Neurophysiological Correlates of WM Retrieval in Schizophrenia During a Serial Position Test with Words or Faces

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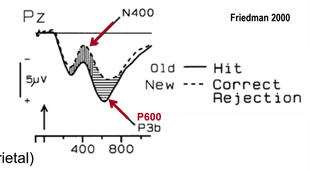
Abstract

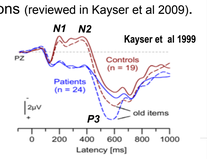
Background: The event-related potential (ERP) 'old/new' effect (enhanced parietal positivity 300-800 ms after correctly recognized repeated items) is a reliable neurophysiologic correlate of conscious recollection, which is reduced in schizophrenia during word but not face recognition (Kayser et al., 1999, 2009, 2010). This study examined whether the task-specificity of this effect also applies to WM retrieval. **Methods**: 67-channel ERPs were recorded from 75 schizophrenic patients and 44 healthy controls (right-handed) during a WM paradigm with words or faces. After sequentially encoding three items (500 ms, 1.5 s SOA), one item was repeated after a 3-s delay (probe), and its serial position was reported. **Results**: ERPs were transformed into reference-free current source density (CSD; spherical spline interpolation) waveforms, which were more positive for probe (old) than encoding (new) items, revealing differences highly similar to recognition memory old/new effects. An unrestricted Varimax-PCA identified positive sources peaking at 281 ms (parietoccipital) and 660 ms (centroparietal). Although both groups performed well in the word task (> 90% correct), probe/encode effects over left lateral-parietal sites for the 660 source were markedly reduced in patients. In contrast, probe/encode effects for this source were comparable in patients and controls for faces, despite poorer performance in patients (72.3±14.3% vs. 88.3±9.5%). **Conclusions**: The findings suggest that neurophysiologic abnormalities of conscious recollection in schizophrenia are specific to tasks requiring phonological encoding and/or semantic processing.

Introduction

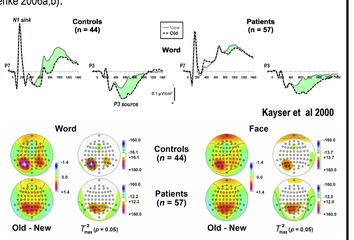
- The typical ERP finding during explicit memory-retrieval tasks (i.e., judging items as being old or new) is the so-called ***Old/New Effect***:
  - begins at 200 – 400 ms
  - lasts 300 – 500 ms
  - mostly posterior
  - words, pictures, faces, etc.
  - overlaps ***N400*** / ***N2*** and ***P600*** / ***P3b***
  - scalp distribution ≠ N2 and P3 topographies
  - dual-process models: familiarity (***FN400***; Curran 1999) vs. conscious recollection (left parietal)



- Few studies have investigated ERP correlates of recognition memory in schizophrenia (e.g., Kayser et al 1999; Matsuoka et al 1999; Guillem et al 2001), but methodological limitations and procedural differences impede efforts to draw general conclusions (reviewed in Kayser et al 2009).



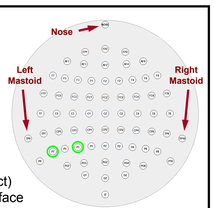
- Whereas the typical behavioral finding is poorer task performance in patients (i.e., reduced recognition accuracy, longer response latency), ERP old/new effects overlapping the late positive complex with a mid-parietal maximum were largely preserved in schizophrenia, suggesting that conscious recollection may not be impaired.
- 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).
- Using a CSD-PCA approach, we found preserved old/new effects in patients over mid-parietal sites but marked old/new source reductions over lateral parietal regions during recognition memory tasks with words (Kayser et al 2009, 2010).



- Moreover, a reduction of left parietal old/new effects in patients was ***not*** observed for faces, despite this being more difficult than recognition memory for words (Kayser et al 2010).

Objective:
- **use CSD-PCA approach to quantify neuronal generator patterns underlying working memory (WM) performance during serial position tests (SPT) with words or faces**
- **because the SPT trial is analogous to a study-test memory paradigm, probe (*old*) items should elicited a greater P3 source than encode (new) items**
- **if this is true, we would predict reduced probe/encode (i.e., old/new) effects in schizophrenia patients compared to controls, particularly for words than faces**

