remediation was compared with table soccer plus cognitive remediation, we found improvement in everyday functioning of schizophrenia patients measured with the Global Assessment of Functioning (GAF) scale, and in social adjustment measured with the Social Adjustment Scale (SAS-II). The ability to work was associated with improvement in verbal memory and processing speed[6].

Short- and long-term verbal memory scores and cognitive flexibility performance were increased in schizophrenia patients and healthy controls receiving the endurance training augmented with cognitive remediation at three months versus six weeks, but this was not observed in those receiving table soccer augmented with cognitive remediation[6]. This finding supports the need to perform long-lasting training programs to improve cognitive deficits in this severely affected patient group. We previously detected an increase in hippocampal volume after a three-month endurance training, but we could not replicate this finding in our second study.

On the basis of the hypothesis that the individual genetic risk load for schizophrenia – which contributes to neuroplastic processes in the brain – plays a role in the response to aerobic exercise, we calculated the schizophrenia polygenic risk score in our sample. Volume changes in the left CA4/DG at three months versus baseline were significantly influenced by polygenic risk score in schizophrenia patients performing aerobic exercise. A larger genetic risk burden was associated with a less pronounced volume increase or even a volume decrease over the course of the exercise intervention[7].

Results of exploratory enrichment analyses reinforced the notion that genetic risk factors modulate biological processes that are tightly related to synaptic ion channel activity, calcium signaling, glutamate signaling, and regulation of cell morphogenesis[7]. Interestingly, the CA4/DG region was again most affected, which corresponds to our post-mortem findings in schizophrenia[3]. We hypothesize that a high polygenic risk may negatively influence neuroplastic processes during aerobic exercise in schizophrenia, indicating a gene x environment interaction.

Besides the need to replicate these findings in independent samples, future studies are needed to identify those patients who benefit from aerobic exercise interventions and to assess the effects of individual genetic and environmental factors on treatment-induced improvements in cognitive abilities. This would contribute to the development of a personalized approach to improve cognition in schizophrenia.

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Cognitive impairment as a diagnostic criterion and treatment target in schizophrenia

Green et al[1] mention the ongoing debate on whether cognitive impairment should be part of the diagnostic criteria for schizophrenia. In the preparatory work for the DSM-5, this impairment was initially proposed for inclusion, yet the final decision was that it requires additional study before being included. I would like to elaborate on this point and on the implications of the inclusion of cognitive impairment as a diagnostic criterion for the treatment of schizophrenia.

Despite the fact that cognitive impairment is as prevalent as delusions, hallucinations or thought disorder, is present even before the development of psychosis, and is persistent rather than intermittent, a number of reasons might have contributed to the decision not to include it in the criterion A for the diagnosis of schizophrenia.

The first reason is that, contrary to the symptoms/signs included in that criterion, which can be elicited and/or observed during a diagnostic interview, cognitive assessment requires the administration of a battery of psychometric tests. This is time consuming and requires specific training and skills that are common in research settings but difficult to apply in daily clinical practice. Moreover, since cognitive impairment in schizophrenia is pervasive rather than test-specific, it is difficult to establish what pattern of dysfunction and what degree of severity should be present to fulfill the criterion. Finally, a cognitive impairment of the magnitude typically manifested in schizophrenia is too common in other mental disorders as well as in the general population to constitute a useful diagnostic criterion *per se*.

Despite these reservations, it is possible that in the next edition of the ICD, and perhaps also the DSM, cognitive impairment will become a criterion rather than an associated feature in the schizophrenia diagnostic category. Indeed, as Green et al point out, knowing something about the level of cognition in a patient would help clinicians and families to anticipate the degree of problems and success in work, school, social functioning, or rehabilitation.

Since cognitive impairment is present in several mental disorders[2], it will certainly appear as a central dimension in systems such as the Research Domain Criteria (RDoC). It is possible that cognitive

dysfunction represents the distal manifestation of a variety of brain disorders, from head trauma to brain degenerative diseases to schizophrenia. It may then be similar to pain, nausea and dyspnea, which represent the distal manifestation of many somatic disorders. This brings forward the question of cognitive impairment as a treatment target.

Over the last four decades, many investigators and pharmaceutical companies have conducted trials in patients with a diagnosis of schizophrenia using constructs of cognitive functioning as the main outcome[3]. Initially, it was believed that second-generation antipsychotics would be able to ameliorate cognitive impairment but, when it became clear that this was not the case, almost every known neurotransmitter was targeted. Basic science and some clinical data pointed out that dopaminergic, nicotinic and NMDA receptors[4-7] might all be a target for pro-cognitive drugs.

The basic design of the trials testing pro-cognitive compounds involved the recruitment of symptomatically stable schizophrenia patients and the administration of the pro-cognitive experimental drug or placebo added to an antipsychotic drug for several weeks to a few months. The add-on design was employed because of the belief that psychosis is the primary abnormality in schizophrenia and/or because of concerns that, in the absence of maintenance treatment with antipsychotics, patients would be destabilized, which in turn would worsen their cognitive performance. A few projects produced positive results in the proof of concept phases but negative results in confirmatory trials.

A range of methodological limitations has been discussed in an attempt to explain the failure of such trials. Selection of specific outcome measures, length of trial, comorbidities, poor patient's cooperation with testing procedures, large placebo effects, overlap with negative symptoms, were only some of these limitations. It could also be hypothesized that, in the add-on design, dopamine blocking antipsychotics impair performance on cognitive tests[8], so that no cognitive improvement can be elicited.

Furthermore, if in many individuals cognitive performance is, in fact, independent of psychosis, this may have important ramifications for study design. The most important implication is that the trials should preferably not include dopamine blocking drugs. Moreover, if indeed psychosis is only coincidentally superimposed on cognitive impairment, then the pharmacological intervention should be effective in patients without schizophrenia and in non-mentally ill individuals with low cognitive performance. Hence, new pharmacological agents should be first tried in these individuals, to avoid the confounding effects of other schizophrenic symptoms and of antipsychotic drugs.

In sum, until a better understanding emerges, although the future editions of the main diagnostic systems will likely include cognitive impairment as a criterion for the diagnosis of schizophrenia, the possibility that the schizophrenia syndrome represents the coincidental manifestation of several distinct mental abnormalities should not be ignored, with the relevant implications for diagnostic systems as well as for pharmacological and non-pharmacological treatments.

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