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Published in:
European Neuropsychopharmacology

DOI:
[10.1016/S0924-977X\(17\)31689-9](https://doi.org/10.1016/S0924-977X(17)31689-9)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Geers, L. M., Pozhidaev, I. V., Ivanova, S. A., Freidin, M. B., Cohen, D., Boiko, A. S., Osmanova, D. Z., Fedorenko, O. Y., Touw, D. J., Semke, A. V., Wilffert, B., Bokhan, N. A., & Loonen, A. J. M. (2017). Association between P-glycoprotein polymorphisms and antipsychotic drug-induced hyperprolactinemia. *European Neuropsychopharmacology*, 27(Supplement 4), S956. [https://doi.org/10.1016/S0924-977X\(17\)31689-9](https://doi.org/10.1016/S0924-977X(17)31689-9)

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(2) In the control region (calcarine area):

At baseline, NAA levels in patients ($n = 3$) and HC ($n = 3$) were close (13.47 ± 0.28 vs 13.48 ± 0.26 mM).

There was no change in the NAA levels after treatment (-0.74% vs -0.14% active group vs sham group).

Conclusion: Noninvasive neurostimulation with high-frequency targeting the medial prefrontal cortex by iTBS opens new therapeutic ways to improve social cognition in patients with schizophrenia. The increase of the NAA one month after iTBS may underlie the social cognition improvement.

References

- [1] Huang, Y-Z, Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2004. Theta Burst Stimulation of the Human Motor Cortex. *Neuron* 45, 201–206. doi:10.1016/j.neuron.2004.12.033.
- [2] Potkin, S.G., Alva, G., Fleming, K., Anand, R., Keator, D., Carreon, D., et al., 2002. A PET Study of the Pathophysiology of Negative Symptoms in Schizophrenia. *Am J Psychiatry* 159, 227–237. doi:10.1176/appi.ajp.159.2.227.
- [3] Dollfus, S., Razafimandimby, A., Maiza, O., Lebain, P., Brazo, P., Beaucousin, V., et al., 2008. Functional deficit in the medial prefrontal cortex during a language comprehension task in patients with schizophrenia. *Schizophr Res* 99, 304–311. doi:10.1016/j.schres.2007.11.016.
- [4] Pomarol-Clotet, E., Canales-Rodríguez, E.J., Salvador, R., Sarró, S., Gomar, J.J., Vila, F., et al., 2010. Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Mol Psychiatry* 15, 823–830. doi:10.1038/mp.2009.146.
- [5] Wijtenburg, S.A., McGuire, S.A., Rowland, L.M., Sherman, P.M., Lancaster, J.L., Tate, D.F., et al., 2012. Relationship between fractional anisotropy of cerebral white matter and metabolite concentrations measured using 1H magnetic resonance spectroscopy in healthy adults. *NeuroImage* 66, 161–168. doi:10.1016/j.neuroimage.2012.10.014.

P.3.d.043 Association between P-glycoprotein polymorphisms and antipsychotic drug-induced hyperprolactinemia

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Background: Regular therapy for schizophrenia includes maintenance antipsychotic treatment. Unfortunately, antipsychotics also have a spectrum of side effects, including metabolic, endocrine, cardiovascular, and movement disorders. One of the common side effects of these drugs is hyperprolactinemia (HPRL) [1]. This side effect is attributed to blockade of dopamine D2 receptors on the membranes of lactotroph cells within the pituitary gland. Certain antipsychotic drugs, e.g. risperidone, are more likely to induce HPRL because of relative accumulation within the adenohypophysis. The strong prolactin-elevating effect of risperidone reflects its relatively high blood/brain concentration ratio, a consequence of it being a substrate for the p-glycoprotein (P-gp, also known as ABCB1) pump [2]. Therefore, P-gp genotypes with

altered functional activity might influence the potential of risperidone to cause HPRL as the changed blood/brain concentration ratio would lead to an altered vulnerability for CNS side effects like parkinsonism. Such side effects are expected to make dose adaptations necessary, which would also decrease exposure of lactotroph dopamine D2 receptors.

Aims: The present study aimed to investigate the influence of polymorphisms of the P-glycoprotein gene (ABCB1 gene) on the prevalence of antipsychotic-induced hyperprolactinemia in patients with schizophrenia.

Methods: We studied the association between polymorphisms of the P-gp gene (ABCB1 gene) and antipsychotic drug-induced hyperprolactinemia in patients with schizophrenia from Siberia. Evaluation of serum prolactin was performed by ELISA using reagents set PRL Test System (USA). Genotyping was carried out on 8 polymorphic variants of the P-glycoprotein gene (rs1045642, rs2032582, rs4148739, rs28401781, rs2235040, rs9282564, rs2235015, and rs2032583). Associations between HPRL and polymorphisms of P-gp gene were established using logistic regression accounting for covariates (age, sex, duration of the disease, and CPZeq). An additive genetic model was tested and the analysis was carried out both in the total sample and in subgroups stratified by the use of risperidone/paliperidone ($N = 76$) or sulpiride/amisulpride ($N = 13$). Bonferroni correction was applied assuming 5 independent tests estimated via the correlation between the SNPs.

Results: 446 Russian patients with schizophrenia were examined, including 225 women and 221 men [3]. The average age of patients was 42.1 ± 1.4 years. No statistically significant associations were obtained in the total sample after correction for multiple-testing. However, the rs2032582 variant appeared to be protective against HPRL in the subgroup of patients using risperidone or paliperidone (OR = 0.17, 95% CI = 0.04–0.79, adjusted $p = 0.041$).

Discussion: Our finding supports the hypothesis that a variant of P-gp gene may influence the likelihood of inducing HPRL in patients using risperidone or paliperidone (i.e. 9-hydroxy-risperidone). This may be related to affecting the blood/brain concentration ratio of the risperidone moiety. In the total sample the association was significant but did not survive correction for multiple testing. Moreover, another variant, rs4148739, was associated to a larger extent than rs2032582. Hence, the variant may affect the affinity of the risperidone moiety specifically without having consequences for the binding and transport of other antipsychotic drugs.

Conclusion: Rs2032582 of the P-gp is negatively associated with risperidone/paliperidone-induced HPRL, but not with HPRL induced by other antipsychotic drugs.

References

- [1] Peuskens, J., Pani, L., Detraux, J., De Hert, M., 2014. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs* 28, 421–453.
- [2] Ejlsing, T., Pedersen, A., Linnet, K., 2005. P-glycoprotein interaction with risperidone and 9-OH-risperidone studied in vitro, in knock-out mice and in drug-drug interaction experiments. *Hum Psychopharmacol* 20, 493–500.
- [3] Ivanova, S.A., Osmanova, D.Z., Freidin, M.B., Fedorenko, O.Y., Boiko, A.S., Pozhidaev, I.V., Semke, A.V., Bokhan, N.A., Agarkov, A., Wilffert, B., Loonen, A.J.M., 2017. Identification of 5-hydroxytryptamine receptor gene polymorphisms modulating hyperprolactinemia in antipsychotic drug-treated patients with schizophrenia. *World J Biol Psychiatry* 18, 239–246.