Format for ANSWERING REVIEWERS

January 10, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 24142-review.doc).

Title: Systems Psychopharmacology

Author: Peter J Gebicke-Haerter

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 24142

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
Reviewer 2445272 : Abbreviations corrected

Reviewer 2445261:
GWAS substantially **shortened** by **erasing** on pp.3 and 4 :
"Consequently, it became mandatory to substantially extend numbers of samples to at least 10,000 patients and even more controls for genome-wide scans to reach the statistical power for identification of potential vulnerability genes of small effect."
"Because single genes were not identified in each of those loci, it could only be concluded that the significant SNPs are only the tip of the iceberg. And…"
"Typically, candidate genes identified in GWAS are not tested for the effects of the gene variants on their expression (no changes, or up- or downregulation) or other functional changes of the gene products, if there are changes of amino acids. Moreover, as stated by the authors of the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC), testing for statistical interaction between all pairs of 125 autosomal SNPs that reached genome-wide significance, revealed no significant interaction after correction for multiple comparisons, from which it has to be concluded, that there is no evidence for epistatic or non-additive effects between the significant loci, and "How variation in these genes impact function to increase risk for schizophrenia cannot be answered by genetics." Hence, the hope to identify common variant alleles with relatively large, additive contributions to a disease phenotype resulted in the disappointing discovery that such variants are uncommon, and the more common ones detected by GWAS studies collectively account for only a small portion of the heritability of the phenotype. In other words, the associations identified do not permit any further conclusions as to their relevance in triggering the disease or to their relevance in its dynamic progress."
"A special problem has even been encountered at the major histocompatibility complex (MHC) locus (see above)."

Additional Tables :
I think, the headlines of each paragraph sufficiently summarize the contents in that **additional tables** can be avoided.

MicroRNAs :

On pp.7 ff the issue of microRNAs has been elaborated in more detail (I am very thankful to the reviewer to have pushed this point):

"They may not only impact on predisposed genetic abnormalities but influence transcription on the epigenetic level (DNA methylations and posttranslational modifications of histone proteins) [39,40] and post-transcriptional events, such as editing of mRNAs or mRNA degradation by si (small interfering) RNAs or micro (mi)RNAs[42]. The latter way of posttranscriptional regulation of gene expression has become very popular to experimentally silence single genes as an alternative to produce gene knock-out animals. In the context of this review, however, it appears to be even more interesting, because those short RNAs (21-25 nucleotides in length) typically are not specific for one mRNA, hence display multi-target functions[43]. Expression levels of several hundreds of mRNAs can be modified by one miRNA, which results in "fine-tuning" of target gene expression. There are several reports delineating the occurrence of altered miRNA expression profiles in psychiatric disorders[44,45]. For example, miRNAs 1202 and 135 turned out to be involved in major depression disorder (MDD), supporting their role in influencing higher brain functions[46,47]. Owing to this relatively new field of research, the molecular mechanisms leading to altered miRNA expression in those disorders are largely unknown. Until recently, experimental and/or computational methodologies capable of detecting accurately and with high resolution miRNA gene transcription start sites (TSSs) were not available, although efforts in this direction have been made several years ago[48,49]. The latter, however, lacked reliable accuracy in experimental techniques, or presented *in silico* algorithms providing low resolution/high false positive rate predictions and heuristics. The first algorithm that surpassed the barrier of 54% sensitivity and 64.5% precision in miRNA TSS identification of the earlier studies by achieving 93.6% sensitivity and 100% precision is MicroTSS[50]. MicroTSS can accurately identify miRNA TSSs in single nucleotide resolution[51]. The interconnection between miRGen v3.0 and other DIANA resources enables users to identify *in silico* as well as experimentally verified miRNA targets on lncRNAs with LncBase[52]. This is very promising progress in getting more insight into regulatory mechanisms of miRNA gene expression and their influence on target mRNAs. A great challenge will be to identify methylation patterns and posttranslational modifications of histones of these genes in health an disease. As a result, effects on protein expression and disturbances of molecular networks in brain disorders may be better understood. Along these lines, it would be important to know, to what extent the products of genes targeted by miRNAs belong to disease networks (see below). Pharmacological interventions on miRNA gene expression would then be reasonable strategies to tackle the problem of the multifactorial origin of chronic psychiatric disorders."

And in CONCLUSIONS on p. 20 :

"Exceptions probably are genes of miRNAs displaying "hub" features as well, that nevertheless may be good pharmacological targets."

Limitations and shortcomings

Limitations and shortcomings of the different mathematical methods and algorithms have been discussed within the text.

Additionally, on p. 20 it has been added:

"In summary, it has to be kept in mind, that the human brain both in health and disease is a biological system distinguished by its extremely high complexity especially on the molecular level. Mathematical approaches to investigate changes on this level still require many improvements, and even greater challenges are confronted when it comes to address dynamic changes of the system. Because, however, this is at the core of biological systems, there is no way around. Reductionistic attempts to understand molecular mechanisms of mental illness are not able to address these issues adequately."

Reviewer 2445374 : --
Reviewer 2445294 : Abbreviations corrected

Reviewer 631881 : Directions for future research
in CONCLUSIONS on p. 20 added :
"……future pharmacological strategies to treat mental disorders may be aimed at targeting "peripheral" molecules with only subtle effects using polypharmacological approaches."

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Psychiatry*.

Sincerely yours,

Peter J. Gebicke-Haerter, Dr.
Professor of Pharmacology & Toxicology