Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Deviation from expected cognitive ability is a core cognitive feature of schizophrenia related to neurophysiologic, clinical and psychosocial functioning

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ARTICLE INFO

Article history:
Received 13 June 2019
Received in revised form
3 October 2019
Accepted 6 October 2019
Available online xxx

Keywords:
Schizophrenia
COGS-2
Deviation from expectation
Neurophysiology
MMN
University of Pennsylvania computerized neurocognitive battery

ABSTRACT

Cognitive functioning in schizophrenia is characterized by a generalized impairment in current cognitive ability based on traditional population-based norms. However, these norms assume a normal cognitive trajectory and do not directly account for illness-related declines from expected cognitive potential. Indeed, schizophrenia patients exhibit even greater deviation between their observed and expected cognitive functioning based on expanded norms that leverage premorbid variables resistant to illness-related features. The current study further quantified the extent to which illness-related features account for this deviation from expectation and assessed its relationship to neurophysiologic (mismatch negativity, P3a, theta oscillations), clinical, and psychosocial functioning in schizophrenia patients. Expected cognitive ability (PENN-CNB global cognition) in patients (n = 684) was calculated using healthy comparison subject (n = 660) weighted regression based on premorbid variables resistant to illness-related decline (demographics, single-word reading, parental education). The magnitude of any deviation between current (observed) and regression-predicted (expected) cognitive ability was calculated. Results indicated that 24% (n = 164) of the total patient population exhibited significant (≥-1.96 SD) deviation between observed and expected global cognitive ability. Interestingly, 20% of the total patient population (n = 136) had "normal" range cognitive performance when using traditional population-based norms, but also had significant deviation from expected cognitive ability. The magnitude of this deviation was associated with more severe neurophysiologic abnormalities, longer illness duration, higher levels of negative symptoms, and worse psychosocial functioning. Assessment of cognitive deviation is thus a complementary metric for characterizing the severity of illness-related cognitive declines in patients, while also reflecting the expression and severity of key endophenotypes of schizophrenia.

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1. Introduction

There is a longstanding debate regarding the characterization of illness-related cognitive decline in schizophrenia patients. Although generalized cognitive impairment is a hallmark of schizophrenia (Bilder et al., 2000; Green et al., 2004; Gur et al., 2015; Hochberger et al., 2016; Swerdlow et al., 2015), research suggests that up to 25% of patients have "normal" cognitive functioning based on traditional performance-based norms (Palmer et al., 1997; Saykin et al., 1991). The heterogeneity in the severity and constellation of cognitive deficits in schizophrenia remains a key variable of interest due to their impact on psychosocial outcomes (Green, 1996; Green et al., 2004; Thomas et al., 2017) and moderating role in treatment engagement and response (Lindenmayer et al., 2017; Mcgurk et al., 2007; Medalia et al., 2019; Wykes et al., 2011).

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https://doi.org/10.1016/j.schres.2019.10.011
0920-9964/Published by Elsevier B.V.

It is possible that the identification of some patients as being "cognitively normal" are errors caused by the traditional approach of classifying cognitive impairment as a discrepancy between a patient's observed performance relative to population-based normative thresholds. Such thresholds typically account for only basic demographic characteristics (age, sex, and education) and classify impairment as performance 0.5-2.0 standard deviations below the population mean (Crawford, 2005; Kessels and Hendriks, 2015; Lezak, 1995). This approach fails to account for illness-related features that could impact both the characterization of cognitive performance as well as the norms themselves. For example, illness-related neurodevelopmental processes in schizophrenia have a direct impact on patient education and academic achievement, features directly linked to expected cognitive ability. Thus, patients with above average premorbid cognitive performance who experience declines may still have performance in the "normal" range despite having a clinically significant decline relative to premorbid expectations (Bilder et al., 2006; Heinrichs et al., 2008; Hochberger et al., 2018; Keefe et al., 2005; Palmer et al., 2009).

A complementary approach for classifying cognitive declines in schizophrenia emphasizes the estimation of premorbid cognitive functioning based on features that are resistant to illness-related decline (Hochberger et al., 2018; Keefe et al., 2005). Single-word reading (widely used as an illness-resistant estimator of premorbid intellectual ability in a variety of populations) (Bright et al., 2002; Gladsjo et al., 1999) combined with parental education and expanded demographic corrections (Kareken et al., 1995; Kremen et al., 2000) significantly improves the estimation of cognitive potential in schizophrenia patients. Integration of these measures in healthy-comparison weighted regression models and examining the deviation between observed and expected cognitive ability may provide a complementary approach to traditional norms when evaluating patient deficits.

