rectional (i.e., higher intelligence – higher schizophrenia risk)[2]. Further analyses indicate a strong protective effect of intelligence on the risk for schizophrenia, and a smaller negative effect of schizophrenia (risk genes) on intelligence[3].

Aspects of cognition are also impaired in relatives of people with schizophrenia, who take an intermediate position between their affected family member and healthy controls[4]. However, the vulnerability to schizophrenia does not appear to be based in an unlucky familial combination of cognitive and environmental risks. An intriguing registry-based study indicates that schizophrenia risk is predicted by the individual's deviation from familial cognitive aptitude (i.e., what is expected from educational attainment and IQ in parents and siblings) and not by cognitive dysfunction *per se*. When cases are matched to controls by educational achievement or IQ, their relatives are found to have better cognitive aptitudes than the corresponding relatives of the controls. These findings point to the existence of a qualitatively different developmental impairment that is associated with schizophrenia risk[5].

A central finding from genome-wide association studies is the link between risk of schizophrenia and the immune system, in particular, the complement system. Studies have identified a new role for complement 4 (C4) in synaptic pruning. Synaptic pruning peaks during adolescence, and is essential for refinement of the CNS and maturation of cognitive abilities. Structurally different variants of C4 genes are associated with differences in C4 expression and with the risk of schizophrenia, supporting the notion that elevated complement activity leading to increased synaptic pruning is a risk factor for schizophrenia. A recent study using patient-derived induced pluripotent stem cells found abnormalities in microglia-like cells and synaptic structures, in addition to increased synaptic pruning in the neuronal cultures. Risk-associated variants of the C4 genes were linked to increased complement uptake in synapses[6]. In line with this, there are indications of poorer memory function linked to increased predicted C4 expression, across patients with schizophrenia and healthy controls[7].

Prospective studies of early cognitive development in children who later developed schizophrenia showed stable deficits in IQ, language, processing speed and executive functioning from infancy. Verbal deficits appear early and are relatively stable, while impairments in processing speed and executive functions increase during adolescence[8]. The widening gap towards healthy adolescence appears mainly to be based in a developmental lag rather than a loss of acquired functions. Studies on groups considered as clinical high-risk (CHR) for psychosis also find significant cognitive dysfunctions. This is particularly the case for those in the CHR group who later experience transition to psychosis. There are, however, no direct indications of a cognitive decline from the prodrome/high-risk state to the onset of the first episode[9].

The main argument for the initial conceptualization of schizophrenia as a neurodegenerative disorder was the presence of cognitive dysfunction and a deteriorating clinical course. However, first episode studies do not find any associations between the duration of untreated psychosis and cognitive dysfunction. Prospective studies of cognitive trajectories from the first episode onwards also show significant cognitive stability, both in short- and long-term. There are some indications of poorer cognitive development in patients with high illness activity during the first year of treatment, but of limited magnitude and balanced by findings of modest cognitive improvements in other subgroups[10].

Taken together, our knowledge about cognition in the early phases of schizophrenia strongly supports the notion of a primarily neurodevelopmental basis for cognitive dysfunction. Cognitive problems may serve as additional stressors increasing psychosis risk, while other symptoms of the disorder may add to cognitive problems. However, current data indicate that cognitive dysfunction is neither a cause nor a consequence of the psychotic process but rather a biomarker of underlying neurodevelopmental problems.

This notion has important clinical implications: while specific treatments may improve one area of dysfunction (cognition or psychotic symptoms) in adults with schizophrenia, this may not translate to other areas. Preventing additional developmental lags in adolescents at high risk might be one of the most effective ways to prevent significant cognitive dysfunction.

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Cognition and disability in schizophrenia: cognition-related skills deficits and decision-making challenges add to morbidity

Schizophrenia contributes 13.4 (95% UI: 9.9-16.7) million years of life lived with disability to the global burden of disease. Its societal costs are immense, with costs derived from productivity loss even larger than direct treatment costs, a pattern observed across different countries and health care systems. Based on these data, disability reduction in schiz-

ophrenia is a priority, yet there are few effective treatments available.

