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ERP/CSD indices of impaired verbal working memory subprocesses in schizophrenia

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Abstract

To disentangle subprocesses of verbal working memory deficits in schizophrenia, long EEG epochs (>10 s) were recorded from 13 patients and 17 healthy adults during a visual word serial position test. ERP generator patterns were summarized by temporal PCA from reference-free current source density (CSD) waveforms to sharpen 31-channel topographies. Patients showed poorer performance and reduced left inferior parietotemporal P3 source. Build-up of mid-frontal negative slow wave (SW) in controls during item encoding, integration, and active maintenance was absent in patients, whereas a sustained mid-frontal SW sink during the retention interval was comparable across groups. Mid-frontal SW sinks (encoding and retention periods) and posterior SW sinks and sources (encoding only) were related to performance in controls only. Data suggest disturbed processes in a frontal-parietotemporal network in schizophrenia, affecting encoding and early item storage.

Descriptors: Schizophrenia, Working memory, Event-related potential (ERP), Principal components analysis (PCA), Current source density (CSD), Laplacian, Slow wave (SW)

Spatial delayed-response tasks probing dorsolateral prefrontal cortex function, which involve remembering the location of a stimulus over a brief delay interval, indicate that impairments in working memory constitute a primary cognitive deficit in schizophrenia (Park & Holzman, 1992). This deficit is present in both medicated and unmedicated patients, during acute psychosis and partial remission, and is related to negative symptoms of schizophrenia (e.g., Carter et al., 1996; Gooding & Tallent, 2002; Park, Püschel, Sauter, Rentsch, & Hell, 1999, 2003). Schizophrenic patients have also shown impairments on a variety of verbal working memory tests (e.g., Bruder, Wexler, Sage, Gil, & Gorman, 2004; Callicott et al., 2000; Conklin, Curtis, Katsanis, & Iacono, 2000; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Wexler, Stevens, Bowers, Sernyak, & Goldman-Rakic, 1998), which appear to parallel their poor spatial working memory (Conklin, Curtis, Calkins, & Iacono, 2005). Although these working memory tasks vary in stimulus content and cognitive demands, they have some basic processes in common. After a stimulus is perceived, a working memory representation must be generated, integrated and maintained within an online buffer, and accessed or manipulated for successful performance. The systems that mediate short-term storage and basic executive processes, such as attending to and manipulating information in working memory, presumably involve prefrontal and anterior cingulate cortex, together with modality- or content-specific posterior regions (e.g., Cohen et al., 1997; Smith & Jonides, 1999). The extent to which these different cognitive processes and their neurophysiological correlates contribute to working memory deficits in schizophrenia is an important and yet unresolved question. Although behavioral findings suggest that dysfunction of both perceptual processing and maintenance of information during delay intervals contribute to visual working memory deficits in schizophrenia (Lencz et al., 2003; Tek et al., 2002), more direct neurophysiologic evidence is needed.

Neuroimaging studies of visual working memory have separated transient brain activity in posterior regions associated with perceptual processing from sustained activity in prefrontal regions associated with maintenance of information (Belger et al., 1998; Courtney, Ungerleider, Keil, & Haxby, 1997; Leung, Gore, & Goldman-Rakic, 2002; Smith & Jonides, 1998). The fine temporal resolution of event-related potentials (ERPs), which measure electrical brain activity time-locked to sensory or cognitive events, in combination with their scalp topography,

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may be particularly helpful to understand the time course of ongoing brain activity during working memory tasks. ERP components occurring at different latencies reflect the spatiotemporal sequence of cortical information processing, ranging from early components that index sensory and attentional processing (P1, N1) in primary and secondary cortices to later components indicative of resource allocation and stimulus evaluation (P3) and further cognitive processing (slow waves) in higher-order cortices. Moreover, ERPs can be readily measured during all phases of a working memory task, thereby enabling the association of stimulus encoding, maintenance, and access during a delayed-response task with specific ERP components and cognitive processes. Recording ERPs can therefore provide unique information about the different stages of cognitive processing that contribute to abnormalities of working memory in schizophrenia, which is not available from behavioral or neuroimaging measures.

Studies in healthy adults have recorded ERPs during match-to-sample paradigms, in which subjects are presented with an initial stimulus (S1) and, after a delay of a few seconds, are required to indicate whether a probe stimulus (S2) matches S1. Several studies have demonstrated that slow wave (SW) potentials during the S1–S2 interval reflect the maintenance or rehearsal of information in working memory (e.g., Löw et al., 1999; Ruchkin, Johnson, Grafman, Canoune, & Ritter, 1992, Ruchkin et al., 1997; Vogel & Machizawa, 2004). Ruchkin et al. (1992) identified two slow wave potentials that varied as a function of verbal working memory load, and suggested that a positive SW with a parietal maximum between 1000 and 3000 ms after S1 onset reflected long-duration encoding and elaboration, whereas a subsequent, left-lateralized negative SW with a frontal maximum reflected rehearsal of phonological information. In accordance with these findings, this research group found a modality-nonspecific, sustained left anterior negativity during visual and auditory verbal working memory tasks (Ruchkin et al., 1997). A similar enhancement of SW negativity over frontocentral sites during a visuospatial delayed-response task was observed by Geffen et al. (1997), who proposed that this "SW memory effect" represents a neurophysiological correlate of maintenance of information in working memory. Both frontal and parietal slow waves have also been shown to increase as a function of working memory load in an *n*-back task (Gevins et al., 1996; McEvoy, Smith, & Gevins, 1998). Notably, these later two studies, as well as the study by Löw et al. (1999), used reference-free Laplacian transformations of the ERP data to sharpen scalp topography and to avoid the interpretational uncertainties stemming from the choice of the EEG recording reference (e.g., linked mastoids or ears), which crucially affects component polarity and topography.

Two studies have found differences between schizophrenic patients and healthy controls in memory-related slow wave effects during visuospatial match-to-sample (Löw, Rockstroh, Harsch, Berg, & Cohen, 2000) and delayed-response tasks (Cameron et al., 2003). Control subjects showed the expected enhancement of negative slow wave over frontal sites during retention intervals, which was attributed to sustained activation of prefrontal working memory. Schizophrenic patients performed more poorly than controls and lacked the slow wave memory effect over frontal regions. Although this may indicate a deficit in the maintenance of information during working memory performance, these studies did not report on earlier ERP components, and so it is possible that impairment during the encoding stage of processing could have contributed to a subsequent abnormality of the negative slow wave. This possibility is suggested by the findings of Javitt, Shelley, Silipo, and Lieberman (2000), who recorded ERPs of schizophrenic patients and controls during a continuous AX-type working memory task, which requires responding whenever a letter X was preceded by a letter A. Schizophrenic patients showed impaired performance that correlated with a decreased frontocentral positivity, which was evident 350–500 ms after onset of incorrect cues. Also, the patients' performance was no more impaired at long (5 s) than short (850 ms) interstimulus intervals, which may support the conclusion that schizophrenic patients are impaired at *forming* but not in *maintaining* working memory representations. However, if storage capacity is limited, such an impairment would be unaffected by the length of the retention interval, rendering these findings inconclusive.

The extent to which impairments of *verbal* working memory in schizophrenia are due to deficits in encoding, integration, or maintenance of information has received less attention. Schizophrenic patients, who perform as well as healthy controls on a screening test of auditory attention and perception, show poorer performance than healthy controls in both auditory and visual versions of the word serial position test, which requires short-term storage of the serial positions of a series of four words (Bruder et al., 2004; Stevens, Donegan, Anderson, Goldman-Rakic, & Wexler, 2000; Wexler et al., 1998). Although Wexler, Donegan, Stevens, and Jacob (2002) suggested that impaired working memory for words in schizophrenia may arise after sensory-specific processing, the stage at which these deficits arise needs further study. By taking advantage of recording ERPs during all phases of the word serial position test, the current study sought to provide measures not only of frontal SW memory effects during the retention interval, but also of earlier ERP components over parietotemporal sites associated with sensory/attentional processing (e.g., N1) and context updating (e.g., P3). On the basis of prior findings (Cameron et al., 2003; Löw et al., 2000; Ruchkin et al., 1992), we hypothesized that healthy adults would show an increase in negative SW during retention, particularly over left frontal sites, but this working memory effect would be less evident in schizophrenia. Given our prior findings during a word recognition memory task (Kayser et al., 1999), in which ERP abnormalities of schizophrenic patients arising as early as 200 ms after word onset were associated with their poorer performance, we hypothesized that schizophrenic patients would also show reduced amplitudes of stimulus-related ERPs (N1, P3) over parietotemporal sites, which should be evident across word presentations (initial words and probe).

One of the purposes of this report was also to demonstrate the potential and effectiveness of a new approach for the analysis of ERP data that overcomes limitations of traditional ERP analysis, which may be particularly problematic when studying psychiatric populations, such as schizophrenia. Reference-free current source density (CSD; surface Laplacian) and temporal principal components analysis (PCA) were combined to fully exploit the spatial and temporal information provided by ERP measures and to identify data-driven components of physiological relevance for this verbal working memory challenge (Kayser & Tenke, 2003, 2005, 2006a, 2006b).

