Cognitive Functioning in Older Adults With Schizophrenia

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Cognitive deficits are thought to be a core feature in schizophrenia and have been found to be strongly associated with impairments in functioning. It is estimated that more than 70% of patients with schizophrenia have cognitive impairment. The aim of this article is to critically review the emerging literature on cognition in older adults with schizophrenia. Specifically, we address the following questions: Are there differences in cognitive functioning between older adults with schizophrenia and their healthy age peers as well as with younger people with schizophrenia? What are the factors associated with cognitive deficits and their interaction over time? What are the life course trajectories of cognitive deficits, especially in later life? Are older adults with schizophrenia more likely to develop dementia, and, if so, does it differ from other dementias? Are there pharmacological and psychosocial interventions that can successfully treat cognitive deficits in older adults with schizophrenia?

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Cognitive deficits are thought to be a core feature in schizophrenia and have been found to be strongly associated with impairments in functioning (1). Neurocognition refers to the ability to correctly perceive, attend to, and remember information, such as verbal fluency, memory, processing speed, reasoning, problem solving, and attention (2, 3). Social cognition refers to mental operations involved to understand, perceive, and interpret the social world, such as detecting emotion in faces and inferring what people are thinking and feeling (2). In the literature, there is a tendency to conflate cognition and neurocognition. It is estimated that more than 70% of patients with schizophrenia have cognitive impairment (4). There is an emerging literature on the course, associated factors, impact, and treatment of cognitive deficits in older adults with schizophrenia. Most of the latter has focused on neurocognitive deficits, although there have been a few recent interventional strategies targeting social cognitive dysfunction.

There is a pressing need to more fully understand the issues affecting cognition in older adults with schizophrenia because people age 55 years and older will soon represent one fourth or more of individuals with schizophrenia in many developed countries (5). In this review, we address several questions. First, are there cognitive differences between older adults with schizophrenia and their age-matched peers? Second, are there cognitive differences between younger and older adults with schizophrenia or among persons with early- and late-onset disorders? Third, what factors are associated with cognitive functioning in older adults with schizophrenia, and how do they interact over time? Fourth, what are the later-life trajectories of cognitive functioning in older adults with schizophrenia? Fifth, are older adults with schizophrenia more prone to develop neurocognitive disorders? If so, how can clinicians distinguish the cognitive impairment of schizophrenia from such disorders? Sixth, what treatment strategies can be used to treat the cognitive problems of older adults with schizophrenia?

To address these questions, we have focused on more recent articles and have strived to reduce unnecessary detail and extensive referencing by citing conclusions from meta-analyses and literature reviews. There is no consensus definition of older adults with schizophrenia, but the literature has typically considered it to be age 55 years and older or, in some instances, age 50 years and older.

COGNITIVE DIFFERENCES BETWEEN ADULTS WITH AND WITHOUT SCHIZOPHRENIA

Most broad-age range studies suggest that schizophrenia is associated with mild premorbid cognitive deficits that are approximately one third to two thirds of a standard deviation below age-matched peers in a control group (6). However, a recent study of people age 50 years and older found that schizophrenia is associated with cognitive deficits that are nearly two standard deviations below cognitive levels of participants in a control group (7). Rajji and Mulsant's (8) cross-sectional literature review of late-life schizophrenia (defined as schizophrenia, schizoaffective, or schizophreniform disorder among individuals age 50 years or older) found that patients with late-life schizophrenia consistently exhibited impaired global cognitive functioning compared with their age-matched healthy peers. Moreover, people with late-life schizophrenia demonstrated specific impairments in executive function, visuospatial ability, and verbal fluency, with

impairment less consistently observed in memory, attention, and working memory. Subsequently, Irani et al. (9) conducted a cross-sectional meta-analysis focused on older adults with schizophrenia (defined as 50 years of age or older, with most participants approximately 65 years of age). The authors found the largest effect in domains associated with language, immediate memory, and executive function. With respect to age of onset, Vahia and colleagues (10) found that persons with early- or late-onset disorders had significantly worse cognitive scores than persons in a healthy control group.

