Auditory Hallucinations and Early Visual Processing Deficits in Schizophrenia: Reference-free ERPs During the Recognition of Words and Faces

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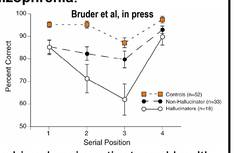
Abstract

Background: Event-related potentials (ERPs) reflect the hierarchy of regional brain activity during the information processing sequence. Reductions of early ERP components in schizophrenia have been inconsistently observed, which may stem from differences in patients' symptoms. Importantly, N1 reductions to tones over left temporal cortex have been reported for psychotic patients during periods of auditory hallucinations. **Methods**: Taking advantage of two 67-channel ERP data sets recorded during recognition memory (RM) and working memory (WM) paradigms using words and faces, we compared right-handed patients who either reported experiencing auditory hallucinations (n = 19/16 for RM/WM) or not (n = 32/35) and healthy adults (n = 44/40). ERPs were transformed into reference-free current source density (CSD) waveforms (spherical spline surface Laplacian), which included a distinct N1 sink (approximate peak latency 150 ms) at inferior lateral-parietal sites (P7/8, P9/10), which was right-lateralized for faces (N170) but strongly left-lateralized for words. CSDs were submitted to unrestricted Varimax-PCA separately for each paradigm to quantify N1 sink activity. **Results & Conclusions**: In both paradigms, N1 sink was substantially reduced in hallucinators compared with controls and non-hallucinators, who did not differ from each other. These N1 sink reductions were most robust for words over the left hemisphere, suggesting an interference of activity in temporoparietal language regions of hallucinators during early visual processing of words, which may contribute to their verbal memory deficits during RM and WM tasks.

Introduction

- Reductions of early visual (e.g., Neuhaus et al 2010; Yeap et al 2006) and auditory (e.g., Salisbury et al 2010) ERP components in schizophrenia are often considered as evidence of **sensory processing deficits**, which may represent an **endophenotype for schizophrenia**.
- **Impairments of memory functions** are one of the most significant **cognitive deficits in schizophrenia**, and yet few studies in this area have addressed the critical problem of biological and clinical **heterogeneity in schizophrenia**.
- Schizophrenic **patients with auditory hallucinations have a greater verbal working memory (WM) deficit** on the auditory word serial position task (WSPT) when compared to non-hallucinators (Bruder et al, in press).



- Using two ERP data sets recorded from a large sample of schizophrenia patients and healthy controls during recognition memory (RM) and working memory (WM) paradigms using words and faces, subgroups were created by separating patients who reported experiencing auditory hallucinations in the past week (SAPS auditory hallucination item ≥ 1) from those who did not.
- The **visual N1 to words is strongly left-lateralized** in healthy adults, with a maximum over the inferior lateral-parietal region (i.e., secondary visual cortex; e.g., Kayser et al 1999, 2007, 2009, 2010).
- The dependency of surface potentials on a **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) are two recurring problems in ERP research, which crucially affect **component interpretation** (e.g., polarity, topography, generator) and **statistical analysis** (e.g., Kayser & Tenke 2003; Tenke & Kayser 2005).
- These limitations can be overcome by combining **reference-free current source density (CSD)** transformations and **temporal principal components analysis (PCA)** to identify relevant, data-driven components (Kayser &Tenke 2006a,b).

Objective:
- use CSD-PCA approach to quantify neuronal generator patterns underlying visual ERPs (i.e., N1 sink activity over lateral inferior-parietal regions)
- compare N1 sink amplitude for schizophrenia patients with and without auditory hallucinations to healthy controls

Participants

Means and Standard Deviations (SD) for Demographic and Clinical Variables

DSM-IV Criteria			Hallucinators		Non-hallucinators		Healthy Controls	
Schizophrenia			Recognition Memory		n = 19, 9 female		n = 32, 14 female	n = 44, 26 female
Paranoid	18	18	Working Memory		n = 16, 8 female		n = 35, 15 female	n = 40, 22 female
Undifferentiated	14	16	Variable		Mean	SD	Mean	SD	Mean	SD
Residual		1	Age (years)		29.8	10.2	28.6	8.0	26.2	6.2
Schizoaffective					32.1	11.2	28.9	8.2	26.7	6.9
Depressed	8	5	Education (years)		14.2	2.6	14.3	2.4	16.3	2.1
Bipolar	7	8			14.0	2.5	14.0	2.7	16.3	2.2
Psychosis NOS	4	3	Handedness (EHI-LQ)		72.8	27.7	75.0	20.2	75.3	20.0
					77.9	25.0	78.3	18.3	74.7	19.7
Medication Status			Verbal IQ (WAIS)		102.7	16.0	102.9	14.9	• no history of any psychopathology or neurology disorder
Unmedicated > 14 days	20	22			103.3	17.8	99.2	16.7	
Clozapine	2	3	Onset age (years)		22.4	6.6	20.8	5.1	
Risperidone	6	7			24.2	6.3	20.4	5.4	
Olanzapine	3	3	Illness duration (years)		7.5	7.6	7.8	9.0	• matched to patients for core demographics
Quetiapine	4	3			7.9	9.0	8.5	8.9	
Ziprasidone	8	7	Total BPRS [a]		45.7	15.8	31.0	10.4	
Aripriprazole	8	6	PANSS general [a]		43.4	13.2	33.3	10.6	
					37.4	13.8	26.9	8.7	
			PANSS positive [a]		35.3	9.3	29.1	8.8	
					19.2	7.4	12.2	5.4	
			PANSS negative [a]		18.8	7.9	13.7	5.3	
					16.6	6.4	12.2	5.2	
					15.9	5.5	12.4	5.3	

