Neuropsychological Performance in Older Patients With Schizophrenia: A Meta-Analysis of Cross-sectional and Longitudinal Studies

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Objective: Cognitive deficits are among the most reliable predictors of functional impairment in schizophrenia and a particular concern for older individuals with schizophrenia. Previous reviews have focused on the nature and course of cognitive impairments in younger cohorts, but a quantitative meta-analysis in older patients is pending. Method: A previously used search strategy identified studies assessing performance on tests of global cognition and specific neuropsychological domains in older patients with schizophrenia and age-matched comparison groups. Both cross-sectional and longitudinal studies were included. Potential methodological, demographic, and clinical moderators were analyzed. Results: Twenty-nine cross-sectional (2110 patients, 1738 comparison subjects) and 14 longitudinal (954 patients) studies met inclusion criteria. Patients were approximately 65 years old, with 11 years of education, 53% male and 79% Caucasian. Longitudinal analysis (range 1–6 years) revealed homogeneity with small effect sizes \( \left(d = -0.097\right) \) being observed. Cross-sectional analyses revealed large and heterogeneous deficits in global cognition \( \left(d = -1.19\right) \) and on specific neuropsychological tests \( \left(d = -0.7 \text{ to } -1.14\right) \). Moderator analysis revealed a significant role for demographic (age, sex, education, race) and clinical factors (diagnosis, inpatient status, age of onset, duration of illness, positive and negative symptomology). Medication status (medicated vs nonmedicated) and chlorpromazine equivalents were inconsequential, albeit under-represented. Conclusions: Large and generalized cognitive deficits in older individuals with schizophrenia represent a robust finding paralleling impairments across the life span, but these deficits do not decline over a 1–6 year period. The importance of considering demographic and clinical moderators in cross-sectional analyses is highlighted.

Key words: schizophrenia/neuropsychology/meta-analysis/elderly

Introduction

Cognitive deficits have been shown to be a strong and reliable clinical predictor of functional impairment in schizophrenia.¹ Several meta-analyses have indicated that when examined cross-sectionally, patients show moderate to large effect sizes across a variety of neuropsychological domains with effect sizes, ranging from \(-0.46 \text{ to } -1.57\), with memory and executive dysfunction representing the more robust impairments.²–⁸ The trajectory of the disorder with aging has been less clear, with ongoing debate about whether schizophrenia follows a neurodevelopmental or neurodegenerative course or some combination thereof. Early descriptions of schizophrenia by Emil Kraepelin as “dementia praecox” led to the contention that cognitive deterioration occurs beyond that found in the initial stages of the illness. Some early studies indicated progressive decline in neurocognitive function with age⁹,¹⁰ but this has been disputed with indications that deficits later in life are typical of normal aging.¹¹–¹³ (Irani, et al., unpublished data) Furthermore, postmortem data from elderly patients with schizophrenia has not shown excess of those neuropathological abnormalities found in typical neurodegenerative disorders such as Alzheimer’s disease,¹⁴ yet chemical markers such as cortical amines and neuropeptides deficits have been associated with more severe cognitive dysfunction in some patients.¹⁵ Reviews of longitudinal studies have indicated either stability in cognitive impairment over a year¹⁶ or no evidence of deterioration among community-dwelling adults.¹⁷ A recent examination of an epidemiological first-episode cohort followed over 10–12 years showed that some aspects of cognition are compromised at initial onset (executive function) and do not deteriorate, while others (visuospatial functions) are spared during the first episode but deteriorate with time.¹⁸ Recently a meta-analysis showed...
improvement in some tasks or no difference for others over 12 months due to cognitive remediation or neuropsychological test practice effects. These conflicting findings continue to raise questions about the longitudinal course of the disorder.

