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Authors

Hochberger, WC
Joshi, YB
Zhang, W
et al.

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Decomposing the constituent oscillatory dynamics underlying mismatch negativity generation in schizophrenia: Distinct relationships to clinical and cognitive functioning

W.C. Hochberger[a,b], **Y.B. Joshi**[b], **W. Zhang**[b], **M.L. Thomas**[c], **the Consortium of Genomics in Schizophrenia (COGS) investigators**, **D.L. Braff**[b], **N.R. Swerdlow**[b], **G.A. Light**[a,b,*,1]

[a]VISN-22 Mental Illness, Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, United States of America

[b]Department of Psychiatry, University of California San Diego, La Jolla, CA, United States of America

[c]Colorado State University, Department of Psychology, Fort Collins, CO, United States of America

Abstract

Abnormalities in early auditory information processing (EAIP) contribute to higher-order deficits in cognition and psychosocial functioning in schizophrenia. A passive auditory oddball paradigm is commonly used to evoke event-related potential (ERP) measures of EAIP reflecting auditory sensory registration and deviance detection, including mismatch negativity (MMN) and P3a responses. MMN and P3a have been extensively studied in healthy subjects and neuropsychiatric patient populations and are increasingly used as translational biomarkers in the development of novel therapeutics. Despite widespread use, relatively few studies have examined the constituent oscillatory elements and the extent to which sensory registration and deviance detection represent distinct or intercorrelated processes. This study aimed to determine the factor structure and clinical correlates of these oscillatory measures in schizophrenia patients (n=706) and healthy comparison subjects (n=615) who underwent clinical, cognitive, and functional characterization and EEG testing via their participation in the Consortium of Genomics in Schizophrenia (COGS-2) study. Results revealed significant deficits in theta-band (4-7 Hz) evoked power and phase locking in patients. Exploratory factor analyses of both ERP and oscillatory measures revealed two dissociable factors reflecting sensory registration and deviance detection. While each factor shared a significant correlation with social cognition, the deviance detection factor had a unique relationship to multiple cognitive and clinical domains. Results support the continued advancement of functionally relevant oscillatory measures underlying EAIP in the development of precognitive therapeutics.

*Corresponding author at: University of California, San Diego, CA, United States of America. glight@ucsd.edu (G.A. Light).
[1]Mail: 9500 Gilman Drive #0804, La Jolla, CA, USA, 92093.

Conflicts of interest

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

Keywords

Schizophrenia; Mismatch negativity; Early auditory information processing; COGS-2

1. Introduction

Schizophrenia is characterized by a constellation of psychosocial and functional deficits driven by a generalized pattern of cognitive impairment (Bilder et al., 2000; Green et al., 2004; Hochberger et al., 2015). Convergent lines of evidence have shown that abnormalities in early auditory information processing (EAIP) underlie widespread impairments in daily cognitive and psychosocial functioning in patients with schizophrenia (Braff and Light, 2004; Javitt, 2009; Light et al., 2015; Light and Braff, 2005a; Rissling et al., 2014; Suga et al., 2016; Thomas et al., 2017). EAIP is commonly measured via mismatch negativity (MMN) and P3a, event-related potentials (ERP) that are translatable across model systems (Avissar et al., 2017; Näätänen et al., 2007; Thomas et al., 2017). Deficits in MMN and P3a are well-documented in schizophrenia, and since they strongly index the functioning of cognitively and functionally relevant networks, they increasingly used as biomarkers in trials of procognitive treatment strategies (Hochberger et al., 2018; Joshi and Light, 2018; Light and Näätänen, 2013; Light and Braff, 2005a; Perez et al., 2017; Swerdlow et al., 2018; Joshi and Light, 2018). Indeed, MMN and P3a are sensitive to both pharmacologic and non-pharmacologic interventions (Dulude et al., 2010; Hochberger et al., 2018; Kantrowitz et al., 2010; Kawakubo et al., 2007; Lavoie et al., 2017; Perez et al., 2017; Swerdlow et al., 2016), and have been extensively used in animal models of schizophrenia with high translational homology (Amann et al., 2010; Featherstone et al., 2015; Todd et al., 2013).

