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Modeling Deficits from Early Auditory Information Processing to Psychosocial Functioning in Schizophrenia

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Access to Data and Data Analysis
MLT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest Disclosures:
Dr. Green has been a consultant to: AbbVie, ACADIA, DSP, FORUM, Lundbeck, and Takeda., he is on the Scientific Board of Luc and has received research support from Amgen and Forum. Drs. Gur and Turetsky have received unrelated research support for investigator-initiated grants from Pfizer and AstraZeneca. Dr. Gur receives royalties from the Brain Resource Center and has been a consultant for Mindprint Learning. Dr. Nuechterlein has received unrelated research support from Ortho-McNeil Janssen Scientific Affairs and has consulted to Wyeth/Pfizer. Dr. Swerdlow has been a paid consultant for Neurocinex. Inc. Dr. Light reports having been a consultant to Neuroverse, Envivo, and Astellas. All other authors have no conflicts of interest to disclose.

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Importance—Neurophysiological measures of early auditory information processing (EAP) are used as endophenotypes in genomic studies and biomarkers in clinical intervention studies. Research in schizophrenia has established correlations among measures of EAP, cognition, clinical symptoms, and functional outcome. Clarifying these relationships by determining the pathways through which deficits in EAP affect functioning would suggest when and where to therapeutically intervene.

Objective—We sought to characterize the pathways from EAP to outcome and to estimate the extent to which enhancement of basic information processing might improve both cognition and psychosocial functioning in schizophrenia.

Design—Cross-sectional data were analyzed using structural equation modeling to examine the associations between EAP, cognition, negative symptoms, and functional outcome.

Setting—Participants were recruited from the community at five geographically distributed laboratories as part of the Consortium on the Genetics of Schizophrenia-2 (COGS-2).

Participants—This well-characterized cohort of schizophrenia patients (N= 1,415) underwent EAP and cognitive testing as well as thorough clinical and functional assessment.

Main Outcome and Measures—EAP was measured by mismatch negativity, P3a, and reorienting negativity. Cognition was measured by the Letter Number Span test and scales from the California Verbal Learning Test - Second Edition, the Wechsler Memory Scale Third Edition, and the Penn Computerized Neurocognitive Battery. Negative symptoms were measured by the Scale for the Assessment of Negative Symptoms. Functional outcome was measured by the Role Functioning Scale.

Results—EAP had a direct effect on cognition (β = 0.37, p < .001), cognition had a direct effect on negative symptoms (β = −0.16, p < .001), and both cognition (β = 0.26, p < .001) and experiential negative symptoms (β = −0.75, p < .001) had direct effects on functional outcome. Overall, EAP had a fully mediated effect on functional outcome, engaging general rather than modality-specific cognition, with separate pathways that either involved or bypassed negative symptoms.

Conclusions and Relevance—The data support a model where EAP deficits lead to poor functional outcome via impaired cognition and increased negative symptoms. Results can be used to help guide mechanistically informed, personalized treatments, and support the strategy of using EAP measures as surrogate endpoints in early stage pro-cognitive intervention studies.
Schizophrenia is characterized by widespread deficits that range from abnormalities in basic information registration and processing\textsuperscript{1,2} to impairments in cognitive\textsuperscript{3–5} and psychosocial\textsuperscript{6} domains. Given the current evidence that cognitive impairments are robust predictors of functional outcome,\textsuperscript{7,8} there is renewed interest in the longstanding challenge of understanding how deficits in information processing contribute to cognitive and psychosocial impairments in schizophrenia.\textsuperscript{9–12} In this paper, we use structural equation modeling\textsuperscript{13} to refine a theory characterizing the mediating pathways that relate impaired information processing to poor functional outcome.\textsuperscript{14} Clarifying the relationships between information processing and outcome can improve the use of novel pro-cognitive therapeutics, such as pharmacologic enhancement,\textsuperscript{15} neuroplasticity-based cognitive training,\textsuperscript{16–19} and neurostimulation,\textsuperscript{20,21} by informing clinicians and researchers when and where to intervene.

