Reference-Free ERP Old/New Effects of Visual Recognition Memory for Words and Faces in Schizophrenic and Healthy Adults

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Abstract

Background: We previously reported a preserved 'old-new effect' (enhanced parietal positivity 300-800 ms to correctly recognized repeated words) in schizophrenia over mid-parietal sites using 31-channel nose-referenced event-related potentials (ERP) and reference-free current source densities (CSD). However, patients showed poorer word recognition memory and reduced left lateral-parietal P3 sources. The present study investigated whether these abnormalities are specific to words. **Methods**: High-density ERPs (67 channels) were recorded from 56 schizophrenic (26 female) and 42 healthy (25 female) right-handed adults during parallel visual continuous recognition memory tasks using common words or unknown faces. To identify and measure neuronal generator patterns underlying ERPs, unrestricted Varimax-PCA was performed using CSD estimates (spherical spline surface Laplacian). **Results**: Two late source factors peaking at 446 ms (lateral parietal maximum) and 723 ms (centroparietal maximum) accounted for most of the variance between 250 and 850 ms. Poorer (76.7±20.1% vs. 85.4±12.6% correct) and slower (818±170 vs. 753±146 ms) performance in patients was accompanied by reduced stimulus-locked parietal sources. However, both controls and patients showed mid-frontal (446 ms) and left parietal (723 ms) old/new effects in both tasks. Whereas mid-frontal old/new effects were comparable across groups and tasks, later left parietal old/new effects were markedly reduced in patients over lateral temporoparietal but not mid-parietal sites, particularly for words, implicating impaired phonological processing. **Conclusions**: In agreement with prior results, ERP correlates of recognition memory deficits in schizophrenia suggest functional impairments of lateral posterior cortex (stimulus representation) associated with conscious recollection. This deficit was more pronounced for common words despite a greater difficulty to recall unknown faces, indicating that it is not due to a generalized cognitive deficit in schizophrenia.

Introduction

- Disturbances of language functions have been hypothesized to be central to both the cause and expression of the schizophrenia syndrome (e.g., Crow, 1997), and may be directly linked to other abnormalities of cognitive function in schizophrenia, including working memory and episodic memory (e.g., Barch, 2005).

- Although abnormalities of temporal lobe structures, which are critically involved in memory processes, have frequently been reported in schizophrenia (e.g., McCarley et al., 1993), few studies have investigated ERP correlates of recognition memory performance in schizophrenia (e.g., Kayser et al., 1999).

- Typical ERP finding during explicit memory-retrieval tasks (*old* or *new* judgement):
  Old-New Effect - enhanced ERP positivity 300-800 ms to correctly-recognized items
  - overlaps two distinct ERP components: *N400*/*N2* and *P600*/*P3b*
  - scalp distribution differs from *N2* and *P3* topographies
  - mostly posterior parietal (conscious recollection, *P600*)
  - also mid-frontal (item familiarity, *FN400*; e.g., Curran, 1999)
  - words, pictures, faces, etc.

- Because ERP effects may be masked by the EEG reference choice, we have analyzed reference-free current source density (CSD) transformations of visual and auditory ERPs recorded during continuous word recognition memory tasks (Kayser et al., 2009). Poorer performance in schizophrenia patients was accompanied by reduced left lateral-parietal old/new effects, particularly for spoken words.

- If a dysfunction in temporal integration and retrieval of semantic information is the main contributor to the recognition memory deficits of schizophrenic patients, it is not surprising that their electrophysiologic correlates are more pronounced for auditory stimuli, which require even greater phonological and acoustic processing resources.

- These previous findings and considerations lead to the hypothesis that group differences in episodic memory will be less prominent for stimuli that are difficult to verbalize, such as faces of strangers.