Individualized regression approaches have demonstrated that a significant number of schizophrenia patients experience illness-related deviations from expected cognitive ability (Bilder et al., 2006; Hochberger et al., 2018; Keefe et al., 2005). This deviation from expectation is associated with greater negative symptom severity and lower psychosocial functioning in patients (Hochberger et al., 2018), and varies across the psychotic illness spectrum – increasing from bipolar disorder with psychosis to schizoaffective disorder to schizophrenia, with greater deviation in more severely affected psychosis biotypes (Clementz et al., 2016; Hochberger et al., 2018). Further, the low familiality estimates of this deviation from expected cognitive ability compared to the familiality estimates for neuropsychological test scores highlights that this deviation is more closely related to the presence and severity of psychotic illness rather than individual or heritable cognitive ability (Hill et al., 2013; Hochberger et al., 2018). The "deviation scores" (residuals) between observed and expected cognitive ability derived from this approach may thus be an index dissociating illness-related burden from other non-illness-related features (Gladsjo et al., 1999; Hochberger et al., 2018; Keefe et al., 2005; Palmer et al., 2009, 1997).

Although promising, gaps remain in the clinical profile associated with this cognitive deviation – particularly regarding its relationship to well established biomarkers. Of these biomarkers, neurophysiologic activity underlying early auditory information processing (EAIP), commonly assessed via electroencephalography (EEG) during passive auditory oddball tasks designed to elicit mismatch negativity (MMN) and P3a event related potentials, presents as an optimal target. EAIP mediates deficits in higher-order cognitive, symptom, and psychosocial functioning in schizophrenia (Javitt, 2015; Light and Näätänen, 2013; Rissling et al., 2014; Thomas et al., 2017). MMN amplitude and theta oscillatory activity are significantly reduced in patients with psychotic illness (Hochberger et al., 2019a,b; Light and Näätänen, 2013), and predict patient response to cognitive training (Hochberger et al., 2019a,b; Perez et al., 2017; Perez et al., 2019). If the severity of deviation from expected cognitive ability is indeed a more explicit indicator of illness-specific processes in psychosis, and EAIP is a direct measure of that process, it should be related to the integrity of EEG activity underlying EAIP without extra variance secondary to non-illness processes included within traditional population-based normative performance metrics. Evaluating patient deviations from expected cognitive ability could thus prove an effective complementary approach when quantifying illness-related burden in psychotic disorders.

This study aimed to further characterize illness-related deviation from expected cognitive ability in schizophrenia patients by: 1) evaluating the extent of this cognitive deviation in patients, and the amount of overlap in classifying patient impairments compared to traditional population-based norms, 2) examining the relationship of this deviation to leading candidate neurophysiologic biomarkers, as well as patient cognitive and clinical characteristics, and 3) determine whether the severity of this deviation accounts for additional variance in accounting for patient deficits in neurophysiologic function, cognition, behavioral symptoms, and psychosocial functioning. First, we hypothesized that patients would exhibit significant discrepancies between observed and regression-predicted global cognitive ability consistent with previous results (Keefe et al., 2005; Hochberger et al., 2018). In addition, we hypothesized that a significant number of patients would exhibit cognitive function in the "normal" range using traditional norms while still having a significant deviation from their observed vs. expected cognitive ability based on regression-predicted estimates derived from individualized factors resistant to illness-related decline. Second, we hypothesized patients with significant deviation from expectation would have greater abnormalities in neurophysiologic functioning (MMN and P3a amplitude, theta oscillations), greater severity of negative symptoms, and worse psychosocial functioning compared to those without significant deviation. Finally, we hypothesized that patient deviation scores would complement traditional population-based norms in ability to predict patient functioning by accounting for additional variance in the neurophysiologic, cognitive, clinical, and psychosocial domains.

2. Methods

2.1. Participants

Recruitment strategy, procedures, and characterization of the study sample have been reported previously (Gur et al., 2015; Light et al., 2015; Swerdlow et al., 2015). Participants included 1290 individuals (HC n = 606, SZ n = 684) tested as part of the 5 site Consortium of Genomics on Schizophrenia (COGS-2) study. Diagnoses were determined using the Structured Clinical Interview for DSM-IV (First et al., 1997). Exclusion criteria included evidence of Axis I psychiatric and neurological disorders other than schizophrenia, head injury, stroke, substance abuse (except nicotine) or a history of psychosis in first degree relatives of healthy comparison subjects. Participant demographics are presented in Table 1.

2.2. Neurophysiologic variables

Neurophysiologic variables of interest consisted of EAIP-associated EEG activity (MMN, P3a, theta evoked power and phase locking). The experimental task, recording, and analytic procedures for EEG variables of interest are previously described by Light et al. (2015) and Hochberger et al. (2019a,b). Briefly, a duration-deviant auditory oddball paradigm consisting of standard

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Table 1
Clinical and demographic characteristics of the sample.

