Insight Into Illness and Cognition in Schizophrenia in Earlier and Later Life

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ABSTRACT

Objective: Impaired insight into illness in schizophrenia is associated with illness severity and deficits in premorbid intellectual function, executive function, and memory. A previous study of patients aged 60 years and older found that illness severity and premorbid intellectual function accounted for variance in insight impairment. As such, we aimed to test whether similar relationships would be observed in earlier life.

Methods: A retrospective analysis was performed on 1 large sample of participants (n = 171) with a *DSM-IV-TR* diagnosis of schizophrenia aged 19 to 79 years acquired from 2 studies: (1) a psychosocial intervention trial for older persons with schizophrenia (June 2008 to May 2014) and (2) a diffusion tensor imaging and genetics study of psychosis across the life span (February 2007 to December 2013). We assessed insight into illness using the Positive and Negative Syndrome Scale (PANSS) item G12 and explored its relationship to illness severity (PANSS total modified), premorbid intellectual function (Wechsler Test of Adult Reading [WTAR]), and cognition.

Results: Insight impairment was more severe in later life (≥ 60 years) than in earlier years ($t = -3.75$, $P < .001$). Across the whole sample, the variance of impaired insight was explained by PANSS total modified (Exp[B] = 1.070, $P < .001$) and WTAR scores (Exp[B] = 0.970, $P = .028$). Although age and cognition were correlated with impaired insight, they did not independently contribute to its variance. However, the relationships between impaired insight and illness severity and between impaired insight and cognition, particularly working memory, were stronger in later life than in earlier life.

Conclusions: These results suggest an opportunity for intervention may exist with cognitive-enhancing neurostimulation or medications to improve insight into illness in schizophrenia across the life span.

Trial Registration: Original study registered on ClinicalTrials.gov (identifier: NCT00832845).

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Impaired insight into illness is a common phenomenon in schizophrenia, with over 50% of patients experiencing moderate to severe insight impairment.[1,2] Impaired insight contributes to medication nonadherence and negative clinical and functional outcomes.[1,3–8] Different dimensions of schizophrenia have different trajectories across the life span. In general, positive symptoms tend to stabilize or attenuate as patients with schizophrenia age.[9–13] In contrast, cognitive function tends to decline at a similar rate as compared to healthy individuals.[9,11–16] Functional capacity also declines with age and remains affected by cognition in later life.[17] A recent review[11] of the literature by our group suggests that the course of insight impairment follows a U-shaped curve. Insight impairment is severe during the first episode of psychosis, modestly improves or stabilizes over midlife, and worsens again in late life.[11] However, the course of insight and its relationship to these other domains of schizophrenia is still to be characterized.

Among adult patients with schizophrenia, insight impairment is associated with illness severity, premorbid intellectual function (ie, IQ), global cognitive function, executive function, and memory.[18,19] By contrast, in a study[20] by our group investigating this relationship among older patients with schizophrenia (≥ 60 years), although cognitive measures were correlated with impaired insight, we did not find they contributed to its variance after controlling for premorbid intellectual function. Specifically, lower premorbid IQ, executive function, working memory, attention, and processing speed were associated with impaired insight, while only illness severity and premorbid IQ contributed to its variance. On the basis of these results, we proposed that, in late life, age-related decline in attention, executive function, and memory might attenuate the relationship between impaired insight and schizophrenia-specific cognitive deficits. By comparison, the relationship between insight and premorbid intellectual function persisted, as the latter is unaffected by aging. However, we did not have a younger comparison group to directly test this model in our late-life schizophrenia study.

As such, in this study, we aimed to investigate the effects of age on insight into illness in schizophrenia in relation to cognition and illness severity across the adult life span. Specifically, we hypothesized (1) illness severity and premorbid IQ would contribute to insight impairment across adulthood, (2) insight impairment would be more severe in later (≥ 60 years) than in earlier (< 60 years) life, and (3) cognitive

Clinical Points

- Impaired insight into illness in schizophrenia appears to be more severe in later life (≥ 60 years) than in earlier life.
- Impaired insight into illness in schizophrenia is a function of illness severity and premorbid intelligence in both earlier and later life.
- The relationships between impaired insight and illness severity and between impaired insight and cognition, particularly working memory, in schizophrenia are stronger in later life than in earlier life.

dysfunction (ie, attention, executive function, and memory) would contribute to the variance of impaired insight in earlier but not in later life independent of premorbid intellectual function.

METHODS

Participants

We analyzed data collected from the baseline assessments of 171 participants with *DSM-IV-TR* diagnoses of schizophrenia or schizoaffective disorder who had consented to participate in 2 studies at our center: (1) a psychosocial intervention trial for older persons with schizophrenia (June 2008 to May 2014) (ClinicalTrials.gov identifier: NCT00832845) and (2) a diffusion tensor imaging and genetics study of psychosis across the life span (February 2007 to December 2013). These studies were approved by the research ethics board of the Centre for Addiction and Mental Health, Toronto, Canada, and all participants provided written informed consent. For group comparisons, participants in "earlier life" were defined as those aged less than 60 years and "later life" as those aged 60 years and older. This age cutoff was chosen based on the inclusion criteria for the psychosocial intervention trial[20] for older persons (greater than 60 years) in schizophrenia. A proportion of the data (n = 50) included in the later-life group was previously published[20] from this trial and contributed to the hypotheses generation for the present work.

