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Olfactory Receptor Neuron Dysfunction in Schizophrenia

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Olfactory impairments are a common feature of schizophrenia. Impairments in odor detection and odor identification are present early in the course of illness and among those at risk for the disorder. These behavioral impairments have been linked to both physiological and anatomical abnormalities in the neural substrates subserving olfaction, including relatively peripheral elements of the olfactory system. The location of olfactory receptor neurons in the nasal epithelium allows noninvasive access to these neurons in living subjects. This offers a unique opportunity to directly assess neuronal integrity *in vivo* in patients. The peripheral olfactory receptor neuron response to odor stimulation was assessed in 21 schizophrenia patients and 18 healthy comparison subjects. The electroolfactogram, representing the electrical depolarization of the olfactory receptor neurons, was recording following stimulation with different doses and durations of hydrogen sulfide, a pure olfactory nerve stimulant. Schizophrenia patients had abnormally large depolarization responses following odor stimulation, independent of clinical symptomatology, antipsychotic medication dosage or smoking history. Although the precise pathophysiological mechanism is unknown, this olfactory receptor neuron abnormality is consistent with several lines of evidence suggesting altered proliferation or maturation of olfactory receptor neuron cell lineages in schizophrenia. It is also consistent with emerging evidence of disruptions of cyclic AMP-mediated intracellular signaling mechanisms, and may be a marker of these disruptions. It unambiguously demonstrates that neurophysiological disturbances in schizophrenia are not limited to cortical and subcortical structures, but rather include even the most peripheral sensory neurons.
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INTRODUCTION

There is increasing evidence that olfactory impairments are a common feature of schizophrenia (Moberg *et al*, 1999). This is not unexpected, because olfactory processing is mediated by many of the same brain areas implicated in the illness, including the ventromedial temporal lobe, basal forebrain, prefrontal cortex, and diencephalon. The olfactory system thus shares a common neural substrate with many of the cognitive and emotion processes that are abnormal in schizophrenia. Behavioral studies have demonstrated impairments in odor detection threshold sensitivity (ie ability to detect the presence of low concentrations of an odorant), as well as odor identification and odor recognition memory. These deficits are present early in the course of illness and, among individuals at high risk for the disorder, they may help to identify those who will eventually develop the full clinical syndrome (Brewer *et al*, 2003). Although olfactory deficits may progress over time (Moberg *et al*, 1997), they are not explained by symptom severity, antipsychotic medication use, or increased smoking among patients (Moberg *et al*, 1999).

These behavioral impairments in olfactory function have now been linked to specific physiological and anatomical abnormalities in the neural substrates subserving olfaction. Chemosensory evoked potential responses originating in the primary olfactory cortex and the gray matter volume of this cortical region are both decreased in schizophrenia patients (Turetsky *et al*, 2003b, c). There is also evidence indicating that these abnormalities extend to more peripheral elements of the olfactory system. MRI scans of the olfactory bulbs have demonstrated reduced bulb volumes in both schizophrenia patients (Turetsky *et al*, 2000) and their unaffected first-degree relatives (Turetsky *et al*, 2003a), suggesting a genetically mediated abnormality. Histological examination of olfactory epithelial tissue, obtained postmortem from schizophrenia patients, has documented the presence of increased numbers of immature olfactory receptor neurons (ORNs; Arnold *et al*, 2001), consistent with disrupted growth and development of these primary sensory neurons.

The location of ORNs in the posterior–superior aspect of the nasal cavity allows direct noninvasive access to these neurons in living subjects. This offers the unique opportunity to directly assess the functional integrity of a specific

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neural substrate, *in vivo*. In this study, we examined the electroolfactogram (EOG) response in schizophrenia patients and healthy comparison subjects. The EOG represents the membrane depolarization of ORNs in response to a chemosensory odorant stimulus. By recording this depolarization response directly from the nasal mucosa, we were able to examine the physiological responsiveness of these peripheral sensory neurons, independent of such factors as subject cooperation, attentiveness, and cognitive ability that typically confound other *in vivo* methods in schizophrenia research. Given the histological evidence of neurodevelopmental dysregulation, we hypothesized that the physiological responses of the neurons would also be abnormal.