COGNITIVE DIFFERENCES BY AGE AND AGE AT SCHIZOPHRENIA ONSET

Whereas the *DSM-5* (11) and *ICD-10* (12) do not distinguish by age of onset, the International Late-Onset Schizophrenia Group (13) proposed that schizophrenia be termed "late-onset schizophrenia" for disorders that have an onset between the ages of 40 and 60 years, and "very-late-onset schizophrenia-like psychosis" for onset after the age of 60 years. The literature has sometimes ignored these demarcations and classified all people developing the disorder at age ≥40 (or 45) as one group. The type with onset between the ages of 40 and 60 years has been thought to be more similar to the early-onset subtype, although subtle differences have been noted between these two types, such as a preponderance of women, a lower level of symptom severity, and lower average antipsychotic dose requirement (14). The very-late-onset type is distinguished by its much higher frequency of diagnosis among women than among men; greater prevalence of persecutory and partition delusions; higher rates of visual, tactile, and olfactory hallucinations; lower genetic load; the absence of negative symptoms or formal thought disorder (13); and possibly a higher standard mortality rate versus older people with early-onset disorder, chiefly because of higher rates of comorbid illness and accidents (15).

Rajji et al. (16) conducted the most comprehensive study examining differences across age groups among people with schizophrenia. They compared people with schizophrenia, age 19–79 years, with their healthy age peers. There was a significant age effect in the group with schizophrenia, with progressive declines in overall cognitive scores as well as all cognitive domains except social cognition. The rate of decline across the various age groups was similar to that observed in the healthy groups. Rajji et al. noted that "deficits occur around the time of onset and do not progress beyond what is observed due to effect of aging over the entire span of adult life" (p. 6). They concluded that although individuals with schizophrenia decline at the same rate as those without the disorder, they cross the threshold of clinical impairment earlier and, thus, exhibit premature aging.

The data are in conflict with respect to cognitive deficits in older patients with early-onset schizophrenia and late-onset schizophrenia. Studies have shown late-onset schizophrenia to have lower, greater, or equivalent levels of cognitive impairment versus early-onset schizophrenia. Some investigators have suggested that there may be a few differences in the cognitive deficit patterns between early- and late-onset schizophrenia that are independent of age or duration of illness, although any definitive conclusions are constrained by methodological differences across studies (17, 18). A serious methodological confounder is the possibility that organic-related psychosis was included among samples with late-onset schizophrenia (17, 18). Although acknowledging the methodological shortcomings and a paucity of comparative studies, Rajji and Mulsant's (8) literature review found that "all the cross-sectional and most of the longitudinal studies were unable to distinguish patients with early-onset schizophrenia from those with late onset in terms of their cognitive profiles" (p. 138). In a large comparative study (N=110 patients with late-onset schizophrenia; N=744 patients with early-onset schizophrenia), Vahia and colleagues (10) found that when duration of illness was considered, the only differences between early- and late-onset schizophrenia were in processing speed and perceptual organization, which were more impaired in the former. Rajji and Mulsant (8) speculated that the lack of differences in cognitive functioning between people with early- versus late-onset schizophrenia—despite having experienced dissimilar durations of illness—suggests differences in the sequence of cognition and psychotic symptoms in the two groups; that is, cognitive decline precedes psychosis in late onset, whereas it follows psychosis in early onset. Finally, two recent studies have found better social cognition scores linked to late-onset schizophrenia and that appeared associated with age of onset rather than age per se (19, 20).

FACTORS ASSOCIATED WITH COGNITIVE FUNCTIONING AND THEIR INTERACTION

Cross-Sectional Studies

In the cross-sectional meta-analysis of older adults with schizophrenia by Irani et al. (9) described earlier, demographic and clinical variables that had the strongest relationship with worse cognitive (global or domain specific) functioning included greater age, female gender, lower education, living in an institution, longer duration of illness, earlier age of onset, and higher levels of positive and negative symptoms. There was also some evidence that Caucasian patients had greater global and domain-specific cognitive impairment; however, the authors cautioned that this finding may reflect reporter bias, such as omitting race or stating only a proportion of Caucasians. Although their analysis did not specifically look at the impact of cognition on daily functioning, the authors noted that the presence of cognitive deficits has been shown to be a strong predictor of functional impairment in schizophrenia.

Kalache and colleagues (21) published a cross-sectional study of cognition and functional competence of individuals with schizophrenia across seven decades of life with ages ranging from 19 to 79 years (mean age = 49 years; 24% of

participants were age 60 years and older). They found that global cognition was associated with comprehension as well as planning, financial, communication, and transportation skills, education, gender, and negative symptoms of schizophrenia. The authors concluded that cognition is a strong correlate of functional competence across the lifespan and that targeting cognitive impairment associated with schizophrenia could improve individuals' function regardless of age.

