Olfaction in the Psychosis Prodrome: Electrophysiological and Behavioral Measures of Odor Detection

COLUMBIA PSYCHIATRY

67th Annual Meeting of the
Society of Biological Psychiatry (SoBP)
in Philadelphia, Pennsylvania, May 3 – 5, 2012

Poster available in high resolution at
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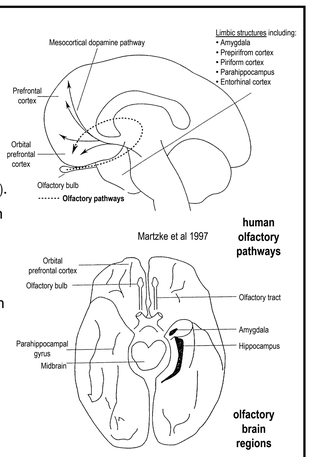
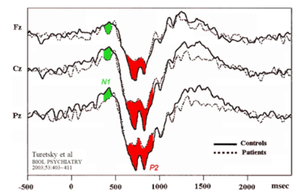
Abstract

Background: Smell identification deficits (SIDs) are relatively specific to schizophrenia and its negative symptoms, and may have predictive value for conversion to psychosis in high-risk individuals (Corcoran et al., 2005). Moreover, event-related potentials (ERPs) to odors are reduced in schizophrenia. This study examined whether prodromal patients show SIDs and abnormal olfactory N1 and P2 potentials seen in schizophrenia. **Methods**: 49-channel ERPs were recorded from 21 prodromal and 20 healthy adolescents (13/13 male; age 21.4±3.5, range 13-27 years) during an odor detection task using three concentrations (strong, medium, weak) of hydrogen sulfide (H_2S) or blank air presented unilaterally by a constant-flow olfactometer (variable ISI 15-21 s). Subjects indicated odor presence via foot pedal. Neuronal generator patterns underlying olfactory ERPs were identified and measured by unrestricted Varimax-PCA of reference-free current source densities (CSD; spherical spline interpolation). **Results**: Replicating previous findings (Kayser et al., 2010), CSD waveforms to H_2S stimuli were characterized by an early N1 sink (345 ms, bilateral centrotemporal) and a late P2 source (580 ms, mid-frontocentroparietal). N1 and P2 varied monotonically with odor intensity (strong > medium > weak) and did not differ across groups. Patients and controls also showed comparable odor detection accuracy and had normal odor identification and thresholds (Sniffin' Sticks). **Conclusions**: Olfactory ERPs directly reflected differences in odor intensity, but there was no evidence of impaired olfactory processing in prodromal patients. Although this contrasts with findings for schizophrenia, it remains to be seen whether olfactory measures may be helpful in predicting conversion to psychosis.

Introduction

- **Olfactory function deficits are common in schizophrenia** (e.g., Moberg et al 1999)**:**
  - higher threshold sensitivity
  - impaired discrimination
  - poorer identification
- Moreover, s**mell identification deficits (SIDs)** may have **predictive value** for conversion to psychosis in high-risk individuals (Corcoran et al 2005).
- Olfactory deficits presumably originate from brain structures also linked to cognitive and emotional disturbances in schizophrenia.
- Neurophysiological studies of olfactory function indicate that event-related potentials (ERPs) to odors (i.e., N1 and P2 amplitudes) are reduced in schizophrenia (Turetsky et al 2003; Kayser et al 2010) and also abnormal in their unaffected first-degree relatives (Turetsky et al 2008).

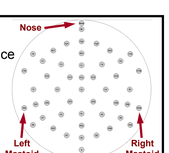




- The dependency of surface potentials on a **recording reference location** (e.g., nose, linked mastoids, average) and the **definition and measurement** of appropriate **ERP components** (e.g., specific time windows for peak or integral amplitudes) are two recurring problems in ERP research, which 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).

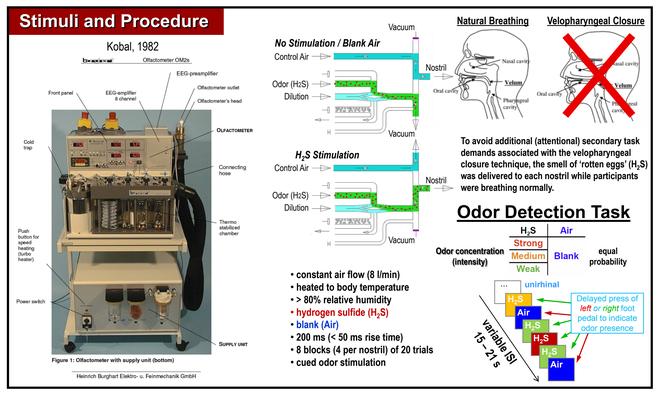
Objective:
- **examine whether young individuals at risk for schizophrenia have deficits in odor thresholds and odor identification (Sniffin' Sticks;** Kobal et al 2000)
- **use CSD-PCA approach to identify and quantify neuronal generator patterns underlying odor detection**
- **evaluate whether prodromal patients also show reduced N1 sink and P2 source amplitudes to hydrogen sulfide (H_2S) odorants previously seen for schizophrenia patients** (Kayser et al 2010)

