Implications of Olfactory Agnosia for Understanding Sex Differences in Schizophrenia

by Lili Kopala and Campbell Clark

Abstract

In our studies, 50 percent of the male patients with schizophrenia have an olfactory agnosia. This finding is of interest because the olfactory neuroanatomical network involves brain regions found to be abnormal in patients with schizophrenia, and this olfactory deficit appears to be sex dependent. This article reviews conceptual models for assessing olfactory function, describes the neuroanatomical structures involved, and reviews the findings of olfactory performance in patients with neurological dysfunction. The findings are then integrated with neuropathological studies of patients with schizophrenia. Finally, as there is increasing evidence for a sex difference in patients with schizophrenia, a model is suggested to account for these differences based on neurodevelopmental and latent lesion hypotheses.

Recently we reported on the presence of an olfactory identification deficit in patients with schizophrenia (Hurwitz et al. 1988). In a subsequent analysis, we found that this deficit was confined to approximately 50 percent of the male patients with schizophrenia (Kopala 1989). Although there are many studies documenting behavioral deficits in patients with schizophrenia, this particular finding may be of special interest for two reasons: (1) The olfactory neuroanatomical network involves many of the brain regions found to be abnormal in patients with schizophrenia. (2) The deficit in olfactory identification appears to be sex-dependent and confined to male patients. The purposes of the current article are to review the conceptual models for assessing olfactory function, to describe the neuroanatomical structures involved in these functions, and to review briefly the findings concerning olfactory performance in patients with neurological diseases or dysfunction. These findings will then be integrated with neuropathological studies of patients with schizophrenia.

Because there is increasing evidence of sex differences in patients with schizophrenia (as illustrated by the articles in this issue), a model should be evolved to account for these differences. Specifically, if these differences reflect a truly different underlying process in the development of schizophrenia, then deviations from normal maturational processes within each sex may explain these differences. Therefore, in the final section of this article, potentially important processes are discussed within a neurodevelopmental model of schizophrenia. This discussion is clearly speculative and is, at best, designed to identify areas worthy of further research.

Neuroanatomical Structure of the Olfactory System

Chemical sensing begins in the olfactory mucosa by specialized neurons with axons that pass through the cribiform plate to the olfactory bulb. From here, the impulses pass through the lateral olfactory tract to the brain. The principal termination of these axons is the piriform cortex in the medial aspect of the temporal lobe (paleocortex). There are, as well, many projections

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to the structures of the limbic system, including the anterior olfactory nucleus, the prepiriform cortex, the periamygdaloid cortex, the olfactory tubercle, and subsequently, the dorsal medial nucleus of the thalamus (Eslinger et al. 1982; Doty and Snow 1987). The secondary projections from the limbic system and dorsal medial nucleus of the thalamus are to the orbitofrontal cortex. The olfactory system is unique in this regard as it is the only sensing system that does not use the thalamus as the primary relay center to cortical structures (Pansky and Allan 1980). The fact that the olfactory system projects to orbitofrontal and medial temporal structures suggests that behavioral examination of the olfactory system in patients with schizophrenia may be sensitive to abnormalities in these structures. Figure 1 schematically represents this system.

**Brief Overview of the Functional Properties of the Olfactory System**

The olfactory system is a hierarchical one in which the peripheral sensing function precedes the more central, higher order information processing that is required for the identification of different odors (Corwin 1989). Olfactory acuity can be defined as the ability to detect an odor. Threshold, a measure of acuity, refers to the lowest concentration of an odorant that an individual can identify. Deficits in acuity can result from insults to the peripheral system—for example, nasal trauma, viral infection, or environmental insults such as noxious agents. The deficits can be temporary or permanent. In contrast, olfactory identification is the ability to name a common odor when presented with an odorant. The peripheral olfactory nervous system must be functioning for the odorant to be perceived. Hence an individual may fail an odor identification task due to either deficits in acuity or identification ability. If olfactory acuity is impaired, then one would label this individual as microsmic or anosmic, depending on the degree of deficit. Similarly, within the terminology of classical neurology, the inability to identify common odors in the presence of normal acuity would be termed an olfactory agnosia. The literature suggests that such a condition can occur in patients who had insults to the cortex and are not aphasic or anosmic (Mair et al. 1986; Varney 1988; Corwin 1989).

