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Oscillatory biomarkers of early auditory information processing predict cognitive gains following targeted cognitive training in schizophrenia patients

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ABSTRACT

Auditory-based targeted cognitive training (TCT) is an effective and well-validated intervention for the treatment of cognitive impairment in schizophrenia patients. Improvements in higher-order cognition, reductions in symptom severity, and increases in psychosocial functioning secondary to TCT are thought to be driven by "bottom-up" enhancement of early auditory information processing (EAIP). Despite strong evidence of efficacy at the group level, there is significant variability in response to TCT, with few well-delineated biomarkers for predicting individual benefit. EEG biomarkers of EAIP are indicators of early-treatment sensitivity that predict full-course TCT outcome; however, further characterization is necessary for biomarker-guided clinical trials. The current study examined baseline and early-treatment sensitivity (i.e., change from baseline after 1 h) in theta band oscillatory activity to deviant stimuli as moderators of full course (30 h) TCT response in treatment-refractory schizophrenia patients randomly assigned to receive either treatment-as-usual (TAU; $n = 22$) or TAU augmented with TCT ($n = 30$). Theta evoked power and phase locking at baseline predicted patient improvements in global cognitive function after 30 h of TCT. Decrease in theta activity to deviant stimuli after 1 h of TCT predicted improvements in verbal learning after 30 h. Exploratory analyses using EEG composite scores had high levels of sensitivity and specificity for identifying patients most likely to benefit from TCT. The integrity of baseline neurophysiologic activity associated with EAIP, as well as the sensitivity of the underlying circuity to change, likely reflects an intermediate therapeutic process underlying the effectiveness of TCT that can be used to predict patient response to treatment.

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1. Introduction

Cognitive impairment and psychosocial disability in schizophrenia and other psychotic disorders have been conceptualized as resulting from a core deficit in early auditory information processing (EAIP) (Braff and Light, 2004; Thomas et al., 2017). Auditory-based targeted cognitive training (TCT) is an effective treatment for improving EAIP through progressive and adaptive tuning of the underlying neural circuitry (Bell et al., 2017; Fisher et al., 2016; Fisher et al., 2010; Thomas et al., 2018a; Thomas et al., 2018b). In turn, TCT-induced improvements in EAIP lead to "bottom-up" gains in higher order cognitive functioning, reductions in clinical symptoms, and improvements in psychosocial functioning (Suga et al., 2016; Thomas et al., 2018a; Thomas et al., 2018b). Although response rates to TCT remain variable, advances in experimental therapeutics have identified several well-validated candidate biomarkers of EAIP which have shown preliminary evidence of both malleable change secondary to TCT, as well as predictive utility for patient outcomes (Biagianti et al., 2017, 2016; Hochberger et al., 2019a, 2019b; Jahshan et al., 2019; Medalia et al., 2019; Perez et al., 2017).

Biomarkers of EAIP reflecting neural system engagement during TCT can be separated into baseline and early-treatment (first-dose) indicators, with some measures predicting treatment outcome. For example, baseline EAIP integrity (reflected by performance on the Tone Matching Test) moderates patient gains in verbal learning, but not global cognitive function or symptoms (Medalia et al., 2019). In addition, the efficiency of baseline auditory processing predicts global and focal cognitive improvements following TCT (Biagianti et al., 2016). Event-related potential (ERP) markers of central auditory system plasticity and discriminability involved in EAIP (mismatch negativity [MMN]

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and P3a) demonstrate utility in predicting patient outcomes from TCT. Baseline MMN activity predicts global cognitive improvement following TCT (Biagianti et al., 2017), while our prior research has shown that MMN and P3a are malleable in response to the first-dose (1 h) of TCT, and that the degree of this sensitivity predicts patient improvements in both verbal learning and reductions in positive symptom severity (Hochberger et al., 2019a, 2019b; Perez et al., 2017).

Deficits in the constituent oscillatory elements of the MMN-P3a response complex are also linked to EAIP in patients with schizophrenia (Hochberger et al., 2019a, 2019b; Javitt et al., 2016; Kaser et al., 2013). Specifically, the strength (evoked power) and inter-trial consistency (phase-locking) in theta oscillations to deviant stimuli and the mismatch difference wave, thought to reflect the integrity of deviance detection during EAIP, have strong and unique relationships to premorbid function, current cognitive ability, and key domains of clinical outcome in schizophrenia patients (Hochberger et al., 2019a, 2019b; Javitt et al., 2016, 2008). Decomposing EAIP into its constituent oscillatory activity offers a distinct advantage of furthering downward translation and characterization of the underlying neural circuitry hypothesized to be engaged by TCT (Javitt, 2015; Kirihara et al., 2012). The utility of oscillatory activity underlying EAIP in predicting TCT outcome, however, has not been examined.