	HC		SZ		P-Value	Effect size
	n = 606		n = 684			
Age	39.31	(13.19)	46.32	(11.36)	<0.000	0.57
Education	13.94	(2.18)	12.70	(2.07)	<0.000	0.58
WRAT Reading Standard Score	106.12	(9.76)	95.26	(12.74)	<0.000	0.96
Maternal Education	13.92	(3.00)	12.43	(3.19)		
Paternal Education	14.17	(3.34)	12.58	(3.64)		
Male	52.6%		70.6%		<0.000	0.19
Female	47.4%		29.4%			
Caucasian	61.4%		41.4%		<0.000	0.22
African-American	21.1%		40.1%			
Other	21.0%		18.6%			
Age of Onset			22.31	(7.26)		
SAPS Global Score			6.94	(4.11)		
SANS Global Score			11.65	(4.74)		
PENN Global Cognition Score	0.01	(0.50)	-0.88	(0.84)		
Deviation Score	0.00	(0.40)	-0.56	(0.73)		
MMN Amplitude	-2.25	(1.18)	-1.25	(0.89)		
P3a Amplitude	2.81	(1.76)	1.46	(1.11)		
Duration EP	28338.60	(43439.62)	8608.89	(10682.61)		
Duration PLF	42.22	(16.35)	25.33	(13.73)		
MMN EP	1689.31	(812.77)	1064.93	(475.15)		

WRAT Reading = Wide-Range Achievement Test, 4th Edition, Reading Subtest Standard Score
SAPS = Scale for the Assessment of Positive Symptoms
SANS = Scale for the Assessment of Negative Symptoms
Penn-CNB = University of Pennsylvania Computerized Neurocognitive Battery
Effect sizes are reported as Cohen's d for continuous variables, and Cramer's V (phi) for categorical variables
Amplitude values are in microvolts (μV)
Evoked power and phase locking are measures of the average area (μV*ms) across the theta frequency layer

($P = 0.90$, 50 ms duration) and duration deviant ($P = 0.10$, 100 ms duration) tones was used. Electroencephalographic data was collected on a custom 2-channel system (San Diego Instruments) from the vertex (CZ) referenced to the left mastoid (full scale setting 0.1, bandpass filter settings 0.5-100 Hz). Eye movement (EOG) activity was collected from electrodes placed mid superior and lateral to the right orbit, and was used for artifact detection. Eye movement artifacts were removed from continuous files via regression-based procedures (Semlitsch et al., 1986), with additional removal of segments with residual artifacts exceeding ± 50 μV. Amplitude values for MMN and P3a were respectively quantified as the mean amplitude from 135-205 ms and 250–300 ms time windows (Light et al., 2015). Processing of stimulus-locked time-frequency data (evoked power [EP] and phase-locking [PLF]) consisted of Morlet Complex Wavelet analyses (parameter = 7) from 1-50 Hz using 50 logarithmic frequency steps, and extracting the area (μV*ms) across the theta frequency layer (4–7 Hz) across a time window of 150–250 ms (Hochberger et al., 2019a,b).

2.3. Cognitive and clinical assessments

Participants were administered comprehensive diagnostic and clinical assessments (Swerdlow et al., 2015). Primary measures of interest included the Wide Range Achievement Test – 4th Edition, Reading Subtest (WRAT-4), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the Scale of Functioning (SOF) (Rapaport et al., 1996), the University of California San Diego Performance-Based Skills Assessment (UPSA) (Patterson et al., 2001), and the global cognition score from the University of Pennsylvania Computerized Neurocognitive Battery (Penn-CNB) (Gur et al., 2015, 2001; 2010; Moore et al., 2015; Swerdlow et al., 2015). Global cognition was computed using an equally-weighted mean of all Penn-CNB subtest "efficiency" scores (the mean of the subtest time and accuracy standardized [z] scores corrected for age and sex) (Moore et al., 2015). To limit the impact of extreme values the global cognition score was Winsorized to a maximum absolute value of 4.0 (Tabachnick and Fidell, 2007).

2.4. Characterizing deviation from expected cognitive ability

2.4.1. Regression model predicting cognitive functioning

Healthy-comparison weighted hierarchical regression was used to predict the global cognition in patients (Gur et al., 2015; Hochberger et al., 2018; Keefe et al., 2005; Light et al., 2015). This method involved first fitting the model on healthy comparison subjects, and then applying the derived model to patients. The first step of the regression equation included age, sex, and race in order to account for demographics, while the second step included paternal and maternal education, and WRAT-IV reading standard scores as an assessment of single-word reading.

2.4.2. Classifying patient impairments in cognitive functioning

Deviation from expected cognitive functioning in patients was classified using two separate measures (Hochberger et al., 2018). In the first, participants falling below the lower bound of a 95% prediction interval (PI) for predicted global cognition was defined as exhibiting a significant deviation. In the second, "deviation scores" were calculated as observed-minus- predicted scores. Impairment in observed cognitive performance (derived from population-based norms) was defined as a z-score of -1.96 or lower, directly corresponding to the lower 95% PI threshold for deviation scores. In total, this provided 2 novel "deviation-based" metrics, and 1 "traditional" metric based on observed cognitive ability, for classifying patient

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cognitive impairment. Chi-square was used to compare the total proportion of individuals across and within groups (healthy comparison, patient) identified as impaired for each criterion (population-based cutoff alone, regression-based cutoff alone, and the overlap across both cutoffs).

2.4.3. Comparison of patient subgroups

Multivariate analysis of variance (MANOVA) using a Bonferroni correction for multiple comparisons was used to compare patients with and without significant deviation from expected cognitive ability (falling below the 95% PI) across premorbid indicators (WRAT reading, patient education, parental education), symptom severity (global SANS and SAPS scores), psychosocial functioning (SOF and UPSA total scores), and EEG biomarkers of EAIP (MMN and P3a amplitude, theta evoked power and phase-locking).