Additionally, most studies have focused on younger populations. The nature and magnitude of cognitive impairments in older patients has received comparatively less attention. In fact the term “older” has been used variably in various studies and reviews. For the current study, we relied on the consensus statement by members of the International Late-Onset Schizophrenia Group and operationally defined it as schizophrenia in an individual over the age of 50 years. Older individuals with schizophrenia continue to constitute a high proportion of hospitalizations and institutionalizations, making the issue of late-life trajectory of schizophrenia an important public health concern. Geriatric schizophrenia has been found to be the most expensive among all medical disorders based on per capita Medicare and Medicaid expenses. Given the substantial personal and economic cost of aging-related cognitive and functional impairments, further clarification of cognitive functioning in older individuals with schizophrenia is needed. Furthermore, a better understanding of the cognitive course of schizophrenia over the life span can also advance our understanding of the neurobiology of the disorder and aid in ongoing efforts focused on early detection and intervention of this complex disorder.

A recent review focused on the nature and course of cognition in late-life schizophrenia in individuals over 50 years of age. This qualitative review suggested that cross-sectional studies show impairments in executive function, visuospatial ability, and verbal fluency, with less consistent deficits in memory, attention, and working memory. Longitudinal findings were interpreted as indicating the presence of cognitive decline around age 65, with early deficits in visuospatial abilities. While this review was conducted thoroughly, it was limited to a qualitative description of the observed deficits, thus lacking important information on the magnitude of the effect.

Here, we extended this line of work by conducting a quantitative meta-analysis of existing studies in older patients with schizophrenia. A meta-analytic approach allowed us to combine the results of several studies to examine synthesized effect sizes, which provide more powerful estimates of true population differences than those derived from a single study. We examined the impact of both global cognitive measures as well as specific neuropsychological domains in older samples of schizophrenia patients as compared with age-matched comparison groups. A separate analysis of longitudinal data was also conducted to more closely examine the course of the disorder. We further sought to clarify the impact of potential moderators such as various methodological, demographic, and clinical variables that have been variously linked to differences between patients and healthy comparison groups.

Methods

Search Strategy

We relied on a search and analytic strategy previously used by Rajji and Mulsant and updated by us in October 2008. Briefly, these authors searched Medline on November 30, 2007 and February 16, 2008, with no date limits using the following search terms: (schizophrenia OR schizoaffective) AND ((cognition) OR (neuropsychology) OR (memory) OR (learning) OR (Wechsler) OR (complex figure) OR (face recognition) OR (spatial perception) OR (line orientation) OR (Purdue) OR (motor dexterity) OR (finger tapping) OR (motor disorder) OR (Stroop) OR (Digit Span) OR (continuous performance) OR (backward masking) OR (Trail Making) OR (Wisconsin Card Sorting Test) OR (IQ) OR (vocabulary) OR (Block Design) OR (word fluency) OR (comprehension) OR (affect recognition) OR (dichotic listening)). Search was limited to “middle age (45–64 years)” OR “middle aged (45 plus years)” OR “all aged (65 and over)” OR “aged (80 and over).” We reviewed titles and abstracts and retained them if they were studies of cognition in older adults with schizophrenia or related disorders, either in a cross-sectional design with an age-matched healthy comparison population or a within-subjects longitudinal design.

Data Extraction

The Meta-analysis Of Observational Studies in Epidemiology standard was followed in the extraction of relevant studies and data. Potential studies were initially reviewed for possible inclusion by 3 authors (E.A.M., F.I., P.J.M.) based on aforementioned criteria. Cross-sectional studies included by Rajji and Mulsant that did not include a comparison group were excluded. Relevant data were extracted and tabulated independently by 2 authors (F.I., S.K.). References for the papers included in this meta-analysis are provided in the online Supplementary Material.

