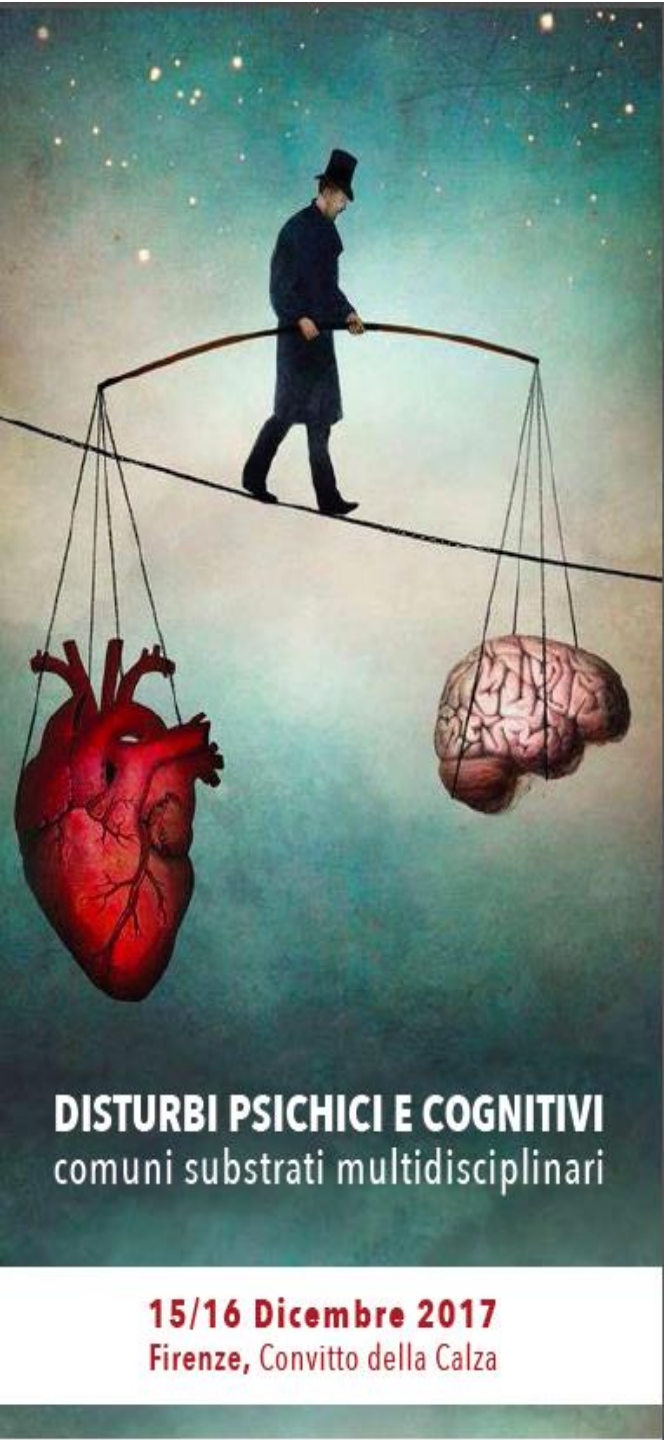

Gli aspetti cognitivi nei "rischi" ed esordi psicotici

Nadia Magnani

UF Salute Mentale Adulti – Grosseto

Azienda USL Toscana sud est

Stati mentali a rischio ed esordi psicotici

……Interazione tra “ambiente” e “vulnerabilità biologica”

The standard research definition of **At Risk Mental State (ARMS)** include:

(1) Genetic Risk and Deterioration Syndrome, a trait/state combination of genetic/familial risk or schizotypal personality disorder with functional decline

(2) Attenuated Positive Symptom Syndrome, considered an early, subtle form of psychotic-like symptoms (less intense and less frequent)

(3) Brief Intermittent Psychotic Syndrome, that are recent, brief, and not seriously disorganizing or dangerous

(associati a riduzione e/o compromissione del funzionamento)

Mod. da: Carrión RE, Correll CU, Auther AM and Cornblatt BA. *Schizophrenia Bulletin* vol. 43 no. 1 pp. 64–74, 2017

A somewhat different classification according to a theoretical model proposing that…

Schizophrenia is rooted in **genetic abnormalities** that affect development of basic brain functions. The underlying brain abnormalities are life-long, relatively subtle and provide the necessary but not sufficient foundation for later illness.

Examples of the **vulnerability factors** on the behavioral level are cognitive deficits, social isolation, and school/work problems.

On their own, these abnormalities, which typically precede positive symptoms by several years, have been shown to lead to various levels of functional disability.

However, according to this model, when combined with the additional predisposition (likely having an independent genetic etiology) to develop positive symptoms, then psychoses evolve.

Therefore, critical to this model is the notion that there are 2 independent processes involved in developing a full-blown psychotic illness. The presence of either one alone can lead to poor long-term prognosis, but the interaction between these 2 pathways is thought to lead to emergence of full-blown psychosis.

……fattori di resilienza

Recognition and Prevention (RAP) Program of the Zucker Hillside Hospital in New York

Carrión RE, Correll CU, Auther AM and Cornblatt BA. *Schizophrenia Bulletin* vol. 43 no. 1 pp. 64–74, 2017