MATERIALS AND METHODS

This investigation was conducted in accordance with the Declaration of Helsinki Principles. All experimental procedures were approved by the University of Pennsylvania Institutional Review Board. Written informed consent was obtained from each subject before the study.

Subjects

The sample included 21 patients with a DSM-IV diagnosis of schizophrenia (14 men, 7 women) and 18 healthy comparison subjects (11 men, 7 women). Patients were recruited from the outpatient psychiatric facilities at the Hospital of the University of Pennsylvania and through outreach at Community Mental Health Centers and family support programs. All patients were stable outpatients at the time of testing. Healthy comparison subjects were recruited through advertisements in community newspapers and neighborhood bulletin boards.

All subjects received a semi-structured psychiatric interview (Diagnostic Interview for Genetic Studies; Nurnberger *et al*, 1994) and the Family Interview for Genetic Studies (Maxwell, 1992). The patients were rated on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983), and Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Ratings were completed by investigators trained to a criterion reliability of 0.90 (intraclass correlation). Patients were excluded for any concurrent Axis I diagnosis other than schizophrenia. Healthy comparison subjects were excluded for any history of an Axis I diagnosis, Axis II Cluster A (schizotypal, schizoid, or paranoid) personality disorder, or family history of an Axis I psychotic disorder. Across groups, subjects were excluded for any history of a neurological disorder, including head trauma with loss of consciousness, any lifetime history of substance dependence, history of substance abuse within the preceding 6 months, or any medical condition that might affect cerebral functioning. Subjects were also excluded for any obvious craniofacial trauma or abnormality, including septal deviation, and for any acute respiratory condition, cold, or allergy.

There were no differences in either age ($t(38) = 0.12$, $p = 0.90$) or gender composition ($\chi^2(1) = 0.13$, $p = 0.72$) between the two groups. Mean age of patients was 37.6 ± 9.7 years; mean age of control subjects was 37.2 ± 10.3 years. There were also no significant differences in smoking status, although there was a trend towards greater smoking among patients. Eight patients were active smokers and thirteen were nonsmokers; three controls were smokers, and fifteen were nonsmokers ($\chi^2(1) = 2.20$, $p = 0.14$). Mean cigarette packs per day was 0.35 ± 0.56 for patients and 0.08 ± 0.19 for controls ($t(38) = 1.95$, $p = 0.06$). Cumulative pack-years of tobacco exposure was 6.93 ± 14.39 for patients and 1.22 ± 3.17 for controls ($t(38) = 1.65$, $p = 0.11$).

Nineteen of twenty-one patients were medicated at the time of testing. Of these, 8 were taking typical antipsychotics, either alone or in combination with a low-dose atypical; 11 were taking solely atypical antipsychotic medications. Mean daily antipsychotic dosage, calculated as chlorpromazine equivalents, was 332 ± 305 mg. Mean age of illness onset was 20.2 ± 5.5 years and mean illness duration was 17.4 ± 9.7 years. Mean total BPRS score for 18 items was 30.6 ± 9.4. This indicates a very mild level of acute symptomatology.

Experimental Procedures

Olfactory stimulation. Odor stimuli were presented by a dynamic multi-odorant air dilution olfactometer (OM4/B; Heinrich Burghart GmbH, Wedel, Germany). This computer-controlled apparatus allows for precisely timed pulses of odorants to be embedded in a constantly flowing air stream with specified temperature and humidity (36.5°C; 80% relative humidity) without transient pressure artifacts. A continuous airstream is delivered to one nasal chamber by a 6 cm long Teflon™ tube with a 4 mm outer diameter inserted approximately 1 cm into one naris. This airstream is then replaced by one of several odorized airstreams for time periods ranging as low as 50 ms, using a nonelectrical vacuum switching device, which allows for the switching of the airstreams without pressure or thermal artifacts. By carefully tuning the switching of the vacuums, the stimulus characteristics can be optimized so that the rise time of the stimulus does not exceed 20 ms. This guarantees that the subject has no additional cues, such as tactile or thermal sensations, which could provide extraneous information about the timing of stimulus presentation. Also, to eliminate any possible auditory cues associated with the opening and closing of the valves, subjects listened to 65 dB continuous white noise presented through insert ear phones.