Methods

Participants

Seventeen inpatients and two outpatients at New York State Psychiatric Institute and 21 healthy volunteers from the New

Table 1. *Means, Standard Deviations (SD), and Ranges for Demographic and Clinical Variables*

	Patients ($n = 13$, 9 male)			Healthy controls ($n = 17$, 8 male)		
Variable	Mean	SD	Range	Mean	SD	Range
Age (years)	30.5	8.4	18–44	27.4	7.6	19–45
Education (years)	13.7[a]	2.3	9–17	15.7	2.3	12–19
Handedness (LQ)[b]	81.7	30.7	−6–100	84.9	18.6	37–100
Verbal IQ (WAIS)	107.4[c]	14.0	90–124			
Onset age (years)	19.9[d]	6.7	12–34			
Illness duration (years)	9.2[d]	6.9	1–20			
Total BPRS[e]	30.2	6.9	21–43			
PANSS[f] general	26.6	7.6	16–38			
PANSS positive	13.5	5.7	7–26			
PANSS negative	9.5	2.5	7–14			

[a]Patients differ significantly from healthy controls, $p = .03$.
[b]Laterality quotient (Oldfield, 1971) can vary between −100.0 (completely left-handed) and +100.0 (completely right-handed).
[c]$n = 7$.
[d]$n = 11$.
[e]Brief Psychiatric Rating Scale.
[f]Positive and Negative Syndrome Scale.

York metropolitan area without a history of neurological illness or substance abuse were recruited for the study. Three participants (2 patients, 1 control), who did not complete the ERP recording session, were not included in the study. In addition, 3 patients with chance performance and participants (1 patient, 3 controls) who did not provide sufficient artifact-free trials for stable ERP waveforms were removed from the study. Table 1 summarizes the major demographic and clinical characteristics of the final sample (13 patients, 17 controls). Patients were comparable to controls in age and handedness (all right-handed except for one ambidextral patient; Oldfield, 1971; all $F[1,28] < 1.2$, all $p > .28$), but had significantly less education, $F(1,28) = 5.3$, $p = .03$. Due to the exclusion of several participants, the groups were not matched for gender; however, the gender composition was not significantly different between groups, $\chi^2(1) = 1.475$, n.s. The available verbal IQ data (Wechsler Adult Intelligence Scale) suggested that the patients' verbal skills were well within normal range. The experimental protocol had been approved by the institutional review board and was undertaken with the understanding and written consent of each participant.

Eight men and 9 women without current or past psychopathology (First et al., 1996), who were paid US$15/h, were compared to 9 men and 4 women meeting DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia (undifferentiated, $n = 3$; paranoid, $n = 4$), schizoaffective disorder (bipolar type, $n = 4$, or depressive type, $n = 1$), or psychosis not otherwise specified ($n = 1$).[1] Diagnoses were based on clinical interviews by psychiatrists and a semistructured interview (Nurnberger et al., 1994) including items from commonly used instruments (e.g., Andreasen 1983, 1984; Spitzer, Williams, Gibbon, & First, 1990). Symptom ratings were obtained using the Positive and Negative Syndrome Scale (Kay, Opler, & Fishbein, 1992). The total Brief Psychiatric Rating Scale (BPRS) score indicated that patients were mildly to moderately disturbed (Table 1). Most patients ($n = 11$) did not receive antipsychotic medications for at least 14 days before testing. Two patients were treated with risperidone (schizoaffective) or aripriprazole (schizophrenia).

Stimuli and Procedure

A visual analogue of the auditory word serial position test (Wexler et al., 1998) was developed, which consisted of four 32-trial blocks (128 trials total), each trial being a sequence of four words, a retention period, a probe word, and a response. Trials began with a light gray rectangle centered on a darker background (monitor distance about 1 m). Participants were instructed to fixate on the rectangle and not move while it was on the screen. Shortly after rectangle onset (1500 ms), a series of four words, each presented in the center of the rectangle for 500 ms and separated by a 1000-ms interstimulus interval, was followed by a 4500-ms delay, after which one of the four words was repeated as a probe (500 ms). Participants had to remember the four words in the order presented and, when prompted by a response screen 1500 ms after probe onset, to indicate its position in the original sequence by pressing one of four buttons on a response pad using their right or left index finger. Signaling the end of this trial, a blank screen (2000 ms) replaced the response screen after 2500 ms. Response hand (L/R) was alternated across blocks (i.e., RLLR or LRRL), with initial response hand counterbalanced across participants.

Eight sets of four words (32 stimuli) were selected from Wexler et al. (1998) to include only items of the same semantic category (e.g., animals, household objects, fruits, clothing), same length (number of characters and syllables), and about the same frequency of occurrence in the English language (Thorndike & Lorge, 1944; see appendix). Thus, the stimuli consisted of very easy to read, well-known nouns for native English speakers, rendering any differences in verbal skills between controls and patients an unlikely confound. Using different Latin Squares, each word within each set occurred exactly once in each of the four positions of the stimulus sequence and once as a probe. The resulting 16 trials/set were distributed over four experimental blocks separated by rest periods, using the same pseudorandomized trial sequence for all participants, in which any given

[1]One 44-year-old male patient had a preliminary diagnosis of schizoaffective disorder at the time of testing. His cardinal symptom consisted of auditory command hallucinations for many years. At discharge, however, the final diagnosis was changed to *psychosis not otherwise specified*. As this individual clearly falls in the range of schizophrenia spectrum disorders, and due to the small sample, this patient was not excluded from the study. Furthermore, CSD waveforms and all crucial ANOVA results were virtually unaffected by including this patient.

four-word set was repeated after eight trials using a different sequence. For task familiarization, an eight-trial training block used different words.[2]

Data Acquisition, Recording, and Artifact Procedures

Using a Lycra stretch cap with tin electrodes, nose–referenced scalp EEG (AFz ground) was continuously recorded from 30 extended 10–20-system locations (4 midline [Fz, Cz, Pz, Oz] and 13 lateral pairs of tin electrodes [FP1/2, F3/4, F7/8, FC5/6, FT9/10, C3/4, T7/8, CP5/6, TP9/10, P3/4, P7/8, P9/10, O1/2]; Pivik et al., 1993), together with bipolar recordings of vertical and horizontal eye movements (impedances at or below 5 kΩ). Continuous EEG data, stimulus trigger codes, and responses were recorded at 200 samples/s through a Grass/Neuroscan acquisition system at a gain of 10 k (5 k for horizontal and 2 k for vertical eye channels) within 0.01–30 Hz (− 6dB/octave).

Volume-conducted blink artifacts were effectively removed from the raw EEG using a spatial singular value decomposition filter generated from identified blinks and artifact-free EEG periods, thereby minimizing topographic distortions (NeuroScan, 2003). This PCA-based blink correction procedure sufficiently reduced eyeblinks over the entire duration of the long ERP epochs, as verified by visual inspection for each participant.

Recording epochs of 10,500 ms (including a 500-ms prestimulus baseline) were extracted off-line from the blink-corrected continuous data, tagged for A/D saturation, and low-pass filtered at 20 Hz (− 24 dB/octave). Epochs contaminated by amplifier block or drift, residual eye activity, muscle, or movement-related artifacts were excluded by a rejection criterion of ± 100 μV on any channel followed by direct visual inspection of the raw data.

Volume-conducted horizontal eye movements, which were systematically prompted by the nature of the task (i.e., reading the word stimuli), were further reduced by computing the linear regressions between the horizontal EOG and the EEG differences of homologous lateral recording sites (i.e., Fp2–Fp1, F8–F7, etc.), and then removing the correlated eye activity by applying ± beta weight/2 to each lateral EEG signal. This correction procedure, which is similar to the approach previously used for a dot enumeration task that also produced horizontal eye artifacts (Bruder et al., 1998), was applied to each epoch to maximize the number of artifact-free epochs.[3] For the same reason, a new, reference-free approach was used to identify artifactual EEG epochs for any given trial (Kayser & Tenke, 2006c), which was based on the electrical distance measure introduced by Tenke and Kayser (2001). Using this measure, channels with extreme values outside a median-based range (Junghöfer, Elbert, Tucker, & Rockstroh, 2000) were flagged, and these artifactual surface potentials were replaced by spherical spline interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989, 1990) from artifact-free channels. A trial was rejected if it contained artifacts in more than eight channels. Artifact detection and electrode replacement was verified by visual inspection.

[2]Stimulus lists with their randomization sequence are available at URL http://psychophysiology.cpmc.columbia.edu/wspt2005stimuli.html.

[3]Applying this horizontal eye artifacts regression approach to EEG epochs or an ERP average computed from these very epochs results in the same corrected ERP average due to its linear nature. However, correcting these artifacts on an EEG epoch level reduces the probability of rejecting an EEG epoch, thereby potentially improving the ERP signal-to-noise ratio by increasing the number of artifact-free trials.

ERP waveforms were averaged from correct, artifact-free trials using the entire 10.5-s epoch. The mean number of trials used to compute these ERP averages were 69.8 ($SD = 18.1$, range 44–98) for patients and 83.0 ($SD = 25.8$, range 42–121) for controls, a statistically insignificant group difference, $F(1,28) = 2.45$, $p > .10$. The mean percentage of artifact-free trials out of all correct trials, which was 75.1% ($SD = 13.1\%$, range 53.2%–92.3%) for patients and 73.8% ($SD = 17.6\%$, range 50.9%–96.8%) for controls, also suggested that findings were not confounded by a group bias in the number of trials entering into any given ERP. Visual inspections of the individual ERP waveforms indicated that the signal-to-noise ratio was satisfactory for each participant. ERP waveforms were screened for electrolyte bridges (Tenke & Kayser, 2001), low-pass filtered at 5 Hz (− 24 dB/octave; cf. Löw et al., 1999, 2000), and finally baseline corrected using the 100 ms preceding onset of the first stimulus.