2.4.4. Predictive utility of deviation scores

Hierarchical multiple regression was used to examine the predictive and incremental utility of deviation scores compared to traditional population-based neuropsychological assessment scores in patients. Each neurophysiologic, clinical, and psychosocial variable was used as the outcome variables with the global cognitive efficiency scores in step 1, and deviation scores in step 2.

3. Results

3.1. Regression model predicting deviation in cognitive ability

Consistent with our hypotheses and previous studies, global cognitive ability in healthy comparison subjects was significantly predicted by a combination of parental education and single-word reading ($R^2 = 0.34$, F [6569] = 48.70, $p < 0.000$). Approximately 4% of healthy comparison subjects and 24% (n = 164) of schizophrenia patients exhibited significant deviation between their observed and predicted global cognition based on the regression cutoff. Further, there were significantly more patients identified as impaired based on the regression cutoff compared to the population-based cutoff (χ^2[1] = 81.09, $p < 0.001$, $\phi = 0.27$) (Fig. 1&2). Of those patients identified as having a cognitive impairment (using either population-based or regression-based thresholds), 80% met criteria for impairment using both population-based ($z \leq$ -1.96) and regression-based cutoffs (observed performance below the 95%PI). Notably, 20% of the total patient population (n = 136) were classified as having cognitive performance in the "normal" range based on population-based norms, but were uniquely identified as having a clinically significant decline in cognition based on their regression-predicted ability (Fig. 2).

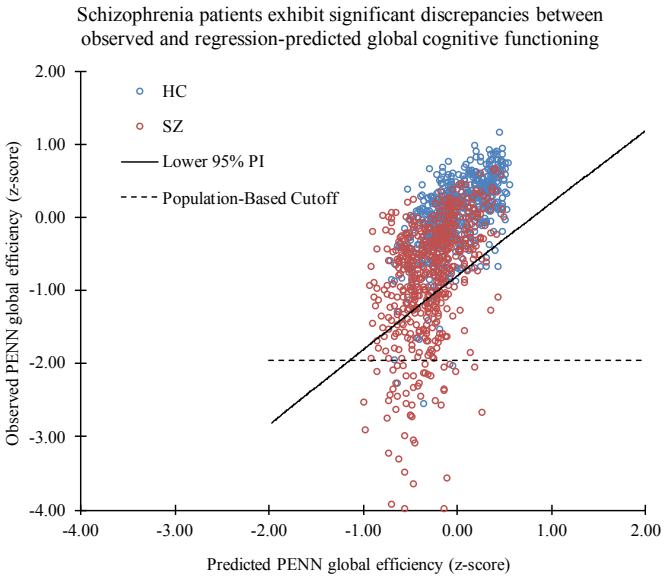

Fig. 1. Comparison of observed and regression-predicted Penn-CNB global efficiency scores in schizophrenia patients and healthy comparison subjects. Solid line represents the lower end of a 95% prediction interval (PI) used to gauge significant deviations between observed and expected ability. Dashed line represents the population-based cutoff ($z \leq$ -1.95) of Penn-CNB global cognition scores used to determine impairment in observed cognitive ability. A total of 24% (n = 164) of SZ patients, and 4% (n = 26) of HCS exhibited significant deviation between observed and expected ability.

3.2. Comparison of patient subgroups based on cognitive deviation

Patients with vs. without significant cognitive deviation could be differentiated based on premorbid functioning, neurophysiologic activity, clinical features, and psychosocial functioning (F [13,485] = 6.06, $p < 0.001$, Wilk's $\lambda = 0.85$, $\eta_p^2 = 0.149$). Group differences on specific variables, and patterns of those differences, are described below.

3.2.1. Premorbid functioning

Compared to patients without significant cognitive deviation, patients with significant deviation had lower estimated premorbid cognitive ability (WRAT reading standard score: F [1500] = 4.57, $p = 0.033$, $\eta_p^2 = 0.009$, x_{Diff} = -2.67, 95% CI_{Diff} = [-5.12, -0.22]) and completed fewer years of formal education (F [1500] = 8.16, $p = 0.004$, $\eta_p^2 = 0.016$, x_{Diff} = -0.59, 95% CI_{Diff} = [-0.99, -0.18]). Although patients with significant deviation had lower maternal education (F [1500] = 10.29, $p = 0.001$, $\eta_p^2 = 0.020$, x_{Diff} = -1.04, 95% CI_{Diff} = [-1.67, -0.40]) there were no group differences in paternal education (F [1500] = 0.70, $p = 0.41$, $\eta_p^2 = 0.001$, x_{Diff} = -0.30, 95% CI_{Diff} = [-0.99, 0.40]).