Hydrogen sulfide (H_2S) was used as the stimulant for the study. Unlike some odorants, which are also astringent, H_2S is a pure olfactory nerve stimulant that does not induce any significant coincidental somatosensory nerve activity. Two different concentrations of H_2S (17.6, 8.8 ppm) were presented at each of four different stimulus durations (100, 500, 1000, 2000 ms). Interstimulus interval was 7.5 ± 2.5 s. At each stimulus duration and concentration, 5–10 odor pulses were presented to each nostril to ensure a representative sampling of the EOG response. The order of nostril and stimulus presentation was randomized across subjects. Subjects were asked to sit quietly in a relaxed awake state and to breathe through the mouth. They were not alerted before stimulus presentation and were not required to respond in any way.

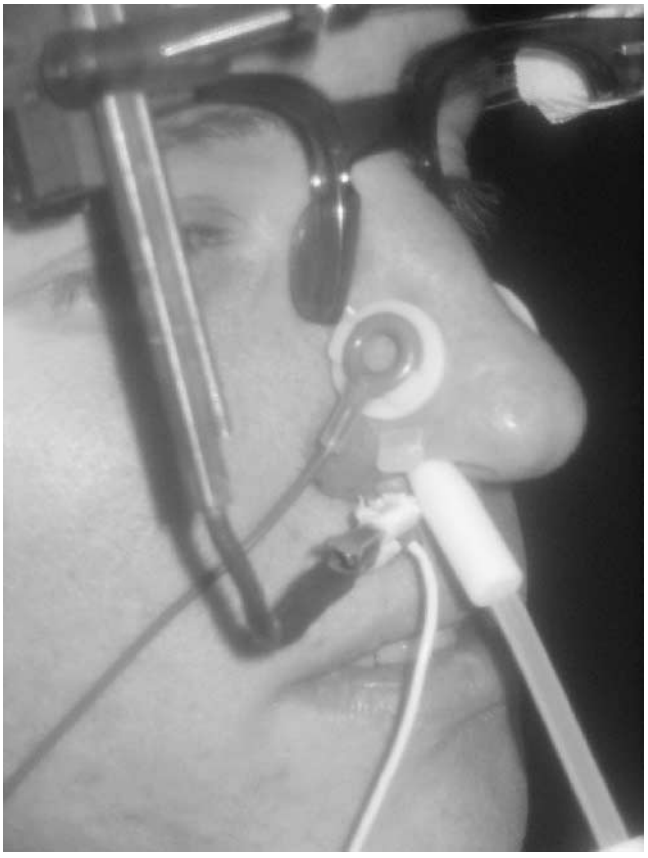

Figure 1 Experimental setup for recording EOG. Odorant is delivered through the large plastic nasal cannula. Wire recording electrode is inserted into the nasal cavity and held in position on the epithelial surface by an adjustable clip mechanism attached to a pair of glasses that are strapped to the head. Circular reference electrode is placed on the external lateral surface of the nose.

EOG recording and data processing. A thin sintered silver–silver chloride wire electrode (0.4×8.0 mm; *In vivo* Metric, Healdsburg, CA) was coated with electrode gel and inserted into the nasal cavity. Under endoscopic guidance, the recording end of the electrode was placed on the posterior superior aspect of the medial surface of the middle turbinate. This is the site that we routinely target for nasal epithelial biopsies, from which we successfully harvest ORNs (Hahn *et al*, 2005). A reference electrode was placed on the external lateral surface of the contralateral nasal cavity and a ground electrode was placed on the forehead. Figure 1 demonstrates the experimental setup for odor stimulus delivery and EOG response recording. Electrical potentials were amplified with an AC-coupled Neuroscan Synamps amplifier (gain: 1000; range: 5.5 mV; resolution: 0.084 μV; bandpass filter settings: 0.10–50.0 Hz). Data were digitally sampled at 250 Hz and written to disk for offline postprocessing. A 2000 ms, 17.6 ppm odorant test pulse was delivered first to ensure that a robust EOG response was elicited, and the recording electrode was repositioned, when necessary, to improve the quality of the recording before the start of data acquisition.