Current Source Density (CSD)

CSD is a mathematical transformation (second spatial derivative; Laplacian), which provides a representation of the direction, location, and intensity of current generators that underlie an ERP topography (Nicholson, 1973; Mitzdorf, 1985). CSD maps represent the magnitude of the radial (transcranial) current flow entering (sinks) and leaving (sources) the scalp (Nunez, 1981). CSD analysis is a reference-free technique that provides topographies with more sharply localized peaks than those of the scalp potential, while eliminating volume-conducted contributions from distant regions (e.g., Tenke & Kayser, 2005; Tenke et al., 1998; Tenke, Schroeder, Arezzo, & Vaughan, 1993). Although it has previously been argued that high-density (i.e., 100 or more recording sites) ERPs are required for obtaining reliable surface Laplacian estimates (e.g., Junghöfer, Elbert, Leiderer, Berg, & Rockstroh, 1997), we have demonstrated that low-density CSD estimates are both adequate and sufficient to summarize group data (Kayser & Tenke, 2006b).

All averaged ERP waveforms were therefore transformed into reference-free current source density estimates using the spherical spline surface Laplacian algorithm suggested by Perrin et al. (1989, 1990) with computation parameters (50 iterations; $m = 4$; smoothing constant $\lambda = 10^{-5}$) previously established for a 31-channel recording montage (Kayser & Tenke, 2006a; Tenke & Kayser, 2005; Tenke et al., 1998). Current source density estimates were expressed as the negative surface Laplacian of the ERP at each electrode based on a unit sphere (radius $r = 1.0$) and converted into $\mu V/cm^2$ units based on a head radius of 10 cm.

Data Reduction and Analysis

To determine common sources of variance in the reference-free transformations of the original ERP data, the averaged CSD waveforms were submitted to temporal principal components analysis (PCA) derived from the covariance matrix, followed by unscaled Varimax rotation (Kayser & Tenke, 2003, 2006a). This approach produces distinctive PCA components (factor loadings) and corresponding weighting coefficients (factor scores), which provide a concise, efficient simplification of the temporal pattern and spatial distribution of neuronal generators (Beauducel, Debener, Brocke, & Kayser, 2000; Kayser et al., 1997, 1999; Kayser, Bruder, Tenke, Stewart, & Quitkin, 2000; Kayser, Tenke, & Bruder, 1998). Unlike ERP factors, CSD factors are independent of the recording reference, resulting in unambiguous component polarity and topography (Kayser & Tenke, 2006a). The correspondence between the time course and topography of

orthogonal, "data-driven" PCA factors and CSD components allows identification and measurement of complex, physiologically relevant factors for further analysis (Kayser & Tenke, 2003, 2006a). Although several limitations of PCA techniques (e.g., misallocation of variance resulting from latency jitter or component overlap) are well known and demand cautious attention, it is important to recognize that more conventional ERP measures are subject to the very same limitations and are probably even more severely affected (cf. Kayser & Tenke, 2005).

Using a MatLab function (appendix of Kayser & Tenke, 2003) that emulates BMDP-4M algorithms (Dixon, 1992), a temporal PCA was computed using 2101 variables (− 500 to 10,000 ms) and 930 observations (30 participants; 31 electrode sites, including the nose). Although it is generally suggested that the number of observations should be several times the number of variables to obtain a stable PCA solution (e.g., Chapman & McCrary, 1995; Guadagnoli & Velicer, 1988), we have found this not to be a problem when using unrestricted solutions (Kayser & Tenke, 2003). In fact, when the current CSD data were down-converted to 50 samples/s, effectively the same PCA solution was observed.

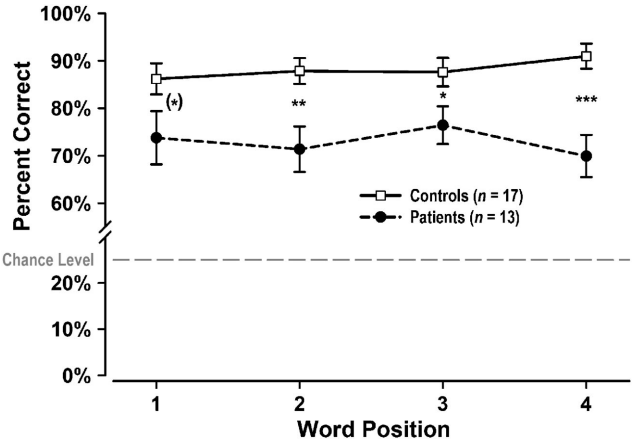

Figure 1. Mean percentage of correct responses (and standard error of the mean) for patients (dashed, circles) and healthy controls (solid, squares) as a function of position of words within the initial series. A chance performance (25%) is marked by a gray dashed line. Simple group main effects are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

Statistical Analysis

Factor scores of meaningful PCA factors were submitted to repeated measures analyses of variance (ANOVA) with group (patients, controls) as the between-subjects factor, including subsets of recording sites at which PCA factor scores were largest and most representative of the associated CSD components (cf. Kayser & Tenke, 2006a; Kayser et al., 2001). These subsets consisted of either midline sites or lateral, homologous recording sites over both hemispheres, thus adding either site or site and hemisphere as within-subjects factors to the design.[4]

Greenhouse-Geisser epsilon (ε) correction was used to compensate for violations of sphericity when appropriate (e.g., Keselman 1998; Picton et al., 2000). The sources of interactions and main effects were systematically examined through contrasts or simple effects (BMDP-4V; Dixon, 1992), while focusing on group effects and sites reflecting distinct source or sink activity. A conventional significance level ($p < .05$) was applied for all effects.

The percentage of correct responses for each probe condition was submitted to repeated measures ANOVA with word position (1, 2, 3, or 4) in the initial series as the within-subject factor and group as the between-subjects factor.

Due to uneven sample sizes for gender (i.e., only 4 female patients were included), gender was not entered as a control factor in statistical analyses. However, analyses including only male patients ($n = 9$) and controls ($n = 8$) yielded essentially the same results as reported below for full samples.

Nonparametric Spearman rank-order correlations (rho) were used to examine, where appropriate, the relation between behavioral performance and prominent CSD components. Fisher-Z transformed correlations were tested for group differences.

Results

Behavioral Data

The mean percent correct was significantly lower for patients (72.9 ± 16.8%) compared with controls (88.2 ± 11.9%; group main effect, $F[1,28] = 11.1$, $p = .03$), and this group difference was observed in all serial positions (Figure 1). However, all schizophrenic patients performed adequately and well above chance (25%) at all four word positions. The position main effect and the Group × Position interaction did not reach statistical significance, both $F(3,84) < 2.1$, $\varepsilon = 0.75$, both $p > .13$.

Average ERP and CSD Waveforms

Grand average ERP waveforms of the surface potentials are shown in Figure 2 for patients (dotted lines) and controls (solid lines). As can be seen, stimulus-specific, short-latency ERP components (i.e., N1 and P3) following each word presentation were prominent at occipital and inferior parietotemporal sites. It should be noted that horizontal and vertical eye movements were comparable across groups, and that blink activity, which was mostly stimulus related (approximate peak latency following word onset 600–800 ms), was effectively removed by the spatial blink filter applied to the continuous data. A negative SW was evident across the entire word presentation sequence for all ERP channels, but was most prominent at mid-frontal locations. Given that the sustained negativity was present at all sites, including the mastoids (TP9/10), when using a nose reference, a linked mastoids reference would yield a positive SW at nose (i.e., a different reference will result in a different pattern of positive and negative SW activity).

The reference-free CSD transformations of the ERP waveforms shown in Figure 2, which eliminate these reference-de-

[4]Additional spatial PCAs were computed for each temporal CSD factor from their rearranged temporal factors scores (i.e., using 30 participants as cases and 31 electrodes as variables). The resulting virtual electrodes (spatial factor loadings; cf. Spencer, Dien, & Donchin, 1999, 2001) and ensuing statistical evaluation of group differences supported both the electrode selections for a specific ANOVA design as well as their statistical outcome. However, because spatial redundancies resulting from the smearing of surface potentials are effectively removed by virtue of the CSD transform, spatial factors tend to load on individual electrodes, thereby limiting the value of the spatial PCA approach for these data. Furthermore, the topography of spatial factors cannot be evaluated statistically and must be taken on face value (i.e., as represented by the loading configuration of a spatial factor), which interferes with the objective of exploring differences in laterality between healthy and psychiatric populations.

