Auditory and Visual Word Recognition Memory (WRM) in Schizophrenia: Stimulus- and Response-Locked Neuronal Generator Patterns

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Abstract

Background: Studying visual WRM with nose-referenced EEGs, we reported a preserved ERP 'old-new effect' (enhanced parietal positivity 300-800 ms to correctly recognized repeated items) in schizophrenia.[1] However, patients showed reduced early negative potentials (N1, N2) and poorer WRM. Because group differences in neuronal generator patterns (e.g., dipole orientation) may be masked by choice of EEG recording reference and component definition, the current study applied a new methodological approach that combines surface Laplacians and principal components analysis. We investigated stimulus modality and disentangled stimulus- and response-related contributions to neuronal generators of WRM. **Methods:** Stimulus- and response-locked 31-channel epochs were recorded from 20 schizophrenic (15 male) and 20 age-, gender-, and handedness-matched healthy adults during parallel visual and auditory continuous WRM tasks.[2] To identify and measure neuronal generator patterns underlying ERPs, unrestricted Varimax-PCA was performed on their reference-free current source densities (spherical splines). **Results:** Poorer (78.2 ±18.7% vs. 87.8 ±11.3% correct) and slower (958 ±226 vs. 773 ±206 ms) performance in patients was accompanied by reduced stimulus-related left parietal P3 sources and vertex N2 sinks (both overall and old/new effects) but modality-specific N1 sinks were not significantly reduced. A distinct, 50-ms post-response mid-frontal sink (FRN) was markedly attenuated in patients. Reductions were more robust for auditory stimuli. However, patients showed increased lateral-frontotemporal sinks (T7 maximum) concurrent with auditory P3 sources. **Conclusions:** Electrophysiologic correlates of WRM deficits in schizophrenia suggest functional impairments of posterior cortex (stimulus representation) and anterior cingulate cortex (response monitoring), primarily affecting memory for spoken words.

Introduction

- Schizophrenia patients show **impairments of verbal episodic memory** [3], which may be linked to **left medial temporal lobe dysfunction**.[4,5]
- One **electrophysiological correlate** of **recognition memory** (judging items as *old* or *new*) is the ERP ***Old-New Effect***:
  - begins at 200–400 ms, lasts 300–500 ms (or longer), more positive to *old*
  - overlaps at least two distinct ERP components: *N400*/*N2* and *P600*/*P3b*
  - scalp distribution differs from *N2* and *P3* topographies
  - mostly left-lateralized posterior parietal (conscious recollection, *P600*)
  - words, pictures, faces, etc.
- Using visual word stimuli, we found poorer WRM and reductions of early negative ERP components (N1, N2) and N2-P3 amplitude in schizophrenia, particularly over the left parietal region, but **no P3 amplitude reductions** and a largely **preserved** ERP **old-new effect**.[1]
- P3 reductions in schizophrenia are **less robust for visual** than auditory stimuli.[6]
- ERP group differences may be masked by the choice of the **EEG recording reference location** (e.g., nose, linked mastoids, average) and the **definition and measurement** of appropriate **ERP components** (e.g., specific time windows for peak or integral amplitudes), which crucially affect **component interpretation** (e.g., polarity, topography, generator) and **statistical analysis**.[7,8]
- These limitations can be overcome by combining **reference-free current source density (CSD)** transformations and **temporal PCA**.[9,10]
- This CSD-PCA approach separated modality-independent old/new effects from stimulus-related parietal P3 source (pre-response) and response-related mid-frontal sink (post-response) activity in 40 healthy adults during visual and auditory WRM tasks.[2]
- By taking advantage of the large sample of healthy adults (N = 40) of this previous study, the current study compared neurophysiologic correlates of visual and auditory WRM in carefully matched samples of 20 schizophrenia patients and 20 healthy controls.

