Vitamin D

McGrath[48] has hypothesized that prenatal exposure to vitamin D deficiency is a risk factor for schizophrenia. The plausibility of this hypothesis is supported by the role of this vitamin in cell growth and differentiation,

Protein-Calorie Malnutrition

Although we consider it more likely that a micronutrient is involved, protein-calorie malnutrition (PCM) should also be considered as a potential explanation for the association between famine and schizophrenia. There is some support from preclinical studies for the biological

Iron

Maternal iron deficiency is known to affect the development of the fetal brain. This may occur through several mechanisms during pregnancy. First, during pregnancy, the needs of the growing fetus and placenta, as well as the increasing maternal red blood cell mass, impose a sub-

Substance abuse and early childhood adverse events

	Schizophrenia	MDD	Controls	Comparison Schizophrenia vs Controls			Comparison MDD vs Controls			Comparison Schizophrenia vs MDD		
	%	%	%	χ^2	O.R.	p	χ^2	O.R.	p	χ^2	O.R.	p
Cannabis abuse	25.5	2	2.4	11.922	**17.11**	**.001**	0.024	-	.876	9.361	**13.68**	**.002**
Cocaine abuse	3.9	-	-	2.040	-	.152	-	-	-	1.644	-	.200
LSD abuse	**2	-	-	1.010	-	.315	-	-	-	0.813	-	.367
Heroin abuse	7.8	-	-	4.163	-	**.041**	-	-	-	3.362	-	.067
Alcohol abuse	3.9	-	-	2.040	-	.153	-	-	-	1.644	-	.200
Adoption	3.9	2.4	2	0.343	-	.558	0.024	-	.876	0.158	-	.691
Father's death	3.9	4.9	2	.343	-	.558	0.613	-	.434	0.050	-	.823
Mother's death	2	-	2	0	-	1.000	0.813	-	.367	0.813	-	.367
Absence of father	15.7	12.2	3.9	3.991	**4.56**	**.046**	2.213	-	.131	0.228	-	.633
Absence of mother	5.9	4.9	3.9	0.210	-	.647	0.050	-	.823	0.045	-	.833
School change	29.4	7.3	11.8	4.857	**3.13**	**.028**	0.509	-	.475	7.050	**5.28**	**.008**
Expulsion from school	5.9	2.4	3.9	0.210	-	.647	0.158	-	.691	0.648	-	.421
Home escape	19.6	4.9	-	9.48	**24.39**	**.002**	2.543	-	.111	4.348	**4.76**	**.037**
Into foster care	2	-	-	1.010	-	.315	-	-	-	0.813	-	.367
Economic difficulties	17.6	26.8	2.2	7.096	**10.71**	**.008**	12.393	**18.33**	**.001**	1.126	-	.289
Neglect of major needs	11.8	9.8	2	3.835	**6.67**	**.050**	2.687	-	.101	0.095	-	.758
Family tensions	43.1	31.7	5.9	19.128	**12.14**	**<.001**	10.551	**7.43**	**.001**	1.260	-	.262
Psychological abuse	29.4	7.3	-	15.841	**41.67**	**<.001**	2.49	-	.114	7.050	**5.28**	**.008**
Physical abuse	37.3	9.8	2	20.151	**26.69**	**<.001**	2.687		.101	9.166	**5.49**	**.002**
Sexual abuse	13.7	4.9	-	6.082	**16.07**	**.014**	2.543		.111	2.016	-	.156
Absence of confident adult	47.1	31.7	13.7	13.393	**5.59**	**<.001**	4.320	**2.92**	**.038**	2.228	-	.136
Absence of peer confident	43.1	26.8	7.8	17.725	**8.91**	**<.001**	6.004	**4.31**	**.014**	2.628	-	.105
Sense of loneliness	60.8	31.7	2	40.982	**77.50**	**<.001**	15.588	**23.21**	**<.001**	7.701	**3.34**	**.006**

Logistic regression analysis. Dependent variables: Diagnosis of Schizofrenia or MDD. Independent variables: Distal risk factors.