Participants had to be clinically stable as operationalized by not having been admitted to a psychiatric hospital within 1 month prior to assessments, having been on a stable dose of an antipsychotic medication during the 4 weeks prior to assessments, and ascertained to be mentally and physically stable based on a clinical assessment by 1 of the study psychiatrists. Participants were excluded if they met criteria for a cognitive disorder secondary to a neurologic or other medical disorder, met criteria for substance abuse or dependence within the 6 months prior to assessments with the exception of caffeine or nicotine, and were treated with electroconvulsive therapy within 6 months of assessments.

Study Measures

Diagnoses were confirmed with the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders-Patient Edition (SCID-I/P).[21] Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).[22] Movement abnormalities and extrapyramidal symptoms were assessed with the Abnormal Involuntary Movement Scale (AIMS)[23] and the Simpson-Angus Scale (SAS),[24] respectively. Insight into illness was assessed using the clinician-rated measure—the PANSS lack of insight and judgment item (PANSS G12). Premorbid intellectual function was assessed with the Wechsler Test of Adult Reading (WTAR).[25] Cognition was assessed using the following tests: Trail Making Test-B time to completion (TMT-B) (executive function),[26] Stroop average color-word time (sustained attention and response inhibition),[27] Letter Number Sequencing (LNS) (working memory),[28] Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) list learning (verbal learning),[29] RBANS delayed free recall (verbal memory),[29] RBANS digit-symbol coding (processing speed),[29] and the Mini-Mental State Examination (MMSE) (global cognition).[30]

Statistical Analyses

Statistical analyses were carried out with PASW software (released 2009, PASW Statistics for Windows, version 18.0; SPSS Inc, Chicago, Illinois). Descriptive statistics were performed for demographic, clinical, and cognitive data. Spearman correlations were used to evaluate the bivariate associations between impaired insight (PANSS G12) and the following: illness severity (PANSS total modified score: total score minus item G12), premorbid intellectual function, and measures of cognition. Spearman correlations were used due to the ordinal nature of the PANSS G12 item. To control for the effect of global cognition, partial correlations were repeated with the cognitive measures controlling for MMSE. Similarly, to control for premorbid intellectual function, these analyses were repeated while controlling for WTAR.

Next, ordinal regression analyses were performed with the variables significantly correlated with impaired insight to assess the degree to which these clinical and cognitive measures predicted impaired insight. The measures selected for these analyses were based on our hypotheses and the strength of associations between these measures and impaired insight in schizophrenia as reported previously.[19] PANSS G12 was the dependent variable. The following predictor variables were entered: PANSS total modified, WTAR, TMT-B, Stroop average color-word time, LNS, RBANS digit-symbol coding, and MMSE. To determine the influence of age, age was subsequently added to the regression analysis. Next, the variable age and the correlated cognitive measures were centered, and the product term age × cognitive measure was additionally entered into the regression analysis to determine whether age moderates the relationship between cognition and insight impairment. Last, any other variables correlated with PANSS G12 (eg, education and AIMS) were additionally entered into the regression analysis to determine their influence. These correlational and regression analyses (with the exception of including the effects of age) were repeated for the earlier- (< 60 years) and later-life (≥ 60 years) groups. As for the regression analysis with the total sample, only the variables

Table 1. Demographic, Clinical, and Cognitive Measures and Their Correlation With Impaired Insight (PANSS G12)

	Total Sample (n = 171)			Earlier Life (19–59 y) (n = 89)			Later Life (60–79 y) (n = 82)			Group Comparison	
Measure	n	χ^2	*P*	n	χ^2	*P*	n	χ^2	*P*	χ^2	*P*
Demographic											
Male	98	−12.9[a]	.227	58	−1.9[a]	.860	40	−16.7[a]	.080	5.42[b]	.067
Female	72			31			41				
	Mean (SD)	*r*	*P*	Mean (SD)	*r*	*P*	Mean (SD)	*r*	*P*	*t*	*P*
Age, y	50.4 (17.4)[c]	0.21	.006*	36.6 (12.6)[d]	−0.10	.367	65.3 (5.4)[e]	0.03	.777	…	…
Age at illness onset, y	25.9 (10.1)	0.14	.073	23.6 (6.8)	0.00	1.000	28.6 (12.4)	0.21	.070	−3.28	.001*
Duration of illness, y	24.1 (16.9)	0.06	.434	12.9 (12.3)	−0.13	.232	36.6 (11.9)	−0.18	.104	−12.63	<.001**
Education	12.6 (2.7)	−0.25	.001*	13.3 (2.2)	−0.26	.014*	11.8 (3.0)	−0.17	.131	3.75	.001**
Chlorpromazine equivalent, mg	254.8 (181.7)	−0.06	.490	250.1 (195.9)	−0.17	.129	260.1 (165.7)	0.20	.089	−0.34	.732
AIMS	1.4 (3.0)	0.20	.008*	0.3 (0.8)	0.08	.456	2.6 (4.0)	0.10	.387	−5.29	<.001**
SAS	2.6 (3.4)	0.13	.082	1.4 (2.1)	0.08	.466	4.0 (3.9)	−0.04	.693	−5.47	<.001**
Cognitive											
MMSE	28.4 (1.9)	−0.31	<.001**	28.9 (1.5)	−0.30	.004*	27.8 (2.1)	−0.17	.118	4.11	<.001**
Premorbid IQ (WTAR)	108.3 (15.0)	−0.32	<.001**	109.6 (14.2)	−0.32	.002**	106.9 (15.8)	−0.30	.006*	1.15	.253
TMT-B	135 (83.4)	0.24	.002*	95.8 (57.0)	0.09	.437	177.3 (86.3)	0.25	.028*	−7.10	<.001**
Stroop Average Color-Word Time	92.7 (11.7)	0.15	.051*	88.2 (10.6)	0.02	.869	97.3 (11.0)	0.16	.158	−5.43	<.001**
LNS	11.8 (4.4)	−0.30	<.001**	13.2 (4.0)	−0.07	.539	10.3 (4.3)	−0.38	.001**	4.32	<.001**
RBANS list learning	24.3 (6.2)	−0.13	.098	27.1 (5.6)	0.06	.615	21.4 (5.5)	0.00	.976	6.59	<.001**
RBANS list recall	4.3 (2.6)	−0.10	.223	5.3 (2.6)	0.18	.107	3.4 (2.3)	−0.15	.170	5.01	<.001**
RBANS digit-symbol coding	36.6 (13.2)	−0.28	<.001**	43.1 (11.2)	−0.09	.427	30.0 (11.8)	−0.30	.008*	7.30	<.001**
Clinical insight											
PANSS G12	2.4 (1.6)	…	…	2.0 (1.3)	…	…	2.9 (1.8)	…	…	−3.75	<.001**
Illness severity											
PANSS total modified[f]	50.2 (14.1)	0.44	<.001**	48.6 (15.0)	0.41	<.001**	51.9 (13.0)	0.45	<.001**	−1.52	.130
PANSS positive	13.6 (5.9)	0.36	<.001**	13.0 (5.2)	0.31	.003*	14.2 (6.4)	0.41	<.001**	−1.28	.201
PANSS negative	13.9 (5.8)	0.38	<.001**	13.5 (5.8)	0.42	<.001**	14.4 (5.8)	0.32	.004*	−0.98	.326
PANSS general modified[g]	22.7 (5.9)	0.32	<.001**	22.1 (6.4)	0.30	.004*	23.3 (5.4)	0.28	.011*	−1.39	.166