PERSPECTIVE

doi:10.1038/nature09563

The environment and schizophrenia

Van Os, Kenis, Rutten, Nature vol 468, 2010

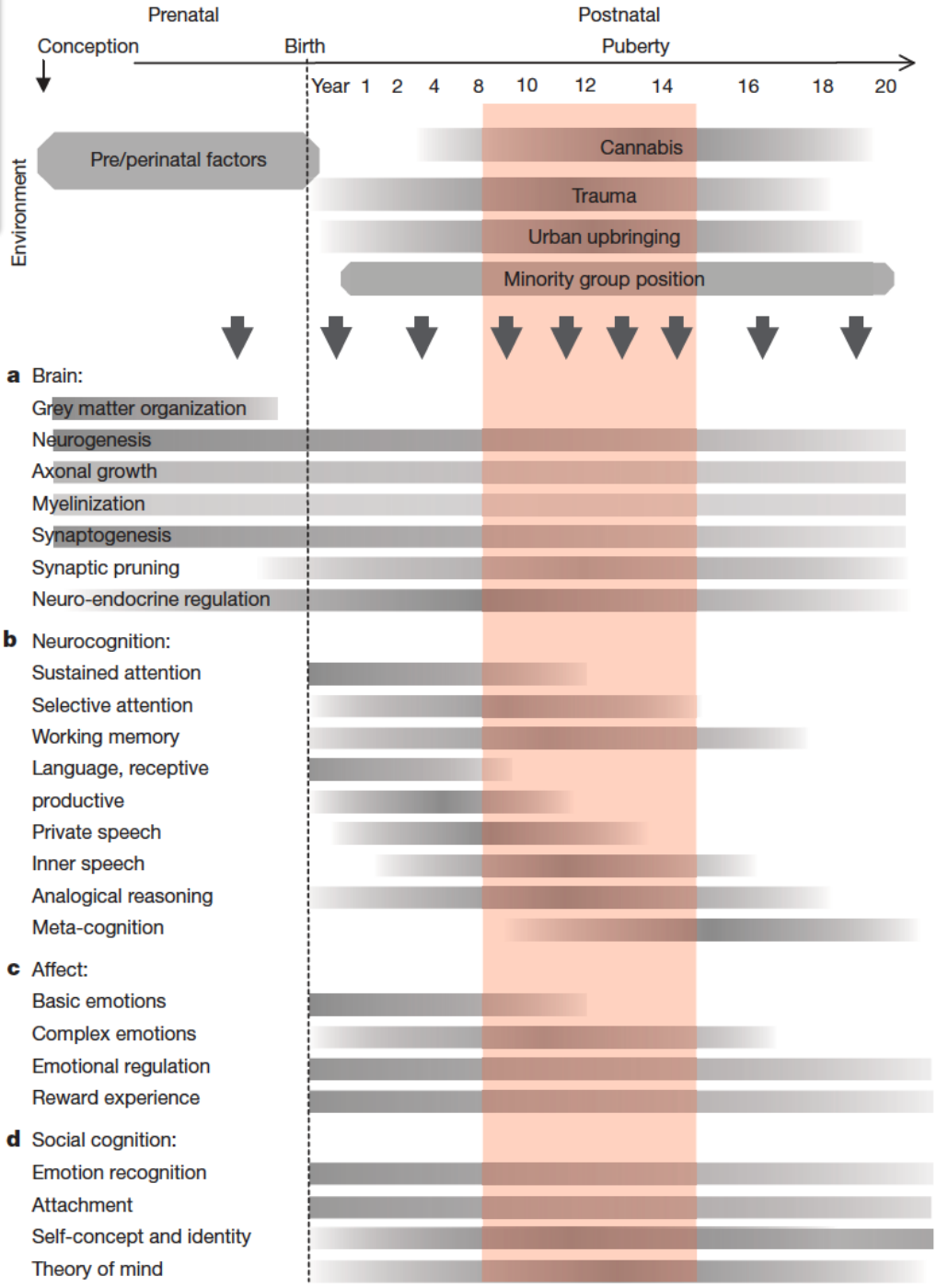

Figure 4 | Schematic illustration of the approximate timing of the development of the human brain, functional abilities, and impact of environmental exposures. Arrows reflect impact of environmental factors associated with psychotic syndrome. Grey bars indicate the approximate developmental periods during which the processes depicted in the column are active (in **a**, around environmental exposures) or are being established/develop (in **b**, **c** and **d**). The grey colour intensities of the bars in **a**–**d**, and around the environmental exposures, indicate the approximate magnitude of the process or the approximate strength of development or maximum exposure over time. The developmental windows for the functional abilities in neurocognition, affect and social cognition (in **b**, **c** and **d**) are only given for the postnatal period. The red box indicates the window of maximum additive environmental impact.

"Approccio dimensionale":

Childhood trauma is associated with the (1)narrow concept of schizophrenia, (2)the broader spectrum of psychotic disorder as well as with (3) subthreshold expressions of psychotic experiences in non-ill people.

J. van Os et al. *Schizophrenia Bulletin,* 2016

Schizophr Bull. 2016 May;4 2(3):542-9.

Different Paths to Core Pathology: The Equifinal Model of the Schizophrenia Syndrome.

Green IW[1], Glausier JR[2].

Jill R Glausier
University of Pittsburgh

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[2]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA glausierjr@upmc.edu.

Abstract

Schizophrenia is a clinically heterogeneous disorder that is perhaps more accurately characterized as "the schizophrenia syndrome." This clinical heterogeneity is reflected in the heterogeneous neurobiological presentations associated with the illness. Moreover, even highly specific neural aberrations that are associated with distinct symptoms of schizophrenia are linked to a wide range of risk factors. As such, any individual with schizophrenia likely has a particular set of risk factors that interact and converge to cross the disease threshold, forming a particular etiology that ultimately generates a core pathophysiology. This core pathophysiology may then produce 1 or more symptoms of schizophrenia, leading to common symptoms across individuals in spite of disparate etiologies. As such, the schizophrenia syndrome can be considered as an *equifinal* entity: a state of dysfunction that can arise from different upstream etiologies. Moreover, schizophrenia etiologies are multifactorial and can involve the interactive effects of a broad range of genetic, environmental, and developmental risk factors. Through a consideration of how disparate etiologies, caused by different sets of risk factors, converge on the same net dysfunction, this paper aims to model the equifinal nature of schizophrenia symptoms. To demonstrate the equifinal model, we discuss how maternal infection and adolescent cannabis use, 2 recognized schizophrenia risk factors, may interact with other genetic, environmental, and/or developmental risk factors to cause the conserved clinical presentation of impaired working memory.

…etiopatogenesi multifattoriale

Neuroscience & Biobehavioral Reviews, Volume 83, December 2017, Pages 226-237

Review article

Epigenetics and gene expression profile in first-episode psychosis: The role of childhood trauma

SimonaTomassi, SarahTosato

Department of Neurosciences, Biomedicine and Movement Sciences, Section of Psychiatry, University of Verona, Verona, Italy

Highlights

- Childhood Trauma (CT) influences epigenetics and gene expression; and is a risk factor for psychosis.
- We included 41 studies on CT, epigenetics, gene expression, and First-Episode Psychosis (FEP).
- DNA hypo-methylation and BDNF reduced gene-expression was shown in FEP with CT. *…perdita del trofismo neuronale*
- SLC6A4 hyper-methylation and hypo-expression was found in healthy subjects with CT.
- FEP itself was also associated with global DNA hypo-methylation.

npj | Schizophrenia

www.nature.com/npjschz

REVIEW ARTICLE OPEN

Early interventions in risk groups for schizophrenia: what are we waiting for?

