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ERP Generator Patterns in Schizophrenia During Tonal and Phonetic Oddball Tasks: Effects of Response Hand and Silent Count

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Abstract

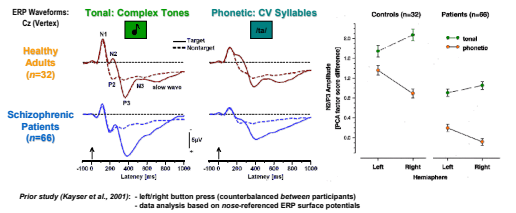
P3 amplitude in schizophrenia has been reported to be more reduced over left than right hemiscalp during auditory oddball tasks, which has been interpreted as left-lateralized dysfunction. However, the contributions of methodological factors (stimulus properties, response mode, recording reference), which affect event-related surface potential (ERP) topographies, remain unclear. We recorded 31-channel ERPs from 23 schizophrenia patients and 23 age- and gender-matched healthy adults (all right-handed) during tonal and phonetic oddball tasks, varying response mode (left press, right press, silent count) also within subjects. Patients performed adequately but were slower. ERP generator patterns were summarized by temporal PCA (unrestricted Varimax) from reference-free current source density (CSD; spherical spline Laplacians) waveforms used to sharpen scalp topographies. CSD factors were unambiguously related to known ERP components and highly comparable between groups. Both groups showed asymmetric frontolateral and parietotemporal N2 sinks and asymmetric centroparietal P3 sources for targets (tonal R>L, phonetic L>R), but patients had reduced frontocentral N2 sinks and reduced midparietal P3 sources. In both groups, left or right press produced opposite, region-specific asymmetries originating from central sites, modulating the N2/P3 complex, and a larger parietal P3 source compared to silent count. Data suggest overall reduced neural generators in schizophrenia during auditory oddball tasks, with both groups showing comparable topographic effects of task and response mode.

Introduction

Medial and lateral temporal lobe regions are involved in the generation/modulation of auditory ERPs. Temporal lobe abnormalities in schizophrenia (STG, hippocampus) may contribute to auditory N2 and P3 reductions in schizophrenia (e.g., McCarley et al., 1993).

Some evidence suggests that *both* structural and functional abnormalities in schizophrenia may affect primarily the left brain (language-related deficit in the supratemporal plane; e.g., Crow, 1990), whereas other evidence suggests that both hemispheres are equally impaired.

Most ERP evidence relied on simple target detection tasks with pure tones. Instead, we used complex tones and syllables as oddball stimuli that require a differential involvement of left and right hemispheric regions, which is reflected in task- and regional-specific N2-P3 asymmetries in healthy adults. However, a large group of patients having schizophrenia spectrum disorders (*n*=66) showed comparable task-specific ERP asymmetries, however, on a lower level (Kayser et al., 2001).



Prior study (Kayser et al., 2001): - left/right button press (counterbalanced *between* participants)
- data analysis based on *nose*-referenced ERP surface potentials

ERP component structure and topography are affected by
- **response demands (e.g., button press vs. silent count)**
- **EEG recording reference (e.g., linked mastoids vs. nose)**

Objective: To what extent are reductions and/or topographic alterations of the N2-P3 complex in schizophrenia affected by these methodological aspects?

Participants

		Schizophrenic Patients (*n* = 23; 15 male)			Healthy Controls (*n* = 23; 15 male)		
Variable		Mean	SD	Range	Mean	SD	Range
	Age (years)	31.2	10.4	18-53	30.5	8.2	21-51
	Education (years)	13.6	2.3	10-18	15.2	1.5	12-18
	Handedness (LQ)[a]	70.7	34.7	0-100	70.3	23.0	5-100
	Onset age (years)	21.7[b]	7.8	8-43			
	Illness duration (years)	7.7[b]	9.0	0-32			
	Total BPRS	39.4[c]	9.8	24-64			
	PANSS general	33.8[c]	9.1	17-58			
	PANSS positive	18.0[c]	5.8	10-29			
	PANSS negative	14.6[c]	4.8	7-23			