We have previously reported a favorable response to TCT in this cohort (Thomas et al., 2018a), as well as first-dose (1 h) sensitivity in MMN and P3a predicting full-course (30 h) treatment outcome in patients who underwent TCT (Hochberger et al., 2019a, 2019b). The current study therefore aimed to characterize the relationship between oscillatory EEG activity and TCT outcome. Based on our prior reports (Hochberger et al., 2019a, 2019b), we hypothesized that TCT would induce sensitive early-treatment (1 h) change in theta-based power and phase-locking to all deviant and difference-wave stimuli, that the degree of this first-dose sensitivity in deviant-related oscillatory EEG would predict post-treatment improvements in verbal learning, and that baseline oscillatory EEG activity would predict improvements in global cognition for patients who underwent TCT. Finally, exploratory analyses were conducted in order to determine whether or not composite indices reflecting baseline and early-treatment sensitivity predictors could be developed with sufficient sensitivity and specificity to predict clinically significant benefit from TCT.

2. Methods

2.1. Participants and design

Detailed report of the current clinical trial and outcomes is described in Thomas et al. (2018a, 2018b). Briefly, patients with chronic schizophrenia or schizoaffective disorder were recruited from a residential treatment program and assigned to receive either treatment-as-usual (TAU; $n = 22$) or TAU augmented with TCT ($n = 30$) (Table 1). Group assignment was determined stratified random sampling (based on age, gender, and ethnicity). The Institutional Review Board of University of California, San Diego approved all experimental procedures (IRB#130874).

2.2. Targeted cognitive training

The current training program involved 6 modules from BrainHQ by Posit Science divided over 3–5 one-hour sessions per week for an approximately total of 30 h of training. Each module used an adaptive algorithm in order to progressively modify item difficulty – ensuring participants were being sufficiently challenged based on any baseline deficit as well as improvements. For full details, see Thomas et al. (2018a, 2018b).

Table 1
Comparison of clinical and demographic variables across patient groups.

	Treatment-as-usual (TAU)	Targeted cognitive training (TCT)	Significance	Effect size
	$n = 22$	$n = 30$		
	Mean (SD)	Mean (SD)		
Age (years)	35.73 (13.00)	33.90 (11.50)	n.s.	0.0007
Education (years)	11.95 (2.17)	11.83 (1.91)	n.s.	0.017
WRAT: Reading SS	91.95 (13.34)	91.37 (13.60)	n.s.	0.005
Gender				
Male	40.9%	50.0%	n.s.	0.045
Female	59.1%	50.0%		
Race				
Caucasian	54.5%	50.0%		
African-American	13.6%	13.3%	n.s.	0.102
Other	31.8%	36.7%		
Clinical diagnosis				
Schizophrenia	54.5%	53.3%		
Schizoaffective disorder	45.5%	46.7%	n.s.	0.012
Age of onset (years)	20.5 (4.96)	18.07 (5.09)	n.s.	0.061
Illness duration (years)	15.23 (12.79)	16.32 (12.89)	n.s.	0.002
SAPS Global Score	4.45 (5.14)	5.04 (4.07)	n.s.	0.002
SANS Global Score	6.18 (3.79)	7.43 (4.33)	n.s.	0.035

WRAT: reading = wide-range achievement test, 4th edition, reading subtest.
SAPS = Scale for the assessment of positive symptoms.
SANS = Scale for the assessment of negative symptoms.
Effect size reported is partial eta-squared for continuous variables, Cramer's phi for categorical variables.

2.3. Cognitive and symptom assessment

The MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2011; Nuechterlein et al., 2008) and the Scale for the Assessment of Positive Symptoms (SAPS) (N. Andreasen, 1984) and Negative Symptoms (SANS) (N. C. Andreasen, 1989) were administered to patients at baseline ($T_{Baseline}$) and upon completion of the study (T_{Post}). Consistent with prior research on this same sample, the MCCB global cognitive composite and verbal learning t-scores (corrected for age and sex) were the primary outcomes.

2.4. EEG recording

Details of the passive auditory oddball paradigm and EEG recording procedures are described in detail by Hochberger et al. (2019a, 2019b). Data was collected from a 64 channel BioSemi ActiveTwo System with a sampling rate of 1 kHz. Eye blinks and movements were recorded using four additional electrodes placed above and below the left eye and the outer canthi of both eyes. Data was collected during a passive auditory oddball paradigm consisting of a pseudorandom sequence of tones including a standard stimulus ($P = .70$, 50 ms duration at 1000 Hz), and five distinct types of deviant stimuli ($P = .30$). These deviant stimuli consisted of a duration deviant (125 ms duration at 1000 Hz) and four novel "pitch sweep deviants" designed to reflect the TCT module of the same name, and were included in order to increase ecological validity. These sweep deviants varied in terms of starting at the standard tone (1000 Hz) or a deviant tone (500 Hz or 1500 Hz), and the direction of the change in pitch (up vs. down) across the sweep. EEG activity across each of the sweep deviants was averaged as there were no significant differences in either evoked power or phase locking across sweep type ($p > .05$). A minimum of 400 duration deviant and 200 of each type of the four distinct sweep deviant trials were collected for each

participant. All patients underwent EEG recording at baseline ($T_{Baseline}$), after their initial completion of either 1 h of cognitive training (TCT) or 1 h of computer games (TAU) ($T_{Initial}$), and upon study completion (T_{Post}).

