Düşünen Adam The Journal of Psychiatry and Neurological Sciences 2014;27:87-93
DOI: 10.5350/DAJPN20142702001

Schizophrenia as a Diagnosis of Exclusion

E. Cem Atbasoglu[1,2], Ahmet Kokurcan[2]

[1]Prof. Dr., Ankara University, Brain Research Center (AU-BAUM), Ankara - Turkey
[2]Psychiatrist, Ankara University, Faculty of Medicine Department of Psychiatry, Ankara - Turkey

Address reprint requests to / Yazışma adresi: Prof. Dr. E. Cem Atbasoglu
Ankara University, Brain Research Center (AU-BAUM), Ankara - Turkey

E-mail address / Elektronik posta adresi: aoglu@medicine.ankara.edu.tr

Replacement of clinical constructs with natural entities has been an ancient challenge for psychiatry. The struggle is reflected in twists of methodology, among which the major paradigm change in the U.S.A. after the seventies is most prominent (1,2). The third edition of the DSM (3) was launched with the main purpose of securing diagnostic reliability; validity would remain a moving target without reliable descriptions. They assumed an atheoretical approach and referred to the polythetically defined clinical categories as disorders, avoiding any reference to etiology. Inherent in this perspective, however, was the presumption that all mental disorders would eventually fit a categorical disease model as their neural substrates were demonstrated (2).

Despite its drawbacks this approach has accelerated research to a great extent, and much effort has been spent to apply neuroscience to mental disorders. Schizophrenia is among the most intensively explored disorders, having enjoyed almost all relevant applications of new technics and robust neuroscience. The initial strategy following the publication of the DSM-III was the identification of core features for schizophrenia. Potential candidates during the eighties were the negative symptoms, originally defined by Andreasen (4). The positive – negative distinction was a fine application of nineteenth century medicine. Andreasen appreciated the legacy of phyicians like Jackson (5) and Bleuler, who made huge contributions to neuropsychiatry with their keen observations: *Our understanding of schizophrenia used to be completely Bleulerian; Kraepelin came into the picture much later* (6). It must be noted here that the introduction of constructs paving the way to good science came from brilliant clinicians' thorough phenomenology. Kendler's (7) aphorism in another context is also worth noting here: *Psychiatric disorders are etiologically complex, and no more "spirochete-like" discoveries will be made that explain their origins in simple terms.* In our view, the patchy reductionism outlined by Kendler is the optimum in behavioral science, and real novelty will originate from sound intuition and creativity in clinical observation grounded on a good grasp of neuropsychiatry (7).

The search for core features continued in the nineties with cognitive deficits. The persistent finding was the replication of Saykin's (8) original research, one of the best designed and reliable studies in the field: Moderate decline in sustained attention (vigilance), executive functions and short-term memory (learning) (8). This profile was in the context of generalized deficits with smaller effect sizes (9,10).

Other studies on cognition included the development of custom-made batteries for use in the necessarily multidisciplinary research to follow as well as with

commercial purposes, to assess medication effects on cognition in schizophrenia. Cognitive dysfunction as the core of schizophrenia was attractive as a new avenue of research for the optimistic scientist, and a commercially attractive novel target for drug development. Much effort and money were spent to replace the antipsychotics with antischizophrenic medications that would hit the "disease" at its core. Recently, a work group developed a new battery of specific subtests. Some proof-of-concept and phase 2 and 3 studies are in progress (11). To this day no procognitive antischizophrenic drug has been discovered (12).

Cognitive deficits and deviations from the norm were explored with contribution from a variety of basic and clinical sciences: Higher temporal and spatial resolution in imaging, afforded by electrophysiology, nuclear medicine and radiology were tried in attempts to observe a specific structural or functional change (13,14).

Efforts directed at defining core features were hardly successful. However, the relatively specific features among them were to constitute the promising leads for the next decade's top priority science and technology—genetics and genomics. At the time when the first draft of the Human Genome Project (2003) was published, research on cognition had provided abundant—if not specific—data (15). Longitudinal folllow-up studies searching for a predictive premorbid pattern ended up defining only a fairly specific pattern of cognitive and electrophysiologic abnormalities. Although none of these abnormalities or any combination of them were good enough to be predictive, they proved valuable as the endophenotypes of schizophrenia, available for the candidate gene studies, which peaked as the new millenium entered (16). The candidate gene approach had, from the start, many advantages and strengths: Specific hypothesis-testing in a case-control design, availability of new information on many functional polymorphisms, convenience compared to linkage studies, which required concordant family members and multiplex families, and above all, the reliability and validity of the investigated phenotypes (17). Patients' nonschizophrenic relatives, individuals with attenuated forms of the disorder and those with subclinical symptoms were the legacy of the previous cognition and prediction research, and they provided the liberty of studying phenotypes that were both heritable and common (18).