Statistical Analyses

Comprehensive Meta-Analysis version 2.0 was used. Mean difference in scores between studies reporting contrasts of schizophrenia patients and comparison groups (cross-sectional) and between time points for patients (longitudinal) were standardized by calculating Cohen’s d, which is the difference between 2 raw means divided by pooled standard deviation (SD). When means and SDs were not available, d was calculated from the reported t or F values. To control for study differences in sample size when mean effect sizes were computed, studies were weighted according to their inverse variance estimates. Effect sizes are typically categorized as small (d = 0.2), medium (d = 0.5), or large (d ≥ 0.8) based on these methods. In order to determine whether mean effect sizes were statistically significant, CI and z-transformation of
effect size were used. The Cochran $Q$-statistic was utilized to assess homogeneity of effect sizes across studies for each cognitive domain.\textsuperscript{25} Significance level of mean effect sizes was computed using fixed effects linear models except when $Q$-statistic revealed significant within-group heterogeneity, in which case a random effects model was used. Possible effect size moderators were examined in those domains with significant heterogeneity, based on the $Q$-statistic and meta-regression techniques. Publication bias was assessed using a funnel plot and mathematically using an adjusted rank correlation test, according to methods of Begg and Mazumdar.\textsuperscript{26} and Eggers.\textsuperscript{27} This provided the number of studies with null effects that have to reside in file drawers to reduce the mean effect size to a negligible level.

Two separate main analyses were conducted. The first examined effect sizes for global measures of cognition, while the second more closely examined effect sizes for specific neuropsychological domains. Ten neuropsychological domains were identified: intelligence estimates, attention, executive functioning, language, memory (immediate, delayed, recognition), motor skills, perceptual abilities, and processing speed. Assignment of neuropsychological tests to selected domain was guided by source articles. In the absence of assignment in source articles, tests were assigned to domain based on consensus discussion between authors (P.J.M., F.I., S.K.). Disagreements about assignment of tests to specific neuropsychological domains were resolved by discussion and consensus. For instance, we decided to place tests of animal fluency in the language domain rather than the executive function domain. Similarly, Wechsler Adult Intelligence Scale-Revised Vocabulary was placed in the IQ estimates domain rather than the language domain.

Results

Publication Bias

Suggestion of publication bias in global cognition was observed, as indicated by an asymmetric funnel plot and significant Begg ($P = .001$, one-tailed) and Egger ($P < .0001$, one-tailed) tests. Publication bias was also evident in neuropsychological domains (Begg test $P < .0001$; Egger test $P < .0001$, one-tailed). To further assess the impact of this publication bias, we calculated a failsafe $N$, which revealed that 7753 “null” studies of global cognition and 7265 null studies of neuropsychological function would have to be located and included in order to and nullify the observed effect. The high number of studies required indicates minimal impact of the publication bias with low likelihood of reducing the effect size of the combined findings to a negligible level.

Sample Characteristics

Twenty-nine cross-sectional (2110 patients, 1738 comparison subjects) and 14 longitudinal (954 patients) studies met inclusion criteria. Detailed demographic, descriptive, and clinical characteristics of the sample as reported in the source articles are presented in table 1. There was variability in studies reporting some patient demographics variables, with poor representation for some categories (eg. 5 studies reporting clinical scale scores).

Overall Analysis

Longitudinal. Analysis of longitudinal studies (mean follow-up of 2.21 ± 1.86 years; range of 1–6 years) for global cognition were homogeneous ($Q_B \ [10] = 12.76, P = .17$) with small effect sizes evident ($d = -0.097, 95\% CI = -0.16 < \delta < -0.03$). Similarly, analysis of neuropsychological domains for longitudinal studies also revealed homogeneity ($Q_B \ [39] = 51.17, P = .092$) with small effect sizes ($d = -0.11, 95\% CI = -0.13 < \delta < -0.08$). Further moderator analyses were not conducted.

Cross-sectional. Analysis of global measures for cross-sectional studies revealed a large overall effect size ($n = 21, d = -1.19, 95\% CI = -1.29 < \delta < -1.11$) that was significantly heterogeneous ($Q_B \ [20] = 325.96, P < .0001$). Similarly, analysis of effect sizes for neuropsychological domains also revealed a large overall effect size ($n = 123$ tests, $d = -1.04, 95\% CI = -1.13 < \delta < -0.95$) that was heterogeneous ($Q_B \ [122] = 634.79, P < .0001$). See figure 1. This indicates that effects sizes between patient and comparison groups differed more than would be expected from sampling error alone, perhaps owing to differences associated with study (or sample) characteristics. Potential moderators that could account for this heterogeneity were examined further as described below.