2.5. EEG processing

Pre-processing utilized a digital filter with a 0.5 Hz low-cutoff (12 dB/oct). Eye movement artifacts were removed via an ocular ICA procedure, with additional removal of segments with residual artifacts exceeding ±100μV. Difference waves were calculated by subtracting ERP's in response to standard tones from those in response to deviant tones. All measures were extracted from a frontal composite (derived from the mean activity of electrodes F1, Fz, F2, FC1, FCZ, FC2, C1, CZ, and C2) across an epoch from −100 to 500 ms. Post-processing of stimulus-locked time-frequency data consisted of Morlet Complex Wavelet analyses (parameter = 7) from 1 to 50 Hz using 50 logarithmic frequency steps. Review of grand average broadband time-frequency plots evidenced theta-band activity (4–7 Hz) as the principal signal in both evoked power and phase locking with no significant activity or group differences in other frequency bands (Supplemental Figs. 1 & 2). As such, the mean activity in the 4-7 Hz frequency layer over the 125-225 ms time window, where overall activity and group differences appeared the largest, was extracted for use in subsequent analyses.

2.6. Statistical analyses

2.6.1. Sensitivity to change in evoked power and phase-locking

The sensitivity (i.e., change over time) of oscillatory EEG secondary to TCT was assessed using linear mixed-models (Hox, 2010) for each dependent variable (duration deviant evoked power and phase locking, duration deviant difference wave evoked power, all sweep deviant evoked power and phase locking, all sweep deviant difference wave evoked power). Each model was fit using the 'lme4' package in *R* (Bates et al., 2015) and included a linear effect of time ($T_{Baseline}$, $T_{Initial}$, and T_{Post}) as a fixed factor with a random intercept for time. Effect sizes for linear mixed models were calculated using R^2 in the 'MuMIn' package (Bartoń, 2018) (small = 0.02, medium = 0.25, large = 0.40) (Cohen, 1988). These values consisted of both conditional R^2 (R^2_C: variance explained by both the fixed and random factors), and marginal R^2 (R^2_M: variance explained by the fixed factors alone).

2.6.2. Prediction of TCT outcome

To determine the predictive utility of theta-band oscillatory EEG difference scores in cognition and clinical symptoms were computed by subtracting baseline ($T_{Baseline}$) from post-TCT (T_{Post}) treatment values. Following our established methods (Hochberger et al., 2019a, 2019b; Perez et al., 2017), early EEG sensitivity was calculated by subtracting activity in the session recorded immediately before ($T_{Baseline}$) from the recording that immediately followed the initial 1 h exposure to TCT ($T_{Initial}$). Regression models were used to predict change in MCCB global cognition and verbal learning t-scores, from the early sensitivity in in theta evoked power and phase locking across each waveform (duration deviant, sweep deviant, duration and sweep deviant difference waves). Consistent with our prior methods (see Hochberger et al., 2019a, 2019b), separate regression models were used for TCT and TAU. Effect sizes for regression analyses are reported as standardized regression coefficients (β: small = 0.02, medium = 0.25, large = 0.40) (Cohen, 1988).

3. Results

3.1. Oscillatory EEG sensitivity secondary to TCT

For duration deviant stimuli both evoked power ($b = -37.35$, SE = 18.26, $t = -2.04$, $df = 49.88$, $p = .046$, $R^2_M = 0.015$, $R^2_C = 0.75$) and phase locking ($b = -0.04$, SE = 0.012, $t = -3.25$, $df = 49.72$, $p = .002$, $R^2_M = 0.035$, $R^2_C = 0.77$) showed significant decreases over time (T_0, $T_{Initial}$, $T_{Baseline}$). Evoked power to the duration deviant difference waveform also significantly decreased over time ($b = -78.40$, SE = 24.80, $t = -3.16$, $df = 49.95$, $p = .003$, $R^2_M = 0.041$, $R^2_C = 0.72$). Conversely, for sweep deviant stimuli, neither evoked power ($b = -17.16$, SE = 18.34, $t = -0.94$, $df = 48.88$, $p = .35$, $R^2_M = 0.003$, $R^2_C = 0.86$) nor phase locking ($b = -0.018$, SE = 0.012, $t = -1.43$, $df = 49.08$, $p = .16$, $R^2_M = 0.008$, $R^2_C = 0.81$) showed a significant linear effect of time. However, there was a significant increase evoked power to the sweep deviant difference waveform over time ($b = -47.74$, SE = 17.20, $t = -2.78$, $df = 48.60$, $p = .008$, $R^2_M = 0.013$, $R^2_C = 0.89$) (see Supplemental Figs. 1 & 2).