Figure 2 illustrates the morphology of the EOG response following presentation of a single 1000 ms puff of H_2S, at different concentrations, in an individual subject. There is a characteristic depolarization that reaches its maximum at ~300 ms, followed by repolarization. The subsequent overshoot and slow return to baseline reflect the low frequency response characteristics of the AC-coupled amplifiers. The initial negative voltage change is highly dependent on the concentration of the odorant, as expected for the EOG originating in ORNs. The absence of an observable response independent of odor concentration confirms that there was no significant somatosensory stimulation or other nonspecific response artifact associated with the odor presentation. The latency and amplitude of the maximum depolarization was measured for each individual EOG waveform, and mean values were computed for each subject for each combination of odor concentration and duration.

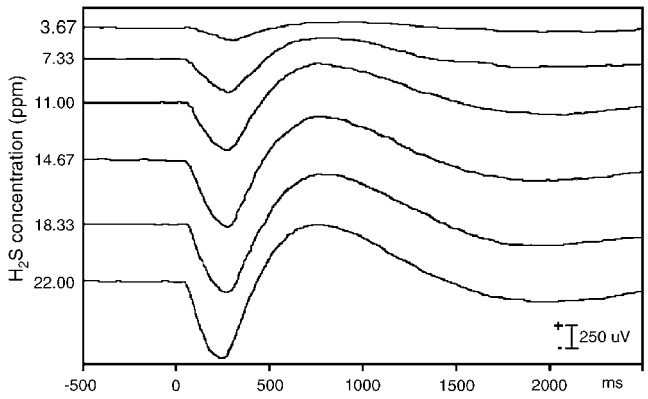

Figure 2 Morphology of the EOG following presentation of a single 1000 ms puff of H_2S, at different concentrations, in an individual subject. This response illustrates the typical dose-dependent depolarization of the olfactory receptor neurons.

Statistical Analysis

Multivariate analysis of variance was used to assess patient–control differences, with diagnosis and smoking status (smoker/nonsmoker) as between-subjects factors, nostril, H_2S concentration and stimulus duration as within-subject factors, and age as a covariate. As normal aging has a significant effect on olfactory abilities (Doty *et al*, 1984), it may be important to account for the impact of this measure on the observed intersubject variance, even when the diagnostic groups do not differ (Miller and Chapman, 2001). Dependent measures, in separate analyses, were mean amplitude and latency of the EOG depolarization response (see Table 1). Significant ($p < 0.05$) multivariate interactions were dissected by *post hoc* univariate contrasts of patient *vs* control responses to each individual class of stimuli having a fixed odor concentration and duration.

RESULTS

EOG Amplitude

There was a significant two-way interaction of diagnosis × odor duration ($F(3102) = 2.72$, $p = 0.049$) and a three-way interaction of diagnosis × odor concentration × odor duration ($F(3102) = 3.94$, $p = 0.011$). As shown in Figure 3, patients had larger EOG amplitudes across all experimental

Table 1 Electroolfactogram Response (mean ± SD)

	Odor concentration: 8.8 ppm		Odor concentration: 17.6 ppm	
	Amplitude (μV)	**Latency (ms)**	**Amplitude (μV)**	**Latency (ms)**
100 ms duration				
Patients	165 ± 85	225 ± 75	387 ± 297	214 ± 69
Controls	129 ± 72	233 ± 95	267 ± 175	209 ± 67
500 ms duration				
Patients	310 ± 175	449 ± 165	650 ± 478	400 ± 158
Controls	242 ± 165	421 ± 149	406 ± 257	417 ± 154
1000 ms duration				
Patients	305 ± 171	497 ± 223	680 ± 475	413 ± 153
Controls	248 ± 168	502 ± 286	389 ± 228	426 ± 167
2000 ms duration				
Patients	295 ± 156	523 ± 163	738 ± 446	432 ± 160
Controls	282 ± 202	625 ± 480	431 ± 268	549 ± 368

conditions, but this group difference was amplified when the odorant was presented either at higher concentration or for longer duration—ie, when the olfactory epithelium was exposed to more odorant molecules. Figure 4 presents the grand average EOG responses for patients and healthy comparison subjects, as well as the median single subject responses, which clearly illustrate this group difference. There was also a two-way interaction of diagnosis × nostril ($F(1,34) = 5.04$, $p = 0.031$). Although the mean patient response was greater for both left and right nostril recordings, this group difference was significantly larger when the odorant was presented to the right nostril. There were no associations within the patient group between mean EOG amplitude and any clinical measures, including scores on BPRS, SANS, SAPS, or GAF rating scales, age of illness onset, illness duration, daily medication dosage or smoking status. In particular, there were no significant differences in the EOG responses of the 8 patients who smoked and the 13 who did not. Nor were there any differences in the responses of the eight patients taking typical antipsychotic medications.

