Unirhinal olfactory identification deficits and convergent lateralized neuropsychological impairment in male patients with schizophrenia

by

Kimberley Patricia Miriam Good

M.Sc., University of British Columbia, 1992

B.Sc., University of New Brunswick, 1989

A thesis submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

in

The Faculty of Graduate Studies

(Graduate program in Neuroscience)

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

April, 1997

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Graduate Programme in Neuroscience

The University of British Columbia
Vancouver, Canada

Date April 30/97

Abstract

Prior research has revealed that olfactory identification ability is impaired in male patients with schizophrenia. Additionally, lateralized differences have been observed in olfactory functioning in normal individuals who have intact sense of smell. The purpose of this study was to determine whether the pattern of olfactory laterality observed in male patients with schizophrenia was different from that observed in non-schizophrenic, normal, male control subjects. In addition, if patients with unirhinal olfactory identification deficits were found, did these individuals have a different profile of neuropsychological impairment relative to those patients with intact sense of smell?

Methods:

Forty-three male in-patients with a DSM-IV diagnosis of schizophrenia and 59 normal male control subjects were assessed unirhinally on three measures of olfactory function: olfactory acuity, identification and discrimination ability. Additionally, a battery of neuropsychological tests sensitive to brain lesions in regions critical to olfaction (left and right temporal and frontal lobes) was also administered.

Results:

No particular pattern of olfactory laterality was observed in either the normal control or the male patient groups on any of the olfactory measures.

Using cutting scores generated from performance of the normal control subjects on the olfactory identification task, patients were classified according to nostril deficit. Three groups were compared: left microsmic (n=12), right microsmic (n=5) and normosmic schizophrenic controls (n=25). On tests of **left** hemisphere function, the **left** microsmic group was preferentially impaired while on tests of **right** hemisphere function, the **right** microsmic group

was preferentially impaired. On demographic and experiential variables, the left microsmic group was impaired on a measure of premorbid IQ (reading of irregular words) and the normosmic group was significantly younger than both other groups.

Discussion and implications .

These data suggest that using a simple, non-invasive measure of unirhinal olfactory identification ability, male patients with schizophrenia could be categorized into subgroups with lateralized brain dysfunction. Those with left hemisphere abnormalities may be those with a neurodevelopmental form of the disorder given their poor reading capacity (an ability which is acquired early in life) despite similarities amongst subgroups on educational achievement and parental socioeconomic status.

Table of Contents

List of Tables

List of Figures

Acknowledgments

I am indebted to the members of my supervisory committee: Dr. Trevor Hurwitz, Dr. Chris Fibiger, and Dr. Holly Tuokko and in particular, to my co-supervisors, Dr. Lili Kopala and Dr William Honer. A superior study was conducted as a result of the unique contributions from each committee member. I extend my sincere appreciation for their input. The additional support and assistance from Dr. Jeff Martzke is gratefully appreciated.

I am also deeply grateful for the assistance provided by Drs. Kulbir Singh, William MacEwan, Lorraine Andrews and Margaret Duke for patient referrals and psychiatric assessments. Barbara Meistrich was instrumental for her role in identifying potential study candidates and making sure that patients met the inclusion criteria *before* I assessed them. The assistance of Dr. A Blokmanis for rhinoscopic examination and cocanization is acknowledged.

To the staff of East 1 at Vancouver Hospital and Health Sciences Center and the staff of West 2 at St. Vincent's Hospital, I extend my thanks for introducing me to patients on the units. My appreciation is also extended to all patients and control subjects who taped their nostrils shut for me.

Several people were extremely helpful with the final manuscript preparation. I would like to thank Mr. Wade Blanchard, M.Sc. for consultation on statistical manipulations, Ms. Coleen Logan for graphic artistry, Ms. Beverly Gillis for editorial assistance, and my father, Mr. Frank Good for proof reading.

A number of personal friends require acknowledgment for their participation (albeit remotely) in this project. To Ms. Kelly Trigg, I extend many thanks for her tenacity in reminding me of what I was capable. I am also very grateful to Ms. Pat Good for showing me how to keep things in perspective. Most importantly, I am deeply grateful to Mr. Greg Stewart for resolutely putting up with me during my numerous crises.

Dedication

This dissertation is dedicated in loving memory of my grandmother, Ms. Patricia M. Brewer, who passed away September 25, 1996. Her strength and determination to maintain an active lifestyle despite chronic illness was a source of great inspiration for me as I struggled through graduate school. She is dearly missed.

CHAPTER 1

INTRODUCTION AND OVERVIEW

1. Introduction

A growing body of evidence indicates that individuals with intact olfactory ability favour their right or their left nostril depending on the olfactory task administered. Specifically, when individuals without olfactory complaints are asked to discern whether two odours are the same or different, a distinct right nostril advantage has been observed (Zatorre & Jones-Gotman, 1990). In contrast, when asked to name an odour, a left nostril advantage has been reported (Hornung et al, 1990). As olfactory pathways travel predominantly within the same hemisphere from which they originate, nostril advantage implies ipsilateral hemispheric superiority for that task. In general, tasks which rely on verbal processing are disrupted more after left rather than right hemisphere lesions whereas the converse is true for functions not readily verbally mediated.

Olfactory pathways project through regions of the brain which are reported to be abnormal in patients with schizophrenia. Therefore, it is not surprising that some patients with schizophrenia are impaired in their ability to identify common odours. Although birhinal olfactory deficits have been reliably demonstrated in patients with schizophrenia (Kopala et al, 1989; Seidman et al, 1992; Wu et al, 1993), only one study has attempted to determine whether the olfactory dysfunction in schizophrenia is lateralized in a pattern different from normal controls (Dunn & Weller, 1989).

Many studies investigating the neuropathology of schizophrenia support increased left hemisphere abnormalities (Petty et al, 1995; Falkai et al, 1995) . These deficits may be more pronounced in males (Suddath et al, 1991). In light of these findings, the purpose of the current

study was to determine whether a different pattern of hemispheric asymmetry for olfactory function was observed in males with schizophrenia relative to that in the normal control population. In an effort to answer this question, 43 males with schizophrenia and 22 normal male control subjects were examined unirhinally on tests of olfactory acuity (detection threshold), identification, and discrimination. In addition, to validate the presence of hemispheric impairment and to further localize the possible regions of brain abnormality, neuropsychological tests sensitive to left or right temporal or frontal lobe damage were administered.

I) Overview of subsequent chapters

This dissertation is divided into five chapters corresponding to the following outline. Chapter 1 consists of a brief introduction and overview to the study. Chapter 2 is a comprehensive review of the literature outlining the background to the study. The third chapter provides a detailed methodology of the study, while chapter 4 surveys the results of the statistical analyses. The fifth chapter discusses the results, suggests conclusions and poses further research questions.

II) Issues related to the study of lateralized olfactory function in schizophrenia

a) Schizophrenia

Schizophrenia is a term which refers to a collection of severe mental disorders resulting from abnormalities in brain structure and function. The characteristic signs and symptoms include hallucinations, delusions, disordered thinking, along with the so-called negative symptoms, such as social and emotional withdrawal. The disorders, which affect one out of every 100 individuals (Hare, 1987), often begin in late adolescence or early adulthood, leaving conservatively 50% of those affected with lifelong disabilities (Maneros, 1993). Affected

individuals suffer greatly and incur a profound burden on care givers and society. In Canada, approximately four billion dollars is spent on the direct and indirect costs of the illness. Individuals receiving a diagnosis of schizophrenia comprise 10% of all the chronically disabled in Canada and occupy 8% of all hospital beds (Pivik & Young, 1994).

The causes of schizophrenia remain unclear. There is evidence supporting a genetic contribution to the etiology. Biological relatives of those with schizophrenia, including biological relatives who were adopted at birth, are at greater risk for developing schizophrenia (Kendler et al, 1985, Kety, 1988). Biological relatives have also been shown to demonstrate "spectrum-like" disorders (Erlenmeyer-Kimling, 1977). Given that the concordance rate for identical twins developing schizophrenia is only 50% (Gottesman, 1991), environmental factors presumably also contribute to illness development.

One of the most appealing and widely accepted models of the etiology of schizophrenia is the "non-lethal" disturbance of fetal development (Kovelman & Sheibel, 1984; Shapiro, 1993; Weinberger, 1987). Specifically, this model suggests that damage occurs during the second trimester of pregnancy when fetal central nervous system (CNS) growth and differentiation are at their peak. At this stage, even a minor disruption in the developmental process may have profound effects. Damage to the CNS may occur as a result of hypoxia, maternal exposure to toxins/viruses, hemorrhage, an inborn error of gene expression or any combination of the above (Shapiro, 1993). The temporal lobe seems to be particularly sensitive to such effects. Neuropathological studies document changes in patients with schizophrenia in temporal lobe cell density (Falkai et al, 1988), neuronal migration and cellular disarray (Kovelman & Sheibel, 1984).

According to the neurodevelopmental hypothesis, obvious symptoms of schizophrenia are not evident in early childhood although mild impairments of attention, motor incoordination and affective expression have been documented (Cornblatt & Erlenmeyer-Kimling, 1985). In late adolescence or young adulthood, the so called "latent lesion" becomes active as affected brain regions mature. Thereafter, signs and symptoms of schizophrenia appear.

b) Olfaction

The olfactory network is a phylogenetically ancient system capable of detecting and discriminating amongst a huge array of odorants. The sense of smell is more highly developed in lower animals who rely heavily on this sense to orient in their environment (macrosomatic organisms). In so called microsomatic organisms, which include humans, olfaction largely determines the pleasantness or unpalatability of the foods we eat, and acts as an early detection system in the event of danger. Despite its documented significance in guiding human behaviour, olfactory function has been largely neglected, both clinically and in the research literature. However, over the last decade, research on human olfaction has burgeoned.

The olfactory pathways project from the olfactory bulbs to areas of the medial temporal lobe. From here, projections proceed to the orbitofrontal cortex either directly or indirectly through the dorsomedial nucleus of the thalamus. Medial temporal regions and dorsomedial nuclei of the thalamus have been reported to be structurally abnormal in patients with schizophrenia (for a review, see Shapiro, 1993).

A commonly reported symptom in dementing disorders such as Alzheimer's, Huntington's and Parkinson's diseases is reduced olfactory capacity (Morgan et al, 1995; Lehrner et al, 1995; Nordin et al, 1995; for a review, see Doty, 1991). Given that each of these disorders involves neurodegeneration of discrete brain regions, a common etiology is unlikely. Olfactory

compromise occurs early in the course of Alzheimer's and Parkinson's disease (Doty et al, 1987; 1988; 1992c). In addition, the degree of olfactory dysfunction is comparable between the two groups of patients. As the olfactory system is affected early in the course of these neurodegenerative disorders, it may be a sensitive marker of early CNS compromise.

Individuals who have undergone removal or damage to the frontal or temporal lobes also have olfactory deficits, when tested birhinally (Potter & Butters, 1980; Jones-Gotman & Zatorre, 1993) or when the two nostrils are tested separately (Zatorre & Jones-Gotman, 1991; Eskenazi et al, 1986; Henkin et al, 1977). Depending on the task employed, impairments have been observed after right hemisphere damage (Zatorre & Jones-Gotman, 1991) as well as after left hemisphere damage (Henkin et al, 1977). Olfactory function does not seem to be disrupted after parietal or frontal lobe lesions which spare orbitofrontal regions (Jones-Gotman & Zatorre, 1988b; Zatorre & Jones-Gotman, 1991).

III) Why study olfaction in schizophrenia?

There have been numerous recent reports describing olfactory dysfunction in patients with schizophrenia. The first study documented that male patients with schizophrenia were more sensitive to the odour of a pheromone than were the normal male control subjects (Bradley, 1984). A subsequent study did not replicate this finding but did indicate that those subjects with schizophrenia performed superiorly when asked to detect amyl acetate (Isseroff et al, 1987). Subsequent studies (with the exception of Serby et al, 1990) were unable to replicate detection threshold differences between patients with schizophrenia and normal control subjects (Kopala et al, 1989,1992) . However, deficits in more "cortical" functions have consistently been reported for patients with schizophrenia. For example, both olfactory identification (Hurwitz et al, 1988) and memory deficits (Wu et al, 1993) have been described in schizophrenia.

Testing olfactory function has the potential advantage of serving as a measure of the integrity of specific brain areas. As olfactory pathways overlap with those brain areas believed to be abnormal in patients with schizophrenia, olfactory testing may be a simple, non-invasive method of evaluating the functioning of these brain areas. Moreover, testing each nostril separately may provide information regarding the relative efficiency of one hemisphere over the other.

IV) Why study only men?

Abnormalities in brain structure and function are more common in male patients with schizophrenia than their female counterparts (Lewine & Seeman, 1995). The most commonly reported morphological sex difference in schizophrenia relates to the size of the lateral ventricles (Lieberman et al, 1992, O'Callaghan et al, 1992). In the normal control population, men were more likely to demonstrate neuroanatomic asymmetry than women (Geschwind & Galaburda, 1987). Most importantly, it is the young men, not the women with schizophrenia who were demonstrably impaired on tasks of olfactory function (Kopala & Clark, 1990).

V) Potential limitations and significance of the study

a) Concerns before commencing the study

Schizophrenia is not likely one disorder, but rather consists of a number of related disorders. Dividing patients with schizophrenia into meaningful subgroups has been unsuccessful and has plagued research endeavors for decades. E. Bleuler recognized the heterogeneity and attached a great deal of importance to it by subtitling his book "The Group of Schizophrenias" (Bleuler, 1911). The heterogeneity is further complicated by the well documented sex differences in age of illness onset and progression.

Females with schizophrenia demonstrate a later age of onset (Lewine, 1988), superior social functioning (Schubart et al, 1986; Prudo & Blum, 1987), a more favorable clinical course (at least until the menopause) (World Health Organization, 1979) and fewer structural brain abnormalities (Raz & Raz, 1990). Nevertheless, men and women with schizophrenia continue to be studied together as a homogenous group and results have been generalized to include male and female patients of all ages.

Other attempts at subtyping have been met with minimal success. Grouping patients according to diagnostic subtype (Diagnostic and Statistical Manual; DSM; APA, 1987) has not proven to be useful in predicting outcome. More recently, classification schemes based on predominant symptomatology have evolved. Specifically, patients exhibiting a preponderance of positive (productive) symptoms are regarded as distinct from those showing prominent negative or deficit symptoms (Crow, 1980; Andreasen & Olsen, 1982). Positive symptoms are reported to be associated with a better response to treatment, fewer structural abnormalities and superior cognitive functioning (Crow, 1980). Negative symptoms have been linked to more structural brain changes, poor response to treatment, and greater cognitive impairment (Crow, 1980).

More recently, applied factor analytic techniques demonstrated that the two syndrome approach is inadequate to explain the variability in symptom presentation (Liddle , 1987; Lindström and von Knorring, 1994). Of these newer systems, Liddle's three syndrome classification is gaining widespread acceptance (Liddle, 1987). Segregation of patients according to predominant symptomotology revealed three unrelated syndromes: Psychomotor poverty (reduced spontaneous movement, affective flattening and poverty of speech), Reality distortion (hallucinations and delusions) and Disorganization (thought form disorder and inappropriate

affect). Each of these syndromes appears to be distinct, demonstrating specific profiles of neuropsychological impairment (Liddle & Morris, 1991) and patterns of cerebral blood flow (Liddle et al, 1992).

However, none of these classification systems has been universally accepted as none has shown substantial predictive powers relative to outcome, response to treatment or elucidating etiology. Until schizophrenia can be reliably and validly subtyped, pooling data from a diverse, broader population, the results of such studies will likely remain inconclusive (Andreasen & Olsen, 1982).

Another issue which limits the interpretability of research is adequate control groups. The choice of comparable control groups is both important and difficult. For example, comparing patients with an age matched group will generally yield a comparison group normally with a higher education level. Schizophrenia, with its early age of onset, tends to truncate an individual's social, educational and occupational achievements, and performance on some neuropsychological measures is related to these experiential variables. Thus, the comparison of two groups who differ on critically related variables on neuropsychological measures is bound to result in significant differences. Yet, matching on the basis of age and education level produces a skewed distribution of normal control subjects who may not be representative of the population from which they are drawn.

To counteract the above mentioned potential confound, some researchers have attempted to equilibrate groups on the basis of parental socioeconomic status (Saykin et al, 1991; Petty et al, 1995). There tends to be a strong correlation between parents and offspring in their ultimate socioeconomic status and IQ. As a consequence, matching on these variables may be most informative.

Assessing human olfactory function in a clinical setting can be challenging. The olfactory mucosa is small and its location, buried deep within the nasal cavities, makes it very difficult to access and study. Equally troublesome is the fact that there is no simple metric which would be analogous to the wavelength of light in the visual system. Odours which are similar in molecular structure can be perceived differently. For example, two molecules with identical chemical composition but with mirror image chemical structure (enantiomers), R and S forms of carvone, smell like spearmint and caraway, respectively (Russell & Hills, 1971). Conversely, one odorant in higher or lower concentrations can be perceived to be different odours.

Assessing olfactory function has been accomplished by various means. Problematic to the systematic study of olfactory function is evaporation and dissipation of certain stimuli. Volatile molecules are used for the assessment of olfactory function and thus are subject to evaporation upon exposure to open air. Hence, the concentration of a given odorant may not be the same at the beginning and end of an experiment. In this regard, tests of olfactory function using microencapsulated odorants have been developed. The concentration of these stimuli are stable for at least 4 years (Doty & Agrawal, 1989).

Further complicating the study of olfactory function is the issue of inconsistent and confusing terminology. For example, testing olfactory discrimination is very different from testing olfactory identification ability. Regrettably, the two terms have been used interchangeably (see Malaspina et al, 1994). Appendix B describes common olfactory tests used. Once a consistent set of terms and definitions are adopted, then data from different centers can be compared.

Another potential concern relates to the issue of testing central and peripheral olfactory structures separately. One would never endeavor to diagnose an auditory agnosia in a hearing

impaired subject. However, higher order olfactory processing is often evaluated without first having determined the integrity of the peripheral sensing structures. In Alzheimer's disease, for example, primary sensory impairment is reported in that olfactory acuity (detection threshold) is reduced (Doty et al, 1987; Serby et al, 1991). Yet, there are numerous papers published suggesting impaired olfactory identification ability in this patient population (Doty et al, 1987; Serby et al, 1991). Regrettably, in the absence of evidence showing intact peripheral sensory ability, the claim of "higher order" (i.e., cortical) processing deficits is suspect.

b) Contributions of the proposed research

In recent years, there has been great interest in olfactory functioning in schizophrenia. Although numerous studies have attempted to delineate the nature and extent of the olfactory deficits, only one study has examined single nostril function. Therefore, the purpose of the current study was to determine whether the olfactory deficit observed in male patients with schizophrenia was lateralized in a manner different than that reported in normal control subjects. As olfactory dysfunction is observed in patients with neurodegenerative disorders and in those who have undergone brain tissue removals, the olfactory deficit observed in male patients with schizophrenia may assist us in localizing brain abnormalities. By assessing each nostril separately, the integrity of ipsilateral (same side) olfactory pathways can be evaluated

2. Overview of the current study

In an attempt to assess the pattern of olfactory laterality in patients with schizophrenia, the following design was implemented. Male patients with the diagnosis of schizophrenia and normal male controls were assessed unirhinally on olfactory acuity (detection threshold), identification and discrimination ability. In addition, a number of neuropsychological tests

which are sensitive to lesions in the left or right hemisphere, frontal or temporal lobes were also administered. The first analysis sought to examine laterality in patients and control subjects. Left/right nostril differences on acuity (detection threshold), identification and discrimination were assessed by comparing patients and control subjects in a 2X2 mixed design ANOVA (group by nostril). In addition, further analyses were performed in order to assess the extent of olfactory dysfunction in these patients. Patients were classified according to unirhinal performance on olfactory identification as normosmic, right nostril microsmic or left nostril microsmic. The profile of neuropsychological impairment was assessed among the groups of patients using a 3X2X2 ANOVA (nostril impairment classification by hemisphere of cognitive task by lobe of cognitive task). In addition, patients within each nostril impairment group were compared on clinical variables to ascertain whether olfactory dysfunction (in one nostril or the other) was related to unique patterns of psychopathology.

CHAPTER 2

BACKGROUND TO THE STUDY

The purpose of this study was to determine: 1)whether male patients with schizophrenia had lateralized olfactory detection, identification and discrimination abilities in a pattern different from that demonstrated by normal subjects and; 2) whether male patients with schizophrenia who demonstrate one sided olfactory identification deficits have a different profile of neuropsychological deficits compared to those whose olfactory status was in the normal range. Therefore, this chapter will first review the current state of knowledge regarding lateralized brain function. Secondly, the relevant anatomy and physiology of normal olfactory function will be reviewed. Thirdly, olfactory function in patients with schizophrenia and other neuropsychiatric disorders will be summarized. Finally, the current understanding of the pathophysiology and neuropsychological function in patients with schizophrenia will be discussed.

1. Cerebral hemispheric lateral asymmetry (laterality)

I) Historical perspectives

Currently, there is little dispute regarding right or left hemisphere cerebral specialization. However, cerebral hemispheric lateral asymmetry has not always been an accepted fact. In the mid 19th century, there were numerous heated debates on the topic of localization of function between the so-called "localizationists" and those who suggested that the brain acted as a whole (Davies, 1971) .

Early in the 1800's, a small group of scientists attempted to explain personality characteristics and cognitive functions by "reading" the bumps and protrusions on a person's skull. Phrenologists, as they were called, based their theory of brain function on four premises:

1) anatomy and physiology of the brain influenced mental behaviour; 2) the mind was not a distinct unit, but was made up of a number of ascertainable faculties; 3) these "faculties" were located in different regions or organs in the brain; and finally 4), greater use of a specific faculty would lead to a larger brain area, much like how exercising a muscle increases its size. According to this line of thought, the volume of specific brain regions would affect the contour of the cranium (Davies, 1971).

These pioneers were instrumental in changing the way that brain function was viewed. The suggestion that the brain was not unitary was extremely controversial. In addition, that different brain regions controlled specific mental activities did not fit with prevailing theories of the time. Nevertheless, the fact that the brain was divided into two hemispheres, which controlled musculature on the contralateral side of the body, was already known at this time and suggested hemispheric specificity. However, this observation had not yet been extrapolated to mental processes.

Although the phrenological viewpoint has since been dismissed, remnants of this theory have persisted and underlie the foundations of modern neuropsychology. In this context, in 1861, Paul Broca was the first to publish (and be taken seriously) that one hemisphere was responsible for a specific mental activity. Using the case study approach, Broca observed that his patient "Tan" who had suffered a stroke in the left hemisphere was unable to speak. At autopsy, Tan was found to have sustained injury to the left inferior frontal convolution, a region now referred to as Broca's area. Broca successfully delineated a region of the brain which was responsible for a particular brain function -namely, language. Not only was Broca successful in convincing other neurologists that the neural circuits involved with a unique function were located in a specific area of the brain, he was also successful at lateralizing function to the left

hemisphere (Walsh, 1985). Once the idea of asymmetrical brain function was accepted, it created the impetus for changing theories of brain function.

II) Measurement of laterality

a) Motoric dominance

Handedness is the most obvious manifestation of cerebral laterality. It is readily observed, evaluated and serves as a relatively crude indicator of cerebral dominance. In over 90% of the general population the left hemisphere is dominant, resulting in right handedness. Early left hemisphere insult was hypothesized to shift motoric dominance from the left hemisphere to the right, resulting in what is referred to as "pathological left handedness" (Satz, 1972). As the left hemisphere develops more slowly than the right, it remains vulnerable for longer periods (Geschwind & Galaburda, 1987). Males are more likely to demonstrate abnormal patterns of cerebral dominance, and as such, it has been suggested that testosterone may further delay the development of the left hemisphere (Geschwind & Galaburda, 1987).

b) Hemispheric dominance for language

Studies of individuals with corpus callosum sectioning or unilateral brain injury leave little doubt that the hemispheres are differentially proficient at certain tasks (Sperry, 1968). Split brain studies have shown that each hemisphere retains the ability to process stimuli. However, for a given task, one hemisphere appears to dominate over the other. For example, if stimuli are quickly presented only to the right visual field, the stimuli can be easily named (visual pathways are contralaterally represented-that is they cross to the other hemisphere). In contrast, if the stimuli are viewed only in the left visual field, they cannot be named. The subject may report that he/she did not see anything, or at the very most, a flash of light. However, the stimuli can be

matched to an object representing the object provided it is manipulated by the left hand (Sperry, 1968).

Language dominance is not always manifest in the left hemisphere. Approximately 90% of individuals who are right handed show the normal pattern of hemispheric laterality for language; specifically, left hemisphere superiority. The pattern of language dominance is neither the same nor reversed in left handed individuals. Approximately 60% of left handers show the usual, left hemispheric superiority for language, whereas the remainder demonstrate an atypical pattern of laterality. Of those who do not show the typical pattern of language dominance, roughly equal proportions are right dominant for language while the other half have bilateral language representation.

Language dominance can be assessed in a number of ways. One such manner is the dichotic listening technique. This procedure involves a series of paired auditory inputs which are presented through different channels to the two ears simultaneously. The subject must repeat as many of the stimuli as he/she can recall. Kimura (1967) demonstrated a strong right ear advantage in the majority of the population. Since the auditory pathways are strongly contralateral, she interpreted this finding as a left hemispheric superiority for language.

A more intrusive, but possibly more reliable method for assessing language dominance is the Wada technique (Wada & Rasmussen, 1960). Language dominance is assessed by intravenously injecting sodium amytal into one carotid artery. This procedure selectively anesthetizes one hemisphere. Language function is temporarily disrupted after the language dominant hemisphere is anesthetized. This procedure, due to its invasive nature, is confined to use in the preoperative period for individuals who require unilateral temporal or frontal

lobectomy. The purpose of the test is to predict those individuals at risk for post surgical amnestic syndrome.

III) Anatomical brain differences between the hemispheres

The cerebral hemispheres are neither structural nor functional mirror images of each other. These left-right differences are most marked in the temporoparietal regions. Specifically, the Sylvian fissure is longer in the left hemisphere in the majority of human brains (Rubens et al, 1976). Similarly, Geschwind and Levitsky (1968) demonstrated differences in the size of the planum temporale in normal subjects. In 65% of the cases, a larger left planum temporale was observed, equal sizes were observed in 24%, whereas a larger right planum temporale was observed in 11%. These asymmetries are presumed to reflect the importance of the left hemisphere for language function (Galaburda et al, 1978).

2. Schizophrenia

I) Neuropathology

The neuropathology of schizophrenia is more subtle and diverse than the gross pathology observed in other well described neurological conditions such as Alzheimer's or Parkinson's diseases. Studies of the neuropathology of schizophrenia have often produced contradictory findings. Nevertheless, neuroanatomic and histopathological abnormalities are now described, suggesting that this disorder is associated with developmental abnormalities affecting limbic and associated brain regions. Newer, more sensitive brain imaging techniques, along with the use of better control groups and greater diagnostic efficiency can be credited for the more reliable findings that are currently being published.

The most consistent finding to date is ventricular enlargement (Johnstone et al, 1976, Bogerts et al, 1985; Kelsoe et al, 1988; Degreef et al, 1992; Lewis, 1996). This finding was first

described on post mortem examination of several patients with schizophrenia in 1871 (Hecker, 1871). Both lateral (DeLisi et al, 1992; Degreef et al, 1992) and third ventricle enlargement (Bornstein et al, 1992) have been reported. Ventricular enlargement *per se* is non-specific and has been demonstrated in a number of neurological disorders (e.g., Alzheimer's disease; Jernigan, 1986). Enlargement of the ventricular system could be secondary to tissue loss or due to a failure in development. Given that gliosis has not been reliably demonstrated in patients with schizophrenia, it is generally believed that abnormal brain development contributes to the structural abnormalities noted. Neuroanatomical findings were demonstrated in patients at first episode and did not seem to progress any further over an 8 year time period (Illowsky et al, 1988).

Another less consistent finding in the gross neuropathology of schizophrenia is widening of the cortical sulci (Pfefferbaum et al, 1988a). This finding is also non-specific in nature (e.g., Alcoholics; Pfefferbaum et al, 1988b) and is more difficult to explain using a neurodevelopmental model. The finding of reduced cranial volume remains equivocal (Gur et al, 1991; Jernigan et al, 1991).

Cytoarchitectural and morphological abnormalities have been described in medial temporal and related frontolimbic structures in schizophrenic brains. Specifically, reduced hippocampal volume (Suddath et al, 1990; Fukuzako et al, 1996), decreased pyramidal cell number (Falkai & Bogerts, 1988), decreased volumes of the amygdala (Barta et al, 1990), decreased cell number and abnormal cytoarchitecture in the entorhinal cortex (Falkai et al, 1988; Jakob & Beckmann, 1994), are reported in schizophrenia.