Longitudinal Studies

Although longitudinal studies are highly desirable and are the gold standard of research, the extant longitudinal literature for cognition in older adults with schizophrenia has many limitations in comparison with the more robust cross-sectional studies described in the previous section. Notably, recruiting and maintaining a sample over time has yielded smaller sample sizes. For example, a 2011 study with an age 50 and older population had a modest N of 32 (22); likewise, a 2015 study with a mean age of 43 years had an N of 30 (23). These numbers are dramatically smaller than recent cross-sectional studies that have 1,000 or more patients per study sample and, thus, are able to draw more robust associations. Although there are several studies that include a portion of older adult patients, there are few longitudinal studies of cognition with purely older adult populations (23–34). Thus, we could identify only 12 longitudinal studies that met criteria for older adult and age 55 years or greater (22, 35–45). There is also a lack of uniformity with respect to the number of assessments and the time interval between these assessments, for example, the shortest period noted was two weeks, and the longest follow-up period was 10 years (32, 33). Szöke et al.'s (46) meta-analysis hypothesized that improvements in test scores with a one month retest interval might result from either real improvement in cognition or a practice effect or a combination of the two. Moreover, the studies with the most number of reassessments had younger mean age starting populations (31). Older age populations were limited to typically a single retest interval. Furthermore, about 85% of older adults with schizophrenia live in community settings; however, most longitudinal studies have been with patients who were chronically institutionalized or patients in a mixed setting from one research institution: Mount Sinai in New York City. The community-based studies were largely from the San Diego Research Group. It is difficult to interpret the results of studies in which inpatients and outpatients are directly compared because patients who have better cognitive performance are more likely to be discharged, and cognitive deficits might serve as one of the selection biases for long-term institutionalization rather than the latter's being a cause of the deficits (26).

In the longitudinal literature, a consensus opinion for predictors of cognition in older adults does not exist (4). This lack of agreement may be a consequence of the limitations described earlier. Harvey and colleagues (38) found that in a population of individuals who were chronically institutionalized, lower levels of education, older age, and the presence of more severe positive symptoms predicted increased risk for cognitive and functional decline (38). Among patients who were institutionalized, worsening cognitive function predicted worse adaptive life skills and was associated with diminished verbal productivity and poverty of speech (35, 36). Studies with participants who were both institutionalized and community-dwelling found that positive and negative symptoms were predictors of cognitive change, that is, declines in these symptoms led to better cognitive functioning (25, 30). In community-dwelling samples, higher cognitive reserve has been shown to predict sustained remission (6). Thompson and colleagues (25) found that cognitive decline was associated with negative symptoms and living in board and care facilities; it was not associated with positive symptoms or antipsychotic use. In a recent naturalistic outpatient follow-up study, Helldin and colleagues (47) analyzed people with schizophrenia, divided into age <70 and ≥ 70 years, and compared characteristics of survivors with their deceased counterparts. They found that those who died performed more poorly in cognitive battery testing and that verbal memory and executive functioning were powerful independent predictors of longevity. The authors concluded that higher cognitive reserve may predict this longevity as it does in healthy populations.

LATER-LIFE TRAJECTORIES OF COGNITIVE FUNCTIONING IN SCHIZOPHRENIA

Investigators have been divided into two schools of thought regarding the lifetime course of cognition in schizophrenia: neurodevelopmental versus neurodegenerative patterns. To date, there has been no resolution of this debate (19). This debate is further complicated by emerging evidence for longitudinal heterogeneity (25, 26); that is, different patterns are observed among individuals with the disorder. The neurodevelopmental process suggests a pattern and rate of cognitive change with aging that appears parallel to that seen in the general population (6, 8, 9, 24, 27, 28, 30, 40, 44). Mild cognitive impairment starts around the onset of the disorder and persists throughout life and across ages (6, 8, 9, 24, 27, 28, 30, 40, 44). Bonner-Jackson and colleagues (29) found that the most dramatic change in cognition was observed at early follow-up assessments within the first 7.5 years. Presumably this cognitive change is close to the index psychotic event, whereas after this period differences in the rate of cognitive decline between people with schizophrenia and controls diminish. This suggests that, except for the typical declines with aging, cognition is somewhat stable in patients with schizophrenia over time after the acute psychotic phase (29). Thus, the neurodevelopmental model is frequently linked to the "static encephalopathy" model because it postulates that there are no marked declines in cognition in the years following the onset of the disorder. A recent meta-analysis by Heilbronner and colleagues (48) provided further confirmation for this pattern. Moreover, a longitudinal study by

Schnack and colleagues (49) comparing magnetic resonance imaging scans of healthy participants and people with schizophrenia (age range = 16–67 years) found that there was an accelerated pattern of brain aging in people with schizophrenia at illness onset and during the initial five years; however, after that period, the rates of decline were comparable between the two groups, although the brain gap stayed constant. Unfortunately, long-term longitudinal neuroimaging studies are not available.