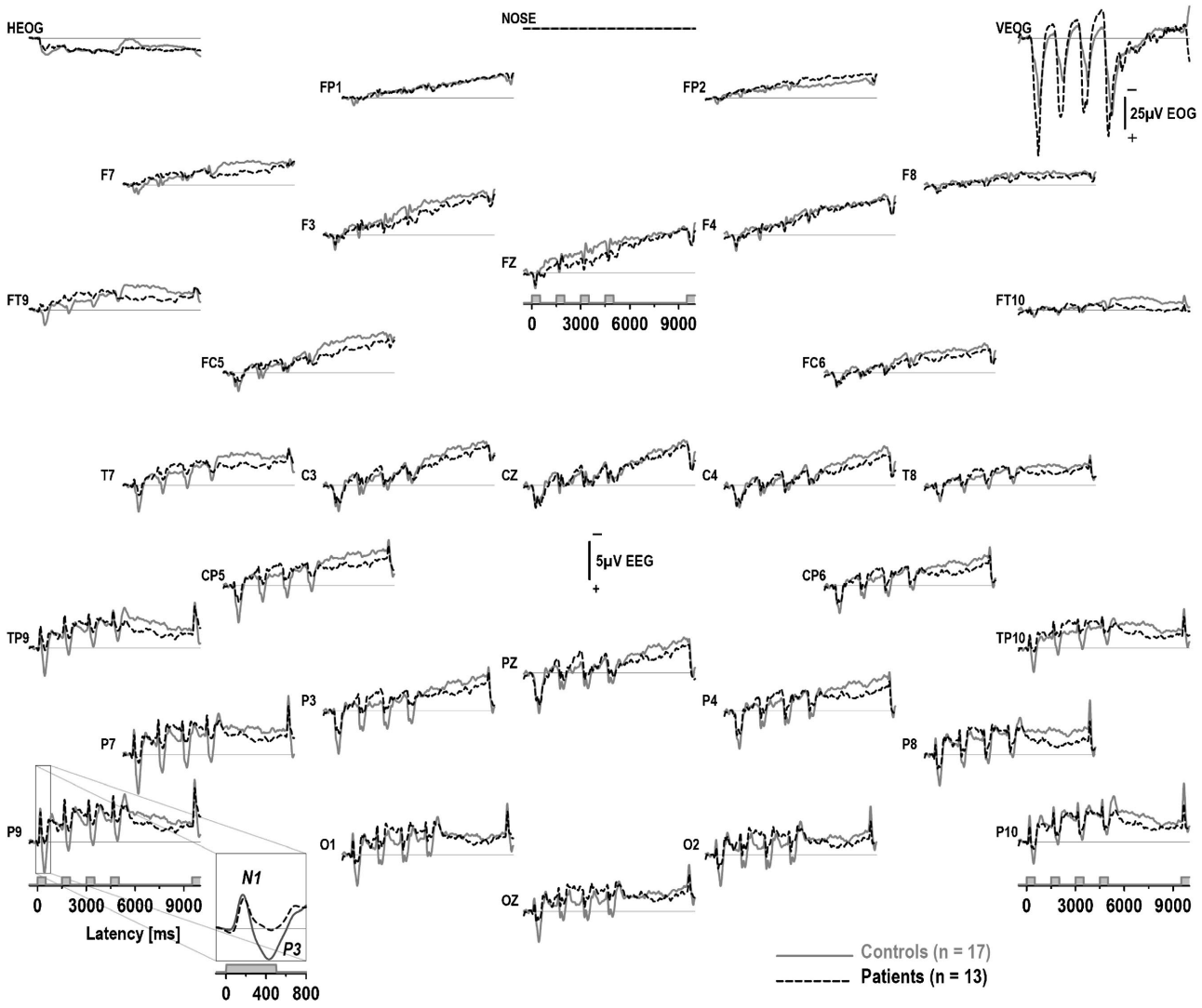

Figure 2. Grand average event-related surface potential (in microvolts) waveforms for 13 patients (dashed black lines) and 17 controls (solid gray lines) at all 30 recording sites using a nose tip reference. Horizontal (HEOG) and vertical (VEOG) electrooculograms (in microvolts) are shown at a smaller scale before blink correction in top corners. Stimulus presentation periods are indicated by gray rectangles above the timelines at sites Fz, P9, and P10. Stimulus–specific ERP components were well defined over the posterior scalp, including N1 (approximate peak latency to previous word onset 170 ms at P9) and P3 (430 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 ERP activity). An overall increase in negative slow wave across the entire 10-s ERP recording epoch is evident at all recording locations (other than the nose reference), however, particularly prominent at mid–frontal scalp sites (e.g, see F3, Fz, F4).

pendent ambiguities, are given in Figure 3, showing sink (negative) and source (positive) activity at each recording site.[5] A distinct stimulus-locked sink-source pattern corresponding to N1 and P3 components was observed after each word presentation, progressing from the occipital region near the inion (Oz) into inferior parietal-temporal sites (see enlarged inset at site P9 in Figure 3). This pattern parallels the presumed activation of striate cortex and the ventral stream, and is characterized by N1 sinks peaking at approximately 180 ms followed by P3 sources peaking at approximately 410 ms after each word onset at site P9. Although the N1 sink amplitudes were comparable across groups, the P3 sources were clearly larger in controls compared to patients at the left inferior parietal sites (e.g., P7, P9), but not at corresponding sites over the right hemisphere (P8, P10). In addition to these stimulus-locked CSD components, slow wave activity spanning the entire 10-s epoch was also observed. A buildup of negative sink activity at mid-frontal sites (Fz), increasing stepwise after each word in the initial series, was observed in controls, and was followed by a sustained slow wave sink during the retention interval preceding the probe word. In contrast, patients largely lacked the stepwise mid-frontal sink increase during the encoding period. They showed, however, comparable sustained slow wave sink activity during the retention period. The mid-frontal sink increase was paralleled by a buildup of (1) positive source activity over occipital (e.g., Oz) and anterior (e.g., Nose) sites and (2) sink activity at inferior parietal-

[5]Animated topographies of CSD waveforms shown in Figure 3 can be obtained at URL http://psychophysiology.cpmc.columbia.edu/wspt2005csd.html.

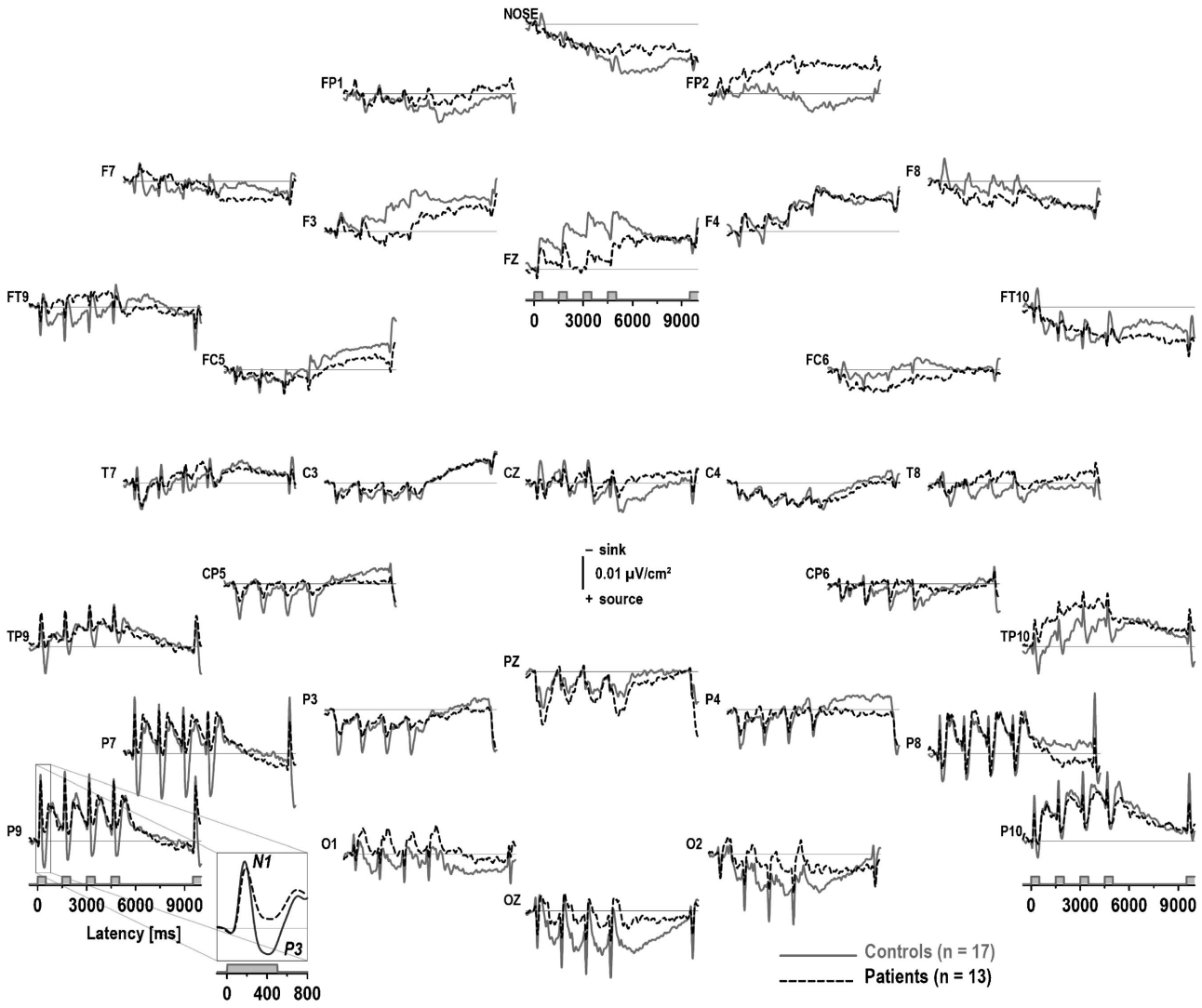

Figure 3. Reference-free current source density (in units of $\mu V/cm^2$) waveforms (spherical spline Laplacians; Perrin et al., 1989, 1990) for 13 patients (dashed black lines) and 17 controls (solid gray lines) at all 31 recording sites. Stimulus presentation periods are indicated by gray rectangles above the timelines at sites Fz, P9, and P10. Distinct CSD components included stimulus-locked inferior lateral-parietal N1 sinks (approximate peak latency to previous word onset 180 ms at P9) and P3 sources (410 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 and occipital source activity during word encoding (up to 6 s; see Fz, P10, and Oz), and a sustained frontocentral sink during the retention period (6–9.5 s; see Fz).

temporal sites, particularly over the right hemisphere (e.g., P10, TP10), on which stimulus-locked sinks and sources were superimposed. These posterior and anterior sinks and sources were fairly comparable in both groups, although the buildup in occipital source activity appeared to be more pronounced in healthy adults, whereas the buildup in right inferior temporal-parietal sink activity appeared to be more pronounced in patients.