It must be noted, however, that all this work, including the invaluable scientist effort and creativity alongside huge amounts of research funding was directed at discovering new information about a single categorical entity. Their value was necessarily dependent on their specificity to the disorder and on the condition that schizophrenia itself was reliable and valid (19).

The following wave of genome-wide and gene-environment-wide interaction studies are more sophisticated in that they use ever-increasing levels of resolution, search for association of many phenotypes with many structural variants and polymorphisms, and take into account epigenetic mechanisms reanalyze with new hypotheses and with the liberty to not focus on schizophrenia as a reliable phenotype (20,21). Our group at Ankara University is among them (22,23).

Confronted with the simple question "what causes schizophrenia?", the answer we can provide with confidence does not really sound satisfactory: Combination of the small effects of many interactions between common alleles—single nucleotide polymorphisms, mostly— and common environmental factors, and the more pronounced effects of some inherited and highly penetrant structural—copy number—variants (24).

Reliability in Psychiatric Assessment

In medical fields utilizing descriptive as opposed to etiologic diagnoses, numerical evidence to reliability is an estimate under the assumption that the context of assessment is either constant or irrelevant. Psychiatric assessment is influenced to a great extent by contextual factors like the quality of the doctor–patient relationship, culturally shaped beliefs and attitudes towards mental illness, relevant value choices, the setting of assessment and conditions of access to health care. Reliable diagnostic assessment takes more than proper compliance with structured questioning and application of standard diagnostic criteria. In fact, the major diagnostic challenge in medicine is the correct detection

and naming of the symptoms and signs. This bears special importance in psychiatric assessment, where interpretation of subjective experience is the basis for the recognition of a great majority of the symptoms. Except for the readily observable abnormalities, assessment is the context of an interpersonal relationship involving the exploration of the complaints and careful observation. The prerequisites for a proper diagnostic formulation are therefore manifold: Establishment and maintenance of an alliance, active and neutral questioning, sufficient knowledge and experience for medical and psychopathological formulation, and free-floating attention for keen observation (25).

The major weakness of an atheoretical psychiatric diagnosis—stipulated by the DSM-III and its successors—arises from the accompanying view that psychiatric disorders, as defined in the current DSM or with their future definitions to be developed by modifying the current DSM definitions, have demonstrable neural substrates, i.e., reduction, the legitimate target of natural sciences, is not impossible for psychiatric disorders—only, it will take more brilliant scientists, more cutting-edge technology and a longer time (26).

How this flawed epistemology was shaped is beyond the scope of this article and has been addressed elsewhere (25). This faith always found followers including very influential psychiatrists. In the title of a frequently quoted article on biological psychiatry, Guze (27) pointed out that biology is the science that psychiatry is founded on: *Biological psychiatry: Is there any other kind?* was acclaimed with its anticartesian overtone, although it was perpetuating the radical error of establishing psychiatric diagnoses as diseases, thereby legitimizing psychiatric examination per se as medical assessment. This standpoint had the unfortunate consequence of depriving the field of the indispensible tool of a general medical assessment and paradoxically cutting its ties with general medicine.

This is a major problem, particularly because behavioral symptoms are ubiquitous. Many non-psychiatric conditions present with abnormalities in psychomotor activity, mood, thought and language. However, the thoroughness of assessment for a non-psychiatric etiology varies across settings and disorders. In general, diagnoses tend to be biased in favor of the physician's specialty and epidemiologic compared to clinical reseach yields higher rates for behavioral disorders (28,29). In a study that reassessed a large epidemiologic cohort for multiple sclerosis (MS) with strict criteria, 16% of the cases with definite MS were found to have initially presented with and treated for psychiatric symptoms. About half of the psychiatric symptom group had also reported complaints attributable to MS, and among them only one fifth had been identified as neurological (30).

