JOURNAL OF PSYCHOPATHOLOGY 2024;30:143-148
DOI: 10.36148/2284-0249-N430

Review

Disorganization in early psychosis: historical and clinical considerations

Arianna Biancalani, Michele Occhionero, Lorenzo Pelizza

Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum University di Bologna, Bologna, Italy

SUMMARY

In the last two decades, the resurgence of the "late neurodevelopment" hypothesis of psychosis has brought into focus Kahlbaum's and Hecker's clinical reports of adolescents who, as a result of a loss of psychic energy, showed a rapidly progressive cognitive impairment leading to functional and behavioral disorganization. In line with their psychopathological descriptions of hebephrenia and heboidophrenia, disorganization could represent a core clinical dimension of early psychosis, especially during its prodromal stages (such as in people with ARMS) and during adolescence. Although under-investigated, disorganized features seem to be associated with early neurobiological alterations, functioning decline, and poorer outcomes and prognosis. Greater clinical attention on disorganization in young help-seeking individuals from researchers and clinicians is thus needed. This paper first summarized past conceptualization of heboidophrenia and hebephrenia as developmental illnesses. Moreover, a literature search was conducted on PUBMED/MEDLINE and PsycInfo, looking for "disorganization" AND "early psychosis" OR "ultra-high risk", OR "clinical high risk" for psychosis. We then discussed recent clinical and neurobiological findings on disorganization in individuals with early psychosis, highlighting its prognostic significance.

Key words: disorganization, clinical high risk, ultra-high risk, early psychosis, psychopathology, neurobiology

Introduction

Disorganization is a common and easily misused term in everyday clinical practice [1]. As a symptom mostly associated with Schizophrenia Spectrum Disorders (SSD), it provides description for a broad range of manifestations, mainly concerning behavior, thought and speech[2]. Dating back to Bleuler [3], the core definition of schizophrenia itself was built around the recognition of a disease where thought (associations), emotions (abnormal affect) and behavior (autistic behavior and ambivalence) seemed to lose coordination and coherence. Consequently, depending on these dimensions, the term "disorganized" may acquire mildly different meanings, as a descriptor[4].

From "Hebephrenia" to disorganization: a journey

When was the concept of disorganization firstly introduced? The first attempt to conceptualize the now-called disorganization features in psychosis is very likely referable to Karl Kahlbaum and Ewald Hecker. In 1871, in an enlightening article by Hecker ("A different version of Vesania Typica - from vē ["out"] + sānus ["sane, healthy"]") [5], the usually deteriorating form of psychosis was described as classically having its first appearance at a *young age*. That new type of Vesania was called "*hebephrenia*" (from the Greek hḗbē = "youth"), a disease "…whose variable symptoms are associated with the tremendous mental and physical changes that occur shortly after the onset of puberty" [6]. Further developing Kahlbaum's first

Lorenzo Pelizza
E-mail: lorenzo.pelizza@unibo.it

How to cite this article: Biancalani A, Occhionero M, Pelizza L, et al. Disorganization in early psychosis: historical and clinical considerations. Journal of Psychopathology 2024;30:143-148. https://doi.org/10.36148/2284-0249-N430

description of "*paraphrenia hebetica*" (basically an early onset psychosis) [7], Hecker argued how hebephrenia not only was characterized by an early onset, but was worth a distinct description of symptomatology, beyond the unitary model of psychosis [8]. What seemed to characterize its presentation was a silly behavior, inappropriate affect, hypochondriac fear, hardly systematized delusions, and hallucinations.

Notably, one of Kahlbaum and Hecker's main contributes to the debate around psychosis was to prioritize, alongside the current neurobiological hypothesis, the role played by psychological factors and developmental issues. In that same article, indeed, he states: "… Ordinarily, puberty and its attendant psychological renewal and transformation of the self are more or less over by this time. But in hebephrenia, this psychological process of puberty – which even under normal conditions displays many prominent symptoms – has become pathologically permanent. The psychological features of this period of transition are pathologically exaggerated at first, but ultimately give way to the specific end stage of hebephrenic dementia" [5].