PCA Component Waveforms

Figure 4 compares the time courses of factor loadings for five CSD factors (i.e., extracted factors 1–4 and 6; 88.2% explained variance after rotation) to CSD waveforms at characteristic sites. CSD factors were labeled using peak latencies of their loadings and corresponding CSD components, identified as distinct CSD sinks and sources. For easy reference and identification, the catch terms ''encoding'' and ''retention'' were used as additional labels for the two SW components. These terms were meant to pragmatically distinguish the corresponding phases of the word serial position test but not to imply an isolated underlying process. Likewise, the labels ''N1 sink'' and ''P3 source'' do not exclusively refer to these identifying sink and source activities but rather to the respective CSD factors, consisting of characteristic time courses and topographies.

Three factors summarized the phasic, stimulus-locked CSD activity corresponding to the N1 sinks (factor 190, 2.1% explained variance), P3 sources (365, 6.0%), and late sinks (825, 4.4%) following each word presentation. Two factors summarized the slow wave activity, corresponding to the gradual increase in regional SW sink and source activity during the encoding period (3910, 33.0%) and the largely sustained SW sink and source activity during the retention interval

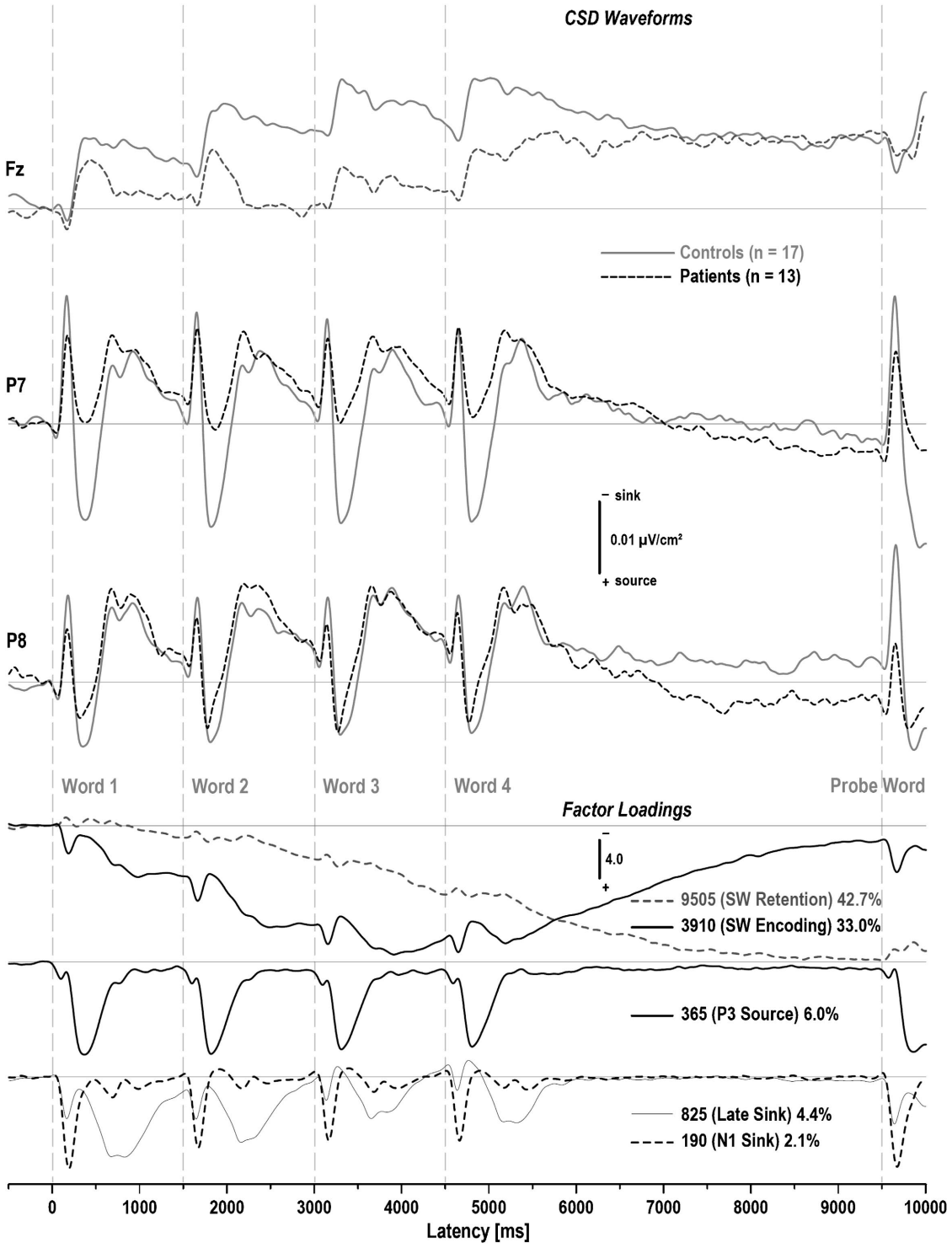

Figure 4. Grand mean current source density (CSD) waveforms (in units of $\mu V/cm^2$) at selected sites (Fz, P7, P8) comparing 13 patients (dashed black lines) and 17 controls (solid gray lines), and time courses of Varimax-rotated factor loadings for five PCA components extracted from all CSD waveforms (Kayser & Tenke, 2003, 2006a). 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 slow wave (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.

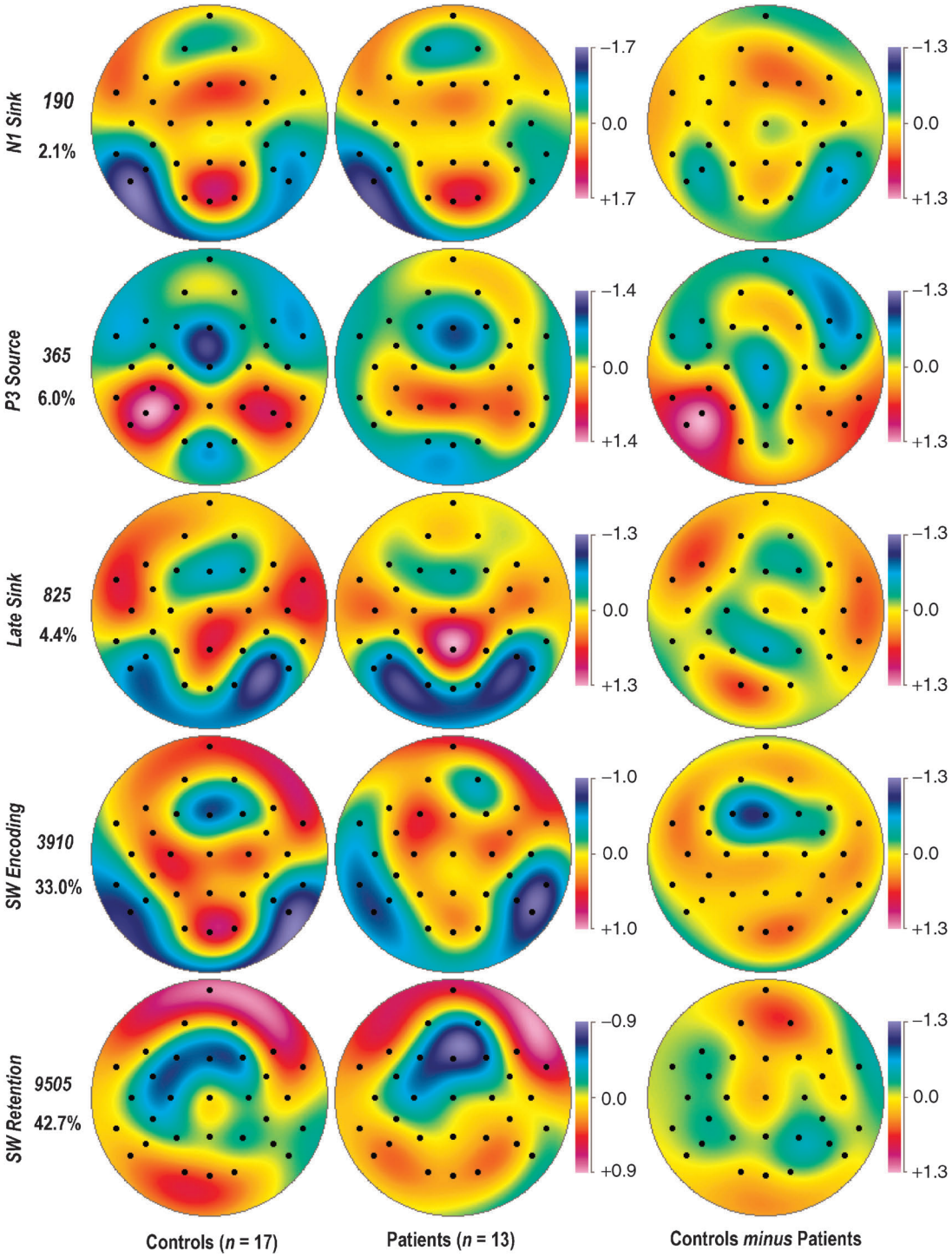

Figure 5. Mean topographies of factor scores for PCA components extracted from CSD (current source density) waveforms for 17 healthy controls (left column) and 13 patients (middle column), and the respective group difference (right column). In a temporal PCA, the factor scores represent the weight of a factor's loadings pattern with each observation (i.e., CSD waveforms observed for each electrode and participant; Kayser & 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 two-dimensional representations of spherical spline surface interpolations (Perrin et al., 1989, 1990) derived from the mean factors scores available for each recording site.