Moderator Analysis—Cross-sectional Studies

Sample Demographics.Age For global cognition, average age of patients ($n = 16$ studies) and comparison subjects were examined ($n = 16$ studies). Analysis revealed a strong relationship between greater age and increased global cognitive deficit in patients ($Z = -7.99, P < .001$) and comparison groups ($Z = -8.48, P < .001$).

Similarly, for neuropsychological domains, there was a strong relationship between greater age and increased neuropsychological deficits in patients ($Z = -6.14, P < .001$) and comparison groups ($Z = -5.55, P < .001$).

Sex Effect of sex composition of samples on global cognition was analyzed by examining percentage of men in the study for comparison subjects ($n = 13$ studies) and patients ($n = 13$ studies). In patients, a greater proportion of men was associated with smaller effect sizes for global measures ($Z = 9.66, P < .00001$), while comparison subjects did not show a significant relationship ($Z = 1.70, P < .087$).

In contrast, for neuropsychological domains, both patients ($Z = 4.94, P < .00001$) and comparison groups ($Z = 2.51, P = .01$) showed that a larger proportion of
men in sample was associated with smaller magnitude of deficit.

**Education**  Education levels of patients (n = 13, Z = 9.44, P < .001) and comparison subjects (n = 12, Z = −5.48, P < .001) were significantly related to effect sizes.

Similarly, for neuropsychological domains, education of patients (Z = 10.58, P < .001) and comparison subjects (Z = 4.25, P < .001) were positively related to effect sizes.

**Race**  The last demographic variable investigated was race, identified in source articles by percentage of Caucasians within comparison (n = 12 studies) and patient groups (n = 12 studies). Effect sizes for global cognitive measures were moderated by percentage of Caucasian patients (Z = −2.98, P = .0028) and comparison subjects (Z = −5.48, P < .001).

Similarly, effect sizes for neuropsychological domains were also moderated by percentage of Caucasian patients (Z = −5.53, P < .001) and comparison subjects (Z = −4.76, P < .001).

**Table 1. Sample Description**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
<th>N (Studies)</th>
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<td>% Male</td>
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<td></td>
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<td>54.55</td>
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<td>63.65</td>
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<td>Patient</td>
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<td>1.71</td>
<td>13.10</td>
<td>8–16</td>
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<tr>
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<td>15.70</td>
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<td>Duration of illness</td>
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<td>10.68</td>
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<td>13</td>
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<td>Scale for Assessment of Negative Symptoms total</td>
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<td>1.71</td>
<td>7.40</td>
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<tr>
<td>Scale for Assessment of Positive Symptoms total</td>
<td>5.94</td>
<td>0.15</td>
<td>6.00</td>
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<td>Positive and Negative Syndrome Scale-Negative</td>
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<td>19.38</td>
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<tr>
<td>Positive and Negative Syndrome Scale-Positive</td>
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<td>3.59</td>
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<td>15</td>
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<td>Brief Psychiatric Rating Scale total</td>
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<td>4.85</td>
<td>33.50</td>
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<td>395.50</td>
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<tr>
<td>Duration of follow-up (years)</td>
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<td>1.86</td>
<td>1.00</td>
<td>1–6</td>
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<tr>
<td>Mixed—other (eg, delusional disorder)</td>
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<tr>
<td>Patient setting</td>
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<td>Inpatient/institutionalized</td>
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<td>Medication status</td>
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<tr>
<td>Mixed</td>
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<td>3</td>
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</tbody>
</table>

*Note:* PANSS, Positive and Negative Syndrome Scale.

**Patient Clinical Characteristics. Diagnosis**  Global cognition studies were mainly comprised of patients with a sole diagnosis of schizophrenia (n = 14), a mixture of patients with schizophrenia and schizoaffective disorder (mixed-sca + sa: n = 3) or a mixture of patients with schizophrenia, schizoaffective disorder, delusional disorder, and psychosis NOS (mixed-other: n = 4). Effect sizes for schizophrenia (d = −1.63, 95% CI = −2.12 < d < −1.14), mixed-sca + sa (d = −1.09, 95% CI = −1.33 < d < −0.65), and mixed-other groups (d = −2.11, 95% CI = −3.50 < d < −0.72) were large but did not differ significantly from each other (Q(2) = 5.39, P = .067).