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 sub-epochs**, 100 ms pre-stimulus baseline, extracted from 9-s epochs spanning a single SPT trial
- ERP averages (artifact-free trials) for matching stimulus pairs (i.e., probe and corresponding encoding item), 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** (-100 .. 1,400 ms = 385 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 identify and quantify neuronal generator patterns underlying the postulated probe/encode (i.e., old/new) effects between approximately 200 and 1,200 ms
- ***CSD data***: evaluate group differences in WM retrieval for words or faces by submitting factor scores at **representative scalp sites** to **repeated measures ANOVA** with *Group* (patients, controls), *Task* (word, face), *Hemisphere* (LH, RH) and Site (as appropriate) as between- and within-subjects factors
- ***Behavioral data***: performance accuracy measures (percent correct, chance levels linearly scaled to 50% correct) submitted to repeated measures ANOVA with *Group* (patients, controls), and *Task* (word, face), *Condition* (serial position [1, 2, 3]) as between- and within-subjects factors

Participants

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

Group	Schizophrenia Patients (*n* = 75)		Healthy Controls (*n* = 44)	
Gender (male/female)	44/31		19/25	
Age (years) [a]	29.4	(8.8)	26.4	(6.6)
Education (years) [b]	13.7	(2.5)	16.3	(2.1)
Handedness (LQ) [c]	76.5	(22.5)	74.7	(19.9)
Verbal IQ (WAIS) [d]	99.9	(16.6)		
Onset age (years)	21.6	(5.9)		
Illness duration (years)	7.9	(8.4)		
Total BPRS [e]	36.9	(13.3)		
PANSS general [e]	31.4	(10.8)		
PANSS positive [e]	15.0	(6.7)		
PANSS negative [e]	15.2	(6.4)		
Schizophrenia, paranoid	25			
Schizophrenia, undifferentiated	23			
Schizophrenia, catatonic	1			
Schizophrenia, residual	1			
Schizoaffective, depressed	11			
Schizoaffective, bipolar	8			
Schizophrenoform	1			
Psychosis NOS	5			
Unmedicated (> 14 days)	32			
Medicated (atypical antipsychotics)	43			

Note. [a] $p = .04$. [b] $p < .001$. [c] LQ: Laterality quotient (Oldfield, 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). [d] $n = 45$. [e] $n = 65$.

no history of any psychopathology or neurology disorder

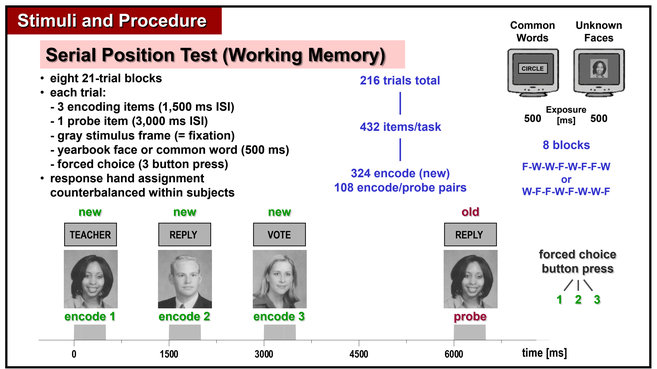
Stimuli and Procedure

Serial Position Test (Working Memory)

- **eight 21-trial blocks**
- **each trial:**
  - **3 encoding items (1,500 ms ISI)**
  - **1 probe item (3,000 ms ISI)**
  - **gray stimulus frame (= fixation)**
  - **yearbook face or common word (500 ms)**
  - **forced choice (3 button press)**
- **response hand assignment counterbalanced within subjects**

216 trials total
432 items/task
324 encode (new)
108 encode/probe pairs

Common Words / Unknown Faces
500 Exposure [ms] 500
8 blocks
F-W-W-F-W-F-F-W or W-F-F-W-F-W-W-F



Behavioral Data

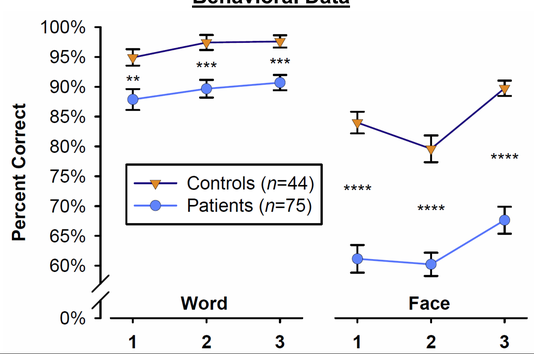


Fig. 1. Mean (±SEM) performance accuracy during the **Serial Position Test (SPT)** using words or faces. Overall, remembering the correct encoding position of probe items was more difficult for faces than words. Patients performed more poorly than controls (Group, $F_{[1,117]} = 44.6$, $p < .0001$), particularly for faces (Group x Task, $F_{[1,117]} = 57.9$, $p < .0001$). Significant group main effects for each task at each encoding position are indicated as follows: ** $p < .01$; *** $p < .001$; **** $p < .0001$.