(9505, 42.7%), accounting together for most of the total CSD variance.[6]

PCA Component Topographies and Statistical Results

Figure 5 shows the PCA topographies for both groups, along with their group difference, for each factor.

N1 sink. Factor 190 (Figure 5, top row) had a negative amplitude at left inferior parietal sites (cold colors at P7, P9), which is entirely consistent with the left-lateralized N1 maximum of the CSD waveforms (Figure 3; cf. also animations referenced in footnote 3). These sinks were paralleled by an occipital source (warm colors at Oz).[7] Two statistical analyses were computed using inferior-parietal sites (P7/8, P9/10, TP9/10) for the sink, and Oz for the source. The ANOVA for the lateral sites revealed a highly significant left-greater-than-right-hemisphere N1 sink across both groups (LH = -1.21 ± 1.24, RH = -0.62 ± 0.89; $F[1,28] = 11.0$, $p = .003$). A significant group × site interaction, $F(2,56) = 3.71$, $p = .04$, $\varepsilon = .87$, originated from a greater N1 sink for controls (-1.10 ± 1.07) than patients (-0.39 ± 1.21) at P7/8, $F(1,28) = 4.94$, $p = .03$. There was no significant group difference for the Oz source. There were no significant correlations of this N1 sink activity with working memory performance.

P3 source. Factor 365 corresponded to a prominent P3 source over lateral parietal sites in healthy adults, which was clearly more medial for patients, who had a Pz maximum (Figure 5, row 2). This posterior positivity coincided with a mid-frontocentral sink in both groups. Three statistical analyses were computed for factor 365 using lateral parietal sites (P3/4, P7/8, P9/10) and Pz for the source activity, and mid-frontocentral sites (Fz, Cz) for the sink. The ANOVA for the lateral parietal sites revealed highly significant effects of group, $F(1,28) = 8.38$, $p = .007$, and Group × Hemisphere, $F(1,28) = 8.81$, $p = .006$, stemming from greater overall and left-greater-than-right amplitude for controls (LH = 1.31 ± 1.25, RH = 0.89 ± 1.02) compared to patients (LH = 0.22 ± 1.28, RH = 0.49 ± 1.04; see group difference map in Figure 5, row 2, right column). However, there was no significant group difference at Pz. Marginally significant effects of group, $F(1,28) = 3.81$, $p = .06$, and Group × Site, $F(1,28) = 3.97$, $p = .06$, were observed for the frontocentral sink, which originated from a somewhat more pronounced vertex sink in controls than patients (simple effect at Cz, $F[1,28] = 8.69$, $p = .006$). P3 source activity recorded at the left mid-parietal P3 site revealed a significant positive correlation with working memory performance across groups only (rho = 0.39, $p = .03$; for controls, rho = 0.18, for patients, rho = 0.26, both n.s.), but this association was not evident at the other sites.

Late sink. Factor 825 corresponded to lateral occipital-parietal sinks and a mid-parietal source that followed the P3 source (Figure 5, row 3; see also Figure 4). Two statistical analyses computed at lateral occipital-parietal sites (O1/2, P7/8, P9/10) for the sink and Pz for the source activity revealed no significant effects except for a site main effect for the sink, $F(2,56) = 3.86$, $p = .05$, $\varepsilon = .63$. This factor was also uncorrelated with working memory performance.

Slow wave encoding. Factor 3910 corresponded to the stepwise increase in SW sink activity at mid-frontal (Fz) and lateral inferior parietal-temporal (P9/10, P7/8, TP9/10) sites during the presentation of the initial four words, paralleled by an occipital (Oz) source (Figure 5, row 4; see also Figure 3), which prompted three statistical analyses. As the mid-frontal sink was shifted to right prefrontal sites (F4, Fp2) in patients, an additional analysis included prefrontal and medial-frontal sites (Fp1/2, F3/4). The analysis for the mid–frontal site Fz revealed a highly significant group difference, $F(1,28) = 9.26$, $p = .005$, confirming the stepwise SW sink increase in controls (-0.74 ± 0.84) but not patients (0.28 ± 1.00; see group difference map in Figure 5, row 4, right column). The analysis for lateral-frontal sites revealed no significant effects except for a right-greater-than-left hemisphere sink (-0.23 ± 1.09 vs. 0.16 ± 1.00; $F[1,28] = 5.60$, $p = .03$). A marginally significant group difference for the Oz source, $F(1,28) = 2.91$, $p < .10$, supported a greater stepwise occipital positive SW increase in controls (0.82 ± 0.97) than patients (0.25 ± 0.80). There were no significant effects for the lateral posterior sink.

Across both groups, SW source at Oz was significantly correlated with working memory performance (rho = .50, $p = .005$), which was marginally significant in controls (rho = .43, $p = .09$) but not patients (rho = .35, n.s.). Likewise, there were significant correlations for SW sink activity at lateral inferior–parietal sites for healthy adults only (at P9 and TP10, both rho = 0.49, both $p < .05$). However, the only significant group difference was observed for site TP10 ($z = -1.85$, $p = .03$). In accordance with the hypothesis that the sink increase at Fz and lateral posterior sites and the occipital source increase may indicate concurrent activity throughout a working memory network, these source-sink differences (i.e., Oz minus Fz, Oz minus P9, Oz minus P10) were significantly correlated with performance across both groups (all rho > .42, all $p < .02$), and these relations were preserved in controls (for Oz–Fz, rho = .44, $p = .08$; for Oz–P9, rho = .56, $p = .02$; for Oz–P10, rho = .59, $p = .01$) but not patients (all rho < .25, n.s.). However, there were no significant group differences for these correlations ($0.81 \leq z \leq 1.30$, $p \geq 0.1$).

Slow wave retention. Factor 9505 corresponded to a sustained mid–frontal (Fz) sink that extended into medial frontocentral regions (F3/4, FC5/6, C3/4), particularly over the left hemisphere, and was largest during the retention interval. As this SW sink was paralleled by sustained anterior (Nose) source activity (Figure 5, row 5; Figure 3), three statistical analyses were computed. There were no significant effects for the midline sites (Fz sink, Nose source). There were also no significant effects at medial frontocentral sites except for a left–greater–than–right hemisphere sink across groups (-0.52 ± 0.94 vs. -0.26 ± 1.00; $F[1,28] = 4.67$, $p = .04$). The amplitude of SW factor 9505 at Fz

[6]To confirm the interpretation that the two long-duration factors 3910 and 9505 measured slow CSD activity during early and late periods of the recording epoch, the surface potential ERPs were low-pass filtered at 0.5 Hz (-24 dB/octave), converted into CSD waveforms, and integrated time window amplitudes (3000–6000 ms and 6000–9500 ms) were computed for both groups. The resulting topographies were highly similar to the ones obtained for the CSD factors (Figure 5, rows 4 and 5), thereby supporting the validity of these factors.

[7]To confirm the interpretation that factors 190 and 365 measure stimulus-related CSD activity independent of the long recording epoch that included five discrete word presentations, a separate PCA was computed from short CSD epochs extracted from the data of the entire epoch, time-locked to the onset of each word (-100 to 500 ms, new 100-ms baseline correction). The first two CSD factors closely corresponded to an N1 sink (165 ms peak latency, 24.5% explained variance) and a P3 source (405 ms, 54.0%), and their factor score topographies for each condition (words 1–4, probe word) were effectively identical with the ones found for factors 190 and 365 (Figure 5, rows 1 and 2), thereby cross-validating the usefulness and legitimacy of these factors.

was inversely correlated with working memory performance across both groups (rho = $-.36$, $p < .05$), and this relation was highly significant in controls (rho = $-.77$, $p < .001$) but not patients (rho = $-.17$, n.s.), a significant group difference ($z = -2.07$, $p = .02$).