Objective:
- compare schizophrenia patients and healthy controls during closely matched auditory and visual continuous word recognition memory tasks
- exploit CSD-PCA approach for improved characterization of ERP old/new effects
- perform separate analysis of stimulus- and response-locked activity

Participants

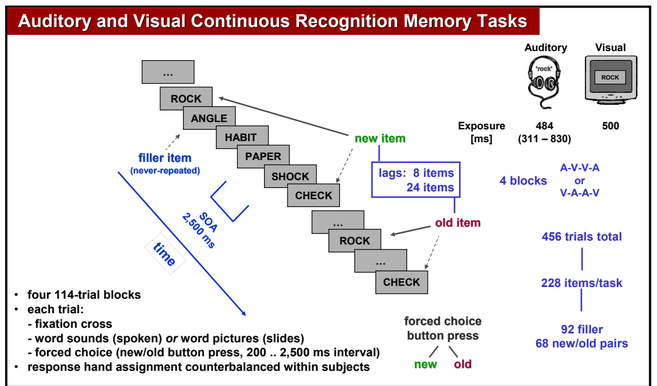
DSM-IV criteria: **schizophrenia** (**paranoid, *n* = 11; undifferentiated, *n* = 4**), **schizoaffective disorder** (**bipolar type, *n* = 3**), **psychosis NOS** (***n* = 2**); med-free for at least 14 days prior to testing (*n* = 11), risperidone (*n* = 3), clozapine (*n* = 2), olanzapine (*n* = 2), aripriprazole (*n* = 1), fluphenazine (*n* = 1)

	Patients (*n* = 20, 15 male)			Healthy Controls (*n* = 20, 15 male)			
Variable	Mean	SD	Range	Mean	SD	Range	
Age (years)	29.0	7.7	19 - 44	28.9	6.4	20 - 42	
Education (years)	13.4	2.2	9 - 16	16.1	2.1	12 - 20	$p < .001$
Handedness (LQ)	79.8	30.8	0 - 100	74.9	24.8	0 - 100	
Verbal IQ (WAIS)	102.4[a]	10.9	87 - 123				
Onset age (years)	21.1	6.1	7 - 35				
Illness duration (years)	6.2[b]	9.7	0 - 37				
Total BPRS	32.8[b]	7.9	22 - 48				
PANSS general	28.4[b]	7.2	16 - 38				
PANSS positive	14.3[b]	5.9	7 - 26				
PANSS negative	12.3[b]	5.5	7 - 27				

Notes. [a] *n* = 7. [b] *n* = 19.

- **no history of any psychopathology or neurological disorder**
- **paid $15/h**

Auditory and Visual Continuous Recognition Memory Tasks



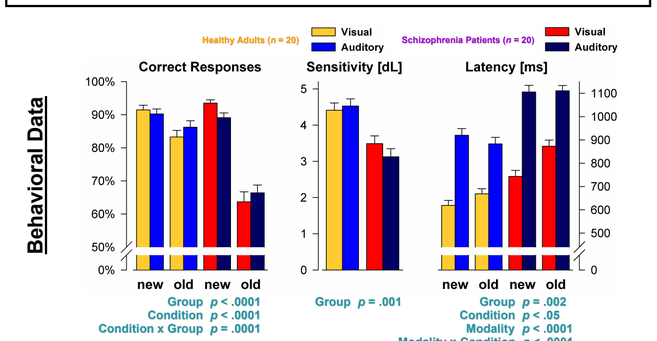
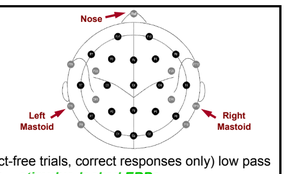


Fig. 1. Mean (SEM) percentage of correct responses, logistic *d'*-like sensitivity measure d_L, and response latency of correct responses revealed well above chance performance for both groups. Still, patients' accuracy was poorer compared to controls, but this was not affected by modality. Patients had also about 200-ms longer response latencies than controls, but this overall group difference did again not interact with modality or condition. However, as expected, mean response latency was about 200-300 ms longer for auditory than visual stimuli, and this modality effect interacted with condition.