Dependent variable	Indipendent variables	Standard Error	p	Odds Ratio	95% Confidence Interval
Schizophrenia[a]	• Urban birth	.454	**.003**	3.931	1.615-9.565
	• First degree relatives with psychosis	.686	**.010**	5.819	1.517-22.321
	• Insufficient weight gain	.862	**.017**	7.808	1.442-42.265
	• Traumatic birth	.388	**.005**	2.954	1.382-6.313
MDD[b]	• Age	.016	**.002**	1.050	1.018-1.082

Logistic regression analysis. Dependent variables: Diagnosis of Schizofrenia or MDD. Independent variables: Early childhood adverse events

Dependent variable	Indipendent variables	Standard Error	**p**	Odds Ratio	95% Confidence Interval
Schizophrenia[a]	• Age	.021	**.044**	0.958	0.919-0.999
	• School change	.615	**.008**	5.178	1.551-17.288
	• Physical abuse	.841	**.023**	6.802	1.308-35.364
	• Sense of loneliness	.522	**.000**	8.636	3.105-24.017
MDD[b]	• Age	.045	**.005**	1.046	1.013-1.079
	• Economic difficulties	.636	**.019**	4.434	1.275-15.421
	• Family tensions	.541	**.045**	2.956	1.025-8.527
	• Physical abuse	.800	**.029**	0.175	.036-.840

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Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies

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Table 2. Results of the separate meta-analyses focusing on specific adverse experiences

	k	OR (95% CI), *p* value	*Q* test	I^2 (%)
Sexual abuse	20	2.38 (1.98–2.87), $p < .001$	$Q = 34.5$, $p < .05$	44.9
Physical abuse	13	2.95 (2.25–3.88), $p < .001$	$Q = 47.8$, $p < .001$	74.9
Emotional abuse	6	3.40 (2.06–5.62), $p < .001$	$Q = 23.1$, $p < .001$	78.3
Bullying	6	2.39 (1.83–3.11), $p < .001$	$Q = 19.1$, $p < .01$	73.9
Parental death	8	1.70 (0.82–3.53), $p = .154$	$Q = 35.4$, $p < .001$	80.2
Neglect	7	2.90 (1.71–4.92), $p < .001$	$Q = 32.9$, $p < .001$	81.8

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REVIEW

Mother–infant interaction in schizophrenia: transmitting risk or resilience? A systematic review of the literature