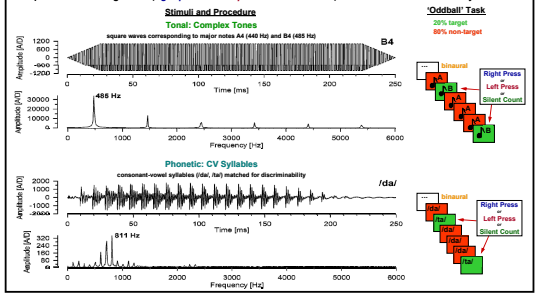
DSM-IV Criteria: Schizophrenia, paranoid (*n*=11); Schizophrenia, undifferentiated (*n*=6); Schizophrenia, disorganized (*n*=1) — *n*=18
Schizoaffective Disorder, depressive (*n*=3); Schizoaffective Disorder, bipolar (*n*=2) — *n*=5
Medication/Status: Olanzapine (*n*=5); Clozapine (*n*=2); Haloperidol (*n*=1); Risperidone (*n*=1); Fluphenazine (*n*=1) — *n*=10
Unmedicated > 14 days — *n*=13

- no history of any psychopathology or neurology disorder
- matched to patients for core demographics

[a]Laterality quotient (range -100 to 100; see Oldfield, 1971). [b]*n* = 21. [c]*n* = 20.

Tonal and Phonetic Oddball Tasks

- **12 80-trial blocks (960 trials total); each block combined one *task* (*tonal* or *phonetic*) with one *response mode***
- **each trial:**
  - **tonal *or* phonetic binaural stimuli (250 ms)**
  - **detect targets (button press or count, 1,750 ms ISI)**
- **response mode assignment (*right press* or *left press* or *silent count*) counterbalanced *within* subjects**



Behavioral Data

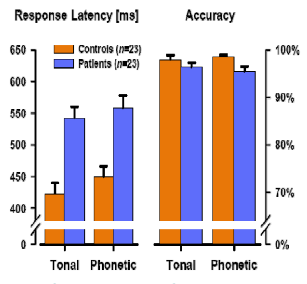


Fig. 1. Mean (SEM) response latency and percentage of correct responses for healthy adults and schizophrenic patients comparing correct button press responses during tonal and phonetic tasks. Schizophrenic patients performed more slowly but adequately. Both groups showed somewhat longer response latencies for phonetic compared to tonal stimuli.

Current Source Densities

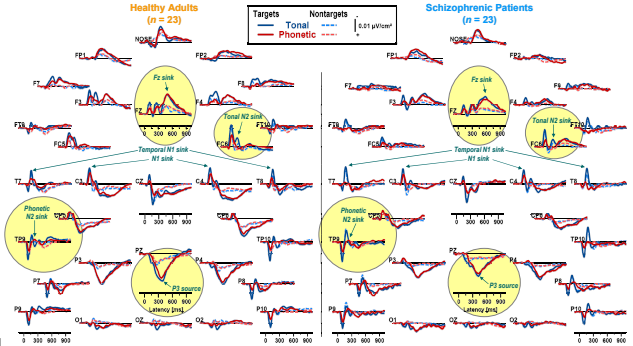


Fig. 2. Reference-free current source density (CSD) [μV/cm²] waveforms (spherical spline Laplacians; Perrin et al., 1989) to targets and nontargets for 23 healthy adults (left panel) and 23 schizophrenic patients (right panel) comparing tonal and phonetic stimuli at all 31 recording sites (averaged across response mode). In both groups, early stimulus-specific CSD components were well-defined over the Sylvian Fissure (central N1 and temporal N1 sinks). Region-specific target effects of N2 sinks (tonal: right-frontocentral, phonetic: left-parietotemporal), mid-parietal P3 sources (P3, Pz, P4) and mid-frontal sinks (Fz) were also evident in both groups, however, appeared to be reduced in patients.