**Olfaction and Neuropsychiatric Illness**

Olfaction deficits have been found in disorders associated with dementia such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Ward et al. 1983; Corwin et al. 1985; Serby et al. 1985; Warner et al. 1986; Moberg et al. 1988). In all three diseases, however, deficits in olfactory acuity usually accompany deficits in olfactory identification. These olfactory deficits appear early in the onset of the disorders and may reflect either peripheral or central dysfunction (Rezek 1987). Interestingly, the degree of dementia in these patients is not strongly related to the olfactory identification performance in these three disorders (Corwin et al. 1985; Moberg et al. 1987). However, olfactory deficits are not found in all organic conditions. For example, Corwin et al. (1985) demonstrated that alcoholics who were either demented or not demented, were able to perform normally on a forced-choice olfactory...
identification test. In contrast, patients with Alzheimer’s disease or Parkinson’s disease scored just above chance levels.

There are two neurological conditions in which olfactory acuity and identification abilities are dissociated and, hence, an olfactory agnosia is present. These two conditions are Korsakoff’s amnestic syndrome and lesions of the orbitofrontal cortex (Potter and Butters 1980; Mair et al. 1983; Jones-Gotman and Zatorre 1988). In Korsakoff’s syndrome, the primary lesions are in the dorsal medial nucleus of the thalamus and the mamillary bodies (Adams and Victor 1985). In contrast, demented alcoholic patients without the amnestic syndrome do not have difficulties in olfactory functions (Corwin 1989). These findings, coupled with the known neuroanatomical network of the olfactory system, suggest that the dorsal medial nucleus of the thalamus may be critical in maintaining normal olfactory identification ability.

The second condition in which this dissociation of olfactory acuity and identification occurs is in patients who have undergone neurosurgery for the treatment of intractable seizure disorders (Potter and Butters 1980; Jones-Gotman and Zatorre 1988). If the orbital regions are spared, identification ability is maintained, while if it is not, deficits in olfactory identification, but not acuity, are present. Neuroanatomically, the dorsal medial nucleus of the thalamus and the orbitofrontal cortex project to each other. When these findings are integrated with the findings for Korsakoff’s patients, the importance of the interaction between the orbitofrontal cortex and the dorsomedial thalamus in maintaining normal olfactory identification becomes apparent.

With respect to olfaction in patients with schizophrenia, there are only two previous reports in the literature and they only examine olfactory acuity. Bradley (1984) and Isseroff et al. (1987) reported increased or normal olfactory acuity, respectively, in patients with schizophrenia. Olfactory identification ability was not measured by these investigators. In our studies, we have found deficits in olfactory identification in a subsample of male patients with schizophrenia. These patients had normal olfactory acuity. This dissociation of olfactory acuity and identification may be considered an olfactory agnosia, hence involving central but not peripheral systems. More recently, data reported by Warner et al. (in press) may be interpreted as a replication of our finding but in medication-free male schizophrenic subjects (Hurtz and Clark, in press). Interestingly, deficits in olfactory function have not been reported in other psychiatric conditions such as depression (Amsterdam et al. 1987). These findings indicate that the deficit in olfactory identification is confined to male patients with schizophrenia. One may infer involvement of the dorsal medial nucleus of the thalamus or the orbitofrontal cortex.

