Auditory Hallucinations in Schizophrenia are Associated with a Neurophysiological Deficit in Early Visual Processing

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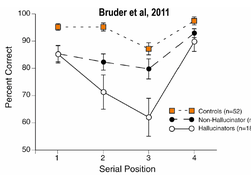
Abstract

Background: Prior studies suggest that auditory hallucinations interfere with processing of spoken words or tones. However, this hypothesis has rarely been tested using event-related potentials (ERPs). We examined visual ERPs of schizophrenia patients who are prone to auditory hallucinations. **Methods**: Using 67-channel ERPs recorded during recognition and working memory paradigms with words or faces, we compared right-handed schizophrenia patients who either reported auditory hallucinations (AH, *n* = 26) or not (NH, *n* = 49) and healthy controls (HC, *n* = 46). ERPs were transformed into reference-free current source density (CSD) waveforms, which included distinct N1 sinks (approximate peak latency 150 ms) over lateral inferior-parietal sites, which were strongly left-lateralized for words but right-lateralized for faces (N170). After individually adjusting for N1 sink peak latency, CSDs were submitted to unrestricted Varimax-PCA to quantify N1 sink activity. **Results**: N1 amplitude was substantially reduced in AH compared with NH and HC, who did not differ from each other. This reduction was present for words and faces in both memory paradigms. The difference in N1 between AH and NH was not due to differences in overall severity of symptoms or performance accuracy, with both groups showing comparable memory deficits. Although N1 reduction in AH was greatest over the left hemisphere and for words, there was no statistical support for N1 reduction to be dependent on stimulus or hemisphere, and all groups revealed similar stimulus-dependent N1 hemisphere asymmetries. **Conclusions**: These findings extend previous reports of auditory N1 reductions in patients with auditory hallucinations, suggesting a broader early perceptual integration deficit that is not limited to the auditory modality and occurs during both verbal and nonverbal memory tasks.

Introduction

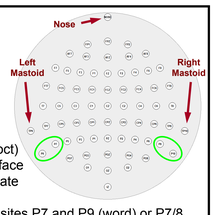
- Reductions of early visual (e.g., Neuhaus et al 2011; Yeap et al 2006) and auditory (e.g., Salisbury et al 2010) ERP components in schizophrenia are often considered as evidence of **sensory (bottom-up) processing deficits**, which may represent an **endophenotype for schizophrenia** (e.g., Javitt 2009).
- **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 2011).



- Several lines of evidence suggest that **auditory verbal hallucinations** involve the **left temporal lobe** (e.g., Badcock & Hugdahl 2012; van Lutterveld et al 2011), suggesting the use of stimuli known to differently engage the left or right hemisphere in early perceptual processing.
- 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), whereas the **visual N1 to faces is right-lateralized** (N170) (e.g., Kayser et al 2010).
- Using two existing 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 (AH)** in the past week (SAPS auditory hallucination item ≥ 1) from **those who did not (NH)**.
- 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 early visual perceptual processing (i.e., N1 sink activity over lateral inferior-parietal regions)**
- **examine whether patients' propensity to experience auditory hallucinations affects early visual processing**
- **if patients prone to having auditory hallucinations show reduced visual N1 sinks to words and/or faces, this would suggest a broader, modality-unspecific, cognitive deficit rather than a deficit caused by acoustical interference (i.e., hearing voices)**

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***: for each memory paradigm, 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), *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

Participants

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

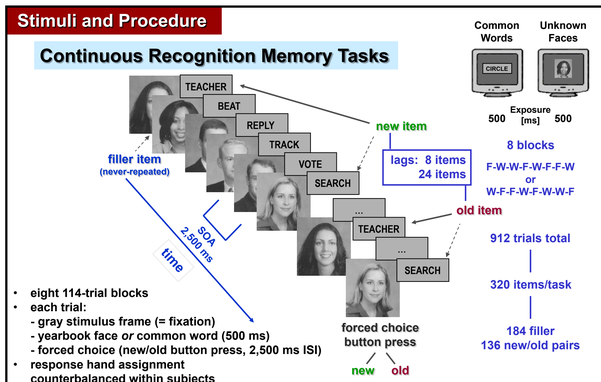
Table 1. Means (SD) for demographic and clinical variables, DSM-IV criteria, medication status, and sample sizes for each paradigm.