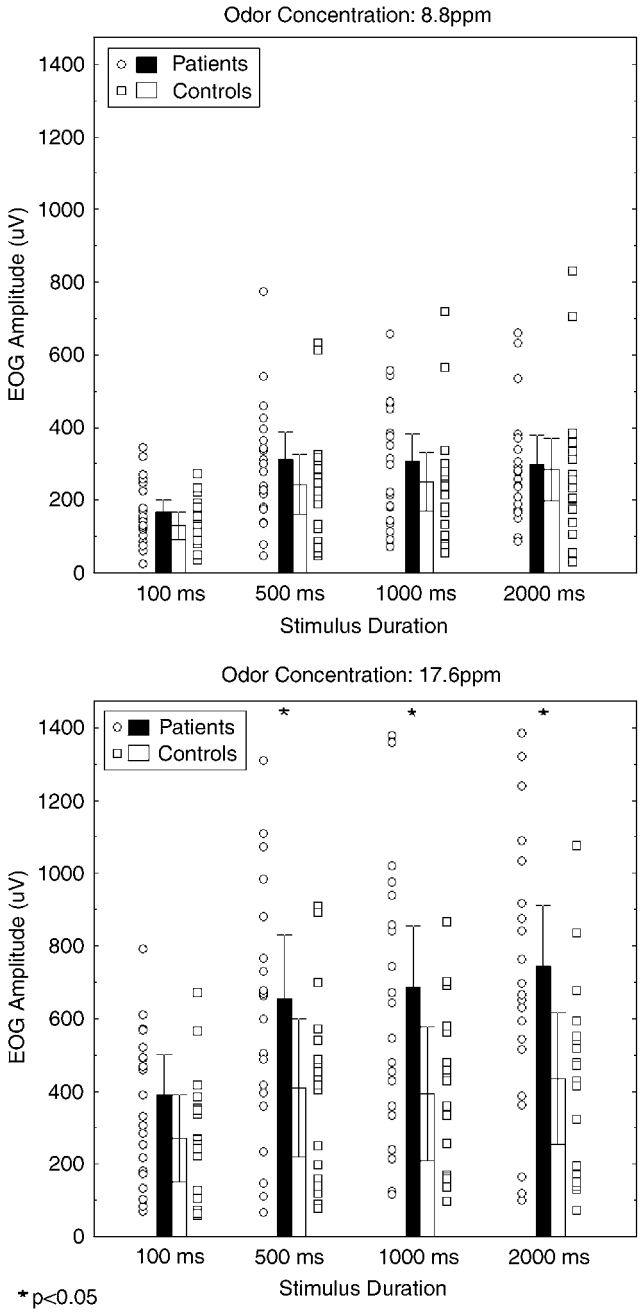

Figure 3 EOG amplitudes for two H_2S concentrations across four different stimulus duration conditions in both patients and healthy comparison subjects. Bar plots indicate mean ± SE. Scatterplots present individual subject responses.

EOG Latency

There was a main effect of odor duration ($F(3102) = 2.93$, $p = 0.037$) on EOG latency, but no other significant effects. The peak EOG response was delayed following more prolonged odor stimulation, but this was independent of diagnosis.

DISCUSSION

The results of this study demonstrate that schizophrenia patients produce abnormally large EOG responses following H_2S stimulation, which are unrelated to acute symptomatology, antipsychotic medication dosage or smoking history. This suggests that disruptions of neural physiology in schizophrenia are not limited to the cortex and subcortical limbic structures, but rather include even the most peripheral sensory neurons. It is thus consistent with an increasing number of reports of abnormalities in primary sensory areas of the cortex (Sweet *et al*, 2007; Turetsky *et al*, 2003b, c) and suggests that the pathological processes of schizophrenia are more ubiquitous than cognition-based models of hypofrontality (Snitz *et al*, 2005) or frontal–temporal dysregulation (Weiss *et al*, 2006) might imply.