Results of Neuropathological Studies in Schizophrenia

A selective review of neuropathological studies of schizophrenia suggests that structures involved in olfaction are also abnormal in these patients. In a review of the previous literature, Weinberger et al. (1983) concluded that limbic system pathology was more common in the brains of schizophrenic patients than control subjects. Jakob and Beckmann (1986) examined 64 (25 male and 39 female) autopssied brains of schizophrenic patients and found 20 with definite cytoarchitectonic abnormalities of the rostral entorhinal region or ventral insular cortex, while a further 20 had equivalent changes in these two regions. In two more recent reports of post-mortem studies of never-medicated schizophrenic patients, Bogerts and his colleagues have found reductions in the brain volume of the medial temporal structures: namely, the amygdala, hippocampus, perihippocampal gyrus, and the entorhinal cortex (Bogerts et al. 1985; Falkai et al. 1988). In the study of Falkai et al. (1988), although the sex distribution was disproportionate, the reduction in volume in the entorhinal cortex was two to three times greater in the male patients (n = 2) than in the female patients (n = 11). Most recently, Casanova and Stevens (1989) have reported gliosis infiltrating the extended amygdala (amygdala, substantia innominata, ventral striatum, septal nuclei, and preoptic hypothalamus). They suggested a relationship between the amygdala and its projections for integration, cognition, perceptions, and emotional behavior, and then linked this relationship to neuroendocrine function. Hippocampal pyramidal cell disorganization has also been found in the brains of schizophrenic patients, most of whom were never exposed to neuroleptics (Altshuler et al. 1987). Although others (Benes et al. 1986; Roberts et al. 1987) did not find gliosis in these structures, one may infer that at least a proportion of patients with schizophrenia have neuropathologic abnormalities in these areas.
From this review one can identify a set of common neuroanatomical structures found to be: (1) abnormal in many of the neuropathological studies of schizophrenia; (2) intrinsic to the neuroanatomy of the olfactory system; and (3) seemingly affected in the behavioral assessment of olfactory function in males with schizophrenia. These structures include the dorsomedial nucleus of the thalamus, the orbitofrontal cortex, and the medial temporal structures of the limbic system.

Sex Differences in the Human Anatomy and the Course of Illness in Schizophrenia

There is a growing body of literature suggesting that male and female patients do differ on a number of pertinent variables. It is of interest to note that the first study reporting enlarged lateral ventricles in patients with schizophrenia examined only male patients (Johnstone et al. 1976). Subsequently, Andreasen et al. (1986), using magnetic resonance imaging, reported that reductions in the volume of the prefrontal cortex were more prevalent in male patients with schizophrenia than in female patients. It cannot be determined, however, whether these decreases in volume are general or confined to specific aspects of the frontal cortex. Ventricular enlargement has been more extensively studied in males than in females with schizophrenia. In studies where enough females were examined, DeLisi et al. (1989) concluded that ventricular enlargement appears as frequently in females. However, in a recent prospective study, Haas et al. (1989) demonstrated that males had greater lateralization of ventricular enlargement than females. Similarly, a greater degree of psychopathology has been associated with smaller corpus callosal size found in male patients with schizophrenia (Gulley et al. 1989).

From these results it is difficult to determine if the described sex differences are a result of sampling bias or represent qualitatively different structural abnormalities in males and females with schizophrenia. More generally, with respect to disease presentation and treatment, sex differences have been reported in the prevalence of neurological signs, response to neuroleptic therapy, and premorbid as well as long-term social adjustment (See- man 1986; Goldstein 1988; Heinrichs and Buchanan 1988). Typically, a higher degree of pathology or maladjustment and a poorer treatment response is found in male patients. In a prospective study, Haas et al. (1989) reported that males with schizophrenia had an earlier age of hospitalization, more negative symptoms at admission, and poorer premorbid functioning. Poorer premorbid functioning in males is associated with more negative findings at discharge, a greater number of hospitalizations, and poorer global functioning. The highest incidence rate for schizophrenia in males is between 15 and 24 years of age, whereas for females, the incidence rate peaks between 25 and 34 years of age (Kaplan and Sadock 1985). These findings may suggest a different etiology, or at least time course, for the observed phenomena of schizophrenia in males and females.