The most widely used metrics of the MMN-P3a response complex are the amplitudes and latencies calculated from the difference wave of ERPs evoked in response to deviant stimuli after subtracting the responses to standard stimuli (Duncan et al., 2009; Näätänen et al., 2007). Schizophrenia patients show significant amplitude reduction in both MMN and P3a, which likely reflects impairment in auditory discrimination and underlying *N*-methyl-D-aspartate receptor (NMDAR) mediated neuroplasticity (Avissar et al., 2017; Garrido et al., 2009; Javitt et al., 1996; Kaser et al., 2013; Näätänen, 2008). Prior research has established that these MMN deficits are heritable and quantitative endophenotypes of schizophrenia and are significantly correlated with key demographic, clinical, cognitive, and psychosocial functioning (Lee et al., 2014; Light et al., 2015; Light and Näätänen, 2013; Light et al., 2012; Light and Braff, 2005a, 2005b; Rissling et al., 2014; Thomas et al., 2017). Moreover, these deficits appear to be stable over time and generalized across patient subgroups, despite the widespread heterogeneity of clinical symptoms and neurophysiological deficits in schizophrenia (Light et al., 2015).

The MMN-P3a response complex can be further characterized via time-frequency analyses of waveform averages and individual trials, reflecting evoked power and phase locking, respectively (Bates et al., 2009; Javitt et al., 2016; Kaser et al., 2013; Lee et al., 2017). These oscillatory measures may offer particular promise in translational studies given their homology of cross-species responses and their amenability for high throughput screening.

Another benefit of this approach is the characterization of stimulus-locked changes in EEG activity across stimulus types combined with potentially greater characterization of the underlying neural circuitry. Oscillatory information underlying mismatch negativity deconstructs the constituent EEG activity into component parts at a cellular level – furthering downward translation which is key to ongoing development of novel therapeutics (Javitt, 2015; Javitt et al., 2008). Profiles resulting from oscillatory measures reflect differential patterns of EEG responses based on stimulus type, wherein patients exhibit differential alpha and theta suppression in response to standard and deviant stimuli, and concurrent impairment in phase locking (Javitt et al., 2016; Kaser et al., 2013; Lee et al., 2017).

This study aimed to examine patterns of oscillatory activity (evoked power, phase locking) in large, well-characterized cohorts of schizophrenia patients (SZ) and healthy comparison subjects (HCS). Based on prior research (e.g., Javitt et al., 2016; Lee et al., 2017), we hypothesized that patients would evidence significant deficits in both evoked theta-band power and phase locking across both standard and deviant stimuli, as well as to the deviant-minus-standard difference-waves. It is unclear whether schizophrenia-related deficits in amplitude, evoked power, and/or phase locking reflect a generalized impairment in establishing coherent responses to all probe stimuli (Featherstone et al., 2018), or if impairments in multiple electrophysiological features are specific to responses to standard vs. deviant stimulus types. We therefore aimed to leverage the large sample of the Consortium of Genomics in Schizophrenia (COGS-2) database to explore the latent factor structure underlying event-related potentials and oscillatory EEG activity. We hypothesized that 1) dissociable factors would be detected that correspond to responses to standard vs. deviant stimuli (rather than a generalized impairment to both stimulus types or type of oscillatory measure), 2) patient factor scores would reflect significant impairment in these factors relative to healthy comparison subjects, 3) these factors would be significantly correlated with key domains of cognitive and clinical functioning.

2. Methods

2.1. Participants

Recruitment strategy, procedures, and clinical characterization of the study sample have been reported previously (Light et al., 2015). Briefly, participants included 1321 individuals (HCS n=615, SZ n=706) recruited and tested as part of the 5 site Consortium of Genomics on Schizophrenia (COGS-2) study. As noted in our previous reports, the group of schizophrenia patients had a greater proportion of males, were significantly older, and completed fewer years of formal education (Table 1). Participant 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 tobacco) or a history of psychotic disorders in first degree relatives of HCS, and inability to detect 1000 Hz tones ≤40 dB.

2.2. EEG data recording

All 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 (full scale setting 0.25, bandpass filter settings 0.5–100 Hz), and was used for artifact detection. All electrode impedances were below 5kΩ.

2.3. Stimuli and procedures

A duration-deviant auditory oddball paradigm (Light et al., 2015) was used. Binaural tones (1 kHz, 85 dB, with 1 ms rise/fall, stimulus onset-to-onset asynchrony 500 ms) were presented while participants were instructed to watch a silent cartoon video. Standard (*P*=0.90, 50 ms duration) and deviant (*P*=0.10, 100 ms duration) tones were presented in pseudorandom order with a minimum of 6 standard stimuli presented between each deviant stimulus.