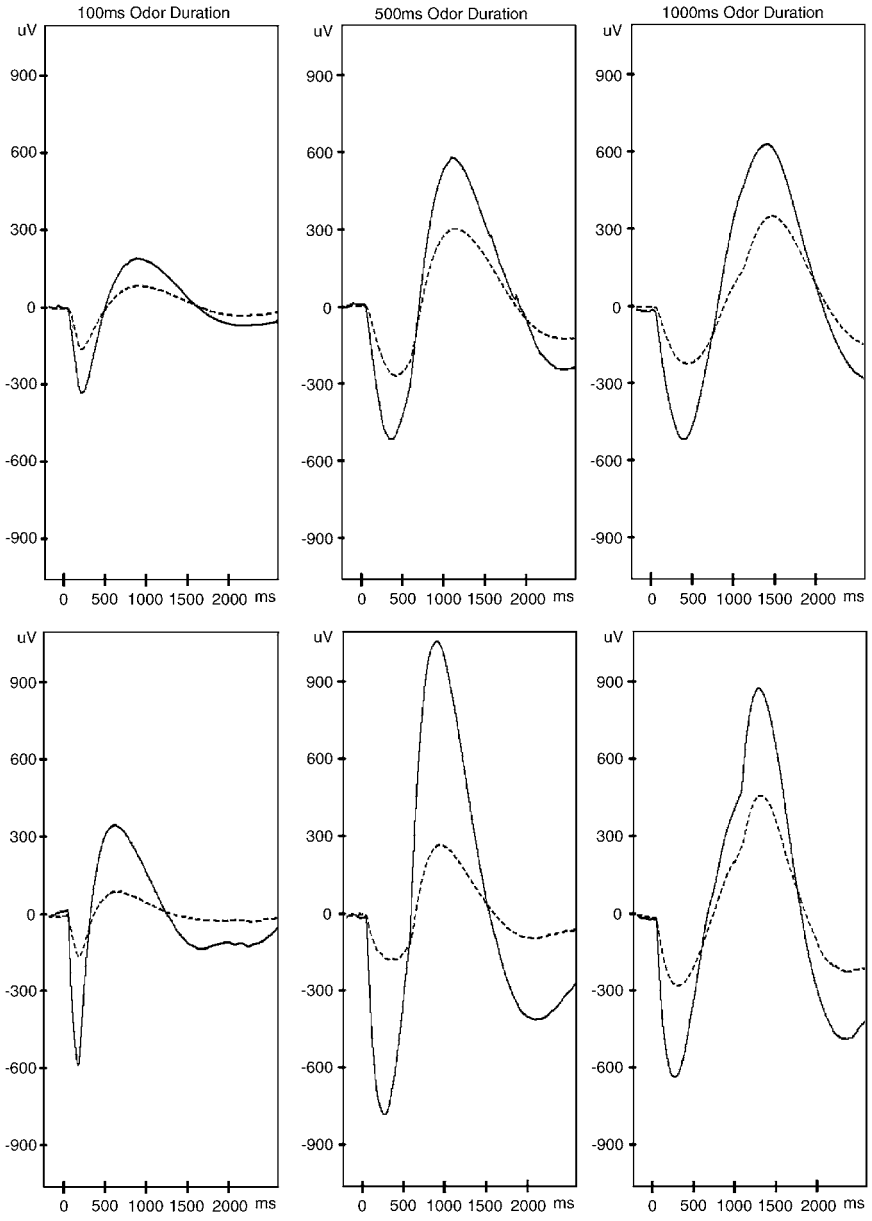

Figure 4 Top: Grand average EOG responses for patients and healthy comparison subjects for 100, 500, and 1000 ms presentations of 17.6 ppm H_2S. Bottom: Representative subject data from the individual patient and healthy comparison subject exhibiting the median response amplitude within their respective groups.

Two aspects of the data require specific comment. First, as indicated in Figure 3, there was a large degree of intersubject variability in EOG responses. This is consistent with *in vitro* findings of large response variability even at the cellular level. For example, among a group of 329 ORNs, all of which exhibited active responses to the odorant cineole, the magnitudes of responses following exposure ranged from 9 to 724 pA (mean ± SD = 215 ± 163 pA; Takeuchi *et al*, 2003). However, this may also reflect, to some extent, differences in placement of the recording electrode on the olfactory epithelium. ORNs are scattered throughout the epithelium in a diffuse and patchy manner, and there are inevitably some between-subject differences in the proximity of the EOG electrode to the olfactory neurons. As comparable variability was seen in the responses of both patients and controls, it is unlikely that this would reflect any sort of systematic bias across the diagnostic groups.