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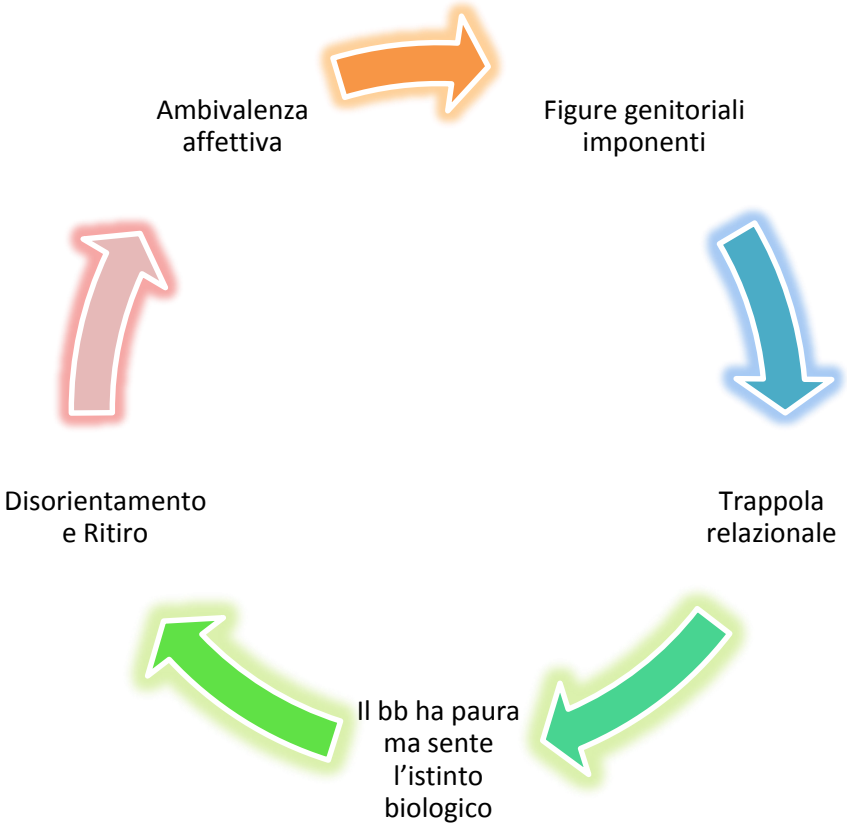
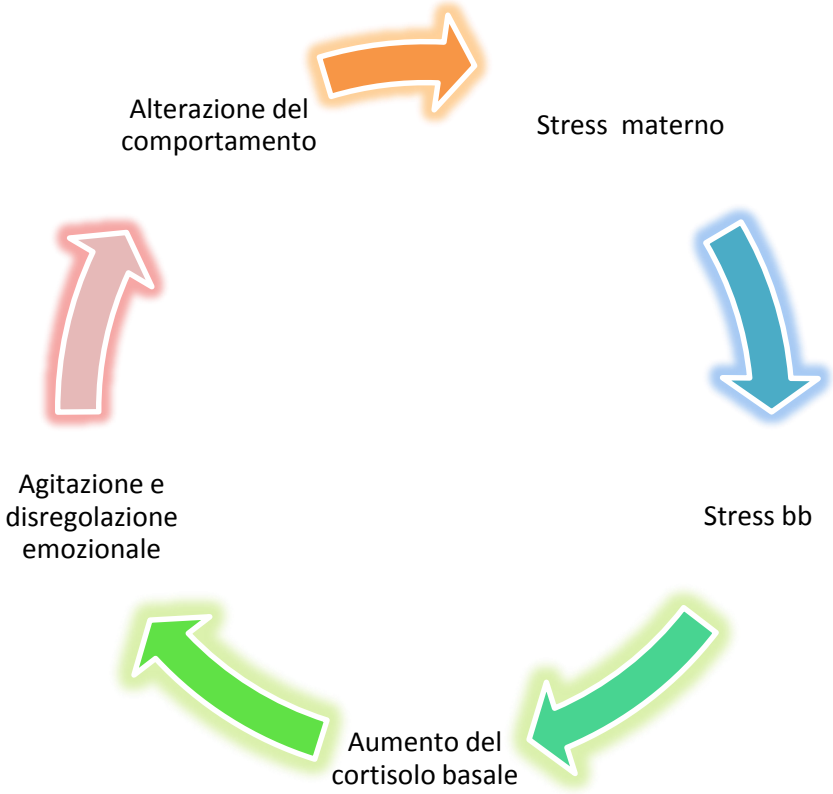
1. What are the characteristics of the studies investigating the early caregiver–infant relationship?
2. What are the characteristics of the early caregiver–infant relationship and what are its correlates?
3. What methodological features are associated with increased risk of bias?

Transmission mechanism 1:
quality of mother– infant interaction



Transmission mechanism 2:
stress-sensitivity (S–S)



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Impact of childhood adversities on the short-term course of illness in psychotic spectrum disorders

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2.1. Participants, setting and procedure

Sixty-two patients ($n=19$ female, age $M=32.2$ S.D. $=10.3$ years) with a primary diagnosis of psychotic spectrum disorder (International Classification of Mental and Behavioral Disorders Tenth Version (ICD-10): F20- F29, World Health Organization, 1992) were recruited from the inpatient pool at the local Center for Psychiatry (see Table 1 for demographic data). Patients met criteria of a diagnosis of schizophrenia F20 (77.4%), 16.1% a diagnosis of schizoaffective disorder, and 4.8% of acute polymorphic psychotic disorder. Forty-one percent of the sample was admitted for diagnosis and treatment of psychoses for the first time, 59% was chronically ill. Symptom severity and global level of functioning were assessed across a four-month period starting at admission. Patients received routine care including maintenance neuroleptic medication, group therapy, physical exercise and adjunct cognitive behavioral psychotherapy if needed. Data assessment (see below) took place in the post-acute phase. Prior to assessment, each participant was informed about the aim and procedure of the study and provided written informed consent. The responsible psychologist or the psychiatrists in charge verified that the patient sufficiently improved to provide informed consent and participate in data assessment. The study was reviewed and approved by the Institutional Review Board (Ethics Committee) of the University of Konstanz.

