MINOR PHYSICAL ANOMALIES AND NEUROPSYCHOLOGICAL PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

by

ANNE-MARIE DONOVAN

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Executive Officer

Howard Ehrlichman, Ph.D.

Richard Bodnar, Ph.D.

Pál Czobor, Ph. D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

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ANNE-MARIE DONOVAN

Advisor: Judith Jaeger, Ph.D.

Individuals meeting conventional diagnostic criteria for schizophrenia comprise a largely heterogeneous group in terms of patterns of clinical course, outcome, neuropsychological performance, family history of mental illness, severity of disability and presence of brain abnormalities. It would seem that a valid classification system for schizophrenia should take these characteristics of illness into account. Over the past fifteen years, the neurodevelopmental model of schizophrenia has emerged; this model proposes the existence of a congenital subtype of schizophrenia in which the putative insult resulting in the illness is from either a genetic predisposition or early environmental hazard occurring at an early point of neurodevelopment. Individuals with this subtype are thought to have an early age of illness onset, insidious onset of illness, poor premorbid cognitive functioning, negative symptoms, cognitive impairment and brain abnormalities. The putative insult causing the illness can also cause minor physical anomalies (MPAs) such as minor abnormalities of the head, face, feet and hands that are of little of no functional or cosmetic consequence. This study explored whether ratings of physical anomalies and craniofacial measurements can distinguish between healthy adults and those with schizophrenia or schizoaffective disorder. Patients had significantly more minor physical anomalies than healthy control subjects. The width of the skull base was significantly greater in patients than in normal control subjects. However, ratings of physical anomalies and craniofacial measurements were not clearly related to putative markers of a congenital subtype including earlier age of onset, poor life functioning and lower scores on neurocognitive tests.

Table of Contents

List of Tables

List of Figures

Introduction

The neurodevelopmental model of schizophrenia proposes that some individuals diagnosed with schizophrenia or schizoaffective disorder have a congenital form of the illness with relatively gross brain abnormalities present at or near birth. Characteristics of this form of illness include poor premorbid functioning and early age of onset. This study explores the degree to which minor physical anomalies (MPAs; subtle differences in physical structures primarily of the head and face) can differentiate schizophrenic and schizoaffective disorder patients with characteristics of a congenital form of illness from those who do not exhibit characteristics of this form of illness. Finding such a relationship may lead to the development of better diagnostic techniques. First, the neurodevelopmental model will be described. Evidence for the neurodevelopmental model is discussed. Finally, MPAs are discussed in terms of their utility in differentiating a neurodevelopmental subtype of schizophrenia.

Purpose of the Research

There were three overall goals of this study. The first was to improve upon current methods of assessing physical deviation. The second goal of this study was to validate the new methods of assessing physical deviation. It is anticipated that objective measurements of the face and head will be more sensitive, relative to rating scales, to the greater physical deviance reported in patients with schizophrenia relative to healthy controls. The third overall goal was to determine if this new method of assessing physical deviance could distinguish a neurodevelopmental subtype among patients with schizophrenia and schizoaffective disorder. It is predicted that increased physical deviance would be associated with other putative indicators of a congenital subtype of schizophrenia including poor cognitive functioning and earlier age of onset.

Heterogeneity of Schizophrenia

Approximately 1% of the population suffers from schizophrenia. Individuals meeting conventional diagnostic criteria for schizophrenia comprise a largely heterogeneous group (American Psychiatric Association, 1994). In order to capture this striking heterogeneity, subtypes are often identified (American Psychiatric Association, 1994, Farmer et al., 1983). However these subtypes are distinguished on the basis of symptoms alone. Examples include the Dignostic and Statistical Manual's (fourth edition) three subtypes (paranoid subtype, catatonic subtype and disorganized subtype) (American Psychiatric Association, 1994), paranoid versus non paranoid types (Nasrallah et al., 1982a; Nasrallah et al., 1982b) process schizophrenia versus reactive schizophrenia (Harrow et al., 1986; Schultz et al., 1979) and 'primarily positive' versus 'primarily negative' symptom subtypes (Garmezy et al., 1959). However, individuals do not simply differ in terms of symptom profiles; they also differ in patterns of clinical course (Carpenter et al., 1988), outcome (Angermeyer et al., 1990; Hafner, H., 1998), neuropsychological performance (Lewine et al., 1996), family history of mental illness (Murray et al., 1992a, 1998), severity of disability (Hafner et al., 1998; Murray et al., 1992a; Shankar et al., 1995) and presence of brain abnormalities (Buchanan et al., 1993; Tamminga et al., 1992). It would seem that a valid classification system for schizophrenia should take these characteristics of illness into account.

The Neurodevelopmental Model of Schizophrenia

The neurodevelopmental model is a proposed classification system based, not only on differences in symptoms, but on family history, neuropsychological performance, brain abnormalities and course of illness. Interest in a neurodevelopmental model of schizophrenia began to emerge in the literature in the mid-1980's (Lewis et al., 1987; McNeil et al., 2000a; (Murray et al., 1992a, 1992b; Murray, 1994; Weinberger, 1995). Several investigators independently described a developmental model of schizophrenia, which posits that, for at least some individuals, schizophrenia is due to brain dysfunction that occurs early in development due to genetic, prenatal or perinatal events. This brain dysfunction impacts later development of the brain such that the onset of symptoms does not occur until late in brain maturation, typically during late adolescence and early adulthood (Weinberger, 1995). Based upon a broad review of genetic, epidemiological, and developmental literature in schizophrenia, Murray and colleagues (1992b) proposed three subtypes of schizophrenia: (1) the congenital subtype, (2) the adult onset subtype and (3) the late onset subtype. The congenital subtype, consistent with the neurodevelopmental subtype, is comprised of individuals whose putative brain insult is thought to be the result of prenatal and/ or perinatal maldevelopment. Individuals with this subtype have an early age of onset, negative symptoms, and cognitive impairment. Premorbid functioning is relatively poor in this group and there is an insidious onset of illness. Among these authors' subtypes, the clinical history, presentation and course of this subtype most closely matches that of Kraepelin's dementia praecox (Kraepelin et al., 1919; Murray et al., 1992b). It is thought that the factor(s) that caused brain development so early in life may have also caused subtle differences in physical features of these individuals, unlike the other subtypes. Therefore, these subtle physical anomalies may serve as a potential biological marker of this illness. This will be described in detail later.

In contrast to the congenital subtype, the adult onset group is characterized predominantly by positive, rather than negative symptoms and an acute and relapsing course of illness. Murray and co-authors proposed that individuals in this group are genetically related to individuals with affective disorder, although this group is likely heterogeneous. Finally, the late onset group consists of individuals whose onset occurs around the age of 60. These patients generally have good premorbid functioning and their illness is thought to reflect progressive brain deterioration (Murray et al., 1992b). Numerous studies have supported a neurodegenerative process for at least some individuals with schizophrenia (for example, Asche et al, 2001; Keshavan, 1999; Lieberman, 1999; Woods, 1998). It is thought that changes in glutaminergic neurotransmission (Keshavan, 1999) and changes in brain derived neurotrophic factors (Asche et. al, 2001) can result in degeneration of brain tissue.

Support for a congenital subtype of schizophrenia comes from a broad range of literature. These different sources will be described including studies of genetics, prenatal development, obstetric complications and premorbid functioning seen in individuals who later develop schizophrenia. Pathophysiological research and evidence of neuropsychological impairment lend further support to the presence of a congenital form of the illness and will be described in greater detail.

Genetics of schizophrenia

Schizophrenia is at least partially heritable. In the general population, there is a lifetime risk of developing schizophrenia of approximately 1% (American Psychiatric Association, 1994). However, in first-degree relatives of schizophrenia, this risk is approximately 15% (American Psychiatric Association, 1994). Twin studies reveal that the genetic component for schizophrenia is necessary, but not sufficient for developing schizophrenia in some cases. In many studies (for example, Kallman et al., 1994), concordance rates for schizophrenia between monozygotic twins have been compared to those for discordant twins. Concordance rates among monozygotic twin pairs are approximately 30-50% (Kendler, 1983; McGue, 1992; Torrey, 1992). If schizophrenia were entirely genetic, the concordance rates between monozygotic twins would be much closer to 100%. The concordance rates for dizygotic twins is approximately 15%, the same rate as other first-degree family members (Kendler, 1983).

Most researchers believe that schizophrenia is a polygenetic disorder (Bray et al., 2001). However, researchers have attempted to find single genes that contribute to the development of schizophrenia. The first candidate genes for schizophrenia were thought to be linked to chromosome 5. In 1995, Bassett and coworkers reported partial trisomy of chromosome 5 in an Asian family that included two members with schizophrenia (Bassett, 1989). Sherrington and colleagues in the same year reported linkage between schizophrenia and two markers in the 5q11-13 region (Sherrington et al., 1988). However these findings were not replicated.