Auditory information processing deficits have been consistently identified in chronic, recent onset, and unmedicated schizophrenia patients as well as individuals at high clinical risk for developing psychosis.\textsuperscript{14} Neurophysiological measures of early auditory information processing (EAP) in schizophrenia correlate with both cognition\textsuperscript{22–24} and functional outcome\textsuperscript{25–28}, can be feasibly measured across diverse settings\textsuperscript{29}, and thus have promising applications as endophenotypes in genomic studies and as biomarkers in clinical outcome studies.\textsuperscript{14,29–36}

In one commonly utilized EAP assessment paradigm, electroencephalography (EEG) recordings are collected while participants passively listen to “standard” stimuli interspersed by deviant “oddball” sounds. EEG recordings are dominated by three peaks labeled mismatch negativity (MMN), P3a, and reorienting negativity (RON). The MMN is thought to index “preattentive” processing of sounds, the P3a is thought to reflect the transition from perception and sensory registration to focal attention or orienting to the stimulus, and the RON is thought to reflect reorienting of attention after distraction.\textsuperscript{37} Together, these components reflect processes underlying auditory perception, auditory learning and memory, and other complex cognitive functions.\textsuperscript{14,38,39} MMN, P3a, and RON arise from broadly distributed patterns of neural activation\textsuperscript{40,41}, and are sensitive to NMDA receptor functioning\textsuperscript{42}—a key component of long-term neuroplasticity.

Reduced MMN, P3a, and RON amplitudes, as well as longer peak latencies, are common features of schizophrenia.\textsuperscript{14,33} A previous analysis of data from the Consortium on the Genetics of Schizophrenia-2 (COGS-2)\textsuperscript{29} showed EAP impairments in schizophrenia with correlations detected between EAP and global cognition, clinical symptoms, and functional outcome; findings that support a growing literature.\textsuperscript{25,26,43–47} Although such correlations underscore the functional significance of EAP deficits, they do not disentangle the multivariate relationships among domains or allow for modelling the cumulative effects of impaired information processing.

Research has suggested that measures of EAP are sensitive to pro-cognitive behavioral and pharmacological therapies,\textsuperscript{48,49} and that changes in EAP might predict improvements in more distant treatment outcomes; that is, outcomes (e.g., work functioning) that are indirectly affected by EAP. This is supported by a bottom-up model suggesting that deficits
in EAP lead to impairments in auditory attention, language, and memory,\textsuperscript{14,22} and that diminished cognition subsequently contributes to defeatist beliefs and other social cognitive phenomena, negative symptoms, and, ultimately, poor functional outcome.\textsuperscript{9,50} Social cognition and clinical symptoms—mainly experiential negative symptoms (i.e., avolition and anhedonia) more so than expressive negative symptoms (i.e., affective blunting/ flattening and alogia)\textsuperscript{51,52}—appear to mediate associations between cognition and functional outcome\textsuperscript{9,53–55} as well as between visual perception and functional outcome.\textsuperscript{9,56,57}

We sought to further clarify the multi-domain pathways relating EAP to functional outcome in schizophrenia using a large sample of patients who participated in the COGS-2 study. In particular, we aimed to examine whether cognition and negative symptoms mediate the EAP-to-outcome relationship. We also sought to estimate the extent to which enhancement of basic information processing might improve both the cognitive and psychosocial functioning of schizophrenia patients in order to provide a benchmark for future intervention studies. We hypothesized: 1) Impairments in EAP would affect negative symptoms via task-modality specific deficits in cognition. That is, measures of EAP would be more closely linked to auditory rather than visual modes of stimulus presentation. Consistent with previous results, we also hypothesized: 2) Negative symptoms would affect functional outcome via separate pathways reflecting a dissociation of experiential and expressive negative symptoms. Lastly, given that EAP is thought to indirectly influence distant outcomes, we hypothesized: 3) Impairments in EAP would indirectly affect functional outcome via a single pathway running through cognition and negative symptoms.

**Method**

**Participants**

Participants included 1,415 unrelated outpatients diagnosed with schizophrenia or schizoaffective disorder that were recruited as part of COGS-2. The average age of participants was 46 (SD = 11), 69% were male, and the average years of education was 13 (SD = 2). Forty-four percent identified their race as White, 39% as African American, 12% as more than one race, 4% as Asian, 1% as Pacific Islander, and less than 1% as Native American. Fourteen percent identified as Hispanic. The average age of illness onset was 22 (SD = 7). Seventy-two percent of participants reported being prescribed atypical antipsychotics, 8% reported being prescribed typical antipsychotics, 10% reported being prescribed both, and 11% reported being prescribed no antipsychotic medication. Test sites included the University of California San Diego, University of California Los Angeles, University of Washington, University of Pennsylvania, and Mount Sinai School of Medicine. Participants were excluded if there was evidence of neurological or Axis I psychiatric disorders other than schizophrenia or schizoaffective disorder. Exclusionary factors also included head injury, stroke, and substance abuse (except tobacco). Diagnoses were verified using the patient edition of the Structured Clinical Interview for DSM-IV.\textsuperscript{58} Urine toxicology screens were used to rule out recent drug use. Additional information on selection criteria are described elsewhere.\textsuperscript{59} Written consent was obtained via methods approved by the local human research protection committees at each testing site.
Measures