ERP Recording and Data Analysis



- ERPs recorded from 30 scalp placements using an electrode cap with a nose reference, 200 samples/s
- 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** (300 ms pre-stimulus), averages (artifact-free trials, correct responses only) low pass filtered at 12.5 Hz (-24dB/oct.), 100 ms baseline correction = ***stimulus-locked ERPs***
- **1,000 ms subepochs** (700 ms pre-response) derived from stimulus-locked ERPs using the same stimulus-locked baseline (100 ms pre-stimulus) = ***response-locked ERPs***
- **reference-free current source densities (CSD)** (spherical splines surface Laplacian [11]) computed for each ERP (sharpen topographies, eliminate volume-conducted activity)
- **stimulus- and response-locked CSDs** separately submitted to ***unrestricted* temporal principal components analysis (PCA)** derived from the covariance matrix [input data matrices: 400 (stimulus-locked samples –300 to 1695 ms) *or* 201 variables (response-locked samples -700 to 300 ms), 2480 observations = 40 participants x 2 conditions (new/old pooled across short and long lags) x 31 electrode sites (including the nose)] **for each modality**, followed by Varimax rotation of covariance loadings [7,9,10], to identify and measure modality-dependent neuronal generator patterns and isolate their stimulus and response contributions
- Meaningful PCA components: factor scores submitted to repeated measures ANOVA using *Group* (patients, controls) as a between-subjects factor and *Condition* (old, new) and *Site* and/or *Hemisphere* (representative subsets of recording locations) as within-subjects factors

Surface Potentials

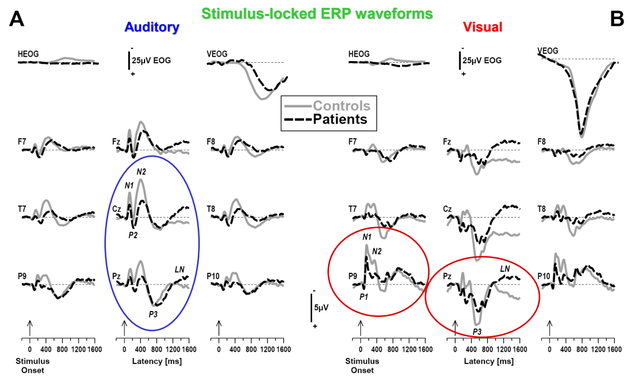


Fig. 2. Nose-referenced, stimulus-locked (-200 to 1600 ms) grand average event-related surface potential (ERP) [μV] waveforms (100 ms prestimulus baseline) for auditory (A) and visual (B) stimuli (averaged across old and new items) comparing 20 patients and 20 healthy controls at selected lateral (F7/8, T7/8, P9/10) and midline (Fz, Cz, Pz) recording sites. Horizontal and vertical electrooculograms (EOG) are shown at a smaller scale before blink correction. Distinct ERP components are labeled for auditory stimuli at Cz (N1, P2, N2), for visual stimuli at P9 (P1, N1, N2), and for both modalities at Pz (P3, LN).