Nonsocial and social cognitive impairment contributes substantially to reductions in everyday functioning and subjective quality of life in persons with schizophrenia. Green et al[1] present and evaluate sophisticated models of the influence of nonsocial and social cognition on functioning, considering moderating variables (e.g., defeatist attitudes, motivation, reward sensitivity) as well as neurobiological correlates and their potential implications. Further, they thoroughly evaluate treatment efforts to date for these deficits, including pharmacological and remediation-based approaches. Among these efforts are exercise interventions, which target physical fitness and have been shown to have beneficial effects on cognitive performance.

Just like with any other chronic disease process, there are multiple factors that contribute to the development of disability in schizophrenia. Obesity and health-related comorbidities are common. Physical fitness is visibly impaired. The presence of these elements shows a correlation with cognitive impairments[2].

One of the issues covered in less detail in Green et al's review is that of functional capacity (the ability to perform everyday functional skills) and its potential mediating effect between nonsocial and social cognition and functional outcomes. In several studies, functional capacity was found to be proximally related to impairments in everyday functioning, with the strongest predictor of deficits in this capacity generally being nonsocial cognition. In addition, when social functional capacity, generally referred to as social competence, is examined for its relationship to functional outcomes, it can be shown that some elements of social cognition predict performance on measures of social competence, which in turn predict informant ratings of everyday social functioning. Thus, impairments in nonsocial and social cognition may be a precursor to functional skills deficits, which then in turn predict impaired everyday outcomes across several domains.

In a related vein, we have recently documented that correlates of poor physical health and fitness are important determinants of disability in schizophrenia that interact with nonsocial and social cognition to complicate functional outcomes. The end result of these physical impairments might prevent people from even leaving their residences and may exacerbate limitations in functional capacity beyond those originating from nonsocial and social cognitive deficits, while generating additional roadblocks to effective deployment of everyday skills that the patients might possess.

We developed a model that integrates these different contributory paths into a unified model of disability in schizophrenia, attempting to isolate the pertinent individual factors (for example, symptoms, cognition, physical functioning) and their interactions, so that they can be approached in a synergistic manner[3].

In analyses of data from the Suffolk County Mental Health Project, we examined the 20-year course of weight gain and its impact on everyday functioning at the 20-year follow-up. We found that weight gain was progressive over the entire period, leading to over 50% of bipolar patients and 60% of schizophrenia patients having a body mass index in the obese range 20 years after diagnosis[4], a striking change from 8% and 20%, respectively, at the time of first diagnosis.

In a separate examination of the everyday functioning of these same patients at the 20-year follow-up, we found that schizophrenia patients, who had a greater prevalence of obesity and worse cognitive performance, also had worse everyday functioning outcomes in terms of sustaining competitive employment and living independently[5]. For both patient samples, cognitive impairment and two indicators of physical functioning, waist circumference and the ability to rapidly and repeatedly rise from a chair (chair stands), were associated with competitive employment. When a logistic regression was used to predict employment, diagnosis accounted for 11% of the variance, with chair stands accounting for 9% and negative symptoms for an additional 5%. The diagnostic effect was likely associated with cognitive differences between the groups, but mobility limitations associated with obesity were excellent predictors of work outcomes. Modeling residential independence, only diagnosis accounted for variance in outcomes.

These findings do not cast any doubt on the importance of cognitive impairments for predictions of everyday outcomes. Rather, they likely suggest that cognitive impairments may contribute to the development of physical limitations. Obesity in schizophrenia is correlated with multiple impairments in nonsocial and social cognition[6]. On the nonsocial side, decision-making regarding dietary choices has been shown to be impaired. Poor dietary quality is common among low socioeconomic status groups, including those with schizophrenia. Fruit and vegetable intake is uncommon compared to the rest of the population. Those dietary choices, combined with the consumption of highly processed energy-dense food, foster obesity[7].

These calorie-dense, highly palatable foods are readily available in industrialized societies, requiring little effort in procurement and preparation. Patients with schizophrenia appear especially vulnerable to this environment, as they consume more food than mentally healthy people, and their food choices are poorer. In addition, very few patients follow a regular physical exercise routine[8] and, amongst those who do, erroneous assumptions about what represents healthy "exercise" prevail. In addition, the same deficits in valuation judgments noted by Green et al in the performance of emotionally neutral problem-solving tasks are present in food choices, with substantial tendencies toward short-term reinforcement rather than delayed gratification and planned food choices.