Objective: ***Compare reference-independent old/new effects for common words and unknown faces in a large sample of schizophrenia patients and healthy adults***

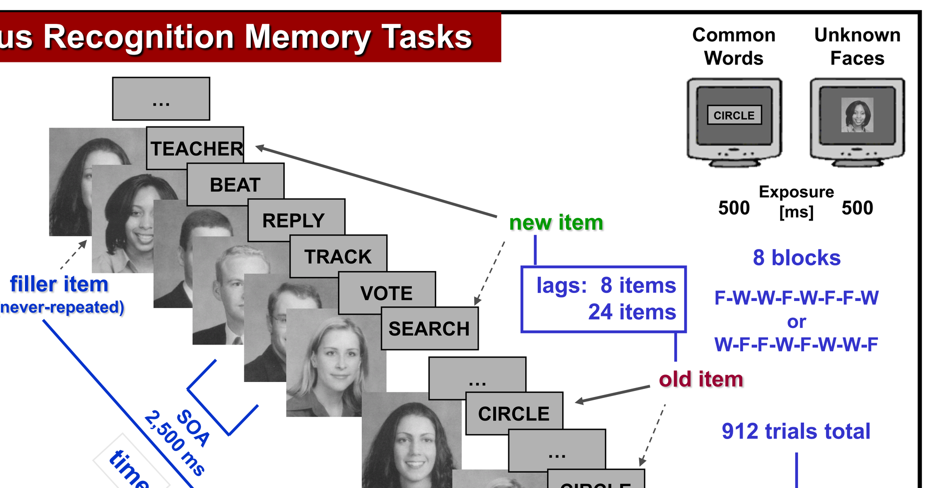
Participants

Means, standard deviations (SD), and ranges for demographic and clinical variables

	Patients (*n* = 56, 25 female)			Healthy Controls (*n* = 42, 26 female)		
Variable	Mean	SD	Range	Mean	SD	Range
Age (years)	29.3[a]	8.5	18 - 56	26.4	6.3	18 - 49
Education (years)	14.4[b]	2.4	10 - 20	16.3	2.1	13 - 25
Handedness (LQ)[c]	75.4	22.4	20 - 100	75.8	20.3	40 - 100
Verbal IQ (WAIS)	103.1[d]	15.5	75 - 133	• no history of any psychopathology or neurology disorder		
Onset age (years)	22.5[e]	5.2	15 - 37			
Illness duration (years)	7.3[e]	7.0	0 - 28			
Total BPRS	36.5[f]	14.3	18 - 88			
PANSS general	30.8[f]	11.9	16 - 77			
PANSS positive	14.9[f]	7.0	4 - 38			
PANSS negative	13.9[f]	5.9	2 - 32			

Note. Gender ratios differ marginally between groups ($\chi^2_{[1]} = 2.87$, $p = .09$); [a] Patients differ significantly from healthy controls ($F_{[1,94]} = 4.17$, $p = .04$); [b] Patients differ significantly from healthy controls ($F_{[1,94]} = 16.7$, $p = .0001$); [c] Laterality quotient (Oldfield, 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed); [d] $n = 35$; [e] $n = 49$; [f] $n = 48$.

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

ERP Recording and Data Analysis

- Continuous DC (24-bit A/D) EEGs using an electrode cap, 67 scalp sites (extended 10-20 system), active recording reference (BioSemi), 256 samples/s
- Amplifier **drift eliminated by second degree Polynomial high pass filter** spanning an entire recording block (approximately 5 min); continuous data exported to Neuroscan format using PolyRex (Kayser, 2009)
- 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 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 [384 variables = samples –100 to 1,395 ms; 26,264 observations = *Subjects* (98) x *Electrode Sites* (67) x *Condition* (new/old) x *Task* (face/word)], followed by Varimax rotation of covariance loadings (Kayser & Tenke, 2003, 2006a, 2006b), to identify and measure neuronal generator patterns
- ***CSD data***: Meaningful PCA components spanning time interval (300 .. 800 ms) of targeted old-new effects: 1) **randomization distributions** of scaled multivariate (entire topography) and univariate (channel-specific) *Hotellings*T^2 statistics computed from factor scores to **identify and evaluate topographic old/new effects** (Maris, 2004; Kayser et al., 2007); 2) factor scores at **representative recording sites** submitted **to repeated measures ANOVA** with *Group* (patients, controls), *Gender* (male/female), *Condition* (new/old), *Task* (face/word), and *Site/Hemisphere* as between- and within-subjects factors to confirm randomization tests
- ***Behavioral data***: Percentage of correct responses, sensitivity (d_L), and mean response latency of correct responses submitted to repeated measures ANOVA with *Group* (patients, controls), *Gender* (male/female), *Condition* (new/old), item *Lag* (short/long), and *Task* (face/word) as between- and within-subjects factors