Adherence to an atheoretical nosology inflates the frequency of comorbidities and deprives the physician of an Occam's razor much needed in the face of a multitude of complex manifestations. Furthermore, the particular emphasis given to comorbidity is paradoxically theoretical for it imposes a proposition—that comorbidity in psychiatry is possible but—probable. Psychiatrists taught to search for comorbidities and encouraged to give multiple diagnoses are more likely to miss an initial common explanation when it is there (31,32).

The brain-disease view is reflected in the dominant academic / professional discourse. Frequent use of confusing expressions such as conditions "mimicking" psychiatric disorders is one example from text-books and articles (33,34). "Mimicry" must, by definition, be attributed to the disorder for which evidence to validity is weaker. The linguistic nuance reveals the field's claim to a more central role in medicine. We must note, however, that this self-assured emphasis on a central role and an effort at strengthening boundaries with other fields are not unique to psychiatry. All branches of medicine have been narrowing their area of interest, subspecialties are growing in number, and clinical collaboration i.e., consultation at the bedside is lagging far behind multidisciplinary research. While special expertise is a necessary component of collaborative science it is not necessarily an asset in clinical practice. In fact, limiting practice to highly specialized expertise is not necessarily an asset or good clinical practice at all times (35).

Heavily stigmatized diagnoses present an additional challenge to reliability, as stigma involves not only

societal discrimination but also a faulty assumption of uniformity among cases. The popular brain-disease emphasis for many mental disorders also encourages the tendency to mistake disorders as diseases, strengthening the uniformity illusion. Signs and symptoms of a disorder that are most conspicuous and easiest to detect tend to be overemphasized in psychiatry as characteristic, if not diagnostic. These are like stigmata whereby, in the original religious sense of the word, others spot sinful behavior and sickness (36). Thus, stigmatized disorders are more vulnerable to diagnostic bias, which is usually an inclination towards overdiagnosis with overreliance on the symptoms that are readily observable even to the untrained eye. Schizophrenia is a good example to this; a hasty diagnosis on the basis of disorganized speech or behavior, low psychosocial functioning, a general slowness or overt negative symptoms is similar to pointing a finger at the sinful and the sick with naive conviction (37).

Heterogeneity of the diagnostic criteria: While all psychiatric diagnoses are defined by multiple features, schizophrenia poses a particular difficulty as the diagnostic criteria for this disorder span almost all mental faculties (38,39). Many Axis I disorders are defined around a central clinical feature, thereby requiring symptom recognition within few mental faculties. Although social anxiety disorder is diagnosed with multiple criteria, its defining feature is simple: Social anxiety. The diagnosis of obsessive-compulsive disorder depends on obsessions, intellectual deficiency on the deficienccy of intellect, and panic disorder on panic episodes that folow a certain pattern (40). For some disorders with relatively complex diagnostic criteria such as bipolar disorder, we have the characteristic symptoms like increased psychomotor activity that are arguably central in the diagnosis of mania. An Autism Spectrum Disorders (ASD) also presents with a multitude of potential conditions, nevertheless it is defined with two main features which involve psychomotor activity and communication (41).

Here we summarize the relatively common conditions that must be explored before formalizing a diagnosis of schizophrenia.

Autism Spectrum Disorder

An initial diagnosis of ASD is rare in adults. This is surprising, given that ASD is not rare and clinical features include neither a shorter life-span nor full recovery. Some of the possible reasons for this findings were previously addressed (42). We will emphasize clinical assessment and differential diagnosis: The low frequency in adult psychiatry can be partly explained with the issues around reliability explored above, resulting in overdiagnosis of some disorders and obscuring others. The official definitions in the DSM-IV TR stipulated that symptoms be present before the age of three, and retrospective review of the earliest years of life would not be easily reliable with individuals assessed for ASD as adults (43). Apart from the poor reliability of a person's past history in comparison to the history of present illness, initial signs of the ASD are within a broad range in terms of severity and the likelihood to be recognized. Furthermore, unlike schizophrenia, for which milder forms, healthy relatives, at risk groups and premorbid characteristics of diagnosed cases have been extensively explored, early manifestations of the milder forms of ASD (the broad autism phenotype, atypical autism, high-functioning autism, Asperger disorder and pervasive developmental disorder not otherwise specified- "PDD-NOS") diagnosed in adulthood have not been retrospectively assessed in large-scale systematic studies. Therefore our current knowledge includes insufficient information about the developmental characteristics of these individuals compared to those with schizophrenia or those who are diagnosed as children (44).