Reduction in neural and glial cell counts has been documented in the dorsomedial nucleus of the thalamus in schizophrenia (Pakkenberg, 1990). Additionally, volumetric measurements have shown smaller thalamic volumes in patients relative to controls (Bogerts et al, 1993).

Frontal lobe pathology in schizophrenia is less well defined. Indirect evidence includes reduced cerebral blood flow in the frontal lobes ("hypofrontality hypothesis"; Weinberger et al, 1986; Andreasen et al, 1992). In addition, reduced efficiency on neuropsychological tests thought to be sensitive to frontal lobe dysfunction (Gruzelier et al, 1988), is also reported. The frontal lobes presumably control purposeful and executive/planning functions (Walsh, 1985). These functions are shown to be impaired in patients with schizophrenia (Goldberg & Gold, 1995). More direct evidence involves neuropathological changes in these brain regions (Benes et al 1986; Benes & Bird, 1987; Akbarian et al, 1993).

II) Neurochemistry

Historically, the neurochemical basis of schizophrenia was believed to be related to overactivity of the mesolimbic dopaminergic system (Kandel & Schwartz, 1985). Dopamine agonists can induce paranoid psychosis resembling the positive symptoms of schizophrenia (Davidson et al, 1987). Classical antipsychotic medications, used to control psychotic symptoms, inhibit dopaminergic transmission by receptor blockade (Seeman et al, 1974). As the olfactory tubercle and other projections along the olfactory pathway are richly dopaminergically enervated, abnormalities in dopamine function are potentially relevant to the study of olfactory deficits in schizophrenia.

III) Neuropsychology

Kraepelin originally speculated that impairments of attention and memory were core symptoms of the disorder and stated that there is "a characteristic and progressive, but not

profound, impairment of memory from the onset of the disease" (Kraepelin, 1902). Currently, evidence suggests extensive cognitive dysfunction beyond simple memory and attention (Kolb & Wishaw, 1983; Blanchard & Neale, 1994). Various authors have suggested that the neuropsychological deficits represent a diffuse pattern of cognitive impairments. Indeed, some patients with schizophrenia are difficult to distinguish from those having sustained brain damage purely on the basis of neuropsychological performance (Goldstein, 1978; Heaton et al, 1978). Deficits are found in verbal and spatial memory, attention/concentration as well as executive functions and speed of information processing (Randolph et al, 1993). Within the global cognitive dysfunction, the left hemisphere may be preferentially affected (Hoff et al, 1992; to be discussed in a later section).

It had been believed that the neuropsychological deficits demonstrated by these patients are secondary to attentional defects (Cullum et al, 1993; Strauss et al, 1993), medication effects (Sweeney et al, 1991) or long term institutionalization (Barton, 1959; Wing & Brown, 1970). Neuropsychological deficits of a similar magnitude to that of chronic patients have been observed in patients with schizophrenia who are experiencing their first psychotic episode (Hoff et al, 1992). Consequently, long term exposure to antipsychotic medication does not seem tenable as an explanatory factor in the genesis of cognitive impairment. Furthermore, consensus has not been reached regarding the effects of psychotropic medications as some have suggested that these drugs may actually improve, rather than worsen, cognitive function (Spohn & Strauss, 1989). With respect to attention, the correlation between neuropsychological measures and the degree of attentional dysfunction appears to be negligible (Seidman, 1992; but see also Sweeney et al, 1991). Long term institutionalization, as well, seems to have little or no effect on cognitive measures when age and education are taken into account (Goldstein et al, 1991)

a) Selective versus generalized deficit:

It is not known which of temporal or frontal lobe functions are relatively more severely impaired. An early report suggested that there was no difference in the magnitude of performance decrements on frontal versus temporal tasks in patients with schizophrenia (Kolb & Wishaw, 1983) but that both were decreased relative to performance on tests sensitive to parietal lobe function. A generalized deficit was also reported in a study assessing neuropsychological impairment in patients who had wide ranging scores on the Wisconsin Card Sorting Test (WCST) suggesting that no consistent pattern of regional neuropsychological deficits can be discerned (Braff et al, 1991).

In contrast, Saykin et al (1991) have shown that superimposed upon a background of diffuse impairment, a selective deficit in memory is observed in patients with schizophrenia. A further study administered tests sensitive to frontal and temporal lobe functioning to patients with schizophrenia and normal subjects who were matched for age and intelligence (Morrison-Stewart et al, 1992). This group found that frontal lobe functions were significantly poorer in patients with schizophrenia than normal control subjects but that temporal lobe functions were not significantly different.

Unfortunately, neuropsychological tests vary substantially in their sensitivity. As a result, comparing the relative performance on one test versus another is not easily accomplished (Randolph et al, 1993). Psychometrically matched tasks are rare. Thus, for example, although a group performs at two standard deviations below the mean of normal control subjects on one test and five standard deviations below the mean on another, the conclusion that performance on the second test is poorer than performance on the first cannot be drawn. The distributions of normal scores on each task may differ from each other due to the sensitivities of each task and not due to

absolute performance. Whether mnemonic or executive functions are more impaired in schizophrenia requires further research.

IV) Laterality in schizophrenia

a) Hemispheric asymmetries in schizophrenia

i) Handedness. Motor asymmetries have been extensively studied in patients with schizophrenia and inconsistent results have ensued (Dvirski, 1976; Fleminger et al, 1977). Some investigations have found no difference between patients with schizophrenia and normal control subjects in the prevalence of left handedness (Wahl, 1976). Others have reported a reversed pattern of handedness, with a higher incidence of left handedness in the control subjects (Fleminger et al, 1977). In contrast, many more studies have shown that left handedness is more common in schizophrenia. In a sample of 200 patients with schizophrenia and 200 normal control subjects, a higher incidence of left handedness was observed in the patient group (Gur, 1977). Dvirski (1976) observed that greater than 14% of patients with schizophrenia were left handed whereas only 8% of normals were observed to be so. Moreover, a larger percentage of patients with schizophrenia have been observed to demonstrate mixed handedness (39%) versus the normal population (23%) (Nasrallah et al, 1981) Current consensus suggest that these observations support a left hemisphere insult resulting in the neuropathology demonstrated. Specifically, those patients who are left handed make up a subgroup who demonstrate abnormal lateralization of the left hemisphere thus causing a shift in cerebral dominance.

ii) Structural changes. Disturbed hemispheric asymmetry has been reported in schizophrenia. Magnetic resonance Imaging (MRI) and Computerized Tomography (CT) studies have shown left hemisphere abnormalities in schizophrenia (Suddath et al, 1989; Shenton et al, 1992). For example, Suddath et al (1990) demonstrated that, overall, the temporal lobes were

smaller on the left than on the right. Subsequently, Shenton and colleagues (Shenton et al, 1992) found specific diminished size of the left parahippocampal gyrus, anterior hippocampus, amygdala and superior temporal gyrus. Barta et al (1990) also showed volume reductions in the left amygdala in patients with schizophrenia.

Post mortem studies are also consistent with the left hemisphere abnormality in schizophrenia. Falkai et al (1992) observed that the normal pattern of asymmetry of the Sylvian fissure was lacking in patients with schizophrenia. Additionally, Crow et al, (1989) demonstrated that enlargement of the lateral ventricles was specific to the left hemisphere in patients with schizophrenia. This finding, led them to propose that schizophrenia was associated with a disturbance in the gene which codes for normal cerebral asymmetry. Although a study of families with schizophrenia does support this theory (Honer et al, 1995), a study investigating brain structure in monozygotic twins discordant for schizophrenia (individuals with identical genomes) does not (Bartley et al, 1993).

iii) Neurochemical abnormalities Very few studies have examined lateralized differences in neurotransmitter function in schizophrenia. In one post mortem study, dopamine in the left amygdala was increased when compared to the right hemisphere. No such lateralized differences were observed in the normal control subjects (Reynolds, 1983). The amygdala receives major dopaminergic input from the ventral tegmental area through the mesolimbic dopaminergic tract (Dalstrom & Fuxe, 1964). The amygdala also receives direct projections from the olfactory bulb (Pansky & Allen, 1980). The mesolimbic dopaminergic tract and its terminals have been implicated in psychosis and may be one of the sites of antipsychotic action (Reynolds, 1983). No study has yet reported lateralized neurochemical distribution in the frontal lobes.

iv) Cognition. Considerable brain imaging and neuropathological evidence has amassed suggesting left hemisphere insult/abnormalities in schizophrenia. Results of neuropsychological studies, however, have produced conflicting outcomes in this regard. The earliest and most compelling evidence to date stems from studies performed by Flor-Henry (1969). Patients with left temporal lobe epilepsy were more likely to demonstrate symptoms similar to that observed in schizophrenia (e.g., hallucinations) than those with right temporal lobe foci whose symptomatology resembled that of affective disorders (Flor-Henry, 1969). From the results of these studies, Flor-Henry suggested that schizophrenia had more in common with left hemisphere dysfunction than right. In accordance with the left hemisphere dysfunction hypothesis, Spitzer et al (1993) suggested that patients with schizophrenia demonstrate a pattern of face recognition similar to patients with left hemisphere lesions. This arrangement was significantly different from that demonstrated by normal control subjects.

Cutting (1994) criticized the Flor-Henry findings by suggesting that the ictal auditory phenomena experienced by the patient with left temporal lobe epilepsy do not resemble the voices experienced in schizophrenia. Cutting has reviewed the literature and cited evidence that individuals with schizophrenia had more in common with groups of patients with *right* rather than left hemisphere abnormalities. Unfortunately, the evidence he sites in support of this hypothesis tends to be anecdotal and not convincing. In the credible studies he does review, those with schizophrenia are compared to control groups (either normal or other psychiatric groups) on tasks which are supposedly sensitive to right hemisphere abnormalities (i.e., facial expression of emotions). As the schizophrenia groups tended to perform more poorly on the tasks of interest than the control groups, the authors concluded that they were more similar to patients with right hemisphere dysfunction. This conclusion cannot be drawn unless a double

dissociation is present (Teuber, 1955). In other words, individuals would have to perform similarly to the control groups on tests sensitive to left hemisphere impairment.

The hemispheric imbalance syndrome model was proposed in an attempt to reconcile the findings of these two contradictory models. In this model, subgroups of patients could be identified who demonstrated a preponderance of positive symptoms such as hallucinations, delusions, and ideas of reference or negative symptoms such as psychomotor retardation, blunted affect and social withdrawal. The active (positive) syndrome was believed to result from activation of the left hemisphere and concomitant loss of function in the contralateral hemisphere. The withdrawn (negative) syndrome was characterized by right hemispheric activation with left hemisphere functional decrements (Gruzelier et al, 1988).

Taken together, these data suggest that demonstrable abnormalities occur in patients with schizophrenia and are most likely to be lateralized to the left hemisphere. The importance of the left hemisphere in processing verbal information is well known; however, how the observed changes in schizophrenia impact on brain- behaviour relationships is not clearly understood.

3. Olfaction

As the "Cinderella of the senses" (Moore-Gillon, 1987), the importance of olfaction has been largely neglected when compared to visual and auditory stimuli for the perception of the environment. In contrast to other members of the animal kingdom, humans have rather poor olfactory ability consequent of having rudimentary olfactory structures. Not only is olfaction considered clinically insignificant by some, but it is also difficult to study (see chapter 1). When the first cranial nerve is assessed in the neurologist's office, testing tends to be cursory and inadequate. However, a number of new test batteries have been developed. These new

techniques have facilitated the assessment of olfactory function in both clinical and experimental settings.

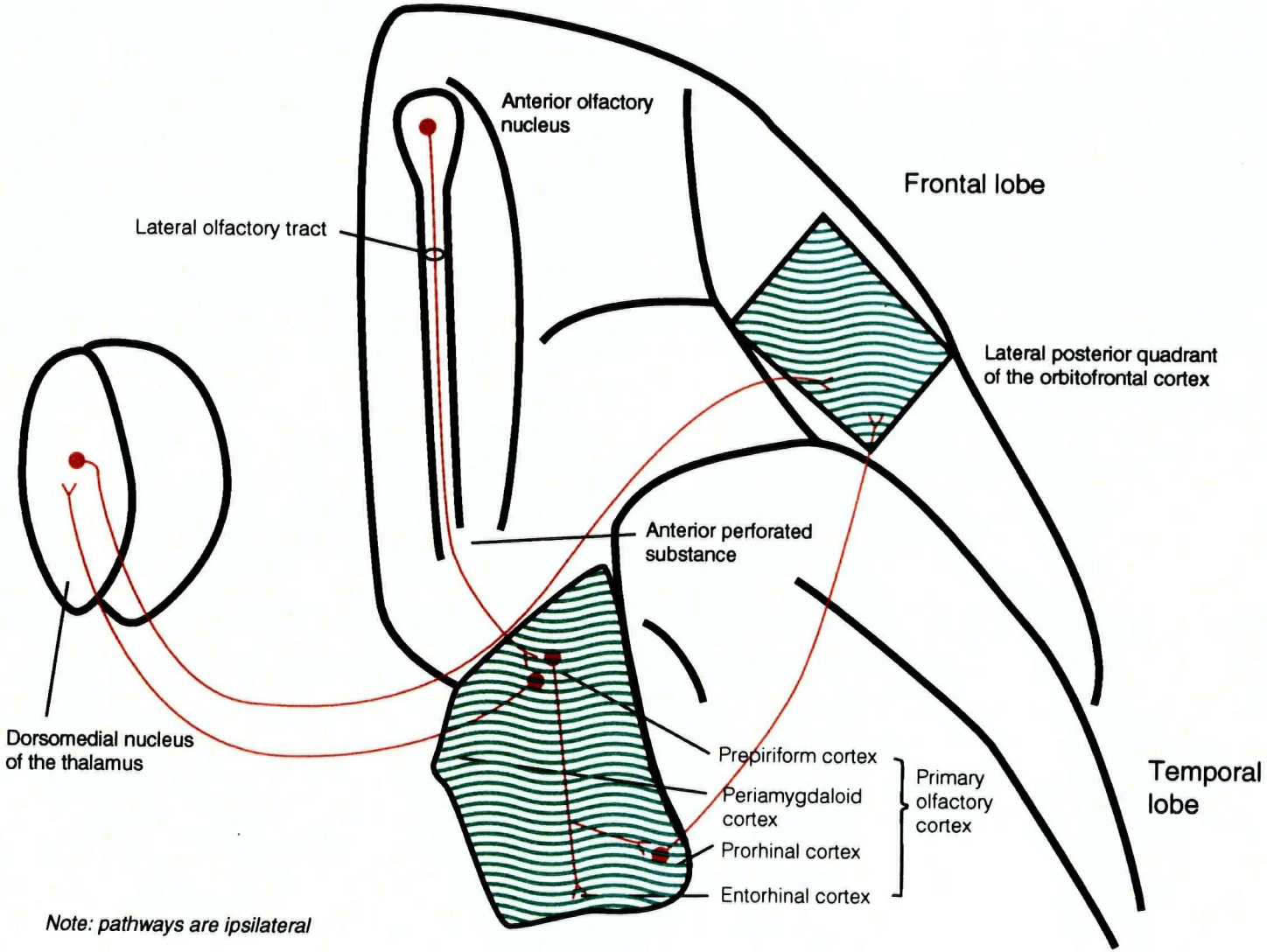
I) Anatomy of the olfactory system

The human olfactory epithelium is located deep within the nasal cavities on the upper portion of the nasal septum and the dorsal portion of the superior turbinate. Olfactory epithelium differs from the surrounding respiratory epithelium by the presence of olfactory receptor neurons, supporting cells, and Bowman's glands. The olfactory epithelium is relatively small, between two and five cm^2 in the average adult and contains approximately six million primary olfactory receptor neurons (Doty & Snow, 1987). These bipolar neurons send out processes which terminate in hair-like cilia. Located on the cilia are specialized proteins called receptors which interact with inhaled odorant molecules. It has recently been noted that approximately 1000 genes which encode approximately 1000 different odour receptors (Buck & Axel, 1991) are located on the rat genome. These receptors interact with one or a small number of odours (Ngai et al, 1993). This finding is in contrast to other sensory systems which rely on a very few receptor types (e.g., 3 classes of photoreceptors to discriminate hue; Rushton, 1955).

The olfactory neuron also gives rise to an axon which coalesces with other axons to form fila (or bundles) which project through perforations in the cribriform plate of the ethmoid bone to project to the olfactory bulbs. Within the olfactory bulbs, tuftlike glomeruli are formed with dendrites from other cell classes. Second order neurons project to distributed cortical and extracortical regions such as the anterior olfactory nucleus (located within the bulb), the anterior perforated substance, corticomedial region of the amygdala, the septal nuclei, the hippocampus, and the primary olfactory cortex. This latter area is comprised of the prepiriform,

periamygdaloid, and entorhinal cortices (See figure 2.1). Secondary olfactory projections subsequently travel from the entorhinal/prorhinal cortices directly to the lateral posterior quadrant of the orbitofrontal cortex. An alternate pathway involves an intermediary synapse within the dorsomedial nucleus of the thalamus (Potter & Nauta, 1979).

Figure 2.1: Orbital surface of the brain showing olfactory pathways



adapted from Potter & Nauta, 1979

Given that the olfactory pathways remain predominantly ipsilateral throughout their trajectory from primary sensory apparatus in one nasal cavity to the cortical processing regions, unirhinal olfactory testing has the potential to assess the olfactory pathways in each hemisphere separately.

Unirhinal olfactory testing of subjects with lateralized, focal brain abnormality is routinely done and the results are then said to reflect unilateral hemispheric performance. However, little attention has been paid to whether testing one nostril singularly tests only one hemisphere. The nasal cavity is divided in two halves by the nasal septum. The intra-nostril barrier extends to the posterior edge of the pharynx, where the pharynx and the nasal cavity meet. Inhaled stimuli enter the nasal cavities, passing over the olfactory mucosa and interacting with receptors. If stimuli are presented only to one nasal cavity, then receptors only on one side would be activated. No study has yet attempted to determine whether stimulation of contralateral receptors occurs if stimuli are only presented to one nasal cavity.

II) Measuring olfactory ability

Testing olfactory function in the clinician's office has traditionally has consisted of presenting a limited number of suprathreshold stimuli to an individual. The "all or none" response would then indicate olfactory status. An individual, unable to detect the presence of the odour of coffee, for example, may be given the diagnosis of anosmia. This procedure lacks precision and is unable to detect malingerers (those who feign disability for financial gain or to avoid some noxious event).

A number of very good clinical tests have been developed in the last two decades to help qualify and quantify olfactory dysfunction. Firstly, to assess olfactory detection threshold, serial dilutions of phenyl ethyl alcohol, diluted in glycerol, seems to be the preferred method. This

stimulus appears to only interact significantly with the receptors of the first cranial nerve (olfactory) and not with the fifth (trigeminal). Although this stimulus is preferred, it is not the most commonly used method. More widespread is the use of n-butanol. This compound does seem to have some irritative properties, resulting in stimulation of the fifth cranial nerve and thus is not suitable for assessment of the olfactory nerve terminals (Doty et al, 1978).

Assessment of more central or cortical aspects of olfaction involve more difficult tasks, ones which involve greater degrees of cognitive processing. Cortical functions such as identification, discrimination and memory are often targeted. Olfactory identification involves matching a verbal label to an odour. The most difficult task is to present an odour and have the subject name it without cues. Forced choice tasks are simpler for the subject as a list of potential names are supplied from which must be chosen the correct response. Olfactory memory tasks simply involve presenting an odour to a subject and after a specified interval, presenting an odour again (same or different). The subject is required to determine if the odour had been previously presented. Olfactory discrimination involves the concurrent administration of two (or more) odours and having the subject determine whether the odours are the same or different. These tasks are described in detail in Appendix B.

III) Olfactory function in control individuals

The sense of smell serves as an early safety signal. Monitoring the external environment for fumes and spoilt food, olfaction serves to alert the individual of potential danger. The sense of smell tends to diminish steadily after the age of 60 years. Eighty percent of normal individuals have severe impairments in odour perception and identification after age 80 (with 50% being completely anosmic) (Doty et al, 1984b). For those aged between 60 and 80, the

prevalence of severe olfactory disturbance is reported to be almost 50% and anosmia at 25% (Doty et al, 1984b).

Younger persons with no complaints about their sense of smell are very good at detecting and discriminating odours. Most individuals can distinguish among at least ten thousand odours; whereas in persons skilled at odour discrimination (e.g., perfumers, wine tasters), this number can be as high as one hundred thousand (Chobor, 1992). Odour *naming* or unaided recall (the ability to name an odour without cues), on the other hand, is performed very poorly by the normal control population. People can easily recognize that the odour is familiar and to categorize it. However, most are deficient at specifying the appropriate verbal label.

IV) Olfactory function in neurological disorders

a) Head injury.

A common sequelae of head injuries is the transient or permanent loss of the ability to smell (Levin et al, 1985). Even relatively minor concussions can result in olfactory dysfunction. The olfactory nerves project through the cribriform plate. During a closed head injury, the brain, which is suspended loosely within the cranial vault, bounces off the inner surfaces of the cranium after impact. The movement of the brain can shear off the axonal filaments projecting through the openings in the skull, leading to post traumatic anosmia (Martzke et al, 1991).

Often concurrent with shearing of the olfactory nerves is damage to the orbital frontal lobes or the temporal poles. Abrasions or lacerations may occur due to the motion of this area across the bony projections on the surface of the cribriform plate. Higher order deficits in olfactory processing after traumatic injury have been discussed (Levin et al, 1985; Martzke et al, 1991).

b) Corpus callosum section

Much has been learned of the neuroanatomy of olfaction from the study of patients with brain lesions and resection. Investigations of patients with focal lesions in brain areas specific to olfaction have helped to assess the relative contribution of each brain area to higher order processing of olfactory information.

In some patients with epilepsy, surgery is required to attenuate seizure activity by preventing the spread of the epileptiform discharge from one hemisphere to the other. The large mass of commissural fibers, the corpus callosum, is transected so as to impair the transfer of electrical impulses. After surgery, these patients appear to be normal; yet, subtle neuropsychological deficits are evident (Bogen, 1993). Sensory information which is only projected to the left hemisphere can be verbalized whereas input reaching only the right hemisphere cannot. Testing olfaction in these patients has given important information regarding the role of each hemisphere in olfactory processing.

Gordon and Sperry (1969) examined unirhinal olfactory identification in patients who had been commissurized for seizure control. In these patients, both the corpus callosum and the anterior commissure were severed. They found that patients could name odours only when stimuli were presented to the left hemisphere (via the left nostril) but not when presented to the right nostril. When the odour was presented to the right nostril and objects representing the odours (e.g., a plastic lemon for the smell of lemon) were presented to the left hand for tactile manipulation, the odour and the object could be matched with a high degree of accuracy. These results lend evidence suggesting that the right hemisphere has the capacity for at least some olfactory processing.

An interesting follow up study was undertaken by Eskenazi et al (1988). Two patients with complete sectioning of the corpus callosum, but with presumably intact anterior commissures, were tested with a number of olfactory tests. Olfactory naming was performed more accurately when stimuli were presented to the left nostril but olfactory naming was also possible when stimuli were presented to the right. These results suggest that olfactory information crossed from the right hemisphere to the left via the anterior commissure.

As it appeared that olfactory information could be processed by each hemisphere, attempts were made to determine the importance of certain brain regions within each hemisphere. Recalling that olfactory pathways project predominantly ipsilaterally to medial aspects of the temporal lobe and to the orbitofrontal cortex, patients were studied who had surgical removal of these cortical areas.

c) Temporal lobe resection (see also Table 2.1)

i) Detection threshold (acuity). Conflicting evidence exists regarding the effects of temporal lobe ablations on olfactory detection thresholds. Some research has shown impaired acuity (Eskenazi et al, 1986; Rausch & Serafetenides, 1975; Martinez et al, 1993), while others have shown no change (Jones-Gotman & Zatorre, 1988b;1993; Zatorre & Jones-Gotman, 1991).

In their pioneering study of olfactory function in patients with temporal lobe resection, Rausch & Serafetenides (1975) examined odour detection and recognition thresholds in 12 patients with temporal lobe removal (7 right, 5 left) and compared them to 10 non-neurological controls. This group observed that patients with temporal lobectomy had lower acuity for pyridine, phenyl ethyl alcohol and pentyl acetate than normal controls but had no reduction in recognition threshold. Similarly, Martinez et al (1993) found reduced acuity in the right nostril but only if it was ipsilateral to the resected hemisphere.

Studies finding no difference in olfactory detection threshold between temporal lobe patients and normal controls are more numerous. In three papers published by Jones-Gotman and Zatorre, no detection threshold deficits were observed in either nostril on unirhinal testing compared to their normal control subjects (Jones-Gotman & Zatorre, 1988a and b; Zatorre & Jones-Gotman, 1991). Other studies came to similar conclusions (Henkin et al, 1977, Eskenazi et al, 1983; 1986). In addition, HM, a subject who underwent unilateral temporal lobe resection and whose contralateral temporal lobe had been damaged, was not impaired on olfactory detection threshold, whereas other higher order olfactory processing tests were distinctly impaired (Eichenbaum et al, 1983).

A lack of consistency as to the stimuli used or the paradigms employed among the various studies may contribute to the discrepant findings. The unique assessment of cranial nerve I requires stimuli that do not irritate the nasal branches of the trigeminal nerve (cranial nerve 5). For example, pyridine, in high concentrations, is a potent trigeminal irritant (Doty et al, 1978) and thus is unsuitable for assessment of olfactory detection threshold. Nevertheless, this compound has been used in older studies (e.g., Rausch & Serafetenides, 1975) making the conclusions drawn from these studies questionable.

Current consensus would suggest that the temporal lobe does not seem to be required for detecting odours. This conclusion is consistent with the rat literature which would suggest that olfactory detection thresholds can only be affected by transections of the lateral olfactory tract and not by cortical resection (Slotnick & Schoonover, 1992). Humans with temporal lobe lesions do, however, demonstrate deficits in higher order processing.

ii) Higher order olfactory processing (Table 2.1). Odour quality discrimination (Eskenazi et al, 1983; Zatorre & Jones-Gotman, 1991) odour matching (Abraham & Mathai,

1983; Sreenivasan et al, 1987), odour memory (Rausch et al, 1977; Eskenazi et al, 1983; Jones-Gotman & Zatorre, 1993; West et al, 1993) and odour recognition and identification (Rausch et al, 1975; Henkin et al, 1977; Eskenazi et al, 1983; Jones-Gotman & Zatorre, 1988a; 1993) have been shown to be affected in patients with temporal lobe removal. Only one study found null findings when assessing higher order olfactory processing in this patient population. Rausch & Serafetenides (1975) did not find olfactory recognition deficits in their group of temporal resection patients relative to their normal control subjects. As previously mentioned, these researchers did find a between-group difference on detection threshold suggesting that an atypical sample may have been studied.

Table 2.1: Effects of frontal and temporal lobe lesions (resections) on olfactory function.

Birhinal stimulus presentation.

Authors	Patient population	n (side of lesion)	Cognitive task	Results
Rausch & Serafetenides, 1975	temporal lobectomy	7 R 5L	detection threshold: recognition threshold:	↓ acuity normal
Rausch et al, 1977	temporal lobectomy	7 R 7 L	odour memory:	↓ odour memory RTL<LTL
Henkin et al, 1977	temporal lobectomy	4R 7L	detection threshold: recognition:	normal poor: L<R
Abraham & Mathai, 1983	temporal lobectomy	14R 10L	smell matching:	RTL<LTL=NC*
Eskenazi et al, 1983	temporal lobectomy	7 L 10 R	detection threshold: discrimination: recognition: memory: odour-visual match: odour naming: odour tactile match: identification:	normal RTL=LTL<NC** RTL=LTL<NC** RTL=LTL<NC** RTL=LTL<NC** RTL=LTL<NC** RTL=LTL<NC**
Jones-Gotman & Zatorre, 1988b	temporal lobectomy frontal lobectomy	35R 36L 18R 11L	identification: (UPSIT)	FL***=TL<NC**
Jones-Gotman & Zatorre, 1993	temporal lobectomy frontal lobectomy	36R 36L 18R 11L	odour memory immed: delay (20 min.): (24hr):	FL=TL<NC FL=TL<NC FL=TL<NC

* RTL= Right temporal lobectomy; LTL= Left temporal lobectomy: NC= Normal control
** No influence of side of lesion
***Only if the lesion includes the orbital surface

Side of the lesion may be important in terms of the extent of impairment demonstrated (see Tables 2.1 and 2.2). The research findings are not consistent. Smell matching (Abraham & Mathai, 1983; Sreenivasan et al, 1987) and odour memory (Rausch et al, 1977; Jones-Gotman &

Zatorre, 1988b; 1993) have been shown to be affected more with right than left temporal lobe resection. This finding is consistent with studies reporting non-verbal memory deficits in other sensory modalities (e.g., tones or visual patterns) in patients with right hemisphere lesions (Lezak, 1983). Other groups have not found any difference in odour memory between groups of patients with right or left temporal lobectomy. Eskenazi et al (1983 and 1986) found that although patients with temporal lobectomy performed more poorly than the temporal lobe epilepsy group and a group of non neurological controls, no difference was noted between the patients with right vs. left temporal lobe removal on an odour memory task.

