

# Electrophysiologic evidence for olfactory dysfunction in schizophrenia: A CSD-PCA study using hydrogen sulfide

Jürgen Kayser<sup>1,2</sup>, Craig E. Tenke<sup>1,2</sup>, Dolores Malaspina<sup>3</sup>, Christopher J. Kroppmann<sup>1</sup>, Nathan A. Gates<sup>1</sup>, Gerard E. Bruder<sup>1,2</sup>

<sup>1</sup> Division of Cognitive Neuroscience, New York State Psychiatric Institute, New York, NY;

<sup>2</sup> Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY;

<sup>3</sup> Department of Psychiatry, New York University School of Medicine, New York, NY

## Abstract

Deficits in odor threshold sensitivity, discrimination and identification are common in schizophrenia, presumably originating from limbic brain structures (e.g., orbital prefrontal cortex, amygdala, piriform cortex) also linked to their cognitive and emotional disturbances. To study the neurophysiological processes underlying olfactory dysfunction in schizophrenia, nose-referenced 30-channel ERPs were recorded from 32 schizophrenic patients and 35 healthy adults (18/18 male) during odor detection of hydrogen sulfide stimuli presented for 200 ms to the left or right nostril at concentrations of 50% or 100% by a constant-flow olfactometer (variable 15-25 s ISI). Time of odor stimulation was not cued. Participants indicated when they perceived a low or high odor intensity. Patients' performance (percentage of missed responses) was not different from healthy controls for high (23% ±16% vs. 23% ±18%) and low (45% ±19% vs. 41% ±20%) intensities. Patients and controls had similar olfactory ERP and CSD waveforms. As previously reported, ERPs referenced to linked mastoids showed a small vertex N1 and pronounced mid-parietal P2, which was larger for high than low odor intensities. However, temporal principal components analysis (unrestricted Varimax rotation of covariance loadings) of the CSD waveforms identified two distinctive PCA factors revealing bilateral fronto-temporal N1 sinks (305 ms peak latency) and a mid-parietal P2 source (630 ms) that were greater for high than low intensities for both patients and controls. In agreement with findings by Turetsky et al (2003), N1 sink and P2 source were markedly reduced in patients for high intensity stimuli, providing further neurophysiological evidence of olfactory dysfunction in schizophrenia. The CSD-PCA methodology uniquely revealed neuronal generator patterns underlying olfactory ERPs that are obscured by volume-conducted, reference-biased surface potentials.

## Introduction

Olfactory function deficits are common in schizophrenia (e.g., Moberg et al 1999):

- higher threshold sensitivity
- impaired discrimination
- poorer identification

These deficits presumably originate from brain structures also linked to cognitive and emotional disturbances in schizophrenia. However, the neurophysiological processes underlying olfactory dysfunction in schizophrenia have only been studied by Turetsky et al (2003) who found reduced N1 and P2 amplitudes.

The dependency of surface potentials on a recording reference location (e.g., nose, linked mastoids, average) and the definition and measurement of appropriate ERP components (e.g., specific time windows for peak or integral amplitudes) are two recurring problems in ERP research, which crucially affect component interpretation (e.g., polarity, topography, generator) and statistical analysis (e.g., Kayser & Tenke 2003; Tenke & Kayser 2005).

These limitations can be overcome by combining reference-free current source density (CSD) transformations and temporal principal components analysis (PCA) to identify relevant, data-driven components (Kayser & Tenke 2006a,b).

**Objective:**

- replicate findings by Turetsky et al (2003)
- use CSD-PCA approach to identify neuronal generator patterns underlying olfactory ERPs

## Participants

Variable	Patients (n = 32; 18 male; 5 smokers)			Healthy Controls (n = 35; 18 male; 6 smokers)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	33.3	9.6	18 - 54	31.7	12.0	18 - 61
Education (years)	14.2	2.7	10 - 20	15.5	1.7	12 - 20
Handedness (LQ) <sup>a</sup>	84.0	18.3	38 - 100	73.6	29.2	6 - 100
Onset age (years)	23.7	6.3	12 - 36			
Illness duration (years)	9.8	8.9	0 - 31			
Total BPRS <sup>b</sup>	28.1	6.6	18 - 42			
PANSS general	23.7	5.8	16 - 36			
PANSS positive	10.8	4.9	7 - 24			
PANSS negative	11.7	3.9	7 - 23			

<sup>a</sup> Laterality quotient (Oldfield, 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed).  
<sup>b</sup> n = 31.