More recently chromosome 6 has been linked to schizophrenia. In a study of 186 Irish families, Wang and coworkers (Wang et al., 1995) reported linkage at the distal end of the short arm of chromosome 6. Schwab and colleagues (Schwab et al., 1995) in a sample of 265 families reported evidence for linkage in 30% of the families in the 6p22-25 region.

Chromosome 22 has also received much attention. Family linkage studies have revealed moderate results (Yan et al., 1998). However, chromosome 22 has received considerable attention because of 22q11 deletion syndrome. With a specific microdeletion of 22q11, velocardiofacial syndrome (VCFS) often results. This syndrome is characterized by cardiovascular problems (Usiskin et al., 1999), neuropsychological impairment (Gerdes et al., 1999) (Holder et al., 1993), brain abnormalities (Eliez et al., 2000) and susceptibility to psychiatric illness (Usiskin et al., 1999; van Amelsvoort, et al., 2001). Approximately 15% of individuals with this specific microdeletion develop schizophrenia (Bassett et al., 1999). However, only 2% of individuals with schizophrenia also have 22q11 deletion syndrome (Bassett et al., 1999; Chow et al., 1999). Individuals with both VCFS and schizophrenia can be considered to have a congenital subtype of the disorder (Bassett et al., 1999) because they have many of the characteristics of this subtype as described by Murray and colleagues. Interestingly, these individuals demonstrate specific minor physical anomalies including narrow palpebral fissures, square nasal root, narrow alar bases, small mouth, cleft palate, malar flatness, and minor ear anomalies (Chow et al., 1999; Usiskin et al., 1999).

Family history studies seem to distinguish between two types of schizophrenia: (1) a chronic type with characteristics consistent with Kraepelin's dementia praecox (Kraepelin, 1919), and (2) a more acute, remitting type that is related to affective disorders. (The former groups would correspond to the congenital subtype, whereas the latter would correspond to either the adult or late onset subtypes.) For example, McCabe and coworkers (1971) reported a morbid risk of affective disorder of 10% in first-degree relatives in schizophrenics with good prognosis. However, in patients with poor prognosis schizophrenia, they found that the rate for affective disorder in first-degree relatives to be only 1.5% (McCabe et al., 1971). Similarly, in the Iowa 500 sample (Clancy, et al., 1973; Kendler, et al., 1988), relatives of schizophrenics with good outcome were at much greater risk for developing affective disorder than relatives of poor outcome schizophrenics. Conversely, for family members of chronically ill schizophrenics, the rates for both chronic schizophrenia and schizotypal personality disorder were relatively high whereas, and the risk of affective disorders was relatively low. Kendler & Tsuang (1988) in a review of studies examining the relationship between risk for psychiatric illnesses and prognosis of the probands concluded that family history of affective disorder was related to good prognosis.

Several findings from the genetic literature help to validate the distinctions between congenital and adult onset subtypes of schizophrenia. There are distinct differences in family risk for affective disorders and schizophrenia between acutely ill and good prognosis schizophrenics and chronic, poor prognosis schizophrenics. In addition, a specific microdeletion of 22q11 in a minority of individuals with schizophrenia results in a profile of characteristics consistent with the congenital subtype of schizophrenia. However, genetic factors may be only partly responsible for the development of schizophrenia. Further support for a congenital form of schizophrenia comes from literature examining the role of prenatal disruption, obstetric complications and poor premorbid functioning in some individuals with schizophrenia.

Prenatal disruption increases risk of schizophrenia

There are many diverse lines of evidence suggesting that risk for schizophrenia can be increased due to some kind of prenatal insult. Increased rates of schizophrenia have been associated with winter births (Baron et al., 1988; Hafner et al., 1987), possible prenatal exposure to infectious agents (Erlenmeyer Kimling et al., 1994; Mednick et al., 1988, 1994; Selton et al., 1999; Suvisaari et al., 1999), poor prenatal nutrition (Hoek et al., 1998), and maternal intrauterine autoimmune response (Hollister et al., 1996). These findings will be discussed below.

Poor prenatal nutrition

The theory that poor prenatal nutrition is etiologically relevant to schizophrenia has been around since the 1950s (Butler et al., 1999; Pasamanick et al., 1956). However, it has received little attention except in the past few years with the publication of the Dutch famine study (Hoek et al., 1998; Lumey, et al., 1995; Susser et al., 1994 , 1998). From October 1944 until May 1945, a famine occurred in the western region of the Netherlands due to German occupation during the war and a severely cold winter; Dutch citizens in this region received food rations of 1,000 calories per day during the height of this famine (Hoek et al., 1999; Susser et al., 1998). In a study by Susser and Lin, examination of Dutch National birth and psychiatric registries revealed that those individuals who were in their first trimester of development during the period of low food rations had an increased risk for developing schizophrenia twenty-four to forty-eight years later. The same relationship was not found for individuals who were in later stages of prenatal development, or those who were born before the famine (Hoek et al., 1999; Susser et al., 1998).

There are very few studies examining the relationship between prenatal nutrition and schizophrenia; however, many other studies support a relationship between poor prenatal nutrition and brain abnormalities. Animal studies have suggested (Butler et al., 1999; Juorio, 1987) that reduction in protein as well as total calories can cause some of the brain abnormalities observed in schizophrenia; they can cause short and long term changes in serotonin and other neurotransmitters, as well as changes in brain morphology, particularly in the hippocampus, (Butler et al., 1999; Juorio, 1987) an area found to be abnormal in some individuals with schizophrenia. In addition, deficiency in folate has been linked to neural tube abnormalities (Hoek et al., 1999).

Seasonality and Winter Birth

More than 50 studies report a 5 to 15% increase in schizophrenia among people born in the winter and spring months (Baron et al., 1988; Waddington et al., 1999a) Consistent with the neurodevelopmental model of schizophrenia, excesses of known neurodevelopmental illnesses are found in individuals who were born in late winter and early spring including mental retardation (Hafner et al., 1987; Waddington et al., 1999a), and autism (Gillberg, 1990; Waddington et al., 1999a). Some reports suggest that winter born individuals who develop schizophrenia are more likely to have no family history of schizophrenia (Hoek et al., 1999; O'Callaghan et al., 1991, 1992) and also have ventricular abnormalities of the brain, particularly among males (Flaum et al., 1990; Hoek et al., 1999). These findings could not be accounted for by anomalous conception patterns of the mothers of individuals with schizophrenia. Most authors believe that gestation and birth in colder months allows the fetus or neonate to be exposed to those unspecified environmental factors that may increase its risk of developing the illness (Butovskaya et al., 1996; Hoek et al., 1999; Waddington et al., 1999b; 1999c).

Prenatal development, influenza and other infectious agents

The literature suggests a relationship between exposure to an infectious agent during prenatal development and increased risk of schizophrenia later in life. Influenza has been the best-studied infectious agent. The first and most famous study linking schizophrenia to influenza is the Helsinki study (Mednick et al., 1994). In 1957, an epidemic of type A2 influenza broke out in Helsinki, Finland for several weeks. Decades later, Mednick's group used data from a national registry to examine the rates of schizophrenia after the influenza epidemic (Mednick et al., 1988; 1994). Two groups were examined. The first group consisted of individuals who were estimated to be in prenatal development during the influenza epidemic and another group that was born just before this epidemic. Individuals who were in the second trimester of development during the epidemic had a 50% greater risk for developing schizophrenia than those who were born before the epidemic and than those who were in their first and third trimester of development (Mednick et al., 1994).

A flurry of studies that examined this relationship soon followed throughout Europe (Barr et al., 1990; Erlenmeyer-Killing et al., 1994; Wright et al., 1995, 1999) and Asia (Izumoto et al., 1999; Kunugi et al., 1995). Although there were some conflicting results (Susser et al., 1994) and methodological differences, the overwhelming majority of the studies found increased rates of schizophrenia in individuals who were in their second trimester (month four to month seven) of development during an influenza epidemic (Kunugi et al., 1995; Takei et al., 1996; Venables, 1996). One Dutch study examined this relationship over a 40-year period and still found the relationship between prenatal influenza in the second trimester and schizophrenia (Barr et al., 1990). Some studies, however found increased rates of schizophrenia in individuals who were in their first trimester of development during likely exposure to influenza (McGrath et al, 1994; O'Callaghan et al, 1994).