Further, impairments in functional capacity, known to be driven by cognitive limitations, are also common in relation to food related skills. Several studies have shown that schizophrenia patients are impaired in their ability to plan for and shop for nutritious meals. Their actual performance of cooking skills is also impaired[9]. Using a series of laboratory-based simulation tests, patients with schizophrenia manifested substantially more impairment in their ability to plan

a meal, shop for ingredients, and actually cook the food than healthy controls. These functional deficits were correlated with the severity of negative, but not positive, symptoms, and with executive functioning, but not memory, deficits.

In conclusion, we suggest that cognitive limitations of people with schizophrenia not only correlate with disability directly, but contribute substantially to other skills deficits (functional capacity; social competence) that exacerbate disability outcomes. Poor health and fitness, which add variance to current cognitive assessments for the prediction of disability, can also be traced back to cognitive deficits. The flow-forward cascade of impaired cognition, particularly in domains of reasoning and problem solving and reinforcement valuation, can lead to deficits in functional capacity which then lead to poor dietary and exercise choices, contributing to poor functional outcome.

Thus, influences on outcomes that appear to be unrelated to cognitive deficits may at least partially originate from cognitive limitations and respond to adequate cognitive enhancing treatments.

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Why are there no approved treatments for cognitive impairment in schizophrenia?

The paper by Green et al[1] details the evidence that cognitive impairment associated with schizophrenia (CIAS) remains a tremendous scourge on the lives of millions of people across the world. It is the aspect of the illness that most accounts for the social isolation and functional disability that plagues most people with schizophrenia for their entire lives.

Yet, tragically, there are no pharmacological or behavioral treatments for CIAS approved by any regulatory agencies across the world. Advances in genetics, biology, pharmacology and technology have facilitated the development of targeted treatments across various areas of medicine, especially in oncology, cardiology and immunology. These advances have transformed some illnesses from devastating, life-threatening events to simple annoyances. Why have the tremendous advances in neuroscience, psychopharmacology and genetics not provided patients with CIAS similar relief?

The most obvious consideration is the amount of investment that is being made in the development of treatments. The 2018 US National Institutes of Health (NIH) budget for research on schizophrenia was $258 million, but for heart disease it was 10 times as much, and for cancer 25 times as much[2]. This disparity is even greater in the pharmaceutical industry, where the overall research and development budget, which in 2017 was $71.5 billion[3], dwarfs government efforts. There are over 1,000 ongoing clinical trials in cancer for every one in CIAS[4] and, contrary to common belief, not because cancer drugs are a safer bet: the latest estimate that a treatment will successfully progress from phase 1 to the US Food and Drug Administration (FDA) approval is 5.1% for cancer indications, very similar to psychiatry at 6.2%[5].

Since many strategies will fail before a success is reached, a large number of attempts is required to find a treatment that is legitimately safe and effective. Further, serendipity flourishes greatest in the most active arenas. Unfortunately, the pharmaceutical industry has not presented nearly as many opportunities for success in CIAS as it has in other illnesses. Perhaps curing cancer is more personally tangible and may appear on the surface to be more morally compelling to investors than improving cognition in the people living in the darkness on the edges of town, and pharmaceutical companies are highly vulnerable to the whims of impressionistic shareholders. It is likely not a coincidence that the drug company listed on clinicaltrials.gov as having the greatest number of ongoing trials for the treatment of CIAS is privately owned.

What may explain why the CIAS trials conducted thus far have not been successful? Are the outcome measures used to assess cognitive and functional change to blame? The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Project developed a cognitive test battery, the MATRICS Consensus Cognitive Battery (MCCB), that was accepted as an FDA gold standard and has been used in most of the later phase trials. Several trials using the MCCB as the primary endpoint have been positive[6], but the one phase 3 program using the MCCB to test the efficacy of an alpha-7 nicotinic agonist was negative and well-publicized. An FDA gold-standard measure is often one of the key components of a registration trial that drug companies are not able to alter, it is thus a natural scapegoat for a failed or negative trial. However, early notions – based on very small samples – that the MCCB had problematic psychometric characteristics were soundly refuted by a