**DSM-IV Criteria**

Schizophrenia, paranoid (n=15)	n=26	Aripiprazole (n=9)	n=29
Schizophrenia, undifferentiated (n=9)		Risperidone (n=7)	
Schizophrenia, catatonic (n=1)		Olanzapine (n=5)	
Schizophrenia, residual (n=1)		Ziprasidone (n=4)	
Schizoaffective Disorder, depressive (n=3)	n=6	Perphenazine (n=2)	Chlorpromazine Equivalents 25-800 mg/day
Schizoaffective Disorder, bipolar (n=3)		Clozapine (n=1)	
		Quetiapine (n=1)	
		Unmedicated > 14 days	n=3

## References

Funding Source: NIMH grants MH066428, MH066597 and MH082393

Kayser J, Tenke CE (2003). Optimizing PCA methodology for ERP component identification and measurement: theoretical rationale and empirical evaluation. *Clin Neurophysiol* 114(12):2307-2325.

Kayser J, Tenke CE (2006a). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks. *Clin Neurophysiol* 117(2):340-368.

Kayser J, Tenke CE (2006b). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. *Clin Neurophysiol* 117(2):369-390.

Kayser J, Tenke CE, Gates NA, Bruder GE (2007). Reference-independent ERP old/new effects of auditory and visual recognition memory: joint extraction of stimulus- and response-related neuronal generator patterns. *Psychophysiology* 44(6):949-967.

Martkic J, Kopala LC, & Good K (1997). Olfactory dysfunction in neuropsychiatric disorders: review and methodological considerations. *Biol Psychiatry* 42(8):721-732.

Moberg P, Agrin R, Gur RE, Gur RC, Turetsky BI, Doty RL (1999). Olfactory dysfunction in schizophrenia: a qualitative and quantitative review. *Neuropsychopharmacology* 21(3):325-340.

Oldfield RC (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1):97-113.

Turetsky BI, Kohler CS, Gur RE, Moberg P (2008). Olfactory physiological impairment in first-degree relatives of schizophrenia patients. *Schizophr Res* 102(1-3):220-229.

Turetsky BI, Moberg P, O'wzar K, Johnson SA, Doty RL, Gur RE (2003). Physiological impairment of olfactory stimulus processing in schizophrenia. *Biol Psychiatry* 53(3):403-411.

Perrin F, Pernier J, Bertrand O, Echallier JF (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalogr Clin Neurophysiol* 72(2):184-187.

11990 Corrigenda EEG 02274. *Electroencephalogr Clin Neurophysiol* 76:565.

Tenke CE, Kayser J (2006). Reference-free quantification of EEG spectra combining current source density (CSD) and frequency principal components analysis (PCA). *Clin Neurophysiol* 116(12):2826-2846.