3.2. Predictors of TCT outcome

3.2.1. Baseline predictors of global cognitive change

Sweep deviant theta evoked power at baseline ($T_{Baseline}$) predicted improvements in MCCB global cognition for patients who underwent TCT ($R^2 = 0.19$, β = 0.44, F [1,20] = 4.53, $p = .047$, 95% CI_B [0.00, 0.023]) but not those in TAU ($R^2 = 0.006$, β = 0.076, F [1,18] = 0.099, $p = .76$, 95% CI_B [−0.14, 0.019]) (Fig. 1A). Similarly, phase-locking to duration and sweep deviant stimuli at baseline ($T_{Baseline}$) predicted improvements in MCCB global cognition for patients who underwent TCT (duration deviant: $R^2 = 0.19$, β = 0.43, F [1,20] = 4.33, $p = .05$, 95% CI_B [−0.16, 55.76]; sweep deviant: $R^2 = 0.29$, β = 0.54, F [1,20] = 7.68, $p = .012$, 95% CI_B [6.48, 46.48]) but not TAU (duration deviant: $R^2 = 0.011$, β = 0.10, F [1,18] = 0.19, $p = .67$, 95% CI_B [−29.77, 45.00]; sweep deviant: $R^2 = 0.008$, β = −0.091, F [1,18] = 0.14, $p = .71$, 95% CI_B [−41.57, 28.94]) (Fig. 1B). All other models predicting MCCB global cognitive change were non-significant ($p > .05$) (Table 2).

3.2.2. Early-treatment sensitivity predicting verbal learning change

For patients who underwent TCT, sensitivity ($T_{Initial} - T_{Baseline}$) in sweep deviant theta evoked power ($R^2 = 0.19$, β = −0.44, F [1,20] = 4.47, $p = .048$, 95% CI_B [−0.053, 0.00]) and theta evoked power to the sweep deviant difference waveform ($R^2 = 0.21$, β = −0.46, F [1,20] = 5.09, $p = .036$, 95% CI_B [−0.057, −0.002) both significantly predicted improvement in MCCB verbal learning (Fig. 2). This pattern was not seen in patients who underwent TAU (sweep deviant evoked power: $R^2 = 0.010$, β = 0.10, F [1,17] = 0.16, $p = .69$, 95% CI_B [−0.038, 0.056]; sweep deviant difference waveform evoked power: $R^2 = 0.00$, β = −0.009, F [1,17] = 0.97, $p = .001$, 95% CI_B [−0.054, 0.052]). All other models predicting change in MCCB verbal learning change were non-significant ($p > .05$) (Table 2).

3.2.3. Exploratory EEG composite score analyses

Across the current study and our prior work (Hochberger et al., 2019a, 2019b) we identified two distinct classes of EEG biomarkers that were significant predictors of TCT outcome. These included: 3 baseline predictors of global cognition improvement (duration and sweep deviant phase locking, sweep deviant evoked power), and 4 early-treatment predictors of verbal learning improvement (duration MMN latency, duration P3a amplitude, sweep deviant theta evoked power, sweep deviant difference wave evoked power). These biomarkers were entered into separate regression models (predicting MCCB global cognition and verbal learning T-score change) in patients who underwent TCT. The standardized predicted values from each model were then saved and used as regression-weighted baseline and early-treatment sensitivity indices. The baseline EEG composite score significantly predicted improvements in global cognition ($R^2 = 0.31$, β = 0.56, F [1,20] = 8.61, $p = .009$, 95% CI_B [1.21,7.23]), the early-treatment sensitivity EEG composite score significantly predicted improvements in verbal learning ($R^2 = 0.41$, β = 0.64, F [1,14] = 9.09, $p = .010$, 95% CI_B [0.88, 5.38]).