2.4. EEG data analyses

All EEG data were processed using BrainVision Analyzer 2.0 (Brain Products GmbH). Pre-processing utilized a digital filter with a 0.1 Hz low-cutoff (12 dB/oct). 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. Standard and deviant waveforms were then generated for each subject, with subsequent difference waves created by subtracting ERPs in response to standard tones from those in response to deviant tones. All measures were extracted from electrode Cz across a −100 to 500 ms epoch. 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 (Brain Products GmbH). Evoked power consisted of the calculation of squared absolute values of the Morlet Complex Wavelet coefficients. Phase locking was also calculated using the Morlet Complex Wavelet, with the phase locking factor (PLF) being the complex values (containing contain both amplitude and phase information for each time-frequency point) derived from the aforementioned wavelet coefficients. As shown in grand average broadband time-frequency plots (Figs. 1 & 2), theta-band activity (4-7 Hz) appeared to be the dominant signal evident in both evoked power and phase locking analyses with no significant activity or group differences in other frequency bands. As such, the area (μV*ms) for the 4-7 Hz frequency layer was then extracted for use in all subsequent statistical analyses.

2.5. Cognitive and clinical assessments

Study participants were assessed on battery of clinical and cognitive measures (Swerdlow et al., 2015), including the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the Wide Range Achievement Test – 4th Edition, Reading Subtest (WRAT-4), and the domain scores from the University of Pennsylvania Computerized

Neurocognitive Battery (PENN CNB: executive-control functions, episodic memory, complex cognitive processing, social cognition, and sensorimotor and motor speed).

2.6. Analytic plan

In order to maximize power and reduce familywise error rate, a multivariate analysis of variance (MANOVA) was used to examine differences in evoked power and phase locking across stimulus type (standard, duration deviant, and deviant-minus-standard differences) across groups (healthy control, schizophrenia). These analyses were performed using a case-control matching function in SPSS, wherein a randomly selected sub-sample of the full dataset were matched on age, sex, and race in order to reduce the potential impact of demographic differences across groups. Sphericity was assessed using Mauchly's Test, with any violations addressed using a conservative approach with a Greenhouse-Geisser correction. Pairwise comparisons utilized a Bonferroni correction.

Exploratory factor analyses using direct oblimin rotation were performed on all EEG variables derived in the current study (i.e., evoked power and phase locking) as well as measures of MMN and P3a amplitude, as previously reported (Light et al., 2015). Kaiser-Meyer-Olkin (KMO) measure was used to determine sampling adequacy, and Bartlett's Test was used to assess sphericity. Initially, separate factor analyses were performed on each group; however, as these models produced identical results, a combined model including both healthy comparison subjects and patients was used in the final analyses.

An additional multivariate analysis of variance (MANOVA) was used to compare factor scores across groups (healthy comparison, schizophrenia). These analyses were performed on the previously described matched sub-sample in order to control for demographic differences across groups. Finally, the rotated factor scores for schizophrenia patients were then correlated with the previously described cognitive test scores, clinical ratings, and demographic variables using multiple correlation in order to examine the profiles associated with these factors. Effect sizes across all analyses were quantified using Cohen's d (d: small=0.20, medium=0.50, large=0.80) and Pearson's correlation coefficient (r: small=0.10, medium=0.30, large=0.50).

3. Results

3.1. ERP differences across patients and controls

Consistent with our hypotheses, evoked power to the standard (F[1874]=4.88, p=0.027, d=0.15), deviant (F[1874]=78.46, $p < 0.001$, d=0.74), and deviant-minus-standard differences (F[1874]=141.72, $p < 0.001$, d=0.81) were significantly reduced in SZ relative to HCS (see Fig. 1). Similarly, phase locking to the standard (F[1874]=53.82, $p < 0.001$, d=0.50), and deviant (F[1874]=222.56, $p < 0.001$, d=1.01) trials was significantly reduced in SZ relative to HCS (see Fig. 2).