Despite the characterizing effort by Kahlbaum and Hecker, it wasn't until Emil Kraepelin included hebephrenia as a subgroup of Dementia Praecox (DP), that this specific mental illness was considered part of the SSD [9]. Indeed, Kraepelin got to the clear and known subdivision of DP in "hebephrenic", "catatonic" and "paranoid" only in the 6th edition of his manual, published in 1899 [10]. For the first time, Kraepelin described hebephrenia as a unitary syndrome (with no severity subdivision), in close and continuous contact with the other two forms of DP. The path through which hebephrenia got included was made of many changes in its description, such as the increasing relevance of psychotic and catatonic symptoms and disorganized behavior, compared to the thought disturbances described by Hecker. This trend was for sure to be read in the light of Kraepelin's attempt to unify the different forms of what he believed DP was, in clear opposition to the manic-depressive psychosis. His effort to create a comprehensive model of the disease inevitably led to the loss of what the term hebephrenia was meant to describe in a specific way (e.g. the close link to puberty and adolescence), yet determined the first relevant conceptualization of the disorganization syndrome [11].

Kraepelin's work, in the wake of the German tradition in the field, determined a shift in psychiatric nosology, which ceased to be based either on etiology or pseudobiological data and started to be found on clinical observations, such as the course of illness [12]. However, in 1911, Bleuler rejected this specific emphasis on prognosis, highlighting the need for a differentiation among the diseases that he believed formed "the group of schizophrenias" [13]. By doing so, not only he gave birth to the modern term, but he also included hebephrenia as a subtype, maintaining Kraepelin's classification. Thanks to this paradigmatic change, hebephrenia kept being diagnosed during the first decades of the 20th century [9].

Despite the growing understanding of the disease, it became progressively clear that many clinical descriptions in psychiatry were still too vague and basically contributed to a general instability of diagnoses, both from a geographical and temporal perspective [9]. On this side, the work of Kurt Schneider was one of the main attempts to avoid subjectivity and reject data coming only from limited observations [14]. His ranks of symptoms, indeed, marked a significant effort to make psychiatric diagnoses – namely, that of schizophrenia – a more reliable tool in the hands of physicians. On that same path, yet in the United States and with a completely different theoretical point of view, the first diagnostic manuals slowly started to be drafted, drawing attention to the potentiality of statistics in nosology [12].

Looking at the history of the Diagnostic and Statistical Manual of Mental Disorders (DSM), hebephrenia was included among schizophrenia subtypes until DSM-5 [15], where all the subtypes were eliminated [16]. Originally known as hebephrenic schizophrenia in DSM-II [17], it was later referred to as "disorganized schizophrenia", marking the relationship between the two terms. What led to the removal of these categories was the increasing acknowledgement that, despite their historical and theoretical meaning, they had low stability and reliability [18]. Also, thanks to the progressive introduction of cluster analytics methods, no significant correspondence was found to support the classification [11]. However, disorganization in early psychosis refers to a cluster of symptoms that can manifest in individuals experiencing the onset of a psychotic disorder (such as schizophrenia). These symptoms typically include disordered thinking, disorganized speech, and disorganized behavior [11].

Disorganized thinking can cause people to have difficulty maintaining a train of thought [13]. People with disorganized speech might speak incoherently, respond to questions with unrelated answers, say illogical things, or shift topics frequently. Signs of disorganized speech often involve loose associations (rapidly shifting between topics with no connections between them), perseveration (repeating the same things over and over again), making up words that only have meaning to the speaker, and/or using rhyming words without meaning. When disorganized thinking is severe, it can be nearly impossible to understand what the person is saying. Disorganized behavior negatively impacts goal-directed behavior. A person with disorganized schizophrenia is likely to have difficulty beginning a specific task (ex:

cooking a meal) or difficulty finishing a task. Independent functioning is exceptionally difficult due to this gross disorganization.

Disorganized behavior can manifest as a decline in overall daily functioning, unpredictable/inappropriate emotional responses, lack of impulse control, behaviors that appear bizarre or lack purpose, and/or routine behaviors (such as bathing, dressing, or brushing teeth) that can be severely impaired or lost [11]. Additionally, inappropriate affect (including the way emotions are expressed) can also be identified. Specifically, people with disorganized emotionality exhibit mannerisms and affect that is inappropriate to the situation (such as laughing at something sad) [13].

The psychometric perspective

During the past 50 years, standardized diagnostic tools (such as scales and scores) started being more and more common in psychiatry[19]. At first, they mainly found their utility in research, yet they gradually became of common use in clinical practice, as well. Since different scales for schizophrenia were rapidly developed, understanding which model fitted at best became a priority in the field.