Table 2.2: Effects of frontal and temporal lobe lesions (resections) on olfactory function. Unirhinal stimulus presentation.

Authors	Patient population	n (side of lesion)	Cognitive task	Nostril			
				R	L	ipsi*	contra *
Eskenazi et al, 1983	temporal lobectomy	10R 7L	detection threshold	N**	N		
Zatorre & Jones-Gotman, 1991	temporal and frontal lobectomy	106	detection threshold odour discrimination	N	N	TL↓ RF↓	LF↓ RF↓
Potter & Butters, 1980	(pre)frontal lesions	5	odour discrimination			↓	N

* ipsi= ipsilateral (same side) to the lesion; contra= contralateral (opposite side) to the lesion
** N=normal (comparable to controls)

Eskenazi et al (1983) also assessed olfactory discrimination in patients with unilateral temporal lobectomy and found that patients were impaired relative to controls but no difference

was found for side of lesion. However, when Zatorre & Jones-Gotman (1991) administered an odour discrimination task unirhinally, deficits were observed in the nostril ipsilateral to the resection.

Researchers also do not agree on whether the side of temporal lobe resection plays any role in the extent of post operative deficit in odour recognition/identification. Odour recognition was found to be worse after *left* temporal lobe resection than after right excision (Henkin et al, 1977) with both patient groups performing more poorly than controls. In contrast, Jones-Gotman & Zatorre (1988b) using the UPSIT, did not note any differential impairment between those with right and those with left removals (see Table 2.2).

Temporal lobectomy, whether left or right is associated with reduced capacity for processing olfactory information. However, patients are lobectomized as a result of a preexisting temporal lobe abnormality. These abnormalities may, in fact, be associated with olfactory dysfunction. This is likely the case. A number of studies have shown that olfactory identification, discrimination and memory are mildly impaired in patients with temporal lobe epilepsy (Carroll et al, 1993; Eskenazi et al, 1986; Abraham & Mathai, 1983) and in epilepsies of other etiologies. The magnitude of the deficits is typically less than what is observed in resection patients. West et al (1993) tested temporal lobe epilepsy patients before and after resection surgery. This group found that olfactory deficits (identification, discrimination and memory) were present in patients pre- and post-operatively and that surgery only accounted for a small portion of the deficit. Martinez et al (1993) reached similar conclusions.

d) Unilateral frontal lobe ablation.

The lateral posterior aspect of the orbitofrontal cortex has important cortico-cortical projections originating in the primary olfactory cortex (Pansky & Allen, 1980). Neurons in this

region seem to be selectively "tuned" to respond to only certain odours in the Macaque monkey (Tanabe et al, 1975). Moreover, removing this area results in selective deficits in olfactory discrimination in primates (Tanabe et al, 1975).

Given the importance of the orbitofrontal cortex for olfactory processing in primates, it is not surprising that olfactory deficits were observed after damage or resection of this region in non-human primates. Potter and Butters (1980) assessed olfactory detection threshold and odour quality discrimination in patients with prefrontal lesions and compared them to patients with a variety of other neurological disorders (Korsakoff's syndrome, brain damage, and 1 patient with thalamic lesion) and normal controls. Both patients with prefrontal lesions and those with Korsakoff's syndrome were distinctly impaired on the odour quality discrimination task. Olfactory detection threshold was better in patients with prefrontal lesions (compared to normal control subjects) but significantly worse in patients with Korsakoff's syndrome. It is unknown why detection threshold should be reduced in Korsakoff's syndrome

Jones-Gotman and Zatorre have shown that after frontal lobe removal, deficits in odour discrimination (Zatorre & Jones-Gotman, 1991), olfactory identification (Jones-Gotman & Zatorre, 1988b), and odour memory (Jones-Gotman & Zatorre, 1993) are observed. These deficits are not observed when the orbitofrontal regions are spared (Jones-Gotman & Zatorre, 1993). Deficits in olfactory identification appear to be worse after orbitofrontal than temporal lobe resection (Jones-Gotman & Zatorre, 1988a). The right orbitofrontal region may be specialized for odour memory (Jones-Gotman & Zatorre, 1993) and discrimination (Zatorre & Jones-Gotman, 1991).

e) Thalamic lesions

The dorsomedial nucleus of the thalamus (DMNT) is an important relay between temporal and frontal lobe olfactory processing. Eichenbaum et al (1980) found that removal of the DMNT in rats produced a milder deficit in odour quality discrimination than did lesioning the frontal cortex. Interestingly, the only study of a human patient with a DMNT lesion was impaired on odour discrimination, but the deficit found was not as pronounced as that observed in patients with frontal lobe damage (Potter & Butters, 1980). More research with larger numbers of patients is required before definitive conclusions can be drawn.

f) Neurodegenerative disorders.

A recent review of literature suggests that many neurodegenerative disorders are associated with olfactory compromise. Patients suffering from Alzheimer's (Doty et al, 1987), Parkinson's (Lehrner et al, 1995) and Huntington's diseases(Moberg et al, 1987), and the Parkinson dementia complex of Guam (Doty et al, 1991a) show alterations in olfactory function on a number of olfactory tasks. In general, the degree of olfactory loss does not seem to be related to disease stage or severity. Neuropathologic studies have shown that each of these disorders is associated with cell death and loss in discrete brain areas and affected regions overlap very little.

i) Alzheimer's disease. One of the first symptoms of Alzheimer's disease (AD) is olfactory dysfunction (Doty, 1991) . A vast literature exists characterizing the compromise in the olfactory system in these patients (Doty et al, 1987; Rezek, 1987; Koss et al, 1988; Murphy et al, 1990; Morgan et al, 1995). Brain areas which are most heavily laden with senile plaques and neurofibrilary tangles, the neuropathological hallmark of this disease, include the frontal, temporal and parietal association cortices (Harrison, 1986). In addition, plaques and tangles are

often found in areas of the brain which are primary or secondary projection areas of the olfactory system (olfactory bulbs, anterior olfactory nucleus, entorhinal cortices; Doty, 1991). Consequently, it is not surprising that olfactory deficits are present.

Regardless of the "higher order" olfactory task used, deficits have been reported in patients with AD compared to age matched control subjects. The degree of olfactory dysfunction is related to the severity of dementia (Waldton, 1974; Knupfer & Speigel, 1986; Murphy et al, 1990) but not to the length of illness, as this symptom may be the first, or at least one of the first symptoms of the illness (Warner et al, 1986). The olfactory dysfunction does not appear to be cognitively based (Warner et al, 1986). When the lexical component is factored out of an olfactory naming test, as in using a picture based olfactory identification test, AD patients remain impaired relative to control subjects (Morgan et al, 1995).

Notwithstanding the seemingly robust finding of higher order olfactory deficits early in the course of the disease in patients with AD, there are contradictory findings in the literature as to the onset of acuity deficits. Some researchers have found that acuity is reduced early in the course of the disease (Doty et al, 1987), whereas others have reported preserved olfactory acuity (Koss et al, 1988) in early dementia. Doty and colleagues suggested that olfactory acuity deficits are present in the earliest definable stages of the disease (Doty et al, 1987). Nordin and Murphy (1996) reported that patients diagnosed with questionable AD were severely impaired on an acuity task. In contrast, Koss et al (1987) reported a dissociation between detection and identification in early stage disease. This group believes that the olfactory deficit is initially central and that the more peripheral sensing component (acuity) fails later.

Down's syndrome (DS) shares neuropathological features with Alzheimer's disease and DS patients almost invariably go on to develop a precocious and aggressive form of AD

(Helmdal et al, 1993). This disorder, like AD, is also associated with olfactory compromise (Helmdal et al, 1993; Helmdal & Corwin, 1989; Warner et al, 1988). Like AD, both identification and detection appear to be affected. Similar to AD, olfactory difficulties do not appear to be attributable to more generalized cognitive limitations (Helmdal et al, 1993).

ii)Parkinson's disease (PD). Evidence from studies of patients with Parkinson's disease indicate that olfactory deficits are a common feature of this disorder. Acuity, discrimination, recognition memory and identification appear to be compromised (Anasari & Johnson, 1975; Ward et al, 1983; Doty et al, 1988; Lehrner et al, 1995) relative to age matched controls. The primary neuropathology of Parkinson's disease involves a degeneration of dopamine containing cells within the substantia nigra (Kandel & Schwartz, 1985), but depletion of dopamine in the olfactory tubercle in PD has also been reported (Bogerts et al, 1983). The extent of olfactory dysfunction does not seem to be related to age, disease stage, duration of illness, extent of motoric symptoms, or cognitive deficits (Doty et al, 1987; 1988; 1989a; 1991b; 1992c; Ward et al, 1983; Quinn et al, 1987). The deficits appear to be bilateral, at least in the early stages of the disease (Hoehen & Yahr stage I or II) and are not affected by antiparkinsonian medication (Doty et al, 1992c) . Similar to Alzheimer's disease, impaired olfactory functioning occurs early in the disease and does not appear to worsen as the disease progresses (Doty et al, 1989a; but see also Anasari & Johnson, 1975).

Interestingly, olfactory function may provide clues to the etiology of Parkinson's disease. Symptoms indistinguishable from those seen in idiopathic Parkinson's disease can occur in younger people who have intravenously administered 1-methyl, 1,4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is the product of a botched attempt at synthesizing Meperidine. The only dissimilarity between the two disorders, apart from the age and speed of

onset, is that MPTP-induced Parkinsonism (MPTP-P) patients lack olfactory dysfunction (Doty et al, 1992b). Progressive supranuclear palsy (PSP), another disorder often misdiagnosed as Parkinson's disease, is also not associated with olfactory compromise (either identification or detection threshold). The mesocorticolimbic regions of the brain in PSP patients (and those with MPTP-P) are relatively spared (Ruberg et al, 1985; Burns et al, 1983), unlike in PD patients which may partially explain why olfactory function is preserved.

The magnitude of the olfactory deficit in patients with Parkinson's disease is comparable to that observed in AD which has led some to speculate a common etiological agent (see Doty, 1991). There has been some suggestion that Parkinson's and Alzheimer's diseases are a result of an inhaled airborne contaminant. An environmental neurotoxin or virus could penetrate the brain via the olfactory epithelium and damage the olfactory pathways "en passant". In animal models, neural destruction has been observed as a result of viral or macromolecules entering the CNS through olfactory receptors (Perl & Good, 1991; Barthold, 1988). Consistent with this view, olfactory neuroepithelium abnormalities have been demonstrated in biopsies of patients with PD and AD (Lanza et al, 1993).

g)Other disorders which have CNS involvement.

i)Kallmann's syndrome. Kallmann's syndrome (KS) is a genetic disorder which is characterized by hypogonadism and anosmia stemming from abnormal expression of the KALIG-1 gene (Cowen & Green, 1993). Midline brain structures are incomplete, leading to aplasia or hypoplasia of the olfactory bulbs (Hudson et al, 1994). In KS, both olfactory acuity and identification are impaired (Youssem et al, 1993).

ii) Human Immunodeficiency Virus. Patients with Human Immunodeficiency Virus infection (HIV), a condition which affects the central nervous system in a large percentage of

patients, are impaired in their ability to identify common odours (Brody et al, 1991). This deficit occurs whether the patient is symptomatic or asymptomatic. Whether these patients have impaired sensitivity as well has not been assessed.

For many of the neurodegenerative and neuropsychiatric disorders, higher order, or cortical processing is believed to be impaired, even when olfactory acuity is also impaired. Conclusions regarding affected brain pathways cannot be drawn in the face of peripheral impairment. In other studies, acuity is not even assessed (or at least not reported). Thus, omission of important information regarding the integrity of peripheral structures also limits the conclusions. Both of these errors are frequently committed in olfactory research (Martzke et al, in press).

V) Olfactory function in psychiatric disorders

a) Depression, anorexia nervosa, panic disorder and obsessive compulsive disorder

In general, patients with psychiatric disorders do not suffer from major impairments in olfactory function (Amsterdam et al, 1987; Warner et al, 1990; Kopala et al, 1995a; Fedoroff et al, 1995; Kopala & Good, 1996). Rather, their sense of smell is comparable to normal control subjects. In patients with obsessive compulsive disorder, olfactory acuity appears to be intact (Gross-Isseroff et al, 1994) but olfactory identification has been reported to be abnormal (Goldberg et al, 1991). The finding of impaired identification was based on a very small sample size and thus, conclusions drawn are questionable. Although patients diagnosed with major depression and anorexia often complain of olfactory hallucinations, these do not seem to be related to abnormal olfactory function. In fact, for olfactory hallucinations to occur, it appears that olfactory function must be intact (at least in patients with schizophrenia; Kopala et al, 1994).

b) Schizophrenia

Given the neuroanatomic overlap between olfactory projection areas and brain regions posited to be affected in schizophrenia, it is perhaps not surprising that olfactory function is impaired in some individuals with schizophrenia. Almost all studies investigating olfaction in this patient population have shown deficits on one or more "higher order" aspects of olfactory function, including olfactory identification (Hurwitz et al, 1988; Kopala et al, 1989; Houlihan et al, 1994) and memory (Wu et a., 1993). Whether there is any change in olfactory detection threshold is not fully resolved. Similarly, further studies are required to assess olfactory discrimination ability in schizophrenia.

The first attempt to formally assess olfactory function in schizophrenia investigated the ability of patients with schizophrenia to detect a steroid hormone, androstenone (Bradley, 1984). In this study, psychotic patients were hypothesized to have abnormally high threshold (low sensitivity) for this steroid. In contrast, psychotic males were found to have *greater* sensitivity to this odour when compared to normal male controls. No differences were noted between psychotic females and normal female control subjects.

A replication study was undertaken to determine whether the results of the Bradley study were artifactual as a small sample size was employed. Isseroff et al (1987) also tested olfactory detection threshold to amyl acetate, in addition to androstenone, in order to control for general olfactory sensitivity in patients with schizophrenia. Schizophrenic males were no different from control subjects in their ability to detect androstenone, while their ability to detect amyl acetate was significantly superior. In a further attempt to assess olfactory detection threshold in patients with schizophrenia, Serby et al (1990) reported impaired olfactory detection threshold for geraniol compared to their sample of normal control subjects.

In contrast, Kopala et al (1989) found no differences in the detection threshold (acuity) of their sample of 41 patients with schizophrenia and 43 normal controls. This group used n-butanol as the stimulus. A later study extended the previous findings reporting that olfactory detection threshold was not impaired in their patient sample relative to control subjects, but this time using a pure olfactory (cranial nerve I) stimulus, phenyl ethyl alcohol (Kopala et al, 1992).

However, there may be a subgroup of patients with schizophrenia who have olfactory acuity deficits. A recent study (Kopala et al, submitted) documents impaired olfactory detection threshold in a group of severely polydipsic patients with schizophrenia.

Given the idiosyncratic methods used for assessing olfactory function in the past, more recent studies employed reliable and valid psychometric methods and have focused on more cortical or central processing of olfactory stimuli. Hurwitz et al, (1988) used the University of Pennsylvania Smell Identification Test (UPSIT) to investigate olfactory identification ability. In this study, patients with schizophrenia were compared to a group of psychiatric (bipolar disorder) and non-psychiatric controls. Only the schizophrenic group was impaired relative to the other two groups. According to standardization data, the schizophrenia group would be classified as being microsmic.

Since then, a number of replication studies have appeared (Seidman et al, 1992; Wu et al, 1993; Houlihan et al, 1994). Numerous potential explanations have been proposed to account for the olfactory deficits in this patient group. Variables such as smoking habit, cognitive impairment and medication level have been entertained as possible contributory factors.

Common clinical perception is that many patients with schizophrenia smoke. Smoking dries out the neuroepithelium, creating the potential for reduced olfactory performance in smokers. Frye et al (1990) demonstrated a significant correlation between the amount and the

number of years smoked (pack-years) and a reduction in olfactory identification ability in a normal population. Having previously been a smoker also contributed to lower scores on the UPSIT. However, the overall effect was small.

Consequently, if smoking had an effect on olfactory identification ability, one would also predict that olfactory acuity would be impaired. Kopala et al (1989) did not find a smoking effect for their sample of patients with schizophrenia. Similar proportions of women and men smoked; however, only the male patients were impaired on UPSIT. Further, Houlihan and colleagues specifically addressed the issue of whether olfactory dysfunction could be attributed to smoking. Patients who smoked were no different on UPSIT scores than those patients who did not smoke. The only effect of smoking was found in the normal control group in which those who smoked had lower scores on the UPSIT when compared to those who did not (Houlihan et al, 1994).

The contribution of antipsychotic medications to the genesis of olfactory dysfunction was assessed in different studies. Hurwitz and colleagues (Hurwitz et al, 1988) demonstrated that although the psychiatric control group they studied were medicated with similar types and amounts of antipsychotic medications, only the schizophrenic group was microsmic. A further study investigated olfactory identification in patients who had been withdrawn from neuroleptic medication and found that this group also had olfactory identification deficits. Finally, Kopala et al (1992) showed that first episode, neuroleptic-naive patients with schizophrenia were similarly impaired in their ability to attach a verbal label to an odour. In all three of these studies, the magnitude of olfactory dysfunction was similar. The findings of these studies do not support the tenet that exposure to antipsychotic medication produces olfactory deficits.

The effects of cognitive and attentional factors were examined in a number of subsequent studies. Serby et al (1990) assessed olfactory function in patients with schizophrenia with two different olfactory tasks: the UPSIT and a yes/no odour identification test. Patients with schizophrenia were found to be impaired on the UPSIT but performed no differently from the normal control subjects on the yes/no task. These results led the investigators to conclude that the deficit manifested by these patients was not specific to the olfactory system, but rather reflected underlying cognitive dysfunction. Seidman et al (1992) did not support this conclusion when they showed that patients with schizophrenia were impaired on UPSIT and WCST but that performance on these two tasks was not correlated. In addition, there was no significant correlation between UPSIT scores and the performance on a test of sustained attention, the Continuous Performance Test (CPT). Kopala et al (1995c) examined whether olfactory deficits could be accounted for by the task complexity. Patients with schizophrenia were impaired in their ability to identify common odours but performed comparably to normal controls on an analogous visual task which had similar processing demands. These findings led this group to conclude that impaired olfactory function could not be accounted for by non-olfactory, cognitive processing load.

4. Laterality of olfactory function

I) Laterality of olfactory function in normal control subjects

Investigations focusing on asymmetry of olfactory processing have predominantly examined subjects who have undergone surgical resection for intractable seizure disorders. For example, patients with right temporal lobectomy have been shown to have greater impairment in olfactory memory than those with left temporal lobectomy (Carroll et al, 1993; Jones-Gotman & Zatorre, 1988a; 1993; Rausch et al, 1977). The opposite pattern may be true for olfactory

recognition (Henkin et al, 1977); specifically, greater impairment in olfactory recognition has been reported after left temporal lobectomy. From these results, it has generally been assumed that the right hemisphere is specialized for processing olfactory memory, while the left hemisphere is responsible for verbal tagging of olfactory material. These results would be consistent with the currently accepted understanding of brain functioning.

In non-neurological/psychiatric subjects, lateralized functioning depends on the task used and the subject sample studied. In young, normal control subjects, the ability to identify odours using the Odour Confusion Matrix (OCM) tends to be superior in the left nostril when compared to the right (Hornung et al, 1990). However, in older subjects (mean age approximately 62 years), the ability to identify odours on the UPSIT does not seem to differ across nostrils (Doty et al, 1992c).

The discrepant findings observed may stem from the differences in age of subjects or the olfactory tasks used. The UPSIT has a very low ceiling as it was designed to assess olfactory function in individuals with impaired sense of smell. Thus, this measure may not be the most sensitive instrument to use to find small differences in the normal control population. The OCM has a higher ceiling and thus may be more suitable measure to assess this question.

A relative right nostril advantage has been shown for olfactory discrimination (Zatorre & Jones-Gotman, 1990; 1991) and olfactory intensity rating (Pendse, 1987). The only study to assess laterality of olfactory memory in normal control subjects with a mean age of 23.6(3.3) found no inter-nostril difference (Bromley & Doty, 1995).

A study undertaken by Zucco and Tressoldi (1988) was designed to assess hemispheric advantage of olfactory processing. The subjects were presented an odour (birhinally). Subsequently, a tachistoscopic screen flashed a verbal label or a picture representing an odour to

either the left or right visual field. The subject was required to determine whether the picture/label matched the odour presented. It was predicted that stimuli flashed to the left visual field (and thus, the right hemisphere) would be processed faster and more efficiently. Faster reaction times were observed when stimuli were presented to the left visual field. When the olfactory stimulus was replaced with an auditory signal (e.g., the odour name was spoken instead of smelled), a right visual field advantage was observed. These authors concluded that the olfactory stimuli "primed" the right hemisphere to respond to the visual label/picture. When an auditory stimulus was presented, the left hemisphere was primed to receive the visual input.

II) Laterality of olfactory function in schizophrenia

Kopala and Clark (1990) reviewed the literature on olfactory deficits in patients with brain lesions and made some suggestions as to the brain region of abnormality likely responsible for the olfactory identification deficits seen in patients with schizophrenia. In this group, olfactory identification was impaired while olfactory acuity (detection threshold) was comparable to a control group. This pattern of olfactory agnosia was similar to that demonstrated by patients with lesions to the orbitofrontal regions or dorsomedial nucleus of the thalamus. Seidman et al (1992) agreed with Kopala and Clark (1990) and suggested that the UPSIT was a probe specific to the orbitofrontal cortex and thus identification deficits were likely to reflect orbitofrontal cortex abnormality.

Lateralizing the olfactory disturbance in schizophrenia has been attempted by two groups. Sreenivasan et al (1987) using a smell matching test, assessed 32 patients with schizophrenia, 30 patients with affective disorder, and 17 patients with neurotic illness. Previous studies using this test found that the degree of smell matching dysfunction increased with the extent of right temporal lobe involvement (Abraham & Mathai, 1983). Those with schizophrenic and affective

disorder had lower scores than did the neurotic controls. The former two groups would be classified as mildly impaired. Comparing the three samples with norms generated from previous publications, Sreenivasan et al (1987) concluded that the patients with schizophrenia and affective disorder had scores that were indicative of right temporal lobe impairment, whereas the neurotic controls performed similarly to control subjects. The comparison mean scores for the temporal lobe epilepsy patients were drawn from a previous publication (Abraham & Mathai, 1983). Of particular note, although patients with schizophrenia performed more similarly to patients with right temporal lobectomies, the mean score for these patients is identical to that previously observed for patients with *left* temporal lobectomies. Thus, the conclusion of right hemisphere involvement is not substantiated. A direct comparison between patients with schizophrenia, temporal lobectomies (left, right) and those with lesions in other brain areas would be more informative.

Subsequently, Dunn and Weller (1989) assessed lateralization of olfactory function in schizophrenia. An olfactory discrimination task was administered to 15 patients with schizophrenia and 15 normal control subjects. These authors found no left-right difference on the olfactory discrimination task in the schizophrenia group. However, a number of methodological flaws clouded the interpretation of the data. Of concern, the olfactory task employed had not been previously reported in the literature, thus its reliability and validity were questionable. Furthermore, the non-tested nostril was occluded by pressing it shut with the index finger. This method is not recommended as it could result in deviation of the nasal septum, partially obstructing the tested nostril. A third caveat to the interpretation of the Dunn and Weller study relates to the number of subjects sampled. Only 15 subjects per group were studied and statistical power may have been compromised, resulting in a type II error. Finally,

and most importantly, a key analysis was not conducted. No inter-nostril difference was observed in the patient group; however, they failed to compare left and right nostril function in the normal control group (or at least did not report the results). As other studies documented lateral asymmetry in olfactory discrimination in the normal control population (Zatorre & Jones-Gotman, 1991), the lack of an inter-nostril difference in the patient group could be an interesting finding.

Clearly, there are differences between the hemispheres with respect to their ability to process different kinds of information. The hemispheric advantage for olfactory processing is task specific; verbally mediated functions are performed superiorly with the left nostril while functions non-verbally oriented are better performed with the right. Additionally, disruptions in olfactory pathways (orbitofrontal and temporal lobe lesions) in each hemisphere tend to be associated with specific decrements in olfactory function (right with olfactory memory; left with olfactory naming).

The olfactory pathways overlap to a great extent in those regions of the brain posited to be abnormal in schizophrenia. Should the left hemisphere be preferentially affected in schizophrenia, testing the sense of smell unirhinally in these patients may uncover a different pattern of olfactory laterality than is observed in the normal control population. Whether olfactory function is abnormally lateralized in patients with schizophrenia has not been adequately assessed. Therefore, the purpose of the current study was to assess olfactory function in each nostril separately in a group of males with schizophrenia and compare their performance to a suitable group of normal male control subjects. The results of this study may allow us to understand how the brain is organized in males with schizophrenia.

CHAPTER 3

METHODS

This chapter will outline the methods used to determine whether the pattern of olfactory laterality in male patients with schizophrenia is different from that observed in normal male control subjects. As no study has yet adequately assessed olfactory laterality on numerous different olfactory tasks concurrently in patients with schizophrenia or normal controls, the results of these analyses will be valuable for understanding lateralized olfactory processing in health and in a disease state. This chapter will also detail the methods used to determine the relationship between lateralized olfactory and neuropsychological deficits. Chapter three consists of the following sections:

I. Subject selection and characteristics

II. Test selection and procedures

III. Administration procedures

IV. Statistical analyses

1. Subject selection

Consecutive admissions of male patients to inpatient psychiatric wards at two mid-sized University-based hospitals (Vancouver Hospital and Health Sciences Center and St. Vincent's Hospital) were screened for inclusion in the present study. Screening occurred during weekly ward meetings. When a potential candidate was identified, he was later approached by the attending psychiatrist and asked if he would participate in a study examining the sense of smell. If he agreed to participate, the study was explained in full and informed consent obtained. Normal control subjects were University of British Columbia and hospital personnel. No subject

was remunerated for participating. This study was approved by the University of British Columbia ethics committee.

I) Inclusion criteria.

The following inclusion criteria were applied. Subjects were: 1) male; 2) between the age of 17 and 60 years; 3) physically healthy; 4) IQ greater than 70; 5) fluent in English; 6) able to give informed consent. In addition, patients: 1) met Diagnostic and Statistical Manual (DSM-III-R) criteria for diagnosis of schizophrenia; 2) were hospitalized for psychotic symptoms and; 3)were treated with antipsychotic medications for at least one month.

II) Exclusion criteria

The following exclusion criteria applied. Subjects were excluded if they had: 1) a history of significant head injury with loss of consciousness exceeding 3 minutes; 2) facial trauma; 3)medical, neurological or other problems which might interfere with the sense of smell (for example, hypothyroidism, Kallmann's syndrome); 4) comorbid diagnosis of severe water intoxication[1] or; 5) past or current substance abuse. Control subjects were excluded if they had ever received a psychiatric diagnosis or if they had a family history of mental illness.

III) Sample size calculation

Sample size calculation was based on estimating requirement to demonstrate a difference between patients and control subjects. Analysis of preliminary data documented a mean left-right difference between patients and controls on UPSIT score of 1.3 with a standard deviation of 1.7. Therefore, the sample size required for a power of .80 and an effect size of .76 was

[1] This exclusion was enforced to rule out gross brain disorganization. There is some suggestion that patients with severe polydipsia and water intoxication may represent a subgroup in whom further brain deterioration has occurred. Our group has recently observed that patients with schizophrenia and severe water intoxication had marked olfactory identification deficits and impaired acuity (Kopala et al, in submission)

computed to be 27 subjects per group. Unequal sample sizes were anticipated as patients were approximately twice as easy to recruit than normal control subjects. As a result, 40 patients and 20 control subjects were required. See appendix C for calculations.

2 Test selection and procedures

I) Test selection

Studies of patients with focal brain abnormalities have contributed to our understanding of how disordered brain function can affect behavior. According to neuropsychological theory, test performance is related to functioning of a specific brain region. The tests used in the current study are believed to be sensitive to impairments in cognitive functions subserved by brain regions implicated as being abnormal in schizophrenia. The neuropsychological battery administered was selective, assessing the domains of interest; specifically, olfactory function, verbal and non-verbal memory, visual and verbal fluency, an estimate of premorbid IQ, and handedness.