Summary and Conclusions

- **Schizophrenia patients had significantly reduced WM performance compared to healthy controls for both words and faces** (Fig. 1).
- **Item repetition during serial position tests yielded robust probe/encode ERP effects that were highly comparable to ERP old/new effects typically observed during explicit recognition memory paradigms.**
- **This included both early mid-frontal (*FN400*) and mid-parietal (300 – 600 ms) as well as late left parietal (600 – 900 ms) probe/encode effects** (Fig. 3).
- **Schizophrenia patients had preserved early probe/encode effects across tasks, suggesting intact retrieval processes associated with familiarity.**
- **In contrast, patients revealed markedly reduced late old/new effects (left lateral-parietal) for words, but not for faces, implicating impaired conscious recollection of verbal material.**
- **The preserved late probe/encode effects for faces in schizophrenia are even more remarkable considering the greater difficulty to remember and/or retrieve unknown faces as compared to common words** (Fig. 1).
- **These findings are in close agreement with those of our previous recognition memory ERP studies in schizophrenia** (Kayser et al 1999, 2009, 2010).
- **Because verbal information is readily stored in a phonological loop, healthy adults may have better (privileged) access to this mechanism than schizophrenic patients, and what seems to be a deficit for patients is rather a selective advantage for controls in phonological and/or semantic encoding and/or retrieval of information.**
- **The notion of a phonological encoding deficit is in agreement with prior findings that reduced late old/new effects in schizophrenia are greater for spoken than read words** (Kayser et al 2009).

Current Source Densities

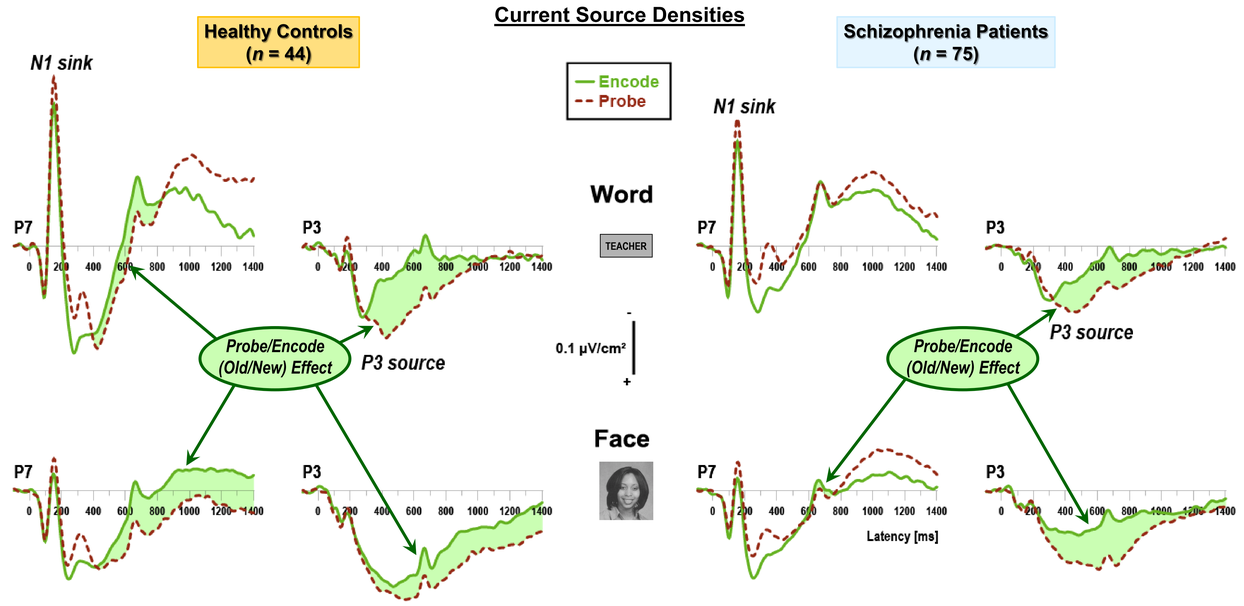
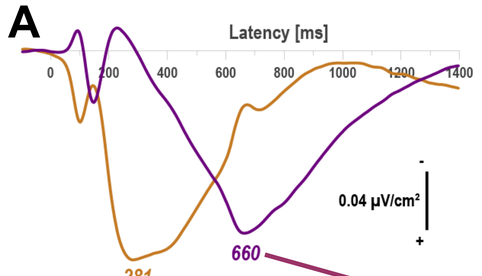


Fig. 2. Grand mean CSD waveforms at left parietal sites (P7, P3) for 44 healthy adults and 57 schizophrenia patients comparing words (top) or faces (bottom) presented during the **encoding** phase (***new***) or **probe** phase (old). ***Probe/encode effects*** (i.e., greater sources to probe than encode items) began at about 200-300 ms and were highly similar to the classical ***old/new effects*** (highlighted in green). Whereas encode/probe effects were clearly present in both groups over medial-parietal sites (P3) for words and faces, only controls revealed substantial probe/encode effects at lateral parietal sites (P7).