In contrast for neuropsychological tests, effect sizes for schizophrenia (d = −1.09, 95% CI = −1.20 < d < −0.98), mixed-sca + sa (d = −0.80, 95% CI = −0.99 < d < −0.61), and mixed-other groups (d = −0.85, 95% CI = −1.02 < d < −0.68) were large and differed significantly (Q(2) = 9.94, P = .007). Post hoc analyses revealed that schizophrenia patients had larger effect sizes than the mixed-sca + sa
group \((Q_B [1] = 9.49, P = .002)\), but there were no significant differences between other groups.

Living Status Patient samples for global studies included inpatients/institutionalized \((n = 3)\), outpatient/community dwelling \((n = 15)\), or mixed \((n = 1)\) groups. Analysis of global cognition revealed heterogeneity of effect sizes by living status \((Q_B [2] = 184.80, P < .0001)\) even when the mixed group sample was excluded due to being represented by only one study \((Q_B [1] = 183.20, P < .0001)\). Inpatients/institutionalized patients were significantly more impaired \((d = -4.92, 95\% CI = -7.81 < \delta < -2.03)\) than outpatients/community-dwelling patients \((d = -1.08, 95\% CI = -1.25 < \delta < -0.91, Q_B [1] = 6.72, P = .01)\).

Analysis of neuropsychological deficits for living status also revealed significant differences by living status \((Q_B [2] = 6.36, P = .041)\). Inpatients/institutionalized patients were more impaired \((d = -1.38, 95\% CI = -1.94 < \delta < -0.83)\) than mixed living status \((d = -0.99, 95\% CI = -1.18 < \delta < -0.80)\), who were more impaired than outpatients/community-dwelling patients \((d = -0.81, 95\% CI = -0.91 < \delta < -0.71)\).

Medication Status To assess possible influences of antipsychotics on observed effect sizes for global cognition, studies were classified as including: (1) medicated \((n = 2)\) studies, (2) unmedicated \((n = 0)\) studies, or (3) mixed (medicated and unmedicated) \((n = 3)\) samples. However, a large number of studies did not report medication status \((n = 16)\). Effect sizes for medicated \((d = -3.25, 95\% CI = -7.81 < \delta < -1.31)\) and mixed group \((d = -0.96, 95\% CI = -1.32 < \delta < -0.59)\) were large and did not differ significantly \((Q_B [1] = 0.96, P = .33)\).

Similarly, for neuropsychological domains, effect sizes for medicated \((d = -1.17, 95\% CI = -1.37 < \delta < -0.97)\) and mixed group \((d = -1.10, 95\% CI = -1.25 < \delta < -0.95)\) were large and did not differ \((Q_B [1] = 0.28, P = .59)\).

Chlorpromazine Equivalents Few studies \((n = 5)\) examined effect of chlorpromazine equivalence on global cognition. Relationship between effect sizes and chlorpromazine equivalents was nonsignificant \((Z = -0.11, P = .90)\) indicating that antipsychotic dose was not a significant moderator. There were not enough studies reporting chlorpromazine equivalents for neuropsychological studies for further analysis.

Age of Onset/Duration of Illness Age of onset of psychotic symptoms significantly moderated effect sizes for global cognition, with later age of onset related to greater cognitive impairment \((n = 7, Z = -3.33, P < .001)\). Similarly, duration of illness was also significantly related to effect sizes for global cognition \((n = 7, Z = 3.19, P = .001)\), with longer duration of illnesses associated with less impairment.

In contrast, for neuropsychological studies, neither age of onset \((Z = 1.52, P = .12)\) nor duration of illness \((Z = -1.95, P = .05)\) was associated with effect sizes.