Animal studies revealed that exposure to the influenza virus during the human equivalent of the second trimester may cause disruption in normal neuronal migration. When pregnant mice were injected with an influenza virus during the equivalent of the second trimester of development, the pups are later found to have neuronal disorganization of cell structure specifically in the anterior two thirds of the hippocampus, similar to post mortem findings in schizophrenia (Fatemi et al., 1999; Scheibel et al., 1993). Similarly, Cotter's group (1997) exposed mice to influenza A in utero at the thirteenth day of gestation. This time was thought to be the developmental equivalent of the second trimester in humans (Cotter et al., 1997; Wright et al., 1999). When the brains of these mice were examined twenty-one days after birth, there was evidence of abnormal organization of hippocampal pyramidal cells, consistent with post mortem findings in schizophrenia. Earlier exposure also causes brain abnormalities. Fatema and coworkers (2002) found that prenatal human influenza viral infection in mice during day 9 of pregnancy leads to pyramidal cell atrophy, macroencephaly and ventromegaly. This finding contradicts Mednick's finding that those in the first trimester of development during influenza famine, do not develop schizophrenia at increased rates (Mednick et al., 1994). However, it is consistent with other studies linking exposure to influenza in the first trimester to increased rates of schizophrenia (McGrath et al, 1994; O'Callaghan et al, 1994).

However, very few cases of schizophrenia were accounted for by possible prenatal exposure to influenza. A meta analysis by Sham and coworkers (1993) estimated that up to 2% of all individuals with schizophrenia (and 4% born in winter months) might have been exposed to influenza prenatally. In addition, only a small minority of mothers who were in the second trimester of pregnancy during an influenza epidemic gave birth to preschizophrenic children. In addition, studies did not find evidence of influenza antibodies in individuals with schizophrenia (Crow et al., 1992).

Some authors suggested that a variety of teratogens can interfere with the development of a fetus and produce schizophrenia including rubella (Brown et al., 1999), radiation (Imamura et al., 1999) cytomegalovirus (Murray et al., 1992c), polio (Suvisaari et al., 1999) herpes (Pandurangi et al., 1994) and toxoplasma gondi (Selten et al., 2002). While many of the agents are known teratogens in other neurodevelopmental disorders, they are understudied in schizophrenia. Other authors suggested that it is not a specific teratogen that increases risk for schizophrenia but rather maternal responses to the teratogenic agent such as fever, nutritional deficiency due to loss of appetite, or immune responses that adversely affects prenatal development (Wright et al., 1993, 1999).

Maternal immune response: Rhesus incompatibility

The Rhesus or RhD factor is a protein found in the blood of some individuals. If a person who does not have the Rhesus factor receives a transfusion of Rh – positive blood, RhD antigens will be produced. Because the gene for Rh-positive blood is the dominant gene, it is possible for a fetus to be Rh positive (from the father) but be carried by an Rh-negative mother. If the Rh negative mother had blood contact with Rh positive blood, perhaps from a previous Rh positive pregnancy or Rh positive blood transfusion, the Rh antigen is more likely to be produced. This can result in RhD hemolytic disease in the developing fetus, which can produce anemia, hepatomegaly and later neuropsychiatric consequences including motor, behavioral and intellectual dysfunction. (Hollister et al., 1996, 1999). This condition rarely affects the first RH-positive fetus; it is five times more likely to occur in later, rather than first pregnancies. Male fetuses appear more susceptible to RhD hemolytic disease than female fetuses.

In a prospective study, prenatal RhD incompatibility was linked to later schizophrenia, (Hollister et al., 1999). The authors followed 9,182 male infants born to 9,006 mothers between 1959 and 1961. Of the mothers whose Rhesus factor was determined, 40% of them were Rh negative. The offspring of those mothers were divided into two categories: those who were Rhesus positive or incompatible (n= 536) and those who were Rh negative or compatible (n= 1,322). Data of psychiatric hospitalizations and diagnosis from 1992 to 1993 was taken from the Danish Psychiatric Hospital Register. By 1992 to 1993, 2.1% of the individuals in the Rh incompatible group developed schizophrenia, whereas only 0.8% of individuals in the Rh compatible group developed schizophrenia. When each group was divided by birth order (i.e., first born versus subsequently born), these authors found that the rate for developing schizophrenia was not significantly different for first born children, but was significantly higher, for subsequently born individuals (Hollister et al., 1999). The authors speculated that the RhD antigen could disrupt fetal development, thereby increasing the risk for schizophrenia. The transfer across the placenta of the anti-D antigen is thought to occur by the second trimester and may cause hemolysis resulting in hypoxia. This can affect multiple brain regions, especially the hippocampus, which is particularly vulnerable to hypoxia. In addition, hepatomegaly and moderate anemia can cause hyperbilirubinemia, in which neurotoxic levels of bilirubin accumulate and cause damage to the basal ganglia, dendate nucleus of the cerebellum, and the hippocampus as well as other brain structures (Laroche, et al., 1987; Rorke, 1992). In some instances, this can result in motor difficulties, sensorineural hearing deficits, or mental retardation (Watchko et al., 1992). Some children who develop from a pregnancy with hemolytic disease can have many of the same characteristics of preschizophrenic children including anxiety, poor volition (Turner et al., 1985), social immaturity (Cannon et al., 1997; Neumann et al., 1995; Turner et al., 1985; Walker et al., 1993), language difficulties (Bearden et al., 2000; Turner et al., 1985; Walker, 1994) lower IQ and motor disturbance (Cannon et al., 2002a; Walker et al., 1994).

The role of obstetric complications in schizophrenia

The relationship between obstetric complications and schizophrenia has been studied extensively using a variety of methods. Obstetric complications (OCs) have been found to be more prevalent and severe by (21% to 40%) in individuals with schizophrenia than in healthy adults (Cannon et al., 1999a , 2000; Cantor-Graae et al., 1997). This finding supports the model that some individuals with schizophrenia are compromised in their development at birth, as proposed for the congenital subtype of schizophrenia. Furthermore, many studies report that OCs are related to clinical characteristics that Murray's group (1992b) has attributed to the congenital form of schizophrenia (Gilvarry et al., 2001; Soorani-Lunsing et al., 1993). Many, but not all studies (Verdoux et al.,

1997) report that obstetric complications are reported more frequently in male patients (Cantor-Graae et al., 1994a, 2000; Foerster et al., 1991; O'Callaghan et al., 1992). Earlier age of onset is also associated with an increased frequency of obstetric complications (Cantor-Graae et al., 1994a, 2000; Foerster et al., 1991; Verdoux et al., 1997) and in some studies this relationship has been found for male schizophrenic individuals only (Kirov et al., 1996). Early developmental difficulties have been associated with increased rates of schizophrenia (Foerster et al., 1991). Obstetric complications have been linked to schizophrenia in individuals who generally have no family history of the illness. In addition, obstetric complications have been correlated with specific brain abnormalities including increased size of lateral and third ventricles, as well as reduced normal asymmetry. In a study of twins discordant for schizophrenia, obstetric complications were related to the presence of minor physical anomalies (Campbell et al., 1978; Cantor-Graae et al., 1994b) and neurological soft signs (Cannon et al., 1999a; Soorani-Lunsing et al., 1993).

However, other studies have failed to find these relationships (Carter-Saltzman & Scarr-Salapatek 1975). This can be attributed to methodological differences across studies. Obstetric complications have been assessed by examination of clinical obstetric records (Jones B. et al., 1998), maternal interview (Cantor-Graae et al., 1998), and prospective studies (Cannon et al., 2002b; Cannon, T. D. et al., 1999a). In addition, there are a variety of scales to assess the number and severity of prenatal and birth complications (McNeil et al., 1997).

Another limitation is that few studies have looked at specific types of obstetric complications. In most studies, the number and severity of obstetric complications are combined to form a single obstetric complication score (McNeil et al., 1997). Some authors criticized this practice and indicated that prenatal and obstetric events may not be independent of each other (Cannon et al., 2002b; Waddington et al., 1999a, 1999c) Perinatal complications such as extended labor or breech birth may reflect a fetus that has been compromised much earlier in development (Altshuler et al., 1987; McNeil et al., 1996). In addition there may be a bias in reporting particular kinds of OCs. For example, more salient events later in pregnancy such as low birth weight and prolonged labor (Rifkin et al., 1994) may be reported more frequently than earlier prenatal complications that may be very serious although not as noticeable. These include early prenatal bleeding in the first trimester (Waddington et al., 1998a, 1999a, 1999b). While one study has attempted to differentiate among types of prenatal and perinatal complications (Ismail et al., 1998b), further research is needed to ascertain what aspects of fetal development can increase risk for schizophrenia.

In support of the congenital subtype of schizophrenia, the risk for developing schizophrenia appears to be greater when prenatal development is impaired, perhaps due to poor prenatal nutrition, prenatal exposure to infectious agents, or maternal immune response impacting the fetus. Greater incidence and severity of obstetric complications have been found in the development of individuals who later have schizophrenia. Individuals who result from such pregnancies and later develop schizophrenia are thought to have brain differences even at birth, although they do not develop the illness until adolescence or early adulthood (Murray et al, 1992; Weinberger, 1995). However, consistent with the proposed congenital subtype, many of these individuals likely have poor premorbid functioning behaviorally, intellectually and emotionally, well before onset of schizophrenia (Murray et al, 1992; Wadding ton, 1999a; Weinberger, 1995). Studies finding poor premorbid functioning in some individuals with schizophrenia support the concept of a congenital subtype of schizophrenia (Cannon-Spoor et al., 1982; Chiders et al., 1990; Guy et. al, 1983).

