The Magic of Movement; the Potential of Exercise to Improve Cognition

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Effective treatment for cognitive dysfunction is the Holy Grail in research for most brain diseases. With the exception of stimulants for attention deficit hyperactivity disorder (ADHD), there is little evidence for any pharmacological intervention to restore cognitive dysfunction once a brain disease is diagnosed. Although future success of new drugs should not be ruled out yet, the many negative results so far suggest that drug interventions may be better to prevent cognitive dysfunction in brain diseases than to treat them once present.

In sharp contrast to the disappointing findings of pharmacological interventions, are the promising results of studies assessing the potential of physical exercise to improve cognition. Both aerobic training and resistance training have the potential to improve cognition, while the combination of both yields the strongest improvement in cognitive functioning. The effect on cognitive functioning has been extensively demonstrated in healthy subjects as have been the effects on brain plasticity, gray and white matter volume, and functional connectivity. In patients with brain diseases, improved cognition after exercise therapy has been reported for patients with Alzheimer’s disease, Parkinson’s disease, major depression, multiple sclerosis, traumatic brain injury, stroke, ADHD and Huntington’s disease. Importantly, exercise also has the potential to slow progression of brain diseases, improve mood, self-esteem, anxiety, and sleep, making it an excellent tool for secondary and tertiary prevention.

Since the beneficial effects of exercise are observed in many different brain disorders, the neurobiological mechanisms underlying these effects are expected to involve general aspects of brain function that are affected in all diseases. This indeed seems to be the case. Firstly, increased cardiac output improves cerebral circulation and optimizes oxygen extraction and glucose uptake of neurons and glia cells. Secondly, neurogenesis is improved, most pronounced in the hippocampal dentate gyrus, which may be secondary to increased neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor. Further, moderate exercise reduces the inflammatory status of the brain, by increasing levels of the anti-inflammatory cytokine interleukin-10, among others, although stringent exercise can have a negative impact on the immune system. Recently, the route to explain the association between cognition and exercise was further elucidated. Expression of peroxisome proliferator-activated receptor-gamma coactivator-1 is increased when skeletal muscles become active. This substance enhances the conversion of the tryptophan metabolite kynurenine to kynurenic acid, thereby lowering kynurenic levels in the blood. Through this mechanism, muscular activity restores the immune balance in the brain.

Given the extensive documentation of the positive effects of exercise on cognitive function, it is surprising that so few studies have investigated its potential for patients with schizophrenia. In 2012, Knöchel et al reviewed studies that used exercise treatment for patients with schizophrenia. They could include only 7 studies, most of them reporting an improvement in symptom severity in the intervention group. Unfortunately, cognition was not systematically assessed in any of these papers. Since 2012, 4 more studies assessed the influence of exercise on schizophrenia, only one of them included cognitive measures and yielded significant improvements in the exercise group.

This field is clearly in its infancy, given the modest sample size of the studies so far, the shortcomings in methodology and the lack in standardizing effects of fitness. In addition, research into the effect of exercise is hindered by the inherent open label nature, as there is no well-matched sham condition available. Moreover, drop-out rates are generally high and only few studies attempt to capture the mechanisms underlying the effect of exercise on the brain. In this issue of Schizophrenia Bulletin, the scanty literature on exercise for patients with schizophrenia is extended by...
3 manuscripts. Malchow et al\textsuperscript{27} included 3 groups: patients with schizophrenia who were offered endurance training for 3 months, augmented in the last 6 weeks with cognitive remediation, a similar group of patients who were provided table soccer for 3 months, again augmented with cognitive remediation in the last 6 weeks and a healthy control group, given the same interventions as the first patient group. They showed superior effects of endurance training over table soccer on symptom severity, depression, and some (but not all) cognitive tasks. The combination of physical exercise and cognitive remediation is new and exciting, yet it blurs the effects of exercise per se. The second study by Svatkova et al\textsuperscript{28} assessed the effect of biking for 6 months on the integrity of white matter connections in patients and controls, as compared with life as usual. In both groups, exercise improved fiber integrity, especially in the motor circuit, while the patients in the control group showed deterioration of fiber integrity over the 6 months of the study. Kimhy et al\textsuperscript{29} demonstrated a 15% improvement in cognition as assessed with the Matrix Consensus Cognitive Battery in the exercise group as compared with 2% decline in the control group. They further showed that increases in the serum levels of BDNF could explain only a small percentage of the improvement in cognition. These three manuscripts once more show that beneficial effects of exercise are ubiquitous, ie, present in patients and controls and manifest in several different areas and are associated with improvements in both brain structures and physical health.

Although the potential of exercise to benefit patients with schizophrenia is promising, the implementation in daily practice is no mean feat. Simply informing patients about the advantages of exercise will not be enough. Even in the healthy population, life style is not easily changed, even though the benefits of activity and fitness are well known. For patients who already experience lack of energy, flat affect, lack of motivation and drive—as part of their disorder—it is even more difficult to engage in fitness training. Side effects from medication, comorbid affective and anxiety symptoms, and low income further complicate the necessary step to start and maintain physical activities. Yet this is the challenge we should take on, as the advantages of this intervention are clear and side effects are few. How can we make physical activity attractive and doable for people with schizophrenia? In order to induce a lasting change in habit, individuals need to believe that a desired outcome can be attained. This outcome differs per patient and therefore tailor-made coaching should be offered. For some, the combination of sports and music may help. For others, a gym teacher who makes a good role model can be helpful. Social support from family or friends can provide the necessary push to leave the house and head for sports. Team sports, such as basketball, may be a means to improve physical condition and social networks at the same time. Perhaps a monetary gain can help patients to regularly perform exercise?

Clearly, this field needs more investigation, especially with well-sampled randomized controlled trials, that creatively overcome the problem of amotivation. In the mean time, clinics might consider investing in sports facilities, such as exercise rooms and sports teachers to trigger some enthusiasm for patients during their stay in the hospital. As the benefits of exercise are not restricted to schizophrenia, various patient groups including those with depression and dementia may benefit from these facilities.

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