Sex Hormones and the Developing Brain

To account for these differences in male and female patients with schizophrenia, one must identify a physiological system that differentiates male and female maturation. One obvious candidate is circulating sex hormones and their effect on brain development. The hormone that determines the normal male brain pattern is estradiol, a female sex hormone (Kandel and Schwartz 1985). In fact, in rats, estradiol is eight times more effective than testosterone in androgenization. In male rats, although testosterone enters the brain, much of it is converted to estradiol, which then is active in masculinizing the nervous tissue. In the female rat brain, estradiol is bound such that the female brain is protected and masculinization does not occur (McEwen 1976). The interplay of androgen and estrogen, rather than either alone, results in the normal sexual differentiation of brain tissue. The sex hormones act on cell receptors and affect gene expression in specific brain regions (McEwen 1976; Kandel and Schwartz 1985; MacLusky et al. 1986; Pelletier et al. 1988). Although estrogen receptors are widely distributed throughout the cortex and subcortical structures, the highest concentrations are found in the amygdala, the hippocampus, and the orbital prefrontal cortex. This distribution is of particular interest given that these structures are also involved in olfaction and have been found to be abnormal in patients with schizophrenia. Note also that psychotic episodes are more likely to occur in females who are estrogen-depleted (e.g., premenstrual, post-partum, and postmenopausal states) (Endo et al. 1978; Kane 1985; Seeman 1986).

With respect to behavior, Goldman and Brown (1975) have demonstrated a sex-dependent age effect for lesions of the orbitofrontal cortex in male and female rhesus monkeys.
When lesions were performed in infancy, males were impaired on behavioral tests at 2.5 months of age whereas similar deficits were not seen in females with comparable lesions until 15–18 months of age. More recently, MacLusky et al. (1986) reported that this differential effect may be eliminated by treating female monkeys with testosterone. Specifically, female monkeys treated with testosterone after sustaining a lesion to the orbitofrontal cortex did not show the normal female pattern, but rather followed the male pattern. This finding suggests that the normal sex difference in this particular response is hormone-dependent and may be sensitive to gonadal steroids in postnatal life (Goldman and Brown 1975). On the basis of these results, Goldman and Brown (1975) suggested that functional specialization of the orbital prefrontal cortex develops more rapidly in males than in females.

Our own findings of an olfactory agnosia in male patients with schizophrenia, as well as the literature cited, suggest that there may be an abnormality in the sex hormone system in a subsample of males with schizophrenia. Specifically, a disruption of this system, whether in the proliferation, migration, specialization, or weeding of estrogen receptors, or in the concentration of estrogen or testosterone, affects the development of the orbitofrontal cortex differentially in males and females. This disruption could produce a latent lesion in males that is triggered at puberty with the known increase in testosterone. In females, this process may be different due to the higher concentration of estrogen and thus result in delayed functional specialization. Such an explanation is consistent with Weinberger’s (1987) neurodevelopmental and latent lesion hypothesis for schizophrenia, but is more specific regarding process. DeLisi et al. (1989) have also postulated a neurochemical model for the effect of sex hormones on the neurotransmitter systems and the possible implications for psychosis and schizophrenia.

With respect to etiology, a number of studies have suggested a relationship between X-chromosome abnormalities and schizophrenia (Crow 1988; Crow et al. 1989; DeLisi et al. 1989). These speculations have included X-linkage models, the pseudosomal portion of the X chromosome, and fragile X (Reiss and Toomey 1986). Hypotheses such as these could explain the suggested disruption in processes and the subsequently observed deficits in our subsample. Specifically, an abnormality of the X chromosome may influence the proliferation, migration, and specificity of the estrogen receptors in the brain or, perhaps, the concentration of circulating sex hormones. As with other genetic disorders (e.g., Huntington’s chorea), there may be a triggering phenomenon that initiates the abnormalities observed in later life. The triggering mechanism may well be puberty, as suggested by the time of onset of illness in males.

In summary, the suggested abnormalities in processes can be tested by identifying patients whose behavioral deficits are consistent with the suggested sites of pathology. The advantage of such an approach, although speculative, is that theoretically based hypotheses can be tested empirically. Clearly, such approaches will not always be successful, but the theory can be refuted or accepted. Note that the suggested disruption in processes would be, in all likelihood, confined to a subsample of patients with schizophrenia. Historically, individuals have been pared from the diagnostic category of schizophrenia by understanding the etiology of their symptoms (e.g., heavy metal poisoning and neurosyphilis). To continue this approach may be the most productive in developing our understanding of schizophrenia.

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