2.2. Measures and instruments

Childhood adversities were screened by the Maltreatment and Abuse Chronology of Exposure (MACE) scale administered as an interview (Isele et al., 2014; Teicher and Parigger, 2011). The MACE scale captures the exposure to ten types of adversity during childhood, up to age 18: parental physical and verbal abuse, parental non-verbal emotional abuse, familial and non-familial sexual abuse, witnessed physical violence towards parents, witnessing violence towards siblings, peer emotional and peer physical violence, emotional and physical neglect). Good psychometric properties of the MACE scale are documented by test-retest reliability, $r=0.91$, $n=75$ at 10 weeks, and correlation coefficients of $r=0.75$ with the Childhood Trauma Questionnaire (Wingenfeld et al., 2010) in a German validation sample (Isele et al., 2014). The MACE MULTI score indicates the number of different types of childhood adversities that reached the defined severity, ranging from 0 to 10. The MACE SUM score indicates the overall severity of exposure to childhood adversities, ranging from 0 ("no childhood adversities at all") to 100 ("reporting maximal exposure to all types of childhood adversities"). Using a median split of the MACE MULTI score ($Mdn=2$), patients of the present sample were assigned to a group with lower level of childhood adversities (0 or 1 types) or higher level of childhood adversities (2 or more types).