## Stimuli and Procedure

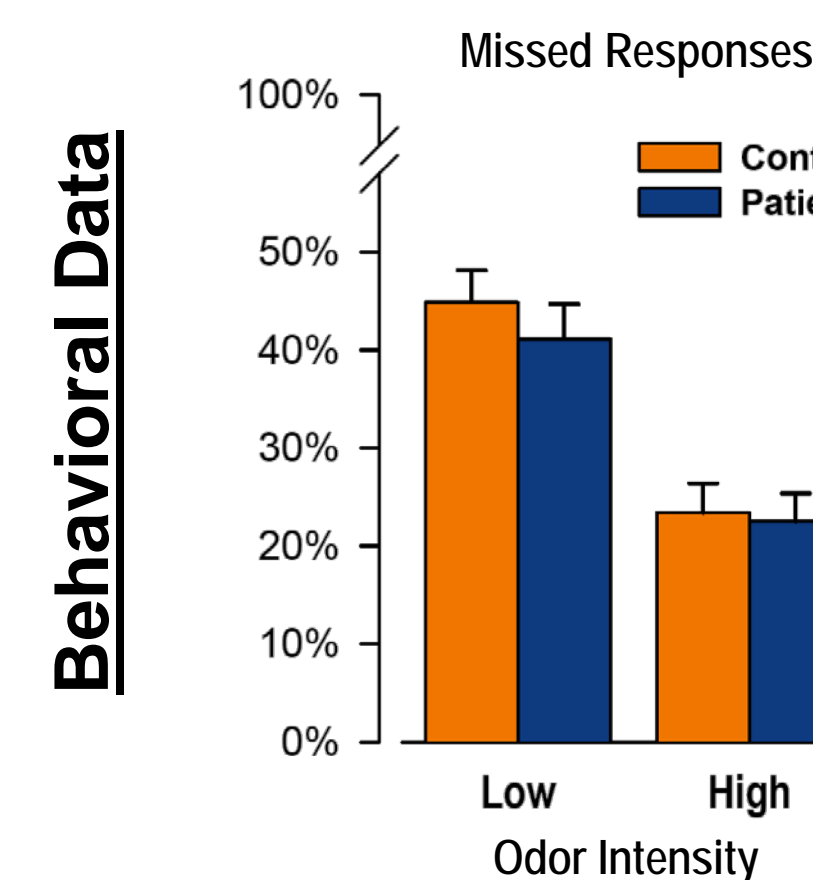
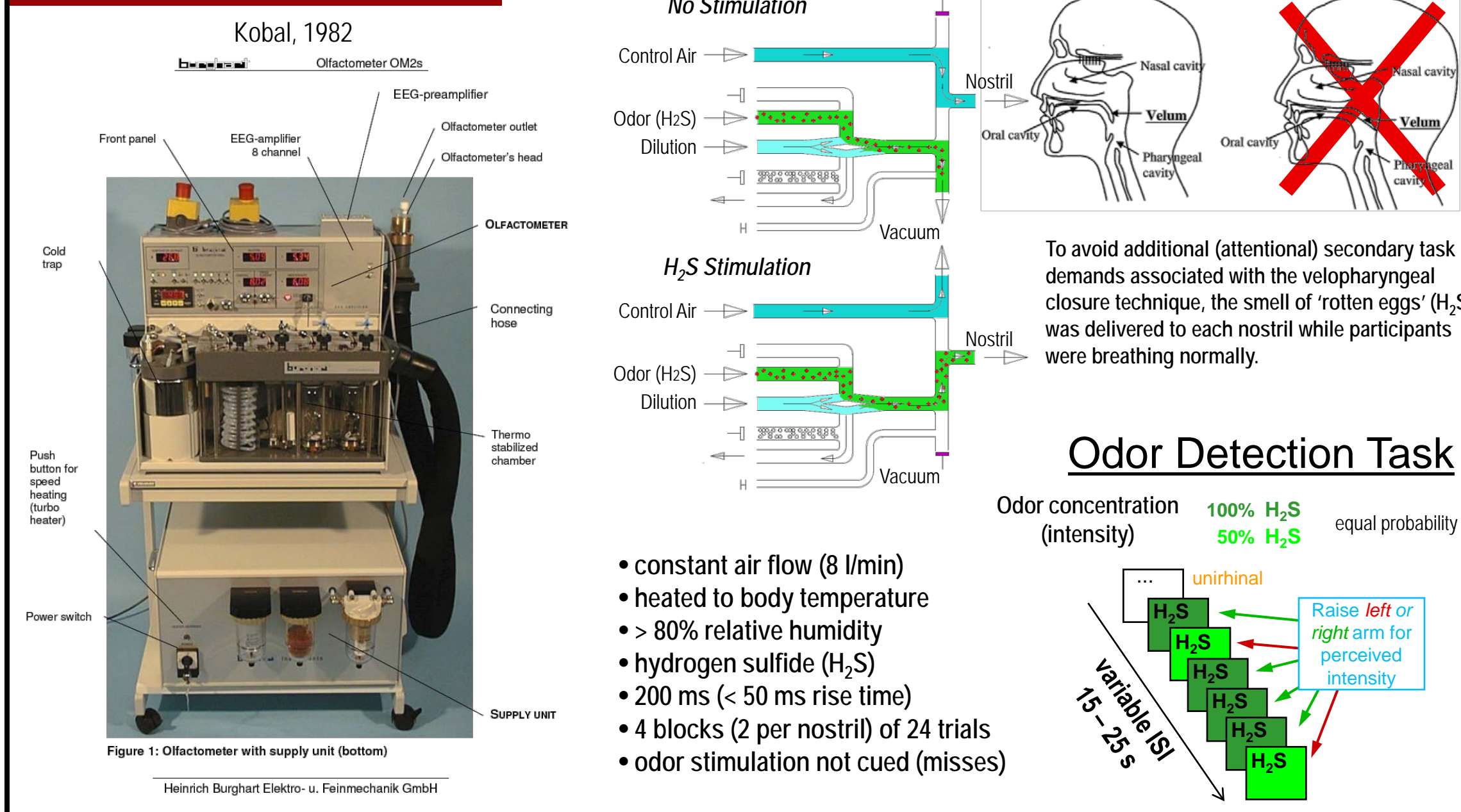