Factor analysis and cluster analysis are two of the most useful statistical methods chosen to make sense of data coming from the administration of such scales [20]. What these statistical tools allow to do is to group variables together, in order to obtain fewer dimensions of symptoms out of the many items assessments are usually made of. Thus, this process simplifies the interpretation of data and allows researchers to verify the reliability of the scales they aim to use. As for schizophrenia, in the 1980s, factor analysis of rating scales brought to the identification of three main subtypes: positive symptoms, negative symptoms and disorganization symptoms [21]. Yet, one limit of this type of analysis is the variability of the number of dimensions that can be found, depending on the number of variables (items of the scales) being used. This basically means that the more items are analyzed, the more sub-syndromes are likely to be found [22].

Nowadays, one of the most reliable tools for schizophrenia is the "Positive And Negative Syndrome Scale" (PANSS) [23]. So far, factor analysis conducted using the PANSS or similar scales for schizophrenia, led to the definition of different main dimensions, ranging from three to seven [24]. Despite such variability, the most used one is the five-factor model of the PANSS, which is made up of the following dimensions: positive factor, negative factor, cognitive factor, excitement, and depression factor [25]. Nonetheless, for reasons including methodological differences and cultural factors [26], no model has gained broad consensus to date[27].

Heboidophrenia: a mild form of hebephrenia

As previously stated, when the concept of hebephrenia was included in Kraepelin's model, it was redefined as a unitary disease, in close link with the other subgroups of Dementia Praecox [10]. In Kahlbaum's view of the disease, on the other hand, hebetic forms of mental disorders were two: hebephrenia and "heboidophrenia"[28,29]. The latter was conceived as a milder form, with better outcomes and fluctuating symptoms, such as thought disorders and a typical "deterioration in morality" [30].

Nowadays, this concept might draw attention to how "disorganization" (which derives from "hebephrenia") is a core psychopathological dimension in early psychosis. That might be worth of investigation even in those forms of "milder" or "upcoming" psychosis, such as At-Risk Mental States" (ARMS) [31,32]. Therefore, starting from this historical background, a narrative review examining the main clinical findings on disorganization in subjects with early psychosis reported in the literature to date was conducted. From a methodological point of view, the search was performed on MEDLINE/PubMed and psycInfo, looking for "disorganization" AND "early psychosis" OR "ultra-high risk", OR "clinical high risk" for psychosis in the "Title/Abstract" field. We exclusively considered papers written in English and published between January 1, 2000 and January 31, 2024. We only found 10 pertinent papers on this topic. Their main findings were discussed in the following sections of this manuscript.

Disorganization in early psychosis: clinical considerations

Interestingly, a relatively recent study [33] investigated the use of the PANSS in Ultra-High Risk mental states (UHR) and conducted factor analysis on those samples. Five factors were derived, namely "positive", "negative", "cognitive/disorganization", "anxiety/depression" and "hostility". The cognitive/disorganization factor included different items, such as conceptual disorganization, grandiosity, unusual thought content, poor attention and disturbance of volition. Despite the similarity to the factor models of PANSS for schizophrenia, no association between the cognitive/disorganization factor and neurocognitive function was found in this study [33]. In this sense, the traditional concept of disorganization (especially within the Kahlbaum and Hecker's description of hebephrenia and heboidophrenia) might shed light on the pathogenesis of psychosis and on neurobiological data recently reported and collected in the last part of neurodevelopment, between adolescence and early youth [34,35]. Indeed, in this critical period of life, the elementary, pre-psychotic symptoms (often in the form of subjective thought and language disturbances, or cognitive anomalous Self experiences) can induce a higher risk of developing psychosis (often in an insidious form

or as a personality disorder, eating disorders, or substance use disorder) [36], which will deform the character of the young person, damaging his/her harmonious development within the social environment [37].

Neural correlates of disorganization in early psychosis

In this respect, in the constitution of what is known as the "Bonn Scale for the Assessment of Basic Symptoms" (BSABS) [38], Huber and Gross followed a positivist model being able to identify an impaired neural substrate whose "lesion" could be identifiable as the cause of the observable behavioral and cognitive alterations typically shown by patients with psychosis (especially schizophrenia). The limbic system was one of the first areas considered in this theory. In particular, Huber regarded the thalamus as the area where the "lesion sine materia" or without evident neurological signs could be the cause of the alterations preceding full-blown psychosis [39]. Indeed, he believed that thalamic alterations were responsible for the disturbance of the filtering function among sensory stimuli, thus affecting the ability to establish a hierarchy in perception selection [40].