II) Test procedures

a) Olfactory

The olfactory tasks were chosen to represent a wide range of olfactory processing abilities and to extend our previous work and work by others (Doty et al, 1992; Dunn & Weller, 1989). Birhinal olfactory identification deficits in patients with schizophrenia have been demonstrated by virtually all groups who have studied this phenomenon (Kopala et al, 1989, 1992; Seidman et al, 1992; Wu et al, 1993; Houlihan et al, 1994). Therefore, the University of Pennsylvania Smell Identification Test (UPSIT) was chosen as the primary olfactory task. The advantage of the UPSIT, in addition to its ease of administration and scoring, is that the test items represent both simple and complex odours (Doty et al, 1990). This feature allows for testing a diverse range of

odours. In addition, a large body of standardization data exists (in excess of 2000 subjects) to which data collected can be compared. The ability to detect odours was assessed using the compound phenyl ethyl alcohol (PEA). This substance was chosen as detection thresholds observed on this measure correlate reasonably well with a number of other odorants (i.e., camphor, isovaleric acid, diallyl sulfide and others) (Yoshida, 1984) and lack of ability to detect this odour presumably reflects general olfactory insensitivity. PEA has also been shown to have minimal trigeminal properties, thus is a "pure cranial nerve I stimulant". Finally, an olfactory discrimination task was chosen as this phenomenon has not been adequately assessed in patients with schizophrenia. Furthermore, olfactory discrimination has been shown to be lateralized in normal subjects.

Olfactory memory has been assessed in patients with schizophrenia (Wu et al, 1993) but was not assessed in the current study. Whether a deficit in olfactory memory truly exists or whether it is simply artifact has yet to be determined (Strauss, 1994).

All olfactory tasks were administered unirhinally (one nostril at a time). The non-tested nostril was comfortably occluded with a suitably sized strip of Microfoam$^{(TM)}$ (3M Company) surgical tape which covered the entire nostril (after a method described by Doty, personal communication). Before testing began and periodically during the session, the tested nostril was clamped shut with the index finger while the subject inhaled through the nose. If any air permeated the tape, it was re-placed in order to prevent stimuli reaching the olfactory receptors in the occluded nostril. All olfactory testing was performed in a well ventilated room at least an hour after the subject had eaten or smoked.

For half the subjects, the left nostril was tested first for each olfactory task; for the other half of the subjects, the right nostril was tested first.

i) Identification. The University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al, 1984a) is comprised of four booklets, each containing 10 test items. Each item is made up of a scent impregnated strip which is activated by scratching and a four choice array of answers.

Given the clinical nature of the population under study and to ensure comprehension, the self administered procedure was not employed. Rather, the examiner scratched the scented strip, handed the book to subject who would inhale the released odour with the unoccluded nostril and make a choice from the four provided answers. If the subject could not identify the odour on first presentation, the procedure was repeated until a choice was made. The first two booklets were administered to one nostril while the last two booklets were presented to the other nostril. Internal consistency reliability has been shown to be high (.92 and above) between the first two booklets and the last two booklets and also between the scores from the first two booklets and the whole test (.85) and between scores from the last two booklets and the whole test (.85) (Doty et al, 1989b). This procedure therefore yielded two scores, with a maximum of 20. It was also administered birhinally to each subject in the initial session to serve as a baseline for comparing unirhinal scores.

ii) Detection threshold (Acuity). In order to assess the integrity of peripheral sensory structures (i.e., cranial nerve I receptors), serial dilutions of the compound phenyl ethyl alcohol (PEA) in glycerol were used (after a method described by Doty et al, 1984a).

Phenyl ethyl alcohol was serially diluted and placed in individual small bottles with openings 2.5 cm in diameter. The forced-choice single staircase began at -6.5 log concentration and increased to -0.5 log concentration in half-log steps. Each bottle was assigned a number

according to its concentration. Therefore, the bottle with the highest concentration of PEA was labeled #1 and the least concentrated, #11. Two bottles were presented to the subject at one time, one containing the diluted PEA, the other containing only the inodorous diluent. The subject's task was to determine which of the two solutions evoked a stronger sensation. If a correct choice was made, the next weaker solution was presented along with a bottle containing diluent only. If an incorrect choice was made, the next stronger solution was presented along with the blank. Subjects were instructed to guess even if they could detect no difference between the two solutions. Threshold was determined when four correct guesses occurred at a given concentration and chance level of correct guesses were made for the next weaker solution. Any subject who performed abnormally low on the threshold task in either nostril did not participate any further in the study.

iii) Discrimination. This task was modified from the UPSIT (Doty et al, 1992a). One booklet containing 16 items made up this test. Each item included three scented strips, two of which were identical odours, the third was different. The different odour was randomly placed in the first, second or third position. The subject's task was to determine the odd odour from the triad after the examiner scratched the scented strips.

For the discrimination task, the administration procedures were as follows. The examiner scratched the strip, and placed it under the subject's nostril, and said "This is strip A (or B or C)". This task was forced choice as the patches were scratched until the subject made a choice. As the colour of the strips may sometimes give visual cues to the strip containing the odd odour, the task was administered to the subject while he was blindfolded. The entire test was administered in this fashion to each nostril, yielding two scores, each out of 16.

III) Neuropsychological tests

a) Frontal lobe functions

i) Verbal Fluency Test (FAS). The Controlled Oral Word Association Test (COWAT), a subtest of the Multilingual Aphasia Examination, was employed as a measure of verbal fluency (Benton, 1968). The examiner presented the subject with a letter of the alphabet and instructed him to dictate as many words that begin with that letter in one minute. The subject was instructed not to use words that are normally capitalized (proper nouns) nor to add many suffixes to one root word. The letters F, A, and S were employed in the current study. The score was the total number of admissible words for all three letters. Age scaled norms were available. This test was chosen as it has been extensively used in the neuropsychological literature in schizophrenia (Kolb & Wishaw, 1983; Goldberg & Weinberger, 1988) and is thought to be a sensitive indicator of brain damage, particularly if the brain lesion is in the left frontal region (Lezak, 1983; Benton, 1968).

ii) Design Fluency Test (Jones-Gotman & Milner, 1977). This test was developed to examine conceptual productivity in the non-dominant hemisphere and has been shown to be sensitive to right prefrontal dysfunction (Jones-Gotman & Milner, 1977). Furthermore, it has been extensively used in studies of neuropsychological functioning in schizophrenia (Kolb & Wishaw, 1983; Morrison-Stewart et al, 1992). There were two conditions, "free" and "fixed". In the free condition, the subject was given a pen and a piece of paper and instructed to draw as many nonsense drawings as he could in five minutes. The subject was directed not to draw anything real (i.e. namable such as a square or an apple) nor to scribble. The words "many" and "different" were emphasized in the directions. The total score was the total number of drawings that conformed to the instructions. If the patient perseverated (i.e., drew the same drawing many

times), only the first drawing was scored. In the second condition, the "fixed" condition, the subject was again asked to draw as many abstract forms as he could, but this time, each drawing had to be composed of exactly four lines. The lines could have been straight or curved. Again, the subject was instructed not to draw anything real (box or peace sign) and to come up with a new drawing each time. The total score was the number of admissible four line drawings created.

b) Temporal lobe functions

i) Benton Visual Retention Test (BVRT). The BVRT is a test of visual memory which is sensitive to problems of inattention, memory span or spatial organization (Lezak, 1983). As well, it is sensitive to non-dominant temporal lobe lesions. Numerous groups have reported results from this task in patients with schizophrenia (Morrison-Stewart et al, 1992) The test is comprised of ten cards. Each card (except the first two) has three figures on it, two large and one small. The small figure is either to the left or the right of the larger figures.

Administration D was employed in the current study. The subject was shown a card for ten seconds; then the card was taken away for fifteen seconds (Administration D, Benton, 1974). The subject was then given a piece of paper to draw the three figures in the correct orientation. The scoring system is elaborate, but enables an overall error score and the types of errors are also scored (i.e., perseverations, omissions, distortions).

ii) Paired Associates Learning. Ten word pairs were presented to the subject, six of which were "easy" pairs or pairs that were easily associated and four pairs which were "hard" or not readily associated. The subject had to recall the second word of the word pair when the first word of the pair was presented. Three trials were administered. This test was used to assess left temporal functioning.

iii) Paragraph memory ("The Cowboy Story", Lezak, 1983). For this test, the subject was read a paragraph. After the initial presentation, the patient was asked repeat all he could remember. The subject's responses were audiotaped and subsequently transcribed. The subject was given credit for all the "ideas" or elements that were similar to the original story. Both the Paired Associates Learning and various forms of Paragraph Memory have been shown to be sensitive to left temporal lobe lesions and have been used a great deal in schizophrenia research (Seidman et al, 1992; Saykin et al, 1991).

c) Miscellaneous measures.

i)The National Adult Reading Test (NART; Nelson & O'Connell, 1978). In older patients who are suffering from neurodegenerative disorders (i.e., Alzheimer's disease), the ability to read complex words remains intact, even when other cognitive functions are impaired (Blair & Spreen, 1989). Consequently, the NART was developed in order to estimate premorbid intelligence in this patient population. This test is comprised of 61 "irregular words" or words that cannot be pronounced using common phonetic rules. Examples of words in the NART list are gaoled and quadruped. The number of words pronounced incorrectly is entered into three prediction equations in order to generate estimations of Verbal IQ (VIQ), Performance IQ (PIQ) and Full scale IQ (FIQ). Scoring procedures were modified to include Canadian and U.S. pronunciations (Blair & Spreen, 1989).

ii) Colour Identification Test (CIT). Inclusion of the CIT was based on previous findings indicating it to be a measure of equivalent attentional load and difficulty level to the UPSIT but which examines a different sensory modality (Kopala et al, 1995c). This task consists of twenty stimulus cards. One colored strip is glued on each stimulus card. For each stimulus card, there is

an additional card with four colored strips glued to it, one of which is identical to colour of the stimulus strip already shown.

For this task, the subject was presented with the stimulus card for a period of at least five seconds, then the card was removed from sight. The paired answer card was then presented to the subject who had to pick from the four choices the colour of the stimulus previously shown. This task had a maximum score of 20.

iii) Edinburgh Handedness scale (Oldfield, 1971). Handedness may be a continuous, rather than a categorical phenomenon. Consequently, a handedness inventory may be more useful for assessing relative unimanual preference rather than asking the subject which hand he prefers to use. The Edinburgh Handedness Scale is a self administered test containing 10 activities which are performed with one hand. The subject's task was to determine whether he preferred to use only his right hand, only his left hand or could use either hand with similar ease. On the answer sheet, two columns are provided for answers, one marked "left" and one marked "right". For each item, the subject placed 2 check marks in the column which corresponds with the hand of greatest preference. If the activity could be performed equally well with either of the hands, a single check is placed in each column. The laterality quotient was computed by summing all checks in each column. For the numerator of the quotient, the total number checks in the "left" column was subtracted from the total number checks in the "right" column. The denominator was achieved by summing the total number of "right" checks with the total number of "left" checks. A quotient was then computed. A negative value is indicative of sinistrality (relative left handedness) whereas a positive value would suggest relative dextrality (right handedness).

d) Psychiatric Rating scales

i) Global Assessment Scale (GAS; Endicott et al, 1976). Degree of psychosocial and symptomatic impairment was determined using the GAS. The scale runs from 0 (unable to care for self) to 100 (superior functioning in a wide range of activities) in 10 point ranges. The clinician rated the subject's level of functioning at around the time of testing (+/- 3 days). A score of 40 or less is indicative of a distortion of reality testing.

ii) Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987). This scale was designed to give qualitative and quantitative documentation of the patient's symptom presentation. There are 30 items on the scale which form three subscales: positive symptoms (e.g., hallucinations, delusions, suspiciousness), negative symptoms (e.g., blunted affect, social withdrawal), and general psychopathology (e.g., somatic concern, poor impulse control). Each item in the scale is rated between a 1 (absent) to 7 (extreme). Three subscale scores (positive, negative and general) arise from this scale. In addition, five separate syndromes can be identified by clustering PANSS items. The GAS and PANSS scores were computed by the patient's attending psychiatrist who was unaware of performance on any of the other behavioral measures employed.

3). Administration procedures

I) Experiment I

Prior to recruiting and testing patients, the feasibility of using unirhinal testing methods to assess unilateral olfactory pathways was determined in normal volunteers. Many different investigations have used unirhinal olfactory testing (Gordon & Sperry, 1969; Zatorre & Jones-Gotman, 1991; Bromley & Doty, 1995). However, none have determined the extent to which olfactory stimuli can cross over to the contralateral nasal cavity and be processed by receptors on

that side. The septum, the cartilaginous structure which acts as a barrier between the two nasal cavities projects only as far back as the opening of the pharynx. Thus, on inhalation or exhalation, a stimulus presented to only one nostril has the potential to cross over to the contralateral nasal cavity and interact with receptors on that side. Should this occur, finding a nostril advantage would be less likely as both hemispheres would be activated.

In an effort to determine whether stimuli could be processed by receptors in the contralateral nasal cavity when presented to one nasal cavity only, reversible ablation of the olfactory receptors was completed on three normal control subjects. Two men and one woman participated in this preliminary study. All were between the ages of 37 and 45, had no complaints related to their sense of smell, and none had any history of significant head injury. Each subject initially underwent direct rhinoscopic examination of both nasal cavities employing a Stortz 0^0 4 mm diameter, rigid, nasal endoscope to rule out any significant structural abnormalities

Figure 3.1 outlines the timeline for olfactory testing and reversible ablation. Baseline olfactory testing was completed including unirhinal assessment using the UPSIT along with the detection threshold task. One nostril was tested at a time while the non-tested nostril was occluded with surgical tape. The subject was instructed to inhale deeply (once) through the nose and to breathe out all inhaled air through the mouth. This procedure helped to minimize the amount of air turbulence within the nasal cavity and thus limit the amount of retronasal airflow. The nostril tested first was random among subjects.

In an initial session, the olfactory mucosa was anesthetized by spraying 1 metered dose (10 mg) of a topical anesthetic, xylocaine, directly onto the olfactory receptors in one nasal cavity. This procedure was inadequate to decrease olfactory performance. Therefore, in a

subsequent session, a more potent topical anesthetic, cocaine, was applied directly to the sensory receptors. Under direct rhinoscopic visualization, a 10% cocaine solution was sprayed onto the olfactory region of the superior dorsum of one nasal cavity between the nasal septum and the middle and superior turbinates. After two minutes, a cotton pledglet, soaked in 10% cocaine, was applied and left in place for 5 minutes before being removed prior to testing.

Figure 3.1 Timeline for cocanization study

Nostril Ultimately Cocanized

Day 1			//	Day 2	
Unirhinal UPSIT acuity	xylocaine	Test N UPSIT N acuity	//	Cocaine	Re-test ⇓UPSIT ⇓acuity

Control Nostril

Day 1			//	Day 2	
Unirhinal UPSIT acuity		Test N UPSIT N acuity	//		Re-test N UPSIT N acuity

The anesthetized (cocanized) nostril was tested first while the un-anesthetized nostril was occluded with surgical tape. Olfactory threshold was assessed first, followed by olfactory

identification. Subsequently, the un-anesthetized nostril was tested. For the acuity and identification tasks, scores from the anesthetized nostril were subtracted from baseline scores. Similarly for the control (non-anesthetized) nostril, the post cocanization score was subtracted from the baseline score. The resulting means were compared with a paired t-test.

II) Experiment II:

The second half of the current study aimed to determine whether the pattern of olfactory laterality in patients differed from that demonstrated by normal control subjects. After having been admitted to hospital and initial clinical assessment completed, the patient was evaluated to determine whether he met inclusion and was not excluded for any reason. If all requirements were met, the primary investigator administered a semi-structured interview focusing on demographic and disease-related information (disease-related information was matched against information obtained by medical chart review). A modification of the Hollingshead scale was employed to ascertain the subject's and his parents' socioeconomic status (Bassett, personal communication; see Appendix A). Any questions the subject may have had concerning the study were answered at this time. After the preliminary interview was completed, the subject was asked to fill out the handedness inventory. Finally, the UPSIT was administered birhinally during this session. Birhinal testing sought to determine the patient's level of motivation and willingness to participate in the study. During this administration of the UPSIT, no feedback was given to the subject as to whether the responses given were correct or incorrect.

After a minimum of two days (but not exceeding seven), the examiner returned to complete the remainder of the olfactory and neuropsychological testing. Olfactory acuity was performed first unirhinally. If a subject had abnormally high threshold (greater than $1 \times 10^{-2\,M}$),

he was disqualified from the study. The order of presentation of unirhinal discrimination and identification and the neuropsychological tests was random.

All the testing was performed in a quiet, secluded, well ventilated room. Testing was done in the morning after the subject had a full breakfast and his regular morning medications. When necessary, administration of the olfactory tests was delayed for 1 hour after smoking. The psychometrist adhered to the predetermined rest breaks in order to minimize the effects of fatigue. If a subject became fatigued or seemed to lack motivation, the examiner ended the session and returned the next day. For normal control subjects, the entire test battery was administered in one setting with appropriate rest breaks. The entire test battery was approximately 2 hours in length.

4. Statistical analyses

I) Experiment I

For the anesthetized and the control nostril, the post-cocanization score was subtracted from the pre-cocanization score. This formula was used for the detection threshold task and the UPSIT. A paired t-test (one tailed) was completed on the scores of both measures.

II) Experiment II

a) Analysis 1

In order to assess the comparability of the subjects enrolled in the current study to those studied previously, the first step was to determine whether the male patients with schizophrenia were impaired on olfactory identification ability. Birhinal UPSIT scores were compared between patients and control subjects using a t-test for independent groups (one tailed). In addition, since the birhinal score presumably reflects the better of the two nostril scores, the left and right

UPSIT scores were added together and a t-test for independent groups (one tailed) was conducted. Finally, the correlation amongst scores on all olfactory tests was run to ascertain the amount of shared variability among the test scores. For this analysis, Pearson correlations and Spearman's rank order correlations were calculated.

b) Analysis 2

To determine whether the pattern of olfactory laterality was similar in patients with schizophrenia to that demonstrated by normal control subjects, two-way repeated measures ANOVAs were performed on olfactory identification, acuity (detection threshold) and discrimination with nostril (left vs. right) as the within-subject variable and diagnostic group (patient versus control) as the between-group variable.

i) Predictions. For olfactory identification, a diagnosis by nostril interaction was predicted. Patients with schizophrenia were expected to perform significantly more poorly in the left than in the right nostril. Normal control subjects were hypothesized not to differ between nostrils on this measure. For the olfactory acuity (detection threshold) measure, neither the main effects nor the interaction was predicted to be significant. Finally, for the olfactory discrimination task, a main effect for nostril was predicted, whereas the main effect of diagnosis and the interaction between the two were not expected to be significant. The right nostril was hypothesized to be better than the left in both groups. As left handed subjects may have a different pattern of brain laterality than right handers, the same analyses were repeated after excluding all left handed subjects.

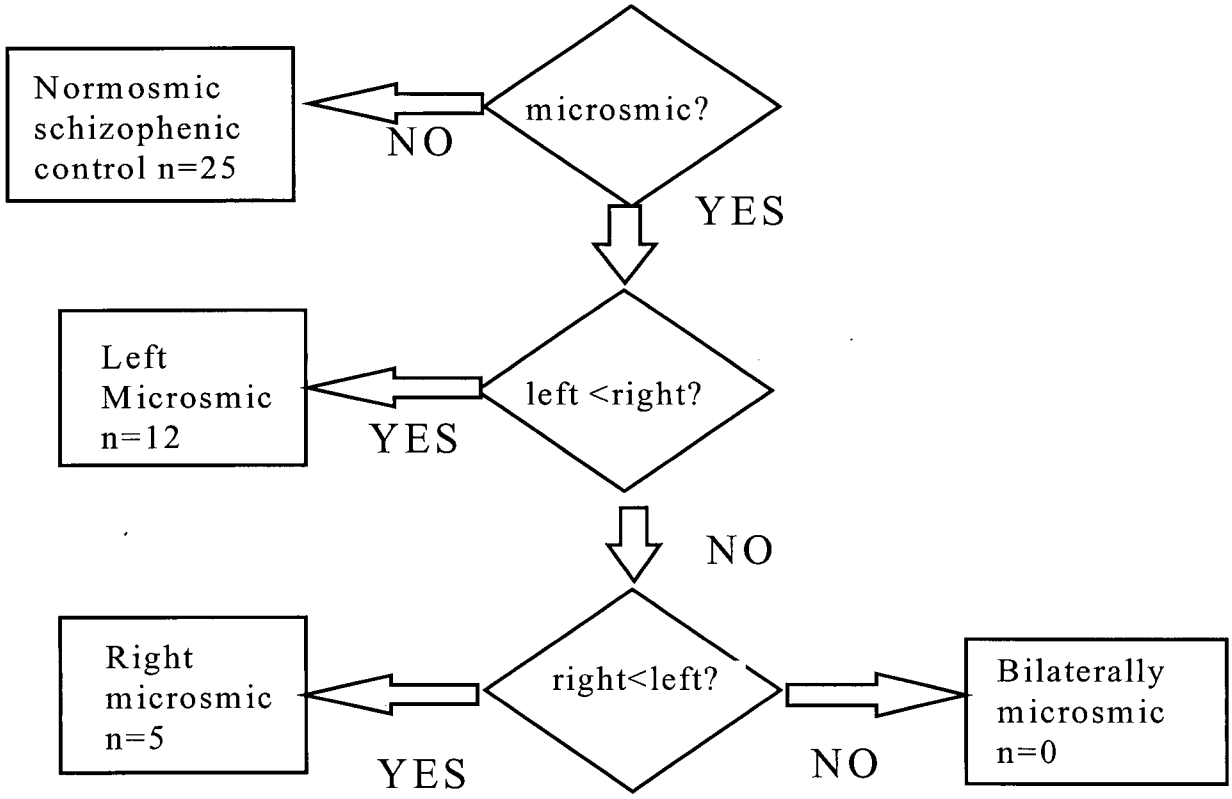
c) Analysis 3

The purpose of this analysis was to explore the relationship between unilateral olfactory deficits and cognitive measures of regional and lateralized brain function. Specific a priori hypotheses were made. Patients with a right nostril identification deficit were hypothesized to demonstrate greater deficits on tests sensitive to right hemisphere dysfunction when compared to left microsmic and normosmic schizophrenia patients. Patients with left nostril identification deficit were predicted to show greater impairment on tests which are sensitive to left hemisphere dysfunction when compared to the right microsmic and normosmic schizophrenia groups.

To address these hypotheses, patients were classified according to unilateral olfactory identification deficit using a two step process. Using a cut off at the 15th percentile of the 59 normal control male subjects (22 subjects from the current study and an additional 37 normal male subjects assessed for a related project. See chapter 4), patients were classified according to nostril deficits. For the first step, any patient who scored below the 15th percentile (for normal control subjects) in either nostril was classified as "microsmic". Any patient who scored above the cutting score in both nostrils was classified as being "normosmic schizophrenic control". In the second step, the microsmic group was further broken down. Patients whose left nostril score was lower than their right nostril score were classified as being "left microsmic". Those in which the right nostril score was lower than the left were considered "right microsmic". Finally, any patients whose left nostril equaled the right nostril were dropped from further study (See Figure 3.2).

Figure 3.2: Patient classification

Patients were classified as microsmic if their left nostril UPSIT score was less than 16/20 or their right nostril UPSIT score was less than 15/20



*Data was incomplete for one subject

Standardized scores were then computed for all cognitive domains using the means and standard deviations of the normal control subjects (z scores). Hence, the mean score for the normal controls for all domains was 0.0 with a standard deviation of 1.0. The cognitive domains

were computed as follows: The combined score for both the "free" and "fixed" conditions made up the non-verbal fluency domain (right frontal). The non-verbal memory domain (right temporal) was computed using the total number of correct reproductions from the Benton Visual Retention test. Age and education corrected scores from the Controlled Oral Word Fluency test were used to compute the verbal fluency domain (left frontal). Finally, the z-scores were computed for each of the immediate recall from the Paragraph memory and the total number of correct pairs recalled for the Paired associates Learning (Hard pairs were multiplied by 2). An average z-score was then computed to determine the verbal memory domain (left temporal).

A mixed design ANOVA was performed on the resultant z scores with olfactory status (right microsmic, left microsmic, and normosmic schizophrenic controls) as the between subject factor while hemisphere (left versus right) and region (frontal versus temporal) were the within-subject factors. Planned orthogonal contrasts were employed to test the a priori hypotheses. All assumptions for the ANOVA were met.

i) Contrasts: It was hypothesized that patients with a right nostril deficit would be preferentially impaired on tests of right hemisphere function relative to the left microsmic and normosmic patients. Patients with left microsmia were expected to perform more poorly on tasks sensitive to left hemisphere impairment relative to right microsmic and normosmic patients. A different pattern of regional specificity of neuropsychological deficits was predicted for both groups of patients with one-sided microsmia compared to the normosmic schizophrenic control subjects. Similar to previous analyses, the left handed subjects were dropped and the analysis was conducted again.

d) Analysis 4

The final analysis sought to determine the relationship between one sided microsmia and psychosocial and symptomatic impairment. Therefore, one-way ANOVAs followed by Tukey's post hoc test were computed among the 3 patient subgroups on the positive, negative and general PANSS subscales. In addition, group differences were analyzed on the five syndrome factors of the PANSS using a series of one-way ANOVAs with Tukey's post hoc test. The five factors, which have been extracted from the PANSS (Lindstrom & von Knorring, 1994), were: the positive factor (P1, P3, P5, G9), the negative factor (N1-4, N6, G7), the excited factor (P4, P7, G8, G14), the anxious-depressed factor (G1-3, G6) and the cognitive factor (P2, N5, G10, G11, G15).

CHAPTER 4

RESULTS

1. Demographics

I) Patient group

In total, 43 male patients with schizophrenia participated in this study. In one subject, complete olfactory test scores were unavailable. The mean age for this group was 30.5 (8.8) years (see Table 4.1). Descriptive values are presented by mean and standard deviation [x±(sd)] unless otherwise stated. This group had, on average, 12.2 (2.8) years of education. Forty two (98%) patients were single (never married) and 1 (2%) was divorced at time of testing. Thirty five patients (83%) were right handed as measured by the Edinburgh Handedness scale (laterality quotient greater than 0). For one patient, handedness was unknown. Patients, on average, had an estimated full scale IQ (premorbid) of 108.2 (9.0) as determined from the NART.

Employment status was measured using a modified Hollingshead scale (Bassett, personal communication; see Appendix A). Sixty five percent of patients were unemployed at time of testing. The current level of occupational achievement was 7.3 (1.6) which suggested that current employment status was between unemployed and unskilled manual labor. On the highest level of occupational achievement, a mean score of 6.0 (1.9) was observed suggesting that, at best, patients had achieved unskilled to semi-skilled manual labor status. Parental occupation was scored and on average, mother's occupational achievement was 5.4(2.5) (between semi-skilled and skilled manual labor) and paternal occupation was 4.2(2.0) representing

between skilled manual labor and low administrative. On average, patients had held their best job for 34.8 (48.1) months (see Table 4.1).

Table 4.1. Demographics for patient and normal control groups (means and standard deviations)

	Patients	Normal controls	p
n	43	22	
age	30.5(8.8)	32.2(7.8)*	ns
education	12.2(2.8)	15.2(3.3)*	<.001
estimated full scale IQ	108.2(9.0)	112.8(7.0)	<.05
length of best employment(months)	34.8(48.1)	84.2(62.4)	<.005
mother's occupation**	5.4(2.5)	4.9(2.4)	ns
father's occupation**	4.2(2.0)	3.2(1.9)	ns
current occupation (subject)**	7.3(1.6)	4.5(2.2)	<.001
highest level of occupational achievement (subject)**	6.0(1.9)	4.1(2.0)	<.005
% married	0	18	<.05
% olfactory hallucinations	42	14	<.05
% smokers	44	32	ns
% left nostril tested first	49	48	ns

*n=59

** modified Hollingshead scale where 1= high executive and 8=unemployed

The mean age of onset of illness (as defined as first hospitalization for the treatment of psychotic symptoms and initiation of antipsychotic medication) was 22.6 (4.0) years. Patients had been treated with antipsychotic medications for 83.0 (99.0) months. This group had 3.5 (4.4) previous admissions to hospital for psychiatric symptoms. Mean GAS score was 34.6(12.0) and mean PANSS positive subscale was 18.6(6.1), negative subscale 26.9(8.6) , and general

psychopathology was 42.6(10.3). Seventeen (42%) patients had experienced olfactory hallucinations at some point in their lives. Disease-related variables can be found in Table 4.2.

Table 4.2. Disease-related phenomena in the patient group.

	Mean	standard deviation
age of illness onset	22.6	4.0
length of treatment (months)	85.0	96.5
number of hospital admissions	3.6	4.4
GAS*	35.2	11.5
PANSS positive**	18.6	6.0
PANSS negative	26.5	8.3
PANSS general	42.8	10.2
% receiving novel antipsychotics	53	
% receiving antiparkinson medications	28	
% receiving antidepressants medications	5	
% receiving anticonvulsant medications	9	
% receiving sedative medications	23	

*Global Assessment Scale
** Positive and Negative Syndrome Scale

All patients were medicated with antipsychotic medications at time of testing. Approximately half of the patients were receiving typical antipsychotics whereas the other half were treated with the newer, atypical compounds (risperidone, clozapine). Medication use can be found in Table 4.3. All dosages were converted into chlorpromazine equivalents for comparison purposes. Formulae for the typical and atypical agents came from Bezchlibnyk-Butler and Jeffries (1996).