Surface Potentials / Current Source Densities

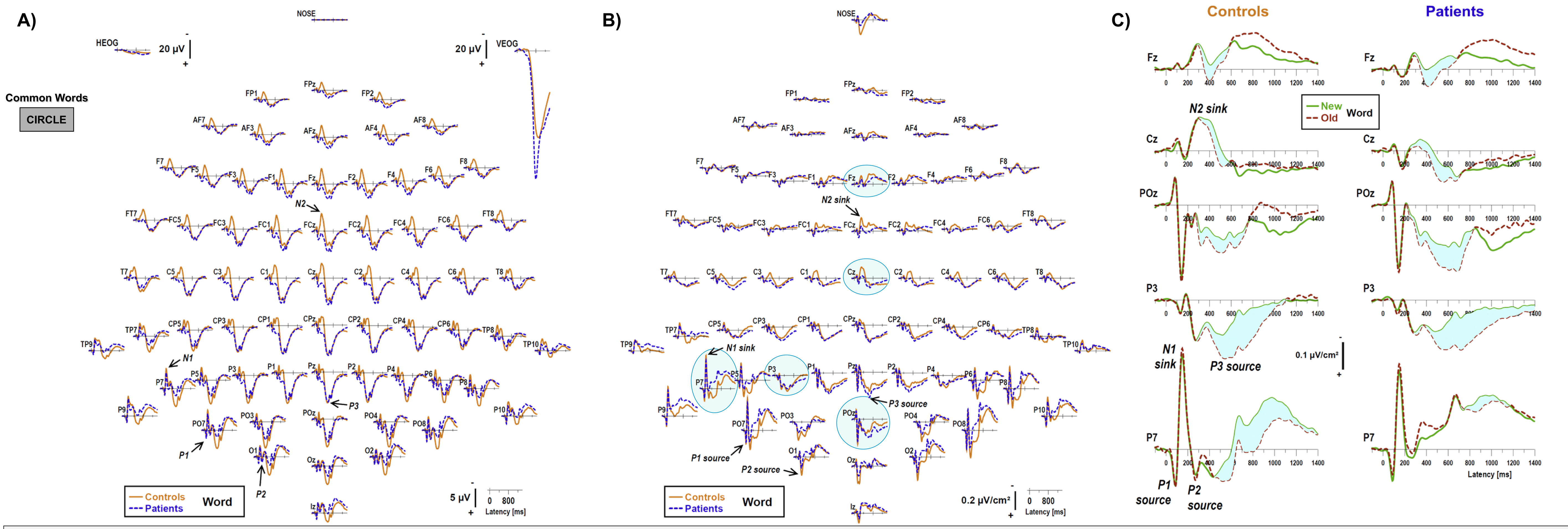


Fig. 1. Grand mean surface potential (ERP) and current source density (CSD) waveforms (-100 to 1400 ms, 100 ms pre-stimulus baseline) for word stimuli comparing 42 controls and 56 patients.

A) Nose-referenced ERPs [μV] averaged across old and new items at all 67 recording sites. Horizontal and vertical electrooculograms (EOG) are shown at a smaller scale before blink correction. Distinct ERP components are labeled at PO7 (P1; approximate peak latency 85 ms), P7 (N1; 150 ms), O1 (P2; 235 ms), FCz (N2; 295 ms), and Pz (P3; 580 ms).