Note. [a] Hallucinators differ significantly from Nonhallucinators ($p \leq .02$).

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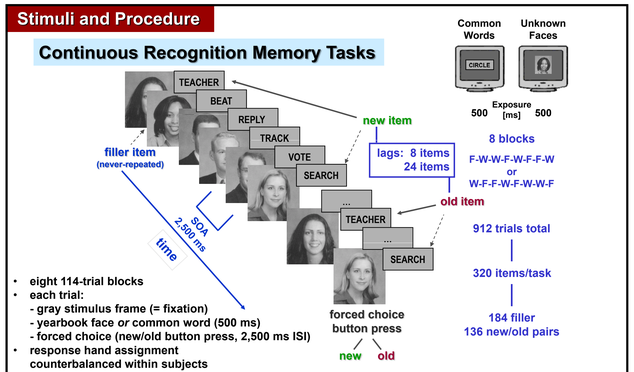
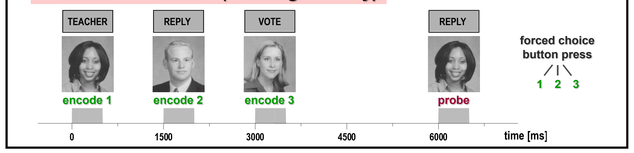
Stimuli and Procedure

Continuous Recognition Memory Tasks

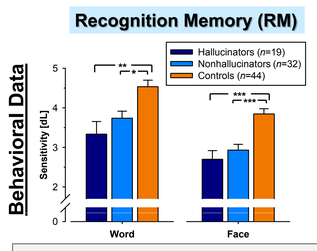


- **eight 114-trial blocks**
- **each trial:**
  - **gray stimulus frame (= fixation)**
  - **yearbook face *or* common word (500 ms)**
  - **forced choice (new/old button press, 2,500 ms ISI)**
- **response hand assignment counterbalanced within subjects**

Serial Position Tasks (Working Memory)



Recognition Memory (RM)



Working Memory (WM)

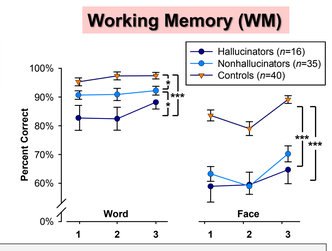
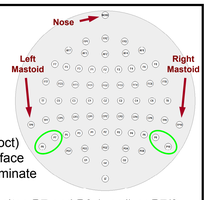


Fig. 1. Mean (±SEM) performance accuracy during RM and WM tasks using words or faces. Overall, remembering faces was more difficult than remembering words. Patients performed more poorly than controls, but hallucinators did not differ from nonhallucinators, except for the WM word serial position task.

ERP Recording and Data Analysis



- Continuous DC (24-bit A/D, 256 Hz) EEGs using an electrode cap, **67 scalp sites**, active recording reference (BioSemi)
- Amplifier drift eliminated by 2nd degree Polynomial high pass filter
- Bipolar horizontal and vertical EOG; **spatial SVD blink reduction**; horizontal eye artifact reduction (epoched EEG, linear regression)
- **1,500 ms epochs**, 100 ms pre-stimulus baseline, ERP averages (artifact-free trials, correct responses only) low pass (12.5 Hz, -24 dB/oct)
- **reference-free current source densities** (CSD; spherical splines surface Laplacian; Perrin et al., 1989) to sharpen ERP topographies and to eliminate volume-conducted activity from distant regions
- **CSDs temporally adjusted for N1 peak latency** for each task, using sites P7 and P9 (word) or P7/8 and P9/10 (face), to create optimized epochs (-50 .. 400 ms) focused on N1 sink activity
- for each paradigm (RM, WM), CSD epochs focused on N1 (-50 .. 400 ms = 116 samples) submitted to ***unrestricted* temporal principal components analysis (PCA)** derived from the covariance matrix, followed by Varimax rotation of covariance loadings (Kayser & Tenke, 2003, 2006a, 2006b), to quantify neuronal generator patterns underlying N1
- ***CSD data***: identify PCA components corresponding to visual N1 sink activity and submit factor scores at **representative inferior lateral-parietal recording sites** to **repeated measures ANOVA** with *Group* (hallucinators, nonhallucinators, controls), *Task* (word, face), *Condition* (RM: new, old, filler; WM: encode, probe), *Hemisphere* (LH, RH) and Site (P7/8, P9/10) as between- and within-subjects factors
- ***Behavioral data***: performance accuracy measures (RM: sensitivity [d_L]; WM: percent correct, chance levels linearly scaled to 50% correct) submitted to repeated measures ANOVA with *Group* (hallucinators, nonhallucinators, controls), and *Task* (word, face), *Condition* (RM: lag [short, long]; WM: serial position [1, 2, 3]) as between- and within-subjects factors

