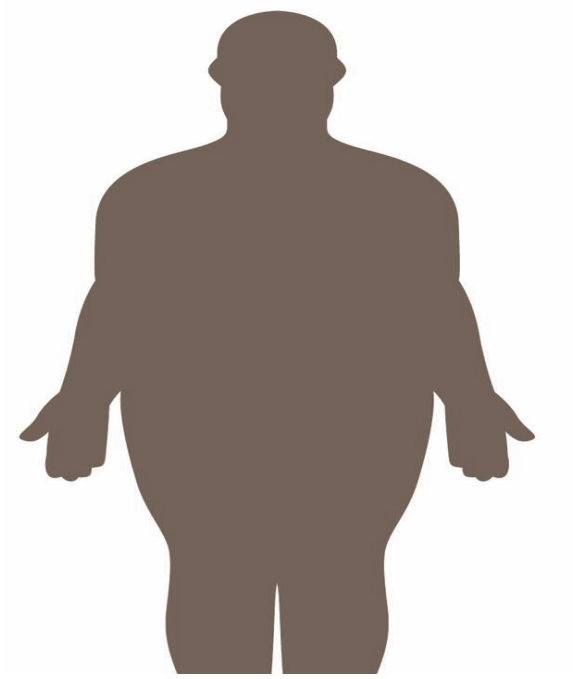
Update on Cognition



Treatment of Obesity and Disability in Schizophrenia

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ABSTRACT

Despite 50 years of pharmacological and psychosocial interventions, schizophrenia remains one of the leading causes of disability. The inability to function in everyday settings includes deficits in performance of social, occupational, and independent living activities. Schizophrenia is also a life-shortening illness, caused mainly by poor physical health and its complications. Dysfunctional lifestyles including sedentary behavior and lack of physical activity prevail, while treatment with adipogenic psychotropic medication interacts with poor performance in screening, monitoring, and intervention that result in shortening of life expectancies by 25 to 30 years. Disability interferes with self-care and medical care, further worsening physical health to produce a vicious cycle of disability. Further, the neurobiological impact of obesity on brain functioning is substantial and relevant to schizophrenia. Simultaneous treatment of cognitive deficits and related deficits in functional skills, ubiquitous determinants of everyday functioning in schizophrenia, and targeted interventions aimed at poor physical health, especially obesity and associated comorbidities, may lead to additive or even interactive gains in everyday functioning in patients with schizophrenia not previously realized with other interventions.

KEY WORDS

Cognition, obesity, schizophrenia, novel treatments, functional capacity

INTRODUCTION

In the past 20 years, there has been a burst of interest in disability in schizophrenia and its determinants. Setting aside symptomatic contributors, research on the causes of disability has focused on the influence of neuropsychological (NP) deficits, now identified as core features of schizophrenia,[1] and more recently on the functional capacity (FC) to perform everyday living skills. Multiple studies in different samples now consistently suggest that these NP- and FC deficits, in conjunction with clinical symptoms and immutable environmental influences (i.e., disability compensation) are responsible, at least correlationally, for a substantial proportion of everyday disability in people with schizophrenia.[2] Yet, despite multiple attempts at treating these deficits, with variable success, along with typically successful pharmacological treatment of symptoms, meaningful reductions in disability have remained elusive.

COGNITION, FUNCTIONAL CAPACITY AND OBESITY

We suggest that one major reason for this reduced level of clinical response is that there are other similarly important potential behavioral, physical, and neurobiological influences on functioning not addressed in studies of

cognitive remediation, pharmacological cognitive enhancement, or psychosocial interventions. We have previously demonstrated that poor physical health, especially derived from obesity and related comorbidities, in conjunction with lifestyle factors, such as minimal exercise and high rates of smoking, is another prevalent source of disability that can also reduce levels of everyday functioning in people with schizophrenia,[3] just like in people without mental illness.[4] Moreover, poor physical health serves to shorten progressively dysfunctional lives of our patients, feeding a vicious cycle of morbidity, disability and premature death.