B) Reference-free CSDs [μV/cm²] derived from ERPs. Distinct CSD components included inferior lateral-parietal P1 sources (approximate peak latency 80 ms at PO7) and N1 sinks (145 ms at P7), occipital P2 sources (225 ms at O1), a central N2 sink (295 ms at FCz), and mid-parietal P3 sources (645 ms at Pz).

C) CSDs at selected midline (Fz, Cz, POz) and left parietal (P3, P7) sites revealed more positive-going current sources for old than new words, overlapping the falling phase of the mid-frontal N2 sink (Fz, Cz) and the subsequent parietal P3 source (POz, P3, P7). The later old/new effects, however, were restricted to medial sites in patients (POz, P3).

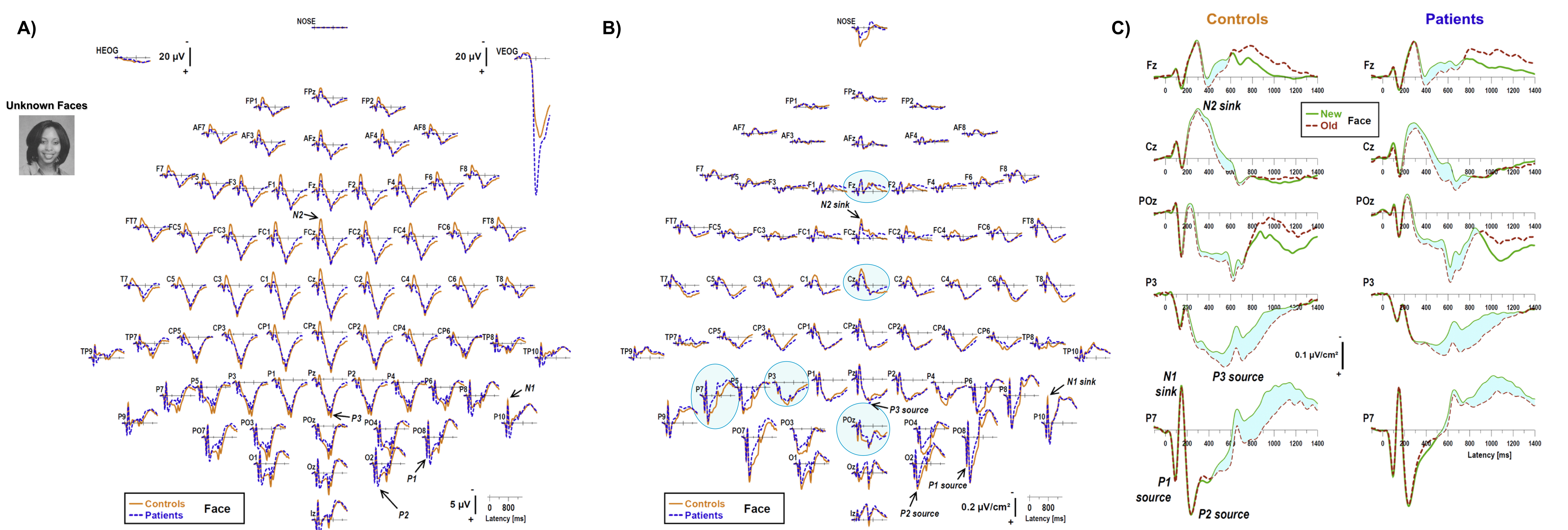


Fig. 2. Grand mean surface potential (ERP) and current source density (CSD) waveforms (-100 to 1400 ms, 100 ms pre-stimulus baseline) for face stimuli comparing 42 controls and 56 patients.

A) Nose-referenced ERPs [μV] averaged across old and new items at all 67 recording sites. Distinct ERP components are labeled at PO8 (P1; approximate peak latency 90 ms), P10 (N1; 150 ms), O2 (P2; 225 ms), FCz (N2; 270 ms), and Pz (P3; 700 ms).