[a]Multinomial logistic regression. [b]χ^2 test. [c]Range, 19–79 years. [d]Range, 19–59 years. [e]Range, 60–79 years. [f]PANSS total score minus item G12. [g]PANSS general score minus item G12.
*Significant at α ≤ .05, ie, before Bonferroni correction.
**Significant at α < .001, ie, after Bonferroni correction for multiple comparisons.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, LNS = Letter-Number Sequencing, MMSE = Mini-Mental State Examination, PANSS = Positive and Negative Syndrome Scale, PANSS G12 = PANSS lack of insight and judgement item, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SAS = Simpson-Angus Scale, TMT-B = Trail Making Test-B time to complete, WTAR = Wechsler Test of Adult Reading.

significantly correlated with impaired insight within each age range were entered into the regression analyses. In the earlier-life group, the following predictor variables were entered: PANSS total modified, WTAR, and MMSE. Education was subsequently added as it also was correlated with PANSS G12 in the earlier-life group. For the regression analysis in the later-life group, the following variables were entered: PANSS total modified, WTAR, TMT-B, LNS, and RBANS digit-symbol coding. Finally, between-group comparisons were performed between the earlier- and later-life groups.

RESULTS

Table 1 presents the demographic, clinical, and cognitive characteristics for the total sample (n = 171) and the earlier-life (n = 89) and later-life (n = 82) age groups, and the Spearman correlations between these measures and the measure of insight impairment (PANSS G12).

Total Sample

As expected, associations were found between PANSS G12 and the PANSS total modified ($r = 0.44$, $P < .001$), WTAR ($r = -0.32$, $P < .001$), TMT-B ($r = 0.24$, $P = .002$), Stroop average color-word time ($r = 0.15$, $P = .051$), LNS ($r = -0.30$, $P < .001$), RBANS digit-symbol coding ($r = -0.28$, $P < .001$), and MMSE ($r = -0.31$, $P < .001$). Age ($r = 0.21$, $P = .006$), education ($r = -0.25$, $P = .001$), and AIMS ($r = 0.20$, $P = .008$) were also correlated with PANSS G12 (Table 1).

After performing partial correlations controlling for MMSE, associations were found between PANSS G12 and age ($r = 0.16$, $P = .036$), education ($r = -0.16$, $P = .035$), AIMS ($r = 0.16$, $P = .038$), PANSS total modified ($r = 0.41$, $P < .001$), WTAR ($r = -0.21$, $P = .007$), TMT-B ($r = 0.23$, $P = .004$), LNS ($r = -0.19$, $P = .019$), and RBANS digit-symbol coding ($r = -0.17$, $P = .036$). Only the partial correlations with PANSS total modified and TMT-B survived correction for multiple comparisons ($P < .005$ after Bonferroni correction, ie, $P \leq .05/11$ comparisons).