The age criterion in the DSM-IV TR limited the diagnosis of these disorders to the setting of child and adolescent psychiatry, and to some extent, to pediatric neurology and general pediatrics, especially for syndomic cases. Review of the medical history concerning the period of 0-3 years is easier and more reliably precise in the case of a young patient; in addition, young patients are more likely to be accompanied by a reliable informant. Furthermore, the terms initial presentation, onset, and initial diagnosis are sometimes used interchangeably (45). It is known that milder cases of neurodevelopmental disorders tend to manifest relatively later, and

identification of a behavior or a cognitive feature as symptomatic is not independent from cultural norms, i.e., the same manifestation of an ASD may be regarded as symptomatic and present to medical care at a later stage of life in some cultures, while it is recognized as abnormal at an earlier age in others (46). The level of information made available by mental health professionals to the public is also an important factor determining the age at initial presentation. In fact this inevitably arbitrary age at presentation is not different in the case of schizophrenia, as suggested by data indicating premorbid deficits and subtle signs in many cases, or the relatively recent concept "duration of untreated psychosis" (45).

The new definition of ASD in the DSM-5 is does not limit the initial manifestations to the first 3 years of life and this provides the liberty to take into account the fact that presentation may vary with the severity of the disorder and cultural attitudes towards aspects of communication and adaptation to change (47).

Our case series of DSM-IV-TR PDD diagnosed as adults is comprised of 64 patients. The total duration of follow-up ranges between 3 months and 17 years. Two patients are deceased (one with suicide, another with unknown cause) and 8 were lost to follow-up. All 3 patients with autistic disorder, 16 of the 21 patients with Asperger disorder and 25 of the 40 patients with PDD-NOS have a history of treatment for schizophrenia or bipolar disorder or schizoaffective disorder. Patients who fulfill the DSM-IV TR criteria for the three disorders at our assessment and follow up come from the Asperger disorder and PDD-NOS groups and are fewer: Nine cases with schizophrenia, 9 with bipolar disorder, 3 with schizoaffective disorder.

Intellectual Disability

Detailed characterization of schizophrenia among individuals with intellectual disability (ID) has been completed in small groups of moderately or severely impaired children. In addition to this, the comorbidity emphasis in psychiatry has resulted in a general weakening of interest in the critical review of a previously established diagnosis. An apparently new clinical manifestation in the context of a developmental or early-onset mental disorder is thus usually assessed under the assumption that it is the presentation of a comorbid disorder, and an alternative explanation explaining both disorders is rarely taken into consideration (48). Despite the higher percentage of overlap between mild intellectual deficiency or borderline intellectual functioning and schizophrenia, their association has not addressed by few studies. A large-scale review of health records suggested that milder forms of ID were more likely to have an additional record of schizophrenia (49). Comorbidity with the less specific category of psychosis was even more frequent. This may be interpreted as an indication of overdiagnosed comorbidity in some cases for which a single disorder could have explain the whole clinical picture. The relatively high frequency of abnormal or maladaptive behavior and brief psychotic episodes in individuals with mild ID further supports this line of reasoning and warns against the potential harm of further stigmatization and the unnecessarily extended period of medical treatment to be brought about by a hasty diagnosis of comorbid schizophrenia (50).

It must be noted that, like schizophrenia, neither of these disorders are diseases per se, and therefore they are not immune to the risk of being stigmatized as uniform and natural entities. The advantage in reviewing the diagnosis of schizophrenia or its judicious use is that the alternatives of ASD and ID have identifiable causes in a greater percentage of the cases. In addition to this clinical advantage, recognition of medical causes might help identify novel causes and mechanisms for the remainder. It might also encourage the physician to question the popular brain-disease model in understanding psychiatric disorders. Overdiagnosis of schizophrenia is not simply a physician error (51).

CONCLUSION

Figures pointing out to satisfactory diagnostic agreement for schizophrenia might well be reflecting a widespread tendency to overdiagnose—or miss the diagnosis of the conditions that might present with psychosis. For disorders that are heavily stigmatized as uniform diseases, high figures of reliability might be misleading and the diagnosis might be more in the eye

of the beholder than in the patient. We suggest particular caution against the overdiagnosis of schizophrenia.