B) Reference-free CSDs [μV/cm²] derived from ERPs. Distinct CSD components included inferior lateral-parietal P1 sources (approximate peak latency 90 ms at PO8) and N1 sinks (145 ms at P10), occipital P2 sources (220 ms at O2), a central N2 sink (295 ms at FCz), and mid-parietal P3 sources (645 ms at Pz).

C) As for words, both groups had more positive-going current sources for old than new faces, overlapping the falling phase of the mid-frontal N2 sink (Fz, Cz) and the subsequent parietal P3 source (POz, P3, P7), with the later old/new effects confined to medial sites in patients (POz, P3).

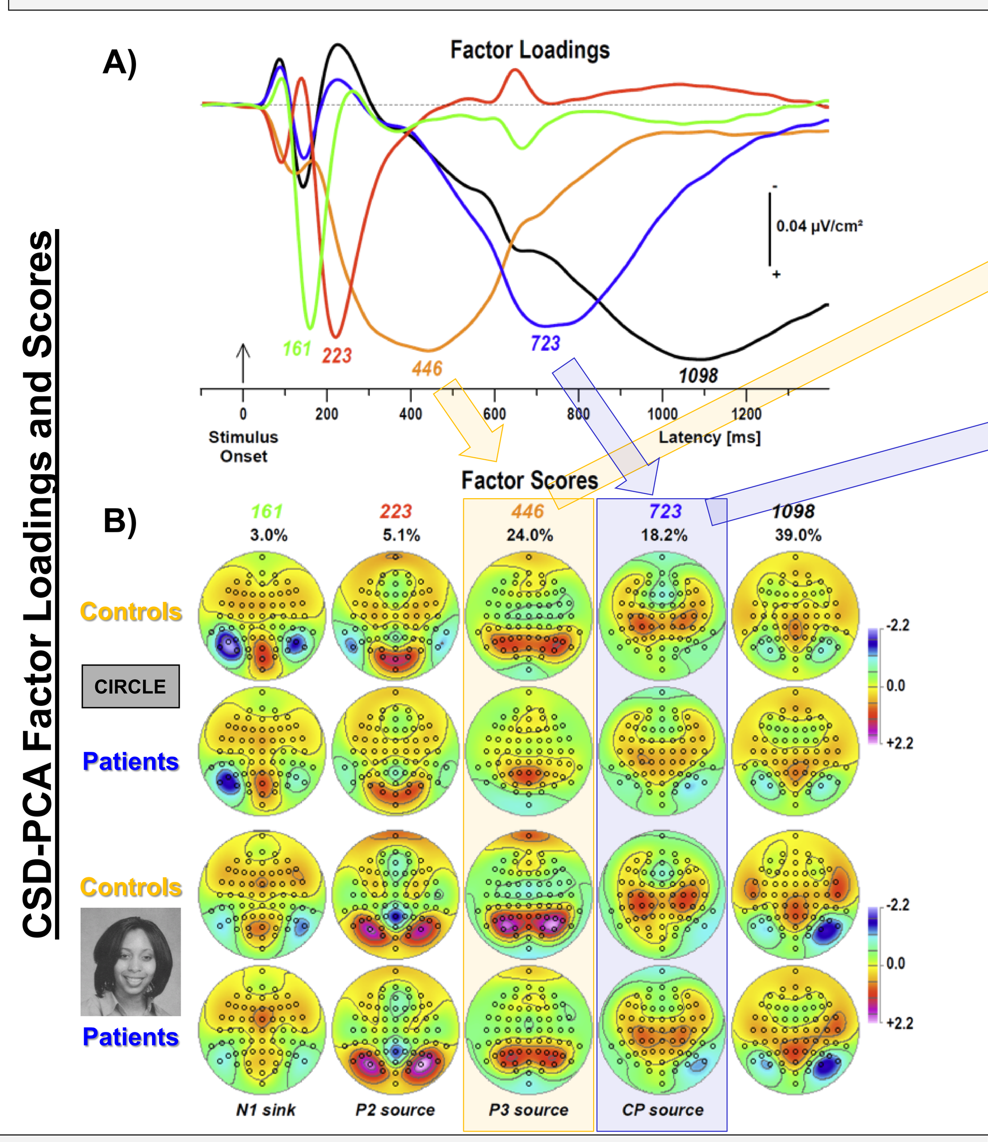


Fig. 3. Unrestricted temporal PCA solution. **A)** Time courses of Varimax-rotated covariance loadings for the first five CSD factors extracted (89.3% total variance explained). **B)** Corresponding factor score topographies (nose at top) for both tasks and groups (pooled across old and new items) with percentage of explained variance. Factors *161*, *223* and *446* clearly corresponded to lateral inferior-parietal N1 sinks (left-lateralized for words), task-specific occipital P2 sources, and parietal P3 sources, respectively. Factor *723* had a more complex topography, with a centroparietal (CP) source maximum accompanied by a mid-frontal and a right inferior occipitoparietal sink.