Table 4.3. Antipsychotic medications prescribed

Medication (generic/trade)	number of patients prescribed
haloperidol/Haldol	1
haloperidol decanoate/ LA haldol	1
loxapine/ Loxapac	5
trifluoperazine/Stelazine	5
flupenthixol/Fluanxol	2
pimozide/Orap	1
chlorpromazine/Largactil	1
thioridazine/Mellaril	1
clozapine/Clozaril	5
risperidone/Risperdal	18
seroquel	1
fluphenazine/Modecate	2
mar327*	1

* Study drug (may have been receiving haldoperidol)

Eleven patients (26%) had been medicated with antiparkinsonian medication (procyclidine, and benztropine), 4 (9%) had been treated with anxiolytics (clonazepam), 2 patients (5%) were prescribed antidepressants (amitryptiline and clomipramine). Ten (23%) patients were also taking concomitant sedative medications. No patient had been prescribed antimanic medications. One patient was being treated with tetrabenazine, a dopamine depletor, for the treatment of severe tardive dyskinesia. All patients had met DSM-III-R criteria for schizophrenia. Subtypes were as follows: disorganized: 3 (7%); catatonic: 5 (12%); paranoid: 6 (14%); residual: 2(5%); and undifferentiated: 20 (47%). One patient received the diagnosis of schizoaffective disorder. Subtype for 6 (14%) patients was unavailable.

The nostril of first presentation was approximately equal with 49% having the left nostril tested first, and 51% having had the right nostril first (see Table 4.1).

II) Normal control group

In total, 59 normal male control subjects were included in the study data. Of these, 37 had only unirhinal olfactory identification scores. For the remaining 22, data was available for neuropsychological and olfactory testing. The mean age of the entire normal control group (all 59 subjects) was 32.2 (7.8) years. The mean education level was 15.2 (3.3) years (see Table 4.1). Forty-seven subjects (80%) were right handed as assessed by a laterality coefficient of greater than 0 on the Edinburgh Handedness Scale. Of the 22 original control subjects, 4 (18%) were married, 17 (77%) were single, and 1 (5%) was divorced. Mean estimated, NART based IQ was 112.8 (7.0). These data are presented in Table 4.1.

Fourteen percent of the normal control subjects were unemployed at time of testing. The current occupational level was assessed to be 4.5 (2.2) which corresponds to having between skilled laborer to low administrative status. The highest level of occupational achievement was scored as 4.1 (2.0) (skilled manual labor to low administrative). Maternal occupation was 4.9(2.4) (also skilled manual labor to low administrative) whereas paternal occupation was 3.2(1.9) (low administrative to middle management). Normal control subjects had been employed for 84.2(63.4) months (see Table 4.1).

Using independent t-tests for continuous variables and Chi squares for categorical, no differences were found between the two groups on age ($t_{(84)}$=.98, p=ns), maternal occupation ($X^2_{(7)}$=7.6, p=ns) and paternal occupation ($X^2_{(6)}$=11.5, p=ns). Inter-group differences were observed for highest level of occupation achievement ($X^2_{(8)}$=23.7, p<.005), education($t_{(98)}$=5.0, p<.001), FIQ ($t_{(51)}$=2.2, p<.05), and marital status ($X^2_{(2)}$=8.7, p<.05). Smokers were found in both groups. Forty four percent of all patients were smokers, whereas only 32% of normal controls smoked (see Table 4.1) but this difference failed to reach significance ($X^2_{(1)}$=.92, p=ns). Of the smokers, the patients smoked 1.0 (.65) packs for 11.8 (8.4) years while normal controls were found to have smoked .4 packs for 12.6(7.4) years. Nineteen percent of patients had been smokers in the past as had 5% of the control subjects. Although 14% (3 subjects) of the normal control subjects claimed to have experienced olfactory hallucinations (which were likely as a result of psychotropic drugs), more patients than control subjects had reported ever experiencing olfactory hallucinations ($X^2_{(1)}$=4.7, p<.05).

2. Experiment I

The purpose of experiment 1 was to determine whether presenting stimuli to one nostril singularly affects the ability for that nostril to detect and identify odours.

In the anesthetized nostril, UPSIT scores were reduced to just above chance levels at 50% of the original (range of decrease of 28% to a decrease of 69%) while acuity scores were reduced

34% from baseline (range decrease of 17% to a decrease of 50%). Changes in the mean scores for the un-anesthetized nostril were negligible. Specifically, the detection threshold task increased 0.2% (range 21% decrease to an increase of 33%) while the UPSIT scores decreased 4% (range decrease of 17% to an increase of 1%). For raw scores pre and post cocanization, refer to table 4.4.

Table 4.4. Mean unirhinal acuity and identification scores for Experiment I

Test	Cocanized nostril*		Control nostril	
	Baseline	**Post**	**Baseline**	**Post**
UPSIT**	18(2.0)	9.0(4.0)	18(0.0)	17.3(2.5)
Acuity	8.3 (2.5)	5.3 (1.5)	8.0(2.0)	7.7(0.6)

* Nostril ultimately cocanized
** University of Pennsylvania Smell Identification Test

Paired t-tests (one tailed) were conducted on the baseline-post cocanization score to ascertain whether there was a significant drop in olfactory scores in the cocanized nostril to warrant the use of unirhinal testing For both the UPSIT and detection threshold task, significant results were observed (UPSIT: $t_{(2)}=5.71$, $P<.05$; detection threshold: $t_{(2)}=3.47$, $p<.05$).

3. Experiment II

I) Analysis 1

A one-tailed independent t-test was completed to determine whether patients with schizophrenia performed worse than normal control subjects on the UPSIT under birhinal testing conditions. The t-value approached, but did not reach significance ($t_{(46)}$=1.57, p<.06) (see Figure 4.1). Thirty percent of patients and 14% of control subjects scored in the microsmic range (<34/40; see Figure 4.1). However, when left and right unirhinal UPSIT scores were summed, patients were significantly impaired relative to control subjects [Sz 32.8(4.0) vs. NC 34.2(3.6)] using a t-test for independent groups (one tailed) $t_{(82)}$=1.8, p<.05)

In the total sample, the interrelations among all olfactory tests were calculated using Pearson's correlation procedure. All inter-correlations between birhinal and left and right UPSIT scores were significant and positive. The highest correlations were between birhinal and right and between birhinal and left UPSIT scores with correlations of .58 (p<.0001) (see Table 4.5). None of the correlations with acuity were found to be significant. Left and right acuity scores did not significantly correlate with each other. Right and left discrimination scores correlated strongly and positively with all other measures (except for being uncorrelated with right and left acuity). The significant correlations ranged from .27 to .49. Spearman's rank order correlations

were also computed. The same pattern of significant correlations was observed, with the exception of a non-significant trend between birhinal UPSIT and right nostril discrimination.

Table 4.5. Intercorrelations among scores on olfactory tasks

	Birhinal UPSIT	Right UPSIT	Left UPSIT	Right Acuity	Left Acuity	Right Discr**	Left Discr**
Birhinal UPSIT	1.00	**.58***	**.58***	.06	.06	**.33*****	**.41***
Right UPSIT		1.00	**.39***	.01	.14	**.50***	**.42***
Left UPSIT			1.00	-.21	.12	**.27***	**.28***
Right Acuity				1.00	.08	-.10	-.03
Left Acuity					1.00	.21	.07
Right Discr.**						1.00	**.42***
Left Discr.**							1.00

* $p<.05$

** Discrimination task

*** Significant correlation with Pearson's technique. Non significant trend with Spearman's technique ($p=.079$).

II) Analysis 2

To investigate whether a left nostril identification deficit was observed in the schizophrenia group on the UPSIT, a two-way mixed design ANOVA was performed on scores from 59 controls and 42 patients.

The nostril main effect was non-significant ($F_{(1,99)}$=.31, p=ns) as was the interaction between nostril and diagnostic group ($F_{(1,99)}$=.13, p=ns). The main effect for diagnosis approached significance ($F_{(1,99)}$=3.41, p=.068).

For the analysis of **discrimination** and **acuity**, scores from the 22 normal control subjects were entered into the equation. On **acuity**, neither the main effects nor the interaction was significant (diagnosis: $F_{(1,55)}$=.05, p=ns; nostril: $F_{(1,55)}$=.06, p=ns; diagnosis by nostril interaction: $F_{(1,55)}$=1.6, p=ns). These findings are in keeping with the predictions generated (see Figure 4.3).

For the **discrimination** task, a right nostril superiority was predicted for both the schizophrenia and control subjects. However, none of the main effects nor the interaction was significant [diagnosis: $F_{(1,62)}$=2.67, p=ns; nostril: $F_{(1,62)}$=.58, p=ns; diagnosis by nostril interaction: $F_{(1,62)}$=.31, p=ns].

The same pattern of results was obtained when only the right handed subjects (Schizophrenia n=35 and normal control subjects: n=47 for the UPSIT analysis and n=18 for the discrimination and acuity analysis) were included. The only difference was on the UPSIT where the main effect for diagnosis was significant ($F_{(1,79)}$=6.53, p<.05).

III) Analysis 3

The next analysis sought to determine whether subgroups of microsmic patients could be identified who had left nostril or right nostril **identification** deficits. The patient group was

subdivided according to unirhinal olfactory identification scores. Using the unirhinal olfactory identification scores from the 59 normal control subjects, the 15th percentile score for each nostril was established. For the left nostril, a cut off score of 16/20 was observed and of 15/20 for the right nostril. Any patient who scored above the cutting score for both nostrils was considered to be the "normosmic schizophrenic controls" (n=25 or 58%). The remaining subjects, those who scored below the cutting score in either nostril were further characterized as to the nostril of worse performance. Those patients whose left nostril score was lower than their right were considered to be "left microsmic" (n=12 or 28%). Those patients whose right nostril score was lower than the left were considered to be "right microsmic" (n=5 or 12%). No patient scored equally in both nostrils but missing data occurred for one patient. See Figure 3.2

The three resulting schizophrenic subgroups (left microsmic, right microsmic and normosmic schizophrenic controls) were compared on demographic measures and disease related variables. The results of these analyses can be found in Table 4.6. No between-group differences were observed for education ($F_{(2,39)}$=2.1, p=ns), age of onset of the disease ($F_{(2,38)=}$1.1, p=ns), chlorpromazine equivalents ($F_{(2,29)}$=1.2, p=ns), GAS scores ($F_{(2,27)}$=1.0, p=ns) PANSS scores (positive subscale: $F_{(2,27)}$=.48, p=ns, negative subscale: $F_{(2,27)}$=1.8, p=ns, general psychopathology subscale: $F_{(2,27)}$=1.6, p=ns). In addition, the three groups did not differ on a non-olfactory measure of naming ability, the colour identification test (CIT) ($F_{(2,35)}$=1.1, p=ns).

Table 4.6. Demographic and disease-related variables for the three olfactory patient groups

	Right microsmic	Left microsmic	Normosmic sz controls	p
n	5	12	25	
age	41.2(6.3)	34.1(11.0)	27.0(5.4)	<.001**
education	12.6(1.3)	10.9(2.8)	12.8(2.8)	ns
estimated full scale IQ	114.8(4.1)	102.6(10.7)	110.6(6.6)	<.01***
age of onset	23.4(4.3)	21.3(5.5)	23.8(3.2)	ns
duration of neuroleptic Rx (wks)	211.2(128.0)	121.2(94.9)	45.2(60.1)	<.0005*
number of previous adm.	11.0(6.9)	4.8(3.1)	1.6(2.3)	<.0001*
GAS	33.2(5.6)	30.1(8.1)	37.5(13.2)	ns
PANSS positive	18.3(6.7)	20.2(5.8)	18.0(6.2)	ns
PANSS negative	18.3(3.8)	25.6(8.9)	28.1(8.0)	ns
PANSS general	34.0(11.4)	46.7(5.2)	42.4(11.1)	ns
Colour identification	15.3(1.7)	15.2(2.1)	16.2(1.9)	ns
medication dosage (CPZ)	573.2(320.1)	381.5(177.3)	396.8(159.5)	ns

* All three groups differ

** Normosmic group differs from both microsmic groups

***Left microsmic group differs from right microsmic and normosmic groups

The three groups differed on estimated premorbid Full Scale IQ as assessed by the NART with the left microsmic group performing significantly worse than the other two groups ($F_{(2,36)}$=5.4, p=<.01) (Tukey's Honestly Significant Difference Post Hoc test). Regarding age, the normosmic group was significantly younger than the other two groups ($F_{(2,39)}$=9.2, p<.001). For duration of neuroleptic treatment, all three groups were significantly different from each other ($F_{(2,37)}$=15.5, p<.0001). On length of illness, right microsmic patients had been ill significantly longer the left microsmic group and normosmic schizophrenic controls. Normosmic schizophrenic controls were no different from left microsmic group ($F_{(2,37)}$=10.7, p<.0003). The

three groups differed on number of previous admissions with the right microsmic group having the highest number of admissions ($F_{(2,37)}$=30.2, p<.0001). Table 4.6 contains the mean scores and standard deviations for these variables

Table 4.7 summarizes the olfactory scores amongst the three groups. A MANOVA was computed on the other olfactory scores (discrimination, acuity and birhinal UPSIT) followed by one-way ANOVAs with Tukey's post hoc test. A significant omnibus result was obtained ($F_{(10,92)}$=2.8, p<.005). The normosmic group scored significantly higher on birhinal UPSIT than the two microsmic groups. In addition, the right microsmic group scored significantly lower than the normosmic group on olfactory discrimination in the right nostril, but not in the left.

Table 4.7. Olfactory-related variables for the three patient groups.

	Right microsmic	Left microsmic	Normosmic sz controls	p
UPSIT (birhinal)	32.5(2.4)	32.7(3.4)	36.6(2.4)	<.0005*
Right acuity	9.2(1.3)	9.3(2.5)	9.9(2.3)	ns
Left acuity	8.4(1.3)	8.8(1.9)	9.6(1.9)	ns
Right discrimination	9.6(3.2)	11.2(2.5)	12.4(2.0)	<.05**
Left discrimination	9.4(3.8)	11.9(1.4)	12.2(2.4)	<.08***

*normosmic group significantly different from both microsmic groups
** right microsmic group significantly different from controls
***non-significant trend

Z-scores were computed for the four cognitive domains: verbal fluency, non-verbal fluency, verbal memory and non-verbal memory (see methods). The z-scores were then entered into a mixed design MANOVA with olfactory status (left microsmic, right microsmic and

normosmic schizophrenic controls) as the between-group factor and hemisphere (right vs. left) and brain region (frontal vs. temporal) as the within subject factors.

The main effects of olfactory status ($F_{(2,36)}$=2.23, p=ns) or hemisphere ($F_{(2,36)}$=.03, p=ns) did not reach significance. However, the main effect for brain region was significant ($F_{(1,36)}$=6.91, p<.05) as were the interactions between olfactory status and region ($F_{(2,36)}$=5.6, p<.01) and olfactory status by hemisphere ($F_{(2,36)}$=3.45, p<.05). The significant interaction between olfactory status and hemisphere was followed up with planned orthogonal contrasts according to the a priori hypotheses generated. The unanticipated region by olfactory status was followed up with Tukey's post hoc test.

For the hemisphere by olfactory status interaction, the first planned comparison involved the left hemisphere tasks, contrasting the left microsmic group to the combined right microsmic and normosmic schizophrenia groups. As predicted, this contrast was significant ($t_{(36)}$=2.7, p<.05). The contrast comparing the right microsmic and normosmic schizophrenia on left hemisphere scores was non-significant ($t_{(36)}$=.69, p=ns). On right hemisphere measures, the right microsmic group was compared to the combined left microsmic group and normosmic schizophrenia group and, consistent with the apriori hypotheses, this contrast was significant ($t_{(36)}$=3.9, p<.05. Comparing the left microsmic group to the normosmic schizophrenia group did

not produce a significant result ($t_{(36)}$= 1.77, p=ns). These results are graphically represented in Figure 4.5.

The unanticipated significant interaction between olfactory status and region was followed up with Tukey's honestly significant test. No pairwise differences were observed (see Figure 4.6).

When the left handed patients (n=7) were omitted from the analysis, the same pattern of means and significant results were observed. The main effect for region was significant ($F_{(1,28)}$=8.74, p<.01) as were the olfactory status by region interaction ($F_{(2,28)}$=3.9, p<.05) and olfactory status by hemisphere interaction ($F_{(2,28)}$=3.3, p<.05).

IV) Analysis 4

The purpose of this analysis was to determine whether psychopathology ratings differed as a function of unirhinal olfactory identification ability. A series of one-way ANOVAs followed by Tukey's post hoc test was employed. No significant differences were found amongst the three groups on PANSS positive, negative or general psychopathology subscales as well as on the five factors (positive, negative, excited, anxious/depressed, and cognitive). For the mean scores and standard deviations, see Table 4.8.

Table 4.8. PANSS subscale and factor mean scores for the three olfactory groups

	Right microsmic	Left microsmic	Normosmic sz controls	p
Subscales:				
positive	18.3(6.7)	20.2(5.8)	18.0(6.2)	ns
negative	18.3(3.8)	25.6(8. 9)	28.1(8.0)	ns
general psychopathology	34.0(11.4)	46.7(5.2)	42.4(11.1)	ns
Factors*:				
positive	11.7(5.5)	13.1(2.8)	11.2(3.8)	ns
negative	14.7(2.5)	19.9(6.7)	23.7(8.1)	ns
anxious/depressed	7.3(4.2)	10.3(3.5)	9.1(4.5)	ns
excited	6.0(3.5)	10.7(3.0)	7.6(3.8)	ns
cognitive	13.0(1.7)	14.0(2.4)	16.1(4.1)	ns

*From Lindström & von Knorring, 1994

Figure 4.1
Experiment II, Analysis 1
Birhinal UPSIT score by diagnosis

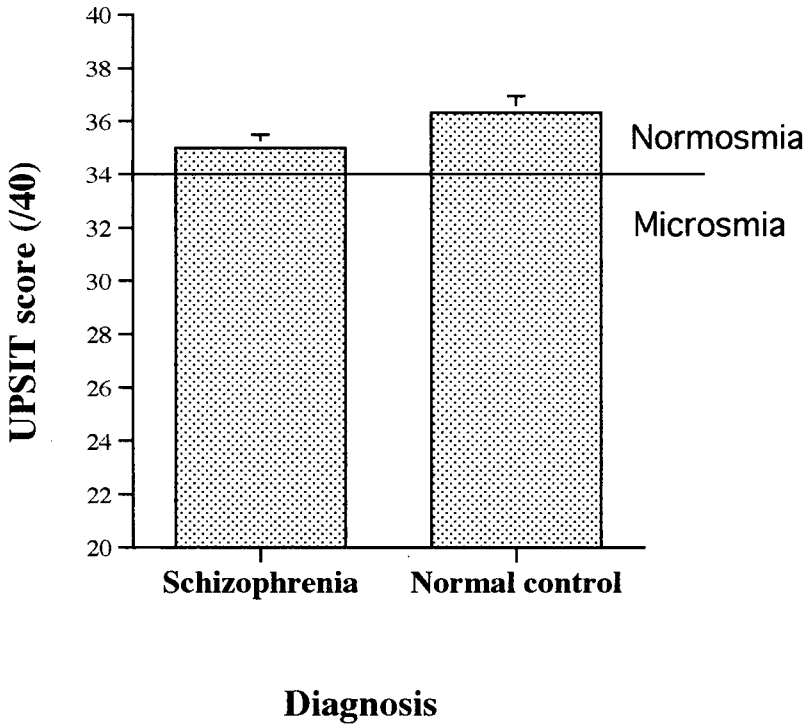
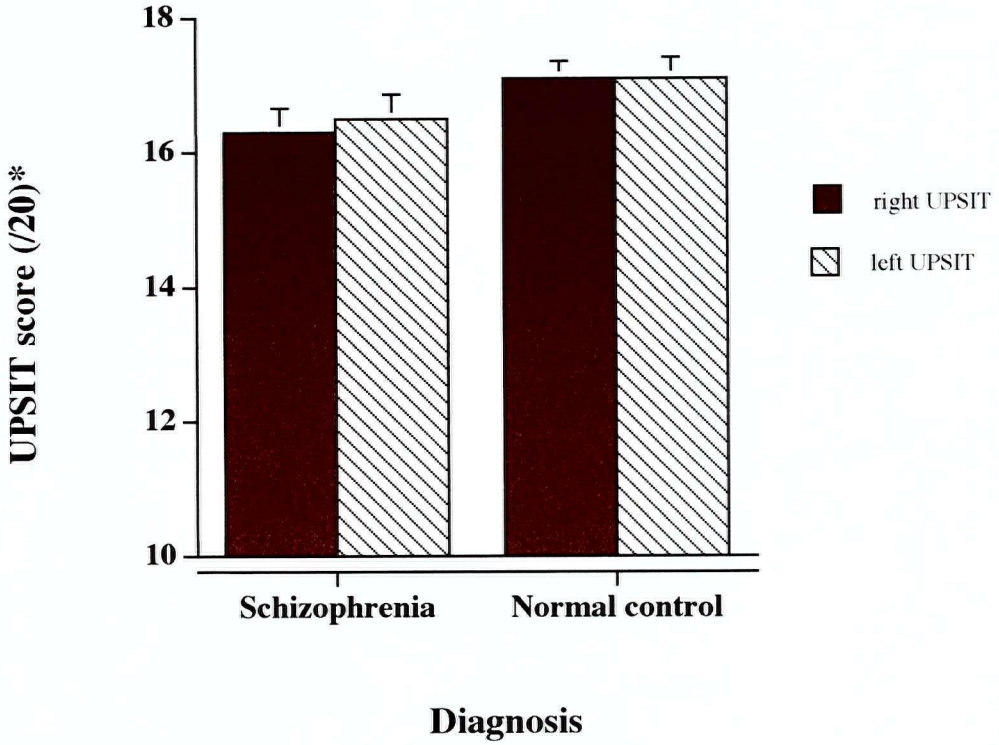


Figure 4.2
Experiment II, analysis 2
Left and right unirhinal UPSIT scores by diagnosis



* Half (2 booklets) of the UPSIT was administered to each nostril

Figure 4.3
Experiment II, Analysis 2
Left and right unirhinal acuity scores by diagnosis

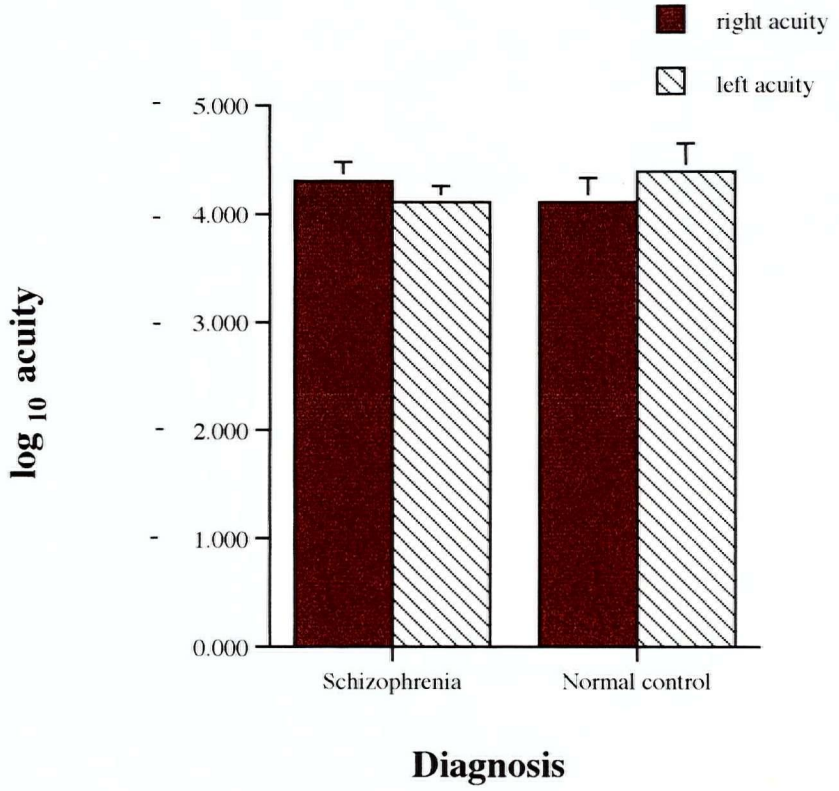


Figure 4.4
Experiment II, Analysis 2
Left and right unirhinal discrimination scores by diagnosis

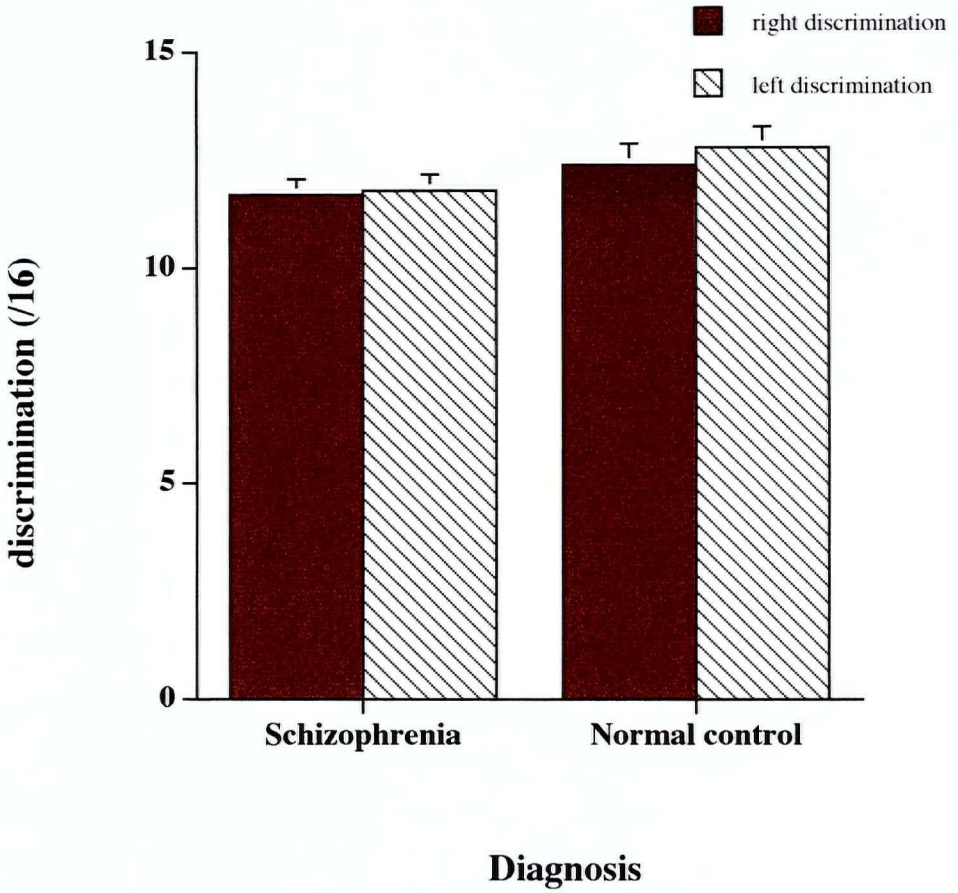
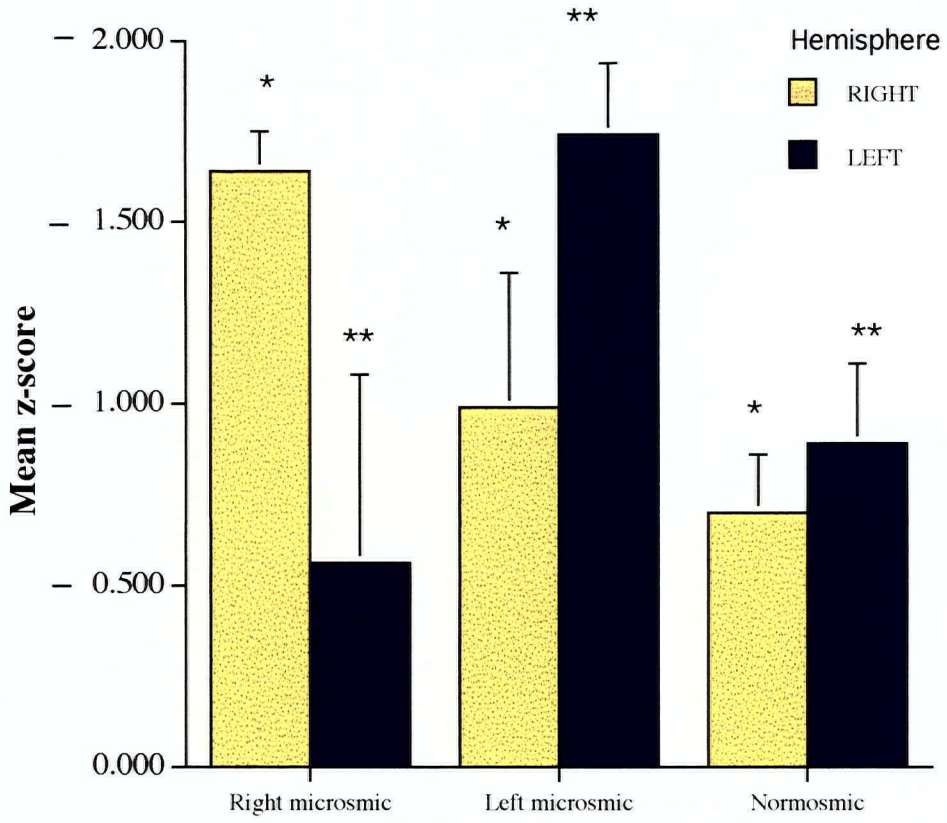


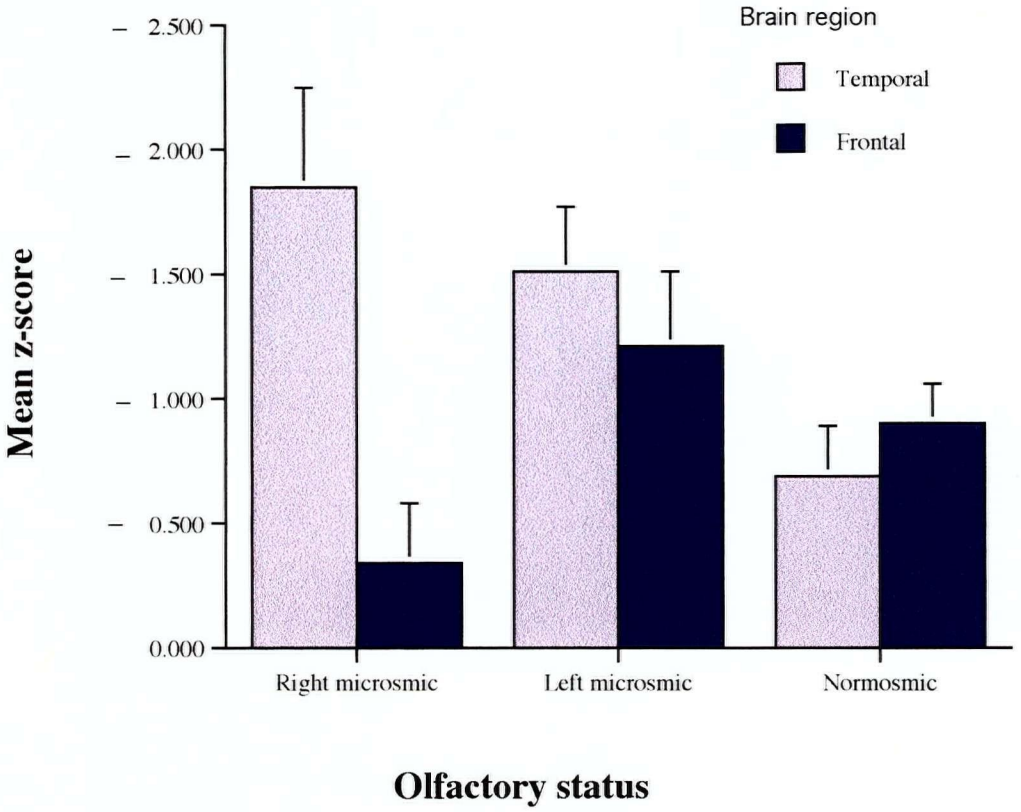
Figure 4.5
Experiment II, Analysis 3
Hemisphere by olfactory status interaction



* On right hemisphere tasks, the right microsmic group scored significantly lower than the combined left microsmic and normosmic groups. Left microsmic and normosmic groups were not different from each other.