By comparison, after performing partial correlations controlling for WTAR, associations were found between PANSS G12 and age ($r = 0.22$, $P = .004$), age at illness onset ($r = 0.18$, $P = .020$), AIMS ($r = 0.20$, $P = .009$), PANSS total modified (0.44, $P < .001$), TMT-B ($r = 0.23$, $P = .004$), LNS ($r = -0.17$, $P = .035$), and RBANS digit-symbol coding

Table 2. Regression Analysis for Impaired Insight Into Illness (PANSS G12) for the Full Sample Across Age Categories (19–79 years)

Predictor	Exp(B)[a]	95% CI	Wald	*df*	*P*
PANSS total modified[b]	1.070	1.045–1.096	31.47	1	<.001*
Premorbid IQ (WTAR)	0.970	0.944–0.997	4.82	1	.028*
TMT-B	1.000	0.994–1.006	0.00	1	.973
Stroop Average Color-Word Time	1.021	0.987–1.057	1.43	1	.233
LNS	0.979	0.877–1.091	0.15	1	.697
RBANS digit-symbol coding	0.973	0.937–1.009	2.13	1	.144
MMSE	1.021	0.790–1.321	0.03	1	.872
Age	1.014	0.991–1.038	1.41	1	.236

[a]Exp(B) represents an odds ratio, eg, for every 1 unit increase in the predictor variable, PANSS total modified, the odds of severe insight impairment increases by 1.070 times.
[b]PANSS total score minus item G12.
*Significant at α ≤ .05.
Abbreviations: LNS = Letter-Number Sequencing, MMSE = Mini-Mental State Examination, PANSS = Positive and Negative Syndrome Scale, PANSS G12 = PANSS lack of insight and judgement item, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, TMT-B = Trail Making Test-B time to complete, WTAR = Wechsler Test of Adult Reading.

Table 3. Regression Analysis for Impaired Insight Into Illness (PANSS G12) in Earlier Life (< 60 years) and Later Life (≥ 60 years)

Predictor	Exp(B)[a]	95% CI	Wald	*df*	*P*
Earlier life					
PANSS total modified[b]	1.050	1.020–1.082	10.82	1	.001*
Premorbid IQ (WTAR)	0.965	0.931–1.000	3.95	1	.047*
MMSE	0.905	0.655–1.252	0.36	1	.547
Later life					
PANSS total modified[b]	1.098	1.055–1.142	21.45	1	<.001*
Premorbid IQ (WTAR)	0.977	0.941–1.014	1.52	1	.218
TMT-B	0.999	0.992–1.006	0.06	1	.804
LNS	0.841	0.720–0.983	4.76	1	.029*
RBANS digit-symbol coding	1.004	0.948–1.063	0.02	1	.887

[a]Exp(B) represents an odds ratio, eg, for every 1 unit increase in the predictor variable, PANSS total modified, the odds of severe insight impairment increases by 1.050 times.
[b]PANSS total score minus item G12.
*Significant at α ≤ .05.
Abbreviations: LNS = Letter-Number Sequencing, MMSE = Mini-Mental State Examination, PANSS = Positive and Negative Syndrome Scale, PANSS G12 = PANSS lack of insight and judgement item, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, TMT-B = Trail Making Test-B time to complete, WTAR = Wechsler Test of Adult Reading.

($r = -0.19$, $P = .014$). Only the partial correlations with age, PANSS total modified, and TMT-B survived correction for multiple comparisons ($P < .005$ after Bonferroni correction, ie, $P \leq .05/11$ comparisons).

The ordinal regression analysis for the total sample revealed that PANSS total modified (Exp[B] = 1.070; 95% CI, 1.045–1.096; Wald $\chi^2_1 = 31.47$; $P < .001$) and WTAR (Exp[B] = 0.970; 95% CI, 0.944–0.997; Wald $\chi^2_1 = 4.82$; $P = .028$) independently contributed to the variance of insight impairment (Table 2). The addition of age (Exp[B] = 1.014; 95% CI, 0.991–1.038; Wald $\chi^2_1 = 1.41$; $P = .236$) did not independently contribute to the variance of insight impairment. Only the addition of the product term age × PANSS total modified (Exp[B] = 1.002; 95% CI, 1.000–1.003; Wald $\chi^2_1 = 6.80$; $P = .009$) contributed to the variance of insight impairment, indicating that an interaction between age and illness severity contributes to impaired insight. This result suggests that age strengthens the relationship between illness severity and impaired insight. Education and AIMS, which were also correlated with PANSS G12, were subsequently added to the analysis. Only AIMS (Exp[B] = 1.156; 95% CI, 1.019–1.312; Wald $\chi^2_1 = 5.081$; $P = .024$) contributed to the variance of impaired insight. However, the independent contribution of AIMS disappeared after the addition of the product term age × AIMS, suggesting age mediates the relationship between abnormal involuntary movements (ie, dyskinesia) and impaired insight.

Earlier Life (19–59 years)

In the earlier-life group, only PANSS total modified ($r = 0.41$, $P < .001$), education ($r = -0.26$, $P = .014$), WTAR ($r = -0.32$, $P = .002$), and MMSE ($r = -0.30$, $P = .004$) were associated with PANSS G12 (Table 1). After performing partial correlations controlling for MMSE, only the association with PANSS total modified ($r = 0.33$, $P = .001$) remained significant. Similarly, after performing partial correlations for WTAR, only the association with PANSS total modified ($r = 0.37$, $P < .001$) remained significant.

