Verbal Working Memory (WM) in Schizophrenia: Event-Related Brain Potential (ERP) Findings for the Word Serial Position Test

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Abstract

Background: Reduced WM is a primary cognitive deficit in schizophrenia. To better determine its functional and neuroanatomical origin (cortical activation during encoding, retention, or retrieval), advanced analytic techniques (current source density, CSD; principal components analysis, PCA; CSD animations) were used to exploit the high temporal resolution underlying 31-channel ERP topographies obtained during a verbal WM task based on the Word Serial Position Test (Wexler et al. 1998). **Methods:** Long EEG epochs (> 10 s; 0.01 Hz high pass) were recorded from 13 schizophrenic (9 male) and 17 healthy adults (8 male) during 128 visual trials consisting of 4 initial words (500 ms exposure, 1,500 ms SOA), a retention period requiring storage of the word sequence (4,500 ms), a probe word (500 ms), and a delayed button press to indicate its correct position. Reference-free CSDs of ERP waveforms were submitted to unrestricted, covariance-based, and Varimax-rotated PCA to identify and measure relevant neuronal generator patterns. **Results:** Poorer performance in patients (72.9±14.3% vs. 88.2±10.8% correct, $p<0.01$) was paralleled by reduced stimulus-related, left-lateralized (inferior-parietal) P3 source asymmetry ($p<0.01$) and amplitude ($p<0.05$) during encoding and retrieval. Healthy adults evidenced a sustained increase in mid-frontal sink activity during word encoding (up to 6 s), which was absent in patients ($p<0.01$). In contrast, a sustained frontocentral sink during the retention period and early, left-lateralized (inferior-parietal) N1 sinks were similar across groups. **Conclusions:** Electrophysiologic correlates of visual verbal WM deficits in schizophrenia suggest a complex disturbance in functional neuronal network processes, primarily affecting the encoding of successive stimuli.

Introduction

- Reduced working memory (WM) is a primary cognitive deficit in schizophrenia (e.g., Park and Holzman, 1992; Bruder et al., 2004).
- The systems that mediate short-term storage and the basic executive processes of selective attention and manipulation of information in WM involve prefrontal and anterior cingulate cortex, together with modality- or content-specific posterior regions (e.g., Smith and Jonides, 1999).
- The fine temporal resolution and scalp topography of event-related brain potentials (ERPs) reflect the spatiotemporal sequence of cortical information processing, ranging from early sensory/ attentional components (P1, N1) to later cognitive components (P3, slow waves).
- Because ERPs can be readily measured during all phases of a WM task (stimulus encoding, maintenance, and retrieval), they can provide unique information about the different stages of cognitive processing that contribute to abnormalities of WM in schizophrenia (e.g., Löw et al., 2000; Cameron et al., 2003), which is not available from behavioral or neuroimaging measures.

Participants

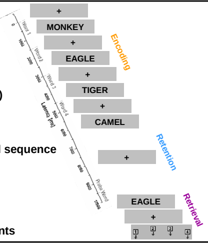
Patients: DSM-IV criteria for **schizophrenia (undifferentiated, *n* = 3; paranoid, *n* = 4)**, **schizoaffective disorder (bipolar type, *n* = 4; depressive type, *n* = 1)**, **psychosis not otherwise specified (*n* = 1)**; med-free for at least 14 days prior to testing (*n* = 11), risperidone (schizoaffective, bipolar type, *n* = 1), aripriprazole (schizophrenic, undifferentiated, *n* = 1).

Controls: **Healthy, right-handed adults (*n* = 17)** with no history of any psychopathology or neurological disorder

	Patients (n = 13, 9 male)		Healthy Controls (n = 17, 8 male)		
Variable	Mean	SD	Mean	SD	
Age (years)	30.5	8.4	27.4	7.6	
Education (years)	13.7	2.3	15.7	2.3	p = .03
Handedness (LQ)	81.7	30.7	84.9	18.6	
Onset age (years)	19.9	6.7			
Illness duration (years)	9.2	6.9			
Total BPRS	30.2	6.9			
PANSS general	26.6	7.6			
PANSS positive	13.5	5.7			
PANSS negative	9.5	2.5			

Word Serial Position Test (WSPT)

- **visual analogue of auditory WSPT (Wexler et al., 1998)**
- **four 32-trial blocks (128 trials total), each trial:**
  fixation cross-hair
  encoding sequence of four words (500 ms, 1,000 ms ISI)
  retention period (4,500 ms delay interval)
  probe word (500 ms) retrieval period (1500 ms)
  response period (2500 ms): press one of 4 buttons to indicate the position of the probe word in the original sequence
  blank screen (2000 ms)
- **response hand (L, R) alternated across the four blocks (i.e., RLLR or LRRL)**
- **initial response hand counterbalanced across participants**