Fig. 1. Mean (SEM) percentage of missed responses revealed equal performance for healthy adults and schizophrenic patients. In both groups, H<sub>2</sub>S stimuli were more often correctly perceived for high than low intensity odors.

## ERP Recording and Data Analysis

- ERPs recorded from 30 scalp placements using an electrode cap with a nose reference, 200 samples/s
- EEG data acquired at .1-30 Hz band pass (-6dB/octave)
- Bipolar horizontal and vertical EOGs; blink reduction (continuous EEG) using spatial SVD; horizontal eye artifacts (epoch EEG) by linear regressions of lateral EEG differences (Fp2-Fp1, etc.)
- 2,000 ms epochs (250 ms pre-stimulus), averages (artifact-free trials, correct responses only) low pass filtered at 12.5 Hz (-24dB/oct.), 100 ms baseline correction
- ERPs re-referenced to linked mastoids (TP9/10) for better comparability to previous OERP research
- reference-free current source densities (CSD) (spherical splines surface Laplacian; Perrin et al 1989) computed for each ERP (sharpen topographies, eliminate volume-conducted activity)
- CSDs submitted to **unrestricted temporal principal components analysis (PCA)** derived from the covariance matrix [401 variables = stimulus-locked samples -250 to 1,750 ms; 4,154 observations = Subjects (67) x Electrode Sites (31) x Intensities (2)], followed by Varimax rotation of covariance loadings (Kayser & Tenke, 2003, 2006a,b), to identify and measure neuronal generator patterns underlying olfactory ERPs
- data were pooled across nostrils because of their blocked presentation order and to obtain more stable ERP waveforms
- data from two meaningful, high-variance CSD factors corresponding to N1 and P2 source submitted to repeated measures ANOVA with group (patients, controls) and gender (male, female) as between-subjects factors, and odor intensity (high, low) as a within-subjects factor
- ANOVA design also included subsets of lateral, homologous recording sites over both hemispheres at which PCA factor scores were largest and most representative of the associated CSD components (cf. Kayser & Tenke 2006a), adding hemisphere and site as within-subjects factors to the design