3.2.2. Neurophysiologic functioning

Patients with and without significant deviation significantly differed in neurophysiologic functioning. Specifically, patients with significant deviation exhibited smaller (i.e., more deficient) MMN (F

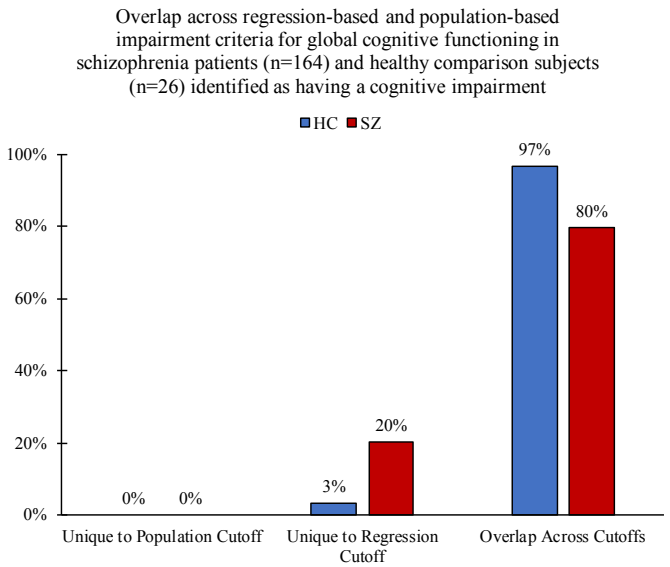

Fig. 2. Overlap across regression-based and population-based impairment criteria (≥-1.96 SD) for Penn-CNB global efficiency scores in schizophrenia patients (n = 164) and healthy comparison subjects (n = 26) identified as having an impairment based on either criterion. Interestingly, 20% of patients (n = 136) with a significant deviation had cognitive functioning within expected limits based on population-based norms alone.

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[1500] = 12.75, $p < 0.000$, $\eta_p^2 = 0.025$, $x_{Diff} = 0.31$, 95% CI_{Diff} = [0.14, 0.48]) and P3a (F [1500] = 10.16, $p = 0.002$, $\eta_p^2 = 0.020$, x_{Diff} = -0.35, 95% CI_{Diff} = [-0.56, -0.13]) amplitudes, as well as lower theta evoked power (F [1500] = 7.92, $p = 0.005$, $\eta_p^2 = 0.016$, x_{Diff} = -3106.81, 95% CI_{Diff} = [-5275.53, -938.08]) and phase-locking (F [1500] = 10.90, $p = 0.001$, $\eta_p^2 = 0.021$, x_{Diff} = -4.42, 95% CI_{Diff} = [-7.05, -1.79]) to duration deviant stimuli, and lower theta evoked power to the deviant-minus-standard (difference) waveform (F [1500] = 13.33, $p < 0.000$, $\eta_p^2 = 0.026$, x_{Diff} = -173.67, 95% CI_{Diff} = [-267.13, -80.22]).

3.2.3. Clinical and psychosocial functioning

Patients with significant deviation had longer illness duration (years: F [1500] = 28.09, $p < 0.000$, $\eta_p^2 = 0.053$, $x_{Diff} = 6.27$, 95% CI_{Diff} = [3.96, 8.62]), greater severity of negative symptoms (SANS total score: F [1500] = 14.53, $p < 0.000$, $\eta_p^2 = 0.028$, $x_{Diff} = 1.79$, 95% CI_{Diff} = [0.87, 2.72]) and lower psychosocial functioning (SOF total score: F [1500] = 14.54, $p < 0.001$, $\eta_p^2 = 0.028$, x_{Diff} = -2.24, 95% CI_{Diff} = [-3.40, -1.09]; UPSA total score: F [1500] = 36.25, $p < 0.001$, $\eta_p^2 = 0.068$, x_{Diff} = -7.94, 95% CI_{Diff} = [-10.53,-5.35]). There were no significant group differences in positive symptom severity (SAPS total score: F [1500] = 1.43, $p = 0.23$, $\eta_p^2 = 0.003$, $x_{Diff} = 0.49$, 95% CI_{Diff} = [-0.31, 1.29]).

3.3. Predictive utility and incremental validity of deviation scores

3.3.1. Neurophysiologic functioning

In patients, global cognition was significantly predicted by MMN (F [1548] = 39.40, $p < 0.000$, $R^2 = 0.093$) and P3a amplitudes (F [1522] = 28.02, $p < 0.000$, $R^2 = 0.051$), evoked theta power to duration deviant (F [1548] = 31.25, $p < 0.000$, $R^2 = 0.052$) and difference waveforms (F [1548] = 35.87, $p < 0.000$, $R^2 = 0.060$), and phase-locking to duration deviant stimuli (F [1548] = 34.63, $p < 0.000$, $R^2 = 0.060$). The addition of deviation scores significantly improved the majority of the prediction models (MMN amplitude: $\Delta F = 36.31$, $\Delta F_p < 0.000$, $\Delta R^2 = 0.059$, total $R^2 = 0.15$; P3a amplitude: $\Delta F = 17.97$, $\Delta F_p < 0.000$, $\Delta R^2 = 0.032$, total $R^2 = 0.083$; Duration deviant evoked power: $\Delta F = 18.83$, $\Delta F_p < 0.000$, $\Delta R^2 = 0.032$, total $R^2 = 0.086$; difference waveform evoked power: $\Delta F = 12.99$, $\Delta F_p < 0.000$, $\Delta R^2 = 0.022$, total $R^2 = 0.080$), but only marginally improved the phase-locking to duration deviant stimuli model ($\Delta F = 3.56$, $\Delta F_p = 0.060$, $\Delta R^2 = 0.006$, total $R^2 = 0.066$). Global cognition accounted for greater variance in each model than deviation scores (MMN amplitude: $ß_{STD}$ = -0.94 vs. 0.68; P3a amplitude: $ß_{STD} = 0.69$ vs. -0.50; duration deviant evoked power: $ß_{STD} = 0.69$ vs. -0.49; duration deviant phase-locking: $ß_{STD} = 0.45$ vs. -0.22; difference waveform evoked power: $ß_{STD} = 0.63$ vs. -0.41) (see Fig. 3).