Neurodegenerative cognitive changes were postulated in the late 19th century by Kraepelin's characterization of the disorder as "dementia praecox" (50). A meta-analysis by Shah and colleagues (51) examining evidence for cognitive decline late in the disorder found a ratio of positive to negative studies of 1.2:1 when control groups were used. In general, investigations of older adults with schizophrenia have found that cognitive deficits may be affected by institutional status, whereas age of onset may not contribute to cognitive functioning. For example, Harvey (50) identified two separate periods of deterioration in schizophrenia patients: the first occurring some time prior to the first psychotic episode and the second beginning at approximately 65 years of age. Harvey and colleagues (45) identified long-term institutionalization as a predictor of late-life decline; however, even after deinstitutionalization, patients continued to worsen cognitively. It was estimated that these patients who were chronically institutionalized—who represent a minority of older adults with schizophrenia—declined cognitively after the age of 65 years by 1 point per year on the Mini-Mental State Exam (MMSE) compared with 3 points per year for patients with Alzheimer's disease (30). Rajji et al.'s (17) review of older patients with schizophrenia concluded that the findings of cognitive decline at age 65 years found in people who are institutionalized might not apply to those who have been living in the community. Indirect support for this hypothesis came from a study by Nemoto and colleagues (26) who found that patients who were chronically institutionalized (mean age = 55 years) showed a small degree of improvement in some cognitive deficits, social functioning, and symptom burden after being transitioned into the community. This finding confirmed the importance of the connection between residential setting and cognition, although this conclusion differed from Harvey's group, who had found that cognition continued to decline in discharged patients (45).

Increasingly, there has been interest in potential for within-group improvement or heterogeneity in cognitive functioning in older adults with schizophrenia. Thompson and colleagues' (25) study of middle-aged and older people with schizophrenia (age 40–100 years) with a mean of 3.5 years of follow-up demonstrated that three subgroups exist with differing trajectories of cognitive ability. One group exhibited relatively high and stable trajectories of cognition (50%); a second group exhibited lower, modestly declining trajectories (40%); and a third group exhibited lower, more rapidly declining trajectories (10%). Even in the latter category, rates of cognitive decline were substantially less than people with Alzheimer's disease. Thompson et al. observed that their findings suggested "a middle-ground between studies of community dwelling outpatients indicating stability and studies using data from institutionalized patients indicating accelerated decline" (p. 95). A somewhat similar heterogeneous pattern was observed in a more recent 52-month follow-up study of 104 community-dwelling people age 55 years and older living in New York City (52). The authors found that 19% of the participants were rapid decliners, 25% were modest decliners, and 56% were stable or improved. Indeed, a notable finding was that 20% of the sample showed a .50 or greater effect size improvement in their cognitive scores (52). There was flux in scores across all cognitive subscales, but memory and executive function showed the most fluctuation. A study by Savla and colleagues (24) similarly found that over a 15-month period, as many participants cognitively improved as declined (about one sixth in each category) among their sample of middle-aged and older people with schizophrenia (mean age = 53 years). Other studies have alluded to heterogeneity in cognitive outcome within older adult populations with schizophrenia (38). This issue was thoughtfully addressed by Shmukler and colleagues (4) in their literature review:

> We accept that the heterogeneous groups of patients may show divergent dynamics of cognitive functioning over time, in particular at different stages of schizophrenia: cognitive deficit in a subset of patients may remain stable throughout the illness, in other cases, cognitive functioning may improve and yet other patients may exhibit the progressive worsening of cognitive deficit. It is also necessary to highlight the possibility of undulating dynamics of cognitive impairment, with periods of deterioration and improvement (for example, due to relapse or remission of symptoms). In addition, it is necessary to take into account the possibility of divergent dynamics of the distinct cognitive domains in the same patient, thus requiring that when single patients are being assessed, the assessor should specifically look at separate cognitive domains. (p. 1008)

DO PATIENTS WITH SCHIZOPHRENIA DEVELOP NEUROCOGNITIVE DISORDERS?