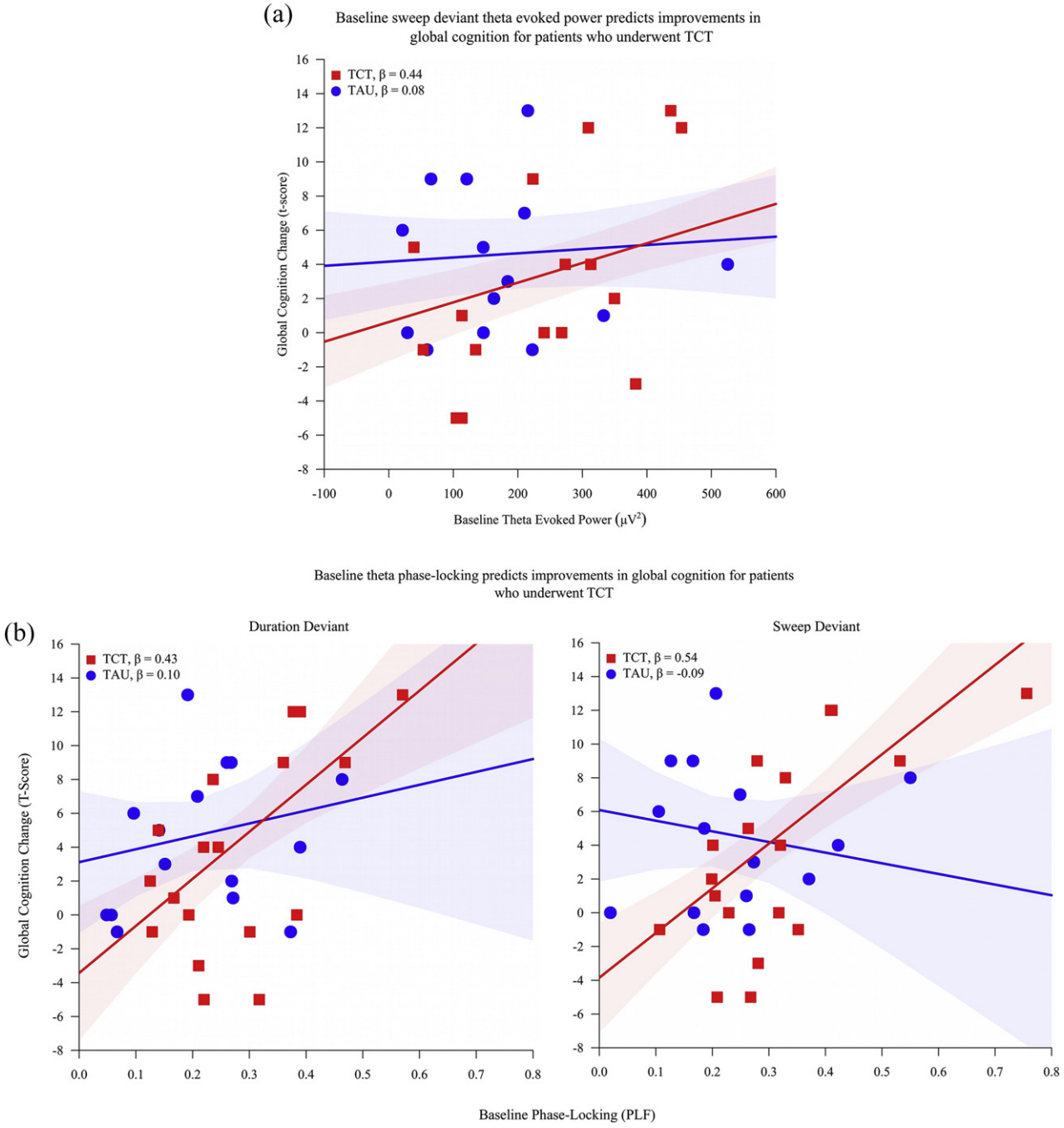


Fig. 1. a. Baseline theta evoked power to sweep stimuli predicts improvements in global cognition for patients who underwent TCT. Shaded regions represent the standard error of the regression line. b. Baseline theta phase-locking to duration deviant stimuli predicts improvements in global cognition for patients who underwent TCT. Shaded regions represent the standard error of the regression line.

Further, each composite score was able to screen for the presence of true cognitive improvements (defined as Cohen's $d \geq 0.2$ via established methods, see Keefe et al., 2017 and Vinogradov et al., 2012) in MCCB global cognition (AUC = 80.6%, $p = .02$, $95\%CI_{AUC}$ [0.62, 0.99]) and verbal learning scores (AUC = 87.3%, $p = .02$, $95\%CI_{AUC}$ [0.66, 1.00]). For baseline activity, ROC analyses demonstrated that a cutoff of $z \geq -0.38$ provided 83% sensitivity and 67% specificity in detecting positive gains in global cognition; whereas for early-treatment sensitivity a cutoff of $z \geq -0.55$ provided 91% sensitivity and 80% specificity in detecting positive gains in verbal learning secondary to TCT. Full estimates of specificity and sensitivity based on specific composite score cutoffs can be found in Fig. 3.

4. Discussion

Advances in procognitive therapeutics have identified baseline and early-treatment neurophysiologic measures of EAIP target engagement that can be used to predict and monitor patient response to TCT (Biagianti et al., 2017, 2016; Hochberger et al., 2019a, 2019b; Medalia et al., 2019; Perez et al., 2017). The current study extends our previous findings of EAIP biomarkers by decomposing event-related potential components into their constituent oscillatory dynamics. Our results demonstrate that theta oscillations underlying the mismatch negativity-P3a auditory deviance response complex (Rissling et al., 2014) measured at the outset of TCT treatment predict patient gains in both global and focal cognitive domains after a full course (30 h) of

Table 2
Regression coefficients (R^2) for all regression models predicting change ($T_{Initial} - T_{Baseline}$) in cognitive outcomes across groups.

