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EDITORIAL

# Genetic and environmental risk factors in neurodevelopmental disorders

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According to the immune hypothesis of schizophrenia, an immune system deregulation possibly influences the risk of schizophrenia. For this reason, Frydecka et al. [1] investigated the influence of serum interleukin-6 (IL-6) level together with the polymorphism in its gene (IL-6–174G/C) plus high-sensitivity C-reactive protein (hsCRP) levels on clinical manifestation and cognition in 151 schizophrenia patients and 194 healthy controls. Compared to controls, patients showed significantly higher serum IL-6 and hsCRP levels and both also were significantly associated with insidious psychosis onset, duration of illness, and chronic plus deteriorating course of schizophrenia. The association between IL-6 and hsCRP and worse cognitive performance also remained positive after complex adjustment, whereas the IL-6–174G/C polymorphism had no influence on the IL-6 level albeit on the severity of positive symptoms. Hence, elevated IL-6 levels are possibly relevant in cognitive impairment and a potential inflammatory biomarker of deterioration in schizophrenia. Besides the effects of risk genes, an interaction with environmental factors such as psychosocial stress plays a role in the pathophysiology of schizophrenia. Since stress seems to be complexly linked to psychotic breakdown, Moritz et al. [2] studied the relevance of two cognitive core biases in psychosis in 30 schizophrenia patients with acute delusional symptoms compared to 29 healthy controls. Added by neuropsychological tests, participants underwent three stressing conditions under which they performed parallel versions of cognitive bias tasks. Under stress, particularly noise, patients in comparison with controls showed an increased jumping to conclusion bias and made more monocausal attributions, increasing under social stress. Since stress seems to negatively affect cognition in psychosis, increasing patient's awareness in this regard might be beneficial for improving positive symptoms. The incidence of psychotic symptoms in the general population is more common than validly diagnosed psychoses and might be associated with the same risk factors. Traumatic stress experience and symptoms of post-traumatic stress disorder (PTSD) have recently been suggested to be related to schizophrenia risk. Ayub et al. [3] conducted a cross-sectional survey in 1291 persons 1.5 years after an earthquake. The association between symptoms of anxiety, depression, PTSD, and psychotic symptoms via logistic regression analysis showed psychotic symptoms to be directly correlated with symptoms of PTSD as well as concurrent symptoms of anxiety and depression. Lower educational level was strongly associated with all regression models. Opposite to a positive association of previous traumatic exposure or past psychiatric history, living in a joint family was negatively associated with hallucinations. In accordance with prior correspondent publications, paranoia was associated with female gender, any other psychiatric symptom with environmental stress factors or history of past psychiatric illness.

Modelling stressors in animal models can be helpful in dissecting gene–environment relationships, but underlie practical limitations which afford protocol standardization as well as appropriate statistical normalization to compare different experiments. To this respect, Badowska et al. [4] merged data of individual measures in two independent wild-type mice studies on psychosocial stress into broader

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categories and calibrated joint effects within each category. After plotting and overlaying the calibrated effect sizes in a single paragraph, intuitive comparison of stress-induced behavioural profiles was feasible. Accordingly, isolation rearing might be a paradigm for studies focusing on positive symptoms, while social defeat might be more relevant for negative and cognitive symptoms. In an animal model, Jiang et al. [5] focused on the molecular mechanisms behind the favourable role of the hippocampal endogenous neurogenesis in brain restoration after another environmental risk factor for schizophrenia, the intrauterine infection. He focused on the potential regulatory capacity of MAPK/ERK signalling on neurogenesis and the associated cognitive performance. In neonatal rats, intrauterine infection could not only induce hippocampal neuronal apoptosis, but also increased the levels of p-ERK, p-CREB, and BDNF, which have been associated with the potential endogenous rescue system. Inhibiting MAPK/ERK signalling, again, led to aggravated hippocampal neuronal apoptosis; decreased neurogenesis; impaired cognitive performances; and down-regulated levels of p-ERK, p-CREB, and BDNF. Thus, the activation of MAPK/ERK signalling presumably plays an important role in promoting survival of newly generated neural stem cells via an anti-apoptotic mechanism, which promote endogenous regeneration.