Effects of Using a 5-Hz Low-Pass Filter

Because the focus of the present study was on slow, long-lasting ERP/CSD components, ERPs were smoothed by a 5-Hz low-pass filter, which is common for this type of ERP research (e.g., Löw et al., 1999, 2000; Ruchkin et al., 1997). However, ERP components of shorter latency, that is, P3 and particularly N1, which are typically not analyzed in these studies, will be affected by such a filter choice (i.e., reduced in amplitude), raising the question of whether this filter distorted the ERP component structure and/or differentially affected the two groups. To address this concern, the unfiltered data (i.e., before applying the additional 5-Hz low pass) were submitted to the same temporal PCA-ANOVA approach described above. With the exception of the original CSD factor 190 (N1 sink), all factors derived from the unfiltered CSD data directly corresponded to the original CSD factors (correlations of corresponding factor loadings, all $r \geq .968$; correlations of corresponding factor score topographies for each group, all $r \geq .996$). The corresponding ANOVA results were virtually identical to those computed with the factor scores of the filtered data. Although the low pass clearly affected the shape of the P3 source (i.e., for both the CSD waveforms and the factor loadings), it did not substantially alter the reported group differences for the P3 source factor scores at lateral parietal sites (group main effect, $F[1,28] = 7.89$, $p = .009$; Group $\times$ Hemisphere interaction, $F[1,28] = 8.02$, $p = .008$).

The original N1 sink factor was split into two distinct CSD factors with similar left-lateralized, inferior parietal topographies, evidently corresponding to N1 and N2 sinks with peak latencies of 145 and 205 ms, which closely matched our previous ERP findings for visually presented words in a continuous recognition memory paradigm (Kayser et al., 1999, Kayser, Fong, Tenke, & Bruder, 2003). Given the frequency properties and temporal proximity of these early sinks, it is not surprising that these neighboring components were merged due to temporal smearing caused by the 5-Hz low-pass filter. The statistical analyses revealed a highly significant left-greater-than-right hemisphere asymmetry across both groups for the N1 sink, $F(1,28) = 10.5$, $p = .003$, but not for the N2 sink, $F(1,28) = 1.8$, n.s. However, no significant group main or interaction effects emerged in the ANOVA for these early CSD factors.

Discussion

Patients having schizophrenia or schizophrenia-spectrum disorders showed poorer verbal working memory than healthy adults, and the extent of their deficit was comparable to that previously seen for schizophrenic patients for a visual version of the word serial position test (Stevens et al., 2000). By exploiting the fine temporal and improved spatial resolution of CSD-transformed ERPs, this study provides evidence that the deficit is at least partially related to cognitive processes involved in the encoding and integration of information into working memory. A left-lateralized, parietotemporal sink with about 190 ms latency after word onset, corresponding to the N1 component, was slightly smaller in patients. A more marked reduction was found for cortical source activity, corresponding to the cognitive P3 potential about 400 ms following word onset, particularly over language-related, left inferior parietal-temporal regions. Moreover, healthy adults showed a buildup of a frontal sink, corresponding to negative slow wave, during the encoding and early storage of the series of words in the word serial position test, which was absent in patients. In contrast, a sustained frontal sink (negative SW) during the retention interval did not differ between patients and controls. Although reductions of memory-related negative slow waves have previously been reported for schizophrenia (Cameron et al., 2003; Löw et al., 2000), the reference-free CSD/PCA estimates derived over the entire 10-s recording epoch (including shorter-latency, stimulus-related N1 and P3 components) allowed an improved description of the timing and topography of cortical activity (i.e., neuronal generator patterns) associated working memory deficits in schizophrenia.

Temporal PCA enabled a comprehensive segregation of brain radial current flow into CSD components corresponding to different stages of cognitive processing. A distinct stimulus-locked sink-source pattern was observed after presentation of each word, progressing anteriorly from the occipital region near the inion into inferior temporal-parietal sites, which parallels the presumed activation of striate cortex and the ventral stream (e.g., Ungerleider, Courtney, & Haxby, 1998). This stimulus-locked activation was superimposed by dissociable, long-lasting positive and negative slow waves, which directly corresponded to the task sequence of stimulus encoding phase, including early storage and item integration and maintenance of the full buffer in working memory during the retention phase.

A left-lateralized negative CSD component (sink) at inferior parietal sites, peaking at about 190 ms after word onsets, corresponded to a stimulus-locked, modality-specific N1 surface potential associated with initial sensory/attentional processing of word stimuli (e.g., Kayser et al., 1999, 2003). Although this component should be interpreted with some caution, because the analysis of the unfiltered CSD waveforms revealed this component to be a fusion of two distinct successive sinks (N1 and N2) with similar topographies, this factor nevertheless provided an appropriate summary measure for the early sink activity. This component was slightly smaller in patients at lateral parietal sites (P7/8), which is in accordance with evidence that deficits in word processing in schizophrenia may begin as early as 200 ms after stimulus onset (e.g., Kayser et al., 1999). Nevertheless, the hemispheric asymmetry of this component, and its amplitude at other sites, was comparable in patient and control groups, suggesting that the impairment in working memory performance in patients is not likely to be due solely to a deficit in an early, sensory/attentional stage of processing linguistic stimuli. This conclusion is supported by findings of Wexler et al. (2002), who used serial position tests designed to bypass perceptual processing of verbal material (e.g., by presenting line drawings of familiar objects and requiring participants to remember the word associated with these pictures), but still observed marked working memory deficits in schizophrenia patients for these tasks. Doniger, Foxe, Murray, Higgins, and Javitt (2002), who found an intact visual N1 in chronic patients, also concluded that the initial stages of ventral stream processing are relatively preserved in schizophrenia.

A positive CSD component (source) peaking about 400 ms after word onsets, corresponding to the cognitive P3 potential, was more prominent at lateral-parietal rather than mid-parietal sites in healthy adults (cf. Kayser & Tenke, 2006a), but was markedly reduced in schizophrenia patients at these lateral sites. Moreover, the left-greater-than-right parietal asymmetry of this

source in healthy adults but not patients closely matches our previous findings for N2/P3 amplitude during a word recognition memory task (Kayser et al., 1999). Studies have found regional hemispheric asymmetries of cognitive ERPs (N2, P3) in healthy adults consistent with the neuroanatomical organization of phonetic and tonal processing (Alexander et al., 1996; Bruder et al., 1999; Kayser & Tenke, 2006a; Kayser et al., 1998, 2001; Tenke et al., 1993). Thus, asymmetric, left-lateralized N1 sinks and P3 sources indexing ventral-occipital visual processing would be expected for linguistic tasks that require decoding of grapheme and orthographic information and accessing the lexicon, therefore relying on language functions subserved by left-hemispheric structures (e.g., the extrasylvian temporo-parietal region, angular gyrus, Wernickes area; e.g., Price, 2000).

P3 amplitude is thought to index late cognitive processes (e.g., stimulus evaluation) and is as such considered to be an electrophysiologic marker of cognitive dysfunction in schizophrenia (e.g., Ford, 1999). Reduction of P3 amplitude in schizophrenia has been one of the most consistent findings in studies using auditory target detection (oddball) tasks, but has been less evident for visual stimuli (Egan et al., 1994; Ford, 1999; Ford et al., 1994; van der Stelt, Frye, Lieberman, & Belger, 2004). Some studies have found a left-lateralized reduction of cognitive ERPs (N2, P3) in schizophrenia, which has been related to asymmetric abnormalities in temporal lobe structures (e.g., Bruder et al., 1999; Kayser et al., 1999; McCarley et al., 1993; O'Donnell et al., 1993, 1999; Salisbury et al., 1998; Turetsky, Colbath, & Gur, 1998; van der Stelt et al., 2004; however, see Kayser et al., 2001), whereas other studies have found symmetric P3 reductions (Ford et al., 1994; Pfefferbaum, Ford, White, & Roth, 1989). If P3 amplitude indexes resource allocation for context updating of working memory (Donchin, 1981; Donchin & Coles, 1988), the reduced left parietotemporal source in schizophrenia may reflect a lateralized linguistic deficit, which would impact on their verbal working memory performance. An impairment in forming phonological word representations for storage and rehearsal could be the basis for, or at least contribute to, verbal working memory impairments in schizophrenia on both visual and auditory versions of the word serial position test (Wexler et al., 2002).

We can offer only a tentative discussion for the third stimulus-related CSD factor summarizing the late occipital sink and mid-parietal source activity following the P3 source. Its peak latency of about 800 ms and sink-source topography is strikingly similar to a CSD component observed in a visual recognition memory paradigm (Kayser et al., 2005), and also to a PCA factor derived from surface potentials in a similar visual word recognition memory task (Kayser et al., 2003). In both studies, these components were observed after a manual response. However, none of these studies included an effective parametric manipulation that could have shed some light on the cognitive significance of this factor, and despite its reproducibility across studies, it is unclear whether this systematic variance qualifies under the concept of a component (cf. Picton et al., 2000) or whether this factor simply gathers variance unrelated to the study's objective (Kayser & Tenke, 2003). The PCA performed on the unfiltered data also revealed a more pronounced secondary loading peak for this factor at 145 ms, that is, coinciding with N1 sink activity, which suggests an association of this factor with perceptual and/or attentional processes. In any event, because the current study revealed no group differences or relations of this late sink activity to working memory performance, further speculations on the meaning of this CSD factor are moot.