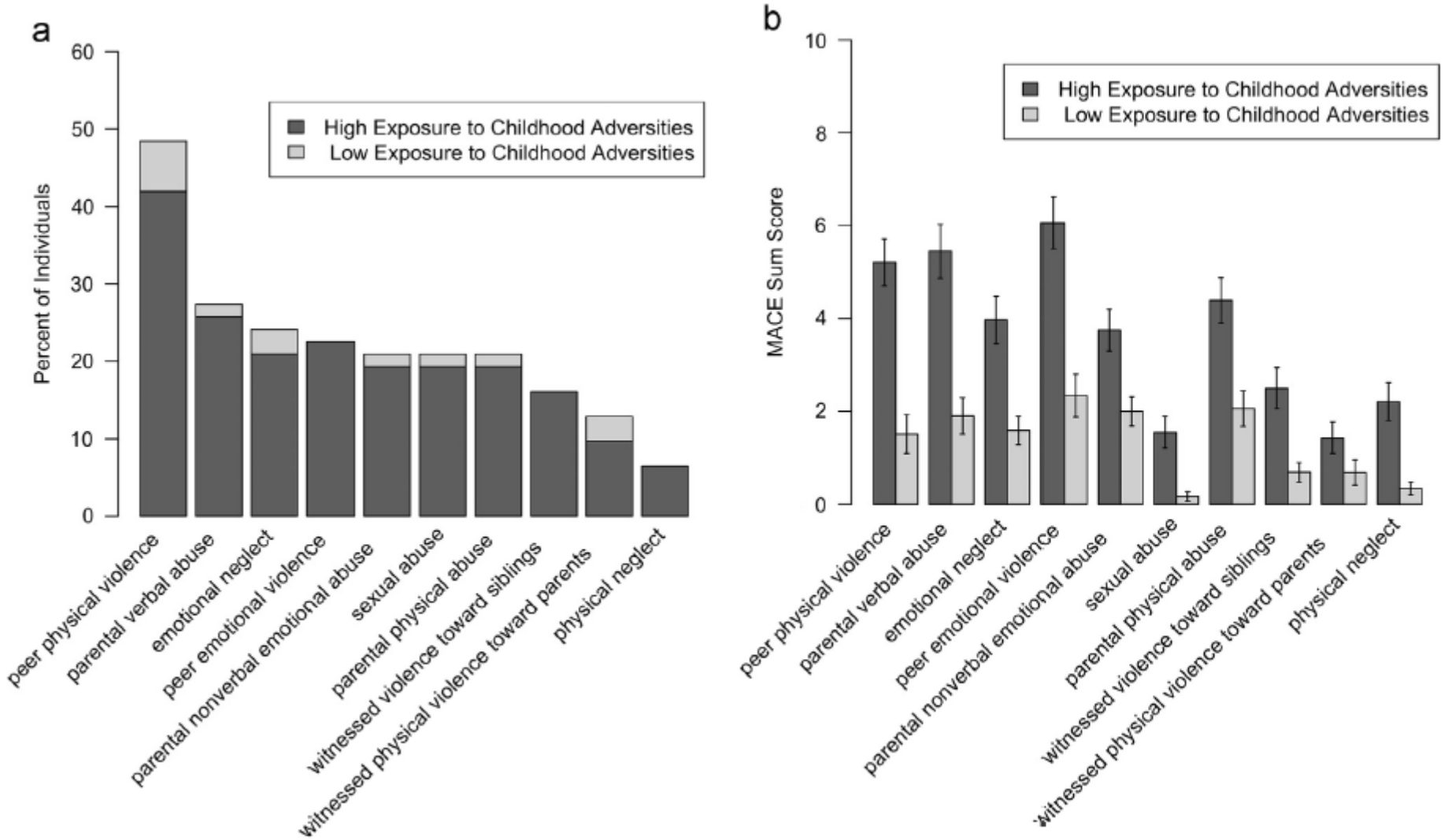

Fig. 1. (a) Prevalence (in %) of each type of childhood adversity as well as (b) severity of childhood adversities per type, separately for the group with high (>1) or low (≤ 1) types of adverse experiences in childhood. The error bars represent the standard deviation.

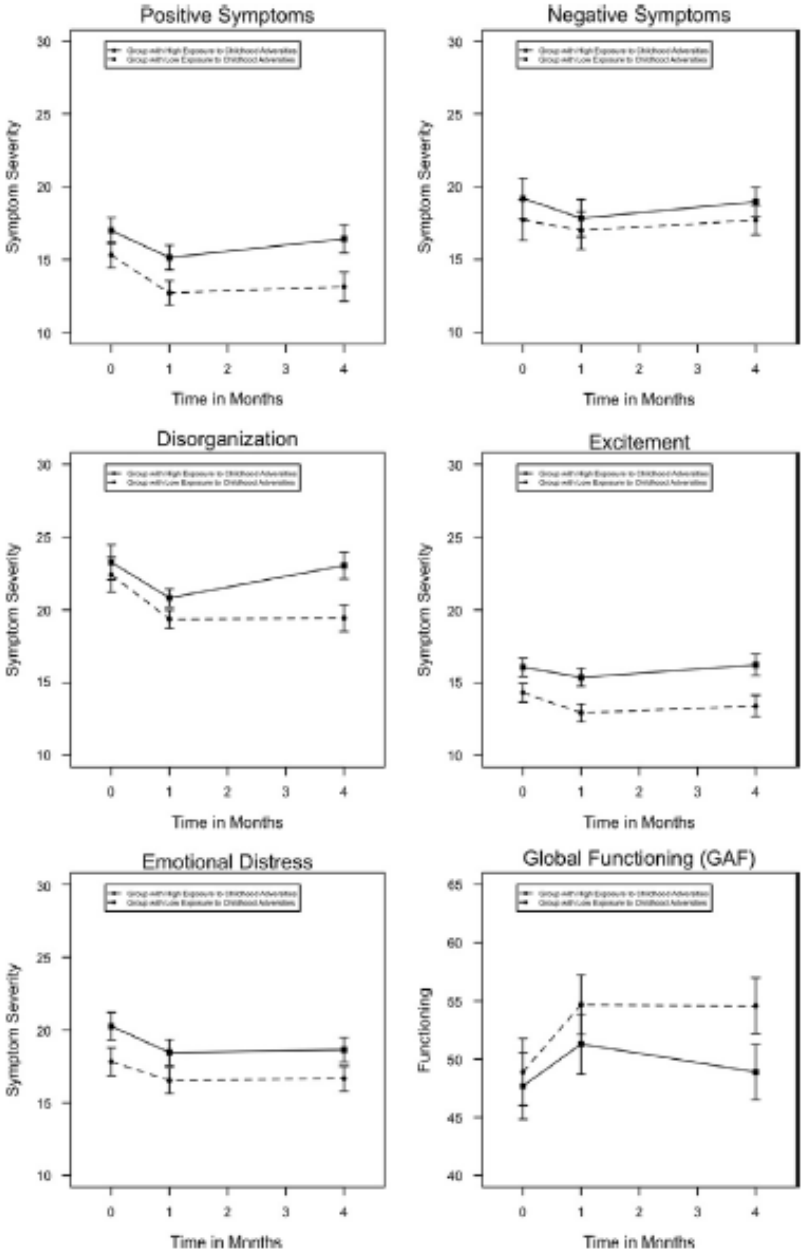

Fig. 2. Course of symptom severities over time measured with the respective dimension of the Positive and Negative Syndrome Scale (PANSS) and global level of functioning. The course is presented separately for the group with high (solid lines) and low (dashed lines) levels of childhood adversities. The error bars represent the standard deviation of the mean.

Table 2
PANSS symptom severity and functioning across a four month observation period of patients with psychotic spectrum disorders reporting low and high levels of childhood adversities.