In the last two decades, especially within the ARMS paradigm [41], an attempt to clarify the neural correlates of "disorganization" as a dimension aimed to better understand the underlying pathogenesis of psychosis and potentially identify predictive neuro-markers of states at high risk of psychosis transition. However, empirical evidence on this topic is still poor. Studies conducted with functional Magnetic Resonance Imaging (fMRI) in UHR subjects are potential areas of exploration, especially when considering disorganization alone [42,43]. Cortical areas under investigation include Prefrontal Cortex, Medial Prefrontal Cortex (MPFC), Anterior Cingulate Cortex (ACC), hippocampus, and Superior Temporal Gyrus (STG) [44]. In this respect, findings are quite conflicting. A meta-analysis [45] showed a reduction in hippocampal volume in UHR subjects, and alterations in the MPFC and ACC that seemed to interfere with the "sense of self". Moreover, these neurobiological alterations appeared to precede the onset of overt psychosis, as well as structural and functional anomalies in the STG, especially in the left hemisphere, appearing early before the onset of attenuated psychotic symptoms. A more recent research [46] particularly specific regarding formal thought disorders and disorganization, assessed Gray Matter Volume (GMV) and White Matter Volume (WMV). Its findings indicated higher GMV within fronto-cingulate regions and lower GMV in occipital regions, which resulted highly predictive of developing formal thought disturbances. These results also suggested that connectivity patterns within and between long-range brain networks could represent relevant early biomarkers of formal thought disorder progression, in line with the disconnection hypothesis of schizophrenia [47,48].

Neurobiological studies on disorganization are very scarce and generally limited to first episode of psychosis. In this respect, a relatively recent research [49] reported that the connectivity of the ACC was related to the severity of disorganized behavior and disrupted domain-general control aspects of information processing in schizophrenia. More elaborate approaches involved network studies that examined the collective functioning of various brain areas. Interesting findings pertained to the Central Executive Network (CEN) and how its alterations were early and detectable in UHR individuals, so becoming promising markers for the staging and progression of psychosis [50]. This approach is less focused on specific brain regions and more on a functional view of networks. In this neuro-functional framework, some studies specifically examined Aberrant Salience (AS), showing that psychotic dimension were in several cases mediated jointly by AS and disorganized domain [51-53]. This approach also brings together positions that once appeared very distant, such as those of the psychodynamic or phenomenological tradition, where concepts like Freud's "pleasure principle" or Blankenburg's "loss of natural evidence" seem to find increasing neuro-functional support [36], and where we hope that disorganization may play a key role as a psychopathological marker to highlight the earliest influences on the overall functioning of patients in the initial deconstruction of their "sense of self".

Conclusions

In recent decades, the resurgence of the "late neurodevelopment" hypothesis of psychosis (especially schizophrenia) has brought into focus Kahlbaum's and Hecker's clinical reports of adolescents who, as a result of a putative loss of psychic energy, showed a rapidly progressive cognitive impairment leading to functional and behavioral disorganization. In line with their psychopathological descriptions of hebephrenia and heboidophrenia, disorganization could represent a core clinical dimension of early psychosis, already during its prodromal stage (such as in people with ARMS) and adolescence. Although under-investigated, disorganized features seem to be associated with early neurobiological alterations and poorer outcomes and prognosis. Greater clinical attention on disorganization in young help-seeking individuals from researchers and clinicians is thus needed.

Conflicts of interest statement

The authors declare no conflicts of interest.

Funding

This paper received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

L.P.: conceptualization;A.B and M.O.: literature search and analysis; A.B., M.O., and L.P.: writing - first draft; A.B.,M.O., and L.P.: writing - final version and reviewing.

Ethical consideration

Ethical approval and inform consent were not sought for the present paper because it is not a research study involving humans.

References

1 Pelizza L, Leuci E, Maestri D, Quattrone E, Azzali S, Paulillo G, et al. Disorganization in first episode affective psychosis: treatment response and clinical consideration from a 2-year follow-up study in a "real world" setting. Rev Psychiatr Salud mental 2023; 16: 151-158. https://doi.org/10.1016/j.rpsm.2021.12.003.