** On left hemisphere tasks, the left microsmic group scored significantly lower than the combined right microsmic and normosmic groups. Right microsmic and normosmic groups were not different from each other.

Figure 4.6
Experiment II, Analysis 3
Region by olfactory status interaction*



* No pairwise comparisons were significant using Tukey's post hoc test.

CHAPTER 5

Discussion and conclusions

1. Caveats to the interpretation of the data:

Before conclusions can be drawn, a number of caveats to the interpretation of the data must be addressed. The patients with schizophrenia studied in the current investigation were relatively young, stable, medicated and male. Many patients were very close to their first contact with the health care system for the treatment of psychosis. Consequently, the results obtained may not be generalizable to older, more chronic males or females with schizophrenia. The constraints on subject inclusion were made so as to maximize the possibility of finding significant results. For example, olfactory identification deficits are almost non-existent in young, female patients with schizophrenia. Additionally, women with schizophrenia were less likely to show lateralized brain abnormalities and thus, may be less likely to demonstrate lateralized olfactory dysfunction. Including both sexes could potentially have obscured any real findings and would have doubled the sample size required.

Although studying a homogeneous sample of drug naive patients would have been preferable to studying those individuals who were medicated, so that any potential medication-induced changes would be eliminated, the rationale for including only medicated patients was four-fold. First, brain abnormalities are present in patients who have never been exposed to neuroleptic medications and may not differ those observed in the chronically medicated (Abi-Dargham et al, 1991; Lieberman et al, 1992; DeLisi et al, 1994). As well, the pattern of neuropsychological impairment and the olfactory deficit do not appear to be progressive [Saykin

et al, 1994 (but see also Bilder et al, 1992); Kopala et al, 1992; Good et al, unpublished observations]. Thus, there would be no clear benefit to studying drug naive patients. Secondly, patients who have not been medicated with antipsychotic medications are likely to be in hospital for their first psychotic episode. Diagnosis is sometimes uncertain. A much larger sample size would have been required to account for the loss of patients over time due to changed diagnosis. Thirdly, patients who are experiencing their first psychotic episode may not be stable, and state-dependent factors may come into play in the neuropsychological assessment, jeopardizing the validity of the results. At first admission patients may be confused, frightened or disoriented and less attentive than patients who are medicated and stabilized. Finally, it is not ethical to withhold antipsychotic medications for psychotic individuals.

Unlike those with Alzheimer's disease, patients with schizophrenia are rarely aphasic. However, poverty of speech may be present. No studies have examined olfactory function in patients with schizophrenia within a lexical processing framework. In Alzheimer's disease, the olfactory deficit is observed even when the lexical component of the olfactory task has been factored out, by incorporating a picture based identification task (Morgan et al, 1995). Our group has recently shown that patients with schizophrenia do not differ from normal control subjects on a picture identification task (Kopala et al, unpublished observations). In this regard, it is unlikely that word finding difficulties form the etiological basis for the olfactory identification deficit in schizophrenia. Clearly, further research is required to extend our understanding of these factors.

Although the literature would suggest that some left handed individuals have atypical patterns of hemispheric laterality, all potential male patients with schizophrenia were screened for participation in the current study. As handedness may be a continuous rather than a

categorical variable, broadening the inclusion criteria would permit analysis of atypical versus typical dominance patterns on olfactory laterality. In the current study, analyses were completed on all patients, followed by the same analyses including only those who were right handed. On only one occasion was a different result found when left handed subjects were excluded.

The regional specificity of neuropsychological tests is not absolute. The ability of a particular task to identify only patients with localized brain abnormalities is poor (i.e., specificity). Certain tests have been shown to be sensitive to regional brain abnormalities, but are by no means specific. For example, the Wisconsin Card Sorting Test has been shown to be performed very poorly by patients with lesions to the dorsolateral prefrontal cortex (Milner, 1963). However, not all patients who have prefrontal lesions, and some individuals who have lesions in other brain regions, show deficits on this task (Anderson et al, 1991).

Clinical neuropsychological assessment involves using a wide ranging battery of tests which assesses overlapping cognitive domains. One task, assessing performance on one aspect of verbal functioning, does not indicate hemispheric or regional brain abnormality. However, there are numerous very sound studies which document group differences on certain neuropsychological tasks. It is therefore appropriate to compare groups of patients with presumed regional impairment on these tasks. As such, the analyses described herein are believed to be valid.

Finally, there are two methodological concerns which should be addressed before conclusions can be drawn. The first is the issue of computing standardized (z) scores using within-study controls versus population means (published norms). There are advantages and disadvantages to each method of computing z-scores. The current study used within-study means for control subjects (n=21). The primary advantage for using sample data for computation

was that for the current study, the patient and control groups were very similar on sociodemographic variables which are assumed to influence performance on neuropsychological measures (age, gender, parental socioeconomic status etc.). The advantage of using population norms relates to the fact that they are normally based on very large sample sizes. However, populations used to generate the norms are typically not well matched to patients with schizophrenia and are not usually stratified according to age and sex (Cannon et al, 1994). Finally, in the case of certain older tests, the comparative group has been known to include patients with schizophrenia as control subjects! Therefore, one could be reasonably confident that z-scores computed were valid benchmarks to which patient groups could be compared.

The second issue related to the assumption of intact acuity in the patient group. Phenyl ethyl alcohol, an odorant thought to excite only receptors of cranial nerve I (olfactory) and not cranial nerve V (trigeminal), was used in the current study. This stimulus has been shown to be very reliable (test-retest reliability=.88; Doty & Kobal, 1995). However, assessing acuity with one odorant may not be sufficient to rule out peripheral sensing abnormalities. Recent investigations into the molecular neurobiology of olfaction have revealed that at least 1000 genes code for approximately 1000 olfactory receptors. Each receptor interacts with one or a small number of odorants (Buck & Axel, 1991). As genetically determined specific anosmias have been reported (for example, isobutyraldehyde; Amoore et al, 1968), it is possible that patients with schizophrenia lack the ability to detect odorants other than phenyl ethyl alcohol. These other odorants may be items found in the identification or discrimination tasks.

There are two reasons why this explanation is unlikely. First, an error pattern analysis has been performed comparing patients with schizophrenia and normal control subjects (Hurwitz et al, 1988). The pattern was similar between patients and controls, suggesting that errors were

essentially random within both groups. One item proved particularly difficult for both patients and control subjects. Errors on this particular item are thought to reflect similarity between the correct response and a distracter (L. Kopala, personal communication). Second, the UPSIT, in full, was administered twice, as was the discrimination task. All items included in the discrimination task are represented in the identification task. As such, if an anosmia to a specific odorant is present, it should have been manifest on both tasks, and in both nostrils. Similar errors were not observed on both tasks, suggesting that peripheral sensing mechanisms were functioning adequately. However, future studies should address this question.

2. Cardinal findings

The cardinal findings of this study are that: 1) unirhinal testing, following strict procedures, can be used to assess the functioning of each olfactory sensing and processing apparatus without interference with receptors in the contralateral nasal cavity; 2) approximately 30% of male patients with schizophrenia were impaired on birhinal olfactory identification testing; on unirhinal testing, 40 % were impaired in one nostril or the other; 3) no consistent pattern of olfactory laterality was observed in either the patient or normal control group on olfactory testing for olfactory detection threshold, identification, or discrimination; 4) unirhinal olfactory identification deficits were not associated with any regional (frontal or temporal) profile of neuropsychological impairment; 5) unirhinal olfactory deficits converged with ipsilateral neuropsychological deficits; 6) unirhinal olfactory function did not correlate with any particular symptom cluster; and 7) differences in age, premorbid IQ and other olfactory scores

were observed amongst the three olfactory subgroups (right microsmic, left microsmic and normosmic controls).

I) Unirhinal testing can be performed following strict procedures.

The main finding of this preliminary study was that unirhinal cocanization of olfactory receptors resulted in reduced olfactory identification and acuity in the nostril which was cocanized but not in the contralateral nostril. Olfactory identification was reduced to just above chance levels while a clinically and statistically significant reduction of acuity was observed. Therefore, it appears that if a number of rules are followed, the administration of stimuli to only one nasal chamber permits the assessment of olfactory pathways only on that side. By ascertaining that the stimulus is only inhaled via one deep inhalation through the nostril of interest, and that the subject exhales through the mouth, one can be sure that the stimulus has only interacted with olfactory receptors on the side of interest.

Numerous studies have demonstrated unilateral olfactory deficits in certain patient groups, and single nostril testing has been the method used (Zatorre & Jones-Gotman, 1991; Doty et al, 1992c). These effects have been reported despite a lack of prior information regarding this stimulus delivery system. If retronasal, contralateral airflow were to have occurred, then any real effects may be attenuated. Addressing this issue before attempting to assess lateralized olfactory function in young patients with schizophrenia was very important given that the degree of olfactory dysfunction observed in this patient group is modest compared to those with Alzheimer's disease. Any confound that even slightly diminishes the effect size is likely to have a significant impact on the results.

Following unirhinal cocanization, olfactory identification ability was reduced to 50% of baseline scores. Detection threshold was reduced by 34%. There are a number of explanations

which could account for these findings. First, there may have been some retronasal air flow and stimuli were able to cross to the opposite nasal cavity and interact with receptors on that side. However, this explanation is not sufficient to explain the results. Precautions were taken to ensure that very little, if any, contralateral airflow occurred. Each subject was instructed to inhale deeply once through the nostril of interest and exhale through the mouth. If stimuli did cross over, then scores closer to baseline would be predicted. As UPSIT scores in the cocanized nostril were close to chance levels post cocanization, it is unlikely that this occurred.

Given the widespread distribution of the trigeminal nerve (cranial nerve V) within the nasal cavities, it is unlikely that the application of cocaine eliminated the function of this sensory system. As some items of the UPSIT are known to activate the trigeminal nerve, it is possible that trigeminal cues were used for detection and identification. Individuals with deficient cranial nerve I (olfactory nerve) function are able to detect odours on the basis of their trigeminal properties (Doty et al, 1978). However, the ability to identify or label odours is distinctly impaired when only trigeminal cues are available (Hudson et al, 1994). Moreover, phenyl ethyl alcohol is believed to be a pure cranial nerve I stimulant (Doty et al, 1978).

A third explanation relates to inadequate application of cocaine, such that not all receptor function was completely ablated. This explanation is the most plausible. The area occupied by the olfactory mucosa is fairly small and compact, yet accommodates approximately 6 million receptors. Some terminals, but not all, may have been anesthetized. Presumably, only a few receptors would be needed for detection to occur. Conversely, stimulation of more receptors would be required in order to facilitate accurate activation of neural systems required for naming an odorant.

II) Birhinal olfactory agnosia was observed in 30% of male patients

According to published norms (Doty et al, 1984a) for males, a birhinal score of 34/40 or less on the UPSIT in males is classified as microsmic. In the current study, only 14% of normal male control subjects were impaired birhinally on the UPSIT whereas approximately 30% of patients were so classified. The percentage of microsmic patients was in keeping with previous findings by our group (Kopala et al, 1989; 1992) and others (Seidman et al, 1992). Previous research by our group has shown that a dissociation between olfactory identification ability and detection threshold was evidenced by male patients with schizophrenia such that an olfactory agnosia was present (Kopala and Clark, 1990). Birhinal olfactory detection threshold was not assessed in the current study, but unirhinal detection threshold was. As no unirhinal olfactory acuity deficits were observed in patients or controls, an olfactory agnosia is presumed to exist in the birhinally microsmic patients.

In contrast to prior publications, the mean score for the patients with schizophrenia did not place the group in the microsmic range. The demographics of patients studied in the current project did not differ substantially from the larger sample of patients studied previously by our research group. All patients in the current study were in-patients, who had been stabilized with antipsychotic medication. All met criteria for diagnosis of schizophrenia, none had any history of head injury, facial fracture, neurological or medical disorder that could account for olfactory dysfunction.

Perhaps the sample of patients studied was not representative of the population of male patients with schizophrenia. Given that mean scores can be highly influenced by extreme scores,

and that the proportion of patients who were in the impaired range is similar to that observed previously, this is likely not the case.

Our research group has recently investigated patients with comorbid diagnoses of schizophrenia and severe polydipsia (water intoxication) and found them to be severely impaired in identification ability and have diminished capacity to detect odours (Kopala et al, submitted). No patient with concurrent diagnosis of water intoxication was included in the current study. It is possible that previous samples included patients with more chronic illness who also had polydipsia. Inclusion of these individuals would potentially result in lower mean olfactory scores for the group.

In the current study, criteria set *a priori* called for the exclusion of individuals who had elevated thresholds. Abnormally high thresholds could be accounted for compromise of peripheral sensation, and thus, including these individuals could potentially confound the data. In some studies by other research groups, this exclusionary criteria was not enforced thus it is possible that an inflated effect sized was reported. The exclusion criteria utilized in the current study are the most prudent and minimized the effects of impaired sensation.

No published norms exist for unirhinal UPSIT. As a result, an arbitrary cutting score at the 15th percentile for normal control subjects was selected to divide the patient group into impaired and non-impaired subgroups. According to this criterion, 17 (40%) were impaired in at least one nostril. The fifteenth percentile was chosen to reflect the outliers in the normal control group and to maximize the number patients with deficits.

There were some patients with birhinal microsmia (n=4) who, when each nostril was tested separately, showed no evidence for reduction of olfactory function in either nostril. Bromley and Doty (1995) observed that birhinal testing in normal individuals tends to produce

higher scores than does testing each nostril separately. Their explanation for the finding is that bilateral stimulation produces a "richer", sharper, overall olfactory experience. Thus, for those patients with birhinal olfactory deficits, unirhinal olfactory scores should also be in the microsmic range.

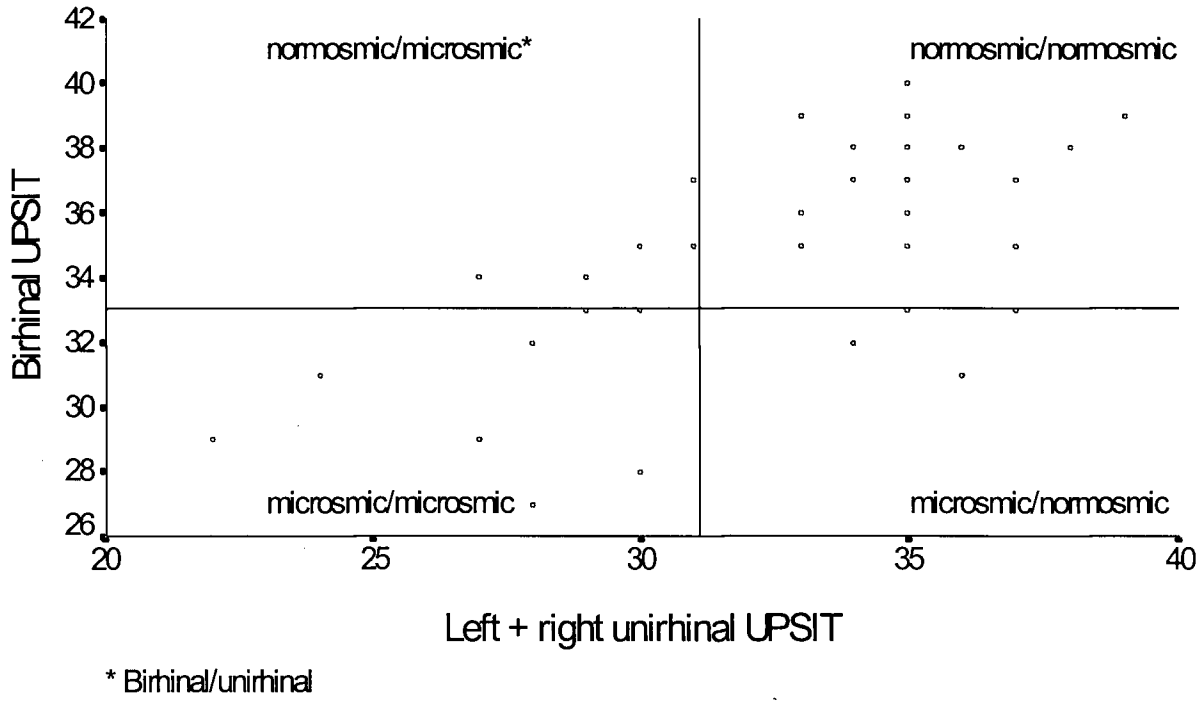
The finding in the current study could be understood within the context of a hemispheric interference model. Using a dual task paradigm, Moscovitch and Klein (1980) presented stimuli through two channels to a single hemisphere or to both hemispheres simultaneously. In contrast to the expected result, simultaneous presentation of stimuli to a single hemisphere produced a slower, rather than faster, activation time. These authors suggested that the convergence of stimuli onto one hemisphere evoked an interference effect. The hemispheres, they speculate, had a limited-processing capacity and did not function as efficiently when overloaded.

The patients in the current study who demonstrate bilateral, but not unilateral, olfactory identification deficits may also be experiencing hemispheric interference. If olfactory identification is ultimately processed in one hemisphere, then information reaching that hemisphere from one nostril may be efficiently processed. Additional information from the opposite hemisphere converging with ipsilateral information may be antagonistic to generalized processing. Thus, when stimuli are presented unilaterally, sensory information may be processed properly. When information is received from too many sources, confusion may occur.

As birhinal identification was always performed first, followed by unirhinal testing (in order to weed out those individuals who were unmotivated or too disorganized to complete all testing), it is also possible that learning occurred. These birhinally microsmic patients may have become more proficient at performing the task upon subsequent administrations. However, feedback was not given regarding the correctness of responses. Furthermore, as can be seen from

the Figure 5.1, the individuals in question scored very close to the criterion for impairment and thus are not true outliers.

Figure 5.1: Scatter plot depicting scores of birhinal and a composite score of unirhinal olfactory identification for patients with schizophrenia



A more likely explanation, however, is that definition of impairment (unirhinal and birhinal) was based on somewhat arbitrary cut off scores. It is possible that categorization into groups based on olfactory status would change with more conservative criteria for impairment.

Interestingly, when the right and left nostril unirhinal UPSIT scores were combined, patients with schizophrenia scored significantly more poorly relative to control subjects. Since birhinal olfactory scores likely represent the better performance of the two nostrils (Hornung et al, 1990), summing the scores across nostrils permits assessment of the contribution of each nostril separately. This finding suggests that unirhinal testing may be more sensitive for finding

impairment in patients with schizophrenia as the confounding effect of the better nostril is reduced.

III) No consistent pattern of laterality was observed in patients or controls

Patients' performance on the discrimination and identification tasks was poorer than control subjects, although not significantly. No nostril effect was observed on either of these two tasks. Neither of the interactions between diagnosis and nostril were significant. The lack of any significant main effect or interaction for the acuity task was anticipated.

a) Identification

The results of the identification task are consistent with some of the existing literature. Doty et al (1992c) administered the UPSIT unirhinally to patients with Parkinson's disease and normal control subjects and found no lateral asymmetry on the UPSIT in either group. In early stage Parkinson's disease, the pathology is more likely to be asymmetric than later in the course of the disease. Hence, any lateralized changes in olfactory regions would be most likely evidenced with olfactory testing at this stage, rather than later in the disease course. Regardless, no asymmetry was observed in these patients, suggesting that both sides of the olfactory system were equally affected.

The UPSIT was designed to assess olfactory identification in patients with olfactory complaints. As such, it has a very low ceiling. Specifically, subjects without olfactory problems or neurological disorders tend to score beyond the ninetieth percentile (Doty et al, 1984a). When scores cluster near the extremes of a task, the probability is lower for finding lateralized dysfunction than if scores are more widely distributed.

In contrast to the Doty et al (1992c) finding, Hornung et al (1990) showed that olfactory identification was more efficient when stimuli were presented to the left nostril than the right.

The olfactory task used in this study was Wright's Odour Confusion Matrix (OCM). The subjects studied in this task were those who had been referred to a taste and smell clinic for subjective olfactory complaints. As such, a different pattern of olfactory laterality than that seen in the normal control population was more likely. The results require replication.

b) Detection threshold (acuity)

No inter-nostril difference was observed in either group on olfactory detection threshold. This was the predicted result and was in keeping with earlier literature.

c) Discrimination.

The results of the current study are at odds with what had been previously reported for olfactory discrimination in normal subjects. Zatorre and Jones-Gotman (1990; 1991) repeatedly found a distinct right nostril advantage on their discrimination task in samples amongst normal subjects. In contrast, the current study population of normal control subjects showed no asymmetry for this task.

Differences in olfactory tasks used between the two research groups could partially explain the discrepant results. Zatorre and Jones-Gotman (1990) used an eight item discrimination task which was comprised of four similar pairs (pairs of odours that have previously been shown to be similar in quality) and four dissimilar pairs of stimuli. They found that performance in the right nostril was much better than the left nostril in their group of young, non-neurologically disordered subjects despite no inter-nostril differences on an acuity task (n-butanol). However, they also observed a significant nostril by similarity interaction. The left-right difference was observed only for the similar items and not for the dissimilar pairs. The discrimination task used in the current study involved three stimuli. Also, triads were chosen based on similarities in odour intensity and pleasantness, and not similarities in odour quality.

Thus, the results of the current study more closely resemble the dissimilar condition in the Zatorre and Jones-Gotman (1991) study.

For patients with schizophrenia, the current results are consistent with the literature. Dunn & Weller (1989) observed no inter-nostril difference on olfactory discrimination task for patients with schizophrenia. Whether this group observed a right nostril advantage for the normal control subjects is unknown.

The choice of the discrimination task in the current study was based on stability of stimuli. In the Zatorre and Jones-Gotman paradigm, stimuli were mixed with a vehicle and kept in jars. This procedure has its limitations. Concentration of stimuli at the beginning of an experiment can differ from concentration at the end of the experiment. The discrimination task chosen for the current study utilized microencapsulated odours, which are not as affected by time (Doty & Agrawal, 1989). Thus, the use of more stable stimuli was ensured. As the stimuli chosen for each item had previously been rated similar in intensity and pleasantness, these properties were less likely to have been used by subjects to differentiate among odorants. This potential confound may not have been taken into account in other studies. Consequently, the results of the current study are possibly more reliable than results generated by studies using other methods.

IV)Unirhinal olfactory deficits did not relate to any specific profile of regional neuropsychological impairment

Kopala and Clark (1990) speculated that, on the basis of results from their own studies and from the study of patients with brain injury, disease or resection, the region of brain

abnormality responsible for the olfactory identification deficit in patients with schizophrenia is located in the dorsomedial nucleus of the thalamus or the orbitofrontal cortex. Seidman et al (1992) concurred with Kopala and Clark, suggesting that subgroups of patients with schizophrenia had orbitofrontal dysfunction.

The premise on which Seidman et al (1992) based their argument of differential frontal lobe deficits comes from the observation that patients with lesions to different subdivisions of the frontal lobes demonstrate dissimilar patterns of symptomatology. Simply, patients with damage to the dorsolateral regions of the prefrontal region are characterized by negative symptoms such as apathy, bradyphrenia, difficulty with initiation of action (but when initiated, hard to change set), perseveration and a lack of spontaneous behaviour. In contrast, the orbitofrontal type can be viewed as a syndrome in which impulses cannot be adequately controlled. Patients with this type of lesion are disinhibited, lack proper social and behavioral controls, are labile and excitable. Thus, the Seidman et al (1992) group suggested that since some patients demonstrated deficits on the Wisconsin Card Sorting Test (WCST; a task that is supposedly specific to dorsolateral prefrontal lesions, DLPFC) and some patients were impaired on the UPSIT (a task that they claim is specific to the orbitofrontal regions, OFC), subgroups of DLPFC and OFC patients exist. Although these neuropsychological data would suggest such a dichotomy, the next logical step, that of assessing predominant symptomatology in each group, was not done. This omission leaves unanswered the question of whether these subgroups do actually represent distinct subtypes of frontal lobe disorders.

Seidman et al (1992) based their conclusions on observations that patients with orbitofrontal lesions/resection showed olfactory deficits that are similar in quality and magnitude to patients with schizophrenia (Jones-Gotman & Zatorre, 1988b; Potter & Butters, 1980).

However, impairment on the UPSIT was observed in patients with temporal lobe resection as well (Jones-Gotman & Zatorre, 1988b).

Brewer et al (1996) have recently refuted the findings of Seidman et al (1992), showing that olfactory identification ability did correlate with WCST performance. These results suggest dorsolateral prefrontal rather than mediotemporal or orbitofrontal dysfunction. This finding can be criticized as reflecting a type I error due to the large number of comparisons made (34). Further, whether the sample studied (Australian) was comparable to the Seidman et al sample (North American) is questionable as the mean UPSIT scores for patients and controls in the Brewer et al study were very low. It is possible that the selective inclusion and exclusion criteria were not enforced in the Brewer et al study, leading to inclusion of individuals with head injury or facial fracture. Additionally, the two studies used different administration procedures for the WCST. The finding in the Brewer et al study of a positive relationship between olfactory function and negative symptoms may be a consequence of the fact that their patient sample demonstrated a predominance of negative symptoms. Furthermore, neither Seidman et al (1992) nor Brewer et al (1996) administered an olfactory detection threshold task limiting the interpretability of the higher order olfactory test results. Taken together, it is impossible to compare the results of the two studies and make any reasonable inferences regarding neuropathology.