		Treatment-as-usual (TAU)	Targeted Cognitive Training (TCT)
Outcome	Predictor		
Global cognition	Baseline sweep deviant evoked power	0.01	0.19*
	Baseline sweep deviant phase locking	0.01	0.29*
	Baseline sweep deviant difference wave power	0.02	0.12
	Baseline duration deviant evoked power	0.01	0.14
	Baseline duration deviant phase locking	0.01	0.19*
	Baseline duration deviant difference wave evoked power	0.01	0.12
Verbal learning	Sweep deviant evoked power sensitivity	0.01	0.19*
	Sweep deviant phase locking sensitivity	<0.01	0.01
	Sweep deviant difference wave power sensitivity	<0.01	0.21*
	Duration deviant evoked power sensitivity	0.12	0.02
	Duration deviant phase locking sensitivity	0.01	<0.01
	Duration deviant difference wave evoked power sensitivity	0.04	<0.01

* $p < .05$.

treatment. Baseline theta evoked power and phase locking predicted global cognitive change, while the sensitivity of theta evoked power after the first exposure to the auditory training exercises predicted focal cognitive change in verbal learning. Composite indices accounted for 31.2% of the variance in global cognition improvements and 41.2% of the variance in verbal learning improvements, both with excellent sensitivity and specificity in predicting clinically significant gains from TCT.

4.1. Oscillatory EEG and TCT

Both event-related (MMN, P3a) and oscillatory (theta-band) EEG activity elicited during passive auditory oddball paradigms are robust, reliable, and valid biomarkers of EAIP target engagement (Hochberger et al., 2019a, 2019b; Light et al., 2015; Light and Näätänen, 2013a). Further, these EAIP-related EEG deficits are core endophenotypes of schizophrenia with well-documented relationships to cognitive and clinical function (Green et al., 2004; Hochberger et al., 2019a, 2019b; Javitt et al., 2016; Kawakubo et al., 2007; Lavoie et al., 2017; Light et al., 2012; Light and Näätänen, 2013b; Rissling et al., 2014; Salisbury and McCathern, 2016; Thomas et al., 2017). Consistent with recent research suggesting that EAIP-related EEG activity reflects an intermediate therapeutic process in TCT, theta oscillatory activity evidenced significant sensitivity in both evoked power and phase-locking across the full course of treatment, with the greatest changes occurring after the first 1 h "dose" of TCT. Taken together with our prior findings showing a similar pattern of MMN and P3a sensitivity (Hochberger et al., 2019a, 2019b; Perez et al., 2017), and recent findings of source redistribution in EEG-associated EAIP neurocircuitry (Perez et al., 2019), it is possible that the neuroplastic effects of TCT reflect an enhancement and dynamic reorganization of the underlying EAIP neurocircuitry, resulting in improvements in cognitive function (Fisher et al., 2010; Hochberger et al., 2019a, 2019b; Javitt et al., 1996; Kaser et al., 2013; Perez et al., 2019, 2014; Todd et al., 2013).

The sensitivity of theta evoked power after the first-dose (1 h) of TCT significantly predicted patient gains in verbal learning from full-course (30 h) treatment. These findings highlight the potential to use neurophysiologic biomarkers to identify individuals who are both acutely sensitive and initially responsive to an intervention and carrying them forward to receive longer-term, therapeutic doses of the intervention in biomarker guided clinical trial designs (Hochberger et al., 2019a, 2019b; Perez et al., 2017). Interestingly, despite no marginal effect of