Premorbid functioning

Poor premorbid functioning provides further support for a congenital form of schizophrenia because it indicates that abnormalities occur long before the actual onset of the illness (Cannon-Spoor et al., 1982; Childers et al., 1990; Guy, et al., 1983) and is consonant with a more insidious onset of illness (Childers et al., 1990; Lewine et al., 1996). Long before the onset of illness, preschizophrenic children demonstrate abnormalities in motor (Lubin, et al., 1962; Walker et al., 1982), neuropsychological (Banaschewski et al., 2000) and social functioning (Cannon et al., 2002a; Kales et al., 1990; Lewine et al., 1978; Neumann et al., 1995; Walker et al., 1993).

Motor functioning

Some children who later develop schizophrenia demonstrate motor abnormalities. Neuromotor deficits have been demonstrated even in infancy. High-risk infants (born to schizophrenic parents) demonstrate abnormalities in both gross and fine motor development as assessed by standardized instruments (Watt et al., 1982). In a prospective study, many individuals who later developed schizophrenia were delayed in the development of motor milestones when assessed at age 2 by maternal interview. Another prospective study revealed that children at age seven, who later developed schizophrenia, demonstrated poor coordination and clumsiness. At age 11, these same children tended to have anomalous hand preference, poor manual skills and articulation difficulties.

Early motor abnormalities in children who later developed schizophrenia were demonstrated in a study by Walker and colleagues (1994). Family films of preschizophrenic children and their siblings were collected and shown to clinicians who were were uninformed of the later diagnosis of the children. The clinicians were asked to rate the presence of neurological soft signs and movements demonstrated on the film. Preschizophrenic children were found to have significantly more neurological and motor abnormality ratings compared to their siblings (Walker et al., 1994).

Neuropsychological, intellectual and academic functioning

Several studies have found that IQs are lower in children who later develop schizophrenia compared to their peers and their siblings (Addington et al., 1993), particularly in males (Bearden et al., 2000). Alyward, Walker and Bettes (1984) performed a meta-analysis of high risk studies and retrospective studies (Watt et al., 1976) and found that the proportion of males in each sample predicted the decrement of the IQ in the preschizophrenic samples (Bearden et al., 2000).

The literature indicated that delayed language development frequently occurs in individuals with child and adolescent onset of schizophrenia (Baltaxe et al., 1995). Moreover, studies revealed language impairments in some individuals with onset of schizophrenia in early adulthood (Cannon et al., 2002a). Jones and colleagues (1994) found that speech milestones were achieved later in preschizophrenic children as compared to their peers. In the same prospective study, speech problems occurred with a higher frequency in preschizophrenic children between the ages of two and fifteen years.

Social adjustment

Poor social and behavioral functioning were found in approximately one third of preschizophrenic individuals in retrospective and prospective studies (Cannon et al., 1997, 1999b; Mueser et al., 1990; Torrey et al., 1994). Teachers of preschizophrenic children more frequently rated them as disagreeable, introverted and emotionally unstable (Done et al., 1994). They engaged more often in solitary play at age four (Jones et al., 1994) and demonstrated withdrawal, social anxiety and acting out behavior in adolescence (Gupta et al., 1995; Jones et al., 1994; Malmberg et al., 1998; Weintraub, 1987). In addition, clinicians, who were uninformed of the later diagnosis, rated preschizophrenic children in home movies as having more unusual facial expression and emotion (Walker et al., 1993).

Developmental factors in support of congenital subtype of schizophrenia

Several lines of evidence supported the presence of a congenital subtype of schizophrenia. Studies of family incidence distinguish between a heritable chronic form of schizophrenia and an acute form that is related to affective disorders. Support for prenatal disruption in some individuals with schizophrenia exists in epidemiological studies that found a relationship between later schizophrenia and prenatal nutritional deficiency, exposure to infectious agents and maternal rhesus blood type incompatibility. In addition, many individuals who later develop schizophrenia were found to demonstrate premorbid behavioral abnormalities including delayed behavioral milestones, neurological soft signs, poor academic functioning, lower IQ, and social maladjustment.

Some studies that examined brain pathology, as well as neuropsychological deficits lend further support for a congenital subtype of schizophrenia. These are described in the next section.

Pathophysiology of schizophrenia

Schizophrenia was thought to be a disorder linked to brain dysfunction, even when it was first described over 100 years ago. Thomas Clouston first hypothesized that developmental insanity (which would include schizophrenia) was likely due to abnormal frontal lobe development; this was reflected in abnormal development of the palate, as the two were proximal (cited by O'Connell et al., 1997a). Kraepelin also hypothesized that the pathology of dementia praecox was related to disturbances of the prefrontal lobes and medial aspects of the temporal lobes (Kraepelin, 1919). Bleuler believed that the etiology of schizophrenia would be linked to the brain as well (1911/ 1950). However, post mortem brain studies in the late nineteenth and early twentieth centuries yielded disappointingly conflicting results (Shenton et al., 2001). This was due to the fact that the methods used at the time could detect large abnormalities, but not the small subtle abnormalities we find in schizophrenia today. With the advent of sophisticated brain imaging techniques, we have really begun to see true brain differences in schizophrenia, even though a comprehensive understanding of the pathophysiology of schizophrenia is still not fully understood, presumably due to the heterogeneity of this illness. The following sections describe neuroanatomical findings in schizophrenia.

According to the classification proposed by Murray's group (Murray, 1994), those with congenital form of schizophrenia manifest some of the more gross anatomical differences observed in individuals with schizophrenia, and some of these anatomical differences would be present well before the onset of illness. In contrast, those with the adult onset of schizophrenia have fewer anatomical differences and perhaps greater neurochemical differences associated with acute and remitting course and their good response to medication. This distinction has not been studied extensively and there is most probably overlap.

Anatomy

Brain pathology in schizophrenia varies among individuals. Approximately 20-30% of patients with schizophrenia do not show any significant brain differences from normal control subjects (Chua et al., 1995; Kasai et al., 2002). However, for others, there are noticeable differences. The following describes brain differences seen in some individuals with schizophrenia.

Whole brain differences

Most MRI studies that compared the whole brain of individuals with schizophrenia to those of healthy control subjects did not find any gross differences between the two groups (Harvey et al., 1997; McCarley et al., 1999), although a minority of studies found reduced volume in schizophrenics (Halliday, 2001). Because there is a large variation between head and brain size in the general population, small reductions in the overall brain may be too subtle for standard MRI techniques to detect (Ward, 2000). In addition, there is great heterogeneity among individuals with schizophrenia; and therefore, perhaps only a small subset has whole brain volume reductions. Jacobsen and colleagues (1998) reported reduced overall brain size in individuals diagnosed with childhood schizophrenia. This finding was consistent with Murray's idea that individuals with the congenital form of schizophrenia have both neuroanatomical abnormalities and an early age of illness onset (Murray et al., 1992b).

Enlarged ventricles

Enlarged lateral ventricles, particularly in the area of the temporal horns, were found in individuals with schizophrenia using pneumoencephalography, CT, and MRI. In monozygotic twin pairs discordant for schizophrenia, many affected twins had larger lateral ventricles (in particular, the left lateral ventricle) compared to their healthy counterparts (Bornstein, 1985). These findings were consistent with postmortem findings of enlarged temporal horn volumes; reduced volume in the amygdala and hippocampus were also observed (Brown et al., 1986; Bogerts et al., 1985; Davis. et al., 1998; Falkai et al., 1986; Sponheim et al., 1991). Enlarged third and fourth ventricles were demonstrated in some studies, although there were fewer studies of the fourth ventricle per se (Shenton et al., 2001; Sullivan et al., 2000; Takeuchi et al., 1994).

These findings are consistent with the neurodevelopmental hypothesis of schizophrenia. Enlargement of the lateral ventricles is present in first episode neuroleptic naïve individuals with schizophrenia, and lateral ventricle enlargement does not appear to worsen with age (DeLisi et al., 1992; Sponheim et al., 1991). This suggests that ventricular enlargement occurs relatively early in life (DeLisi et al., 1992; James et al., 1999; Sponheim et al., 1991). Furthermore, characteristics of the congenital subtype appear to be related to ventricular enlargement. Enlargement of the lateral ventricles is correlated with disability (unemployment) and negative symptoms (Pearlson et al., 1984, 1989). Interestingly, one of the few studies that examined the relationships between the brain and minor physical anomalies demonstrated that enlarged third ventricle was correlated with an increase of minor physical anomalies in schizophrenia (O'Callaghan et al., 1995).