ERP Recording and Data Analysis



- ERPs recorded from 49 scalp sites using an electrode cap with a nose reference
- EEG data acquired at .01-30 Hz band pass (-6dB/octave), 200 samples/s
- **blink reduction** (continuous EEG) **using spatial SVD**; interpolated bipolar horizontal and vertical EOGs; 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) low pass filtered at 12.5 Hz (-24dB/oct.), 100 ms baseline correction
- ERPs **re-referenced to linked mastoids (TP9/10)** for 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)
- data were **pooled across nostrils** because of their blocked presentation order and to obtain more stable ERP/CSD waveforms (i.e., to improve the overall signal-to-noise ratio)
- **CSDs** submitted to ***unrestricted* temporal principal components analysis (PCA)** [401 variables = stimulus-locked samples –250 to 1,750 ms; 8,036 observations = 41 *Subjects* x 49 *Recording Sites* x 4 *Conditions*], followed by Varimax rotation of covariance loadings (Kayser & Tenke 2003, 2006a,b)
- CSD-PCA: identify and measure neuronal generator patterns underlying olfactory ERPs from meaningful, high-variance CSD factors corresponding to N1/P2 sinks and sources
- submit factor scores (and behavioral measures of odor detection) to **repeated measures ANOVA** with *group* (patients, controls) and *gender* (male, female) as between-subjects factors, and odor *intensity* (weak, medium, strong) as a within-subjects factor (*hemisphere* and *site* to reflect CSD topography)

Stimuli and Procedure



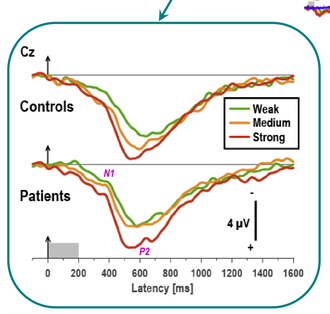
Participants

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

	Prodromal Patients (*n* = 21; 13 male; 5 smokers)			Healthy Controls (*n* = 20; 13 male; 2 smokers)			
Variable	Mean	SD	Range	Mean	SD	Range	*p*
Age (years)	21.4	3.8	13 - 27	21.7	3.3	16 - 27	
Education (years)	13.8	2.5	9 - 19	14.4	1.8	12 - 18	
Handedness (LQ) [a]	65.7 [b]	36.9	-40 - 100	78.8 [c]	49.1	-100 - 100	
SIPS positive [d]	11.3	4.4	4 - 20	0.6	0.9	0 - 3	<.001
SIPS negative [d]	12.2	6.1	3 - 27	1.1	1.7	0 - 6	<.001
SIPS disorganization [d]	6.8	3.4	1 - 13	0.4	0.8	0 - 2	<.001
SIPS general [d]	8.4	4.2	0 - 14	0.5	1.1	0 - 4	<.001
SIPS global [d]	47.2	7.1	33 - 60	83.5	7.0	68 - 95	<.001

Note. [a] Laterality quotient (Oldfield 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). [b] *n* = 16. [c] *n* = 18. [d] *Structured Interview for Prodromal Symptoms* (SIPS; Miller et al 2003) subscales: positive symptoms; negative symptoms; disorganization symptoms; general symptoms; global assessment of function.

Surface Potentials (ERP)



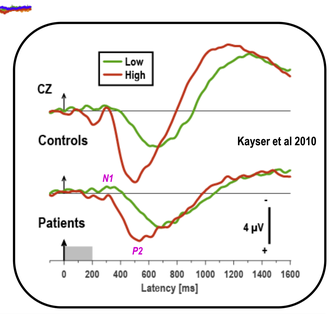


Fig. 3. Grand average OERP waveforms for weak, medium, and strong H_2S stimuli (pooled across groups) and *blank air* at all 49 sites using a linked-mastoids reference (TP9/10). Prominent deflections at about 350 ms (*N1*) and 600 ms (*P2*) at vertex (Cz) are comparable to previous OERP findings using H_2S as olfactory stimuli in healthy adults and schizophrenia patients in a different paradigm (Kayser et al 2010).