PANSS symptom severity	Group with low childhood adversities		Group with high childhood adversities		*t-Test*
	M	S.D.	*M*	S.D.	
Positive symptoms					
First assessment	15.31	4.83	17.00	5.86	$t(60) = -1.23$, $p = 0.224$
1 month follow up	12.71	4.46	15.14	5.58	$t(54) = -1.80$, $p = 0.078$
4 month follow up	13.14	5.30	16.43	5.54	$t(49) = -2.16$, $p = 0.035$*
Negative symptoms					
First assessment	17.72	7.52	19.21	7.21	$t(60) = -0.80$, $p = 0.430$
1 month follow up	17.00	6.82	17.86	7.57	$t(54) = -0.45$, $p = 0.658$
4 month follow up	17.71	5.84	18.96	5.87	$t(49) = -0.75$, $p = 0.455$
Disorganization					
First assessment	22.41	6.48	23.27	5.94	$t(60) = -0.55$, $p = 0.588$
1 month follow up	19.36	4.69	20.82	6.27	$t(54) = -0.99$, $p = 0.327$
4 month follow up	19.43	4.92	23.04	5.47	$t(49) = -2.48$, $p = 0.017$*
Excitement					
First assessment	14.31	3.44	16.06	3.33	$t(60) = -2.03$, $p = 0.047$*
1 month follow up	12.93	3.29	15.36	4.63	$t(54) = -2.26$, $p = 0.028$*
4 month follow up	13.39	3.96	16.22	4.48	$t(49) = -2.39$, $p = 0.021$*
Emotional distress					
First assessment	17.83	5.11	20.27	4.97	$t(60) = -1.91$, $p = 0.061$
1 month follow up	16.54	4.73	18.46	5.78	$t(54) = -1.37$, $p = 0.178$
4 month follow up	16.68	4.55	18.65	4.44	$t(49) = -1.56$, $p = 0.126$
GAF score					
First assessment	48.90	15.45	47.71	14.75	$t(60) = 0.31$, $p = 0.759$
1 month follow up	54.68	13.67	51.30	14.85	$t(53) = 0.88$, $p = 0.383$
4 month follow up	54.59	12.50	48.91	15.22	$t(48) = 1.45$, $p = 0.154$

Note. Mean (*M*), Standard Deviation (S.D.), PANSS = Positive and Negative Syndrome Scale, GAF = Global Assessment of Functioning.

* indicates $p < 0.050$.

Conclusioni dello Studio

- Ci sono differenze rilevanti tra i pazienti con schizofrenia e disturbo depressivo maggiore in materia di fattori di rischio distali ed esperienze traumatiche dell'infanzia.

- Una storia familiare di psicosi tra i parenti di primo grado , inadeguato aumento di peso della madre , deficit nutrizionali , infezioni e perdita ematiche durante la gravidanza e modalità traumatica del parto sono significativamente più frequenti tra i pazienti schizofrenici .

- Inoltre la nascita in ambiente urbano , parto traumatico , l' aver subito abusi fisici in epoche precoci della vita, aver provato sentimenti di solitudine nei primi periodi di vita può predisporre allo sviluppo di Schizofrenia .

- Al contrario , tensioni familiari e difficoltà economiche incontrate prima dei 16 anni tenderebbero a predisporre allo sviluppo di sintomi depressivi .

I fattori di rischio distali sembrano essere più rilevanti per lo sviluppo della Schizofrenia che per quello di un Disturbo Depressivo Maggiore.

Considerazioni Generali

- Esiste un'evidente correlazione tra le Avversità esperite durante le epoche precoci della vita e l'evoluzione dei due Disturbi Psichiatrici.

- Fattori che attengono maggiormente alla sfera individuale come Abusi fisici, senso di solitudine e cambiamenti scolastici predisporrebbero allo sviluppo di Schizofrenia.

- Fattori di tipo ambientale\ familiare come difficoltà economiche, tensioni all'interno del nucleo familiare sembrerebbero essere correlati allo sviluppo di DDM.

La collaborazione pediatria-psichiatria

Esistono numerose ragioni …

- ✓ Osservazione precocemente di fenomeni che altrimenti verrebbero individuati tardivamente (quando non sono modificabili)

- ✓ Prevenire patologie neurodegenerative invalidanti intervendendo su fattori di rischio precoci dell'infanzia.