Current Source Densities

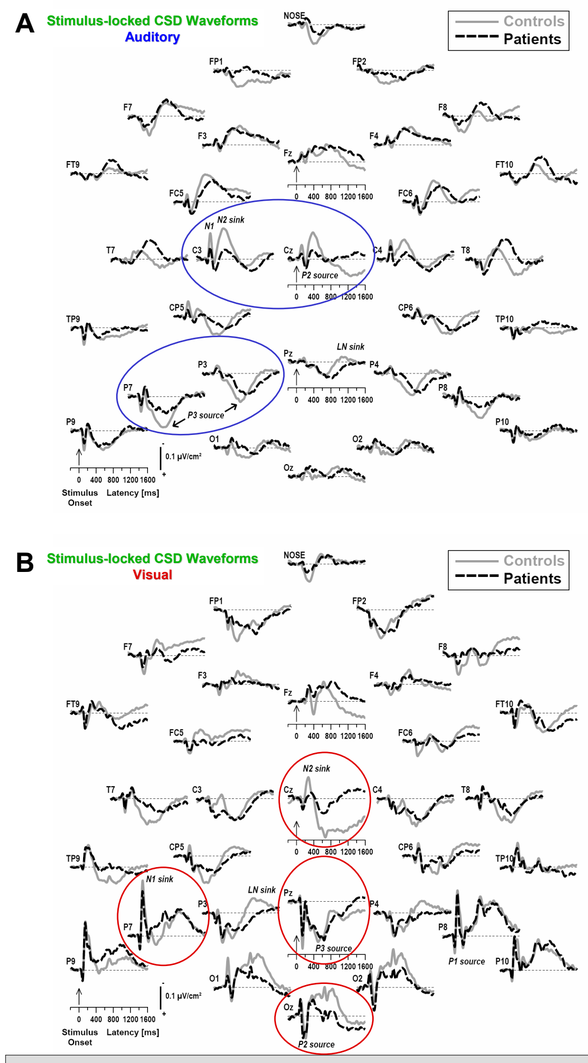


Fig. 3. Stimulus-locked, reference-free current source density (CSD) [μV/cm²] waveforms (spherical spline Laplacians) for auditory (A) and visual (B) stimuli (averaged across old and new items) comparing 20 patients and 20 controls at all 31 sites. Distinct *auditory* CSD components included central N1 and N2 sinks (approximate peak latencies 120 and 420 ms at C3 for controls), central P2 (200 ms at Cz) and lateral-posterior P3 sources (620 ms at P7). Distinct *visual* CSD components included inferior lateral-parietal N1 sinks (approximate peak latency 145 ms at P7 for controls), occipital P2 sources (210 ms at Oz), a central N2 sink (270 ms at Cz), and mid-parietal P3 sources (500 ms at Pz).

Stimulus-locked

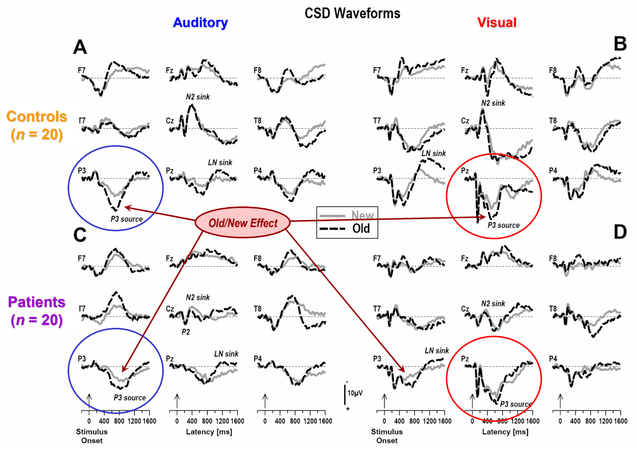


Fig. 4. Stimulus-locked CSD waveforms from controls (A, B) and patients (C, D) for auditory (A, C) and visual (B, D) stimuli comparing old and new stimuli at selected lateral (F7/8, T7/8, P3/4) and midline (Fz, Cz, Pz) sites. Increased medial- and mid-parietal P3 sources (P3/4, Pz) and lateral-frontal sinks (F7/8) were seen for old compared to new auditory and visual stimuli in both groups. These old/new effects, however, were generally smaller in patients.