Paradigm	Recognition Memory (RM)						Working Memory (WM)					
Group[a]	AH (*n* = 19)		NH (*n* = 32)		HC (*n* = 44)		AH (*n* = 21)		NH (*n* = 47)		HC (*n* = 44)	
Gender (male/female)	10/9		18/14		18/26		12/9		26/21		19/25	
Age (years)	29.8	(10.2)	28.6	(8.0)	26.2	(6.2)	30.6	(11.0)	28.8	(8.0)	26.4	(6.6)
Education (years)[b]	14.2	(2.6)	14.3	(2.4)	16.3	(2.1)	13.6	(2.8)	13.8	(2.6)	16.3	(2.1)
Handedness (LQ)[c]	72.8	(27.7)	75.0	(20.2)	75.3	(20.0)	74.5	(28.3)	78.2	(19.4)	74.7	(19.9)
Verbal IQ (WAIS)[d]	102.7	(16.0)	102.9	(14.9)			102.9	(18.0)	98.0	(15.4)		
Onset age (years)	22.4	(6.6)	20.8	(5.1)			22.8	(6.1)	21.1	(6.0)		
Illness duration (years)	7.5	(7.6)	7.8	(9.0)			7.9	(9.0)	7.7	(8.4)		
Total BPRS[e]	45.7	(15.3)	31.1	(10.3)			47.7	(15.5)	32.7	(9.8)		
PANSS general[e]	37.6	(13.4)	27.1	(8.7)			39.4	(13.7)	28.4	(7.8)		
PANSS positive[e]	19.4	(7.3)	12.4	(5.3)			20.4	(7.2)	12.8	(5.4)		
PANSS negative[e]	17.1	(6.6)	12.5	(5.4)			18.2	(7.4)	14.1	(5.7)		
Schizophrenia, paranoid	6		12				8		14			
Schizophrenia, undifferentiated	4		10				6		16			
Schizophrenia, catatonic									1			
Schizophrenia, residual									1			
Schizoaffective, depressed	3		5				2		7			
Schizoaffective, bipolar	5		2				4		4			
Psychosis NOS	1		3				1		4			
Unmedicated (> 14 days)	9		11				11		18			
Medicated (atypical antipsychotics)	10		21				10		29			

Note. [a] AH: Auditory hallucinators; NH: Nonhallucinators; HC: Healthy controls. Group overlap across paradigms: AH, *n* = 14; NH, *n* = 30; HC, *n* = 42. [b] RM, WM: AH, NH differ significantly from HC (all $p \leq .002$). [c] LQ: Laterality quotient (Oldfield, 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). [d] RM: AH, *n* = 11; NH, *n* = 22; WM: AH, *n* = 14; NH, *n* = 29. [e] RM: AH differ significantly from NH (total BPRS, PANSS general, PANSS positive, all $p \leq .001$; PANSS negative, $p = .01$); WM: AH (*n* = 18) differ significantly from NH (*n* = 45; total BPRS, PANSS general, PANSS positive, all $p \leq .001$; PANSS negative, $p = .03$).

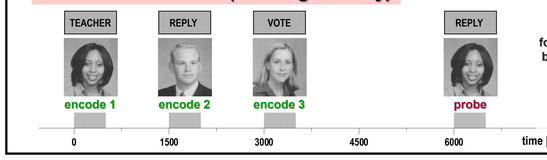
Stimuli and Procedure

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)



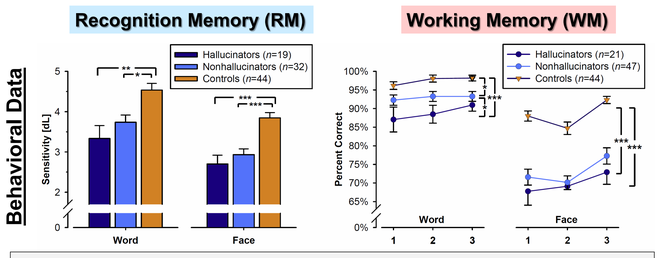


Fig. 1. Mean (±SEM) performance accuracy during RM and WM tasks using words or faces. Overall, remembering faces was more difficult than remembering words. Patients performed more poorly than controls, but hallucinators did not differ from nonhallucinators, except for the WM word serial position task.