2 Pelizza L, Leuci E, Maestri D, Quattrone E, Azzali S, Paulillo G, et al. Examining disorganization in patients with first episode psychosis: Findings from a 1-year follow-up of the 'Parma early psychosis' program. Early Interv Psychiatry 2022; 16: 552-560. https://doi.org/10.1111/eip.13198.

3 Bleuler E. Dementia Praecox or the Group of Schizophrenias. International Universities Press, New York (NY), 1950.

4 Moskowitz A, Heim G. Eugen Bleuler's Dementia praecox or the group of schizophrenias (1911): a centenary appreciation and reconsideration. Schizophr Bull 2011; 37: 471-479. https://doi.org/10.1093/schbul/sbr016.

5 Hecker, E. Die Hebephrenie. Virchows Arch fur pathol Anat Physiol fur klin Med 1871; 52: 394-429. https://doi.org/10.1007/BF02329963.

6 Wilmanns K, Berrios GE, Kraam A. Ewald Hecker (1843-1909). Hist Psychiatry 2002; 13: 455-465. https://doi.org/10.1177/0957154X0201305207.

7 Quinn DK. Kahlbaum's forms of catatonia. Psychosomatics 2013; 54: 504-505. https://doi.org/10.1016/j.psym.2013.02.006.

8 Sedler MJ. The legacy of Ewald Hecker: a new translation of "Die Hebephrenie". Am J Psychiatry 1985; 142: 1265-1271. https://doi.org/10.1176/ajp.142.11.1265.

9 Kendler, KS. The development of Kraepelin's mature diagnostic concept of hebephrenia: a close reading of relevant texts of Hecker, Daraszkiewicz, and Kraepelin. Mol Psychiatry 2020; 25: 180-193. https://doi.org/10.1038/s41380-019-0411-7.

10 Kraepelin E. Psychiatrie: ein lehrbuch für studirende und aerzte, sechste vollständig umgearbeitete Auflage. Barth, Leipzig, 1899.

11 Pelizza L, Leuci E, Maestri D, Quattrone E, Azzali S, Paulillo G, et al. Disorganization in first episode schizophrenia: treatment response and psychopathological findings from the 2-year follow-up of the "Parma Early Psychosis" program. J Psychiatr Res 2021; 141: 293-300. https://doi.org/10.1016/j.jpsychires.2021.07.015.

12 Shorter E. The history of nosology and the rise of the diagnostic and statistical manual of mental disorders. Dialogues Clin Neurosci 2015; 17: 59-67. https://doi.org/10.31887/DCNS.2015.17.1/ESHORTER.

13 Maatz A, Hoff P, Angst J. Eugen Bleuler's schizophrenia—a modern perspective. Dialogues Clin Neurosci 2015; 17: 43-49. https://doi.org/10.31887/DCNS.2015.17.1/amaatz.

14 Moritz S, Gawęda Ł, Carpenter WT, Aleksandrowicz A, Borgmann L, Gallinat J, Fuchs T. What Kurt Schneider really said and what the DSM has made of it in its different editions: a plea to redefine hallucinations in schizophrenia. Schizophr Bull 2024; 50: 22-31. https://doi.org/10.1093/schbul/sbad131.

15 American Psychiatric Association (APA). Diagnostic and Statistical Manual of mental disorders, 5th Edition (DSM-5). APA Press, Arlington (VA), 2013.

16 Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. Schizophr Res 2013; 150: 3-10. https://doi.org/10.1016/J.SCHRES.2013.05.028.

17 American Psychiatric Association (APA). Diagnostic and Statistical Manual of mental disorders, II Edition (DSM-II). APA Press, Washington DC, 1968.

18 McGlashan TH, Fenton WS. Classical subtypes for schizophrenia: literature review for DSM-IV. Schizophr Bull 1991; 17: 609-632. https://doi.org/10.1093/schbul/17.4.609.

19 Maust D, Cristancho M, Gray L, Rushing S, Tjoa C, Thase ME. Psychiatric rating scales. Hand Clin Neurol 2011; 106: 227-237. https://doi.org/10.1016/B978-0-444-52002-9.00013-9.