Olfactory pathways travel from primary sensory receptors to medial temporal regions, then on to the orbitofrontal regions, either directly or indirectly through the dorsomedial nucleus of the thalamus. As medial temporal regions appear to be a relay between sensory receptors and final processing region, abnormalities in these brain areas, if they exist, could potentially degrade the olfactory signal. Thus, even if the final processing zone is located within the frontal

lobes, a defect along the pathway could limit the amount of information that reaches that region. Lesions, therefore, anywhere along the pathway may result in olfactory identification deficits that are similar in quality and magnitude to those demonstrated by patients with orbitofrontal lesions.

A possible explanation for the lack of association of olfactory deficits with frontal lobe tasks i s the lack of specificity of the neuropsychological tests used. Both frontal tasks used are sensitive to impairment in the prefrontal regions. However, it is unlikely that they are specific to lesions to the orbitofrontal cortex. Finding a task which is sensitive to orbitofrontal regions has proven to be difficult. Martzke et al (1991) administered a number of frontal lobe tasks to patients who were completely anosmic secondary to their closed head injury. As orbitofrontal regions are often damaged during a closed head injury (sliding over the bony projections of the orbital plate; Silver et al, 1994), this group made the assumption that orbitofrontal regions were also injured.

Out of all the neuropsychological tests administered by this group, only performance on the Tinkertoy Test (Lezak, 1983) was commonly impaired for anosmic trauma victims. Thus, the neuropsychological tests used in the current study may not be the most sensitive to OFC dysfunction. Martzke et al (1991) also administered the Controlled Oral Fluency Test (but not Design Fluency) with no success in predicting olfactory dysfunction.

While there is very little anatomical/neuropathological data to support orbitofrontal cortex (OFC) abnormalities in patients with schizophrenia, olfactory pathways culminate in this region. This region has been targeted as a possible site for the olfactory identification deficit. Post mortem studies of individuals with schizophrenia show neuropathological abnormalities in the temporal lobes although the findings are not uniform across all subjects. Larger sample sizes

in each of the olfactory deficit groups will be required to determine whether the regional specificity of olfactory dysfunction is observed.

V) Unirhinal olfactory identification deficits converged with lateralized neuropsychological impairment.

Patients with left nostril microsmia were uniquely impaired on tests which are sensitive to impairment of the left hemisphere, while patients with right nostril microsmia were impaired on tests sensitive to right hemisphere dysfunction. This finding implies that in each microsmic group, the hemisphere on the implicated side was in some way abnormal. Even when those patients who were left handed were dropped from the analysis, the same pattern of neuropsychological impairment was apparent.

The neuropsychological tests employed in the current study were not psychometrically matched. The different sensitivities of the neuropsychological measures created a potential dilemma for investigating the relative performances between the hemispheres. However, a double dissociation was present in the current study. A double dissociation exists when a lesion (lesion A) produces behavioral change in one group (Group X) but not in another(Group Y). A second lesion (lesion B) produces a behavioral change in the second group (Group Y) but not the first (Group X) (Teuber, 1955). Thus, neuropsychological tests sensitive to left hemispheric lesions were performed more poorly by the left microsmic group but comparable to controls by the right microsmic group. Similarly, neuropsychological tests sensitive to right hemisphere lesions were performed poorly by the right microsmic group but comparable to controls for the left microsmic group.

The results of this analysis are unique and do not fit with any particular model of brain dysfunction in schizophrenia. These results suggest that one sided olfactory deficits have

validity by virtue of the presence of convergent hemispheric abnormalities. The hemisphere imbalance model of schizophrenia is the most similar (Gruzelier et al, 1988). In this model, patients with schizophrenia can be subgrouped according to relative symptom presentation. Those with prominent positive symptoms are more likely to have increased activation of the left hemisphere and concomitant reductions in the right hemisphere. The opposite is true for those who have relatively greater negative symptoms (activation of the right, reduction in the left). Contrary to the above model, patients in the current study were not subgrouped according to symptoms, but by abnormal scores on olfactory/neuropsychological tasks. As the PANSS subscales are not synonymous with the positive and negative symptoms used to classify patients in the Gruzelier et al study, this could account for the fact that the olfactory impairment groups did not differ on PANSS subscale scores.

Membership in the three olfactory groups was based on unirhinal performance on the UPSIT. Given that the right microsmic group was impaired on the discrimination task relative to the left microsmic and the normosmic schizophrenia controls, a role for the right hemisphere in odour discrimination is supported. This finding is consistent with the literature. Zatorre & Jones-Gotman (1991) reported that the right orbitofrontal cortex is specialized for olfactory discrimination. Olfactory discrimination was impaired in both the right and left nostril after right frontal lobectomy.

In the current study, those patients with right nostril microsmia also show right hemispheric neuropsychological deficits. In addition, significant reduction was observed on right discrimination and a trend towards poorer performance for the left nostril. The sample size of the right microsmic group was small, which may have contributed to the significant trend. Only larger samples sizes will determine whether right hemispheric abnormality (as assessed by

impaired right nostril UPSIT) is associated with impaired discrimination in both nostrils. If such is the case, this would be strong evidence for right orbitofrontal cortex involvement in a subgroup of male patients with schizophrenia.

VI) Amongst the patient subgroups, differences were observed on age, IQ and other olfactory scores

Twelve patients demonstrated a left nostril impairment whereas only five showed impairment in the right nostril. The remainder of subjects (25) were normosmic. The three groups did differ on age, with the normosmic group being the youngest, followed by the left microsmic and right microsmic groups. Our previous research has shown that approximately the same proportion of male patients are microsmic (birhinally) when they are neuroleptic naive and at first presentation than when they are medicated (Good et al, in preparation). Patients who were identified as being microsmic at first episode were also microsmic on re-testing on average two years later, after having been stabilized with medication. As such, it is unlikely that age alone can account for the deficit observed in the current study.

It is possible that the differences in disease-related variables were an age related artifact. Age of onset of the disease was not different among the three groups. However, length of illness, duration of neuroleptic treatment and number of hospital admissions did differ. All these variables increase with the passing of time and thus would be greater for those patients who are older. As such, it is not possible to determine whether these variables are related in any way to one sided olfactory deficits.

As no asymmetry of olfactory acuity was observed amongst the three groups of patients, lateral asymmetry of peripheral sensing is not able to explain one sided olfactory deficits. As well, no differences among the groups were observed on a task which is similar in processing

load, suggesting that attentional factors were not likely responsible for the deficit. Dosage of antipsychotic medications (measured in chlorpromazine equivalent units) was not different among the groups, nor was extent of psychopathology as measured by the GAS and PANSS.

The patient subgroups differed on a premorbid measure of IQ, as estimated by the NART. The left microsmic group performed significantly worse than both the right microsmic group and the normosmic controls. The NART is a reading task; thus, performance is dependent on intact verbal functioning. It is a skill which *is* normally acquired before the onset of schizophrenic symptoms and is influenced by education level. As the left microsmic group was impaired on the NART but was not different than the other two groups on education level, it is possible that this group suffered from impaired brain maturation which potentially impaired early acquisition of language. Future studies will examine whether early brain insult was more likely in the left microsmic group by comparing the prevalence of pre- and perinatal events.

The two cerebral hemispheres do not develop at an equal rate, with the left lagging behind the right. This delay leaves the hemisphere vulnerable for longer periods of time. It is possible that if a brain insult is required for ultimately developing schizophrenia, perhaps the timing of insult that is the critical variable. The three subgroups may represent the effects of insults occurring in different stages of development. The proportion of patients within each subgroup is also consistent with this hypothesis, given the percentage of time that the brain is vulnerable.

3. Implications

The results of the current study may increase our understanding of the behavioral consequences of the pathological processes in schizophrenia. Currently, neuropsychological and neuropathological studies are conducted on heterogeneous groups of patients with schizophrenia

and thus it is not surprising that inconsistent results exist. For example, Raz and Raz (1990) performed a meta analysis on the results of several studies investigating sex differences in ventricle to brain ratios in schizophrenia. These investigators found that the size of the difference between patients and controls increased as the proportion of males included also increased. In addition, different subgroups of patients with different patterns of neuropathology may exist relating to their relative age of onset (Smith et al, submitted). The heterogeneity of schizophrenia diminishes the likelihood of finding significant effects.

The power of the current study relates to the fact that using a short, non-intrusive task such as the UPSIT, patients with putative left or right hemispheric abnormality can be identified. Parsing out homogeneous clusters of patients is crucial for increasing our understanding of the neural substrate of these disorders.

The subgroups of patients identified in the current study suggest that there are a group of male patients who have schizophrenia who are relatively young, demonstrate mild neuropsychological impairments, but do not appear to have brain abnormalities in olfactory regions (normosmic schizophrenic controls). A second group of patients exists who appears to be impaired on left sided hemispheric tasks (including the UPSIT). These patients are also young and have a lower premorbid IQ than all other patients. This particular group may have a neurodevelopmental form of schizophrenia which is different from the other groups as the left hemisphere is preferentially affected. A final group, those with right hemisphere abnormalities, is older and performs poorly on an olfactory discrimination task. Additional research is required to attempt to determine the meaning of the different subgroups.

An alternate framework in which to interpret the finding of the current study is within the context of hemispheric specificity for decoding emotion. Disturbance of affect and the inability

to interpret the emotions of others are common in schizophrenia (Edwards et al, 1997). The right hemisphere, particularly the temporal lobe, plays a major role in comprehension and expression of emotion (Tucker et al, 1995). Although schizophrenia has not been strongly thought of as a disorder of the right hemisphere (however, see Cutting, 1994), the right microsmic group may fit this category while left microsmia may represent defects in verbal associative function.

4. Suggestions for future research

The current study included only male patients with schizophrenia as a subgroup of males have been consistently shown to have olfactory deficits. As laterality has been shown to differ between men and women, and also in men and women who have schizophrenia, extending the current study to include women may provide information regarding gender differences in lateral organization of the brain.

That the olfactory groups differed on age deserves further study. In general, olfactory function declines monotonically with age after about the fifth decade. Roughly fifty percent of patients studied in the current study were experiencing their first hospitalization for psychotic symptoms and thus were in the early stages of the illness. All had been medicated for at least a month, but it is unknown whether unilateral olfactory deficits are present in male patients with schizophrenia before being exposed to antipsychotic agents. Studying first episode, drug naive patients with unirhinal olfactory techniques may shed some light on this issue.

The putative subgroups should be compared on measures which may be more sensitive to neurodevelopmental versus neurodegerative processes. A future study will assess brain changes over time (first episode and follow up) relating them to olfactory groups. In addition, measures of obstetrical complications will be added.

Zucco & Tressoldi (1988) designed a very interesting study which attempted to delineate hemispheric dominance for olfactory recognition. Using a tachistoscopic presentation of words or pictures, and presenting odours birhinally, they found that accuracy was better and latencies were shorter when stimuli were presented to the right hemisphere. This paradigm could be extended for use with patients with schizophrenia and normal control by presenting the olfactory stimuli unirhinally.

As neuroimaging techniques are becoming more sophisticated, a further extension of the current study would involve assessing structural or functional abnormalities in patients within each olfactory impairment group. Using magnetic resonance imaging (MRI), positron emission tomography (PET) or functional MRI, brain regions of interest (those which are involved in olfactory processing) could be visualized and functional capacity assessed and related to olfactory identification deficits. If the subgroups do have validity, it is possible that the neuropathological substrate may also differ within these subcategories.

It may also be interesting to test whether the right microsmic subgroup are impaired on a measure of emotional expression.

The results of the current study contributed to our understanding of olfactory function in healthy controls and in diseased states. The research design is unique and may provide a basis for further studies of schizophrenia and related disorders.

References

Abi-Dargham A, Jaskiw G, Suddath RL, & Weinberger DR. (1991). Evidence against progression of in vivo anatomical abnormalities in schizophrenia. Schizophrenia Research, 5(3), 210.

Abraham A, & Mathai KV. (1983). The effect of right temporal lobe lesions on matching smells. Neuropsychologia, 21(3), 277-281.

Akbraian S, Bunney WE, & Potkin SG. (1993). Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbance of cortical development. Archives of General Psychiatry, 50, 169-177.

American Psychiatric Association (1987). Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Press.

Amoore JE, Venstrom D, & Davis AR. (1968) Measurement of specific anosmia. Perceptual and Motor Skills, 33, 143-164.

Amsterdam JD, Settle RG, Doty RL, Abelman E, & Winokur A. (1987). Taste and smell perception in depression. Biological Psychiatry, 22, 1477-1481.

Anasari KA, & Johnson A. (1975). Olfactory function in patients with Parkinson's disease. Journal of Chronic diseases, 28, 493- 497.

Anderson SW, Damasio H, Jones RD, & Tranel D. (1991). Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. Journal of Clinical and Experimental Neuropsychology, 13(6), 909-922.

Andreasen NC, & Olsen S. (1982). Negative v positive Schizophrenia. Archives of General Psychiatry, 39, 789-794.

Andreasen NC, Rezai K, Alliger R, Swayze VW, Flaum M, Kirchner P, Cohen G, & O'Leary DS. (1992). Hypofrontality in neuroleptic- naive patients and patients with chronic schizophrenia. Archives of General Psychiatry, 49, 943-958.

Barta P, Pearlson G, Powers R, Richards S, & Tune L. (1990). Auditory hallucinations and smaller superior temporal gyral volumes in schizophrenia. American Journal of Psychiatry, 147, 1457-1462.

Barthold SW. (1988). Olfactory neural pathway in the mouse hepatitis virus nasoencephalitis. Acta Neuropathologica, 76, 502- 506.

Bartley AJ, Jones DW, Torrey EF, Zigun JR, & Weinberger DR. (1993). Sylvian fissure asymmetries in monozygotic twins: a test of laterality in schizoprhenia. Biological Psychiatry, 34, 853- 863.

Barton R (1959). Institutional Neurosis. Bristol: John Wright.

Benes FM, & Bird ED. (1987). An analysis of the arrangement of neurons in the cingulate cortex of schizophrenic patients. Archives of General Psychiatry, 44, 608-616.

Benes FM, Davidson J, & Bird ED. (1986). Quantitative cytoarchitechtural studies of the cerebral cortex of schizophrenia. Archives of General Psychiatry, 43, 31-35.

Benton AL. (1968). Differential behavioural effects in frontal lobe disease. Neuropsychologia, 6, 53-60.

Benton A (1974). A test of three dimentional constructural praxis: Manual. University of Iowa: Neurosensory Center Publication.

Bezchlibnyk-Butler KZ, & Jeffries JJ (1996). Clinical handbook of psychotropic drugs. Seattle: Hogrefe & Huber Publishers.

Bilder RM, Lipschutz-Broch L, Reiter G, Geisier SH, Mayerhoff DI, & Lieberman JA. (1992). Intellectual deficits in first- episode schizophrenia: Evidence for progressive deterioration. Schizophrenia Bulletin, 18(3), 437-448.

Blair J, & Spreen O. (1989). Predicting premorbid IQ: A revision of the National Adult Reading Test. Clinical Neuropsychologist, 3(2), 129-136.

Blanchard JJ, & Neale JM. (1994). The neuropsychological signature of schizophrenia: Generalized or differential deficit. American Journal of Psychiatry, 151(1), 40-48.

Bleuler E (1911; English translation J Zinken, 1950). Dementia Praecox, or the Group of Schizophrenias. New York: International Universities Press.

Bogen JE. (1993). The Callosal Syndromes. Heilman KM, & Valenstein E (Eds.), Clinical Neuropsychology (third edition), (pp. 337-406). New York: Oxford University Press.

Bogerts B, Hantsch J, & Herzer M. (1983). A morphometric study of the dopamine-containing cell groups in the mesencephalon of normals, Parkinson patients and schizophrenics. Biological Psychiatry, 18, 951-962.

Bogerts B, Meertz E, & Schonfeldt-Bausch R. (1985). Basal ganglia and limbic pathology in schizophrenia. Archives of General Psychiatry, 42, 784-791.

Bogerts B, Lieberman JA, Ashtari M, Bilder RM, Degreef G, Lerner G, Johns C, & Masiar S. (1993). Hippocampus-amygdala volumes and psychopathology in chronic schizophrenia. Biological Psychiatry, 33, 236-246.

Bornstein RA, Schwarzkopf SB, Olson SC, & Nasrallah HA. (1992). Third ventricle enlargement and neuropsychological deficit in schizophrenia. Biological Psychiatry, 31(9), 954-61.

Bradley EA. (1984). Olfactory acuity to a pheromonal substance and psychotic illness. Biological Psychiatry, 19, 899-905.

Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, & Zisook S. (1991). The generalized pattern of neuropsychological deficits in outpatients with chronic

schizophrenia with heterogeneous Wisconsin Card Sorting Test results. Archives of General Psychiatry, 48, 891-898.

Brewer WJ, Edwards J, Anderson V, Robinson T, & Pantelis C. (1996). Neuropsychological, olfactory, and hygiene deficits in men with negative symptom schizophrenia. Biological Psychiatry, 40, 1021-1031.

Brody D, Serby M, Etienne N, & Kalkstein DS. (1991). Olfactory identification deficits in HIV infection. American Journal of Psychiatry, 148, 248-250.

Bromley SM, & Doty RL. (1995). Odor recognition memory is better under bilateral than unilateral test conditions. Cortex, 31, 25-40.

Buck L, & Axel R. (1991). A novel multigene family may encode odorant receptors: A molecular basis for odor recognition. Cell, 65, 175-187.

Burns RS, Chiueh CC, & Market SP. (1983). A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by 1-methyl-4-phenyl-1,,2,3,6,-tetrahydropyridine. Proceedings from the National Academy of Sciences, 80, 4546-4550.

Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, Moberg P, & Price RA. (1994). Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. Archives of General Psychiatry, 51, 651-661.

Carroll B, Richardson JTE, & Thompson P. (1993). Olfactory information processing and temporal lobe epilepsy. Brain and Cognition, 22, 230-243.

Chobor KL. (1992). A neurolinguistic perspective of the study of olfaction. New York: Springer-Verlag.

Cornblatt BA, & Erlenmyer-Kimling L. (1985). Global attentional deviance in children at risk for schizophrenia: speicificity and predictive validity. Journal of Abnormal Psychology, 94, 470-486.

Corwin J, Serby M, Conrad P, & Rotrosen J. (1985). Olfactory recognition deficits in Alzheimer's and Parkinsonsian dementias. IRCS Medical Science, 13, 260.

Cowen MA, & Green M. (1993). The Kallmann's syndrome variant (KSV) model of the schizophrenias. Schizophrenia Research, 9, 1- 10.

Crow TJ. (1980). Molecular pathology of schizophrenia: More than one process? British Medial Journal, 280, 66-68.

Crow TJ, Ball J, Bloom SR, Brown R, Bruton CJ, Colter N, Frith CD, Johnstone EC, Owens DG, & Roberts GW. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry. Archives of General Psychiatry, 46, 1145-1150.

Cullum CM, Harris JG, Waldo MC, Smernoff E, Madison A, Nagamoto HT, Griffith J, Adler LE, & Freedman R. (1993). Neurophysiological and neuropsychological evidence for attentional dysfunction in schizophrenia. Schizophrenia Research, 10, 131-141.

Cutting JC (1994). Evidence for right hemisphere dysfunction in schizophrenia. in David AS, & Cutting JC (Eds), The Neuropsychology of Schizophrenia (pp. 231-242). Hillsdale: Lawrence Erlbaum Associates.

Dahlstrom A, & Fuxe K. (1964). Evidence for the existance of monamine containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiologica Scandinavica, 62(suppl.232), 1-55.

Davidson M, Keefe RS, Mohs RC, Siever LJ, Losonczy MF, Horvath TB, & Davis KL. (1987). L-dopa challenge and relapse in schizophrenia. American Journal of Psychiatry, 144, 934-938

Davies JD (1971). Phrenology: Fad and science. US: Yale University Press.

Degreef G, Ashtari M, Bogerts B, Bilder RM, Jody DN, Alvir JMJ, & Lieberman JA. (1992). Volumes of ventricular system subdivisions measured from magnetic resonsnce images in first-episode schizophrenic patients. Archives of General Psychiatry, 49, 531- 537.

DeLisi LE, Hoff AL, Kushner M, Calev A, & Stritzke P. (1992). Left ventricular enlargement associated with diagnostic outcome of schizophreniform disorder. Biological Psychiatry, 32, 199-201.

Delisi L, Hoff AL, Neale C, Kushner M. (1994). Asymmetries in the superior temporal lobe in male and female first episode patients: measures of the planum temporale and superior temporal gyrus by MRI. Schizophrenia Research, 12, 19-28

Doty, R. (1991). Olfactory dysfunction in neurodegenerative disorders. Getchell TV, Doty RL, Bartoshuk LM, & Snow JB (Eds.), Smell and Taste in Health and Disease Vol. Ch. 47, (pp. 735- 751). New York: Raven Press.

Doty RL, & Snow JB. (1987). Olfaction. Goldman J, The Principles and Practice of Rhinology (ch 45), (pp. 761-785). : John Wiley & Sons, INC.

Doty RL, & Agrawal U. (1989). The shelf life of the University of Pennsylvania Smell Identification Test (UPSIT). Laryngoscope, 99(4), 402-404.

Doty RL, & Kobal G. (1995). Current trends in the measurement of olfactory function. Doty RL (Ed.), Handbook of olfaction and olfaction, (pp. 191-225). New York: Marcel Decker, Inc.

Doty RL, Brugger WE, Jurs PC, Orndorff MA, Snyder PJ, & Lowry LD. (1978). Intranasal trigeminal stimulation from odorous volatiles: Psychometric responses from anosmic and normal humans. Physiology and Behavior, 20, 175-185.

Doty RL, Shaman P, & Dann M. (1984a). Development of the University of Pennsylvania Smell Test: A standardized microencapsulated test of olfactory function. Physiology and Behaviour, 32, 489-502.

Doty RL, Shaman P, Applebaum SL, Giberson R, Sikorski L, & Rosenberg L. (1984b). Smell identification ability: changes with age. Science, 226, 1441-1443.

Doty RL, Reyes PF, & Gregor T. (1987). Presence of both odor identification and detection deficts in Alzheimer's disease. Brain Research Bulletin, 18, 597-600.

Doty RL, Deems D, & Stellar S. (1988). Olfactory dysfunction in Parkinson's disease: A general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology, 38, 1237- 1244.

Doty RL, Riklan M, Deems DA, Reynolds C, & Stellar S. (1989a). The olfactory and cognitive deficits of Parkinson's disease: evidence for independence. Annals of Neurology, 25, 166-171.

Doty RL, Frye RE, & Agrawal U. (1989b). Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. Perception and Psychophysics, 45(4), 381-384.

Doty RL, Perl DP, Steele J, Chen KM, Pierce JD, Reyes P,& Kurland LT. (1991a). Odor identification deficit of the parkinsonism-dementia complex of Guam: Equivalence to that of Alzheimer's and idiopathic Parkinson's disease. Neurology, 41(suppl 2), 77-80.

Doty RL, Perl DP, Steele JC, Chen KM, Pierce JD, Reyes P, & Kurland LT. (1991b). Olfactory dysfunction in three neurodegenerative diseases. Geriatrics, 46(suppl 1), 47-51.

Doty R, Smith R, McKeown D, & Raj J. (1992a). Psychophysical tests of human olfactory function: Factor analytic evidence that most measure a common sensory domain. Chemical Senses,

Doty RL, Singh A, Tetrud J, & Langston JW. (1992b). Lack of major olfactory dysfunction in MPTP-induced Parkinsonism. Annals of Neurology, 32, 97-100.

Doty RL, Stern MB, Pfeiffer C, Gollomp SM, & Hurtig HI. (1992c). Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 55, 138-142.

Doty RL, Golbe LI, McKeown DA, Stern MB, Lehrach CM, & Crawford D. (1993). Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. Neurology, 43, 962-965.

Dunn TP, & Weller MP. (1989). Olfaction in schizophrenia. Perceptual and Motor skills, 69, 833-834.

Dvirski EA. (1976). Functional asymmetry of the cerebral hemispheres in clinical types of schizophrenia. Neuroscience and Behavioral Physiology, 7, 236-239.

Edwards J, Pattison PE, Jackson HJ, & Wales R. (1997). Emotion recognition in first-episode schizophrenia: facial expression, affective prosody and emotional names. Schizophrenia Research, 24(1-2), 101-102.

Eichenbaum H, Shedlack KJ, & Eckmann KW. (1980). Thalamocortical mechanisms in odor-guided behvavior. I. Effects of lesions of the mediodorsal thalamic nucleus and frontal cortex on olfactory discrmination in the rat. Brain, Behavior and Evolution, 17, 255- 275.

Eichenbaum H, Morton TH, Potter H, & Corkin S. (1983). Selective olfactory deficits in case HM. Brain, 106, 459-472.

Endicott J, Spitzer R, & Fleiss J. (1976). The Global Assessment Scale: a procedure for measuring overall sensitivity to psychiatric disturbance. Archives of General Psychiatry, 33, 766- 771.

Erlenmeyer-Kimling L. (1977). Issues pertaining to prevention and intervention in genetic disorders affecting human behavior. Albee GW, & Joffe JM (Eds.), Primary Prevention in Psychopathology, (pp. 68-91). Hanover, NH: University press of New England.

Eskenazi B, Cain WS, Novelly RA, & Friend KB. (1983). Olfactory functioning in temporal lobectomy patients. Neuropsychologia, 21(4), 365-374.

Eskenazi B, Cain WS, Novelly RA, & Mattson R. (1986). Odor perception in temporal lobe epilepsy patients with and without temporal lobectomy. Neuropsychologia, 24(4), 553-562.

Eskenazi B, Cain WS, Lipsitt ED, & Novelly RA. (1988). Olfactory functioning and callosotomy: A report of two cases. Yale Journal of Biology and Medicine, 61, 447-456.

Falkai P, & Bogerts B. (1986). Cell loss in the hippocampus of schizophrenics. European Journal of Psychiatry and Neurological Science, 236, 154-161.

Falkai P, Bogerts B, & Rozumek M. (1988). Limbic pathology in schizophrenia. The entorhinal region. A morphometric study. Biological Psychiatry, 24, 515-521.

Falkai P, Bogerts B, Greve B, Pfeiffer U, Machus B, Folsch-Reetz B, Majtenyi C, & Ovary I. (1992). Loss of sylvian fissure asymmetry in schizophrenia. A quantitative post mortem study. Schizophrenia Research, 7, 23-32.

Falkai P, Bogerts B, Schneider T, Greve B, Pfeiffer U, Pilz K, Gonsiorzeyk C, Majtenyi C, & Ovary I. (1995). Disturbed planum temporale asymmetry in schizophrenia. A quantitative post-mortem study. Schizophrenia Research, 14(2), 161-176.

Fedoroff IC, Stoner SA, Anderson AE, Doty RL, & Rolls BJ. (1995). Olfactory dysfunction in anorexia and bulimia nervosa . International Journal of Eating Disorders, 18(1), 71-77.

Fleminger JJ, Dalton R, & Standage KF. (1977). Handedness in psychiatric patients. British Journal of Psychiatry, 131, 448-452.

Flor-Henry P. (1969). Schizophrenia-like reactions and affective psychoses associated with temporal lobe epilepsy: etiological factors. American Journal of Psychiatry, 126, 400-403.

Frye RE, Schwartx BS, & Doty RL. (1990). Dose-related effects of cigarette smoking on olfactory function. Journal of the American Medical Association, 263(9), 1233-1236.

Fukuzako H, Fukuzako T, & Hashiguchi T. (1996). Reduction in hippocampal formation is caused mainly by its shortening in chronic schizophrenia: assessment by MRI. Biological Psychiatry, 39, 938-945.

Galaburda AM, Sanides F, & Geschwind N. (1978). Human brain: cytoarchitectonic left-right asymmetries in the temporal speech area. Archives of Neurology, 35, 812-817.

Geschwind N, & Levitsky W. (1968). Human brain: left-right asymmetries in temporal speech regions. Science, 161, 186-187.

Geschwind N, & Galaburda A (1987). Cerebral lateralization: Biological mechanisms. Cambridge MA: MIT Press.

Goldberg TE, & Weinberger DR. (1988). Probing prefrontal function in schizophrenia with neuropsycholgical paradigms. Schizophrenia Bulletin, 14(2), 179-183.

Goldberg TE, & Gold JM. (1995). Neurocognitive deficits in schizophrenia. Hirsch SR, & Weinberger DR (Eds), Schizophrenia, (pp. 146-162). Oxford: Blackwell Science Ltd.

Goldberg ED, Goldberg RJ, & Vannoppen B. (1991). Sense of smell and obsessional behaviour. American Journal of Psychiatry, 148(12), 1757.