Iris E Sommer[1], Carrie E Bearden[2], Edwin van Dellen[1], Elemi J Breetvelt[1], Sasja N Duijff[1], Kim Maijer[1], Therese van Amelsvoort[3], Lieuwe de Haan[4], Raquel E Gur[5], Celso Arango[6], Covadonga M Díaz-Caneja[6], Christiaan H Vinkers[1] and Jacob AS Vorstman[1]

Intervention strategies in adolescents at ultra high-risk (UHR) for psychosis are promising for reducing conversion to overt illness, but have only limited impact on functional outcome. Recent studies suggest that cognition does not further decline during the UHR stage. As social and cognitive impairments typically develop before the first psychotic episode and even years before the UHR stage, prevention should also start much earlier in the groups at risk for schizophrenia and other psychiatric disorders. Early intervention strategies could aim to improve stress resilience, optimize brain maturation, and prevent or alleviate adverse environmental circumstances. These strategies should urgently be tested for efficacy: the prevalence of ~1% implies that yearly ~22 in every 100,000 people develop overt symptoms of this illness, despite the fact that for many of them—e.g., children with an affected first-degree family member or carriers of specific genetic variants—increased risk was already identifiable early in life. Our current ability to recognize several risk groups at an early age not only provides an opportunity, but also implies a clinical imperative to act. Time is pressing to investigate preventive interventions in high-risk children to mitigate or prevent the development of schizophrenia and related psychiatric disorders.

npj Schizophrenia (2016) **2,** Article number: 16003; doi:10.1038/npjschz.2016.3; published online 9 March 2016

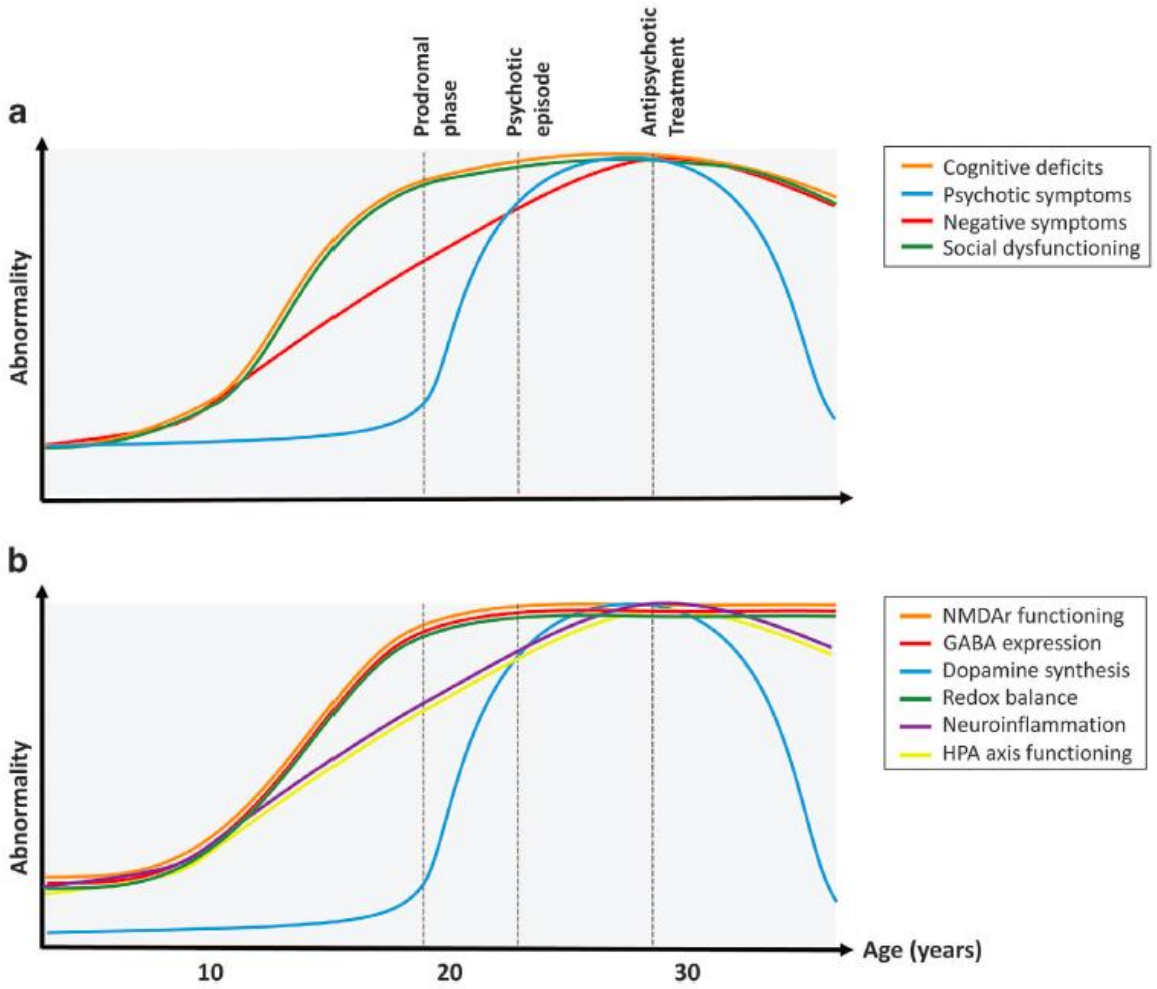

Figure 1. Hypothesized typical course of schizophrenia. (**a**) shows the clinical course of the disease. (**b**) shows the hypothesized course of the underlying molecular mechanisms.

Stati mentali a rischio ed esordi psicotici

……dimensioni psicopatologiche

Schizophr Bull. 2016 Dec 29. pii: sbw178. doi: 10.1093/schbul/sbw178. [Epub ahead of print]

The Search for Environmental Mechanisms Underlying the Expression of Psychosis: Introduction.

van Os J[1,2], Reininghaus U[1,3], Meyer-Lindenberg A[4].