Early auditory information processing (EAP)—Details on deriving MMN, P3a, and RON components are provided elsewhere.\textsuperscript{29} Briefly, an auditory oddball paradigm consisting of frequently presented tone “standards” interspersed with infrequent duration-increment “deviants” was employed following established procedures.\textsuperscript{25} Waveforms to standard and deviant stimuli were calculated by averaging EEG responses to each stimulus type. Deviant minus standard difference waveforms were calculated for the MMN, P3a, and RON components.

Cognition—Measures of cognition with an auditory mode of stimulus presentation included total correct scores from the Total Learning (List A Trials 1–5) and Recognition Hits subscales from the California Verbal Learning Test - Second Edition (CVLT-II),\textsuperscript{60,61} Letter Number Span test,\textsuperscript{52,63} and Letter Number Sequencing subtest from the Wechsler Memory Scale Third Edition.\textsuperscript{63,64} Measures of cognition with a visual mode of stimulus presentation were all from the Penn Computerized Neurocognitive Battery\textsuperscript{65–68} and included accuracy scores from the Visual Object Learning Test, the Penn Letter-N-Back Test, the Penn Face Memory Test, and the Penn Word Memory Test.

Negative symptoms—Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS).\textsuperscript{69} The SANS includes five interviewer-rated global ratings: Affective Flattening or Blunting, Alogia, Avolition-Apathy, Anhedonia-Asociality, and Attention. Research suggests that negative symptoms often separate into expressive and experiential factors.\textsuperscript{9,70,71} Attention ratings were not included in the analyses.

Functional Outcome—Functional outcome was assessed using the Role Functioning Scale.\textsuperscript{72} The Role Functioning Scale includes four interviewer-rated role functions: Working Productivity, Independent Living and Self-Care, Immediate Social Network Relationships, and Extended Social Network Relationships.

Analyses

Structural equation modeling\textsuperscript{13,73} was used to summarize relationships among measures described in the previous sections using latent variables, and then to test the plausibility of causal associations among these constructs. Our measurement model (M0) consisted of EAP, cognition for stimuli presented aurally (hereafter auditory cognition), cognition for stimuli presented visually (hereafter visual cognition), expressive negative symptoms, experiential negative symptoms, and functional outcome. To determine whether causal effects were mediated by specific versus nonspecific pathways, path models additionally assumed higher-order cognition (hereafter cognition) and higher-order negative symptoms (hereafter negative symptoms) constructs. We fitted a series of path models to the data that were designed to test the plausibility of the three causal hypotheses. Models are shown in Figure 1.

The specific-deficits model (M1) assumed that impairments in EAP affect task-modality specific deficits in cognition—which in turn increase negative symptoms—and that
expressive and experiential negative symptoms directly affect functional outcome through separate pathways. We then fitted competing models to the data to test specific hypotheses. In the nonspecific-cognitive-deficits model (M2), which was designed to test hypothesis 1, we restricted the causal pathway between EAP and negative symptoms to run through the cognition factor alone. In the nonspecific-negative-symptoms model (M3), which was designed to test hypothesis 2, we restricted the causal pathway between cognition and functional outcome to run through the negative symptoms factor alone. In the direct-EAP model (M4), which was designed to test hypothesis 3, we allowed EAP to have a direct (i.e., non-mediated) effect on functional outcome.

Model parameters were estimated using the latent variable analysis (lavaan) package for R. Models were compared using distinguishability ($\omega^2$) and closeness ($z$) test statistics, comparative fit index (CFI), root mean square error of approximation (RMSEA), Akaike information criterion (AIC), and Bayesian information criterion (BIC). CFI values in the range of .90 to .95 or greater and RMSEA values in the range of .08 to .06 and lower are typically considered acceptable. Smaller AIC and BIC values indicate better fit. For additional information on the estimation approach see the online supplemental material.