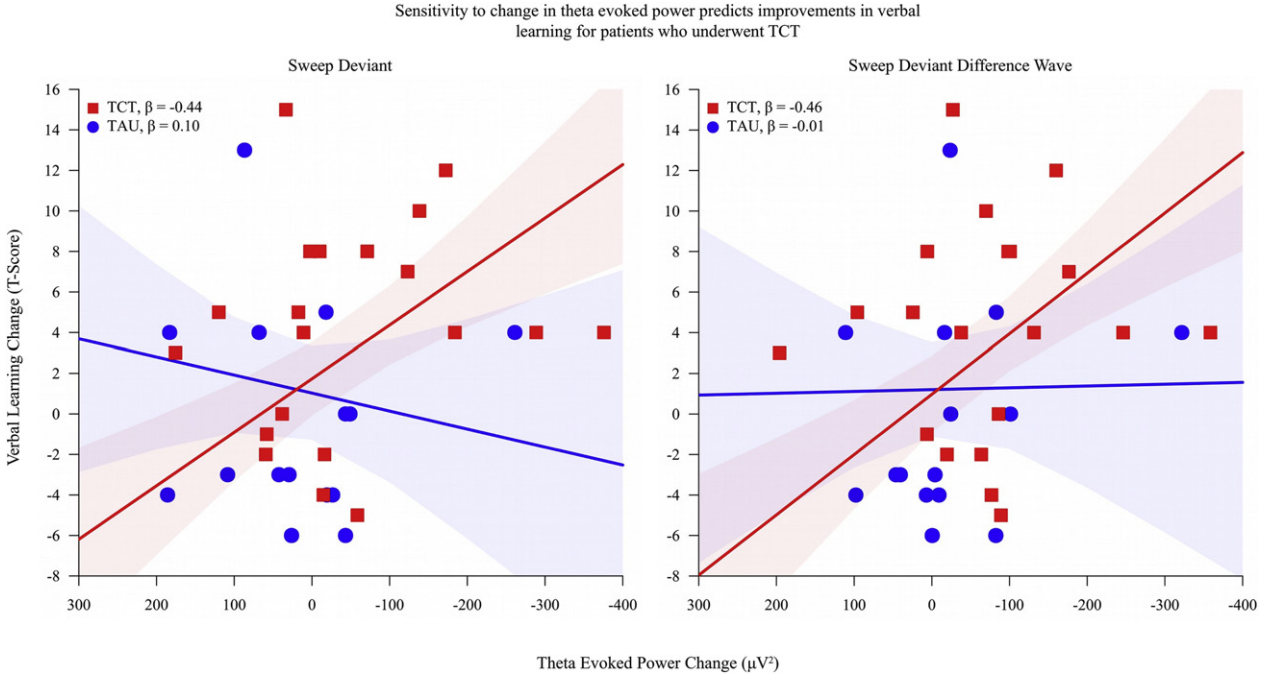
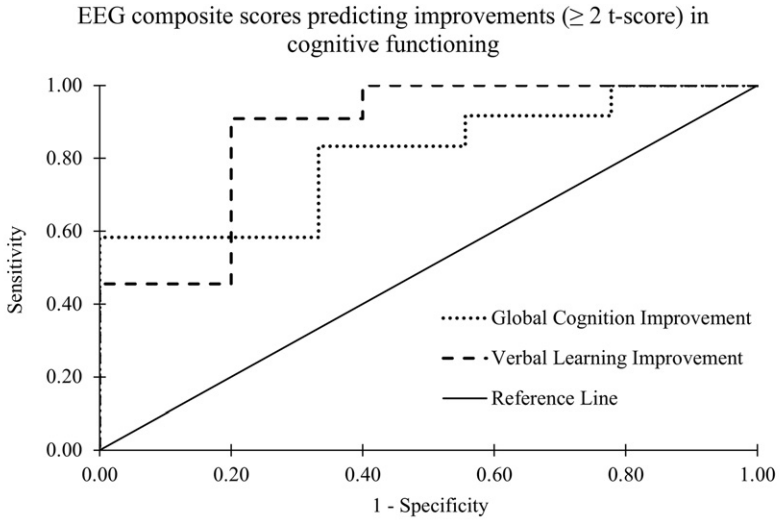


Fig. 2. Sensitivity to change in theta evoked power to the sweep deviant stimuli difference waveform predicts improvements in verbal learning for patients who underwent TCT. Shaded regions represent the standard error of the regression line.



Prediction of Global Cognition Improvement						
Z-Score Cutoff	≥ -1.22	≥ -0.65	≥ -0.38	≥ -0.07	≥ 0.03	≥ 0.55
Sensitivity	100%	92%	83%	58%	58%	42%
Specificity	22%	44%	67%	78%	89%	100%

Prediction of Verbal Learning Improvement						
Z-Score Cutoff	≥ -1.35	≥ -0.96	≥ -0.74	≥ -0.55	≥ 0.18	≥ 0.49
Sensitivity	100%	100%	100%	91%	46%	27%
Specificity	20%	40%	60%	80%	100%	100%

Fig. 3. ROC curve for EEG composite z-scores (baseline and sensitivity to change) cutoffs that can be used to detect true cognitive improvements (Cohen's $d \geq 0.2$; ≥ 2 t-score) in global cognition and verbal learning for patients who underwent TCT.

TCT on global cognition at the group level (Thomas et al., 2018a), the current data found that baseline theta evoked power and phase-locking predicted individual changes in global cognitive functioning secondary to TCT. Thus, patient responsivity to sensory stimuli also has a trait-like utility for predicting global cognitive improvement. Although baseline (trait) MMN activity has been demonstrated to predict global cognitive improvement following TCT (Biagianti et al., 2017), these data are the first to extend these findings to the constituent oscillatory dynamics underlying EAIP, as well as assess both baseline and early-treatment sensitivity measures as predictors of a full course of TCT.

4.2. Implications for gauging patient response to TCT

Patient improvements in cognitive functioning, symptom severity, and functional outcome at the group level are well-documented (Fisher et al., 2016; Mcgurk et al., 2007; Thomas et al., 2018a; Thomas et al., 2018b; Wykes et al., 2011) despite the high variability in individual responses (Murthy et al., 2012). Biomarker-guided clinical trials have identified several neurophysiologic measures of EAIP target engagement that can be used as individualized predictors of TCT outcome (Biagianti et al., 2017; Hochberger et al., 2019a, 2019b; Perez et al., 2017). Our results support the use of multiple neurophysiologic features at baseline and following initial exposure to TCT as an effective means of determining, at the outset of treatment, individuals who are most likely to benefit from therapeutic "doses" of TCT. Baseline evaluation would serve the role of establishing the general propensity for patient cognitive change secondary to the intervention, while assessment of early-treatment sensitivity would directly evaluate a patient's individual neural system engagement in response to the specific modality of TCT. Further, this stage-based model would allow for multiple points of triage for future research examining points of enhancement in patient treatment response (e.g., pharmacologic augmentation, adjunct psychosocial interventions, etc.) (Swerdlow et al., 2018).