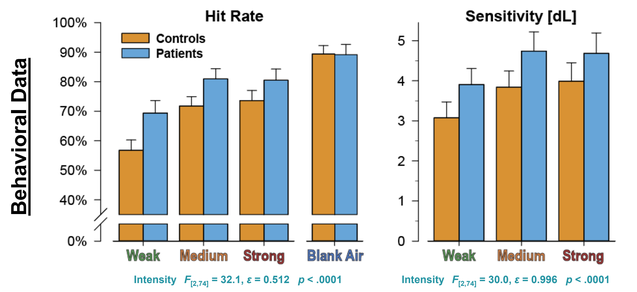


Fig. 1. Mean (SEM) percentage of correctly detected H_2S stimuli and correctly rejected blank air trials (pooled across nostrils). Whereas both healthy controls and prodromal patients showed a monotonic increase in performance with greater odor intensity, patients showed somewhat better performance than controls (Group, $F_{[1,37]} = 4.15$, $p < .05$). However, the *d'*-like sensitivity measures d_L (no response bias; cf. Snodgrass & Corwin 1988) revealed no significant group difference (Group, $F_{[1,37]} = 2.38$, $p = .13$).

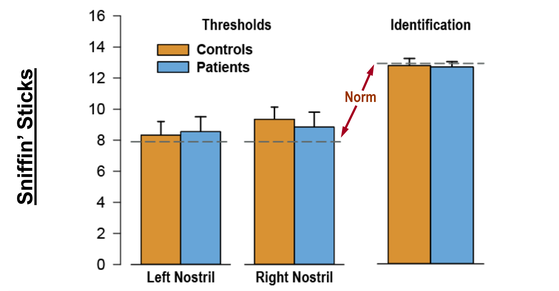


Fig. 2. Nasal chemosensory performance (Sniffin' Sticks; Kobal et al 2000) revealed normal scores of left and right nostril odor thresholds and odor identification for healthy controls and prodromal patients. There were no significant Group main effects or Group x Nostril interaction effects for either measure of olfactory function (all $F < 1.0$ *n.s.*).

Current Source Densities (CSD)

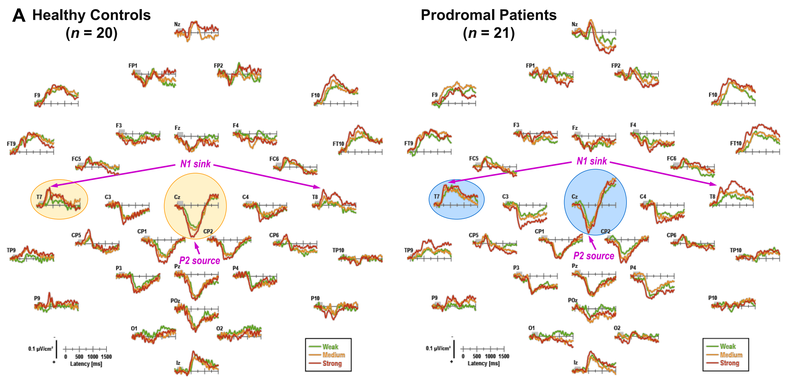


Fig. 4. Grand mean CSD waveforms for controls and patients comparing H_2S stimuli of weak, medium, and strong intensity at 32 selected sites **(A)** and at sites T7 and Cz **(B)**.
A) Across odor intensities and groups, CSDs revealed distinct bilateral fronto-temporal N1 sinks (approximate peak latencies 280 - 430 ms at T7) and mid-centroparietal P2 sources (500 - 700 ms at Cz), which were accompanied by frontolateral sinks. **B)** N1 sinks and P2 source appeared to be highly comparable in prodromal patients and healthy controls.

CSD-PCA Factor Loadings

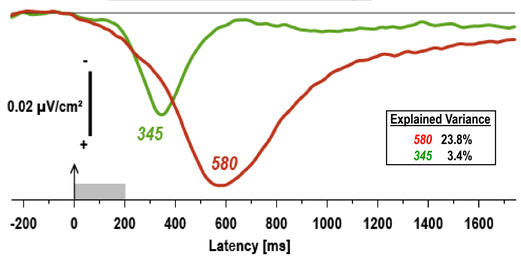


Fig. 5. Unrestricted PCA solution using olfactory CSD waveforms. The time courses of the factor loadings identified two factors corresponding to sinks and sources associated with the olfactory N1/P2 complex (i.e., peak loadings between 200 to 900 ms).