NP and decision-making deficits worsen obesity. A substantial component of the development of obesity in schizophrenia may be related to deficits in decision-making, broadly defined. This is perhaps not surprising given the near ubiquitous presence of NP deficits. Cognitive and FC limitations worsen multiple relevant aspects of self-care across neuropsychiatric conditions. In this context, it is possible that patients with schizophrenia, for example, either never acquire or cannot exercise the skills necessary to successfully maintain a healthy weight or control food intake and caloric expenditure, just like their disrupted skills deployment interferes with functionality in social, residential, or vocational-related areas.[5]

Aside from (usually chronic) treatment with adipogenic psychotropic medication, this particularly detrimental neurobiological background meets with an equally detrimental environment. Poor dietary quality, for example, is common in individuals with schizophrenia.[6] Fruit and vegetable intake is uncommon. That and the consumption of highly processed, energy-dense food, characteristic in the diets of individuals with schizophrenia, foster obesity.[7] Moreover, these calorie-dense, highly palatable foods are readily available; and they are usually among the most affordable and accessible food choices, requiring little effort in procurement and preparation. Palatability and energy density of food are closely related with human food preferences.[8] Patients with schizophrenia appear especially vulnerable to these influences, as they consume more food than mentally healthy population comparisons, and their food choices are poorer still. In addition, very few patients follow a regular physical exercise routine,[9] and among those who do, erroneous assumptions about the constitution of healthy and goal-directed "exercise" prevail.[10] At the same time, sedentary behavior, perhaps complicated by anhedonia and other interfering negative symptoms or by sedative effects of psychotropic medication, is widespread.[11,12]

Obesity worsens NP and functional deficits. Cognitive and FC deficits can not only worsen obesity, obesity and associated medical comorbidities can worsen neurocognitive performance. In otherwise mentally healthy individuals, elevated body mass index (BMI) has independently been associated with reduced cognitive performance,[13] related to changes in brain structure and function,[14] and reduced decision-making capacity related to food choices and exercise behavior.[15] Sequelae of chronic hyperlipidemia and poor glycemic control and, of manifest, hypertension and diabetes likely contribute to and cause deficits across a variety of cognitive domains.[16] The extent of cognitive dysfunction seen in adults with obesity is highly variable,[17] perhaps caused by interactions or additive effects with related metabolic comorbidities and varying aging effects. Chronic hyperglycemia and long duration of diabetes, for example, are both associated with increased development of cognitive dysfunction by themselves and in conjunction with other metabolic risk factors, including obesity, and worsen over time.[18]

DEVELOPMENT OF NOVEL INTERVENTION STRATEGIES

The United States Public Health Service and practice guidelines from the American Diabetes Association and the NHLBI[19] recommend the use of behavioral lifestyle modification (BLM)—usually a combination of diet, exercise, and behavioral techniques—as a first-line approach to reduce excess body weight and attendant metabolic complications prior to the use of adjunctive pharmacotherapy. Several large-scale studies utilizing BLM, including the National Institute of Diabetes and Digestive and Kidney Disease-sponsored Diabetes Prevention Program[20] (NIDDK) and the Action for Health in Diabetes trial[21] (Look AHEAD) confirm highly significant and clinically meaningful effects on these parameters (i.e., obesity reduction, glucose control). A healthy lifestyle incorporating moderate exercise is necessary for cardiovascular disease risk reduction and may be vital for optimal brain health.[22] Participation in exercise alone is related to better NP function. Changes in dietary patterns associated with weight-loss treatments may also improve cognition;[23] dietary manipulations have been found to affect cognitive function depending on their energy content and macronutrient composition.[24,25]