Clinical Symptoms The Positive and Negative Syndrome Scale\(^{28}\) was administered by 7 global cognition studies. Both positive \((Z = -6.76, P < .001)\) and negative \((Z = -6.71, P < .001)\) symptoms were significant moderators, with greater cognitive impairment associated with higher levels of severity in both symptom domains. Neuropsychological studies were not examined further due to inadequate representation.

discussion
Cross-sectional Approach

The current meta-analytic review provides a quantitative analysis of cognition later in life in schizophrenia. Prior cross-sectional comparisons of younger schizophrenia patients have yielded medium to large effect sizes \((d = -0.46 \text{ to } -1.57)\) across multiple neuropsychological domains.\(^{2,4}\) Our study extended cross-sectional findings to a large sample of older patients with schizophrenia who were approximately 65 years old, with 11 years of education, 53\% male and 79\% Caucasian. Consistent with effect sizes from younger cohorts, our results indicated large overall effect sizes for global measures of
cognition ($d = -1.19$) as well as specific neuropsychological domains ($d = -1.04$). This suggests that on average cognitive performance of older patients with schizophrenia is more than one SD below that of an age-matched comparison group on global and domain-specific neuropsychological measures. The very large fail-safe number makes the “file drawer” problem, which is a limitation of some meta-analyses, negligible.

While it is clear that there are large impairments in schizophrenia patients’ cognitive functioning across the life span, the issue of selective cognitive deficits in specific neuropsychological domains remains outstanding. Because there are significant impairments observed in general intelligence or global deficits across tasks, some have argued for a nonspecific impairment in schizophrenia. We found large effect sizes for global measures such as IQ estimates ($d = -0.84$) and global cognition ($d = -1.19$) as well as large effects for the other neuropsychological domains. This supports the presence of a generalized impairment. Relative comparisons of effect sizes across neuropsychological domains showed strongest effects in domains associated with language ($d = -1.30$), immediate memory ($d = -1.25$), and executive function ($d = -1.14$). In younger cohorts, the general trend in the literature has also been that the strongest effect sizes are associated with tests of episodic memory (particularly free recall), and processing speed, with the least (but still medium to large effect size differences) associated with measures of crystallized verbal knowledge and visual-spatial skill. Thus, similar to younger cohorts, older patients with schizophrenia also showed a large magnitude of effect for multiple cognitive deficits in varying patterns rather than any single isolated cognitive impairment.

**Longitudinal Course**

Are cognitive deficits later in life in schizophrenia typical of normal aging or is there evidence of progressive decline in cognitive function with age? There have been contradictory findings in prior longitudinal studies that have attempted to examine the neurocognitive trajectory of the disorder with aging. Our use of a meta-analytic approach permitted clarification and quantification of effect size estimates in this population. Our analysis of existing data from longitudinal studies in older patients indicated small and homogeneous effects for both global cognitive measures ($d = 0.097$) as well as across a variety of neuropsychological domains ($d = -0.11$). Small effect size estimates indicate that on average, over a 1–6 year follow-up period, there are no more changes in older schizophrenia patients’ cognitive performance than would be expected from sampling error alone. In addition, homogeneity of effect size estimates indicates that this effect is robust and not readily moderated by sample or study characteristics that may seem relevant. This argues against a neurodegenerative course for schizophrenia over a 1–6 year period.

Yet, schizophrenia is a disorder characterized by significant heterogeneity in symptoms and course of illness. Prior contradictions in the literature may have been influenced by a subgroup of patients who have shown a chronic course of institutionalization associated with progressive cognitive and functional decline. Lower levels of education, older age, and more severe positive symptoms have been shown to characterize this subset of approximately 30% of institutionalized patients who manifest worsening functional and cognitive status. Furthermore, even in relatively higher functioning groups of community-dwelling outpatients with schizophrenia, there has been some recent support for the presence of cognitive decline associated with depletion of available processing resources at lower processing loads. Age-associated cognitive worsening on more complex components of information-processing tests has been observed, with indications that age-related changes in cognition in schizophrenia may be a function of both the course of the illness and the processing demands of the cognitive measure of interest. The literature upon which this meta-analysis was based used traditional paper–pencil measures of neuropsychological functioning which can differ in sensitivity from tests for which parametric difficulty manipulations can be performed. Thus, while we found small effect sizes and homogeneity in our analysis of longitudinal data, the impact of an underrepresented subgroup of chronically institutionalized “poor outcome” patients and some community-dwelling elderly outpatients may be dampened in a meta-analytic approach.

