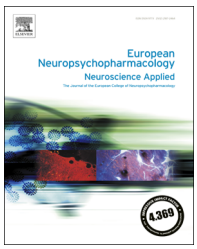
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



The inverse link between genetic risk for schizophrenia and migraine through NMDA (N-methyl-D-aspartate) receptor activation via D-serine ☆

Sandra Van der Auwera[a,*], Alexander Teumer[b], Johannes Hertel[a], Georg Homuth[c], Uwe Völker[c], Michael J. Lucht[a], Franziska Degenhardt[d,e], Thomas Schulze[f,g], Marcella Rietschel[h], Markus M. Nöthen[d,e], Ulrich John[i], Matthias Nauck[j], Hans Jörgen Grabe[a]

[a]*Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Ellernholzstraße 1-2, 17475 Greifswald, Germany*
[b]*Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany*
[c]*Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany*
[d]*Institute of Human Genetics, University of Bonn, Bonn, Germany*
[e]*Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany*
[f]*Department of Psychiatry and Psychotherapy, University Medical Center, Göttingen, Germany*
[g]*Institute of Psychiatric Phenomics and Genomics (IPPG), Ludwig-Maximilians-University, Munich, Germany*
[h]*Division of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*
[i]*Institute of Social Medicine and Prevention, University Medicine Greifswald, Greifswald, Germany*
[j]*Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany*

Received 15 July 2015; received in revised form 18 February 2016; accepted 24 March 2016

KEYWORDS
Migraine;
D-serine;
Serine-racemase;

Abstract
Schizophrenia has a considerable genetic background. Epidemiological studies suggest an inverse clinical association between schizophrenia and migraine. However, it is unclear to what extent this inverse comorbidity can be explained by genetic mechanisms or by schizophrenia-related

☆Polygenic risk score for schizophrenia in migraine.

*Correspondence to: Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Ellernholzstraße 1-2, 17475 Greifswald, Germany. Tel.: +49 0 3834 86 22165; fax: +49 0 3834 86 6886.
E-mail address: auweras@uni-greifswald.de (S. Van der Auwera).

http://dx.doi.org/10.1016/j.euroneuro.2016.03.019

Please cite this article as: Van der Auwera, S., et al., The inverse link between genetic risk for schizophrenia and migraine through NMDA.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.03.019

NMDA hypo-/ hyperactivation; Schizophrenia

behavioral factors. For both disorders hypotheses of glutamate N-methyl-D-aspartate (NMDA) receptor dysfunction have been developed in the past. We hypothesized that both conditions share common genetic factors with inverse effects, primary in the glutamatergic system and genes involved in NMDA activation.

Data from the population based Study of Health in Pomerania ($N=3973$) were used. Based on the results from the recent genome-wide association study for schizophrenia, we calculated polygenic scores (PRS) for subsets of SNPs with different p-value cutoffs and for biological subentities. These scores were tested for an association of distinct biological pathways with migraine.

The PRS for schizophrenia was inversely associated with migraine in our sample. This association was exclusively based on the genome-wide hits and on single nucleotide polymorphisms near or within genes encoding proteins involved in glutamatergic neurotransmission. This association could be attributed to a single intronic variant rs4523957 in *SRR* encoding serine-racemase. Additional expression quantitative trait loci analyses of functional variants in *SRR* and gene-by-gene interaction analyses further supported the validity of this finding.

SRR represents the rate limiting enzyme for the synthesis of D-serine, an important co-agonist of the NMDA receptor. According to our results, a decreased versus increased activation of NMDA receptors may play a role in the etiology of schizophrenia, as well as in migraine.

1. Introduction

Schizophrenia is a disabling psychiatric disorder with a high heritability indicating that genetic mechanisms are involved in its etiology (Wray and Gottesman, 2012). Although the precise molecular mechanisms still remain unclear, there is substantial evidence for changes in several neurotransmitter systems (Laruelle, 2014). Great progress has been made through genome-wide association studies (GWAS) identifying a huge number of genetic variants that may contribute to the pathophysiology (Sullivan et al., 2012). The latest step in uncovering these mechanisms was taken by the schizophrenia GWAS performed by the Psychiatric Genomics Consortium (PGC) with nearly 37,000 cases. In total, 108 genome wide significant independent loci clustering in neuronal calcium signaling, glutamatergic neurotransmission or neurodevelopment pathways were identified (SCZ Working Group of the PGC, 2014).

At the clinical level schizophrenia is associated with many comorbid diseases, e.g. decreased risk for rheumatoid arthritis and increased risk for epilepsy, metabolic disorders and circulatory system diseases (Sørensen et al., 2014; Sellgren et al., 2014). Although these comorbidities are often attributed to medication side-effects and poor health habits in schizophrenia patients (Sørensen et al., 2014), the question arises to what extent they share a common biological basis that can be identified through genetic analysis. With regard to an association between schizophrenia and migraine, there is conflicting evidence (Kuritzky et al., 1999; Baptista et al., 2012; Birgenheir et al., 2013). Subjects with schizophrenia have found to be at decreased risk for migraine in observational studies whereas other studies report a positive association between schizophrenia and migraine. Birgenheir et al. (2013) observed a positive association between chronic pain and people with schizophrenia or bipolar disorder in a sample of veterans. They investigated the joint burden of several pain conditions in individuals affected by traumatic war-related events. Thus, the results of this study should not be generalized to patients suffering from schizophrenia in every day clinical settings. Smith et al. (2013) reported a higher rate of multiple physical-health comorbidities, including migraine, in people with schizophrenia or a related psychosis in primary care. Although the rate of migraine in both samples was relatively low (0.8% versus 0.7%) the difference was nominal significant on a 5% level ($P=0.03$) but without taking into account the possibility of medication side effects. Thus, both studies cannot be taken as strong support for a positive association between schizophrenia and migraine in the general population. One study (Baptista et al., 2012) examined migraine life-time prevalence in schizophrenic patients, healthy controls and in unaffected first-degree relatives. The frequency of migraine was 14.9% in the controls compared to 8.3% in schizophrenic patients and only 3.5% in their first-degree relatives. Especially the low frequency of migraine in first-degree relatives of schizophrenia patients who are not influenced by medication effects points to a genetic component and minimizes the contribution of behavioral factors associated with schizophrenia. Although little is known about the association and coheritability between both disorders, this inverse clinical association suggests that genetic factors might inversely transmit the risk for one disorder but protect against the other.

On the molecular level, the putative involvement of the glutamatergic system in both disorders has led independently to hypotheses of opposite glutamate related effects (Laruelle, 2014; Anttila et al., 2010). In schizophrenia there is evidence for a primary hypofunction of the NMDA (N-methyl-D-aspartate receptor) receptors which is supposed to disinhibit the dopaminergic system (Sendt et al., 2012). This model is supported by the recent GWAS findings for schizophrenia (SCZ Working Group of the PGC, 2014) where a number of gene loci involved in glutamatergic neurotransmission were significantly associated with schizophrenia. Also for migraine, GWAS results indicated an involvement of glutamatergic

Please cite this article as: Van der Auwera, S., et al., The inverse link between genetic risk for schizophrenia and migraine through NMDA.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.03.019