R. Krishaber, student of C. Bernard, A.A. Mehrabyan noted that in case of the phenomena of depersonalization, sensory perception in general is deeply distorted, and ordinary impressions from the outside world are not enough. The data obtained can have a dimensionally-informative and differential-diagnostic significance.

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## APPROACH AND CHALLENGE OF FIRST EPISODE SCHIZOPHRENIA TREATMENT IN ADOLESCENTS

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Treating first episode schizophrenia in adolescents is one the leading therapeutical challenges in psychiatry. The symptoms appear earlier and it is diagnosed earlier than ever before, which brings unique issues with treatment.

Developmental processes in adolescents often hide the symptoms of the illness, while they are also dealing with specific conflicts of growing up that are specific for this developmental period. Diagnosing the illness is not the only difficulty, as choosing an appropriate treatment is difficult due to the limited choices in this age group. It is important to approach every adolescent individually and administer treatment that follows their lifestyle, while also reacting to difficulties appropriately to achieve remission and prevent relapses.

### IZAZOV I PRISTUP LIJEČENJU PRVE EPIZODE SHIZOFRENIJE U ADOLESCENATA

Danas je liječenje prvih epizoda shizofrenije u adolescenata jedan od vodećih terapijskih izazova u psihijatriji. Bolest nastupa kod sve mlađih osoba i sve se ranije dijagnosticira, što donosi specifičnu problematiku.

Razvojni procesi kod adolescenata često prikrivaju simptome bolesti, a oni i zbog posebnosti ovog razvojnog doba moraju riješiti specifične konflikte odrastanja. Prepoznavanje i postavljanje dijagnoze nije jedina poteškoća, već i odabir odgovarajuće terapije koja je u ovoj populaciji limitirana. Važno je pristupiti adolescentu individualno i odrediti terapiju koja prati životni stil mlade osobe te reagirate na poteškoće na vrijeme kako bi se postigla remisija i spriječili relapsi.

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## ANALYSIS OF THE ASSOCIATION OF THE POLYMORPHIC LOCUS RS6280 OF THE DRD3 GENE WITH THE DEVELOPMENT OF PARANOID SCHIZOPHRENIA

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Schizophrenia is a common mental disorder caused by synergic effects of multiple genetic and environmental factors. Heritability of up to 80% has been reported for schizophrenia; however, the precise etiology of this disease remains inconclusive. Several investigators have suggested that dysregulated dopaminergic neurotransmission has a role in the pathogenesis of schizophrenia.

Dopamine receptor D3 (DRD3) is a candidate gene for evaluating an association between dopaminergic neurotransmission and schizophrenia risk. Ser9Gly is a functional SNP that yields a protein with altered dopamine-binding affinity. The substitution of serine with glycine is thought to yield D3 autoreceptors with a higher affinity for dopamine and more robust intracellular signaling.

We studied functional polymorphic locus in 1 exon - rs6280 (c.25G> A, p.Gly9Ser) of the DRD3 in 258 paranoid schizophrenia (PSz) patients and in 350 controls from Bashkortostan region (belonged to Russian and Tatars ethnic groups), using PCR-RFLP.

In the sample of Tatars with paranoid schizophrenia, the rs6280*G allele was significantly more frequent, at 45.83%, compared to the controls at 36.86% (p=0.024, OR=1.45 CI95% 1.06-1.99). In Tatars with a continuous type of PSz, the frequency of the rs6280*S/G genotype was significantly higher (p=0.033, OR=1.8 CI 95% 1.06-3.07) than in the controls. The frequency distribution of genotypes and alleles in Tatars with episodic type of paranoid schizophrenia and in the control group of individuals was similar.

The results obtained by us agree with the data of studies of this polymorphic locus in other populations. The association of SNP rs6280 of the DRD3 gene was detected in Europeans (allele rs6280*G) (Vehof et al. 2012). The absence of association of SNP rs6280 of the DRD3 gene with the development of PSz in Russians confirms the interethnic differences in the susceptibility to the development of multifactorial diseases and is consistent with the results of a number of studies that also do not establish the role of this SNP in the development of schizophrenia in European (Paweł et al. 2010) and in Asian populations (Tee et al. 2011).

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## PROTEIN AGGREGATION AND INSOLUBILITY AS A BIOLOGICAL COMPONENT OF CHRONIC MENTAL ILLNESS

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Major mental illnesses such as schizophrenia and chronic depression are acknowledged to have biological underpinnings, however intense analysis has demonstrated their genetic background to be extremely complex, with very few obvious targets for future therapeutic approaches. Major neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis, also have complex genetic backgrounds, but can nevertheless be characterised by the presence of insoluble aggregates of a very few specific proteins in the brain. These proteins are often toxic, and contribute to the worsening of patients' symptoms with time. Taking inspiration from this, we and others have begun investigating the existence of similar protein aggregates in the brains of patients with chronic mental illnesses.

Through biochemical approaches based on isolating the insoluble protein fractions of patient brain samples, five proteins have now been identified with the potential to form aggregates in major mental illness. Three of these (DISC1, dysbindin-1 and NPAS3) were investigated as they are encoded for by previously described genetic risk factors. The remaining two (CRMP1 and TRIOBP-1) were identified through hypothesis-free proteomics approaches, and represent proteins which had not been previously associated with mental illness. All five have the potential to form aggregates in the brain of schizophrenia patients, with some also been implicated in this way in bipolar disorder and major depression.

We are now embarking on a comprehensive program to characterise these five proteins and the role in which their aggregation plays in major mental illness. This will occur principally at the cell biology level: determining the mechanisms through which aggregates form and their consequences on neuronal development and function. A particular focus will be on interactions between the proteins, and the extent to which aggregation of one protein can affect the aggregation propensity of the others. In parallel, the five proteins will be studied in the blood of patients with schizophrenia, in order to determine their viability as diagnostic markers.

A major hurdle in the development of biological diagnoses and rational therapeutics for major mental illness is the lack of well-characterised molecular targets, a direct effect of their genetic complexity. By bypassing genes and instead focussing on downstream proteins, it is hoped that the development of such new techniques can be greatly accelerated.