The diagnosis of schizophrenia must be one of exclusion, despite the misleading importance attached to the disorder in official nosology.

Acknowledgement

Partially supported by the European Community's Seventh Framework Programme under gran HEALTH-F2-2010-241909 (Project EU-GEI).

REFERENCES

1. Kendler KS. An historical framework for psychiatric nosology. Psychol Med 2009; 39:1935-1941.
2. Wilson M. DSM-III and the transformation of American psychiatry: a history. Am J Psychiatry 1993; 150:399-410.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-III (third edition), Washington DC, 1980.
4. Andreasen NC. Negative and Positive Schizophrenia Definition and Validation. Arch Gen Psychiatry 1982; 39:789-794.
5. Pearce JM. Positive and negative cerebral symptoms: the roles of Russell Reynolds and Hughlings Jackson. J Neurol Neurosurg Psychiatry 2004; 75:1148.
6. Andreasen NC. The evolving concept of schizophrenia: from Kraepelin to the present and future. Schizophr Res 1997; 28:105-109.
7. Kendler KS. Toward a philosophical structure for psychiatry. Am J Psychiatry 2005; 162:433-440.
8. Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry 1991; 48:618-624.
9. Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Arch Gen Psychiatry 1999; 56:749-754.
10. Atbasoglu EC, Ozguven HD, Saka MC, Olmez S. Relative sparing of executive functions in the early phase of schizophrenia. J Neuropsychiatry Clin Neurosci 2005; 17:510-516.
11. Marder SR, Fenton W. Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. Schizophr Res 2004; 72:5-9.
12. Lee H, Dvorak D, Kao HY, Duffy ÁM, Scharfman HE, Fenton AA. Early cognitive experience prevents adult deficits in a neurodevelopmental schizophrenia model. Neuron 2012; 75:714-724.
13. Fu CH, Costafreda SG. Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. Can J Psychiatry 2013; 58:499-508.
14. Atluri G, Padmanabhan K, Fang G, Steinbach M, Petrella JR, Lim K, Macdonald A 3rd, Samatova NF, Doraiswamy PM, Kumar V. Complex biomarker discovery in neuroimaging data: Finding a needle in a haystack. Neuroimage Clin 2013; 3:123-131.
15. International HapMap Consortium. The International HapMap Project. Nature 2003; 426:789-796.
16. Gottesman II, Gould TD. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. Am J Psychiatry 2003; 160:636-645.
17. Van Os J, Rutten BP. Gene-environment-wide interaction studies in psychiatry. Am J Psychiatry 2009; 166:964-966.
18. Modinos G, Iyegbe C, Prata D, Rivera M, Kempton MJ, Valmaggia LR, Sham PC, van Os J, McGuire P. Molecular genetic gene-environment studies using candidate genes in schizophrenia: a systematic review. Schizophr Res 2013; 150:356-365.
19. Atbasoglu EC. Letter to the Editor: What have official classifications ever done for psychiatric genomics? Implications for DSM-V schizophrenia. Psychol Med 2011; 41:219-220.
20. Psychiatric GWAS Consortium Coordinating Committee, Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, Kelsoe J, Lehner T, Levinson DF, Moran A, Sklar P, Sullivan PF. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. Am J Psychiatry 2009; 166:540-556.
21. Harvey PD. CNTRICS. Psychiatry (Edgmont), Matrix Medical Communications 2008; 5:57-59.
22. Guloksuz S, Mance OC. Schizophrenia. TÜBİTAK Bilim ve Teknik Dergisi 2012; 530. (Turkish)
23. Gumus-Akay G, Karabulut HG, Tukun A. What is biobanks, what do they serve? TÜBİTAK Bilim ve Teknik Dergisi 2012 530:48-51. (Turkish)
24. Owen MJ. Implications of genetic findings for understanding schizophrenia. Schizophr Bull 2012 ;38:904-907.

25. Atbasoglu EC, Guloksuz S. Science, Psychiatry, and the DSM. Turk Psikiyatri Derg 2013; 24:202-212. (Turkish)

26. Bolton D. Postempiricism and Psychological Theory. J Clin Child Psychol 1999; 28:550-552.

27. Guze SB. Biological psychiatry: is there any other kind? Psychol Med 1989; 19:315-323.

28. Lolas F. The axiological dimension of psychiatric diagnosis. Acta Bioethica 2009; 15:148-150.

29. De Groot JAH, Bossuyt PMM, Reitsma JB, Rutjes AWS, Dendukuri N, Janssen KJM, Moons KGM. Verification problems in diagnostic accuracy studies: consequences and solutions. BMJ 2011; 343:4770.