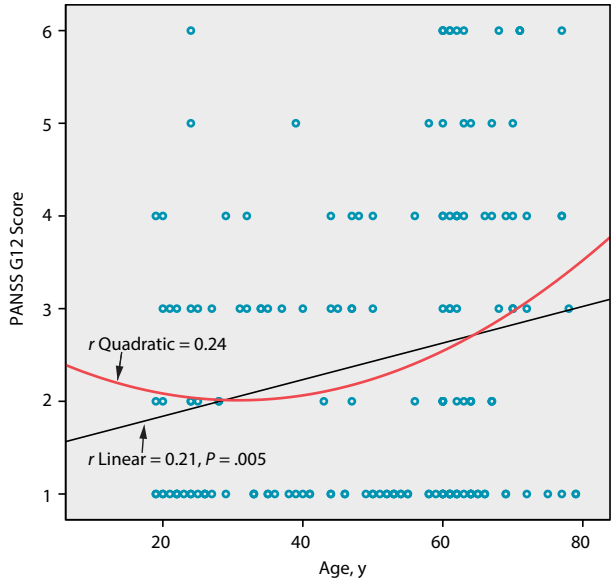
The ordinal regression analysis for the earlier-life group revealed that only PANSS total modified (Exp[B] = 1.050; 95% CI, 1.020–1.082; Wald $\chi^2_1 = 10.82$; $P = .001$) and WTAR (Exp[B] = 0.965; 95% CI, 0.931–1.000; Wald $\chi^2_1 = 3.95$; $P = .047$) contributed to the variance of insight impairment (Table 3). The addition of education, which was correlated with PANSS G12, did not independently contribute to the variance of insight impairment in the earlier-life group, but it eliminated the independent contribution of WTAR.

Later Life (60–79 years)

In the later-life group, PANSS total modified ($r = 0.45$, $P < .001$), WTAR ($r = -0.30$, $P = .006$), TMT-B ($r = 0.25$, $P = .028$), LNS ($r = -0.38$, $P = .001$), and RBANS digit-symbol coding ($r = -0.30$, $P = .008$) were correlated with PANSS G12 (Table 1). After performing partial correlations controlling for MMSE, associations remained with PANSS total modified ($r = 0.49$, $P < .001$), WTAR ($r = -0.29$, $P = .009$), TMT-B ($r = 0.25$, $P = .028$), and LNS ($r = -0.33$, $P = .004$). Only the partial correlations with WTAR and LNS remained significant after correction for multiple comparisons ($P \leq .01$ after Bonferroni correction, ie, $P \leq .05/5$ comparisons). After performing partial correlations controlling for WTAR, associations remained with PANSS total modified ($r = 0.52$, $P < .001$) and LNS ($r = -0.23$, $P = .048$); however, only the relationship with PANSS total modified was significant after correcting for multiple comparisons ($P \leq .01$ after Bonferroni correction, ie, $P \leq .05/5$ comparisons).

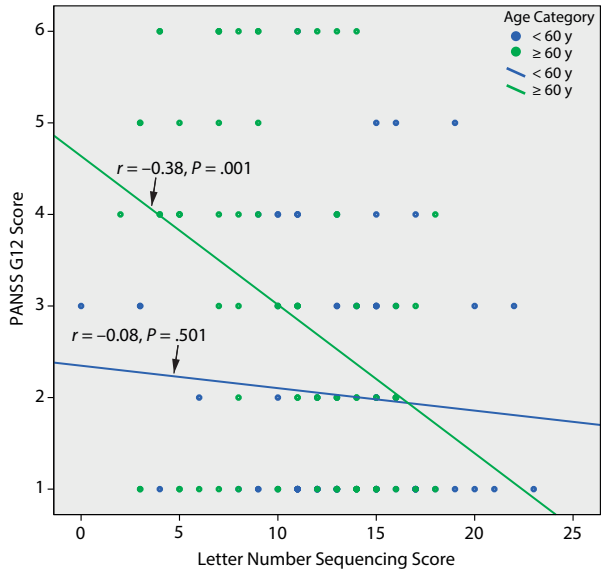
The ordinal regression analysis for the later-life group revealed that PANSS total modified (Exp[B] = 1.098; 95% CI, 1.055–1.142; Wald $\chi^2_1 = 21.45$; $P < .001$) and LNS (Exp[B] = 0.841; 95% CI, 0.720–0.983; Wald $\chi^2_1 = 4.76$;

Figure 1. Relationship Between Age and Impaired Insight Into Illness in Schizophrenia



Abbreviation: PANSS G12 = Positive and Negative Syndrome Scale lack of insight and judgment item.

Figure 2. Effect of Age (earlier life [< 60 years] vs later life [≥ 60 years]) on the Relationship Between Impaired Insight Into Illness and Working Memory (LNS score)



Abbreviations: LNS = Letter Number Sequencing, PANSS G12 = Positive and Negative Syndrome Scale lack of insight and judgment item.

$P = .029$) contributed to the variance of insight impairment (Table 3).

Comparison Between the Earlier- and Later-Life Groups

Significant group differences were found for all demographic, clinical, and cognitive variables between the earlier- and later-life groups (Table 1), including PANSS G12 ($t_{169} = -3.75$, $P < .001$) (Supplementary eFigure 1), with the notable exceptions of chlorpromazine equivalents ($t_{154} = -0.34$, $P = .732$), WTAR ($t_{167} = 1.15$, $P = .253$), and PANSS total modified ($t_{169} = -1.52$, $P = .130$).

DISCUSSION

To our knowledge, this study is the first to investigate the effects of age on insight into illness in relation to cognition and illness severity across the adult age range in patients with schizophrenia. The main findings of this study are that (1) impaired insight in schizophrenia across adulthood is a function of illness severity and premorbid intellectual function; (2) insight impairment is more severe in later life (≥ 60 years) than in earlier life (Figure 1 and Supplementary eFigure 1); and (3) the associations between impaired insight and illness severity (Supplementary eFigure 2) and between impaired insight and cognition, in particular working memory deficits (Figure 2), are stronger in later life than in earlier adulthood.