Abnormal asymmetry

Imaging studies of the brain found that the normal brain extends further anterior on the right and posterior to the left (called torque) and the left planum temporale (underlying the Sylvian fissure) is larger than the right. Studies of cerebral asymmetries in some patients with schizophrenia revealed reversals and reduction of normal asymmetry, and these differences are likely neurodevelopmental in origin (Cowell et al., 1999; DeLisi et al., 1997; Luchins, et al., 1979, 1982; Risch et al., 1990). Consistent with a congenital subtype of the disorder, early age of illness onset was associated with greater disturbance in normal brain asymmetry (Maher et al., 1998). Disturbance of normal asymmetry is not specific to schizophrenia and was also found in neurodevelopmental disorders such as dyslexia (Annett, 1999; Cowell et al., 1999; Saugstad, L. F., 1999).

Temporal lobe findings

Abnormalities of the temporal lobes, hippocampus and entorhinal cortex were found in individuals with schizophrenia (Falkai et al., 1992; Lawrie et al., 2002; Maher et al., 1998). MRI studies revealed volume reductions in the temporal lobe (Axelrod et al., 1994; Lawrie et al., 2002) present in some individuals during their first episode of schizophrenia (DeLisi et al., 1992; Shenton et al., 2001). Abnormal cell orientation and placement in the entorhinal cortex (Arnold et al., 1991) and hippocampus (Dwork, 1997) found in postmortem studies of schizophrenic brains, were thought to be due to aberrant cell migration during prenatal development (Arnold. et al., 1991; Bunney et al., 1997). In addition to these findings, many studies failed to find gliosis in these regions, a sign that would indicate brain insult occurring well after birth (Bunney et al., 1995). Taken together, it appears as though these abnormalities occurred prior to or around the time of birth, lending further support to a congenital subtype of schizophrenia.

In addition, abnormalities in these regions have been linked to characteristics that Murray attributes to a congenital form of schizophrenia. Cytoarchitectural abnormalities (of the limbic allocortex) were found specifically in individuals with hebrephrenic or disorganized types of schizophrenia. Reduced left hippocampal volume was found in patients with schizophrenia who had a significant history of pregnancy and birth complications (Shenton et al., 2001). McNeil's group (2000a) reported a relationship between smaller bilateral hippocampi and labor and delivery complications in the schizophrenic twin of MZ pairs discordant for schizophrenia. Because the hippocampus and subiculum are particularly sensitive to the effects of prenatal and perinatal hypoxia, it is thought that pregnancy complications resulting from hypoxia in the developing fetus may predispose individuals to developing schizophrenia.

Frontal lobe abnormalities

MRI studies yield equivocal findings for structural abnormalities in individuals with schizophrenia (Benes et al., 1991; Bilder, et al., 1995; Halliday, 2001; Test et al., 1990). Small subtle differences in the whole prefrontal cortex might be too difficult to detect by present MRI capabilities. However these differences have been observed in post-mortem studies; Selemon and coworkers found an 8% reduction in prefrontal cortical thickness in schizophrenia reduction that was not statistically significant, although they found abnormalities in the cell density of the prefrontal cortex (Selemon et al., 1995).

One reason for failing to find small subtle differences in the prefrontal cortex using MRI may be attributed to the fact that most studies examine the entire frontal cortex, which is made up of regions that are, to some degree, functionally heterogeneous (Hoff et al., 2001). Some studies that examined the structure of the prefrontal cortex in schizophrenia found that individuals with schizophrenia demonstrating a predominance of negative symptoms have reduced volumes of gray matter in the left prefrontal cortex (Grossberg, 2000). A CT study also revealed that frontal portions of the interhemispheric fissure were greater in negative than in positive symptom patients (Bogerts et al., 1991). Although no differences were found between samples of individuals with schizophrenia and healthy controls, differences were seen between those patients with predominantly negative symptoms and healthy controls. Goldberg and coworkers (Goldberg et al., 1995a) reported between 7 and 15% volume reductions n the middle frontal middle medial and right-sided fronto-orbital subregions in schizophrenia. Gur and coworkers (Gur et al., 2000) studied male and female patients with schizophrenia and matched controls, and reported reduced prefrontal gray matter in dorsolateral regions of 9% in men and 11% in women. Dorsomedial volume reductions were evident only in male patients and orbitofrontal volume reductions were evident only in female patients. In addition, a larger dorsal cortex was correlated within the patient groups with better performance on abstraction and attentional measures whereas smaller volume in the orbitofrontal regions in female patients was correlated with poorer premorbid functioning, more negative symptoms and depression. Barge's group (1999) reported no differences between controls and schizophrenia in parcellated prefrontal regions, although these investigators noted a correlation between left and right prefrontal gray matter volume reduction and decreased performance on tests of verbal recall visual memory and semantic fluency. Further reduced orbitofrontal volume was correlated with more negative symptoms. These findings, taken together, suggest that dividing the frontal cortex into subregions is important not only for detecting volume differences but also for examining the association between reduced prefrontal volume and clinical and cognitive deficits.

Functional imaging studies of this region that utilized PET, SPECT and cerebral blood flow revealed that some individuals with schizophrenia have decreased prefrontal functioning during tasks such as Wisconsin Card Sorting Test, eye tracking, spatial working memory (Andreasen et al., 1992; Goldberg et al., 1987; Ragland et al., 1998; Weinberger et al., 1986a). Poor performance on the Wisconsin Card Sorting Test, particularly in individuals with negative symptoms, has been associated with hypofrontality (Goldberg et al., 1987; Weinberger et al, 1986a). There was some evidence that prefrontal hypofunction is associated with negative symptoms (Pantelis et al., 2001). In monozygotic twins discordant for schizophrenia, relative hypofrontality was observed in the affected twins during executive functioning tests. In addition, hypofrontality was observed in patients with schizophrenia at first episode who are medication free. Therefore hypofrontality that is present at illness onset is not completely heritable and is unrelated to chronicity of illness or medications (Berman et al., 1992).

Generalized deficits

Overall, there appear to be cognitive deficits in individuals with schizophrenia. On broad batteries of neuropsychological tests, individuals with schizophrenia performed approximately one standard deviation worse than controls (Pantelis, et al., 2001; Saykin et. al., 1994). Similarly, in monozygotic twin pairs discordant for schizophrenia, the affected twins' performance on tests of intellectual functioning, was on average about 10 points less than the unaffected twins (Goldberg et al., 1995b).

However, not all individuals with schizophrenia appeared to suffer with similar levels of impairment. Between forty to sixty percent of individuals with schizophrenia fell into the impaired range on tests of neuropsychological functioning (Elvevag et al., 2000a). There was considerable heterogeneity regarding neuropsychological functioning (Elvevag et al., 2000a; Zalewski et al., 1998). Two independent studies (Baxter et al., 1998; Goldberg et al., 1995c) found that patients with thought disorder or predominantly negative symptoms demonstrated greater neuropsychological impairment than individuals with a preponderance of positive symptoms. Similarly, females demonstrated less cognitive impairment than males (Haas, et al., 1991). Some studies seemed to indicate that there is a decline in general cognitive functioning with onset of illness, whereas others indicated that some individuals with schizophrenia demonstrated low IQ and academic difficulties as children (Hoff et al., 1999; Jones et al., 1994). Such discrepancies may support Murray's hypothesized subtype of schizophrenia; a congenital subtype with poor premorbid neuropsychological functioning, male preponderance, characterized by disorganization and negative symptoms as compared to adult onset with neuropsychological impairment developing around the time of illness onset (Murray et al., 1992b).

Because there is general cognitive impairment in many individuals with schizophrenia, it is difficult to assess the degree to which specific neuropsychological functions are impaired. To demonstrate a specific dysfunction, performance within a particular domain must be significantly lower than the already lowered general neuropsychological dysfunction. The following sections describe some neuropsychological domains that have received considerable attention in schizophrenia. Few of these studies however distinguish among subtypes of the illness.

Attention

Kraepelin (1919) recognized attention as a central feature of schizophrenia. Individuals with schizophrenia perform poorly on a number of attention paradigms in both auditory and visual modalities (Randolph et al., 1998). Deficits in simple attention functions were seen, such as unusually slow and variable reaction time (even after motor slowing was accounted for). Poor selective attention was demonstrated in individuals with schizophrenia using the Span of Apprehension test, dichotic listening tasks or visual tasks that required the patient to selectively attend to relevant information while ignoring unimportant information (Gold et al., 1993). Slowed perceptual processing was also demonstrated on backward masking tasks (Braff, 1993). People with schizophrenia also performed poorly on tasks assessing vigilance (the ability to sustain attention over time) by making an abnormally high number of omission errors even in simple versions of continuous performance (CPT) tasks (Buchanan et al., 1997; Cornblatt et al., 1994). Deficits in the alerting, shifting, and response preparation aspects of attention were suggested by their inability to benefit from regular preparatory or warning intervals, as well as the poor use of cues to facilitate their performance (Elvevag et al., 2000a, 2000b).