30. Skegg K, Corwin PA, Skegg DC. How often is multiple sclerosis mistaken for a psychiatric disorder? Psychol Med 1988; 18:733-736.

31. Berrios GE. The History of Mental Symptoms: Descriptive Psychopathology Since the Nineteenth Century. Third ed., Cambridge: Cambridge University Press, 2002; 172-208.

32. Berrios GE, Chen EY. Recognising psychiatric symptoms. Relevance to the diagnostic process. The British Journal of Psychiatry 1993; 163:308-314.

33. Testa A, Giannuzzi R, Daini S, Bernardini L, Petrongolo L, Gentiloni Silveri N. Psychiatric emergencies (part III): psychiatric symptoms resulting from organic diseases. Eur Rev Med Pharmacol Sci 2013; 17(Suppl 1):86-99.

34. Lebon S, Mayor-Dubois C, Popea I, Poloni C, Selvadoray N, Gumy A, Roulet-Perez E. Anti-N-methyl-D-aspartate (NMDA) reseptor ensephalitis mimicking a primarypsychiatric disorder in an adolescent. J Child Neurol 2012; 27:1607-1610.

35. Sharfstein SS, Dickerson FB. Hospital psychiatry for the twenty-first century. Health Aff 2009; 28:685-688.

36. Kingdon D, Taylor L, Ma K, Kinoshita Y. Changing name: changing prospects for psychosis. Epidemiol Psychiatr Sci 2013; 22:297-301.

37. Gerlinger G, Hauser M, De Hert M, Lacluyse K, Wampers M, Correll CU. Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions. World Psychiatry 2013; 12:155-164.

38. Keshevan MS, Kaneko Y. Secondary psychoses: an update. World Psychiatry 2013; 12:4-15.

39. Bhati MT. Defining psychosis: the evolution of DSM-5 schizophrenia spectrum disorders. Curr Psychiatry Rep 2013; 15:409.

40. Wittchen HU, Heinig I, Beesdo-Baum K. Anxiety disorders in DSM-5: an overview on changes in structure and content. Nervenarzt 2014; 85:548-552.

41. Hastings RP, Brown T. Behavior problems of children with autism, parental self-efficacy, and mental health. Am J Ment Retard 2002; 107:222-232.

42. Pinder-Amaker S. Identifying the unmet needs of college students on the autism spectrum. Harv Rev Psychiatry 2014; 22:125-137.

43. Bevan Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. Schizophr Res 2012; 135:164-169.

44. Nylander L, Gillberg C. Screening for autism spectrum disorders in adult psychiatric outpatients: a preliminary report. Acta Psychiatr Scand 2001; 103:428-434.

45. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The Association Between Autism Spectrum Disorder and Psychotic Experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) Birth Cohort. J Am Acad Child Adolesc Psychiatry 2013; 52:806-814.

46. Hollander E, Phillips AT, Yeh CC. Targeted treatments for symptom domains in child and adolescent autism. Lancet 2003; 362:732-734.

47. Shattuck PT, Seltzer MM, Greenberg JS, Orsmond GI, Bolt D, Kring S et al. Change in autism symptoms and maladaptive behaviours in adolescents and adults with an autism spectrum disorder. J Autism Dev Disord 2007; 37:1735-1747.

48. El-Fishawy P, State MW. The Genetics of Autism: Key Issues, Recent Findings, and Clinical Implications. Psychiatr Clin North Am 2010; 33:83-105.

49. Morgan VA, Leonard H, Bourke J, Jablensky A. Intellectual disability co-occurring with schizophrenia and other psychiatric illness: population-based study. Br J Psychiatry 2008; 193:364-372.

50. Atbasoglu EC, Sakarya D, Gumus Akay G, Sakarya A, Tukun A. Fragile-X premutation in adult psychiatry: four cases and overview of clinical presentation. Turk Psikiyatri Derg 2013; 24:63-67. (Turkish)

51. Lee H, Dvorak D, Kao HY, Duffy ÁM, Scharfman HE, Fenton AA. Early cognitive experience prevents adult deficits in a neurodevelopmental schizophrenia model. Neuron 2012; 75:714-724.