Second, although lateralized cerebral findings are commonplace in schizophrenia research, it is surprising to see such lateralized effects extend to the level of primary sensory receptors. However, it is well known that the right hemisphere is better adapted to processing olfactory inputs than the left (Doty *et al*, 1997). We previously observed a similar lateralized right-sided abnormality when we assessed olfactory bulb volumes in unaffected first-degree relatives of schizophrenia patients (Turetsky *et al*, 2003a). Other studies have demonstrated larger right olfactory bulbs, as a consequence of normal development, in diverse species (Heine and Galaburda, 1986; Prasada Rao and Finger, 1984). There is also evidence that the two bulbs

contain different levels of modulating neurotransmitters and enzymes (Dluzen and Kreutzberg, 1996; Rodriguez-Gomez *et al*, 2000). If the right and left olfactory bulbs, which are the axonal targets for the peripheral ORNs, are structurally and functionally distinct then the dysregulation that gives rise to elevated ORN responses in patients could also be one that is manifested primarily on the right side. If this is the case, then an understanding of the normal structural and functional asymmetry of the peripheral olfactory system could provide an important clue to the etiology of this abnormality in schizophrenia.

At this point, though, the pathophysiological mechanisms that might underlie this abnormality are not entirely clear. There appear to be at least three different possibilities: (1) the absolute number of olfactory neurons is greater in schizophrenia patients, hence the observed EOG response is more robust; (2) there is a loss of specificity of olfactory receptor expression in schizophrenia, such that the number of neurons that respond to a particular odorant is increased even if the absolute number of neurons is not; (3) the magnitude of the membrane depolarization current of individual ORNs is increased, so that the recorded EOG response is greater even if the number of responding neurons is unchanged. These alternative mechanisms should not be considered mutually exclusive and there is, in fact, some indirect evidence to support each of them.

With regard to the total number of olfactory neurons, Arnold *et al* (2001) reported that olfactory epithelial tissue obtained at autopsy from schizophrenia patients had increased numbers of immature GAP43 + neurons relative to p75NGFR + precursor stem cells, compared to epithelial tissue obtained from healthy individuals. Similarly, cultures of olfactory neuroepithelial tissue biopsied from living schizophrenia patients exhibited increased mitosis and greater cell proliferation than olfactory tissue cultures derived from healthy subjects (Féron *et al*, 1999; McCurdy *et al*, 2006). Finally, gene expression profiling of olfactory epithelial tissue found increased expression of multiple genes related to cell proliferation, differentiation and neurogenesis in schizophrenia (McCurdy *et al*, 2006). Collectively, these findings indicate that there is increased neuronal proliferation associated with dysregulated olfactory receptor development in schizophrenia. The observation of increased EOG amplitude is consistent with, and may be a marker of, this increased cell proliferation.

This process may also be exacerbated by a loss of selectivity of olfactory neurons. Normally, a given olfactory neuron expresses only one olfactory receptor on its membrane surface, restricting its response to a specific odorant molecule configuration (Ronnett and Moon, 2002). There is evidence, however, that such selectivity can be altered, as in the case of the alteration of olfactory function with normal human aging (Rawson *et al*, 1998). Perhaps more importantly, electrophysiological studies of olfactory development also indicate that the olfactory epithelium of immature animals is highly nonselective, with individual olfactory neurons responding to many different odorants (Gesteland *et al*, 1982). Selectivity appears to be acquired only later in development. As the basic finding of Arnold *et al* (2001) was an increased density of immature rather than mature neurons in schizophrenia, it is possible that this would translate into an increased number of neurons that respond nonselectively to H_2S. Although this is a plausible hypothesis, specific evidence remains lacking.