## Surface Potentials

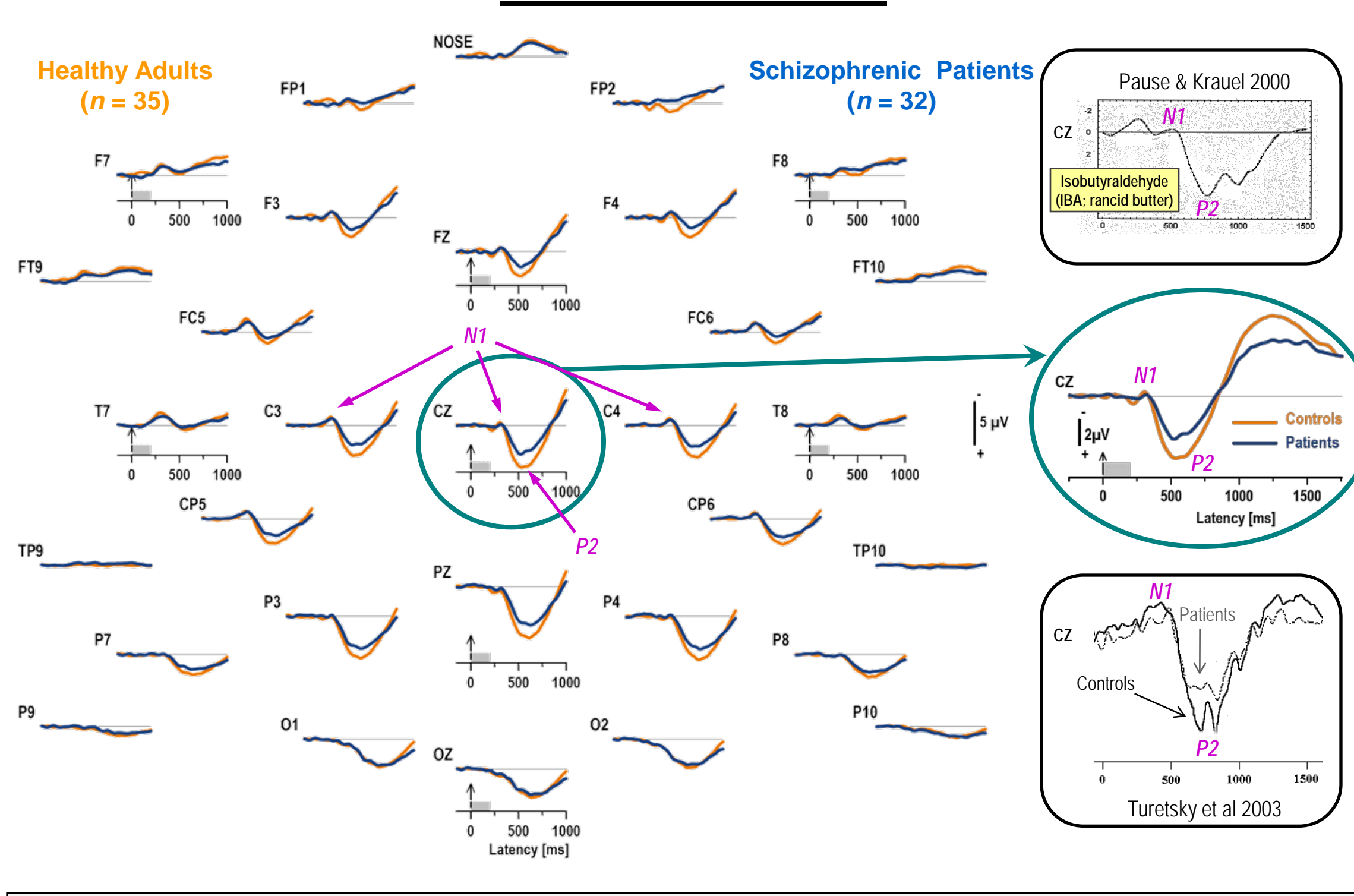


Fig. 2. Grand average OERP waveforms for controls and patients at all 31 sites using a linked-mastoids reference (TP9/10). Prominent deflections at about 300 ms (N1) and 600 ms (P2) at vertex (Cz) are comparable to previous OERP findings also using H<sub>2</sub>S stimuli (Turetsky et al 2003) or similar odors of negative valence (Pause & Krauel 2000). As found by Turetsky et al 2003, patients showed smaller P2 amplitudes than controls.

