Neuronal generator patterns of olfactory event-related potentials (OERP) in schizophrenia

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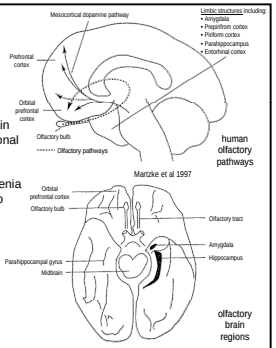
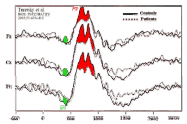
Abstract

Background: Deficits in odor threshold sensitivity, discrimination and identification are common in schizophrenia, presumably originating from brain structures also linked to their cognitive and emotional disturbances. 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. **Methods**: Nose-referenced 30-channel ERPs were recorded from 32 schizophrenic and 35 healthy adults (18/18 male) during an odor detection task. Hydrogen sulfide (H_2S) stimuli (200 ms duration) at concentrations of 50% and 100% were presented to the left or right nostril by a constant-flow olfactometer (variable ISI 15-25 s). Time of odor stimulation was not cued. Subjects indicated whether they perceived a low or high odor intensity. To identify and measure neuronal generator patterns underlying ERPs, unrestricted Varimax-PCA was performed on their reference-free current source densities (spherical splines). **Results**: Patients' behavioral performance was on par with that for healthy controls for high (22.5 vs. 23.4% misses) and low (41.1 vs. 44.9%) odor concentrations. Patients showed similar olfactory ERP and CSD waveforms when compared to controls, but their N1 sink (300 ms, bilateral frontotemporal maximum) and P2 source (615 ms, mid-parietal maximum) amplitudes were smaller. However, both groups had greater N1 sinks and P2 sources to high than low odor intensities. **Conclusions**: OERP amplitude reductions to H_2S stimuli in schizophrenia appear to reflect reduced activity in frontocentral, midline frontopolar, and parietal regions.

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

Means, Standard Deviations (SD), and Ranges for Demographic and Clinical Variables

Variable	Patients (*n* = 32; 18 male; 5 smokers) Mean	SD	Range	Healthy Controls (*n* = 35; 18 male; 6 smokers) 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) [a]	84.0	18.3	38 - 100	73.6	29.2	6 - 100	
Onset age (years)	23.7	6.3	12 - 36				
Illness duration (years)	9.6	8.9	0 - 31				
Total BPRS [b]	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				

- no history of any psychopathology or neurology disorder
- matched to patients for core demographics

[a] Laterality quotient (Oldfield, 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed).
[b] *n* = 31.

DSM-IV Criteria:
- Schizophrenia, paranoid (n=15)
- Schizophrenia, undifferentiated (n=9)
- Schizophrenia, catatonic (n=1)
- Schizophrenia, residual (n=1)

n=26

- Schizoaffective Disorder, depressive (n=3)
- Schizoaffective Disorder, bipolar (n=3)

n=6

Medication Status:
- Aripriprazole (n=9)
- Risperidone (n=7)
- Olanzapine (n=5)
- Ziprasidone (n=4)
- Perphenazine (n=2)
- Clozapine (n=1)
- Quetiapine (n=1)

n=29

Chlorpromazine Equivalents 25-800 mg/day

Unmedicated > 14 days

n=3

References

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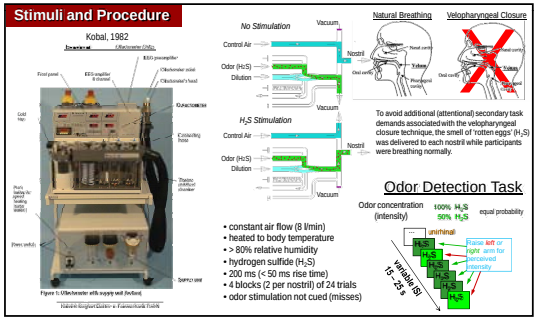
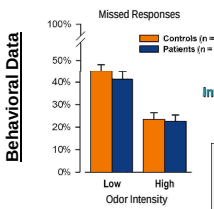
Stimuli and Procedure

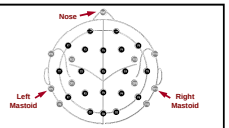




Intensity $F_{[1,63]} = 77.2$ $p < .0001$

Fig. 1. Mean (SEM) percentage of missed responses revealed equal performance for healthy adults and schizophrenic patients. In both groups, H_2S 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 (epoched 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