J. van Os et al

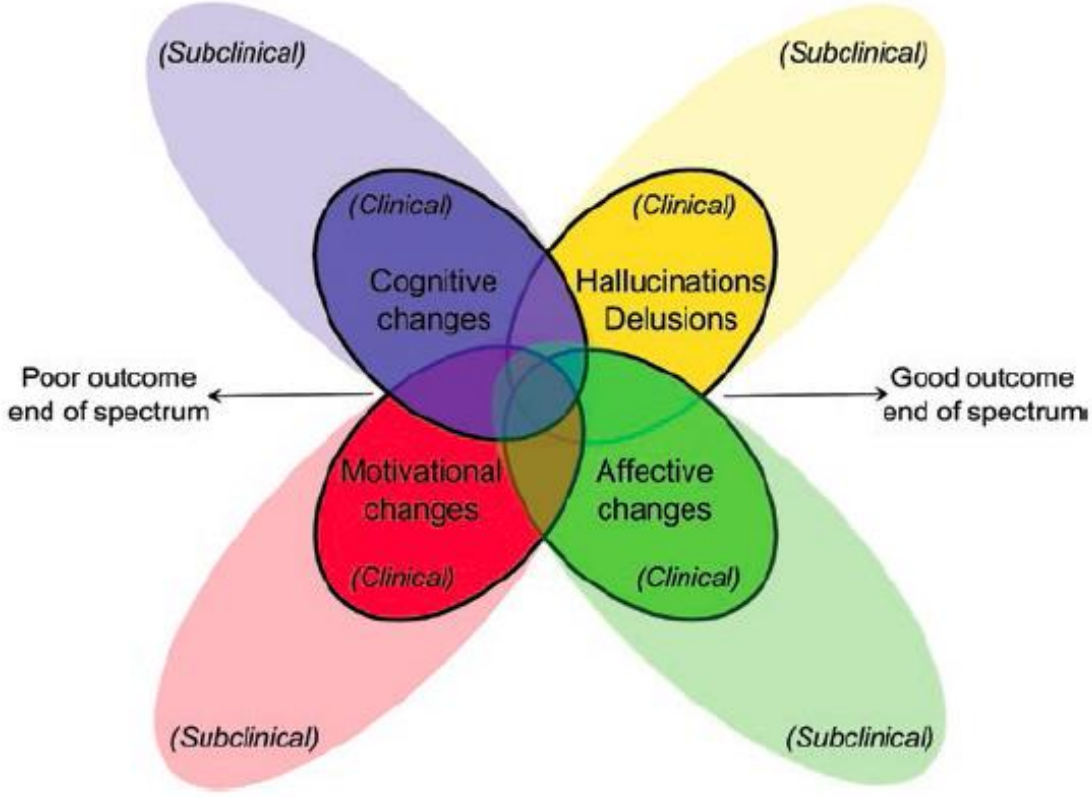

Fig. 1. Phenotypic complexity of psychosis: overlapping dimensional domains of psychopathology with clinical and subclinical expression.

These dimensions are "transdiagnostic," in the sense that they are expressed in varying degrees across the diagnostic categories making up the clinical psychosis spectrum.

And their ***cognitive, neural, and social mechanisms*** are likely transdiagnostic as well.

Schizophr Bull. 2017 Jan;43(1):64-74.

A Severity-Based Clinical Staging Model for the Psychosis Prodrome: Longitudinal Findings From the New York Recognition and Prevention Program

Carrión RE, Correll CU, Auther AM and Cornblatt BA

Clinical staging improved the possibility of intervening during the psychosis prodrome to limit progression of illness. The current study aimed to validate a novel 4-stage severity-based model with a focus on clinical change over time and risk for conversion to psychosis. One hundred seventy-one individuals at clinical high risk (CHR) for psychosis were followed prospectively (3 ± 1.6 y) as part of the Recognition and Prevention (RAP) program and divided into 4 diagnostic stages according to absence/presence and severity of attenuated positive symptoms. Twenty-two percent of the combined sample recovered (no prodromal symptoms) by study outcome. The negative symptoms only subgroup had the highest symptom stability (70%), but the lowest conversion rate at 5.9%. The subgroup with more severe baseline attenuated positive symptom levels had a higher conversion rate (28%) and a more rapid onset when compared to the moderate attenuated positive symptom subgroup (11%). Finally, the Schizophrenia-Like Psychosis (SLP) subgroup showed low stability (3%), with 49% developing a specific psychotic disorder. The proposed stage model provides a more finely grained classification system than the standard diagnostic approach for prodromal individuals. All 4 stages are in need of early intervention because of low recovery rates. The negative symptom only stage is possibly a separate clinical syndrome, with an increased risk of functional disability. Both subgroups with attenuated positive symptoms are appropriate for studying the mechanisms of psychosis risk, however, individuals with more severe baseline positive symptoms appear better suited to clinical trials. Finally, the SLP category represents an intermediate outcome group appropriate for preventative intervention research but questionable for inclusion in prodromal studies of mechanisms.

Schizophrenia Research 184 (2017) 32–38

Using clinical information to make individualized prognostic predictions in people at ultra high risk for psychosis

Andrea Mechelli [a,*], Ashleigh Lin [b], Stephen Wood [c,d], Patrick McGorry [e,f], Paul Amminger [e,f], Stefania Tognin [a], Philip McGuire [a], Jonathan Young [g], Barnaby Nelson [e,f,1], Alison Yung [h,i,1]

Measures to prediction "converters" vs "non-converters"