3.2 Exploratory factor analyses

An exploratory factor analysis using unweighted least squares factoring with direct oblimin rotation was performed on EEG variables for both schizophrenia patients and healthy

comparison subjects. As expected, KMO and Bartlett's Test were within acceptable ranges (KMO=0.78; $\chi^2[21]=3058.20$, $p < 0.001$). Examination of scree plots revealed two distinct factors (see Fig. 3). These factors clearly sorted according to the stimulus type (i.e., standard vs. deviant/difference) rather than the type of measure (i.e., phase locking vs. evoked power/amplitude). Variables related to deviant stimulus processing (deviant and difference evoked power, deviant phase locking, MMN amplitude, P3a amplitude) loaded onto the first factor ("deviance detection"), which accounted for approximately 62% of variance in the model. Variables related to standard stimulus processing (standard evoked power and phase locking) loaded onto the second factor ("sensory registration"), which accounted for approximately 17% of the variance in the model. Rotated factor loadings are shown in Table 2.

3.3 Characterization of EEG factors

3.3.1. Factor score comparison across groups—Consistent with our hypotheses, schizophrenia patients exhibited a significant and robust deficit in both deviance detection ($F[1827]=158.15$, $p < 0.001$, $d=0.88$) with significant but less-severe impairments in sensory registration ($F[1827]=13.90$, $p < 0.001$, $d=0.26$), when factor scores were compared across groups (see Table 3).

3.3.2. Correlations with patient profiles—Correlation analyses using EFA-derived EEG factor scores revealed significant relationships among demographic, clinical, cognitive, clinical, and functional variables (Fig. 4). Notably, the "deviance detection" factor showed small-to-moderate relationships with executive functions (abstraction and flexibility, working memory), non-verbal memory, premorbid function, and patient outcome (psychiatric hospitalization rate) – a pattern which was not seen for the "sensory registration" factor. However, both factors significantly were correlated with social cognition.

4. Discussion

The current findings identified significant reductions of theta-band evoked power and phase locking underlying standard, deviant, and difference waveforms, consistent with previous research (Javitt et al., 2016; Lee et al., 2017). Although not directly evaluated in the current study, comparison of effect sizes of oscillatory EEG and ERP amplitude measures suggest that the integration of both metrics can provide complementary information regarding EAIP. The magnitude of patient deficits in oscillatory EEG warrants continued examination – particularly regarding its relationship to patient functioning in key clinical and cognitive domains (Hochberger et al., 2018; Lee et al., 2014; Light and Näätänen, 2013; Light and Braff, 2005a, 2005b; Perez et al., 2017; Rissling et al., 2014), as well as the development of novel CNS therapeutics (Javitt, 2015; Javitt et al., 2008; Lainscsek et al., In Press).

Factor analyses of ERP and oscillatory EEG revealed the presence of unique profiles based on stimulus-type, rather than whether the measure was derived from single trials (i.e., phase locking) vs. averages (i.e., evoked power). This structure is consistent with models of automatic and attention-dependent auditory processing as hypothesized by Näätänen et al. (2011). Interestingly, although both factors contributed a substantial amount of variance, the deviance detection factor was byfar the largest contributor to the model (62% of the

variance), though responses to standard stimuli (sensory registration factor) did contribute to a non-trivial proportion of variance (17%).

As expected, when factor scores were compared across groups schizophrenia patients exhibited significant deficits in both deviance detection and sensory registration. Prior research has characterized EAIP deficits in schizophrenia in terms of both ERP (Lee et al., 2014; Light et al., 2015; Light and Näätänen, 2013; Light et al., 2012; Light and Braff, 2005a, 2005b; Rissling et al., 2014; Thomas et al., 2017) and oscillatory measures (Javitt et al., 2016; Lee et al., 2017). The current findings are the first to link this pattern of impairments to deficits in two distinct factors underlying EAIP. Although patients exhibited impairment in the initial sensory registration of auditory stimuli the effect was small; the primary factor driving patient deficits was impairment in deviance detection. Indeed, this pattern could also be seen across metrics, where the individual variables with high loadings on the deviance detection factor generally accounted for medium-to-large effect sizes regardless of metric (i.e., single-trial vs. averages). This pattern of results underscores both the relative importance of deviance detection abnormalities rather than sensory registration impairments in schizophrenia, as well as the use of multi-feature electrophysiologic composite indices to derive latent factors of complex neural activity.