CSD-PCA Factor Loadings and Scores



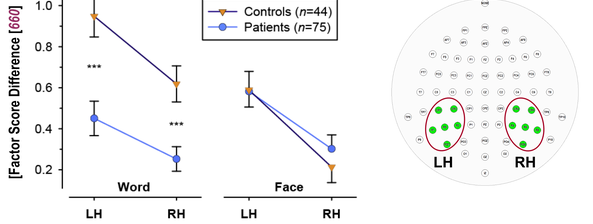


Fig. 4. Mean (±SEM) probe/encode effects for the late source (***660***) at lateral centroparietal sites, which was markedly reduced in patients for words (Group x Task, $F_{[1,117]} = 17.0$, $p = .001$). Across groups and tasks, late probe/encode effects were greater over the left than right hemisphere (Hemisphere, $F_{[1,117]} = 46.4$, $p < .0001$). Significant group main effects for each task and hemisphere (LH: left, RH: right) are indicated: *** $p < .001$.

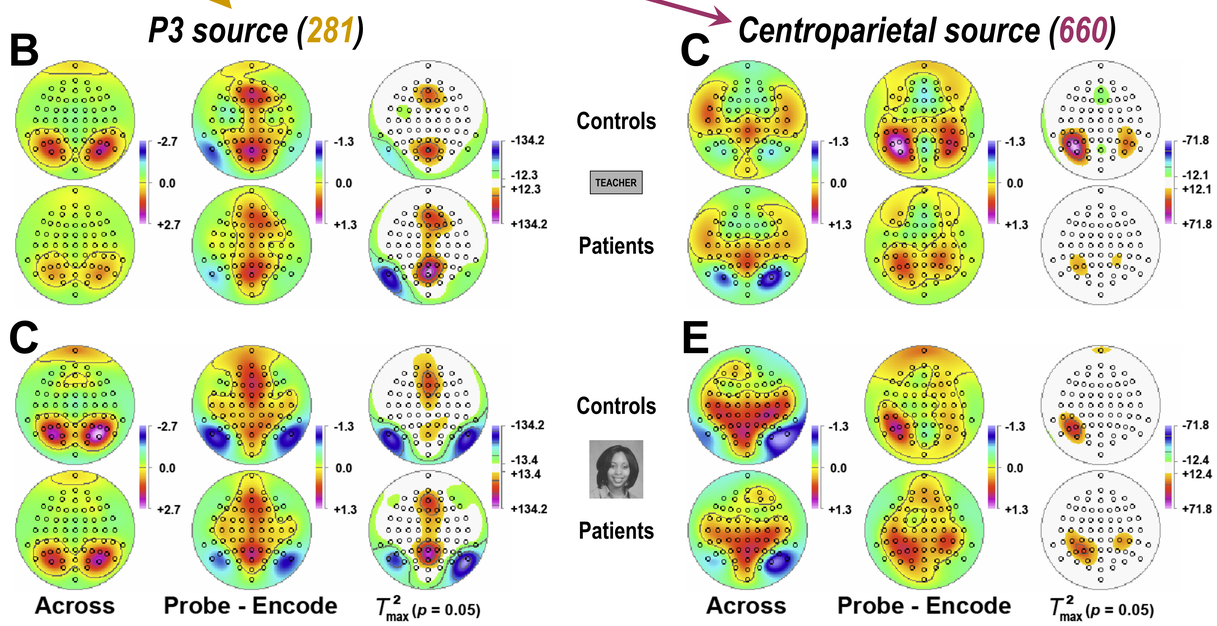


Fig. 3. The unrestricted Varimax-PCA identified late sources peaking at ***281*** ms (18.5% explained variance) and ***660*** ms (15.0%), which accounted for most of the variance during the typical time interval for old/new effects (**A**). The probe/encode differences for these sources showed the same topographies as the old/new effects for recognition memory tasks. Both groups showed robust early (***281***) probe/encode effects at mid-parietal and mid-frontal sites (**B**, **C**). However, whereas controls had robust probe/encode effects over left lateral-parietal sites for the late centroparietal source (***660***) in the word task, these were markedly reduced in patients (**C**). In contrast, the probe/encode effects for this source were comparable in patients and controls for faces (**E**; see Fig. 4 above for ANOVA means).

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