Goldstein G. (1978). Cognitive and perceptual differences between schizophrenics and organics. Schizophrenia Bulletin, 4, 160-185.

Goldstein G, Zubin J, & Pogue-Geile MF. (1991). Hospitalization and the cognitive deficits of schizophrenia: The influences of age and education. The Journal of Nervous and Mental Disease, 179, 202-206.

Good KP, Martzke JS, Honer WG, Kopala LC. Stability of olfactory deficits in first-episode, neuroleptic naive patients with schizophrenia. In preparation.

Gordon HW, & Sperry RW. (1969). Lateralization of olfactory perception in the surgically separarated hemispheres of man. Neuropsychologia, 7, 111-120.

Gottesman II (1991). Schizophrenia genesis: The origins of madness. New York: WH Freeman.

Gross-Isseroff R, Luca-Haimovici K, Sasson Y, Kindler S, Kotler M, & Zohar J. (1994). Olfactory sensitivity in major depressive disorder and obsessive compulsive disorder . Biological Psychiatry, 35, 798-802.

Gruzelier J, Seymour K, Wilson L, Jolley A, & Hirsch S. (1988). Impairments on neuropsychological tests of temporohippocampal and frontohippocampal functions and word fluency in remitting schizophrenia and affective disorders. Archives of General Psychiatry, 45, 623-629.

Gur RE. (1977). Motoric laterality imbalance in schizophrenia. A possible concomitant of left hemisphere dysfunction . Archives of General Psychiatry, 34, 33-37.

Gur R, Mozley D, Resnick S, Shtasel D, Kohn M, Zimmerman R, Herman G, Atlas S, Grossman R, Erwin R, & Gur R. (1991). Magnetic resonance imaging in schizophrenia. Archives of general psychiatry, 48, 407-412.

Hare EH. (1987). Epidemiology of schizophrenia and affective psychoses. British Medical Bulletin, 43(3), 514-530.

Harrison PJ. (1986). The pathogenesis of Alzheimer's disease: Beyond the cholinergic hypothesis. Journal of the Royal Society of Medicine, 79, 347-352.

Heaton RK, Boade LE, & Johnson KL. (1978). Neuropsychological test results associated with psychiatric disorders in adults. Psychology Bulletin, 85, 141-162.

Hecker E. (1871). Die Hebephrenie. Arch Pathol Anat Physiol Klin Med, 52, 394-409.

Helmdal P, & Corwin S. (1989). Olfactory identification in Down's syndrome. Journal of Clinical and Experimental Neuropsychology, 11, 65.

Helmdal P, Corwin J, & Oster H. (1993). Olfactory identification in Down's Syndrome and idiopathic mental retardation. Neuropsychologia, 31(9), 977-984.

Henkin RI, Comiter H, Fedio P, & O'Doherty D. (1977). Defects in taste and smell recognition following temporal lobectomy. Transactions of the American Neurological Association, 102, 146- 150.

Hoff AL, Riordan H, O'Donnell D, Stritzke P, Neale C, Boccio A, Anand AK, & DeLisi LE. (1992). Anomalous lateral sulcus asymmetry and cognitive function in first-episode schizophrenia. Schizophrenia Bulletin, 18(2), 257-269.

Honer WG, Bassett AS, Squires-Wheeler E, Falkai P, Smith GN, Lapointe JS, Canero C, & Lang M. (1995). The temporal lobes, reversed asymmetry and the genetics of schizophrenia. Neuroreport, 7, 221-224.

Hornung DE, Leopold DA, Mozell MM, Sheehe PR, & Youngentob SL. (1990). Impact of left and right nostril olfactory abilities on binasal olfactory performance. Chemical Senses, 15(2), 233-237.

Houlihan DJ, Flaum M, Arnold SE, Keshavan M, & Alliger R. (1994). Further evidence for olfactory identification deficits in schizophrenia. Schizophrenia Research, 12, 179-182.

Howell DC. (1987) Statistical Methods for Psychology. Boston Mass: PWS-Kent Publishing company.

Hudson R, Laska M, Berger T, Heye B, Schopohl J, & Danek A. (1994). Olfactory function in patients with hypogonadotropic hypogonadism: an all-or-none phenomenon? Chemical Senses, 19(1), 57-69.

Hurwitz T, Kopala L, Clark C, & Jones B. (1988). Olfactory deficits in schizophrenia. Biological Psychiatry, 23, 123-128.

Illowsky BP, Juliano DM, Bigelow LB, & Weinberger DR. (1988). Stability of CT scan findings in schizophrenia: results of an 8 year follow up study. Journal of Neurology, Neurosurgery and Psychiatry, 51, 209-213.

Isseroff GR, Stoler M, Ophir D, Lancet D, & Sirota P. (1987). Olfactory sensitivity to androstenone in schizophrenic patients . Biological Psychiatry, 22, 922-925.

Jakob H, & Beckmann H. (1994). Circumscirbed malformations and nerve cell alterations in the entorhinal cortex of schizophrenics: pathologenetic and clinical aspects. Journal of Neural Transmission, Genetics Section, 98,83-106.

Jernigan T, Zisook S, Heaton R, Moranville J, Hesselink J, & Braff D. (1991). Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. Archives of General Psychiatry, 48, 881-890.

Johnstone E, Crow T, Frith C, Husband J, & Kreel L. (1976). Cerebral ventricual size and cognitive impairment in chronic schizophrenia. Lancet, 2, 924-926.

Jones-Gotman M, & Milner B. (1977). Design Fluency: The invention of nonsense drawings after focal cortical lesions. Neuropsychologia, 15, 653-674.

Jones-Gotman M, & Zatorre RJ. (1988a). Contribution of the right temporal lobe to odor memory . Epilepsia, 29, 661.

Jones-Gotman M, & Zatorre RJ. (1988b). Olfactory identification deficits in patients with focal cerebral excision. Neuropsychologia, 26(3), 387-400.

Jones-Gotman M, & Zatorre RJ. (1993). Odor recognition memory in humans: Role of right temporal and orbitofrontal regions. Brain and Cognition, 22(182-198),

Kandel ER, & Schwartz JH (1985). Principles of Neural Science. New York: Elsevier.

Kay S, Fiszbein A, & Opler L. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizoprhenia Bulletin, 13, 262-275.

Kelsoe J, Cadet J, Pickar D, & Weinberger D. (1988). Neuroanatomy in schizophrenia: a controlled magnetic resonance imaging study. Archives of General Psychiatry, 45, 533-541.

Kendler KS, Gruenberg AM, & Tsuang MT. (1985). Psychiatric illness in first degree relatives of schizophrenic and surgical control patients. Archives of General Psychiatry, 42, 770-779.

Kesslak JP, Cotman CW, Chui HC, van den Noort S, Fang H, Pfeffer R, & Lynch G. (1988). Olfactory tests as possible probes for detecting Alzheimer's disease. Neurobiology of Aging, 9, 399-403.

Kety SS. (1988). Schizophrenic illness in the families of schizophrenic adoptees: findings from the Danish national sample. Schizophrenia Bulletin, 14, 217-222.

Kimura D. (1967). Functional asymmetry of the brain in dichotic listening. Cortex, 3, 163-178.

Knupfer L, & Spiegel R. (1986). Differences in olfactory test performance between normal aged, Alzheimer and vascular type dementia. International Journal of Geriatric Psychiatry, 1, 3-14.

Kolb B, & Wishaw IQ. (1983). Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. The Journal of Nervous and Mental Disease, 171(7), 435-443.

Kopala L, & Clark C. (1990). Implications of olfactory agnosia for understanding sex differences in schizophrenia. Schizophrenia Bulletin, 16(2), 255-261.

Kopala LC, & Good KP. (1996) Olfactory identification ability in patients with panic disorder. Journal of Psychiatry and Neuroscience

Kopala L, Clark C, & Hurwitz TA. (1989). Sex differences in olfactory function in schizophrenia. American Journal of Psychiatry, 146, 1320-1322.

Kopala L, Clark C, & Hurwitz T. (1992). Olfactory deficits in neuroleptic naive patients with schizophrenia. Schizophrenia Research, 8, 245-250.

Kopala L, Good K, & Honer WG. (1994). Olfactory hallucinations and olfactory identification ability in patients with schizophrenia and other psychiatric disorders. Schizophrenia Research, 12, 205-211.

Kopala LC, Good K, Goldner EM, & Birmingham CL. (1995a). Olfactory identification ability in anorexia nervosa. Journal of Psychiatry and Neuroscience, 20(4), 283-286.

Kopala LC, Good K, & Honer WG. (1995b). Olfactory identification ability in pre- and postmenopausal women with schizophrenia. Biological Psychiatry, 38, 57-63.

Kopala L, Good K, Martzke J, & Hurwitz T. (1995c). Olfactory deficits in schizophrenia are not a function of task complexity. Schizophrenia Research, 17, 195-199.

Kopala LC, Good, KP Good, Koczapski AB, & Honer WG. Olfactory deficits in patients with schizophrenia and severe polydipsia (in submission, Biological Psychiatry).

Koss E, Wieffenbach JM, Haxby JV, & Friedland RP. (1987). Olfactory detection and recognition in Alzheimer's disease. Lancet, 14, 622.

Koss E, Weiffenbach JM, Haxby JV, & Friedland RP. (1988). Olfactory detection and identification performance are dissociated in early Alzheimer's disease. Neurology, 38, 1228- 1232.

Kovelman JA, & Scheibel AB. (1984). A neurohistological correlate of schizophrenia. Biological Psychiatry, 19(12), 1601-1621.

Kraepelin E (1902; English translation by AR Diefendorf, 1907). Clinical Psychiatry. New York: MacMillen.

Lanza DC, Moran DT, Doty RL, Trojanowski JQ, Lee JH, Rowley JC, Crawford D, & Kennedy DW. (1993). Endoscopic human olfactory biopsy technique: A preliminary report. Laryngoscope, 103, 815-819.

Lehrner J, Brucke T, Kryspin-Exner I, Asenbaum S, & Podreka I. (1995). Impaired olfactory function in Parkinson's disease. Lancet, 345, 1054-1055.

Levin HS, High WM, & Eisenberg HM. (1985). Impairment of olfactory recognition after closed head injury. Brain, 108, 579- 591.

Lewine R. (1988). Gender and Schizophrenia. Tsuang M, & Simpson J (Eds), Handbook of Schizophrenia Vol. 3, (pp. 379-203). : Elsevier Science Press.

Lewine RJ, & Seeman MV. (1995). Gender, brain and schizophrenia: anatomy of differences/differences of anatomy. Seeman MV, Gender and Psychopathology,Washington, DC: APA Press.

Lewine R, Hudgins P, Brown F, Caudle J, & Risch SC. (1995). Differences in qualitative brain morpholology findings in schizophrenia, major depression, bipolar disorders and normal volunteers. Schizophrenia Research, 15, 253-259.

Lewis S. (1996). Structural brain imaging in biological psychiatry. British Medical Bulletin, 52, 465-473.

Lezak MD (1983). Neuropsychological Assessment. New York: Oxford University Press.

Liddle PF. (1987). The symptoms of chronic schizophrenia. A re- examination of the positive-negative dichotomy. British Journal of Psychiatry, 151, 145-151.

Liddle PF, & Morris DL. (1991). Schizophrenic syndromes and frontal lobe performance. British Journal of Psychiatry, 158, 340-345.

Liddle PF, Friston KJ, Frith CD, & Frakowiak RS. (1992). Cerebral blood flow and mental processes in schizophrenia. Journal of the Royal Society of Medicine, 85, 224-227.

Lieberman J, Bogerts B, & Degreef G. (1992). Qualitative assessment of brian morphology in acute and chronic schizophrenia. American Journal of Psychiatry, 149, 784-794.

Lindstrom E, & von Knorring L. (1994). Changes in single symptoms and separate factors of the schizophrenic syndrome after treatment with risperidone or haloperidol. Pharmacopsychiatry, 27, 108-113.

Malaspina D, Wray AD, Friedman JH, Amador X, Yale S, Hasan A, Gorman JM, & Kaufmann CA. (1994). Odor discrimination deficits in schizophrenia: Association with eye movement dysfunction. Journal of Neuropsychiatry and Clinical Neuroscience, 6, 273-278.

Maneros A. (1993). Editorial. Triangle, 31(4), 123-125.

Martinez BA, Cain WS, de Wijk RA, Spencer DD, Novelly RA, & Sass KJ. (1993). Olfactory functioning before and after temporal lobe resection for intractable seizures. Neuropsychology, 7, 351-363.

Martzke JS, Swan CS, & Varney NR. (1991). Posttraumatic anosmia and orbital frontal damage: Neuropsychological and neurospychiatric correlates. Neuropsychology, 5(3), 213-225.

Martzke JS, Kopala LC, & Good KP. Olfactory dysfunction in neuropsychiatric disorders: review and methodological considerations. Biological Psychiatry (in press).

Milner B. (1963). Effects of different brain lesions on card sorting. Archives of Neurology, 9, 90-100.

Moberg RJ, Pearlson GD, Speedie LJ, Lipsey JR, Strauss ME, & Folstein SE. (1987). Olfactory recognition: Differential impairments in early and late Huntington's and Alzheimer's Diseases. Journal of Clinical and Experimental Neuropsychology, 9, 650-664.

Moore-Gillon V. (1987). Testing the sense of smell. British Medical Journal, 294, 793-794.

Morgan CD, Nordin S, & Murphy C. (1995). Odor identification as an early marker for Alzheimer's disease: Impact of lexical functioning and detection sensitivity. Journal of Clinical and Experimental Neuropsychology, 17(5), 793-803.

Morrison-Stewart SL, Williamson PC, Corning WC, Kutcher SP, Snow WG, & Merskey H. (1992). Frontal and non-frontal lobe neuropsychological test performance and clinical symptomatology in schizophrenia. Psychological Medicine, 22, 353-359.

Moscovitch M, & Klein D. (1980). Material-specific perceptual interference for visual words and faces: Implications for models of capacity limitations, attention and laterality. Journal of Experimental Psychology: Human Perception and Performance, 6(3), 590-604.

Murphy C, Gilmore MM, Seery CS, Salmon DP, & Lasker BR. (1990). Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. Neurobiology of Aging, 11, 465-469.

Nasrallah AH, Keelor K, van Shroeder C, & Whitters MN. (1981). Motoric lateralization in schizophrenic males. American Journal of Psychiatry, 138, 1114-1115.

Nelson HE, & O'Connell A. (1978). Dementia: The estimation of premorbid intelligence using the new adult reading test. Cortex, 14, 234-244.

Ngai J, Dowling MM, Buck L, Axel R, & Chess A. (1993). The family of genes encoding odorant receptors in the channel catfish. Cell, 72, 657-666.

Nordin S, & Murphy C. (1996). Impaired sensory and cognitive olfactory function in questionable Alzheimer's disease. Neuropsychology, 10(1), 113-119.

Nordin S, Paulsen JS, & Murphy C. (1995). Sensory- and memory- mediated olfactory dysfunction in Huntington's disease. Journal of the International Neuropsychological Society, 1, 281-290.

O'Callaghan E, Redmond O, & Ennis J. (1992). Abnormalities of cerebral structure in schizophrenia on magnetic resonance imaging: Interpretation in relation to the neurodevelopmental hypothesis. Journal of the Royal Society of Medicine, 85, 227- 231.

Oldfield RC. (1971). The assessment and analysis of handedness. The Edinburgh Inventory. Neuropsychologia, 9, 97-113.

Pakkenberg B. (1990). Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. Archives of General Psychiatry, 47, 1023-1028.

Pansky B, & Allan D (1980). Review of Neuroscience. New York: MacMillan Press.

Pendse SG. (1987). Hemispheric asymmetry in olfaction on a categorical judgement task. Perceptual and Motor Skills, 64, 495- 498.

Perl DP, & Good PF. (1991). Aluminium, Alzheimer's disease and the olfactory system. Annals of the New York Academyn of Science, 640, 8-13.

Petty RG, Barta PE, Pearlson GD, McGilchrist IK, Lewis RW, Tien AY, Pulver A, Vaughn DD, Casanova MF, & Powers RE. (1995). Reversal of asymmetry of the planum temporale in schizophrenia. American Journal of Psychiatry, 152(5), 715-721.

Pfefferbaum A, Zipursky RB, Lim KO, Zatz LM, Stahl SM, & Jernigan TL. (1988a). Computed tomographic evidence for generalized sulcal and ventricular enlargement in schizophrenia. Archives of General Psychiatry, 45, 633-640.

Pfefferbaum A, Rosenbloom M, Crusan K, & Jernigan TL. (1988b). Brain CT changes in alcoholics: effects of age and alcohol consumption. Alcohol Clinical and Experimental Research, 12, 81-87.

Pivik RT, & Young S. (1994). Schizophrenia Research: Time for a national strategy. Journal of Psychiatry and Neuroscience, 15(5(suppl. 1)), 2-5.

Potter H, & Nauta WJH. (1979). A note on the problem of olfactory associations of the orbitofrontal cortex in the monkey. Neuroscience, 4, 361-367.

Potter H, & Butters N. (1980). An assessment of olfactory deficits in patients with damage to prefrontal cortex. Neuropsychologia, 18, 621-628.

Prudo R, & Blum H. (1987). Five year outcome and prognosis in schizophrenia. A report from the London Field Research Centre of the International Pilot Study of Schizophrenia. British Journal of Psychiatry, 150, 345-354.

Quinn NP, Rossor MN, & Marsden CD. (1987). Olfactory threshold in Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry, 50, 88-89.

Randolph C, Goldberg TE, & Weinberger DR. (1993). The neuropsychology of schizophrenia. Heilman and Valenstein (Eds), Clinical Neuropsychology (3rd ed),: Oxford Press.

Rausch R, & Serafetinides EA. (1975). Specific alterations of olfactory function in humans with temporal lobe lesions. Nature, 225, 557-558.

Rausch R, Serafetinides, & Crandall PH. (1977). Olfactory memory in patients with anterior temporal lobectomy. Cortex, 13, 445- 452.

Raz S, & Raz N. (1990). Structural brain abnormalities in the major psychoses: a quantitative review of the evidence from computerized imaging. Psychological Bulletin, 108, 93-108.

Reynolds G. (1983). Decreased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. Nature, 305, 527-529.

Rezek DL. (1987). Olfactory deficits as a neurological sign in dementia of the Alzheimer type. Archives of Neurology, 44, 1030-1032.

Rubens AB, & Mahowald MW. (1976). Asymmetry of lateral (Sylvian) fissures in man. Neurology, 26, 620-624.

Ruberg M, Javoy-Agrid F, & Hirsch E. (1985). Dopaminergic and cholinergic lesions in progressive supranuclear palsy. Annals of Neurology, 18, 523-529.

Rushton WAH. (1955). Foveal photopigments in normal and colourblind. Journal of Physiology, 129, 41-42.

Russell GF, & Hills JI. (1971). Odor differences between enantiomeric isomers. Science, 172(987), 1043-1044.

Satz P. (1972). Pathological left handedness: An explanatory model. Cortex, 8, 121-135.

Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, & Stafiniak P. (1991). Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Archives of General Psychiatry, 48, 618-624.

Saykin AJ, Shtasel D, Gur RE, Kester DB, Mozley LH, Stafiniak P, & Gur RC. (1994). Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Archives of General Psychiatry, 51, 124-131.

Schubart C, Krumm B, Biehl H, & Schwarts R. (1986). Measurement of social disability in a schizophrenic patient group. Definition, assessment and outcome over 2 years in a cohort of schizophrenic patients of recent onset. Social Psychiatry, 21(1), 1-9.

Seeman P, Wong M, & Lee T. (1974). Dopamine receptor block and nigral fibre impulse blockade by major tranquilizers. Federations Proceedings, 33, 246.

Seidman LJ, Talbot NL, Kalinowski AG, McCarley RV, Faraone SV, Kremen WS, Pepple JR, & Tsuang MT. (1992). Neuropsychological probes of fronto-limbic system dysfunction in schizophrenia. Schizophrenia Research, 6, 55-65.

Serby M, Larson P, & Kalkstein D. (1990). Olfactory sense in the psychoses. Biological Psychiatry, 28, 830.

Serby M, Larson P, & Kalkstein D. (1991). The nature and course of olfactory deficits in Alzheimer's disease. American Journal of Psychiatry, 148(3), 357-360.

Shapiro RM. (1993). Regional neuropathology in schizophrenia: Where are we? Where are we going. Schizophrenia Research, 10, 187-239.

Shenton ME, Kikinis R, Jolesz FA, Pollak SP, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, & McCarley RW. (1992). Abnormalities of the left temporal lobe and thought disorder in schizophrenia. The New England Journal of Medicine, 327(9), 604- 612.

Silver J, Yudofsky S, & Hale RE. (1994). Neuropsychiatry of traumatic brain injury. New York: American Psychiatric Press Inc. (page 59).

Slotnick BM, & Schoonover FM. (1992). Olfactory pathways and the sense of smell. Neuroscience and biobehavioral reviews, 16, 453- 472.

Sperry RW (1968). Mental unity following surgical disconnection of the cerebral hemispheres. New York: Academic Press.

Spitzer M, Seyyedi S, & Schiementz C. (1993). Pronounced right hemisphere advantage in schizophrenic patients performing a face matching task. Schizophrenia Research, 188.

Spohn HE, & Strauss ME. (1989). Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. Journal of Abnormal Psychology, 98(4), 367-380.

Sreenivasan KV, Abraham A, & Verghese A. (1987). Right temporal lobe functions in psychiatric disorders. Indian Journal of Clinical Psychology, 14, 40-42.

Strauss ME. (1994). Olfactory memory deficits in schizophrenia: differential deficit or psychometric artifact. Schizophrenia Research, 12, 89-90.

Strauss ME, Buchanan RW, & Hale J. (1993). Relations between attentional deficits and clinical symptoms in schizophrenia outpatients. Psychiatry Research, 47, 205-213.

Suddath RL, Casanova MF, Goldberg TE, Daniel DG, Kelsoe JR, & Weinberger DR. (1989). Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. American Journal of Psychiatry, 146(4), 464-472.

Suddath R, Christison G, & Torrey E, Casanova MF, & Weinberger DR. (1990). Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. New England Journal of Medicine, 322, 789-794.

Sweeney JA, Haas GL, Kelip JG, & Long M. (1991). Evaluation of the stability of neuropsychological functioning after acure episode of schizophrenia: one year followup study. Psychiatry Research, 38, 63-76.

Tanabe T, Yarita H, IIno M, Ooshima Y, & Takagi SF. (1975). An olfactory projection area in orbitofrontal cortex of the monkey. Journal of Neurophysiology, 38, 1269-1283.

Teuber H. (1955). Physiological Psychology. Annual Review of Psychology, 6, 267-296.

Tucker DM, Luu P, Pribram KH. (1995). Social and emotional self-regulation. Annals of the New York Academy of Sciences, 769, 213-239.

Wada J, & Rasmussen TR. (1960). Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. Journal of Neurosurgery, 17, 266-272.

Wahl FO. (1976). Handedness in schizophrenia. Perceptual and Motor Skills, 42, 944-946.

Waldton S. (1974). Clincial observations of impaired cranial nerve function in senile dementia. Acta Psychiatrica Scandinavica, 50, 539-547.

Walsh K (1985). Neuropsychology: A clinical Approach. Edinburgh: Churchill Livinstone.

Ward, C., Hess, W., & Calne, D. (1983). Olfactory impairment in Parkinson's disease. Neurology, 33, 943-946.

Warner MD, Peabody CA, Flattery JJ, & Tinklenberg JR. (1986). Olfactory deficits and Alzheimer's disease. Biological Psychiatry, 21, 116-118.

Warner, M., Peabody, C., & Berger, P. (1988). Olfactory deficits and Down's Syndrome. Biological Psychiatry, 23, 836-839.

Warner, M., Peabody, C., & Csernansky, J. (1990). Olfactory functioning in schizophrenia and depression. Biological Psychiatry, 27, 457-467.

Weinberger DR. (1987). Implications of normal brain development for the pathogenisis of schizophrenia. Archives of General Psychiatry, 44, 660-669.

Weinberger DR, Berman KF, & Zec RF. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. Archives of General Psychiatry, 43, 114-124.

West SE, Doty RL, O'Connor MJ, & Sperling MR. (1993). Pre- and post-operative studies of olfactory function in patients with anterior temporal lobectomy. Chemical Senses, 18, 649.

Wing JK, & Brown GW (1970). Institutionalization and schizophrenia. London: Cambridge University Press.

World Health Organization (1979). Schizophrenia: an international follow up study. Chichester: Jonh Wiley.

Wu J, Buchsbaum M, Moy K, Denlea N, Kesslak P, Tseng H, Plosnaj D, Hetu M, Potkin S, Bracha S, & Cotman C. (1993). Olfactory memory in unmedicated schizophrenics. Schizophrenia Research, 9, 41-47.

Yoshida M. (1984). Correlation analysis of detection threshold data for "standard test" odors. Bull Fac Sci Eng Chuo Univ, 27, 343-353.

Youssem DM, Turner WJ, Li C, Snyder PJ, & Doty RL. (1993). Kallmann Syndrome: MR evaluation of olfactory system. American Journal of Neuroradiology, 14, 839-843.

Zatorre RJ, & Jones-Gotman M. (1990). Right nostril advantage for discrimination of odors. Perception and Psychophysics, 47(6), 526-531.

Zatorre RJ, & Jones-Gotman M. (1991). Human olfactory discrimination after unilateral frontal or temporal lobectomy. Brain, 114, 71-84.

Zucco GM, & Tressoldi PE. (1988). Hemispheric differences in odor recognition. Cortex, 25, 607-615.

Appendix A: Modified Hollingshead socioeconomic status rating scale (A. Bassett, personal communication)

Rating	Status
1	Higher executive: owner/manager large business, professional (MD, CPA, lawyer, engineer, professor)
2	Medium executive: owner/manager medium business, other professional (RN, MSW, teacher, programmer)
3	Middle management: owner/manager small business, semi-professional (computer operator, surveyor)
4	Lower administrative, technical, supervisory (bookkeeper, head typist, sales, draftsman)
5	Skilled manual labour (typist, cashier, machinist, carpenter, hair stylist, complex machine operator)
6	Semi-skilled manual labour (receptionist, waitress, apprentice, taxi driver, machine operator)
7	Unskilled labour (factory worker, messenger, cleaner, farm helper, baby-sitter)
8	Unemployed/homemaker
9	Unknown

Appendix B: Definitions for common olfactory tasks used

Term	Definition
Acuity (detection threshold)	A measure of the lowest concentration of a particular olfactory stimulus required to activate the receptor neurons resulting in the detection of that odour.
Odour Identification	A measure of an individual's ability to perceive and name an odorant. Three types are common: a simple naming task where the subject must supply a name for the given odorant; a yes-no odour identification test where the subject must decide whether the odour presented matches the verbal label "is this a skunk?"; or multiple choice odour identification test (UPSIT) in which a list of odour names is provided for each stimulus.
Odour Discrimination	A measure of an individual's ability to differentiate between a set of odorants. The simplest form is to state whether two odours are the same or different. A common task involves having the subject pick the odd odour out of a series of odorants, all of which are identical except for one. Accurate performance on these tasks requires intact acuity but not identification (or naming) of the odorant.
Odour Recognition	A measure of an individual's ability to ascertain whether the odour is familiar to him/her. Correct identification is not required. The simplest type requires the subject to state whether a stimulus has ever been experienced.
Odour Memory	A similar measure to the odour quality recognition task in which a stimulus is presented to the subject. After a short or long delay, the subject is required to pick the target odorant from a series of odours presented.

Appendix C: Sample size calculations

Using preliminary patient data on unirhinal UPSIT, (n=5), a mean left-right difference between patients and controls of 1.3 with a standard deviation of 1.7 was observed. The effect size formula is below:

$$\gamma = \frac{\mu_1 - \mu_2}{\sigma}$$

$$\gamma = \frac{1.3}{1.7} = .76$$

For a power of .80, tabled values (Howell, 1987) projects the δ as 2.8. The power calculation formula is shown below

$$\delta = \gamma\sqrt{\frac{n}{2}} \quad \text{or rearranged } n = 2\left(\frac{\delta}{\gamma}\right)^2 \text{ or } n = 2\left(\frac{2.8}{.76}\right)^2$$

$$n = 27.1 \text{ per group}$$

But, patient to normal control subject recruitment is, on average, 2:1. Therefore, $n=n_h$ (harmonic n) can be used to calculate the number of subjects per group when the group sizes are uneven.

$$n_h = \frac{2n_1n_2}{n_1 + n_2}$$ and since $n_1=2n_2$ and $n_h= 27.1$

Then, $$27.1 = \frac{2(2n_2)n_2}{(2n_2)+n_2} = \frac{4n_2^2}{3n_2}$$

Or: $n_2= 20$ and $n_1 =40$

(All equations from Howell, 1987)