Many studies have explored the relationship between impaired insight and cognition in individuals with schizophrenia; however, few have included individuals with schizophrenia who were older than 60 years.[11] Consistent with our previous findings in later life,[20] illness severity and lower premorbid intellectual function contributed to the variance of impaired insight across the adult age range. To put this in perspective, for every 10-point increase in illness severity (ie, PANSS total modified), a person with schizophrenia is twice as likely to have severe insight impairment. For every 20-point increase in IQ (ie, WTAR standardized score), the patient with schizophrenia is nearly half as likely to have severe insight impairment. A recent meta-analysis[18] found that global cognition, IQ, memory, executive function, and Wisconsin Card Sorting Test (WCST) categories achieved and perseverative errors were related to impaired insight into illness in schizophrenia. In the present study, we also found that measures of cognitive function, ie, attention, executive function, working memory, and processing speed (Table 1), correlated with impaired insight, but did not independently contribute to its variance across the adult age range.

The literature suggests the course of insight impairment follows a U-shaped curve, where insight impairment is more severe during the first episode of psychosis, modestly improves over midlife, and worsens again in late life.[11] In support of this conceptualization, although age was not a predictor of insight across the life span, we found that insight appears to be less severe or remains stable over midlife and then declines again in later life (Figure 1 and Supplementary eFigure 1). Data from first-episode patients are required to test whether impaired insight is more severe in this stage of illness compared to later stages. Impaired insight was notably worse in those aged 60 years or older in comparison with those aged less than 60 years (Table 1, Supplementary eFigure 1). This finding is consistent with a prior study[31]

that found insight impairment was worse in those older than 56 years in comparison with younger age groups. The decline of insight into illness in later life may be a function of age-related cognitive decline.[11,14,15] These changes could be related to neuroanatomical alterations, such as brain atrophy or reduced neuroreceptor density that may contribute to premature aging and greater insight impairment in later life.[11,15]

In earlier life, illness severity, education, global cognition, and premorbid IQ were associated with impaired insight, but only illness severity and premorbid IQ contributed to its variance. Contrary to our expectations, cognitive measures of attention, executive function, and memory were not correlated with impaired insight in the earlier-life group as was found in the aforementioned meta-analysis.[18] The degree to which studies that included older patients (≥ 60 years) may have influenced the relationship between impaired insight and cognition in this meta-analysis[18] is unclear, as the effects of age were not specifically addressed. Further, our study did not include the WCST, which may be a more sensitive marker of executive dysfunction than TMT-B, the measure used in the present study. Another possibility is that our study may not have the statistical power to detect the small, but significant correlations ($r < 0.2$) between impaired insight and cognition in younger patients with schizophrenia.[18]

In contrast to the earlier-life group, impaired insight in later life was additionally associated with executive function, working memory, and processing speed. However, only illness severity and working memory deficits (ie, LNS) independently contributed to its variance (Table 3). Overall, this result is consistent with our prior study[20] of insight into illness in late-life schizophrenia (≥ 60 years), which is expected due to the overlap in sample. Additionally, in our later-life group, illness severity was an even stronger predictor of insight impairment than it was for the earlier-life group. The reason for this finding could be that better cognitive function in earlier life mitigates the negative impact of illness severity on insight.

To understand the relationships among cognitive function, schizophrenia, and aging, we have considered that cognitive dysfunction in late-life schizophrenia may involve two separate processes, one related to aging (ie, age-related decline in attention, memory, and executive function)[32,33] and another specific to the illness itself.[20,34] Contrary to our expectations, our results from across adulthood indicate that the relationship between impaired insight and cognition is stronger in later life rather than attenuated. In other words, age-related cognitive decline appears to accentuate the association between impaired insight and cognitive dysfunction, particularly deficits in working memory (Figure 2), executive function, and processing speed.

Our study is limited by a few factors. First, this study is a cross-sectional analysis of a convenience sample, and thus it is difficult to make causal inferences about the effects of age on insight into illness and other variables of interest. Ideally, the effects of aging should be explored prospectively using a single sample with a longitudinal design. However, there are practical limitations to carrying out such a study, leaving cross-sectional approaches as the next best alternative. Second, as previously mentioned, our study did not include the WCST, which is reliably related to impaired insight in schizophrenia and may be a more sensitive marker of executive dysfunction than the TMT-B.[18] Future studies of insight into illness in schizophrenia should include the WCST and consider using measures of insight into illness in schizophrenia that assess the various domains of insight impairment.[35–37] The PANSS item G12, however, is highly correlated with other, more comprehensive instruments.[38] Last, although the aim of the present work was to investigate the effects of age on insight into illness in schizophrenia in relation to cognition and illness severity in earlier and later life, this study is limited by the lack of inclusion of other factors that are related in a complex way to insight into illness and cognition in schizophrenia, including cognitive insight,[18,39] mood,[40,41] negative symptoms,[42] function,[43,44] and quality of life.[45] Future investigations should make attempts to include these other factors.