Attentional deficits in schizophrenia are of particular importance because they were found in unaffected family members (Cannon et al., 1994; Faraone et al., 1995), schizotypal personality disorder (Docherty, 1993; Kent. et al., 1994) and children who were thought to be at risk for schizophrenia (Cornblatt et al., 1999; Freedman et al., 1998). In addition, correlations between attentional tasks and other tests of neuropsychological functioning were relatively low, supporting the idea that attentional deficits were not merely related to general neuropsychological deficits.

Executive Functions

Clinically, patients with schizophrenia resemble those with frontal lobe insult in their demonstration of poor social judgment, planning ability, and insight as well as aspontaneity, anhedonia and affective flattening (Randolph et al., 1998). Patients with schizophrenia have impaired performance on NP tests sensitive to frontal lobe dysfunction (Fossati et al., 1999). Impaired performance has been reported on tests of abstract reasoning (Fucetola et al., 2000) and poor fluency (Gilvarry et al., 2001; Paulsen et al., 1995). Deficits with problem solving, concept formation, set shifting are apparent on their performance on tests such as the Wisconsin Card Sorting Test (Axelrod et al., 1994; Beatty et al., 1993; Velligan, 1995) and the Category test of the Halstead Reitan Battery (Johnson-Selfridge et al., 2001). Specifically, on the Wisconsin Card Sorting Test, patients with schizophrenia make perseveratory and incorrect responses even in the face of feedback to the contrary (Goldberg et al., 1991). The tenacity of the deficit was revealed by Goldberg et al. (1987) who demonstrated that the deficit remained even after explicit instruction on how to complete the Wisconsin Card Sorting Test (WCST) (Goldberg et al., 1994). Some researchers found problem solving ability to be impaired in individuals with schizophrenia who have normal or even supernormal IQ (Heinrichs et al., 1993). These findings suggested that difficulties with problem solving tasks do not merely reflect a general decline in general neuropsychological functioning. Several studies demonstrated that patients with schizophrenia had reduced blood flow in the dorsolateral prefrontal cortex during the WCST relative to healthy controls (Berman et al., 1986) (Weinberger et al., 1986a, 1986 b; 1988). Reduced cerebral blood flow was not found when other neuropsychological tests were assessed; normal activation of the right parietal cortices was found when patients performed Raven's progressive matrices (Fry, 1978).

Memory

Memory impairments are among the most reliable neuropsychological deficits found in schizophrenia (Brebion et al., 2000; Gold et al., 1993). Gold and colleagues (1993) reported that the majority of their schizophrenic sample performed relatively lower on the WMS-R than on the Wechsler Adult Intelligence Scale. Impaired memory functioning has been demonstrated in schizophrenia on a wide range of paradigms implicating multiple stages of memory. Deficits have been observed in the encoding, consolidation, retrieval and recognition of both visual and verbal material (Gold et al., 1993; Goldberg et al., 1991). Patients with schizophrenia demonstrate slow rates of learning (Elvevag et al., 2000a) and some studies indicate that they have rapid forgetting (Landro et al., 1993). Both recall and recognition appear to be impaired, with recall relatively worse than that of normal control subjects compared to recognition (Calev, 1984; Paulsen et al., 1995). Priming appear to be impaired in individuals with schizophrenia; however, procedural memory is relatively intact (Keshavan, 1999). In a large sample of patients, nearly 50% of individuals scored in the moderately-severely impaired range (Gold et al., 1993). The finding of significant memory impairment in schizophrenia was consistent with the structural and functional abnormalities found in the medial temporal lobes (Lawrie et al., 1998; Tamminga, 1997; Tamminga et al., 1992), as mentioned previously, as this area plays a crucial role in mnemonic functioning.

Language function

Clinically, some schizophrenic patients demonstrate language difficulties including alogia, incoherence, loose associations and neologisms. Language impairments have been reported in individuals with schizophrenia, although much less consistently than in other neuropsychological domains such as attention and executive functioning (Barr et al., 1989; Leentjens et al., 1998). Linguistic studies in schizophrenia have revealed difficulties in language comprehension, as well as deficits in problems with use of language in a social context (Baltaxe et al., 1995; Condray et al., 1995). Language impairments have been seen in children who are later diagnosed with schizophrenia as well as first episode patients (Baltaxe et al., 1995), indicating that in some individuals, language impairment was present prior to illness onset, a characteristic of the proposed congenital subtype. Dysfunction of language is consistent with left temporal lobe dysfunction. Gur and coworkers suggested that language dysfunction in schizophrenia may be caused by left hemisphere inactivation (Gur, 1977).

Motor and visuomotor coordination

Some studies reported significant motor dysfunction in patients with schizophrenia relative to patients with other psychiatric disorders as well as normal controls (Walker et al., 1982). For example, Gold's group found that finger tapping speed of schizophrenic patients was slower than individuals with temporal lobe epilepsy (Gold et al., 1994). Similarly deficits were seen on tasks of visuomotor integration including

Digit Symbol (Gold et al., 1993), Trail Making Test Form A (Arango et al., 1999; Flashman et al., 1996; Franke et al., 1993) and Perdue Pegboard (Jablensky, 2001). These tests were thought to be sensitive to global brain dysfunction. Motor deficits found in schizophrenia seemed to be relatively mild and cannot be readily distinguished from general cognitive deficit (Gold et al., 1993). However, others reported that performance in schizophrenia on simple motor tasks such as finger tapping speed, finger dexterity and motor grip strength is not significantly worse than it is in individuals with affective disorder (Goldberg et al., 1993; Klahr et al., 1995). Other studies reported difficulty with motor function prior to illness onset. These discrepant reports may reflect differences among individuals with schizophrenia.

Heterogeneity of neuropsychological dysfunction in schizophrenia

Not all individuals with schizophrenia appear to suffer with similar levels of neuropsychological impairment. Between 40-60% of individuals with schizophrenia fall in the impaired range on tests of neuropsychological functioning. There is considerable heterogeneity regarding neuropsychological performance (Gold et al., 1993; Klapow et al., 1997). Independent studies reveal that patients who generally demonstrate thought disorganization and those with prominent negative symptoms tend to have worse neuropsychogical performance than that of patients with positive symptoms (Baxter et al., 1998; Goldberg et al., 1995c). Similarly, females tend to have fewer and less severe neuropsychological impairment than males (Goldstein et al., 1994; Moriarty, et al., 2001).

Neuropsychological deficits are primary in schizophrenia

It has been suggested that neuropsychological deficits in schizophrenia were "functional impairments," secondary to other factors such as institutionalization, medication, poor motivation or symptoms. In the past, clinicians frequently tried to use performance on neuropsychological tests to distinguish individuals with organic impairment from those with 'functional impairments,' such as those with schizophrenia (Green, 1998). It was assumed that individuals with organic impairment had poorer performance on neuropsychological tests. However, raters who tried to categorize individuals as "organically" or functionally impaired based only on scores from neuropsychological tests, correctly categorized people with only a 52% accuracy rate. This was just slightly above the 50% expected from chance (McMahon et al., 1994). There was nothing inherent in the impairment to distinguish the two groups; the explanation that individuals with schizophrenia had "functional impairments" was thus based on circular reasoning (McMahon et al., 1994). Further research examining the relationships between NP impairment and variables such as long term institutionalization, medication and psychopathological symptoms seemed to indicate that neuropsychological functioning is a core feature of schizophrenia rather than an epiphenomenona (Elvevag et al., 2000a). These findings are summarized below.

Institutionalization and NP impairments

Institutionalization was thought to cause neuropsychological dysfunction because there is a lack of environmental stimulation. Actual studies, however, did not support this assumption (Harrow et al., 1987). Marked cognitive deficits were found in first episode patients, indicating that the neuropsychological impairments could not be attributed to institutionalization because they occurred prior to institutionalization (Mohamed et al., 1999). Johnstone found no decline in Mini-mental state examination with increased lengths of hospitalization (Johnstone et al., 1985). Studies showed no difference in neuropsychological functioning between individuals who were continuously hospitalized and those that were intermittently hospitalized (Harrow et al., 1987). Finally, a study examining the relationship between neuropsychological functioning and age, education, and length of hospitalization revealed that length of hospitalization did not account for a significant portion of variance in scores on neuropsychological tests in a sample of 245 patients (Goldstein et al., 1991).

Medication

Previously, some clinicians believed that neuropsychological impairment was merely the result of medication. Several lines of research refute this idea. As stated previously, neuropsychological impairments have been found in first episode patients who were medication naïve. Similarly, some neuropsychological impairments are found in unmedicated first-degree relatives of individuals with schizophrenia (Elvevag et al., 2000b). Some individuals who were chronically medicated did develop tardive dyskinesia as a result from taking neuroleptic medication; however, anticholinergic medication, used to combat the motor side effects, were reported to have some adverse effects on memory (Tyrka et al., 1995).