**Moderators**

While moderator variables did not influence effect size estimates of cognition in longitudinal studies, in cross-sectional studies, a number of moderators impacted the large effect size deficits between patients and comparison groups. For instance, greater cognitive impairment was associated with greater age in patients and comparison groups for both global and specific neuropsychological domains. While general decline in cognition associated with aging is not a novel finding, the lack of differentiation between older patients and comparison groups further supports a normative course associated with aging in schizophrenia.

Sex was also an influential moderator, with greater domain-specific neuropsychological impairment associated with a lower percentage of males in the sample for both patients and comparison groups. For global cognition, however, only male patients showed a relationship. Among younger patients, women tend to have less severe symptoms and better outcomes, yet fewer sex differences have been reported in elderly and highlights an area requiring further study.

Greater global and domain-specific cognitive impairment was also associated with lower levels of education for patients and comparison groups. Prior work has
indicated that lower education is associated with lower levels of cognitive and functional capacity in older schizophrenia patients. Here, our findings suggest that educational attainment has a normative impact on cognition later in life but does not differentially impact patients with schizophrenia.

Race is another important demographic moderator that has not been well examined in geriatric schizophrenia. Our analysis indicated that a higher percentage of Caucasian patients and comparison subjects in samples is associated with greater global and domain-specific cognitive impairment. This suggests that race moderates scores on cognitive tests later in life in both patient and normative samples. Yet, caution is required in generalizing these findings because the majority of studies examined in the current analysis either omitted reporting race or stated only the proportion of Caucasians in the sample. Because many neuropsychological measures do not have acceptable diagnostic accuracy when used among people who are not Caucasian, well-educated, native English-speaking, and middle to upper class, our understanding of the complex relationship between race and cognitive test performance in schizophrenia would benefit from inclusion of more diverse samples representative of our growing cultural diversity.

With regard to patient clinical characteristics, patients diagnosed with schizophrenia showed greatest domain-specific neuropsychological impairment, followed by a mixed group of those diagnosed with schizophrenia or schizoaffective disorder. Lastly, a more heterogeneous group of psychotic patients with schizophrenia, schizoaffective disorder, delusional disorder, or psychosis NOS showed the smallest effect sizes. Prior empirical and meta-analytic studies have shown consistently that degree of neuropsychological impairment in schizophrenia is worse than degree of cognitive impairment in other affective and nonaffective schizophrenia spectrum disorders. Interestingly, there was no difference in effect sizes for global cognitive measures. This highlights the value of not exclusively focusing on global screening measures when examining cognition in schizophrenia because a more extensive battery can detect more subtle changes in cognition.

With regard to living status for cross-sectional studies, inpatient/institutionalized patients showed larger effect sizes for global and domain-specific neuropsychological measures, as compared with a mixed group of inpatients and outpatient/community dwelling individuals. Studies focused on outpatient/community dwelling patients showed the smallest effect sizes. Institutionalized patients with schizophrenia are by definition a more severely ill group, and prior work has supported the ability of cognition to predict lower levels of functional outcome in geriatric inpatients as compared with outpatients.

Surprisingly, greater global cognitive impairment was associated with shorter durations of illness and later ages of onset for global cognitive measures and not associated with specific neuropsychological domains. This contradicts prior work indicating that earlier ages of onset and longer duration of illnesses are associated with more severe positive symptoms, poorer social, and occupational outcomes. Our analysis did not distinguish between patients with early ages of onset (prior to 40 years), late onset (after 40 years), or very late age of onset (after 60 years). This was due to inconsistencies in source papers on diagnostic systems and nomenclature, which limited our ability to more clearly differentiate between groups. Recent international consensus on face validity and clinical utility of using appropriate diagnostic categories for age of onset in schizophrenia may reduce future ambiguity.