In summary, impaired insight in schizophrenia across adulthood appears to be, in part, a function of illness severity and premorbid intellectual function. Age appears to strengthen the relationship between impaired insight into illness and illness severity and between impaired insight and cognition, in particular working memory. That is, in later life, illness severity and cognitive deficits have a greater influence on insight impairment in schizophrenia than in earlier life. This opens the future possibility for the use of noninvasive neurostimulation techniques[46] or cognitive-enhancing drugs[47] to improve cognition and insight into illness in schizophrenia. It remains unclear the degree to which medications, particularly high-dose antipsychotics and drugs with anticholinergic properties may contribute to insight impairment in later life.[48,49] As with our previous study[20] in late-life schizophrenia, the results of the present study also underline the importance of premorbid intellectual function as a reliable predictor of insight into illness across adulthood and the potential benefit of early intervention to treat the cognitive impairment that can occur prior to the manifestation of the full schizophrenia syndrome.[50] Early intervention is also supported by the evidence that first-episode[51] and younger patients[52] have significantly greater improvement in insight into illness following a psychotic episode than multiepisode or older patients, which suggests these groups may have a greater capacity for developing insight into illness than those in later phases of schizophrenia. Last, future longitudinal studies are still required to determine whether impaired insight in schizophrenia is static or amenable to change independent of fluctuations in illness severity.

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National Institute of Mental Health, Canada Foundation for Innovation, OMHF, Brain & Behavior Research Foundation/NARSAD (BBRF), Ontario Ministry of Research and Innovation, and CAMH Foundation. **Dr Graff-Guerrero** reports receiving support from National Institutes of Health (NIH), CIHR, OMHF, Conacyt, Instituto de Ciencia y Tecnología del DF (ICyTDF), BBRF, the Ontario Ministry of Health and Long-Term Care, the Ontario Ministry of Research and Innovation Early Research Award, and Janssen. **Dr Pollock** receives research support from NIH, CIHR, Brain Canada, Ontario Brain Institute, and CAMH Foundation; has been a member of the advisory board of Lundbeck Canada (final meeting, May 2009); was a member of the advisory board of Forest (final meeting, March 2008); has served one time as a consultant for Wyeth (October 2008) and Takeda (July 2007); and was a faculty member of the Lundbeck International Neuroscience Foundation (final meeting, April 2010). **Dr Mulsant** currently receives research support from Brain Canada, CIHR, NIH, CAMH Foundation, Eli Lilly (medications for a NIH-funded clinical trial), and Pfizer (medications for a NIH-funded clinical trial); has received research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial) and Pfizer/Wyeth (medications for a NIH-funded clinical trial); has received honorarium from Pfizer; and has received travel support from Roche. He directly owns stocks of General Electric (less than $5,000). In the past 5 years, **Dr Rajji** has received research support from Brain Canada, BBRF, Canada Foundation for Innovation, Canada Research Chair, CIHR, Ontario Ministry of Health and Long-Term Care, Ontario Ministry of Research and Innovation, NIH, and W. Garfield Weston Foundation. **Drs Menon** and **Mamo** report no conflict of interest.

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Supplementary material: See accompanying pages

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Supplementary material follows this article.

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Supplementary Material

Article Title: Insight Into Illness and Cognition in Schizophrenia in Earlier and Later Life

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List of Supplementary Material for the article

1. eFigure 1 — Impaired insight into illness in schizophrenia in Earlier Life (< 60 years) versus Later Life (≥ 60 years)

2. eFigure 2 — The effect of age, i.e. Earlier Life (<60 years) versus Later Life (≥60 years) on the relationship between impaired insight into illness and illness severity (PANSS Total Modified)