Following genome-wide associated loci with autism of a former study, Zhang et al. [6] undertook sequencing analysis of the coding regions, UTR, and flanking splice junctions of the adenosine monophosphate deaminase 1 (*AMPD1*) gene in previously not included 830 Han Chinese autism patients and 514 healthy controls. They detected 14 novel variants in the coding sequence, including three synonymous mutations and 11 missense variants, though 10 of the latter only in the patient group for which reason the authors performed conservative and functional prediction to figure out the possible roles of these missense mutants. Further carried out were mitochondria activity and lactate dehydrogenase assays in the lymphoblast cell lines of five patients, which resulted in p.P572S and p.S626C showing decreased mitochondrial complex I activity, and p.S626C increased lactate dehydrogenase release in medium. Thus, mutational variants in *AMPD1* seem to contribute to autism risk in this specific population and that mutant protein contributes to disease development operating via mitochondria dysfunction and cell necrosis. The DiGeorge (22q11DS) syndrome is a copy number variant disorder encompassing manifold clinical presentations such as hypocalcaemia, learning disabilities, and symptoms of schizophrenia. Based on the hypothesis of early childhood hypocalcaemia influencing the 22q11DS neurobehavioral phenotype, Muldoon et al. [7] extracted albumin-adjusted serum calcium levels from 151 newborn up to 19.5-year-old patients of a longitudinal 22q11DS cohort. When subsequently assessing the association between the lowest measured calcium level (mean age 6.2 months) and scores on the CSBS-DP ITC (mean age 14.7 months) in a subset of 20 infants from this group, they found a significant association between lower calcium and greater impairment in the social, speech, and symbolic domains of the CSBS-DP ITC. These findings should be re-examined in a larger cohort under a longitudinal approach.

Hypothesizing the interaction between novelty and relevance to be of note to test the aberrant salience hypothesis of schizophrenia, Bachiller et al. [8] in their EEG study aimed at quantifying differences between distractor (i.e. novelty) and target (i.e. novelty and relevance) tones in an auditory oddball paradigm. Measuring EEG activity in 31 schizophrenia patients and 38 controls using Shannon spectral entropy (SE) and median frequency (MF) showed healthy controls to display a larger SE decrease in response to target stimulus than in response to distractor tones which was accompanied by a significant and widespread reduction in MF. In contrast, in response to both target and distractor tones, patients showed a significant reduction in changes in SE irrelevant of treatment prior to EEG recording. Significant changes in SE were additionally inversely correlated to positive and total symptoms severity, for which reason SCH seems to be associated with reduced response to both novelty and relevance during an auditory P300 task. To investigate whether increased resting-state power of gamma oscillations in fact is associated with autism spectrum disorder (ASD), van Diessen et al. [9] retrospectively studied routine EEG recordings of 19 ASD patients and 19 matched controls. While relative resting-state condition gamma spectral power was variable, it on average increased significantly in children with ASD. Since this effect persisted after exclusion of electrodes associated with myogenic gamma activity, increased resting-state gamma activity indeed seems to characterize a subset of ASD, and the well-tolerated EEG could routinely be inserted in the clinical assessment.

## References

1. Frydecka D, Misiak B, Pawlak-Adamska E, Karabon L, Tomkiewicz A, Sedlaczek P, Kiejna A, Beszłej JA (2014) Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0533-5
2. Moritz S, Köther U, Hartmann M, Lincoln TM (2015) Stress is a bad advisor. Stress primes poor decision making in deluded psychotic patients. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-015-0585-1
3. Ayub M, Saeed K, Kingdon D, Naeem F (2014) Rate and predictors of psychotic symptoms after Kashmir earthquake. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0561-1

4. Badowska DM, Brzózka MM, Chowdhury A, Malzahn D, Rossner MJ (2014) Data calibration and reduction allows to visualize behavioural profiles of psychosocial influences in mice towards clinical domains. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0532-6
5. Jiang P, Zhu T, Xia Z, Gao F, Gu W, Chen X, Yuan T, Yu H (2015) Inhibition of MAPK/ERK signaling blocks hippocampal neurogenesis and impairs cognitive performance in prenatally infected neonatal rats. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-015-0588-y
6. Zhang L, Ou J, Xu X, Peng Y, Guo H, Pan Y, Chen J, Wang T, Peng H, Liu Q, Tian D, Pan Q, Zou X, Zhao J, Hu Z, Xia K (2014) AMPD1 functional variants associated with autism in Han Chinese population. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0524-6
7. Muldoon M, Ousley OY, Kobrynski LJ, Patel S, Oster ME, Fernandez-Carriba S, Cubells JF, Coleman K, Pearce BD (2014) The effect of hypocalcemia in early childhood on autism-related social and communication skills in patients with 22q11 deletion syndrome. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0546-0
8. Bachiller A, Lubeiro A, Díez Á, Suazo V, Domínguez C, Blanco JA, Ayuso M, Hornero R, Poza J, Molina V (2014) Decreased entropy modulation of EEG response to novelty and relevance in schizophrenia during a P300 task. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0525-5
9. van Diessen E, Senders J, Jansen FE, Boersma M, Bruining H (2014) Increased power of resting-state gamma oscillations in autism spectrum disorder detected by routine electroencephalography. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-014-0527-3