ERP Recording and Data Analysis

- Continuous EEGs using an electrode cap , 30 scalp sites (4 midline, 26 homologous lateral) referenced to nose, acquired at .1-30 Hz band pass (-6dB/oct.), 200 samples/sec
- Bipolar horizontal and vertical EOGs; **blink reduction** (continuous EEG) **using spatial PCA**; horizontal eye artifacts (epoched EEG) by linear regressions of homologous EEG differences (Fp2 - Fp1, F8 - F7, etc.)
- **10,500 ms epochs**, 200 ms pre-stimulus baseline, ERP averages (artifact-free trials, correct responses only) low pass filtered at 5 Hz (-24dB/oct.), 100 ms baseline correction preceding onset of the first stimulus
- **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 [2201 variables = samples –500 to 10,000 ms; 930 observations = *Subjects* (30) x *Electrode Sites* (31)], followed by *unscaled* Varimax rotation (Kayser & Tenke, 2003), to disentangle temporally and spatially overlapping CSD components
- Meaningful PCA components: factor scores (**Fig. 5**) submitted to **repeated measures ANOVA** using ***Group* (patients, controls)** and **representative subsets of CSD recording sites** as design factors
- Behavioral data: percentage of correct responses for each probe condition (i.e., the word position in the initial series) submitted to repeated measures ANOVA with *Group* (patients, controls) and *Position* (1, 2, 3, or 4)
- Nonparametric Spearman rank-order correlations (*rho*) used to examine, where appropriate, the relation between behavioral performance and prominent ERP measures

Behavioral Data

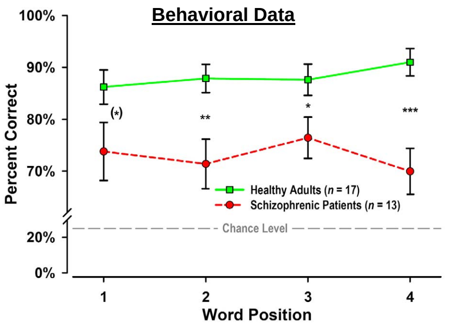


Fig. 1. Mean percentage of correct responses (and standard error of the mean) for patients (dashed, circles) and healthy controls (solid, squares) as a function of position of words within the initial series. A chance performance (25%) is marked by a gray dashed line. Simple group main effects are indicated as follows: *** $p < .001$; ** $p < .01$; * $p < .05$; (*) $p < .10$.

Surface Potentials

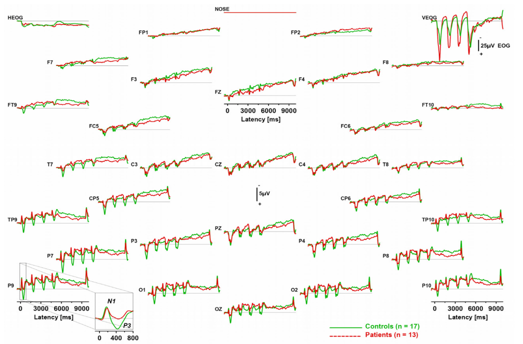


Fig. 2. Grand average event-related potential (ERP) [µV] waveforms for 13 patients (red lines) and 17 controls (green lines) at all 31 recording sites (nose reference). Horizontal (HEOG) and vertical (VEOG) electrooculograms are shown at a smaller scale before blink correction in top corners. Stimulus-specific ERP components were well-defined over the posterior scalp, including N1 and P3 following each word presented at 0, 1.5, 3, 4.5 and 9.5 s (e.g., prominent at left hemisphere site P9; see inset for enlargement of initial ERP activity). A continuous increase in negative slow wave (SW) is particularly evident at mid-frontal scalp sites (e.g, see F3, Fz, F4).

Current Source Densities

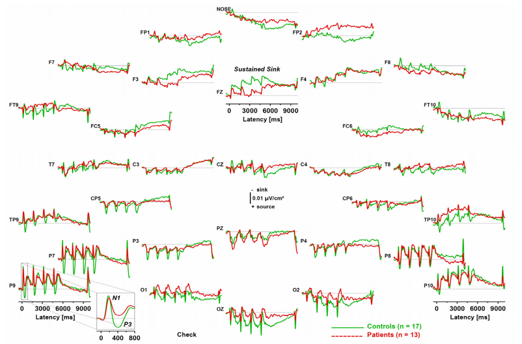


Fig. 3. Reference-free current source density (CSD) [µV/cm²] waveforms (spherical spline Laplacians; Perrin et al., 1989, 1990) for 13 patients (red lines) and 17 controls (green lines) at all 31 recording sites. Distinct CSD components included stimulus-locked inferior lateral-parietal N1 sinks (approximate peak latency to previous word onset 170 ms) and P3 sources (400 ms) following each word presented at 0, 1.5, 3, 4.5 and 9.5 s (e.g., prominent at left hemisphere site P9; see inset for enlargement of initial CSD activity), a stepwise increase in mid-frontal and right lateral-parietal sink activity during word encoding (up to 6 s; see Fz and P10), and a sustained frontocentral sink during the retention period (6 to 9.5 s; see Fz).