Positive symptoms and NP impairment

Neuropsychological impairment in schizophrenia is not secondary to positive psychopathological symptoms. In one study, atypical neuroleptics were used to alleviate hallucinations and delusions in individuals with schizophrenia; deficits in memory and problem solving ability remained even after amelioration of symptoms (Goff et al., 2001). Overall, there is little correlation between symptoms and neuropsychological deficits (Schuldberg et al., 1999). In addition there is high test-retest reliability on neuropsychological tests in individuals with schizophrenia despite clinical state (Elvevag et al., 2000b).

Minor Physical Anomalies in Patients with Schizophrenia

Minor Physical Anomalies (MPAs) are subtle structural differences of the head, face, feet and hands that are typically of little of no functional or cosmetic consequence (Green, 1998). Examples include malformed and/or asymmetrical ears, furrowed tongue, high palate, and curved fifth finger (Waldrop & Halverson, 1971). In the late 1800s, Thomas Clouston first noticed palatal anomalies in a proportion of mentally ill patients that he categorized a having suffered from “adolescent insanity” (Clouston, 1891). When Kraepelin later distinguished between dementia praecox and manic depressive illness, most of Clouston’s adolescent insanity cases would have been categorized as suffering from dementia praecox (O’Connell et al., 1997b). Kraepelin, himself, noted that physical anomalies occurred in a proportion of dementia praecox cases (Kraepelin et al., 1919). However, for most of the twentieth century, the popularity of psychoanalytic interpretations of schizophrenia resulted in a paucity of research examining organic components to schizophrenia. Over the past twenty years, research indicated that MPAs occur in schizophrenic patients more frequently and with greater severity than in comparison groups including healthy subjects (Green et al., 1989), non-schizophrenic twins from discordant twin pairs (Cantor- Graae et al., 1994b), and patients with other Axis I diagnoses (Lohr et al., 1993). Approximately thirty-five percent of schizophrenic patients (Green et al., 1994a) are estimated to have a high incidence of physical anomalies. Because MPAs are thought to be indicators of early developmental abnormalities present at birth, Murray hypothesized that MPAs occur only in individuals having the congenital subtype of the schizophrenia (Murray et al., 1992a). MPAs are thought to develop from approximately the ninth through the fifteenth week of gestation, a period of time important in the development of such anterior midline brain structures as the hippocampi and temporal lobes (Cantor-Graae et al., 1994b ; Green et al., 1994b; McNeil et al., 2000b; Waddington et al., 1999a, 1999c, 1999d). Therefore, MPAs may be a valuable marker for this congenital subtype of schizophrenia.

In this next section, classical methods of assessing MPAs in schizophrenia are described. Research examining the relationship between MPAs and other putative signs of congenital subtype is discussed and newer methods for assessing craniofacial dysmorphology in schizophrenia will be described.

Prenatal Development: the relationship between brain development and craniofacial development.

The relationship between prenatal development of the brain and craniofacial structure has not been studied extensively, although it is generally accepted that they are inter-related. Prenatal face and brain are both derived from the same layer of the notochord, the ectoderm; development of these structures is temporally proximal, as well. In addition, the skull, which is derived from neural crest cells and the mesoderm influences the development of brain structures (Kjaer, 1995).

Early in prenatal development, by the 15^{th} day, the region that will become the human head is already formed on the anterior portion of the notochord, called the prechordal area. The surface ectoderm of the prechordal region will later become the face and the epithelial layer of the prechordal area, or the neuroectoderm, will become the brain. The pituitary develops in the frontal and anterior area of the notochord (Kjaer, 1995).

There is an open rostral neuropore on this prechordal region that closes around the 28^{th} day of development. After this closure, the progenitors of the face appear on the ectoderm of the prechordal region. These are the nasal placode, the optic placode, the maxillary process and the mandibular process. At this time there is an outgrowth of the mesenchyme of the notochord separating what will become the face and what will become the brain. From the mesenchyme the craniofacial development will ultimately occur in the following sequence: mandible, maxilla, palatine bone (hard palate), cranial base and then tooth development (Kjaer, 1995).

Near the time of the mesenchyme outgrowth separating the face and the brain, neural crest cells are released from the juncture of the neurectoderm and ectoderm to create two bulges that will form the cerebral hemispheres and gradually cover the brain stem. These neural crest cells are released in a manner that corresponds to the frontonasal process, the maxillary process and the mandibular process (Kjaer, 1995). An insult occurring near this time of development or even after this time, may result in the findings of Deutsch, that dysmorphology of the frontonasal and maxillary regions are related to a skewed midline in the posterior regions of the brain in individuals with schizophrenia (Deutsch et al., 2000). The forebrain neuroectoderm develops in close relationship with the optic placode, olfactory optic and optic placodes (Kjaer, 1995).

The development of the skull base, found to be wider in patients with schizophrenia in this and other studies is in its cartiligenous form when the pituitary gland is in place. It appears as though the pituitary is encased in an orifice of the sphenoid body of the skull base. Some studies have found a close correlation between the development of the pituitary and the development of the skull base (Kjaer, 1995). Other studies have found that the development of the skull base is important for supporting and inducing the development of the other craniofacial structures (Degani et al., 2002).

At week 11, ossification of the skull base begins at the most posterior aspects of plates surrounding what will become the foramen magnum (Degani et al., 2002). At the same time, frontonasal growth is occurring and midbrain structures are developing at this time (Kjaer, 1995). The hippocampus begins development around week nine or ten and the entorhinal cortex is developing between weeks nine and a half to thirteen and half. At around week eleven the hemispheres of the brain are small and do not fully cover the midbrain and the hindbrain (Kjaer, 1995). Prenatal disruption occurring around this time can affect all of these structures and other midline structures such as the thalamus and hypothalamus. Midline brain abnormalities are thought to develop in schizophrenia between weeks nine to fourteen. In a review by Waddington and coworkers (Waddington et al., 1999b), the authors predicted that during this time of rapid face growth, disruptions to anterior brain development can result in elongation of the anterior portions of the face. Reductions in gray matter found in schizophrenia appear to be in the more anterior regions (prefrontal, and temporoparietal regions) rather than in more posterior regions (parietal and parietoccipital regions) (Waddington et al., 1999b). In addition, cytoarchitectural abnormalities found in postmortem studies of frontal areas and anterior portions of temporal lobe are thought to occur around weeks thirteen to fifteen (Waddington et al., 1999b, 1999c).

Disruption occurring during the first trimester when the above events are occurring can result in craniofacial dysmorphology found in schizophrenia in this and other studies including increased skull base width (by causing increased width to the middle cranial fossa), narrowing and elongation of the lower two thirds of the face and dysmorphology of fronto- nasal- maxillary regions (Waddington et al., 1999b).

In addition to the temporal and spatial proximity of the development of these structures, these structures appear to be under the influence of the same genes. For example, disruption of the *Barx* genes, a class of homeobox genes located on chromosome 11q 25 and expressed in craniofacial structures during prenatal development (Hjalt & Murray, 1999), can result in disruption to the development of craniofacial structures and neural structures such as the dorsal midline structures, as well as anterior embryonic structures. *Wnt* genes, which are responsible for encoding a large family of growth factors, encode intracellular signaling molecules important in prenatal development. Reduced expression of this gene has been found in schizophrenia, particularly in the subiculum and the hippocampus. Reelin, a protein that acts as a signpost for migrating neurons has been found to be reduced in schizophrenia, particularly in the areas of the frontal cortex, hippocampus, striatum and the cerebellum (Kjaer, 1995; Waddington et al., 1999b).

Insufficient vitamins that are important in embryonic development may result in maldevelopment. Retinoic acid is involved in the differentiation of neural crest cells (brain and face development), as well as cells in the mesochyme (skull development)

(London, 2000). Disruptions in retinoic acid signaling may account for a range of neural and craniofacial dysmorphogensis (Chaudhuri, 2000; Gelowitz et al., 2002). Over the past few years, prenatal vitamin D deficiency has been proposed as a cause of schizophrenia (McGrath, 1999), however the exact effects it may have on the development of the brain and on craniofacial structures has not yet been fully explored.