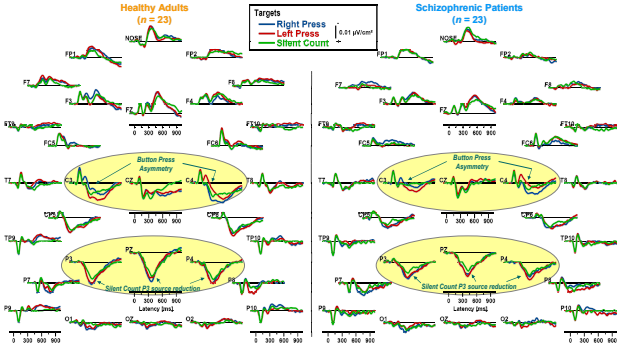
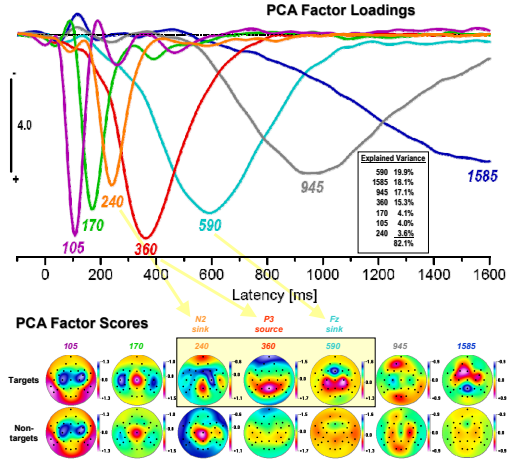


Fig. 3. Reference-free current source density (CSD) [μV/cm²] waveforms (spherical spline Laplacians; Perrin et al., 1989) to targets for 23 healthy adults (left panel) and 23 schizophrenic patients (right panel) comparing right press, left press, and silent count at all 31 recording sites (averaged across tonal and phonetic tasks). A sustained medial-central sink activity contralateral to the responding hand (button press conditions) was superimposed on N2 sinks and P3 sources in both groups (sites C3 and C4). Moreover, both groups showed a reduced P3 source for silent count compared to both button press conditions (sites P3, Pz, and P4).

PCA Factor Loadings



PCA Factor Scores

Fig. 4. Time courses and percentage of explained variance of Varimax-rotated covariance loadings for the first five PCA components, and corresponding factor score topographies of task means (pooled across group and condition). CSD factors *240*, *360* and *590*, which closely corresponded to subcomponents of the N2/P3 complex, were selected for further analysis of target-related activity.

Topographies of PCA Factor Scores

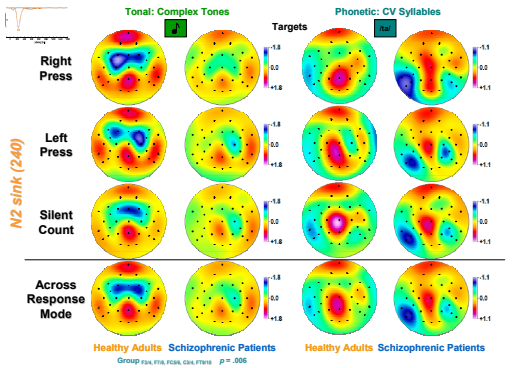


Fig. 5. Mean *N2 sink (240)* topographies of PCA factor scores for 23 healthy adults and 23 schizophrenic patients for tonal and phonetic targets. Medialfrontal N2 sinks in the tonal task were reduced in schizophrenia, but left parietotemporal N2 sinks in the phonetic tasks were well-preserved in schizophrenic patients. Response mode effects were particularly evident in the tonal task but comparable across groups.

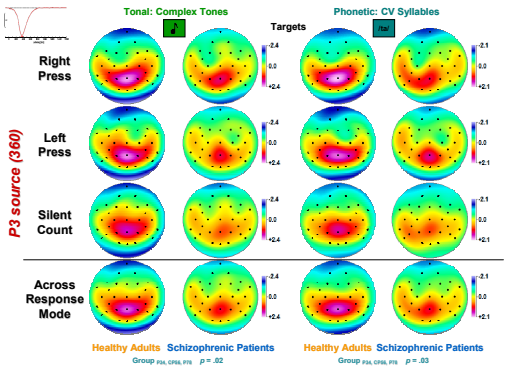
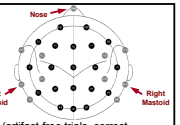


Fig. 6. Mean *P3 source (360)* topographies of PCA factor scores for 23 healthy adults and 23 schizophrenic patients for tonal and phonetic targets. Midparietal P3 sources were reduced in schizophrenia for both tasks. Response mode effects were evident in both tasks, depressing P3 source activity for button presses at medial-central sites contralateral to the response hand, but were again comparable across groups.