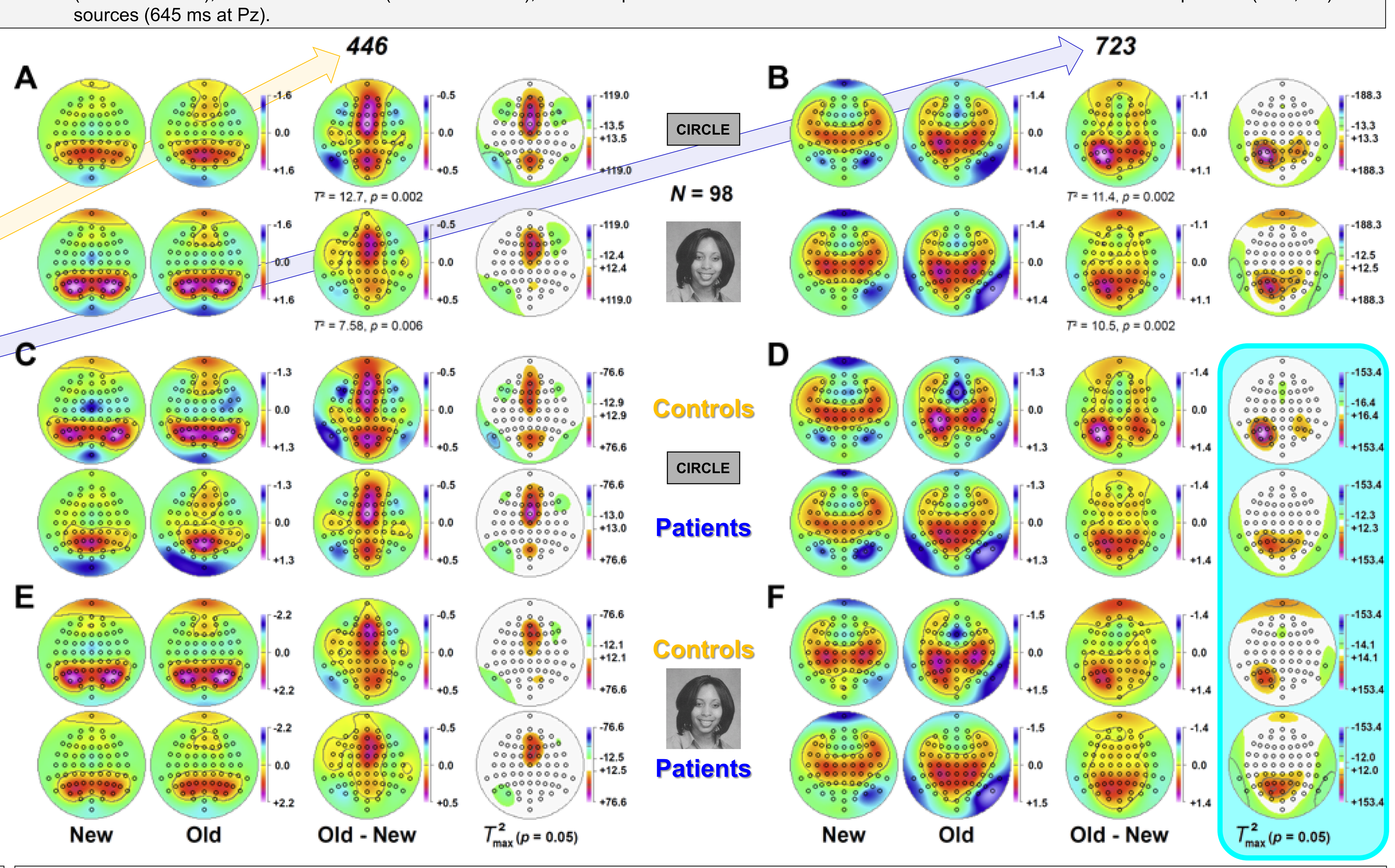


Fig. 4. Statistical evaluation of topographic old/new effects using randomization tests for paired samples for CSD factors *446* and *723* with prominent loadings between 300 and 800 ms, performed across groups for each task **(A, B)**, and separately for 42 controls and 56 patients for words **(C, D)** and faces **(E, F)**. Shown are the mean factor score topographies for new and old items and their respective old-minus-new difference (multivariate Hotelling's T^2 statistics are reported for the total sample), and squared univariate (channel-specific) paired samples T statistics thresholded at the 95th quantile ($p = 0.05$) of the corresponding randomization distribution (maximum of all 67-channel squared univariate paired samples T statistics). To facilitate comparisons of the max(T^2) topographies with the underlying sink-source difference