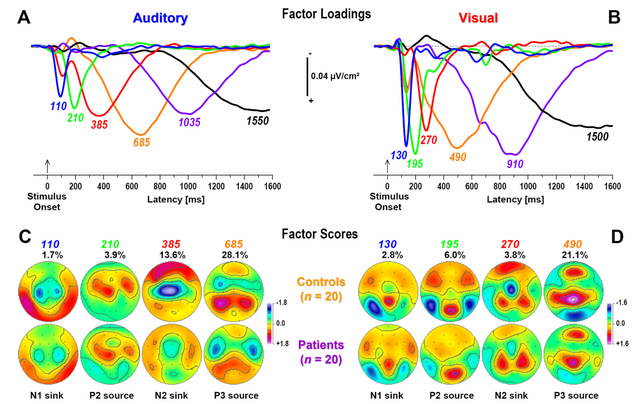


Fig. 5. Unrestricted PCA solutions using auditory (A, C) or visual (B, D) stimulus-locked CSD waveforms. A, B: Time courses of Varimax-rotated covariance loadings for the first six CSD factors extracted for auditory (86.5% total variance explained) or visual (85.2%) stimuli. Labels indicate the peak latency of the factor loadings relative to stimulus onset. C, D: Corresponding factor score topographies (nose at top) with percentage of explained variance for the earliest four factors in each PCA solution (peak latency < 900 ms) corresponding to N1 and N2 sinks and P2 and P3 sources for each modality, separately plotted for controls and patients. Across modalities, the vertex N2 sink was significantly reduced in patients compared to controls (at Cz: auditory factor *385*, $F_{[1,38]}$=9.79, p=.003; visual factor *270*, $F_{[1,38]}$=6.94, p=.01). There were no significant group differences for N1 sink (auditory factor *110* at C3/4; visual factor *130* at P7/8, P9/10, O1/2).

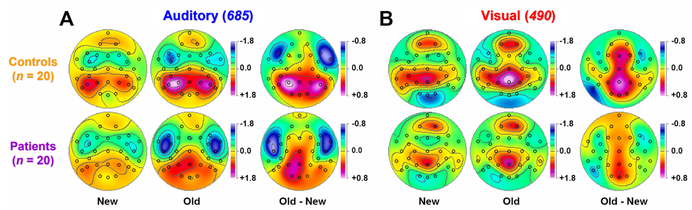


Fig. 6. Mean topographies of CSD factor scores for PCA components corresponding to auditory (A; factor *685*) and visual (B; factor *490*) stimulus-locked P3 source. Topographies are shown for new and old stimuli and their respective old-minus-new difference for controls and patients. Marked old/new effects were observed over parietal sites (auditory at P3/4, P7/8, CP5/6; visual at Cz, Pz; both $F_{[1,38]}$>26.7, both p<.0001), but were more robust in controls than patients (group × condition at P3/4, P7/8, CP5/6: auditory, $F_{[1,38]}$=13.2, p =.0008; visual, $F_{[1,38]}$=5.22, p=.03). Moreover, patients had overall reduced auditory P3 source ($F_{[1,38]}$=19.5, p=.0001). P3 source was less left-lateralized in patients (simple hemisphere effects for controls only). The parietal P3 source was accompanied by lateral frontotemporal sinks, which were increased in patients at lateral-temporal sites only (at T7/8, $F_{[1,38]}$=14.3, p=.0005).

Summary and Conclusions

- **Poorer performance in patients was paralleled by reduced left-lateralized parietal P3 source amplitude and asymmetry.**
- **A stimulus-related, left-lateralized parietal old/new effect was present in patients but reduced compared to controls.**
- **These reductions in schizophrenia were more robust for the recognition memory of spoken (auditory) than read (visual) words.**
- **These neurophysiologic effects are not due to slower responses in patients as demonstrated by the response-locked analysis.**
- **Because early neuronal generators (N1) were largely preserved, perceptual and attentional deficits in schizophrenia are not likely the cause for these impairments in word recognition memory.**
- **However, prominent vertex N2 reductions (ACC) in schizophrenia across modalities suggest a stimulus categorization deficit.**
- **Marked reductions of a mid-frontal response-related negativity (FRN) implicate anterior cingulate cortex (ACC) dysfunction in schizophrenia.**
- **Electrophysiologic correlates of WRM deficits in schizophrenia suggest functional impairments of posterior cortex (stimulus representation) and ACC (response monitoring).**