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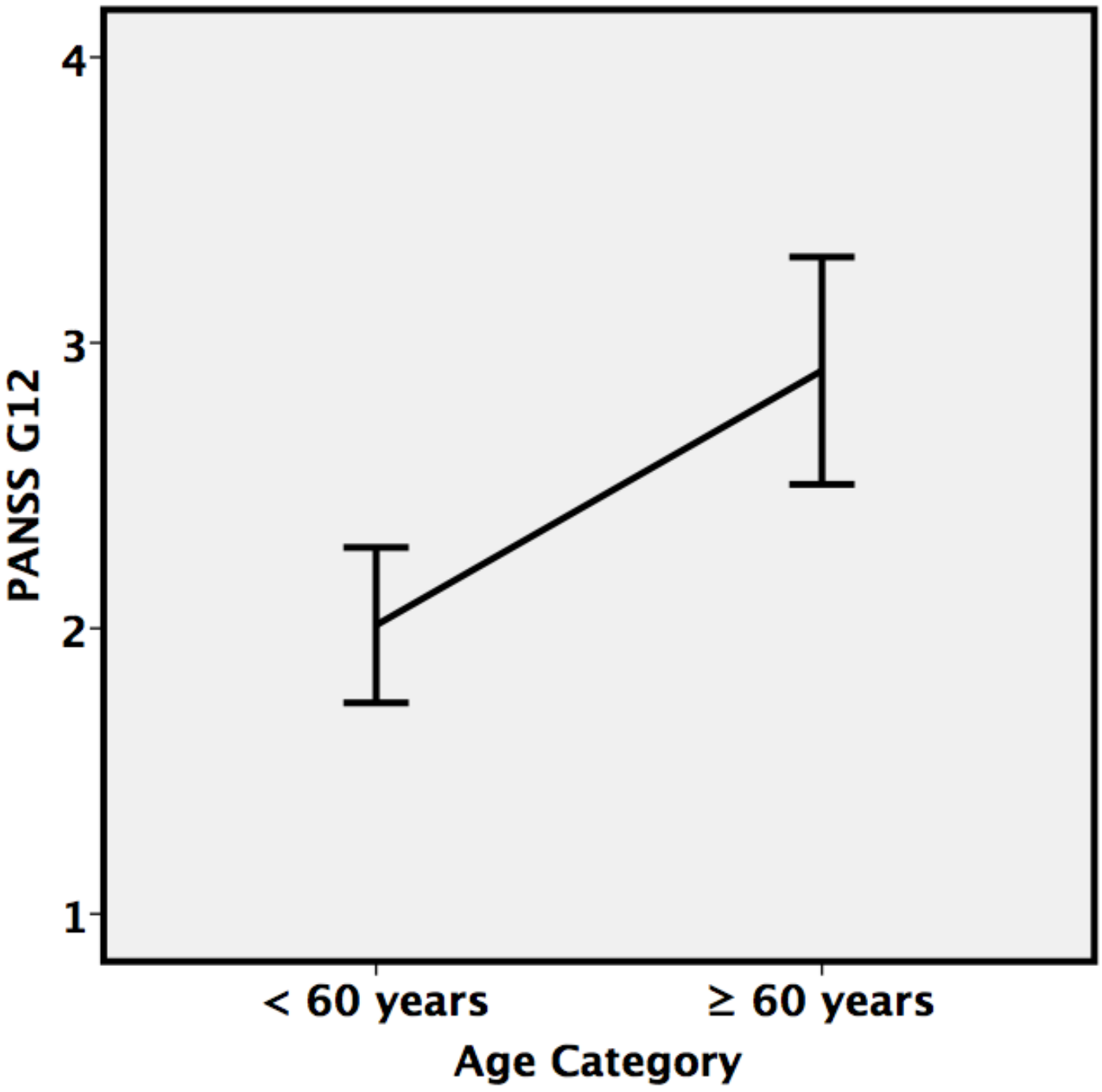
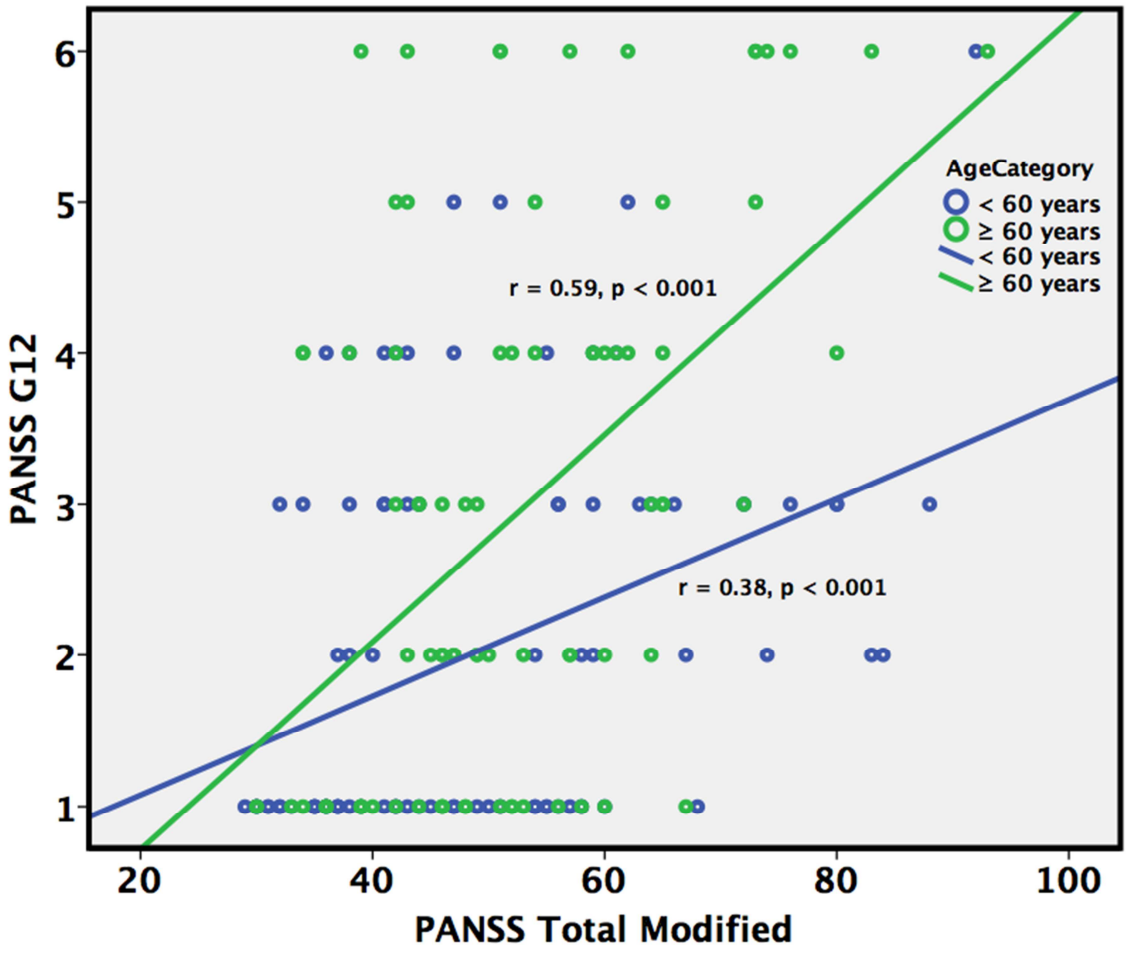


Supplementary eFigure 1. Impaired insight into illness in schizophrenia in Earlier Life (< 60 years) versus Later Life (≥ 60 years). Error bars = 2 SE



Supplementary eFigure 2. The effect of age, i.e. Earlier Life (<60 years) versus Later Life (≥60 years) on the relationship between impaired insight into illness and illness severity (PANSS Total Modified)