## Current Source Densities

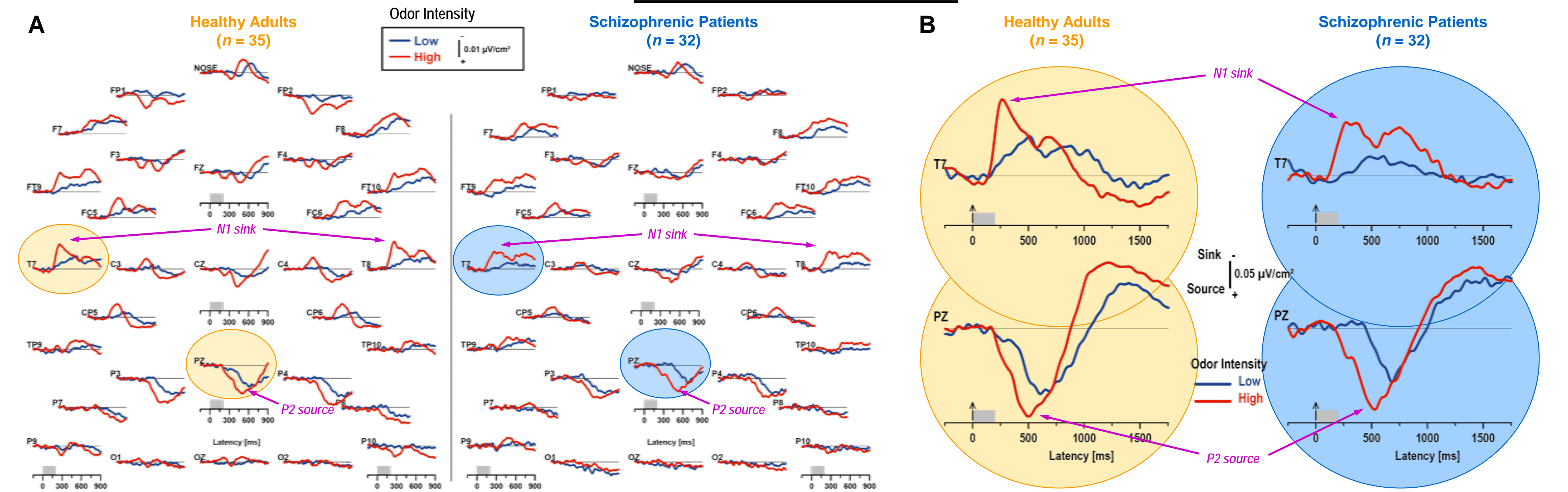


Fig. 3. Grand mean reference-free CSD waveforms for controls and patients comparing low and high concentrations of H<sub>2</sub>S stimuli at all 31 sites (A) and enlarged at sites T7 and Pz (B). A) For high intensity stimuli, both groups had distinct bilateral fronto-temporal N1 sinks (approximate peak latencies 260 ms at T7) and mid-parietal P2 sources (520 ms at Pz). For low intensity stimuli, N1 sink and P2 source amplitudes were reduced and their peak latencies were delayed. B) Compared to healthy adults, N1 sinks and P2 source appeared to be reduced in schizophrenic patients. However, both groups showed comparable intensity-related effects on both CSD components.