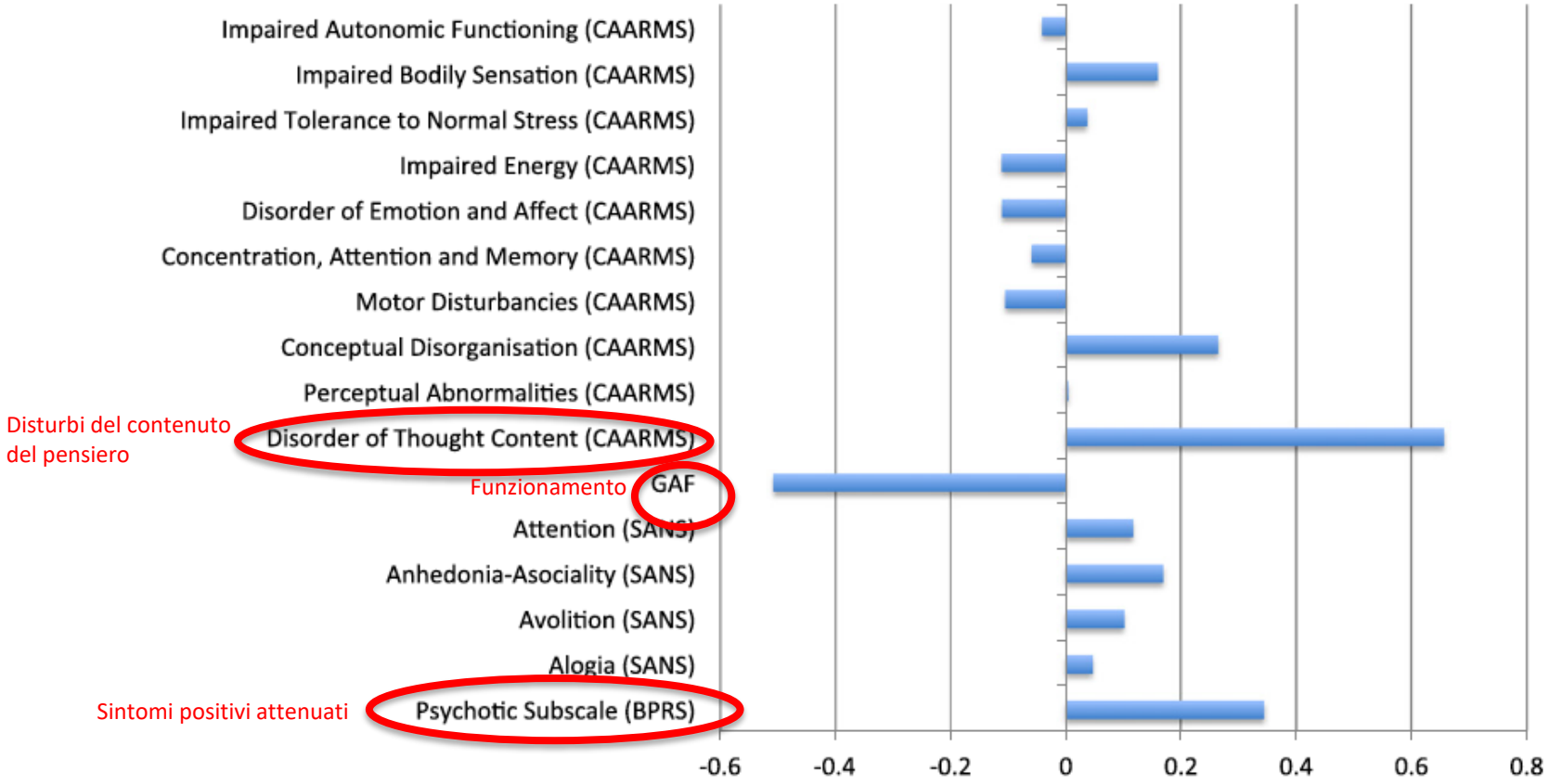

Fig. 1. Relative contributions of clinical measures to prediction of long-term clinical outcome (i.e. converters versus non-converters). A positive weight value indicates that a measure contains valuable information for identifying converters, whereas a negative value indicates that it contains valuable information for identifying non-converters.

Schizophrenia Research 184 (2017) 32–38

Using clinical information to make individualized prognostic predictions in people at ultra high risk for psychosis

Andrea Mechelli [a,*], Ashleigh Lin [b], Stephen Wood [c,d], Patrick McGorry [e,f], Paul Amminger [e,f], Stefania Tognin [a], Philip McGuire [a], Jonathan Young [g], Barnaby Nelson [e,f,1], Alison Yung [h,i,1]

Measures to prediction "poor" vs "good functioning"

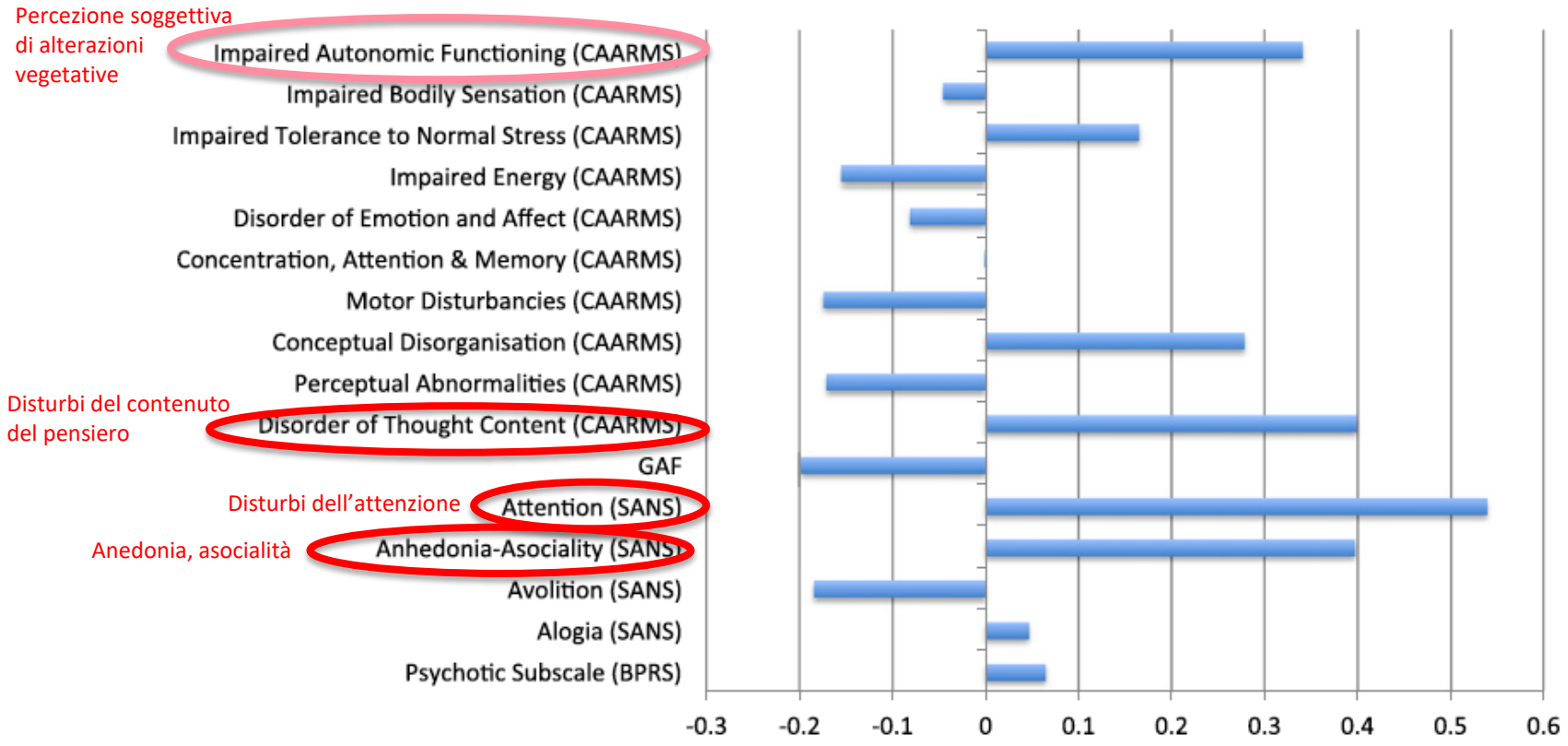

Fig. 2. Relative contributions of clinical measures to prediction of long-term functional outcome (i.e. poor versus good functioning). A positive weight value indicates that a measure contains valuable information for identifying low-functioning individuals, whereas a negative value indicates that it contains valuable information for identifying high-functioning individuals.