Higher positive and negative symptomology was associated with greater global cognitive impairment. In studies with younger cohorts, higher levels of positive and negative symptoms have been associated with longer durations of hospitalization, increased overall symptoms, decreased ability to meet basic needs, and decreased quality of work later in life. In older samples, positive symptoms may diminish with age, although age has also been found to not markedly alter course of symptoms at least among patients who stay in treatment. Medication status (medicated vs nonmedicated) and chlorpromazine equivalents were also examined and found to be inconsequential. However, because few studies reported medication information, this is considered a tentative finding in an area requiring more rigorous study. This is particularly important because older patients may have received large amounts of first-generation antipsychotic medications, which may contribute to cognitive problems. Further attention to pharmacologic and nonpharmacologic interventions is required in this population given the support for early and stable cognitive impairment through late life in schizophrenia.

**Limitations**
The current study has some limitations worthy of discussion. First, our cross-sectional analysis was limited in its inclusion of studies that only included a comparison group. While this allowed comparisons of effect sizes between patient and age-matched comparison groups, it omitted studies that relied exclusively on patients’ adjusted standard scores based on normative data. Yet, the calculation of effect sizes based on published normative data is often based on disparate populations of controls who can also vary across studies and increase the variance as to make interpretation of the effects difficult. We sought to use the most straightforward approach by examining differences between matched patients and comparison subjects as this is the format most often used in meta-analytic studies of this type. Secondly, there are some limitations shared by the studies that provide the source data for the current analysis. While the samples had a mean age of 65 years, there was a wide range...
represented in the original studies (ages 48–78). This heterogeneity in age groups considered to be older raises some concern about truly capturing the cognitive course of late-life schizophrenia. This is most relevant for the hypothesis arguing for greater, nonlinear cognitive decline in late life observed beyond a critical age (ie, 65 years) in poor outcome patients with schizophrenia, yet this is a limitation of the existing literature and a potential area of future focus. Finally, our analysis of available longitudinal data included only 14 studies for which the duration of follow-up ranged from 1 year to 6 years. Relative to the cross-sectional studies, the existence of fewer longitudinal studies for relatively short durations of follow-up likely reflects the inherent practical and resource limitations of conducting long-term research and may impact recruitment and retention rates. While this limits our ability to comment on the course of schizophrenia beyond this time period, it also highlights the need for more longitudinal studies that span longer durations of time.

Conclusions
There has been increased emphasis on the importance of cognition in understanding the neurobiology, functional status, and outcome of schizophrenia. This has led to increased focus on identifying and evaluating treatments to enhance cognition in schizophrenia, with hope that this can translate into improved outcome for patients. Older patients with schizophrenia form an especially vulnerable group who make up a high proportion of hospitalizations and institutionalizations, making the issue of late-life trajectory of schizophrenia an important and costly public health concern. Thus far, there have been contradictions in the literature about the nature and course of cognitive deficits in this population. The use of a quantitative meta-analytic approach allowed us to combine the results of several studies to examine synthesized effect sizes estimates of differences in cognition in schizophrenia. Our results indicated that on average, over a 1–6 year follow-up period, there was no more decline in older schizophrenia patients’ cognitive performance than would be expected from sampling error alone. Yet, consistent with findings in the literature on younger patients there continue to be large and generalized impairments in both global and domain-specific neuropsychological functions in older patients relative to their age-matched peers. These effect size estimates in cross-sectional studies were moderated by a number of sample characteristics such as inpatient/institutionalization status, higher positive and negative symptomology, lower education, older age, male gender, race, and age of onset/duration of illness. This highlights the need to pay close attention to these moderators when examining cognitive functioning across the life span in schizophrenia. Overall, cognitive impairments in schizophrenia are robust later in life but do not decline over a 1–6 year period. Any future research in this area needs to focus on the longer term course, ensure inclusion of both global and detailed neuropsychological measures, and pay close attention to the significant moderator variables outlined here. The stability of cognitive deficits in schizophrenia throughout the life span further highlights the need for early identification and prevention efforts in order to interfere early in the disease process, improve quality of life for patients, and ultimately reduce the significant public health burden posed by schizophrenia across the life span.

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Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org/.

References