In schizophrenia patients, these latent factors were significantly associated with functioning across a variety of cognitive domains including premorbid function, and key clinical characteristics (number of psychiatric hospitalizations). Notably, EEG activity related to deviant stimulus processing showed significant correlations with several key domains of higher-order cognitive (executive functions, non-verbal memory, social cognition, premorbid function) and clinical functioning (number of psychiatric hospitalizations). Interestingly, the sensory registration factor was not uniquely related to any key domains of patient functioning. Thus, these data are the first to demonstrate that EAIP in patients is related to two functionally and quantitively distinct subprocesses with meaningful contributions to key patient outcomes, with the majority of this effect being driven by patient deficits in deviance detection.

4.1. Limitations

The use of a simplified (2-channel) recording system in this large multisite study precluded the examination of other much more powerful and sensitive EEG metrics that can only be derived from high-density recordings (e.g., source analysis, PCA of EEG waveforms). While this system served its original purpose of basic characterization of MMN and P3a for large-scale genomic association studies, it is important to emphasize that high- and low-density recording systems take comparable amounts of time for preparation, but high-density records offer the added benefit of substantial improvements in signal-to-noise ratios via the use of advanced preprocessing algorithms that capitalize on the spatiotemporal relationships contained within the recordings. In fact, it is widely understood that scalp-channel measures of averaged event-related potentials (ERPs) mix contributions from distinct cortical source-area generators and non-brain sources of artifacts (e.g., electrical line noise, muscle, eye blinks, eye movements) thus diluting the functional relevance of channel-based ERP measures. Independent component analysis has emerged as a gold-standard for disentangling

brain and artifact sources for the more precise removal of artifacts and quantification of cortical source contributions. Moreover, even if only simple correlations from a single electrode or region is ultimately desired, higher density arrays substantially improve the sensitivity to detect patient deficits, clinical correlations, and response to interventions (e.g., Rissling et al., 2014). Other advantages of higher-density recordings include improved quality assurance and data verification via inspection of individual response topographies and global field power to give confidence that a questionable quality recording provided plausible responses. Certainly, source localization and other advanced analytic approaches for mechanistic exploration of important findings can only be pursued with higher density recordings.

It is also important to note that although the correlational analyses performed in this large sample identified several statistically significant associations, the effect sizes for the correlations between the factor loadings and the aforementioned cognitive, clinical, and demographic variables were only modest. It is notable that ~21% of the variance in the current EFA model could not be explained and is therefore considered residual error. It is likely that the improved data processing afforded by higher density recordings would have been more sensitive to group deficits and clinical correlations but this assertion must be empirically tested. Finally, the current quantification focused primarily on stimulus-locked EEG, though the examination of other novel (i.e., induced, non-linear) EEG activity is another area of intensive focus for future studies (Lainscsek et al., In Press).

4.2 Conclusion and future direction

Amidst a range of electrophysiologic metrics used to quantify EEG deficits in schizophrenia patients, a pattern of two distinct factors reflecting sensory registration and deviance detection were found in the current analyses. Moreover, patient deficits were primarily accounted for by deviance-detection, which was also correlated with cognitive function and key demographic variables related to illness. Taken together, these findings suggest that the greatest contributor to EAIP deficits in schizophrenia patients is related to deviance-detection, which also contributes to higher order impairment in clinical, cognitive, and psychosocial functioning. Future research would benefit from further examination of EEG composite scores which could be used to advance the development of CNS therapeutics (Yash and Light, 2018).