The *DSM-5* (11) made the decision that the cognitive impairment accompanying schizophrenia is different from Neurocognitive Disorders, which have more clear neurological etiologies. Section III of the *DSM-5* contains criteria for assessing the level of cognitive impairment. However, this decision on classification has created diagnostic conundrums, especially when older adults with schizophrenia experience declines in cognitive functioning.

Because of the increased propensity for patients with schizophrenia exposed to second-generation antipsychotic medications to develop metabolic syndrome, which is a risk factor for both Alzheimer's disease and vascular dementia, it is reasonable to postulate that older adults with schizophrenia might be more likely to develop neurocognitive disorders. Nonetheless, the data in support of this notion

have not been compelling. First, the only available study that has investigated the prevalence of metabolic syndrome in older patients with schizophrenia did not report a higher prevalence than their age peers (53). Second, estimates of dementia are confounded by the fact that people with schizophrenia have cognitive deficits arising earlier in the disease course that are progressively worsened by typical age-associated cognitive decline. Consequently, as many as half of the people with schizophrenia may meet the cognitive cutoffs for mild dementia (54). For example, a large-scale study using outpatient data by Hendrie et al. (55) (mean age = 70 years) reported that patients with schizophrenia were diagnosed as having dementia twice as much as patients without schizophrenia (64% vs. 32%). However, Hendrie et al. conceded that

> The lack of a significant effect on mortality of the diagnosis of dementia in the patients with schizophrenia . . . in contrast to the increased effect of a dementia diagnosis in the total sample . . . raises the possibility that at least in some cases physicians are misidentifying patients in these older, difficult-to-evaluate, patients with schizophrenia. (pp. 7–8)

There are few longitudinal studies examining the incidence of dementia in older people with schizophrenia. Shah and colleagues (51) found only three longitudinal studies comparing people with schizophrenia with a nonschizophrenia control group; all were conducted on people with late-onset disorder, and follow-up ranged from three to 10 years. Two of the studies reported an increased prevalence of dementia, and one did not. None of the studies controlled for risk factors or noted the types of dementia that arose.

Friedman and colleagues (30) observed that the cognitive decline experienced by people with schizophrenia who were chronically institutionalized and who showed accelerated declines in cognition beginning at age 65 years is distinctive in its course compared with Alzheimer's disease. Studies of patients with Alzheimer's disease have demonstrated a mean annual rate of decline on the MMSE between 2 and 5 points annually, whereas the patients with schizophrenia had a mean decline of 1 point annually over a six-year follow-up study. A longitudinal study by Palmer and colleagues (44) found that there were comparable cognitive changes for patients with late-onset schizophrenia, patients with early-onset schizophrenia, and a control group of persons without schizophrenia, whereas the groups with Alzheimer's disease had significantly greater declines. Moreover, in postmortem examinations of older adults with schizophrenia, it has been noted that there is minimal neurodegenerative brain pathology typical of Alzheimer's disease pathology such as neurofibrillary tangles or senile plaque formation (56).

"Very-late-onset schizophrenia," which develops after age 60 years, is a more disputed domain with respect to outcome. On the basis of one study, a higher proportion of patients with very-late-onset schizophrenia versus their healthy age peers may go on to develop a type of dementia by 3- to 4.6-year follow-up, although incidence found was small (4.40% vs. 2.15%) (57). However, it remains unresolved as to whether late-onset psychosis is a triggering factor or a prodromal form of dementia; that is, it's essentially a misdiagnosis (58). Biological markers of schizophrenia with a later onset have been elusive, and no specific neuropathological substrate has been identified (10). Hahn et al.'s (59) review of neuroimaging studies that compared early-onset and late-onset schizophrenia reported differences in eight of 10 studies, but these were not consistent across studies.

Increased microglial activity and neuroinflammatory processes have been implicated in both schizophrenia and various neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (60). It is unclear whether this might place older adults with schizophrenia at greater risk for such neurodegenerative disorders. Interestingly, a small study by Takano and colleagues (61) found an association between microglial activation and both age and duration of illness among persons with schizophrenia.