3.3.2. Clinical and psychosocial functioning

Global cognition was significantly predicted by illness duration (years: F [1538] = 109.01, $p < 0.000$, $R^2 = 0.17$). Further, global cognition significantly predicted negative symptom severity (global SANS: F [1548] = 23.82, $p < 0.000$, $R^2 = 0.042$) and psychosocial functioning (SOF total score: F [1550] = 26.73, $p < 0.000$, $R^2 = 0.046$; UPSA total score: F [1543] = 79.95, $p < 0.000$, $R^2 = 0.13$). The addition of deviation scores significantly improved each model (illness duration: $\Delta F = 177.41$, $\Delta F_p < 0.000$, $\Delta R^2 = 0.21$, total $R^2 = 0.38$; global SANS: $\Delta F = 5.44$, $\Delta F_p = 0.020$, $\Delta R^2 = 0.009$, total $R^2 = 0.051$; SOF total score: $\Delta F = 4.55$, $\Delta F_p = 0.033$, $\Delta R^2 = 0.008$, total $R^2 = 0.054$; UPSA total score: $\Delta F = 4.35$, $\Delta F_p = 0.038$, $\Delta R^2 = 0.007$, total $R^2 = 0.14$), while simultaneously accounting for a greater proportion of variance in both negative symptoms ($ß_{STD} = 0.27$ vs. -0.046) and psychosocial functioning (SOF: $ß_{STD}$ = -0.24 vs. 0.011; UPSA: $ß_{STD} = 0.57$ vs. -0.23). Although deviation scores accounted for the largest shared variance in the illness duration model ($R^2 = 0.17$ vs. 0.21), examination of standardized beta coefficients suggests that global cognition accounted for more variance ($ß_{STD}$ = -1.59 vs. 1.26). Indeed, although the initial model predicting positive symptom severity from global cognition was non-significant (F [1545] = 1.65, $p = 0.20$, $R^2 = 0.003$), the model became significant with the addition of deviation scores (F [1545] = 4.23, $p = 0.015$, $R^2 = 0.015$). Further, deviation scores accounted for the largest shared variance when predicting illness duration ($R^2 = 0.012$ vs. 0.003) (see Fig. 3).

4. Discussion

Cognitive impairment is a key characteristic of schizophrenia due to its prevalence, severity, and relationship to major domains of neurophysiologic, clinical, and psychosocial function (Green et al., 2004; Gur et al., 2015; Hill et al., 2013; Hochberger et al., 2016; Light et al., 2012; Perry et al., 2000; Rissling et al., 2014; Swerdlow et al., 2015; Thomas et al., 2017). Neuropsychological assessment based on population-based norms remains the gold standard for evaluating current cognitive functioning in schizophrenia and other disorders (Crawford, 2005; Kessels and Hendriks, 2015; Lezak, 1995). The current study examined illness-related deviations from expected ability to characterize the severity of cognitive deficits among patients with schizophrenia. Consistent with prior research, a significant proportion (24%) of schizophrenia patients exhibited illness-related declines in cognition, which appear to be dissociable from heritable cognitive ability (Hochberger et al., 2018). Further, although there is substantial overlap between population-based and regression-based impairment thresholds, a significant subset (20%) of patients evidenced “normal” range cognition but actually have significantly reduced performance relative to their expected ability. Importantly, the severity of this illness-related deviation is connected to, and predictive of, patient clinical symptoms and functional impairment, as well as translational biomarkers of neurophysiologic functioning.

4.1. Implications for the etiology of cognitive deficits in schizophrenia

Advances in experimental therapeutics have emphasized the importance of biomarkers that can be used to confirm neural target engagement (Insel, 2015). The consistency of the current findings with prior research suggests that deviation (i.e., the degree of decline from premorbid expectations) in cognitive ability is one such marker that directly reflects illness-specific processes in schizophrenia. Regression-based approaches offer the advantage of directly estimating cognitive ability based on individualized factors. The low heritability of these regression-based deviation scores also allows for the differentiation of inherited cognitive ability from illness-related declines resulting in more precise estimates of illness-specific cognitive impairments (Hochberger et al., 2018; Keefe et al., 2005). Importantly, traditional methods may underestimate the true extent of illness-related cognitive impairment in schizophrenia, particularly in individuals with above average premorbid cognitive ability or potential. Examining deviations from expected cognitive ability circumvents this limitation by directly estimating illness-related cognitive burden. Indeed, 20% of patients in the current study exhibited significant declines from expected cognitive ability while having “normal” range current cognitive ability. Not only does this highlight the utility in assessing for relative performance deficits, but it directly accounts for report of “normal” cognitive functioning in schizophrenia patients (Palmer et al., 1997; Saykin et al., 1991; Strassnig et al., 2018).