**Results**

Correlations between indicators are reported in Figure 2 (for descriptive statistics see eTable 1). Model fit statistics are reported in Table 1. The measurement model (M0) provided acceptable fit. M0 parameter estimates are shown in Figure 3. Our initial path model—the specific-deficits model (M1; eFigure 1)—also provided acceptable fit. Therefore, we continued with tests of the three primary hypotheses.

**Do impairments in EAP affect negative symptoms via task-modality specific deficits in cognition?**

There was no significant difference in model fit comparing the specific-deficits model (M1) to the nonspecific-cognitive-deficits model (M2; eFigure 2), and the latter produced better or equal CFI, RMSEA, AIC, and BIC statistics. Thus, the data do not support the hypothesis that impairments in EAP affect negative symptoms via task-modality specific deficits in cognition.

**Do negative symptoms affect functional outcome via separate experiential and expressive negative symptoms pathways?**

The specific-deficits model (M1) was distinguishable from, and fit the data significantly better than the nonspecific-negative-symptoms model (M3 eFigure 3). The former also produced better CFI, RMSEA, AIC, and BIC statistics. Thus, the data support the hypothesis that negative symptoms affect functional outcome via separate experiential and expressive negative symptoms pathways.
Do impairments in EAP affect functional outcome via a single pathway running through cognition and negative symptoms?

Although distinguishable, there was no significant difference in model fit comparing the specific-deficits model (M1) to the direct-EAP model (M4; eFigure 4); however, the latter produced better CFI, RMSEA, AIC, and BIC statistics. Thus, there is evidence to suggest that, counter to hypothesis 3, EAP has a direct effect on functional outcome. To explore this further, we noted that cognition was more strongly associated with functional outcome than with negative symptoms (see Figure 3), which is not consistent with the assumption that negative symptoms fully mediate the relationship between cognition and functional outcome. This suggests that an omitted pathway between cognition and functional outcome could be the cause of the nearly significant pathway between EAP and functional outcome. To determine this, a fifth model, the direct-cognition model (M5; eFigure 5), was tested where a direct path from cognition to functional outcome was estimated. The direct-cognition model (M5) was distinguishable from, and fit the data significantly better than the specific-deficits model (M1). The direct-cognition model (M5) also produced better CFI, RMSEA, AIC, and BIC statistics when compared to both the specific-deficits model (M1) and the direct-EAP model (M4), suggesting that cognition rather than EAP has a direct effect on functional outcome.

What are the pathways from EAP to functional outcome?

We next fitted the final model that combined all previously accepted hypotheses and ad hoc findings (M6). The parameter estimates for this model are reported in Figure 4. EAP has a direct effect on cognition that is not specific to either auditory or visual task modalities. In turn, poor cognition has both direct and indirect effects on functional outcome. The indirect effect is mediated by negative symptoms, in general, and experiential negative symptoms, in particular. The final model (M6) was distinguishable from, and fit the data significantly better than the specific-deficits model (M1), and produced the best CFI, RMSEA, AIC, and BIC values of all models fitted to the data.

What is the impact of EAP on cognition and functional outcome?

Based on parameter estimates for the final model (M6), the effect (in standardized units) of EAP on cognition was estimated to be $\beta = 0.37$ ($p < .001$) and the total effect of EAP on functional outcome was estimated to be $\beta = 0.14$ ($p < .001$). That is, in the current sample, there was an approximately one-third standard deviation difference in cognition and a one-seventh standard deviation difference in functional outcome for every standard deviation difference in EAP.

Discussion

The present study clarified the multivariate relationships among measures of EAP, cognition, negative symptoms, and functional outcome in schizophrenia. Results supported the hypothesized information processing bottom-up model whereby EAP deficits contribute to cognitive impairments,14,22 which are followed by negative symptoms and reduced functional outcome.9,50 Consistent with our hypothesis, experiential negative symptoms exerted a much stronger effect on functional outcome than did expressive negative
symptoms (hypothesis 2). We also found that the effect of EAP on functional outcome was fully mediated by cognition and negative symptoms (hypothesis 3); but results suggest separate pathways that either involve or bypass negative symptoms. Impairments in EAP appear to be comparably associated with both auditory and visual domains of cognitive functioning. Because EAP arises from a broadly distributed network, results lend support to the view that measures of EAP generally reflect impaired brain functioning rather than a specific deficit in auditory information processing.