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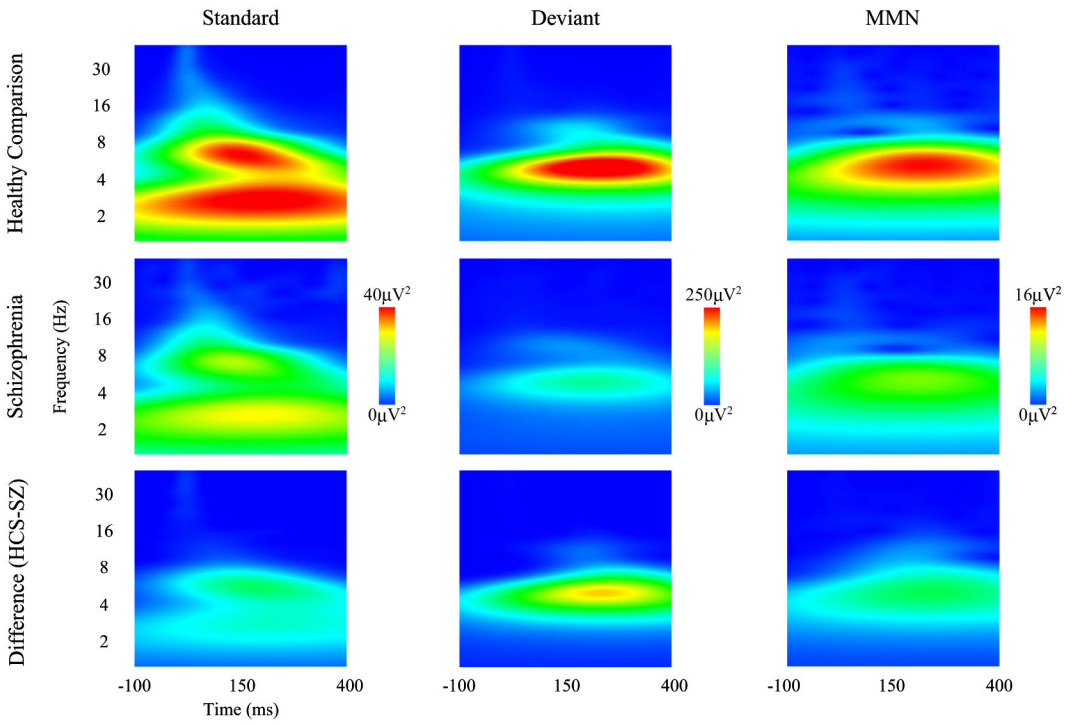

Fig. 1.

Evoked power across frequency bands separated across stimuli type (standard, duration deviant), MMN (standard minus deviant), and group (healthy comparison subjects, schizophrenia, healthy comparison minus schizophrenia).

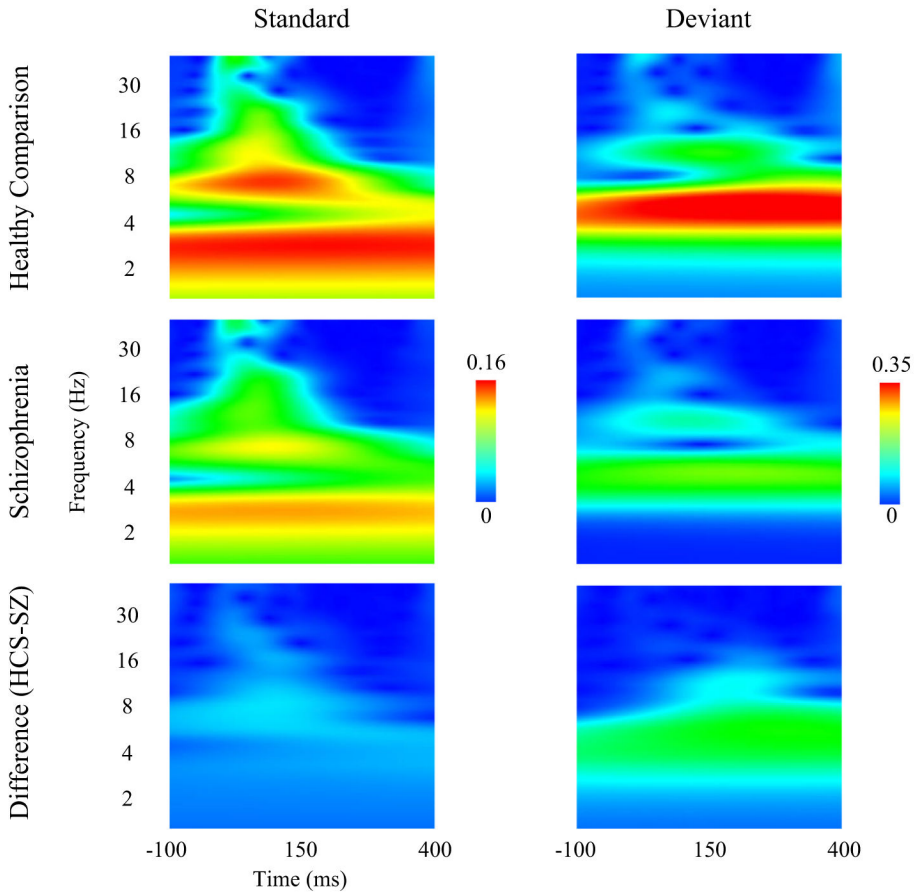

Fig. 2.