Net effect of weight loss interventions and cognitive outcomes appear to be related to baseline BMI. Pursuant to at least four weeks of a behavioral weight loss intervention, resulting in modest weight loss of 2kg or more, significant changes in at least

one cognitive domain (e.g., executive function, memory, attention) has been identified when baseline BMI is in the obese range (BMI≥30kg m^2).[26] Different lines of research suggest a positive influence of regular physical activity on the self-regulation of eating habits by enhancing the sensitivity of the physiological satiety signaling system, adjusting macronutrient food choices or requirements, and/or changing the hedonic response to food stimuli. Physical exercise builds the cognitive resources, namely "top-down" control, necessary to block high salience impulsive actions (e.g., highly palatable food) that may lead to overeating and weight gain. As such, physical activity is a "gateway behavior" that may induce people to improve their diets over time. Concurrent with these findings in healthy adults, patients with schizophrenia show similar benefits derived from physical exercise,[27] including hippocampal plasticity and improvements in NP functioning.[28]

Unfortunately, patients with schizophrenia have been systematically excluded from most large scale lifestyle interventions, withholding effective and potentially salutogenic treatments.[29] Subjectively perceived adherence issues, perhaps stemming from symptomatic deterrents (i.e., positive symptoms), and objectively measured cognitive and functional capacity deficits may render it difficult for patients to access and subsequently successfully acquire the proper short- and long-term skill set necessary to learn to use BLM, just like other, unrelated skills (e.g., work-related or social skills) that also require opportunity and practice in a structured manner.

Several BLM treatment options have since become available for patients with schizophrenia and have shown various degrees of effectiveness,[30] which we suggest is a direct result from cognitive and functional capacity limitations, among other unrelated reasons. The common denominator is that all these BLM based programs require cognitive capabilities, but the cognitive and functional capabilities themselves may have been interfering with skills acquisition. This is because every BLM teaches predominantly behavioral skills aimed at controlling food intake and choices (i.e., picking the right foods and portion size and understanding the different types of food [e.g., starch, protein, fats]), cooking, shopping (selection of food items), control of eating behaviors, planning and implementing activities (i.e., structure the day, use public transportation, walk daily, use stairs in lieu of elevator, substitute sedentary time with physical activity), and adhere to a physical exercise schedule, all of which are cognitively demanding tasks.

BLM and CRT. The cognitive and FC limitations inherent in schizophrenia seem quite likely to reduce the chances of success with a teaching intervention such as BLM alone. Improving cognition through Cognitive Remediation Therapy (CRT) has been shown to increase the success of and fidelity to other learning-based interventions.[31] The caveat here is that cognitive remediation alone produces robust improvements in cognition, but has limited transfer to everyday behavior as a stand-alone treatment without concurrent psychosocial interventions. This restricted transfer of skills occurs in spite of robust improvements in neurocognition. Limited opportunities to learn and utilize relevant new skills might explain why cognitive improvements need to be supplemented by other rehabilitative therapeutic opportunities.[32] In other words, transfer of cognitive gains to everyday behaviors likely requires time and opportunities to practice new skill sets and for others to adapt to these changes. In these cases, CRT can potentiate effects of other learning-based treatments, making them larger and more durable. We surmise that the implementation of BLM program, in their usual structured manner, is an ideal vehicle to facilitate such skills transfer. This is a critical point, because many of the components of successful health-related interventions involve learning and performing new skills. The addition of CRT may also increase persistence and durability of BLM in schizophrenia, and salutatory effects may be maintained after cessation of the BLM, without continuing intervention. Similar effects have repeatedly been reported in combined interventions of CRT and other psychosocial interventions.

Future applications. Effective new ways to reduce disability associated with schizophrenia are urgently needed so that affected patients can function in community settings. Obesity-related physical morbidity, common in schizophrenia, may exacerbate the functional deficits produced by cognitive, symptomatic and functional capacity limitations. These physical limitations further reduce real-world performance in areas where the intrinsic limitations of schizophrenia are also operative, and interactive influences may result. Moreover, physical health limitations are underappreciated, albeit easily accessible and potentially treatable risk factors. Given the widespread failure of adequate maintenance of weight loss interventions in healthy and mentally ill populations, the addition of cognitive remediation to BLM has the potential to have an effect on real-world outcomes similar to and possibly larger than that previously found for combined therapies aimed at cognitive impairments and functional skills training.

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