Eur Child Adolesc Psychiatry. 2016 Oct;25(10):1091-102. doi: 10.1007/s00787-016-0832-7. Epub 2016 Feb 26.

Attenuated psychotic and basic symptom characteristics in adolescents with ultra-high risk criteria for psychosis, other non-psychotic psychiatric disorders and early-onset psychosis.

Lo Cascio N[1,2], Saba R[2], Hauser M[3,4,5], Vernal DL[6], Al-Jadiri A[3], Borenstein Y[3], Sheridan EM[3], Kishimoto T[3,4,5,7], Armando M[1], Vicari S[1], Fiori Nastro P[2], Girardi P[8], Gebhardt E[2], Kane JM[3,4,5,9], Auther A[3,4], Carrión RE[3,4,5], Cornblatt BA[3,4,5], Schimmelmann BG[10], Schultze-Lutter F[10], Correll CU[11,12,13,14].

Abstract

While attenuated psychotic symptoms (APS) and basic symptoms (BS) are the main current predictors of psychosis in adults, studies in adolescents are scarce. Thus, we (1) described the prevalence and severity of positive, negative, disorganization, general, and basic symptoms in adolescent patients at ultra-high risk for psychosis (UHR), with other non-psychotic psychiatric disorders (PC) and with early-onset psychosis (EOP); and (2) investigated BS criteria in relation to UHR criteria.

Sixty-nine 12–18-year-old adolescents (15.3 ± 1.7 years, female = 58.0 %, UHR = 22, PC = 27, EOP = 20) were assessed with the structured interview for prodromal syndromes (SIPS) and the schizophrenia proneness instrument-child and youth version (SPI-CY). Despite similar current and past 12-month global functioning, both UHR and EOP had significantly higher SIPS total and subscale scores compared to PC, with moderate-large effect sizes. Expectedly, UHR had significantly lower SIPS positive symptom scores than EOP, but similar SIPS negative, disorganized, and general symptom scores.

Compared to PC, both EOP and UHR had more severe basic thought and perception disturbances, and significantly more often met cognitive disturbances criteria (EOP = 50.0 %, UHR = 40.9 %, PC = 14.8 %).

Compared to UHR, both EOP and PC significantly less often met cognitive-perceptive BS criteria (EOP = 35.0 %, UHR = 68.2 %, PC = 25.9 %). BS were significantly more prevalent in both EOP and UHR than PC, and UHR were similar to EOP in symptom domains.

Given the uncertain outcome of adolescents at clinical high-risk of psychosis, future research is needed to determine whether the combined assessment of early subjective disturbances with observable APS can improve the accuracy of psychosis prediction.

Schizophrenia Research 174 (2016) 71–76

Cognitive functioning in individuals at ultra-high risk for psychosis, first-degree relatives of patients with psychosis and patients with first-episode schizophrenia

Cai-Lan Hou [a,1], Yu-Tao Xiang [b,*], Zhong-Lei Wang [c,1], Ian Everall [d], Yi Tang [a], Chengjia Yang [a], Ming-Zhi Xu [a], Christoph U. Correll [e], Fu-Jun Jia [a,**]

Objective: The aim of the present study was to investigate and compare cognitive functioning of first-degree relatives of people with schizophrenia who were also at ultra-high risk (UHR) for psychosis with patients with first-episode (FE) schizophrenia, first degree relatives of patients not fulfilling UHR criteria (FDR), and healthy control (HC) subjects.

Method: Forty subjects in each gro
neurocognitive test battery, includi
Word Test (attention), Digit Symbol
bal Leaning Test-Revised (HVLT-R, v

Results: Functioning in all the cognit
groups. After controlling for covar
$P < 0.001$), DST ($F_{(7160)} = 38.9$, $P <$
Test ($F_{(7160)} = 36.2$, $P < 0.001$), St
$P < 0.001$) between the four groups,
between the FE and FDR groups, wh
group had the poorest cognitive fun

Conclusion: The results indicate that
memory exist in both UHR and FDR
and UHR and schizophrenia, longitu

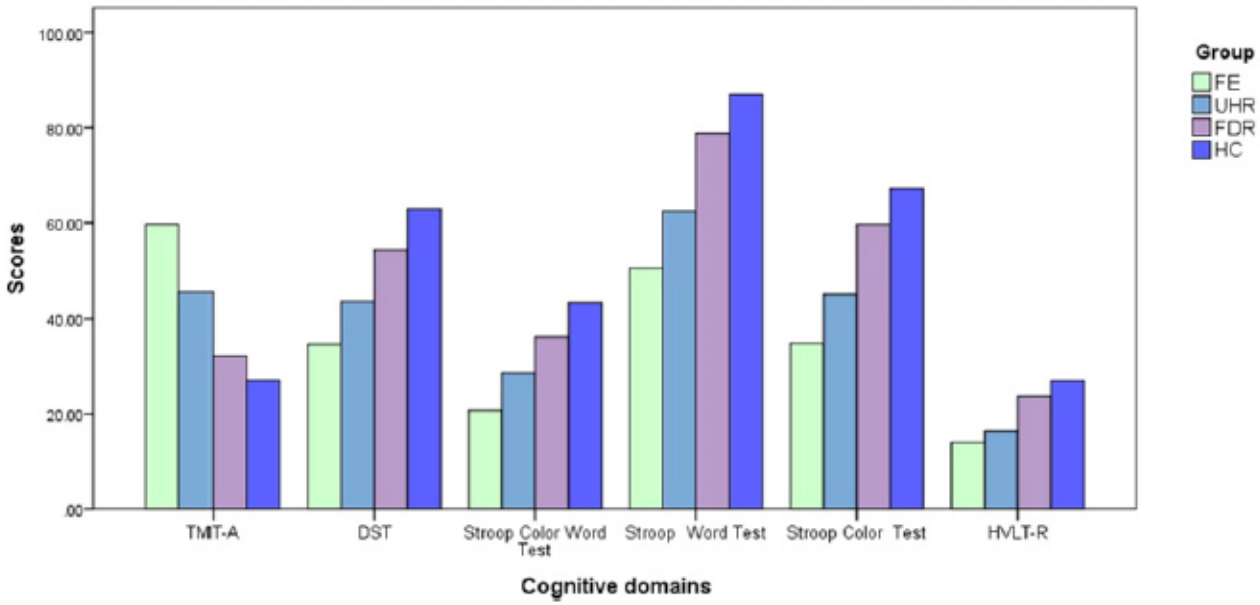

Fig. 1. Neurocognitive performances of different groups.