Phase locking (inter-trial coherence) across frequency bands separated across stimuli type (standard, duration deviant, MMN [standard minus deviant]), and group (healthy comparison subjects, schizophrenia, healthy comparison minus schizophrenia).

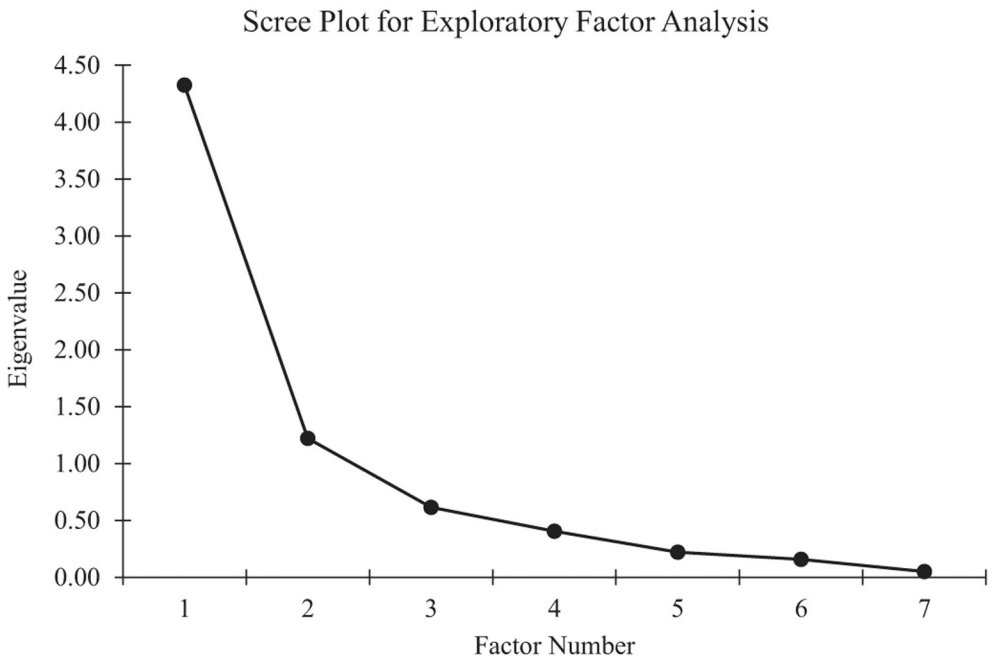

Fig. 3.

Scree plot of the eigenvalues for factors derived from exploratory factor analyses on healthy comparison subjects and schizophrenia patients.

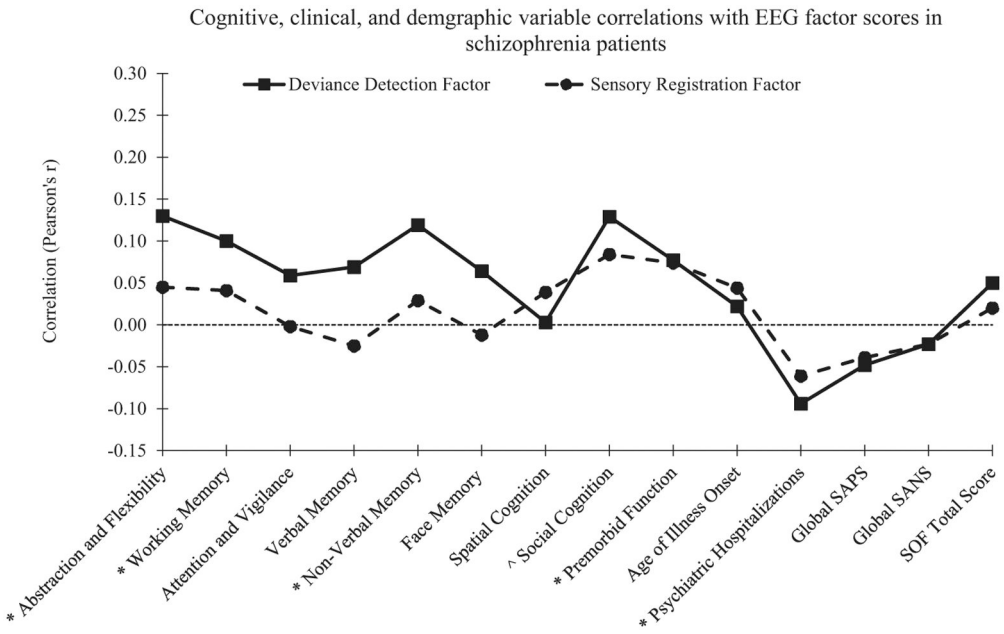

Fig. 4.

