

Answers to reviewer and editor are directly inserted in the manuscript file under track changes option.

All corrections and amendments are highlighted in color across the text.

In response to Reviewer #1:

"The authors should add somewhere a statement that they will not deal in their selective review with these issues. They should state this in both introduction and report it among Limitations (they should add a small subsection just before Conclusions)."

Answer: Although genetic risk factors and pharmacogenomics in the field of psychiatry are promising strategies to predict or mitigate the therapeutic response of medication, and thus to inform medication selection and dosing decisions, the focus in this review will be on the adaptation of new transdisciplinary diagnostic methods like neuroimaging and concurrently administered psychopathological questionnaires and the implementation of the results into treatment using various advanced biomedical treatment methods like ECT, TMS, tDCS and DBS.

The comprehensive approach towards modifying dysfunctional SN and DMN found in patients with schizophrenia is likely to require a combination of pharmacogenomic testing to inform pharmacotherapy selection and dosing decisions in order to restore the aberrant plasticity of brain networks, together with targeted neurostimulation to trigger network reorganization. However, this approach and the specific mechanisms that influence the complex abnormal interactions between the Salience network and the Default mode network are not fully comprehended and need further investigation.

In response to Reviewer #1:

In 4.1. Electro-convulsive therapy: "ECT was first performed by Ugo Cerletti in 1938 [48]". The authors should add after Cerletti "and his team", as several eminent doctors, like Lucio Bini and Franco Accornero were present and who had a role in the development of what they called electroshock

Answer: ECT was first performed by team of physicians led by Ugo Cerletti and Lucio Bini in 1938, alongside with Ferdinando Accornero who contributed for the development of what they called electroshock leading to the replacement of less effective biological interventions like deep sleep therapy and insulin shock therapy.

In response to Reviewer #1:

In their discussion of rTMS, the authors should mention the recent development of deep TNS, which compared to the rTMS, stimulates deeper portions of the prefrontal cortex and may be more effective in depression. Its advantage is a more diffuse stimulation area that may recruit more neuronal circuits at the expense of precision.

Answer: Despite the promising applications of TMS, in about 30% of cases the standard procedure misses the target area, as it only allows stimulation of focal areas just below the skull. Deep TMS (dTMS) has been implemented to overcome these drawbacks. dTMS offers all the advantages of conventional TMS with the benefit to stimulate deeper brain zones with lower focal distribution of the electric field. Some studies have been conducted on the use of conventional TMS for the treatment of auditory hallucinations in drug-resistant patients with schizophrenia, which have shown that the method is moderately effective. In this sense, we propose inhibitory dTMS as a therapeutic intervention targeting temporal, frontal, and parietal areas, taking into account data from functional

neuroimaging that established that hallucinations are accompanied by transient hyperactivity in specific zones – STG, PFC, ACC, inferior parietal cortex, etc. and dTMS may be even more effective than conventional TMS due to greater stimulus depth. In addition, dTMS can even be used as a method to modulate the function of the insula directly, unlike standard TMS, in which this area is inaccessible and can only be reached indirectly. Restoring the function of the insula and the networks in which it participates will further improve the function of the SN as a dynamic switch between DMN and FPN. Finally, our paradigm in tr-fMRI can also be applied as a tool for monitoring TMS, with good enough accuracy and reliability of the method.