Polygenic Risk Scores may in part explain the differences in disease processes. "A Polygenic Risk Score is the sum of trait-associated alleles across several genetic loci, typically weighted by effect sizes derived from a genome-wide association study" (62). Liebers et al. (63), who conducted an 8616 genotyping and clinical study of middle-aged and older adults followed over an average of 10 years, found "evidence for different degrees of association between polygenic risk for SCZ and genetic risk factors for ALZ on cognitive function and decline, highlighting potential differences in the pathophysiology of cognitive deficits seen in SCZ and ALZ" (p. 984). The presence of the established *APOE4-TOMM40* risk loci was strongly associated with lower cognitive scores of patients with Alzheimer's disease, particularly the subsets of language, attention, and verbal memory. Meanwhile, schizophrenia polygenic risk alleles are associated with general modest cognitive decline specifically in attention and spatial working memory. In summary, a preponderance of evidence—histopathological, clinical studies, and polygenic risk scores—suggests real differences in the genetic susceptibility, cognitive limitations, and disease progression of older adults with schizophrenia in comparison with people with Alzheimer's disease.

STRATEGIES FOR TREATING COGNITIVE PROBLEMS AMONG PEOPLE WITH SCHIZOPHRENIA

Pharmacologic Approaches

It is important to remember that many older persons with schizophrenia take prescription and nonprescription medications that have anticholinergic effects. Individuals approaching advanced years are more sensitive to the anticholinergic effects of medications, especially with respect to their impact on cognition. Thus, clinicians must regularly review medication regimens, and when feasible, consider alternatives to anticholinergic medications.

Because there have been few pharmacological trials of cognitive enhancers in older adults with schizophrenia, we provide a brief review of strategies that might have applicability to older populations. With respect to younger samples, Buoli and Altamura (64) concluded that there was little support for the superiority of antipsychotic drugs versus placebo for the enhancement of cognition, and they pointed to a need to consider alternative pharmacological strategies. To this end, Choi et al. (65) published a meta-analysis reviewing 26 double-blind, placebo-controlled studies to determine the efficacy of novel adjunctive pharmacotherapy for cognitive deficits in schizophrenia. The authors reported that acetylcholinesterase inhibitors (AChEIs)—such as donepezil, rivastigmine, and galantamine—produced marginal improvement in verbal learning and memory and moderate improvements on spatial learning and memory. The proglutamate-glutamatergic agonists (i.e., D-cycloserine, D-serine, D-alanine, sarcosine) improved negative symptoms of psychosis but did not improve measures of cognitive function. Lastly, the proserotonin-serotonergic agonists (i.e., tandospirone, mianserin) improved positive symptoms but had no significant effect on cognition. The authors concluded that the marginal benefits provided by AChEIs might maximize treatment effects if they were used in conjunction with cognitive remediation therapy.

A meta-analysis of three random controlled trials of memantine (66–68), which acts on glutamine receptors to block excessive influx of calcium ions in the channels of *N*-methyl-D-aspartate receptors, found significant improvements in some cognitive functions among people with schizophrenia, although individual studies have been mixed. Encericline, an alpha-7 acetylcholine nicotinic receptor agonist, has shown promise enhancing cognitive skills in two small studies (69, 70). Koola and colleagues (68) suggested combining memantine with galantamine, which in addition to AChEI action also has unique effects on alpha-7 nicotinic acetylcholine receptors. This combination has had modest synergistic effects on cognition among people with Alzheimer's disease. Finally, in one of the few studies focusing on people with schizophrenia who are more than 50 years of age, Deutsch and colleagues (71) found some cognitive benefits combining galantamine with cytidine diphosphate choline, a dietary source of choline that might prevent reductions in the receptor's sensitivity that often occur with the former. With respect to social cognition, there have been a few exploratory studies with younger samples of men with schizophrenia that found that people given oxytocin performed better on social skills training (72, 73).

Nonpharmacologic Approaches

Hybrid approaches to cognitive therapy seem to be better than single-focus approaches. Thus, Mueller et al.'s (74) meta-analysis of 15 controlled studies of integrated psychological therapy—a technique that combines neurocognitive and social cognitive remediation with therapy for social skills and interpersonal problem solving—showed a significant medium to high effect size, independent of age group (age <40 years and age ≥40 years), on global cognition, neurocognition, social functioning, psychopathology, and an overall measure of all outcome variables. The integrated psychological therapy effects in middle-aged patients were significantly higher on the global cognitive score, neurocognition, and social cognition compared with younger patients. By contrast, Kontis and colleagues (75) and McGurk and Mueser (76) found cognitive remedial therapy had significant effects on younger but not older patients with schizophrenia. A problem in the literature has been the narrow age range across most studies; the average age of participants was 36 years, and 70% of studies had an average age within five years of this mean (77).