Summary and Conclusions

- **Despite poorer, but nonetheless adequate, RM and WM performance** (Fig. 1), **schizophrenia patients had highly comparable N1 sink peaks and topographies compared to controls** (Figs. 2-3).
- **Auditory hallucinators had substantially reduced N1 sinks for words *and* faces compared to controls and nonhallucinators** (Fig. 4), **independent of memory paradigm.**
- **Although this reduction was greatest over the left hemisphere and for words, there was no statistical support for N1 reduction to be dependent on stimulus or hemisphere, and all groups revealed similar stimulus-dependent N1 hemisphere asymmetries.**
- **This neurophysiological deficit in early visual processing can not be explained by differences in overall symptom severity, which was unrelated to N1 sink amplitude** (Fig. 4, follow-up analysis), **.**
- **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).
- **Findings suggest that an association between reduced N1 and auditory hallucinations is not limited to the auditory modality but occurs for visual processing as well.**
- **Using unambiguous, high-contrast and meaningful visual stimuli (i.e., words and faces) during RM and WM paradigms, we found no evidence that the N1 sink reduction resulted from a deficit in earlier visual processing (i.e., as indicated by P1; Fig. 2).**
- **Instead, auditory hallucinations (or the underlying dysfunctional processes) may interfere with a subsequent stage of cognitive processing beginning about 150 ms after word or face onset, likely coinciding with stimulus categorization.**
- **This implies a deficit in the integration of incoming perceptual information as reflected by N1 (i.e., top-down modulation of bottom-up processing involving the ventral occipito-temporal stream).**
- **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

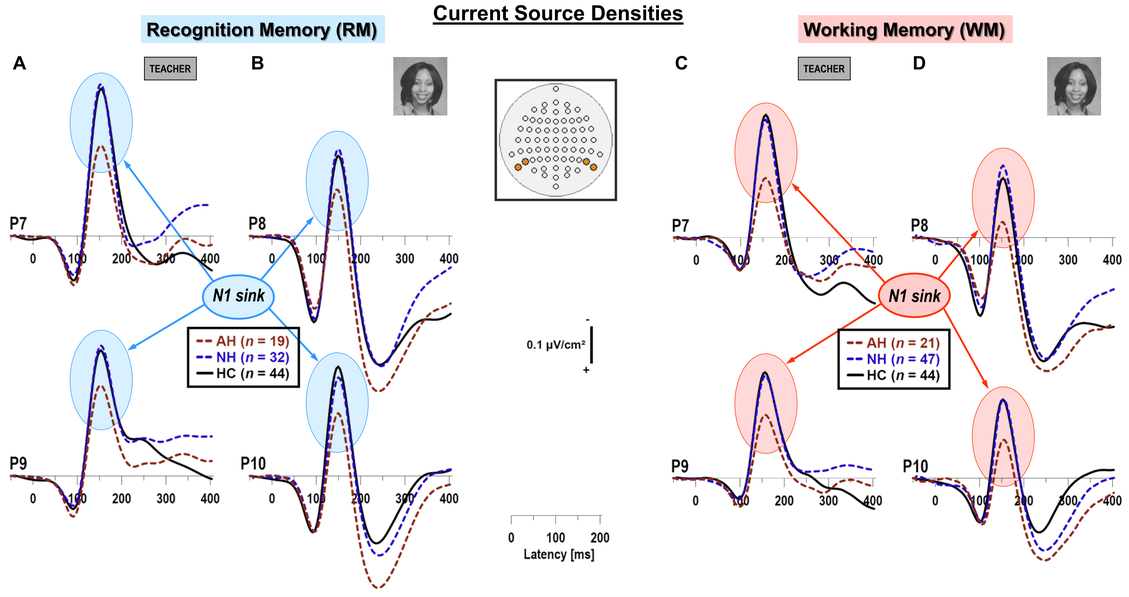


Fig. 2. Grand mean reference-free CSD waveforms for **auditory hallucinators (AH)** , **nonhallucinators (NH)**, **healthy controls (HC)** during RM and WM paradigms using words (**A**, **C**) or faces (**B**, **D**). Shown are inferior lateral-parietal sites where N1 sink (approximate peak latency 150 ms) was 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 **HC** and **NH**, visual N1 sink amplitude appeared to be markedly reduced in **AH**.