ERP Recording and Data Analysis



- ERPs recorded from 30 scalp placements using an electrode cap with a nose reference
- EEG data acquired at .1-30 Hz band pass (-6dB/octave)
- Bipolar horizontal and vertical EOGs; **blink reduction** (continuous EEG) **using spatial SVD**; horizontal eye artifacts (epoched EEG) by linear regressions of lateral EEG differences (Fp2-Fp1, etc.)
- **2,000 ms epochs**, 200 ms pre-stimulus baseline, ERP averages (artifact-free trials, correct responses only) low pass filtered at 12.5 Hz (-24dB/oct.), 100 ms baseline correction
- **reference-free current source densities** (CSD; spherical splines surface Laplacian; Perrin et al., 1989) computed for each ERP (sharpen topographies, eliminate volume-conducted activity from distant regions)
- CSDs submitted to ***unrestricted* temporal principal components analysis (PCA)** derived from the covariance matrix [401 variables = samples –200 to 1,800 ms; 17,112 observations = *Subjects* (46) x *Electrode Sites* (31) x *Task* (2) x *Response Mode* (3) x *Condition* (2)], followed by Varimax rotation of covariance loadings (Kayser & Tenke, 2003, 2006a,b), to identify and measure neuronal generator patterns
- ***CSD data***: Meaningful PCA components spanning time interval (200 .. 800 ms) of targeted ERP components within the N2-P3 complex: factor scores at representative recording sites (for targets only) submitted to repeated measures ANOVA with *Group* (patients, controls), *Gender* (male, female), *Task* (tonal, phonetic), *Response Mode* (right press, left press, silent count) and *Site/Hemisphere* as between- and within-subjects factors
- ***Behavioral data*** (button press responses only): Percentage of correct responses and mean response latency of correct responses submitted to repeated measures ANOVA with *Group* (patients, controls), *Gender* (male, female), *Task* (tonal, phonetic) and *Response Hand* (right, left) as between- and within-subjects factors

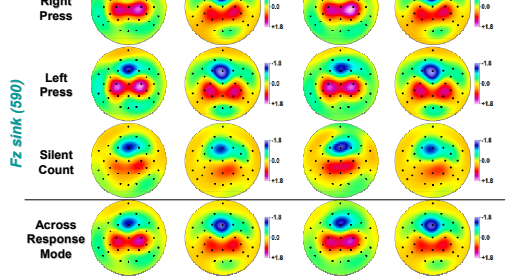


Fig. 7. Mean *Fz sink (590)* topographies of PCA factor scores for 23 healthy adults and 23 schizophrenic patients for tonal and phonetic targets. Response-related midfrontal sinks were comparable across tasks and groups as was the corresponding medial-central source activity, which was, however, smaller for silent count compared to button presses. Generator patterns underlying this late CSD component were again highly similar in both groups.

Summary and Conclusions

- **All oddball tasks produced distinct CSD components and topographies that were concisely summarized by temporal PCA and directly reflect the known neurophysiolology of auditory processing and response requirements**
- **The reference-free CSD components were highly comparable in schizophrenia patients and controls, revealing asymmetric, task-dependent N2 sinks and P3 sources that were equally modulated by response mode**
- **Tonal N2 sinks over frontocentral sites (but not phonetic N2 sinks over parietal sites) and P3 sources over mid-parietal sites were reduced in patients, indicating overall reduced neural generators in schizophrenia during auditory oddball tasks**
- **These reductions were not, however, a function of electrode site and response mode, which together with preserved phonetic N2 sinks challenges the notion that left-lateralized P3 reductions in schizophrenia during simple auditory oddball tasks with pure tones reflect language-related dysfunctions in schizophrenia**
- **Asymmetric reductions in prior studies likely result from different sample characteristics (e.g., severity or chronicity) rather than response mode**
- **Transient stimuli (pure tones < 50ms) used in prior studies may be processed differently than the longer 250 ms stimuli used in this study (Tallal et al., 1998)**

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