This pattern of results has potential implications for biomarker guided treatment development. Until recently, the prevailing view of schizophrenia has been that cognitive impairments are largely immutable to rehabilitative efforts and serve as a bottleneck to optimal psychosocial functioning. Findings that cognitive impairments are not fixed, but can be enhanced via pharmacologic, neuroplasticity-based cognitive training, neurostimulation, or combined treatment approaches (e.g., Pharmacologic Augmentation of Cognitive Therapies) offers the hope of at least some functional recovery, even for patients with chronic illness. The parameter estimates obtained in this study would conservatively predict that an intervention producing a 1 standard deviation improvement in EAP—or, approximately, a 1 microvolt change in the average amplitude of MMN, P3a, or RON—would produce Cohen’s d improvements of 0.78 and 0.28 for cognition and psychosocial functioning respectively. The number needed to treat (NNT) with an EAP intervention in order to have one additional success would be 2.38 for cognition and 6.37 for functional outcome. Although the time course is unclear, research has shown that event-related potentials, such as MMN, are modifiable. Given that treatment responses vary, neurophysiological biomarkers of EAP might contribute to treatment algorithms designed to predict the likelihood of patient benefit. Additional research is needed to characterize the neural substrates that engender a positive treatment response and can be leveraged to guide a mechanistically informed, personalized intervention approach.

The results of this study should be interpreted in light of key limitations. First, we used statistical modeling to explore the plausibility of causal associations. Experimental studies are needed to support causal associations among the constructs. Second, EAP data were obtained from a 2-channel recording system. Although this is generally sufficient for detecting large effect size deficits in schizophrenia patients, it is inadequate for reliably quantifying the magnitude of subtle treatment-related effects. Higher density recordings offer substantial improvements in artifact reduction and for decomposing cortical source dynamics attributable to a drug or cognitive training intervention. Third, as in the vast majority of studies of schizophrenia patients, medications were not experimentally controlled. The variable and complex medication regimens of patients cannot be convincingly disentangled via cross-sectional analyses (cf. ). Fourth, the omission of constructs such as social cognition and defeatist beliefs limits the completeness of our EAP-to-outcome interpretive framework (cf. ). Unfortunately, we lacked a sufficient number of social cognitive measures to be used in structural equation modeling.

Overall, the present findings point to a key role for EAP in terms of developing comprehensive diagnostic and treatment approaches. Recovery from mental illness may be most feasible when conventional treatments targeting symptoms, motivation, self-efficacy,
and socioenvironmental barriers are combined with intensive remediation of basic information processing. Future research in this area will advance personalized and data-driven treatment by indicating when and where to intervene in order to affect various endpoints between EAP and outcome.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Path Models for the Associations Among Early Auditory Information Processing, Cognition, Negative Symptoms, and Functional Outcome Constructs
EAP = Early Auditory Information Processing
Figure 2.
Correlations among Observed Indicators of Early Auditory Information Processing, Cognition, Negative Symptoms, and Functional Outcome

CVLT-II = Second Edition of the California Verbal Learning Test; SANS = Scale for the Assessment of Negative symptoms; RFS = Role Functioning Scale.
Figure 3.
Measurement Model (M0)
Associations between nodes—observed variables (squares) and latent variables (circles)—are represented by edges (lines) that can be either directed (single-headed arrow) or undirected (double-headed arrow). Coefficients for the completely standardized solution are reported in the figure. CVLT-II = Second Edition of the California Verbal Learning Test; SANS = Scale for the Assessment of Negative symptoms; RFS = Role Functioning Scale. * indicates statistical significance at $p < .05$. 
Figure 4.
Final Path Model (M6)
Associations between nodes—observed variables (squares) and latent variables (circles)—are represented by edges (lines) that can be either directed (single-headed arrow) or undirected (double-headed arrow). Coefficients for the completely standardized solution are reported in the figure. CVLT-II = Second Edition of the California Verbal Learning Test; SANS = Scale for the Assessment of Negative symptoms; RFS = Role Functioning Scale. * indicates statistical significance at $p < .05$. 
<table>
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Note. $\omega^2 =$ distinguishability test statistic (vs. M1); $z =$ Vuong closeness $z$ test statistic (vs. M1); CFI = comparative fit index; RMSEA = root mean square error of approximation; AIC = Akaike information criterion; BIC = Bayesian information criterion; 

* $p < .05$; 
** $p < .01$; 
*** $p < .001$; 

n.s. = models not significantly different.