Disturbi della cognizione sociale

….inferenze sullo stato mentale degli altri, teoria della mente (false credenze)

…..decodifica delle emozioni altrui

…..percezione sociale

….dare un senso a se stessi, agli altri e alle situazioni sociali

…attribuzione della causalità degli eventi (bias)

Disfunzioni cognitive e soprattutto deficit dell'intelligenza sociale e della "teoria della mente", si sono rivelati possibili indici nel prevedere il rischio di transizione e l'outcome funzionale.

Schizophrenia Research 189 (2017) 146–152

Mapping structural covariance networks of facial emotion recognition in early psychosis: A pilot study

Lisa Buchy [a,*], Mariapaola Barbato [a], Carolina Makowski [b], Signe Bray [c,d], Frank P. MacMaster [e,f], Stephanie Deighton [a], Jean Addington [a]

Our data suggest that early psychosis may be characterized by an underlying reduction in brain network integration in facial emotion recognition networks (right fusiform face area, superior parietal cortex, orbitofrontal cortex).

Psychiatry Research: Neuroimaging 259 (2017) 34–41

Neural basis for inferring false beliefs and social emotions in others among individuals with schizophrenia and those at ultra-high risk for psychosis

Yosuke Takano[a], Yuta Aoki[a,b], Noriaki Yahata[a], Yuki Kawakubo[c], Hideyuki Inoue[a], Norichika Iwashiro[a], Tatsunobu Natsubori[a], Shinsuke Koike[a], Wataru Gonoi[d], Hiroki Sasaki[d], Hidemasa Takao[d], Kiyoto Kasai[a], Hidenori Yamasue[a,e,*]

Both the UHR and schizophrenia groups were characterized by hyperactivity in superior temporal sulcus and hypoactivity in inferior frontal gyrus

Schizophr Res. 2016 March ; 171(1-3): 176–181. doi:10.1016/j.schres.2016.01.017.

Social Cognition over time in Individuals at Clinical High Risk for Psychosis: findings from the NAPLS-2 cohort

North American Prodrome Longitudinal Study

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

The CHR group performed poorer on all tests of social cognition across all time points compared to HCs.

Curr Top Behav Neurosci. 2017;30:397-409. doi: 10.1007/7854_2015_427.

Social-Cognitive Deficits in Schizophrenia.

Mier D[1], Kirsch P[2].

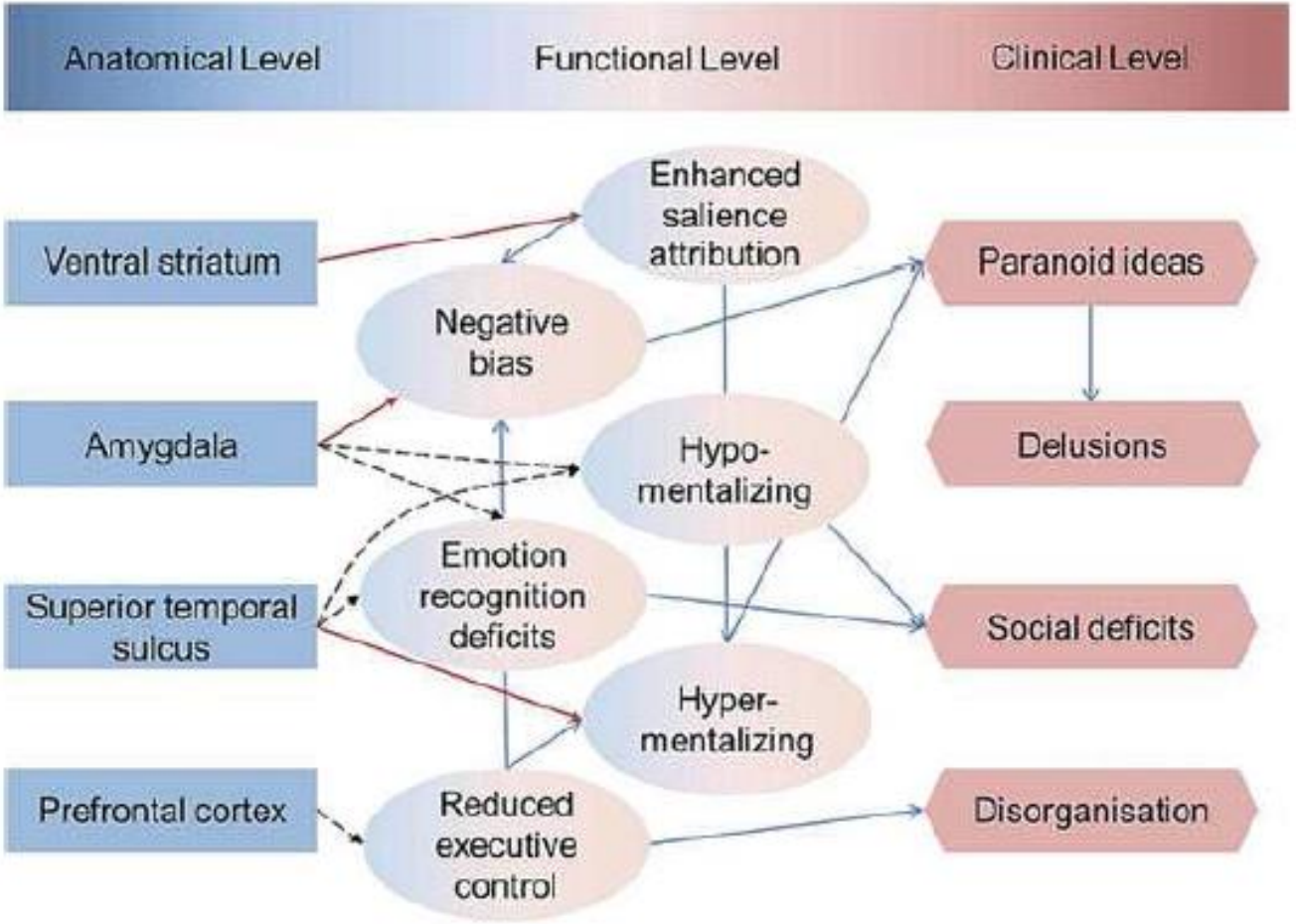

Fig. 1 Model combining the social brain with the dopamine hypothesis to explain the development of schizophrenia pathology. *Note*: *Blue arrows* Leads to, *Red arrows* Hyperactivation, *Dotted arrows* Hypoactivation

