mates exposed to antipsychotic medications exhibited the same degree of brain volume loss observed in the post-mortem human studies[6]. This is yet another example of group differences not being obvious indices of underlying neuropathology.

Similarly, group differences in functional magnetic resonance imaging and EEG measures have been interpreted as representing a core neurocognitive impairment. Though widespread practice, the assumption that differential neurophysiological activation during neurocognitive tasks indicates neurocognitive impairment is a fallacy that has plagued the neuroscience literature broadly[7]. For example, in Green et al's description of dorsolateral prefrontal cortex (DLPFC) activation, they indicate that some studies find hypoactivation and others hyperactivation of the DLPFC. It is unlikely that both hypoactivation and hyperactivation suggest impairment, yet this is the interpretation that is made. Additionally, group-level neurophysiological differences do not indicate impairment. Musicians show increased neural tissue volume in some regions and decreased volume in others[8]. This does not suggest that musicians have a neurocognitive impairment, but that they have specialized knowledge from repeated practice. Presumably individuals given a diagnosis of schizophrenia have had experiences – such as trauma, exclusion, and positive symptoms – to a greater degree than the general population, which would be expected to manifest in differential neurophysiology.

The developmental course of test performance is often cited as evidence that impaired neurocognition is a core and stable feature of schizophrenia. As Green et al describe, poorer performance is observed prior to onset of the first episode of psychosis and remains relatively stable after a diagnosis is given. However, negative symptoms are also present prior to the onset of the first episode, and both poor neurocognitive performance and negative symptomatology appear to emerge at similar periods of development (approximately age 9) in individuals who later develop schizophrenia[9]. Thus, it is possible that poor neurocognitive performance represents a consequence of negative symptoms such as amotivation, or that other variables (e.g., negative bias and beliefs) may lead to the development of both negative symptoms and poor neurocognitive performance. For example, childhood trauma has been associated with later performance on neurocognitive tests, and laboratory induced social exclusion impairs subsequent neurocognitive performance in healthy individuals[10].

It is also worth emphasizing that neurocognitive performance has failed to predict who will develop a psychotic disorder among individuals at clinical high risk. If neurocognition were a core feature, then it should be associated with the development of the disorder. It would seem more likely that group differences in test performance do not reveal a distinct feature of schizophrenia, but instead an epiphenomenon that arises from amotivation, negative attitudes, trauma history and other aspects of the disorder.

Finally, language matters. It is unfortunate that the authors refer to "schizophrenia patients" throughout the manuscript. Similar to the other absolute terms – "deficit" and "impairment" – this term has inaccurate connotations. Nobody is just a patient, just a diagnosis, or just a collection of deficits. The science of schizophrenia would benefit from focusing on the whole person, with the mental health challenges that make up the diagnosis being just part of the full picture. Knowing the person at his/her best; and being able to accurately and dynamically assess his/her strengths, positive attributes, and beliefs will all be invaluable in this effort. Ultimately, the distance between the person given a diagnosis of schizophrenia and the typical citizen might grow very small indeed.

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DOI:10.1002/wps.20645

Cognition in schizophrenia: a marker of underlying neurodevelopmental problems?

The paper by Green et al[1] provides an extensive and in-depth review of cognition in schizophrenia, supporting the argument that cognitive dysfunction is a core feature of the illness. However, the authors do not fully explore how knowledge about cognition can inform us about the nature and development of schizophrenia. Is cognitive dysfunction a cause, a consequence or a marker of illness?

Both schizophrenia and general cognitive ability are heritable, with a broad polygenic basis. Genome-wide association studies have identified significant associations between intelligence and educational attainment, as a proxy for general cognitive abilities, and genes involved in central nervous system (CNS) development and synapse regulation. Some of these genes overlap with vulnerability genes for schizophrenia. These genetic associations are primarily negative (i.e., higher intelligence – lower schizophrenia risk), but some of them are bidi-

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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DOI:10.1002/wps.20646

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-