In recent years, there have been a few hybrid cognitive therapeutic programs that have been developed specifically for middle-aged and older adults with schizophrenia (mean ages in studies = 51–60 years). First, the Functional Adaptation Skills Training (78, 79) intervention targets six areas of everyday functioning: medication management, social skills, communication skills, organization and planning, transportation, and financial management. For example, participants engage in two 3-minute role-plays in which they simulate interactions with a new neighbor and a landlord, respectively. A 24-week randomized controlled trial (78) found that those in the Functional Adaptation Skills Training intervention improved considerably in everyday living skills and social skills but not in medication management skills. Second, the Helping Older People Experience Success (80) program focuses on psychosocial and preventive health care. It consists of the following modules: Communicating Effectively, Making and Keeping Friends, Making the Most of Leisure Time, Healthy Living, Using Medications Effectively, and Making the Most of a Health Care Visit. A three-year follow-up found that compared with a treatment-as-usual group, the intervention group was associated with improved community living skills and functioning, greater self-efficacy, lower overall psychiatric and negative symptoms, and greater acquisition of preventive health care (80). Third, the Cognitive Behavioral Social Skills Training (81) intervention consists of three modules that participants complete twice: Thought-Challenging Module (e.g., "I'm too old to learn"), Asking for Support Module, and the Solving-Problems Module. In a 24-week trial, compared with the treatment-as-usual group, the intervention group performed significantly more social functioning activities, achieved greater cognitive insight, and demonstrated greater skill mastery, although general skill at social functioning activities did not differ significantly from the control group.

SUMMARY

The key findings from our review are summarized below:

- Older adults with schizophrenia exhibited greater overall cognitive deficits compared with their healthy age peers;

differences were found across most cognitive domains, with executive dysfunction being the most frequently observed.

- Compared with their younger counterparts, older adults with schizophrenia had greater deficits in overall scores and in nearly all cognitive domains.
- Data conflict regarding differences in cognition between early- versus late-onset schizophrenia. The reviews and reports with the largest data sets conclude that there are no substantial differences in cognitive profiles despite differences in duration of illness.
- Cross-sectional studies of older adults with schizophrenia found cognitive impairment to be associated with impaired functional abilities, greater age, female gender, lower education, institutional residential status, longer duration of illness, earlier age of onset, and greater positive and negative symptoms.
- Longitudinal studies of older adults with schizophrenia found that cognitive decline was predicted by lower education, older age, and more positive symptoms; cognitive impairment predicted greater impairment in adaptive social skills.
- Trajectories of cognitive functioning suggest longitudinal heterogeneity. Group cross-sectional data indicate that for people who are not institutionalized, there is a typical age-related decline in cognition after initial impairment around the time of illness onset. For people who are institutionalized (15% of older adults with schizophrenia), there seems to be a substantial worsening of cognition after age 65 years. Within-group longitudinal data of middle-aged and older people with schizophrenia in the community showed considerable heterogeneity: Most people seemed to be cognitively stable; however, about one fifth showed more rapid decline, and one fifth showed improvement.
- With respect to risk for dementia, as many as half of older adults with schizophrenia may meet criteria for dementia because of early cognitive deficits followed by typical age-associated declines in cognition. Longitudinal studies produced mixed results with respect to conversion to dementia. Patterns of decline, neuropathology, and polygenetic findings, even among groups who were more chronically hospitalized, did not resemble those of Alzheimer's disease.
- Studies using broad age samples have found marginal benefits from acetyl cholinesterase inhibitors and mixed results from memantine for enhancing cognition. Using a hybrid approach—that is, combining neurocognitive and social cognitive techniques—has yielded some favorable outcomes in controlled clinical intervention studies of middle-aged and older adults with schizophrenia.
- Although prospective analysis is the gold standard of study designs, it has been difficult to draw firm conclusions from longitudinal cognitive data of older adults with schizophrenia because of the relatively few studies and small samples versus cross-sectional studies, inconsistencies in the length of follow-up periods, and the conflation of early- and late-onset cases. Although the proportion of older adults with schizophrenia is approaching one fourth of all people with schizophrenia, only 1% of the schizophrenia literature has focused on older people (5). Indeed, there is a compelling need to target more research toward this population.

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