4.2. Relationship to key domains of patient functioning

Illness-related deviation in cognitive function not only represents a core cognitive feature of schizophrenia, but is also

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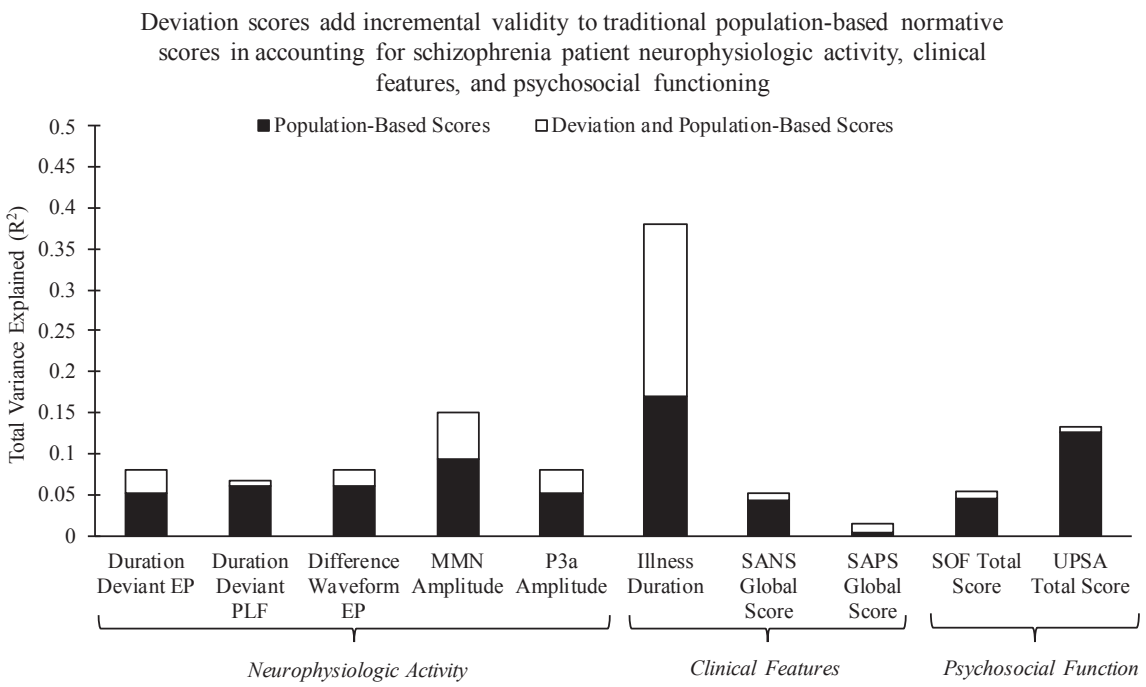

Fig. 3. Total variance explained (R^2) in accounting for schizophrenia patient neurophysiologic activity, clinical features, and psychosocial functioning using population-based scores alone (black bar) or the combination of population-based scores with deviation scores (black bar + white bar). The combination of population-based and deviation scores accounted for significantly more total variance explained than either metric alone in several key areas of patient functioning and outcome.

associated with clinical symptomatology. Patients with significant deviation from expected ability evidenced longer illness duration, greater negative symptom severity, and lower psychosocial functioning, and deviation scores predicted functioning in several of these domains better than traditional population-based norms. This pattern did not hold when examining EEG biomarkers of EAIP, which were better predictors of population-based normative cognitive performance than they were of deviation scores. These findings suggest that deviation scores may have greater utility in predicting clinical features of illness whereas neurophysiologic biomarkers appear to be more linked to current cognitive function. This may be due to the primary importance of current neural integrity necessitating an absolute threshold for efficient functioning, rather than illness-related declines that may not necessarily cross such a threshold. Unsurprisingly, a combination of both deviation and traditional approaches provided the best and most comprehensive predictions of patient functioning across domains. Finally, the relationship between the severity of cognitive deviation and longer illness duration suggests that the presence of this cognitive decline in patients may reflect progressive neurodegeneration akin to Kraepelin's early descriptions of dementia praecox. Modifiable risk factors (such as anticholinergic medication burden) that also contribute to relative declines in cognition would thus present as key treatment targets for recovery-oriented procognitive interventions in both early onset and chronic longstanding psychosis (Eum et al., 2017; Joshi et al., 2019).

These data also suggest a relationship between illness-related cognitive deviations and deficits in EAIP, which have been proposed as surrogate endpoints in early-stage procognitive intervention studies due to their causal contributions to cognitive, clinical, and psychosocial functioning in schizophrenia (Light and Näätänen, 2013; Thomas et al., 2017). Indeed, based on these relationships, it is possible that illness-related deviation from expected cognitive ability could be used alone, or in conjunction with baseline cognitive functioning, to predict and monitor patient outcomes to procognitive interventions (Biagianti et al., 2016; Hochberger et al., 2019a,b; Perez et al., 2017).