Time Courses of PCA Factor Loadings

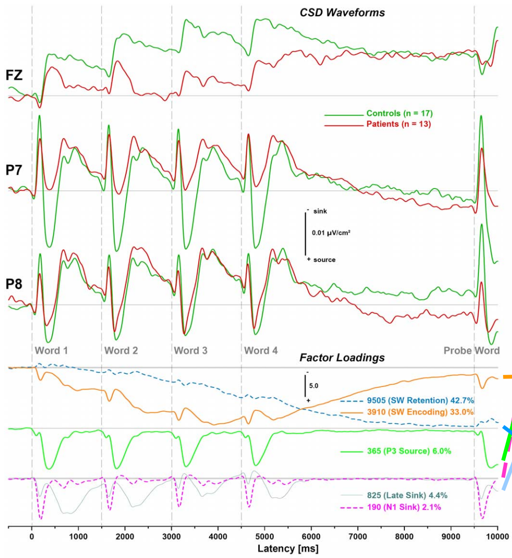


Fig. 4. Grand mean current source density (CSD) waveforms [µV/cm²] at selected sites (Fz, P7, P8) comparing 13 patients (red lines) and 17 controls (green lines), and time courses of Varimax-rotated factor loadings for five PCA components extracted from all CSD waveforms (Kayser and Tenke, 2003, submitted). In a temporal PCA, the factor loadings represent the relative contribution of each time point to a factor. Stimulus onsets for each initial word and the probe word are indicated by long, dashed gray lines intersecting the time scale. CSD factor labels (with percentage of explained variance) indicate the peak latency of the factor loadings, with brief functional interpretations of factors given in parentheses. Note that the peaks of factors 190 and 365 coincide in both groups with the respective amplitudes of the N1 sinks and P3 sources at lateral inferior-parietal sites (P7/8) following each word presentation, whereas the long duration loadings of factors 3910 and 9505 parallel SW sink activity at mid-frontal sites (Fz), that is, an initial SW sink increase during the encoding period for healthy adults, and a sustained SW sink during the retention period for both groups.

Topographies of PCA Factor Scores

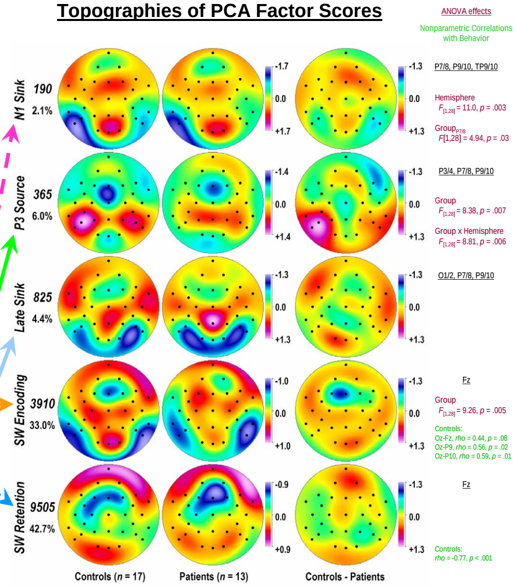


Fig. 5. Mean topographies of factor scores for PCA components extracted from CSD (current source density) waveforms for 17 healthy controls (left column) and 13 patients (middle column), and the respective group difference (right column). In a temporal PCA, the factor scores represent the weight of a factor's loadings pattern with each observation (i.e., CSD waveforms observed for each electrode and participant; Kayser and Tenke, 2003). CSD factors (with percentage of explained variance and corresponding CSD component label) are ordered from top to bottom according to the peak latency of the factor loadings. Black dots indicate the spherical positions of the 31-channel EEG montage (nose at top). Note that the same symmetric scale was used for all difference maps, whereas symmetric scales optimized for score ranges across groups were used for the original topographies. All topographic maps are 2D-representations of spherical spline surface interpolations (Perrin et al., 1989, 1990) derived from the mean factors scores available for each recording site.

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Summary and Conclusions

- **Poorer performance in patients was paralleled by reduced left-lateralized (inferior-parietal) P3 source amplitude and asymmetry during encoding and retrieval.**
- **Healthy adults evidenced a sustained increase in mid-frontal sink activity during word encoding (up to 6 s), which was absent in patients.**
- **In contrast, a sustained frontocentral sink during the retention period and early, left-lateralized (inferior-parietal) N1 sinks were similar across groups.**
- **CSD slow wave activity at frontal and content-specific posterior regions was correlated with WM performance in healthy adults only.**
- **Electrophysiologic correlates of visual verbal WM deficits in schizophrenia indicate a complex disturbance in functional neuronal network processes, primarily affecting the encoding of successive stimuli.**