## CSD-PCA Factor Loadings and Scores

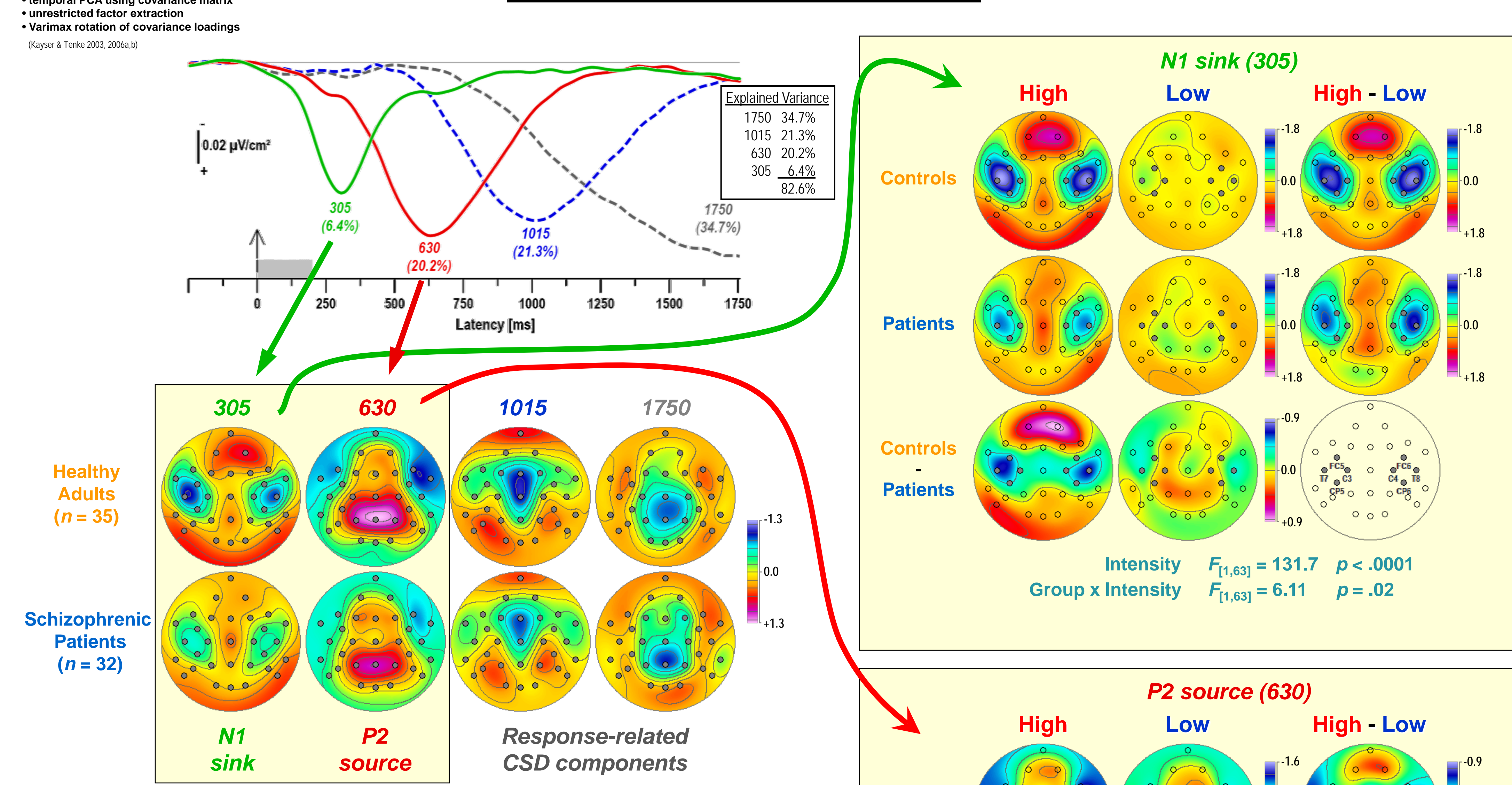


Fig. 4. Unrestricted PCA solution using olfactory CSD waveforms. The first four PCA factors explained most of the systematic CSD variance (82.6% after rotation). The time courses of the factor loadings (top) and the corresponding factor score topographies (bottom) identified two factors corresponding to N1 sink (peak latency 305 ms, lateral frontotemporal maximum) and P2 source (630 ms, mid-parietal maximum). Two later factors had a frontocentral (1015 ms) or parietal (1750 ms) midline sink maximum, suggesting a close correspondence to the response requirements in this task (i.e., raising left or right hand; cf. Kayser et al 2007), and were therefore not further analyzed.

## Summary and Conclusions

- Patients and controls produced highly comparable ERP/CSD waveforms/topographies (Figs. 2-4).
- greater bilateral frontotemporal N1 sink (- 300 ms)
- mid-parietal P2 source (- 600 ms)
- concisely summarized by temporal PCA
- Patients' performance was not different from controls for both odor intensities (Fig. 1).
- However, N1 sink and P2 source were markedly reduced in patients for high intensity stimuli (Fig. 5).
- provides further neurophysiological evidence of olfactory dysfunction in schizophrenia (Turetsky et al 2003)
- Reductions of olfactory ERP/CSD components may be candidate risk biomarkers of schizophrenia (cf. Turetsky et al 2008), warranting further study of high risk individuals, such as young people identified as prodromal to psychosis.
- The N1 sink generator pattern appears to be unique for olfactory stimuli, whereas P2 source (Figs. 4-5) is highly comparable to visual and auditory P3 source topographies (e.g., Kayser et al 2007).
- CSD-PCA methodology can clarify the basic component structure of olfactory ERPs.