4.3. Limitations

Although there are commonly accepted thresholds for classifying cognitive deficits, there remains variability in the literature, with most thresholds ranging from 0.5-2.0 standard deviations below the population mean. Specific estimates and comparisons across population- and regression-based approaches would vary as a function of the specific impairment threshold – directly impacting the interpretation of the current data. To best account for this variability, the current study applied a threshold of 1.96 SD below the mean to best correspond with the threshold for significant deviation between observed and expected ability (i.e.: performance below the lower 95% PI). Although this cutoff was ideal from a comparative and statistical standpoint, it did not allow for the inclusion of patients with mild impairments. Similarly, our use of the PENN global composite efficiency score (compared to accuracy or time scores) might underestimate the severity of impairment by failing to fully account for the accumulation of multiple deficits across domains. Despite its validity as an illness-resistant predictor of premorbid ability, single word reading ability may nonetheless be vulnerable to disruption secondary to illness-related neurodevelopmental abnormalities and educational disruptions common in psychotic disorders. Finally, the current study was a cross-sectional analysis of deviation scores, longitudinal studies examining the stability of cognitive deviation over time would be beneficial, particularly given the current finding suggesting a relationship between these deviation scores and illness duration.

4.4. Conclusion and future direction

Illness-related deviation from expected cognitive ability represents an emergent and complementary method for characterizing the severity of cognitive declines in schizophrenia and perhaps

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other neurodevelopmental disorders. This cognitive deviation has been previously demonstrated to be independent of heritable ability and specific indicator of illness-related cognitive burden. The severity of this deviation has been consistently linked to the expression and severity of key endophenotypes of schizophrenia. The strong relationship between this illness-related deviation and EEG biomarkers of EAIP, previously demonstrated to be early-treatment indicators of patient response to procognitive therapeutics (e.g., Hochberger et al., 2019a,b), warrants further consideration. It is possible that the degree of illness-related deviation may reflect an intermediate process that can be used to gauge the likelihood of treatment gains either alone or in conjunction with traditional population-based norms.

Acknowledgements

The writing of this manuscript was supported by the Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs. The authors wish to thank the COGS investigators including Dr.'s Calkins, Green, Greenwood, Lazzeroni, Nuechterlein, Pela, Radant, Seidman, Siever, Silverman, Stone, Sugar, Turetsky, and Tsuang. In addition, the authors wish to thank all of the participants and support staff that made this study possible, including the following key personnel: University of California San Diego (R01-MH065571; MH042228, MH079777, MH087889, MH094320, Brain Behavior Research Foundation, Sydney R. Baer Jr. Foundation): Joyce Sprock, Richard Sharp, Barbara Haugeland, Lauren Belleville, Stacy Langton, Daniel Mathias, Natalie McCarthy, Marlena Pela, Erich Riesen, Maria Bongiovanni. Mount Sinai School of Medicine (RO1-MH065554): Rui Ferreira, Carolyn Khanian, Denise Poche-Jetter, Rebecca West. University of California Los Angeles (RO1-MH65707): William Horan, Mark Sergi, Amanda Bender, Lusineh Gharapetian, Robert Hubert, Heidi Kuppinger, Trinh Luu, Ian Mathis, Mark McGee, Anaceci Myers, Felice Reddy, Amber Tidwell, Christen Waldon, Katie Weiner. University of Pennsylvania (RO1-MH65578): Amy Cassidy, Erich Dress, Colin Gallagher, Mary March, Kathleen McKenna, Alison Mott, Michael Pato, Jan Richards, Kosha Ruparel, Chandni Singh. University of Washington (R01-MH65558): Kate B. Alvey, Andrew C. David, Sean P. Meichle, Denise O. Pritzl, Sean Meichle, Sandra Perry, Annelise Sullivan, Jane Whetstone, Jake Wolf-Saxon.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.10.011.

Role of the funding source

Other than providing support, the National Institute of Health did not have any further role in the writing of this manuscript.

Conflicts of interest

Dr. Light reports having been a consultant to Astellas, Boehringer-Ingelheim, Heptares, Neuroverse, NeuroSig, and the National Aeronautics and Space Administration (NASA). Dr. Swerdlow has been a consultant for Genco Sciences, Ltd., and Neurocine Inc. All other authors declare that they have no conflict of interest.

Contributors

Dr. Hochberger is the lead author and was responsible for data analyses and manuscript preparation. Dr.'s Thomas and Joshi were involved in supplementary data analyses and select portions of the manuscript. Dr.'s Swerdlow, Braff, R.E. Gur, R.C. Gur, and Light were involved in all aspects of the Consortium of Genomics of Schizophrenia (COGS-2) project including: obtaining funding, data collection and study design, data processing and quality control, and overseeing the development of the current manuscript and data analyses. Additionally, Dr. Light is the corresponding author.

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