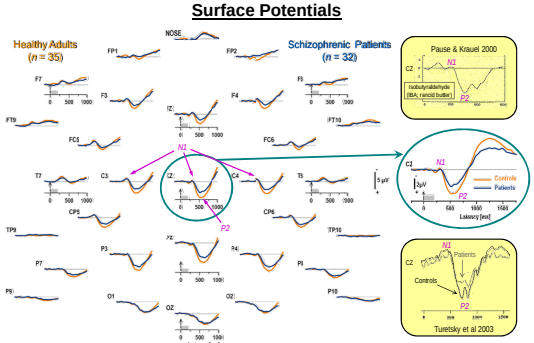


Fig. 2. Grand average OERP waveforms for controls and patients at all 31 sites using a linked-mastoids reference (TP9/10). Prominent deflections at about 300 ms (*N1*) and 600 ms (*P2*) at vertex (Cz) are comparable to previous OERP findings also using H_2S stimuli (Turetsky et al 2003) or similar odors of negative valence (Pause & Krauel 2000). As found by Turetsky et al 2003, patients showed smaller P2 amplitudes than controls.

Current Source Densities

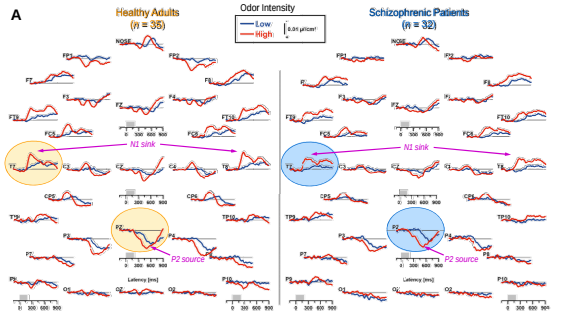
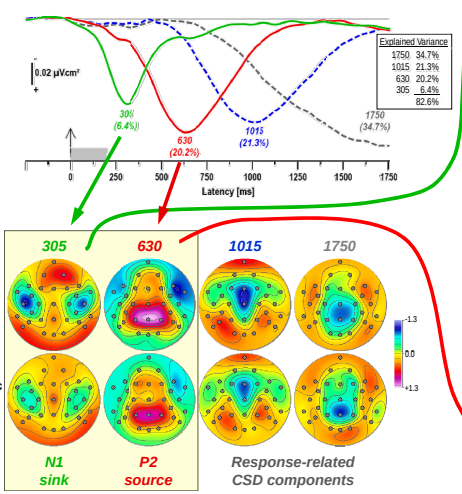


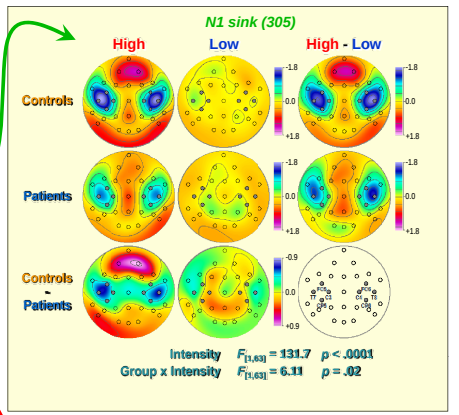
Fig. 3. Grand mean reference-free CSD waveforms for controls and patients comparing low and high concentrations of H_2S stimuli at all 31 sites (A) and enlarged at sites T7 and Pz (B).
A) For high intensity stimuli, both groups had distinct bilateral fronto-temporal N1 sinks (approximate peak latencies 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

- temporal PCA using covariance matrix
- unrestricted factor extraction
- Varimax rotation of covariance loadings

(Kayser & Tenke 2003, 2006a,b)





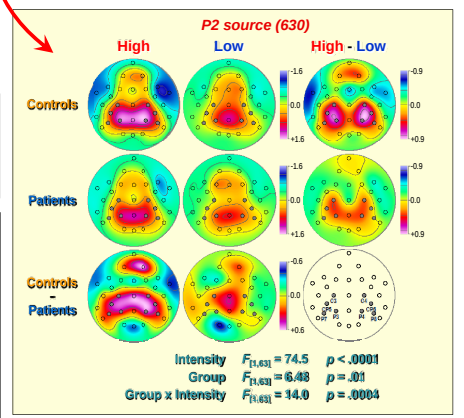


Fig. 4. Unrestricted PCA solution using olfactory CSD waveforms. The first four PCA factors explained most of the systematic CSD variance (82.6% after rotation). The time courses of the factor loadings (top) and the corresponding factor score topographies (bottom) identified two factors corresponding 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

  } greater for high than low H_2S odor intensities
- 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_2S 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_2S stimuli.