20 Jablensky A. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. Dialogues Clin Neurosci 2010; 12: 271-287. https://doi.org/10.31887/DCNS.2010.12.3/ajablensky.

21 Liddle PF. The symptoms of chronic schizophrenia. Br J Psychiatry 1987; 151: 145-151. https://doi.org/10.1192/bjp.151.2.145.

22 Jones R. Factor Analysis. Br J Gen Pract 2018; 68: 403. https://doi.org/10.3399/bjgp18X698417.

23 Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull 1987; 13: 261-276. https://doi.org/10.1093/schbul/13.2.261.

24 Jiang J, Sim K, Lee J. Validated five-factor model of Positive and Negative Syndrome Scale for schizophrenia in Chinese population. Schizophr Res 2013; 143: 38-43. https://doi.org/10.1016/j.schres.2012.10.019.

25 Shafer A, Dazzi F. Meta-analytic exploration of the joint factors of the Brief Psychiatric Rating Scale - Expanded (BPRS-E) and the positive and negative symptoms scales (PANSS). J Psychiatr Res 2021; 138: 519-527. https://doi.org/10.1016/j.jpsychires.2021.04.016.

26 van der Gaag M, Hoffman T, Remijsen M, Hijman R, de Haan L, van Meijel B, et al. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophr Res 2006; 85: 280-287. https://doi.org/10.1016/J.SCHRES.2006.03.021.

27 Fleischhacker W, Galderisi S, Laszlovszky I, Szatmári B, Barabássy Á, Acsai K, et al. The efficacy of cariprazine in negative symptoms of schizophrenia: post hoc analyses of PANSS individual items and PANSS-derived factors. Eur Psychiatry 2019; 58: 1-9. https://doi.org/10.1016/j.eurpsy.2019.01.015.

28 Healy D. Catatonia from Kahlbaum to DSM-5. Aust N Z J Psychiatry 2013; 47: 412-416. https://doi.org/10.1177/0004867413486584.

29 De Page L, Englebert J. Heboidophrenia and pseudo-psychopathic schizophrenia: current knowledge and critical perspective. Psychopathology 2018; 51: 227-233. https://doi.org/10.1159/000488768.

30 Kraam A. Phillips P. Hebephrenia: a conceptual history. Hist Psychiatry 2012; 23: 387-403. https://doi.org/10.1177/0957154X11428416.

31 Allan SM, Hodgekins J, Beazley P, Oduola S. Pathways to care in at-risk mental states: a systematic review. Early Interv Psychiatry 2021; 15: 1092-1103. https://doi.org/10.1111/eip.13053.

32 Pelizza L, Leuci E, Quattrone E, Paulillo G, Pellegrini P. The "Parma At-Risk mental states" (PARMS) program: general description and process analysis after 5 years

of clinical activity. Early Interv Psychiatry 2023; 17: 625-635. https://doi.org/10.1111/eip.13399.

33 Yang Z, Lim K, Lam M, Keefe R, Lee J. Factor structure of the positive and negative syndrome scale (PANSS) in people at ultra-high risk (UHR) for psychosis. Schizophr Res 2018; 201: 85-90. https://doi.org/10.1016/j.schres.2018.05.024.

34 Maggini C, Dalle Luche R. Genealogia della schizofrenia: ebefrenia, dementia praecox, neurosviluppo. Feltrinelli, Milano, 2018.

35 Biancalani A, Occhionero M, Leuci E, Quattrone E, Azzali S, Paulillo G, Pupo S, Pellegrini P, Menchetti M, Pelizza L. Disorganization in individuals at clinical high risk for psychosis: psychopathology and treatment response. Eur Arch Psychiatry Clin Neurosci 2024; Jun 25. https://doi.org/10.1007/s00406-024-01855-3.

36 Maggini C, Dalle Luche R. An overview on Hebephrenia: a diagnostic cornerstone in the neurodevelopmental model of Schizophrenia. Hist Psychiatry 2022; 33: 34-46. https://doi.org/10.1177/0957154X211062534.

37 Schmidt A, Crossley NA, Harrisberger F, Smieskova R, Lenz C, Riecher-Rössler A, Lang UE, McGuire P, Fusar-Poli P, Borgwardt S. Structural network disorganization in subjects at clinical high risk for psychosis. Schizophr Bull 2017; 43: 583-591. https://doi.org/10.1093/schbul/sbw110.