Summary and Conclusions

- **Patients and controls revealed highly comparable N1 sink peaks and topographies** (Figs. 2-3).
  - approximate 150 ms peak latency
  - inferior lateral-parietal maximum (P7/8, P9/10)
  - concisely summarized by temporal PCA

  } Word: LH >> RH; Face: LH < RH
- **Across memory paradigms, hallucinators had markedly reduced N1 sinks for words *and* faces compared to healthy controls and nonhallucinators, particularly over the left hemisphere** (Fig. 4).
- **In contrast, both hallucinators and nonhallucinators performed more poorly than controls across paradigms and both word and face tasks; however, hallucinators performed more poorly than nonhallucinators during the *word* working memory paradigm** (Fig. 1).
- **These findings are consistent with N1 reductions to tones in psychotic patients during periods of auditory hallucinations as opposed to symptom-free intervals** (Hubl et al 2007) **and fMRI evidence revealing differences between hallucinators and nonhallucinators** (Ford et al 2007; Wible et al 2009).
- **Results provide further neurophysiological evidence of early visual processing deficits in schizophrenia.**
- **While these findings support the value of a symptom-based approach for dealing with the heterogeneity of schizophrenia, visual N1 reductions may not represent a biological marker for schizophrenia *per se*.**

Current Source Densities

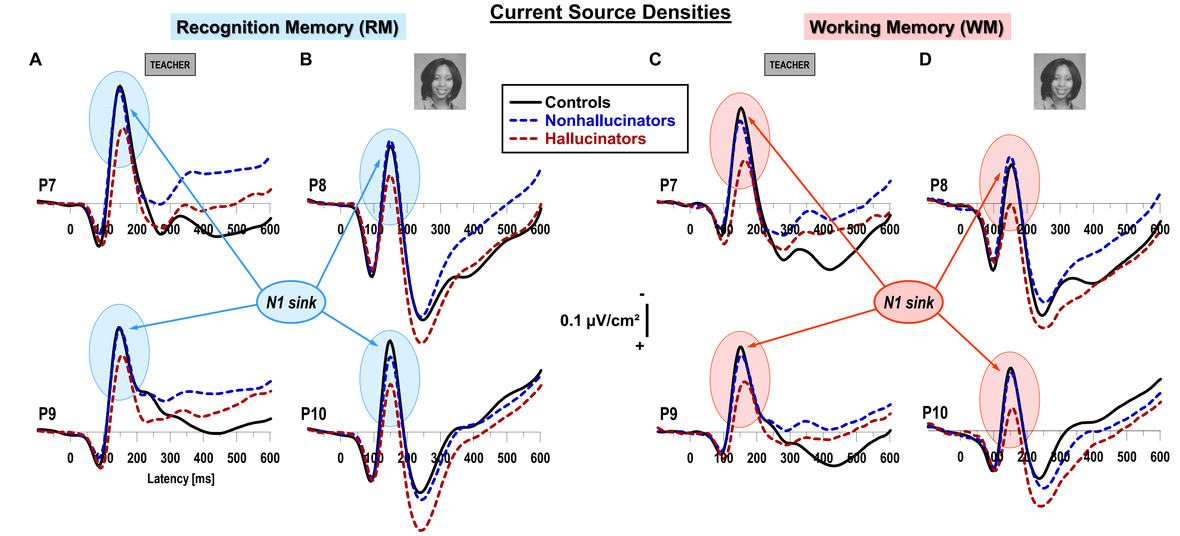


Fig. 2. Grand mean reference-free CSD waveforms for **controls**, **nonhallucinators**, and **hallucinators** during RM and WM paradigms using words (**A**, **C**) or faces (**B**, **D**). Shown are inferior lateral-parietal sites where N1 sink (approximate peak latency 150 ms) was most prominent: over the left hemisphere for words (**P7**, **P9**) and over the right hemisphere for faces (**P8**, **P10**). Whereas virtually no difference in N1 sink amplitude was observed between healthy controls and schizophrenic patients not reporting auditory hallucinations, visual N1 sink amplitude appeared to be markedly reduced in hallucinators.