…..Disturbi cognitivi ed outcome

Schizophrenia Research (2017)

The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia

Susie Fu [a,b], Nikolai Czajkowski [a,c], Bjørn Rishovd Rund [a,b,*], Anne-Kari Torgalsbøen [a]

[a] Department of Psychology, University of Oslo, PO Box 1094, 0373 Oslo, Norway
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[c] Division of Mental Health, Norwegian Institute of Public Health, PO Box 4404, 0403 Oslo, Norway

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Functional outcome
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ABSTRACT

Although cognitive impairments are consistently linked to functional outcome in chronic schizophrenia, the relationship remains unclear for patients with first-episode schizophrenia. The objective of this present study was to determine whether there are distinct developmental trajectories for functional outcome in patients with different levels of baseline cognition. The present study has a multi-follow-up design, and includes data from six follow-ups over four years. Assessments were conducted yearly, apart from the first year where assessments were conducted every six months. A total of 28 patients with first-episode schizophrenia participated in the study, with 79% of patients retained at the 4-year follow-up. Cognition was assessed with MATRICS Consensus Cognitive Battery. Functional outcomes were obtained through Global functioning: Social and Global functioning: Role. Data were analyzed with linear multilevel models. Results suggest steady improvements in social and role functioning among the patients across the four year period. Baseline attention, verbal learning, and verbal working memory were significantly associated with social outcome. Role functioning was significantly associated with attention, verbal working memory, and reasoning/problem solving. Furthermore, the rate of change in social outcome varies among patients depending on their baseline level of attention and verbal working memory, with the lowest scoring group showing the least improvement over the years. The subgroup of patients with the largest cognitive impairments at the onset of the disorder shows limited improvements in social functioning compared to higher functioning groups.

The HELPER programme: HEalthy Living and Prevention of Early Relapse – three exploratory randomised controlled trials of phase-specific interventions in first-episode psychosis

Max Marshall, Christine Barrowclough, Richard Drake, Nusrat Husain, Fiona Lobban, Karina Lovell, Alison Wearden, Tim Bradshaw, Christine Day, Mike Fitzsimmons, Rebecca Pedley, Ruth Piccuci, Alicia Picken, Warren Larkin, Barbara Tomenson, Jeff Warburton and Lynsey Gregg

NHS
National Institute for Health Research

Chapter 1 Cognitive remediation workstream: IMproving PArticipation in Cognitive Therapy (IMPACT) – a randomised controlled trial

This chapter has been published in a shorter format as Drake R, Day J, Picucci R, Warburton J, Larkin W, Husain N, *et al.* A naturalistic, randomized, controlled trial of cognitive remediation combined with cognitive–behavioural therapy after first-episode non-affective psychosis. *Psychol Med* 2014;**44**:1889–99. Available on CJO2013. doi:10.1017/S0033291713002559.

Abstract

Background: Schizophrenia can be an intractable illness and so it is important to understand how far combining therapies creates synergy. Cognitive remediation (CR), which improves neuropsychological deficits, might combine well with cognitive–behavioural therapy (CBT), which improves symptoms.

Hypothesis: Following a first episode of non-affective psychosis, CR will enhance the efficacy and efficiency of subsequent CBT.

Methods: *Diagnostic and Statistical Manual of Mental Disorders* – Fourth Edition (DSM-IV) non-affective psychosis patients aged 18–35 years who were on waiting lists for routine CBT from NHS early-intervention services were randomised to receive either computerised CR over 12 weeks supported by a trained support worker or time-matched social contact (SC). All then received 6–30 weeks of CBT. The primary outcome was the Psychotic Symptom Rating Scales, blind-rated at baseline, after remediation (12 weeks) and after CBT (42 and 54 weeks). Secondary outcomes included duration of CBT, cognition, insight, other symptoms, relapse and self-esteem.

Key findings

- Cognitive remediation after first episodes of non-affective psychosis improved executive function but no other neuropsychological test scores.
- After CR, the duration of CBT was much shorter but there was no difference in efficacy.
- At the end of CBT, those who had received CR had significantly better insight.

(World Psychiatry 2017;16:200–206)

A critique of the "ultra-high risk" and "transition" paradigm

Jim van Os[1,2], Sinan Guloksuz[1,3]

[1]Department of Psychiatry and Psychology, Maastricht University Medical Centre, Maastricht, the Netherlands; [2]King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK; [3]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

The transdiagnostic expression of psychotic experiences in common mental disorder (anxiety/depression/substance use disorder) is associated with a poorer prognosis, and a small minority of people may indeed develop a clinical picture that meets criteria for schizophrenia. However, it appears neither useful nor valid to observe early states of multidimensional psychopathology in young people through the "schizo"-prism, and apply misleadingly simple, unnecessary and inefficient binary concepts of "risk" and "transition". A review of the "ultra-high risk" (UHR) or "clinical high risk" (CHR) literature indicates that UHR/CHR samples are highly heterogeneous and represent individuals diagnosed with common mental disorder (anxiety/depression/substance use disorder) and a degree of psychotic experiences. Epidemiological research has shown that psychotic experiences are a (possibly non-causal) marker of the severity of multidimensional psychopathology, driving poor outcome, yet notions of "risk" and "transition" in UHR/CHR research are restrictively defined on the basis of positive psychotic phenomena alone, ignoring how baseline differences in multidimensional psychopathology may differentially impact course and outcome. The concepts of "risk"

It may be more productive to consider the **full range of person-specific psychopathology** in all young individuals who seek help for mental health problems, instead of "policing" youngsters for the transdiagnostic dimension of psychosis.

Instead of the relatively inefficient medical high risk approach, a **public health perspective**, focusing on **improved access** to a low-stigma, high-hope, small scale and youth-specific environment with acceptable language and interventions may represent a more useful and efficient strategy.