CSD-PCA Factor Loadings and Scores

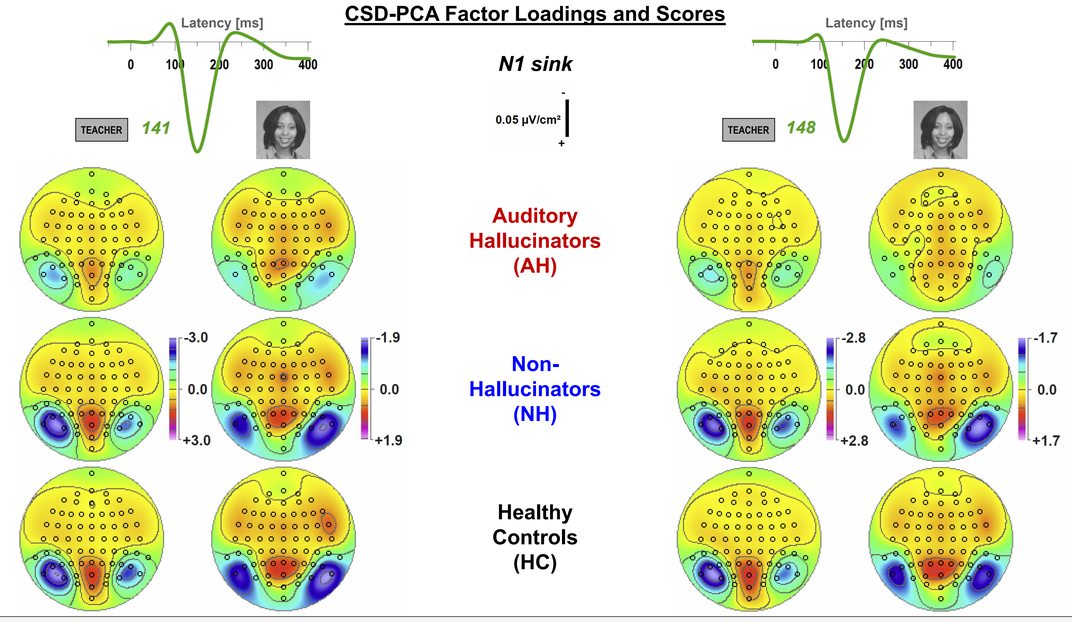


Fig. 3. Unrestricted PCA solutions using CSD subepochs optimized for N1 sink identification and quantification. For each paradigm, one PCA factor uniquely corresponded to prominent N1 sinks over inferior lateral-parietal sites (RM: 141 ms peak latency, 16.4% explained variance; WM: 148 ms, 14.8%). Across memory paradigms, N1 sinks were strongly left-lateralized for words (columns 1 and 3), and slightly right-lateralized for faces (columns 2 and 4). **AH** patients had substantially reduced N1 sinks compared to **NH** patients and **HC**.

ANOVA Means

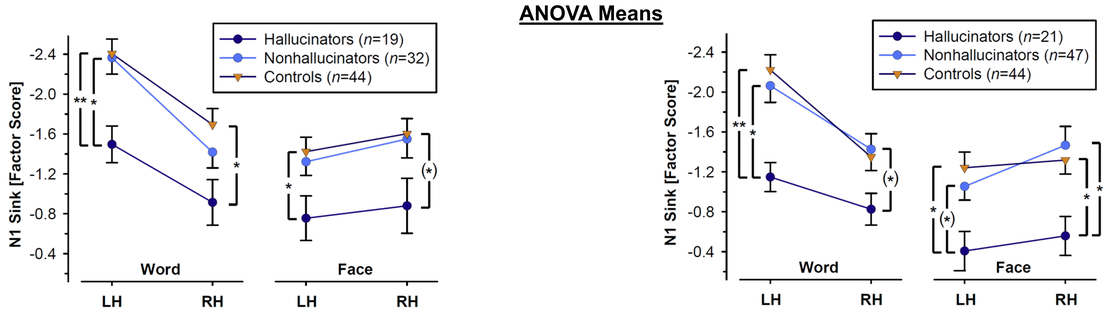


Fig. 4. Mean (±SEM) **N1 sink amplitude** (mean scores of factors *141* [RM] and *148* [WM]) at inferior lateral-parietal sites (P7/8, P9/10) comparing auditory hallucinators, non-hallucinators, and control participants. For both paradigms, overall main effects of *Group* (RM: $F_{[2,92]} = 3.13$, $p < .05$; WM: $F_{[2,109]} = 3.64$, $p = .03$) originated from reduced N1 sinks in **hallucinators** compared to **controls** and **nonhallucinators**, whereas **controls** and **nonhallucinators** did not differ in N1 sink amplitude. Significant contrasts between groups for each paradigm, task, and hemisphere (LH: left; RH: right) are indicated as follows: (*) $p \leq .10$; * $p \leq .05$; ** $p \leq .01$.
Follow-up analysis: To address the potential confound of **differences in symptom severity** between **hallucinators** and **nonhallucinators** (cf. Table 1), repeated measures ANCOVA were computed for patients with PANSS ratings, using the total BPRS score as a between-subjects covariate. All critical effects were maintained in these analyses, because the total BPRS score and all PANSS subscales did not substantially co-vary with N1 sink amplitude (correlation range: RM, $n = 51$, $-.08 \leq r \leq .21$, all $p \geq .14$; WM, $n = 63$, $-.05 \leq r \leq .20$, all $p \geq .20$).

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