Combined with our prior work (see Hochberger et al., 2019a, 2019b), a total of 3 separate baseline EEG biomarkers, 4 separate early-treatment EEG biomarkers, were derived that could be used to predict patient improvements in global cognition and verbal learning respectively. Exploratory analyses using a standardized regression-weighted "sensitivity index" for monitoring the likelihood of improvements secondary to TCT was able to account for approximately 31.2% of the variance in TCT-related global cognition gains, and 41.2% of the variance in TCT-related verbal learning gains. When used as a screening measure to determine the likelihood of a patient benefiting from TCT, these indices presented with high levels of sensitivity and specificity (see Fig. 3). It is possible that these composite scores could thus be used to screen patients at baseline and after the first dose of TCT as a gauge of full course TCT response, informing the appropriateness of continued treatment. However, results from these exploratory analyses are tentative pending validation and refinement in a more robust sample combined with additional demographic, clinical, cognitive, or neurophysiologic variables.

4.3. Limitations

The current findings should be interpreted in the context of some limitations. First, symptom acuity and severity have been suggested as possible moderators of TCT outcome (Lindenmayer et al., 2017), and are particularly relevant to the current study given the cohort of treatment refractory patients recruited from a community-based inpatient care facility. However, prior report on this same sample did not find that symptom severity significantly moderated TCT outcome (Thomas et al., 2018a). Findings from this current study, while important in demonstrating significant TCT benefit among impaired cohorts of patients who need cognitive training the most, might not apply to early illness or less impaired patient populations, particularly given the heterogeneity and complexity of patients and possible secondary impacts on TCT. Nonetheless, the use of combining multiple neurophysiologic features

at baseline and following initial exposure to TCT, presents a promising model for ongoing evaluation of patient outcomes. Second, as noted in our prior reports, attrition was higher in patients who underwent TCT compared to TAU; however, no significant clinical or demographic predictors of attrition could be identified. Thus, it is likely that the higher attrition rate was secondary to the higher time demands required for daily participation in TCT, rather than the intervention itself (Thomas et al., 2018a; Thomas et al., 2018b).

4.4. Future directions

Although no dose-dependent TCT response was observed in the current study (Thomas et al., 2018a) other studies have suggested that more intensive and comprehensive dosing of TCT yields greater stability of long-term gains (Fisher et al., 2009; Fisher et al., 2010; Vinogradov et al., 2012). In addition, although several biomarkers have been proposed to moderate TCT outcome, none of this research has been examined continuously across TCT training sessions, and there is little research examining the long-term stability of the malleability in these EEG biomarkers. Future research would thus benefit from continuous examination of the dose-response relationship to TCT, its intersection with EEG biomarkers predictive of TCT, and the potential stability of the observed sensitivity in EEG activity. Preliminary research examining changes in the EAIP-associated EEG neural substrates have also suggested that TCT induces a dynamic reorganization of the neural architecture and associated resource allocation (Perez et al., 2019) which holds notable benefit for further refinement of potential EEG profiles that can be used to accurately and efficiently gauge patient response to TCT and other procognitive interventions. Finally, validation of the "TCT sensitivity indices" proposed in the current study, particularly regarding the calculation of clinically relevant change thresholds (i.e.: sensitivity and specificity), remains a key step in advancing the clinical application of TCT and improving patient outcomes.

4.5. Conclusion

The advent and refinement of valid and reliable biomarkers that can be used to predict and gauge patient response to procognitive interventions has brought with it the start of a veritable "golden age" of procognitive therapeutics (Vinogradov et al., 2013). Both event-related and oscillatory EEG activity underlying EAIP have been shown to undergo malleable change secondary to TCT. These EEG biomarkers have been demonstrated to predict full-course treatment gains in focal and global cognitive ability in patients with treatment refractory schizophrenia. A tentative optimization of these biomarkers in the form of regression-weighted EEG composite scores also demonstrated utility with high levels of specificity and sensitivity in detecting improvements in global cognition and verbal learning in patients; however, these findings were merely exploratory – replication and validation on a more robust sample is needed before any firm conclusions can be drawn. Despite this, the present results provide an important foundation for the development of clinically relevant neurophysiologic biomarkers that can be applied to refine clinical practice and patient outcomes.

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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 Molina and Treichler, Mr. Nungaray, Ms. Cardoso, and Ms. Sprock were involved in data collection, data processing and quality control, and select portions of the manuscript. Dr. Swerdlow was involved in aspects of the study design and select portions of the manuscript. Dr. Light is the corresponding author and was involved in all aspects of the 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.

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Other than providing support, funding sources for the current manuscript and study did not have any further role in the writing of this manuscript.

Declaration of competing interest

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