Another possibility is that the magnitude of the EOG response is increased at the level of the individual neuron—ie, that there are alterations in the intracellular signal transduction pathways that lead to increased membrane depolarization. The binding of an odorant to an olfactory receptor results in increased levels of intracellular cyclic AMP (cAMP). cAMP functions as a second messenger, causing cyclic nucleotide-gated ion channels to open and cations to enter the cell. There is a strong correlation between the magnitude of this transmembrane current, which produces the observed EOG response, and the levels of adenylyl cyclase activation and cAMP accumulation within olfactory neurons (Lowe *et al*, 1989). There is increasing evidence to suggest that this intracellular signaling cascade may be dysregulated in schizophrenia. An early study, using B lymphocytes, found increased adenylyl cyclase activity and cAMP accumulation in cells from schizophrenia patients following stimulation with forskolin, which binds to a high affinity site on the catalytic subunit of adenylyl cyclase (Natsukari *et al*, 1997). More recently it has been shown that DISC1, the schizophrenia susceptibility gene located on chromosome 1q42, acts intracellularly to sequester phosphodiesterase, the enzyme responsible for the degradation of cAMP, and to release it in response to elevated levels of cAMP (Millar *et al*, 2005). Alterations of the quantity or function of the DISC1 protein will therefore necessarily alter the regulation of cAMP levels. Similarly, a polymorphism of the *GNAS1* gene on chromosome 20q13, which codes for the α-subunit of the G protein that stimulates adenylyl cyclase, has been associated with deficit syndrome schizophrenia (Minoretti *et al*, 2006). Alterations of this protein would affect the production, rather than the degradation, of cAMP following stimulation. Alterations in cAMP levels could also be a secondary effect of either glutamatergic (Chetkovich and Sweatt, 1993) or dopaminergic (Neves *et al*, 2002) dysregulation, both of which have been implicated in schizophrenia pathophysiology. Although these associations support the idea that cAMP signaling is disrupted in schizophrenia, the status of olfactory signal transduction in this disorder has yet to be examined.

We cannot, at this time, delineate the relative contribution of each of these potential mechanisms to the abnormalities we have observed. Any one of these disturbances at the level of the epithelial receptor could, presumably, lead to the olfactory sensory perceptual deficits that are observed in behavioral studies of odor identification and threshold detection sensitivity. Future studies using olfactory epithelial biopsy material are required to clarify the relationship between the electrophysiological and biochemical responses of ORNs. The extent to which these abnormalities generalize to other odorants may also shed light on their underlying mechanisms, because odorants differ substantially in the level of adenylyl cyclase excitation that they produce (Sklar *et al*, 1986). The extent to which this finding is specific to certain groups of odorants needs to be determined, as does its specificity to schizophrenia. Olfactory neurons from bipolar patients exhibit abnormal responses to odor stimulation in culture (Hahn *et al*, 2005), but it is not clear if their EOG responses are similar to or

different from those of schizophrenia patients. The specificity of this finding to schizophrenia, its relationship to observed psychophysical olfactory deficits, and its status in unaffected individuals at genetic risk for the disorder are all questions that have yet to be investigated.

Finally, although we observed no association between EOG amplitude and either the dosage or class (typical *vs* atypical) of antipsychotic medication, we cannot entirely rule out the possibility that these findings are a consequence of patients' use of antipsychotic medications, which may have altered dopaminergic activity in the nasal mucosa in a manner that is not dose-dependent. Recent *in vitro* evidence from slice preparations of the mouse olfactory epithelium (Hegg and Lucero, 2004) indicates that exogenous dopamine can decrease the odor-induced responses of ORNs through inhibition of L-type voltage-gated Ca^{2+} channels. D_2 dopamine receptor antagonism can completely reverse this response inhibition and return neuronal excitability to normal. Importantly, though, a D_2 receptor antagonist alone does not appear to amplify the odor-induced ORN response. Also, previous studies have demonstrated odor-induced cortical evoked potential abnormalities in schizophrenia patients independent of medication status (Turetsky *et al*, 2003b), as well as in healthy unmedicated first-degree relatives (Turetsky *et al*, 2008). Nevertheless, altered mucosal dopaminergic activity in patients, either as a primary dysfunction of the illness or as a secondary response to pharmacological treatment, could have contributed to our findings. It will therefore be very important to determine, in future studies, whether new-onset unmedicated schizophrenia patients, individuals with prodromal symptoms, or unaffected family members exhibit similar EOG abnormalities.

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DISCLOSURE/CONFLICT OF INTEREST

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