Patients who converted to psychosis (*n* = 3)

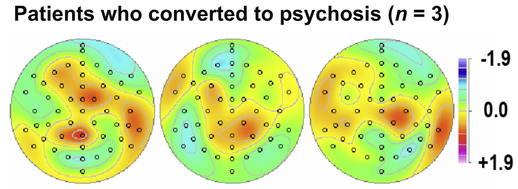


Fig. 8. Three prodromal patients who converted to psychosis revealed marked reductions in P2 source (cf. Fig. 7). These patients also differed from nonconverters in odor detection (d_L: weak, *M* = 1.3 ±1.7; medium, *M* = 1.7 ±1.7; strong *M* = 1.3 ±1.7; cf. Fig. 1) and odor thresholds (left nostril, *M* = 2.7 ±1.4; right nostril, *M* = 3.3 ±2.5; cf. Fig. 2, left panel), but not in odor identification (*M* = 11.7 ±1.5; cf. Fig. 2, right).

Summary and Conclusions

- **Prodromal patients and healthy controls showed highly comparable odor detection** (Fig. 1)**, nasal chemosensory performance** (Fig. 2)**, and ERP/CSD waveforms** (Figs. 3 and 4) **and topographies** (Figs. 6 and 7)**.**
- **CSD component structure and topography were highly comparable to previous findings using H_2S stimuli** (Kayser et al 2010)**.**
- **Both N1 sink (lateral temporal maximum) and P2 source (mid-centroparietal maximum) varied monotonically with the introduced parametric variation of odor intensity, but this was not different in prodromal patients and healthy controls.**
- **Although findings provide no evidence of abnormal olfactory function in individuals at risk for psychosis** (Corcoran et al 2005)**, an important question is whether those who convert to psychosis differ from those who do not convert.**
- **The available preliminary data from three converters** (Fig. 8) **is extremely encouraging as this suggests that behavioral and neurophysiological deficits in olfactory processing may have predictive value for conversion to psychosis.**

CSD-PCA Factor Score Topographies

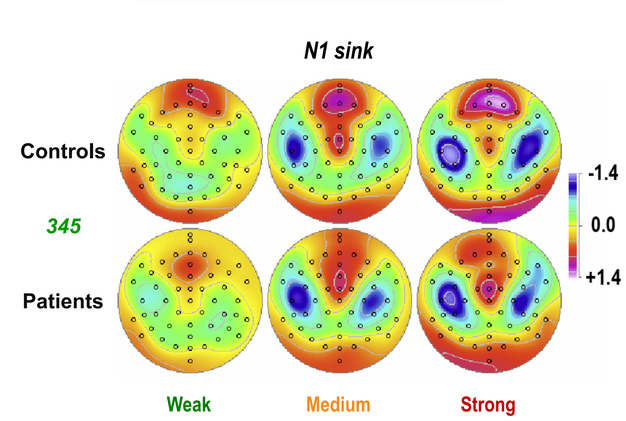


Fig. 6. N1 sink (factor *345*) topographies revealed distinct lateral temporal sinks likewise for controls and patients, which varied monotonically with weak, medium, and strong H_2S stimuli (Intensity, $F_{[2,74]} = 26.1$, $p < .0001$). There were no effects involving Group (all $F < 1.0$, *n.s.*).

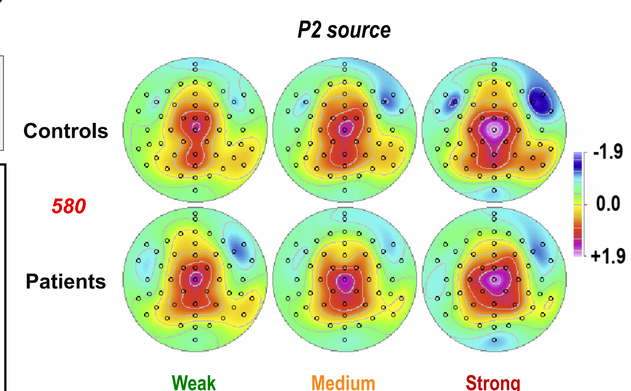


Fig. 7. P2 source (factor *580*) topographies showed a vertex maximum that increased monotonically for weak, medium, and strong H_2S stimuli at mid-frontocentroparietal sites (Intensity, $F_{[2,74]} = 13.4$, $p < .0001$) in both controls and patients (all effects involving Group, $F < 1.0$, *n.s.*). However, the corresponding sink at lateral frontotemporal sites was more sensitive to odor intensity in controls than patients (Group x Intensity, $F_{[2,74]} = 3.96$, $\varepsilon = 0.91$, $p = .02$).

References

Supported by grant MH086125 from the *National Institute of Mental Health (NIMH)*

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