CSD-PCA Factor Loadings and Scores

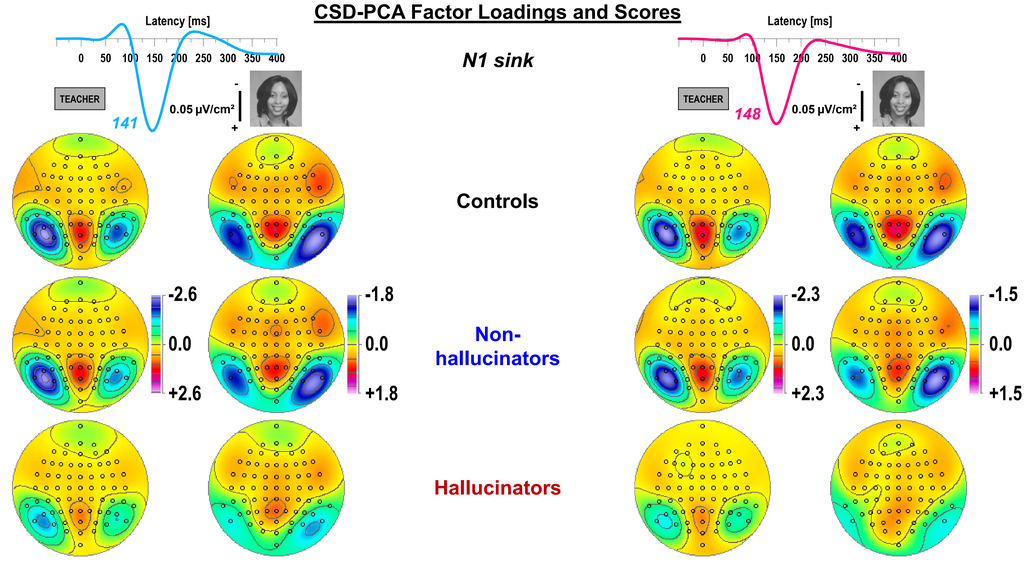


Fig. 3. Unrestricted PCA solutions using CSD subepochs optimized for N1 sink extraction. For each paradigm, one PCA factor uniquely corresponded to prominent N1 sinks over inferior lateral-parietal sites (RM: 141 ms peak latency, 16.4% explained variance; WM: 148 ms, 14.4%). Across paradigms, N1 sinks were strongly left-lateralized for words (columns 1 and 3), and slightly right-lateralized for faces (columns 2 and 4). In contrast to **controls** (top row) and **nonhallucinators** (middle row), **hallucinators** had markedly reduced N1 sinks with attenuated hemispheric asymmetries.

ANOVA Means

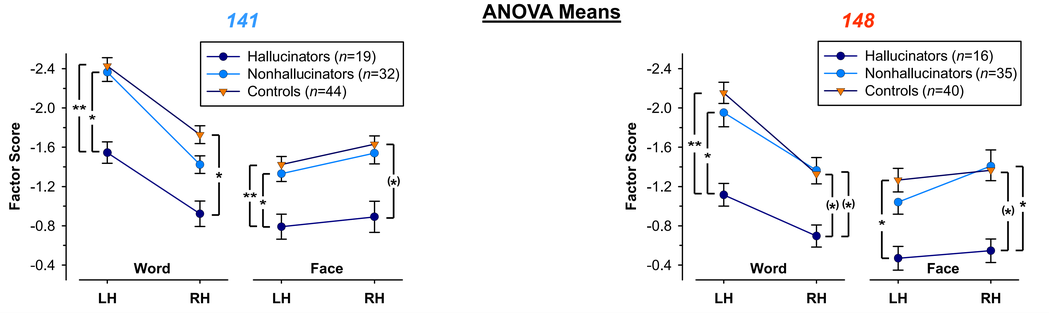


Fig. 4. Pooled means (±SEM) of **N1 sink** (mean scores of factors *141* [RM] and *148* [WM]) at inferior lateral-parietal sites (P7/8, P9/10) with ANOVA significance levels of simple group comparisons for each task and hemisphere. For both paradigms, overall main effects of *Group* (RM: $F_{[1,92]} = 3.20$, $p = .04$; WM: $F_{[1,88]} = 2.95$, $p = .06$) originated from reduced N1 sinks in **hallucinators** compared to **controls** (RM: $p = .02$; WM: $p = .02$) and **nonhallucinators** (RM: $p = .06$; WM: $p = .04$), whereas **controls** and **nonhallucinators** did not differ in N1 sink amplitude.