Cognitive and clinical/demographic variable loadings onto the extracted stimulus-driven EEG factors for schizophrenia patients. Significant correlations ($p < 0.05$) are denoted by asterisks (*) for only the first factor, plus signs (+) for only the second factor, and up-arrows (^) for both factors.

Table 1

Cognitive, clinical, and demographic characteristics of the sample

	HCS	SZ	*P*-value	Effect size
	n=615	n=706		
Age	39.32 (13.16)	46.19 (12.68)	< 0.000	−0.53
Education	14.92 (2.17)	12.69 (2.08)	< 0.000	1.05
WRAT reading	106.12 (9.76)	95.24 (12.66)	< 0.000	0.97
Male	40.8%	54.2%	< 0.000	0.16
Female	36.6%	22.6%		
Caucasian	61.3%	41.9%	< 0.000	0.22
African-American	21.3%	39.9%		
Other	17.4%	18.1%		
Age of onset		22.31 (7.22)		
SAPS global score		6.97 (4.14)		
SANS global score PENN CNB		11.66 (4.79)		
Abstraction and flexibility	0.00 (1.00)	−0.75 (0.95)	< 0.000	0.77
Working memory	0.07 (0.95)	−1.03 (1.73)	< 0.000	0.82
Attention and vigilance	0.09 (0.77)	−0.62 (1.31)	< 0.000	0.68
Verbal memory	0.02 (0.87)	−0.56 (1.10)	< 0.000	0.59
Non-verbal vigilance	0.01 (0.89)	−0.66 (0.90)	< 0.000	0.75
Face memory	0.00 (0.91)	−0.74 (1.05)	< 0.000	0.76
Spatial cognition	0.09 (0.95)	−0.57 (1.24)	< 0.000	0.60
social cognition	0.05 (0.94)	−0.93 (1.39)	< 0.000	0.84

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=PENN Computerized Neurocognitive Battery.

Effect sizes are reported as Cohen's *d* for continuous variables, and Cramer's V (phi) for categorical variables.

Table 2

Rotated factor loadings from EFA of healthy comparison and schizophrenia patient EEG data.

	Deviance detection	Sensory registration
Deviant evoked power	0.84	
Deviant phase locking	0.88	
Difference wave evoked power	1.00	
MMN amplitude	−0.74	
P3a amplitude	0.79	
Standard evoked power		1.00
Standard phase locking		0.46

Small loadings (< 0.30) are suppressed.

Table 3

EEG variable and factor score comparisons across groups.

	HCS n=585	SZ n=676	*P*-value	Effect size
Evoked power				
Standard stimulus	2855.62 (3761.55)	2311.93 (3513.50)	0.027	0.15
Deviant stimulus	22,072.47 (22,877.02)	9283.49 (11,569.59)	< 0.000	0.74
Difference-wave	1547.09 (676.84)	1068.23 (498.94)	< 0.000	0.81
Phase locking				
Standard stimulus	19.23 (9.42)	14.88 (8.07)	< 0.000	0.50
Deviant stimulus	40.36 (15.88)	25.50 (13.49)	< 0.000	1.01
Amplitude				
MMN	−2.25 (1.18)	−1.25 (0.89)	< 0.000	−0.97
P3a	2.81 (1.76)	1.46 (1.11)	< 0.000	0.94
Factor score				
Deviance detection	0.34 (0.94)	−0.40 (0.74)	< 0.000	0.88
Sensory registration	0.18 (1.02)	−0.079 (0.97)	< 0.000	0.26

Evoked power and phase locking values are the area (μV * ms) across the 4-7 Hz frequency layer.

Amplitude values are calculated in microvolts (μV).

Effect sizes are reported as Cohen's *d*.