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Response-locked

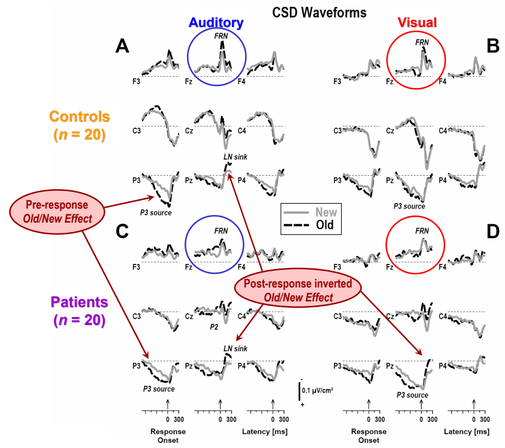

Fig. 7. Response-locked CSD waveforms (-700 to 300 ms, 100 ms baseline preceding *stimulus* onset) at selected midline (Fz, Cz, Pz) and adjacent medial sites (F3/4, C3/4, P3/4) comparing new and old items for each group and modality. A distinct mid-frontal response-related negativity (FRN) terminated the preceding P3 source in all conditions, giving rise to a late inverted old/new effect (LN sink) over mid-posterior sites. However, the focal Fz sink was markedly reduced in patients.

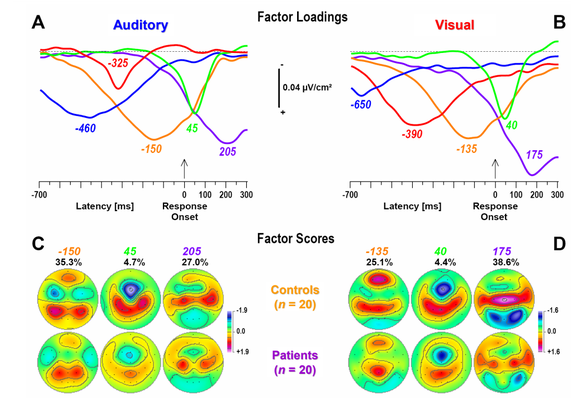

Fig. 8. Unrestricted PCA solutions using auditory (A, C) or visual (B, D) response-locked CSD waveforms. A, B: Time courses of Varimax-rotated covariance loadings for the first five CSD factors extracted for auditory (90.7% total variance explained) or visual (92.6%) stimuli. C, D: Corresponding factor score topographies for the three factors in each PCA solution corresponding to P3 source (peak latencies -150 and -135 ms), FRN (45 and 40 ms), and LN sink (205 and 175 ms) for each modality. The response-related midfrontal auditory sink (factor *45*: Fz) was significantly reduced in patients compared with controls ($F_{[1,38]}$=9.16, p=.004).

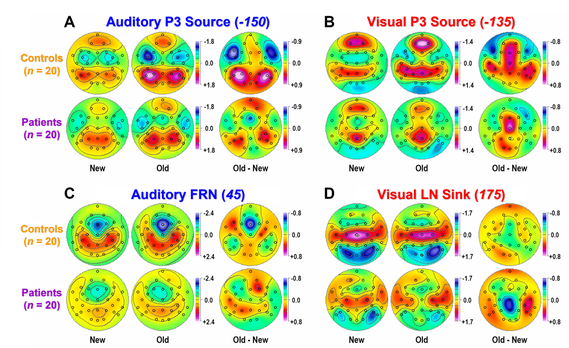

Fig. 9. Mean topographies of CSD-PCA components corresponding to auditory (A; factor *-150*) and visual (B; factor *−135*) response-locked P3 source, auditory FRN (C; factor *45*) and visual LN sink (D; factor *175*). The response-locked P3 source effects largely matched the stimulus-locked data. An old-greater-than-new auditory FRN (*45* at Fz) was present in controls only ($F_{[1,38]}$=10.5, p=.003) but not patients ($F_{[1,38]}$<1.0, *ns*). The visual LN sink (factor *175* at O1/2) was reduced in patients ($F_{[1,38]}$=10.8, p=.002), but inverted old/new effects at mid-centroparietal sites (Cz, Pz; $F_{[1,38]}$=46.0, p<.0001) were more robust in patients (group × condition, $F_{[1,38]}$=11.6, p=.002).

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