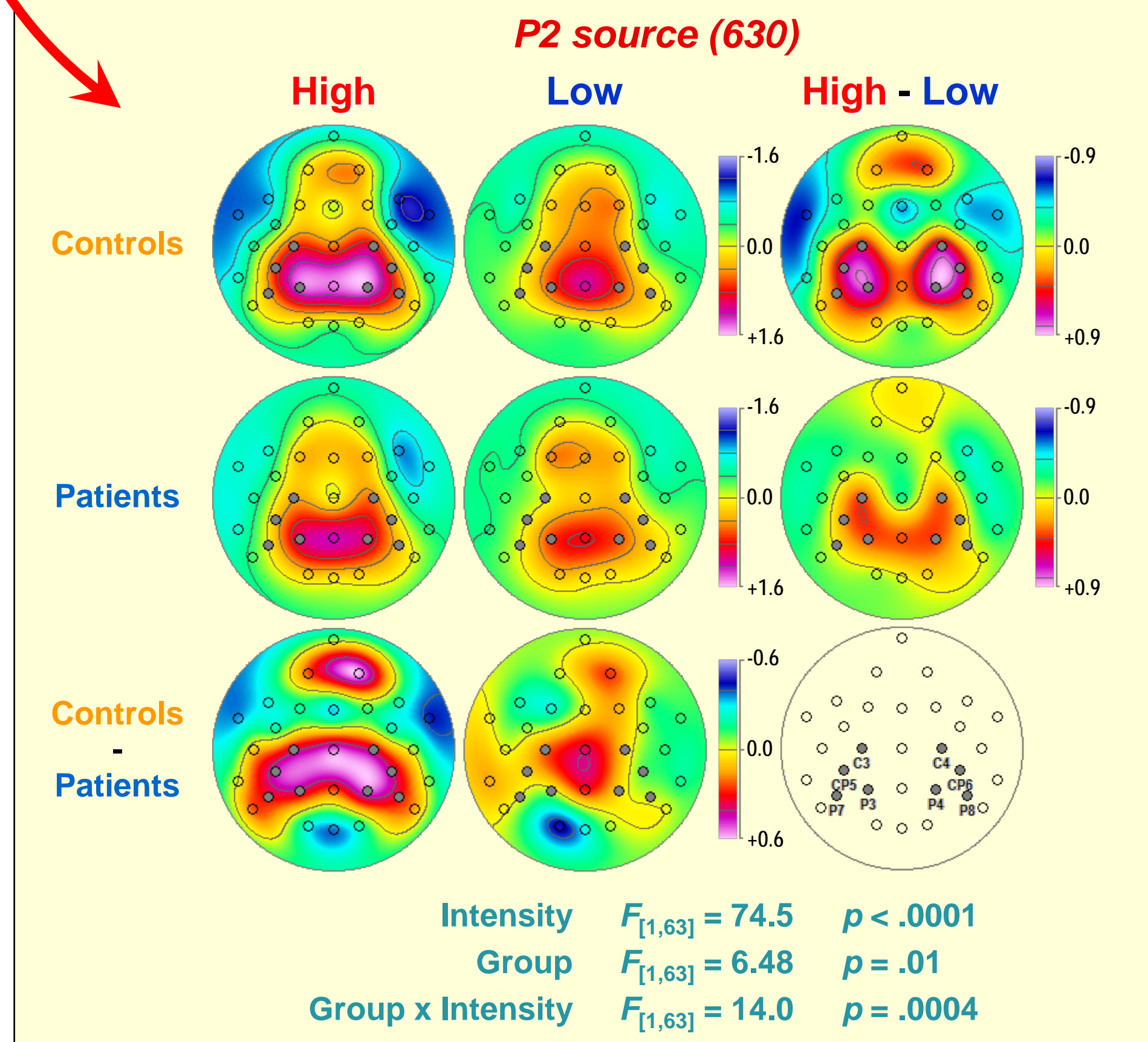


Fig. 5. Statistical evaluation of group and intensity effects for N1 sink (CSD factor 305) and P2 source (630) using repeated measures ANOVA at selected subsets of lateral recording sites (cf. grayed locations). Shown are the mean factor score topographies for high and low intensity H<sub>2</sub>S stimuli for each group and their respective differences. Both CSD components revealed highly significant intensity effects across groups. Nevertheless, N1 sink and P2 source were significantly reduced in patients compared to controls, particularly for high intensity H<sub>2</sub>S stimuli.