topographies, the sign of the difference at each site was applied to the respective T^2 value, which is otherwise always positive. All topographies are two-dimensional representations of spherical spline interpolations (m = 2; λ = 0) derived from the mean factors scores or T^2 statistics available for each recording site.

Behavioral Data

	Correct Responses		Sensitivity [d_L]		Latency	
Effect[a]	F	p	F	p	F	p
Group	25.1	<.0001	14.1	.0003	4.81	.03
Condition[b]	123.5	<.0001	-		52.5	<.0001
Condition × Group[b]	21.7	<.0001	-		15.6	.0002
Task	20.0	<.0001	30.0	<.0001	5.84	.02
Condition × Task[b]			-		6.47	.01

[a] For all effects, df = 1, 94. Only F ratios with p < .05 are reported.

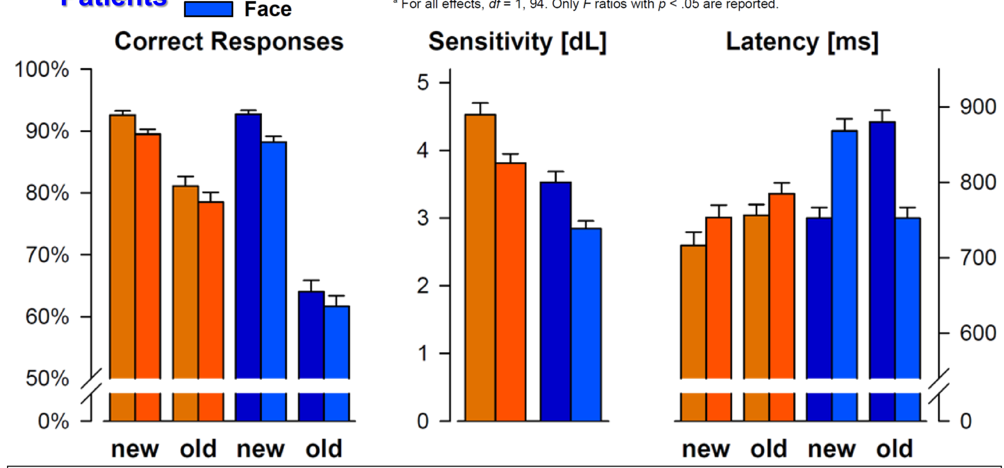


Fig. 5. Mean (±SEM) percentage of correct responses, sensitivity, and response latency for controls and patients comparing recognition memory for words or faces.