38 Huber G, Gross G. The concept of basic symptoms in schizophrenic and schizoaffective psychoses. Recenti Prog Med 1989; 80: 646-652.

39 Uyttendaele T, Bouckaert F. Cenesthetic schizophrenia revisited. Tijdschr Psychiatr 2012; 54: 770.

40 Gross G. The "basic" symptoms of schizophrenia. Br J Psychiatry 1989; Suppl.: 21-25.

41 Yung AR, Yuen H, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005; 39: 964-971. https://doi.org/10.1080/j.1440-1614.2005.01714.x.

42 Karlsgodt KH, van Erp TGM, Bearden CE, Cannon TD. Altered relationships between age and functional brain activation in adolescents at clinical high risk for psychosis. Psychiatry Res Neuroimaging 2014; 221: 21-29. https://doi.org/10.1016/j.pscychresns.2013.08.004

43 Jalbrzikowski M, Hayes RA, Wood SJ, Nordholm D, Zhou JH, Fusar-Poli P, et al. Association of structural magnetic resonance imaging measures with psychosis onset in individuals at clinical high risk for developing psychosis. JAMA Psychiatry 2021; 78: 753. https://doi.org/10.1001/jamapsychiatry.2021.0638.

44 Luna LP, Radua J, Fortea L, Sugranyes G, Fortea A, Fusar-Poli P, et al. A systematic review and meta-analysis of structural and functional brain alterations in individuals with genetic and clinical high-risk for psychosis and bipolar disorder. Progress Neuropsychopharmacol Biol Psychiatry 2022; 117: 110540. https://doi.org/10.1016/j.pnpbp.2022.110540.

45 Jung WH, Jang JH, Byun MS, An SK, Kwon JS. Structural brain alterations in individuals at Ultra-high Risk for psychosis: a review of magnetic resonance imaging studies and future directions. J Korean Med Science 2010; 25: 1700. https://doi.org/10.3346/jkms.2010.25.12.1700.

46 Buciuman, MO, Oeztuerk OF, Popovic D, Enrico P, Ruef A, Bieler N, et al. Structural and functional brain patterns predict formal thought disorder's severity and its persistence in recent-onset psychosis: results from the PRONIA study. Biol Psychiatry Cog Neurosci Neuroimaging 2023; 8: 1207-1217. https://doi.org/10.1016/j.bpsc.2023.06.001.

47 Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis. Schizophr Res 2016; 176: 83-94. https://doi.org/10.1016/j.schres.2016.07.014.

48 Prasad K, Rubin J, Iyengar S, Cape J. Global network disorganization underlying psychosis high risk states. Schizophr Res 2023; 255:67-68. https://doi.org/10.1016/j.schres.2023.03.033.

49 Pan Y, Dempster K, Jeon P, Théberge J, Khan AR, Palaniyappan L. Acute conceptual disorganization in untreated first-episode psychosis: a combined magnetic resonance spectroscopy and diffusion imaging study of the cingulum. J Psychiatry Neurosci 2021; 46: E337-E346. https://doi.org/10.1503/jpn.200167.

50 Ma X, Yang WFZ, Zheng W, Li Z, Tang J, Yuan L, Ouyang L, et al. Neuronal dysfunction in individuals at early stage of schizophrenia: a resting-state fMRI study. Psychiatry Res 2023; 322: 115123. https://doi.org/10.1016/j.psychres.2023.115123.

51 Chen Q, Chen X, He X, Wang L, Wang K, Qiu B. Aberrant structural and functional connectivity in the salience network and central executive network circuit in schizophrenia. Neurosci Lett 2016; 627: 178-184. https://doi.org/10.1016/j.neulet.2016.05.035.

52 Howes OD, Hird EJ, Adams RA, Corlett PR, McGuire P. Aberrant salience, information processing, and dopaminergic signaling in people at Clinical High Risk for Psychosis. Biol Psychiatry 2020; 88: 304-314. https://doi.org/10.1016/j.biopsych.2020.03.012.

53 Ceballos-Munuera C, Senín-Calderón C, Fernández-León S, Fuentes-Márquez S, Rodríguez-Testal J. Aberrant salience and disorganized symptoms as mediators of psychosis. Front Psychology, 13: 878331. https://doi.org/10.3389/fpsyg.2022.878331.