Negative frontal slow waves have been observed in many ERP studies using S1–S2 paradigms with healthy adults, although these studies used considerably shorter encoding and retention intervals (e.g., Bosch, Mecklinger, & Friederici, 2001; Löw et al., 1999). The stepwise increase in mid-frontal negative SW during the encoding interval presumably reflects the increase in working memory load from the first to last word in the series of this verbal working memory task (cf. Mecklinger & Pfeifer, 1996; Ruchkin et al., 1992, 1997). Likewise, the ensuing sustained negative SW, extending particularly into left medial-frontocentral regions, resembles the frontal, left-lateralized negative SW during stimulus retention observed in a verbal match-to-sample task, which was interpreted as indexing retention-rehearsal operations in working memory (Ruchkin et al., 1992, 1997). However, more recent ERP evidence suggests that negative frontal slow waves may index selective, attentional processes required for working memory, which are mediated by the prefrontal cortex (Bosch et al., 2001). Nevertheless, the left frontal maximum of negative SW is consistent with neuroimaging studies showing activation in left inferior frontal gyrus during verbal working memory tasks, including the word serial position test (Smith & Jonides, 1998; Stevens, Goldman-Rakic, Gore, Fulbright, & Wexler, 1998).

The first slow wave component identified by temporal PCA provided a measure of the stepwise increase of mid-frontal SW negativity (sink) after each word in the word serial position test, which was markedly reduced in schizophrenia patients. Similarly, patients tended to show a reduced buildup of a concurrent occipital source. At the same time, the groups did not differ in a corresponding increase of sink activity at lateral inferior parietal-temporal sites. This pattern of findings is consistent with an impairment in the encoding and early storage of words into working memory, which likely involves modality-specific posterior cortices and also a deficit in the integration and active maintenance of new information in the short-term working memory buffer, which likely involves prefrontal and anterior cingulate cortex (e.g., Cohen et al., 1997; Smith & Jonides, 1999). However, due to the lack of parametric manipulation, the current study does not allow a further delineation of these subprocesses (e.g., the contribution of short-term buffer capacity). In contrast, there was no significant difference between patients and controls in the second slow wave component, as both patients and controls showed sustained SW negativity over frontocentral sites during the word retention interval. Thus, despite the marked group differences in parietotemporal P3 and frontal SW activity during word presentations and the 1-s interstimulus intervals, there was no evidence that frontal negative SW during the retention interval, which may reflect continued maintenance of phonological representations in working memory (Ruchkin, Grafman, Cameron, & Berndt, 2003), was abnormal in schizophrenia. Although this may seem at odds with reports of less frontal enhancement of SW negativity in schizophrenia during maintenance of visuospatial information (Cameron et al., 2003; Löw et al., 2000), differences in cognitive tasks (visuospatial vs. verbal) and/or data analysis (e.g., these studies did not use reference-free CSD transformations to sharpen ERP topographies or PCA to separate different spatially and temporally overlapping slow wave components) could well account for the difference in findings. We did, however, find that the slow wave component associated with sustained mid-frontal sink activity during the retention interval was correlated with performance in healthy adults in this word serial position test, but not schizophrenia patients. Further study

of frontal and posterior SW activity in schizophrenia during both verbal and visuospatial working memory tasks would be of value.

Studies in monkeys and humans indicate that a distributed cortical network involving prefrontal and parietal regions mediates performance in working memory tasks (Goldman-Rakic, 1999; Smith & Jonides, 1998; Tek et al., 2002). Electrophysiologic studies provide evidence that sustained coactivation of prefrontal and posterior cortical systems is involved in the short-term storage in working memory (Ruchkin et al., 2003). Consistent with the hypothesis that concurrent SW source and sink activity in these regions indicates activation of this working memory network, word serial position test performance of healthy adults was correlated with SW activity at mid-occipital (source) and mid-frontal/inferior-parietal (sinks) sites, as well as with differences of these regional sink-source activities. In contrast, these correlations were absent or reduced in schizophrenia patients. These findings are consistent with dysfunction of a verbal working memory network involving prefrontal and parieto-temporal regions (e.g., Kim et al., 2003; Winterer, Coppola, Egan, Goldberg, & Weinberger, 2003).

A critical issue is the extent to which reduced current sinks and sources are due to poorer word serial position test performance. In this regard, it is important to note that only *correct* trials entered into the ERP analyses, which strongly suggests that patients were attending and performing the task during theses trials. Moreover, the overall level of performance in patients was well above chance (73% correct compared to 25% correct by chance), which further indicates that patients were adequately performing during this test. Conversely, one may also wonder why we observed any electrophysiologic differences between patients and controls, given that only correct trials were analyzed. Reductions of P3 amplitude have typically been found even in simple ''oddball'' tasks where patients and healthy controls show almost perfect accuracy, indicating that ERP and performance indices measure different aspects of information processing and do so with different sensitivity (e.g., behavioral measures will not differentiate between random and ''true'' performance within chance range). To further address this issue, future studies could include parametric variations (e.g., varying the number of words in the sequence) to examine the influence of word serial position test difficulty and/or performance level on ERP/CSD differences between patients and controls.

Some limitations should be noted. First, the patient sample was relatively small and heterogeneous. We have not, however, found differences in stimulus-related ERPs peaking at intermediate latencies (N1, N2, P3) between patients meeting DSM-IV criteria for schizophrenia versus schizoaffective disorder (Bruder et al., 2001), and both diagnostic groups display similar deficits in visual working memory (Gooding & Tallent, 2004). Second, in the absence of a nonverbal task, it is not clear whether abnormalities in patients are specific to verbal working memory. Previous ERP studies in healthy adults have reported functional and topographical dissociations of slow waves during object, spatial, and verbal working memory tasks (e.g, Bosch et al., 2001; Mecklinger & Pfeifer, 1996), suggesting not only different neuronal generators, but also considerable stimulus and paradigm specificity. Nevertheless, the left-greater-than-right hemisphere N1 sink and P3 source at lateral-parietotemporal sites and slow wave at frontocentral sites are consistent with the asymmetry previously reported for phonetic processing and rehearsal of verbal material (Kayser & Tenke, 2006a; Kayser et al., 1998, 2001; Ruchkin et al., 2003). To further address these issues, we are now recording ERPs of larger samples of schizophrenia patients and healthy adults during serial position tests with both words and faces. Third, EEG was not recorded with DC amplifiers, possibly reducing overall SW amplitude; however, because the observed SW frequencies were well above the filter cutoff (0.01 Hz high–pass), a 3-dB attenuation of the lowest frequencies is unlikely to differentially affect the two groups, and even larger group differences would be expected for true DC recordings. Rather, these filter properties may have improved data quality by preventing slow drifts common with DC recordings. Fourth, ERPs have excellent temporal but limited spatial resolution. This limitation was to a certain extent addressed by using reference-free CSD estimates, which provide measures of radial current flow that are more sharply localized than scalp potentials and quite effectively summarize neuronal generator patterns even with a low-density ERP montage (Kayser & Tenke, 2006a, 2006b).

Despite these limitations, this preliminary study, if nothing else, illustrates the potential of a new data analytic strategy that more fully exploits the temporal and spatial information provided by ERPs. It is remarkable that a recent meta-analysis of studies using behavioral measures arrived at almost the same conclusions, suggesting that working memory deficits in schizophrenia may arise from problems in stimulus encoding and/or early maintenance (Lee & Park, 2005). Furthermore, the consistency of behavioral working memory deficits in schizophrenia across verbal and visuospatial paradigms led the authors to state that ''it may be more useful to parse the cognitive processes necessary for successful performance in working memory tasks into dissociable, temporal components'' (Lee & Park, 2005, p. 603). The current strategy appears to be well suited for this purpose. This analytic approach was successfully applied to a small clinical sample using a long EEG epoch (as opposed to using a large sample of healthy adults with a short ERP epoch; Kayser & Tenke, 2006a), both of which are typically a challenge to ERP research. CSD estimates yielded a reference-free description of current generators underlying surface ERPs during a verbal working memory test, and temporal PCA enabled derivation of components corresponding to different cognitive subprocesses (e.g., sensory processing, encoding and integration of memory representations, and maintenance of this information during a retention interval), which uniquely and comprehensively summarized processing aspects previously addressed in isolation. The findings provide support for the hypothesis that verbal working memory deficits in schizophrenia involve a disturbance of frontal and parietal-temporal processes mediating encoding and early storage of working memory representations.

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APPENDIX

Four-word sets of test and practice stimuli (word frequency given by Thorndike and Lorge, 1944).

Set				
		Test stimuli		
1	DUCK (49)	GOAT (50)	GOOSE (45)	WOLF (50)
2	CLOCK (50)	FORK (31)	SPOON (33)	STOOL (16)
3	BASKET (50)	CANDLE (43)	HAMMER (34)	PENCIL (40)
4	ALMOND (8)	CARROT (9)	MELON (5)	PEANUT (7)
5	BEACH (50)	CLOUD (100)	FIELD (100)	PLANT (100)
6	BOOT (37)	DRESS (100)	SHIRT (47)	SHOE (100)
7	BELL (50)	CARD (50)	DESK (50)	LOCK (50)
8	CAMEL (18)	EAGLE (38)	MONKEY (23)	TIGER (30)
		Practice stimuli		
9	ANKLE (21)	CHALK (13)	FLUTE (9)	JUICE (37)
10	ARM (100)	BOX (100)	DOG (100)	LEG (100)
11	OCEAN (100)	RECORD (100)	WAGON (50)	WINTER (100)
12	BREAD (50)	FENCE (50)	MATCH (50)	SKIRT (50)
13	FINGER (100)	MOUNTAIN (100)	TABLE (100)	WATER (100)
14	BARN (45)	BUSH (50)	DEER (35)	LAMP (50)
15	LETTER (100)	PAPER (100)	RIVER (100)	SHOULDER (100)
16	APPLE (50)	ENGINE (50)	FLOWER (100)	HOTEL (50)