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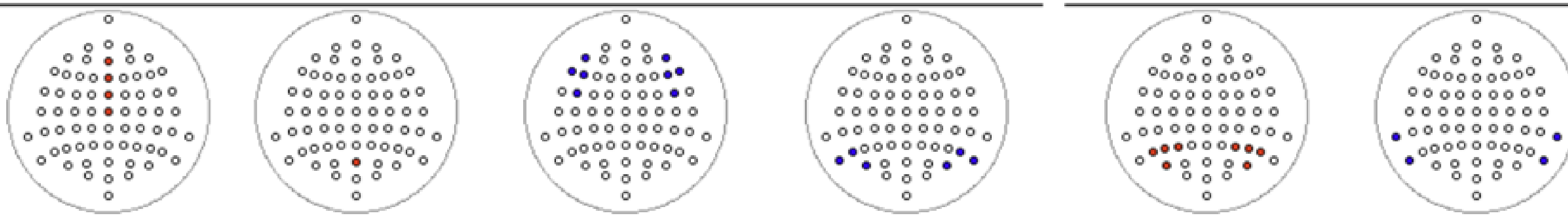
Summary and Conclusions

- Compared to healthy controls, **patients had poorer recognition memory for *both* words and faces**, which agrees with evidence of impaired episodic memory in schizophrenia (e.g., Barch, 2005).
- In contrast, the electrophysiologic findings revealed a task-specific impairment of episodic memory processes in schizophrenia. Reference-free CSDs confirmed largely preserved old/new effects in patients over mid-parietal sites but **marked old/new source reductions in patients over lateral parietal regions for words** (cf. Kayser et al., 1999, 2009). These late old/new effects, **however**, were **comparable in patients and controls for faces**, despite face recognition being the more difficult episodic memory task.
- The late parietal old/new source effects were preceded by **prominent mid-frontal old/new effects across tasks and groups**, reminiscent of mid-frontal old/new effects (*FN400*) seen in healthy adults (e.g., Curran, 1999).
- These **CSD-PCA findings replicate robust reductions of late old/new effects over left lateral temporoparietal, but not mid-parietal, regions in schizophrenia**. They also suggest that these abnormalities are **specific to word recognition memory**, implicating impaired phonological stimulus representation and/or encoding involving left parietal-temporal regions associated with language-related processes.

Sites selected for repeated measures ANOVA models performed on CSD factors ***446*** (P3 source) and ***723*** (CP source) are indicated by marked locations (red: old/new effects; blue: inverted old/new effects).

Summary of *F* ratios from repeated measures ANOVA performed on CSD-PCA factors at selected sites



	Factor (Sites)					
	446 P3 source				***723*** CP source	
	(AFz, Fz, FCz, Cz)	(POz)	(AF7/8, F7/8, F5/6, FC5/6)	(P7/8, P9/10, PO7/8)	(P3/4, P5/6, P7/8, PO7/8)	(P9/10, TP9/10)
C	147.6 ****	40.7 ****	46.7 ****	28.5 ****	87.4 ****	78.3 ****
G	4.16 *			8.94 **	4.95 *	3.10
C × G			3.31		8.06 **	15.3 ***
T	31.2 ****		22.1 ****	24.3 ****	9.84 **	6.48 **
T × G	5.41 *	8.13 **		5.16 *		
T × C	10.3 **	16.4 ****	10.6 **		23.5 ****	4.15 *
T × C × G					4.36 *	
H	-	-	3.17	12.4 ***	44.5 ****	26.3 ****
H × C	-	-	6.58 **	17.1 ****	102.6 ****	2.76
H × C × G	-	-			6.82 **	
H × T	-	-			5.56 *	34.5 ****
H × T × G	-	-			2.95	
H × T × C	-	-	17.5 ****			

Note. G = Group (patients, controls); T = task (word, face); C = condition (new, old); H = hemisphere (left, right). Only *F* ratios with $p < .10$ are reported for effects pooled over gender and site (subsets as indicated; for all tabled effects, df = 1, 94).

- Effect not applicable.

* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$, **** $p \leq .0001$.