Assessing MPAs – the Waldrop and Halverson Scale

Most studies of craniofacial dysmorphology in schizophrenia to date have used some version of the Waldrop and Halverson scale (Waldrop & Halverson, 1971) to assess MPAs. This is a checklist used to assess the presence and severity of eighteen possible anomalies of the head (fine electric hair, hair whorls, head circumference, low seated ears, adherent ear lobe, malformed ears, asymmetrical ears, soft ears), face (epicanthus, telecanthus, high steepled palate, furrowed tongue, tongue with smooth-rough spots) hands (curved fifth finger, single transverse palmer crease) and feet (big gap between first and second toe, syndactyly, third toe longer than second toe). The Waldrop and Halverson scale was originally created about thirty years ago to assess MPAs in a sample of hyperactive Caucasian children. Several variations of this scale were used in schizophrenia research. One popular variation, modified by Green and colleagues (Green et al., 1987; 1989), used a stricter standard for determining telecanthus. Other authors omitted particular items, such as fine electric hair and hair whorls that may not be relevant to individuals who are of African-American descent. Still, other authors omitted some items for which they could not attain good interrater reliability (McGrath et al., 1995).

Although use of this scale indicated the presence of MPAs in some individuals with schizophrenia, it was criticized for having some drawbacks. Because the scale was originally created for Caucasian children, it may not be generalizable to adults or to non-Caucasian individuals. For example, items such as fine electric hair are never found in African-American individuals. In addition, epicanthus, a skinfold at least partially covering the lacrimal caruncle of the eye, is not anomalous for many individuals of Asian descent. Many researchers argued that the Waldrop and Halverson Scale is not sensitive to all of the anomalies found in schizophrenia. Indeed, two separate studies revealed increased prevalence of minor physical anomalies in schizophrenics that were not assessed by the Waldrop and Halverson Scale (for example heterochromia, thin upper lip and retarded toe) (Ismail et al., 1998b; Schiffman et al., 2002). Because it is a rating scale, it was also criticized for allowing too much room for subjectivity (Lane et al., 1997). In particular, even when examiners attempt to be uninformed of the diagnosis, the behavior or appearance for some individuals with schizophrenia may reveal psychiatric abnormalities, and thus influence what the rater would expect to find.

Since the time that the congenital form of schizophrenia was proposed, many researchers attempted to find relationships between MPAs as assessed by the Waldrop and Halverson scale and characteristics of the congenital subtype (Green et al., 1987, 1994b; Guy, et al., 1983; Lawrie et al., 2001; Lobato et al., 2001; Lyon et al., 1989). To review, those with the congenital form of schizophrenia are expected to be predominantly male with poor premorbid functioning, early age of onset, more negative symptoms, structural brain abnormalities, and neuropsychological deficits (Murray et al., 1992a). Research examining the relationships between MPAs (as assessed by the Waldrop and Halverson Scale) and these characteristics is described below.

MPAs and obstetric complications.

Several studies examined the relationship between MPAs and obstetric complications with inconsistent results. In two studies, O'Callaghan's group found a relationship between early prenatal bleeding and increased scores on the Waldrop and Halverson Scale (O'Callaghan et al., 1991; Waddington et al., 1998b). Alexander's group found a trend between MPAs and obstetric complications (Alexander et al., 1994). In monozygotic twins discordant for schizophrenia, increased Waldrop and Halverson scores were found in twins with the greatest number of obstetric complications (Cantor-Graae et al., 1994b). However, McGrath's group found no relationship between MPAs and OCs (McGrath et al., 1995). One potential reason for these discrepancies may be different methods of assessing prenatal and obstetric complications. Another potential reason is the inherent heterogeneity of the illness; however, most of the studies had moderately large samples (at least 40 subjects).

The relationship between MPAs and premorbid adjustment

Four studies to date examined the relationship between premorbid social adjustment and MPAs, with only one getting some estimate of premorbid cognitive functioning (Guy, et al, 1983; Ismail et al, 1998; McGrath et al, 1995; O'Callaghan et al, 1995). One study found a relationship between more numerous and severe MPAs and poorer composite scores on the Phillips Premorbid Adjustment Scale and the Vocabulary subtest of the WAIS-R (Guy et al., 1983). Because performance on the vocabulary subtest is less sensitive to brain insult, it is frequently used to estimate premorbid cognitive functioning. These preliminary results seem to indicate that MPAs may not be related to premorbid social adjustment but may be related to pre-illness cognitive functioning.

The relationship between MPAs and age of illness onset

Several authors tried to determine a relationship between age of onset and MPAs as well. The literature tended to support an earlier age of onset in males who are thought to have a more chronic and severe course of illness. Therefore, finding a relationship between MPAs and earlier age of onset would support the neurodevelopmental hypothesis of schizophrenia. Although one study found this relationship (Green et al., 1989), others did not (Akabaliev et al., 1998; Lohr et al., 1993). Green and coworkers in 1989 found that individuals with an age of onset (age at first hospitalization) before age eighteen had more numerous and severe MPAs than individuals with an age on onset after age eighteen (Green et al., 1989). However, most of the subjects with the early age of onset were males. Several other studies, however, found no relationship between age of onset and MPAs. For example, Akabeliev's group (1998) found that MPAs not related to age of onset as assessed by medical records and family interview age at first diagnosis of mental illness. Some potential factors that may have caused discrepancies among these studies include inherent heterogeneity of the illness, and the different methods of determining age of onset.

MPA and brain abnormalities in schizophrenia

In many neurodevelopmental disorders, prenatal events result in both brain abnormalities and physical anomalies. An example of this is Fetal Alcohol Syndrome. Individuals with FAS frequently suffer from some level of mental retardation and have particular physical anomalies such as epicanthus and malar flattening (Autti-Ramo et al., 1992; Day et al., 1991; Riese, 1989; Tennes et al., 1980). The brain and face are of ectodermal origin and their development is temporally close. It is expected that abnormal development of one region may impact adjacent regions. Because precursors of the brain and the face are close to each other in the fetus, maldevelopment of one may impact the development of the other. Similarly, development of the brain and face occur at the same time. Therefore, prenatal insult at the time of brain develop can impact the development of the face, causing minor physical anomalies. (Waddington et al., 1999a, 1999b). Because of this, two groups examined the relationship between brain structures and MPAs in schizophrenia. Alexander assessed the possible relationship between ventricular -brain ratio, area of the third ventricle (as assessed by CT scan) and MPAs as assessed by the Waldrop scale in 41 individuals with schizophrenia, eight subjects with bipolar disorder, 19 subjects with "mental handicap" and 14 healthy control subjects. The authors found, within the schizophrenia group only, that higher MPA scores were related to larger third ventricle size (Alexander et al., 1994). However, McGrath's group (1995), found no relationship between MPAs and lateral or third ventricle volume in seventy-nine subjects with schizophrenia. In an MRI study conducted by O'Callaghan and colleagues, MPAs were unrelated to lateral ventricle volume for the overall sample. However, they found that three individuals with more numerous and severe MPAs had qualitative anomalies of some aspects of the ventricular system (O'Callaghan et al., 1995). Due to the fact that the only two studies examining this relationship yielded contradictory results, more research needs to be done to elucidate the relationship between MPAs and brain abnormalities.

MPAs and neuropsychological dysfunction in schizophrenia

A handful of studies examined the relationship between NP functioning and MPAs in schizophrenia with unclear results. Ismail's group (2000) examined the relationship between an extended battery of neuropsychological tests such as the verbal memory test, Digit Span, verbal fluency and the Wisconsin Card Sorting Test and found that performance on these tests was unrelated to ratings of minor physical anomalies. Some studies found relationships between tests relying on motor speed, but not other tests of neurocognitive functioning. Green et al, 1994 found that MPAs were related to a test of neuromotor speed, but not tests of attention. O'Callaghan and coworkers found that greater MPA scores were related to poor performance on Trail making Test Part B (O'Callaghan et al., 1991). In a small battery of neuropsychological tests, McGrath found partial support for a relationship between neuropsychological functioning and MPAs; increased MPA scores were related to poor performance on a graphesthesia test for the right hand, but not verbal subtests of the WAIS or the NART (McGrath et al., 1995). However, other studies found some relationship between tests thought to reflect early cognitive functioning. Guy et al (1983) found that a combination of the Vocabulary subtest and Phillips Premorbid Adjustment Scale accounted for most of the variance in ratings of minor physical anomalies. In 1995, O'Callaghan's group found that estimates of poor premorbid intelligence were related to greater number and severity of MPA scores in females but not males (O'Callaghan et al., 1995). The inconsistencies across these studies can be attributed to differences in neuropsychological tests used and to the heterogeneity of neuropsychological functioning in schizophrenia. However, some studies find a positive relationship between MPAs and tests consistent with early cognitive dysfunction (WAIS Vocabulary and NART). Most studies fail to find a relationship between tests sensitive to later brain changes, such as tests of attention, and MPAs. However, no study examined these two types of cognitive tests within the same study. If, in the same study, a relationship was found between MPAs and poor performance on tests reflecting early neurocognitive functioning and no relationship was found between tests sensitive to later brain changes (such as tests of attention), this would lend support to the neurodevelopmental subtype of schizophrenia. To date, no study examining MPAs has distinguished between these two types of neuropsychological tests.

MPAs and gender

It has been proposed that, of the individuals with schizophrenia, the preponderance of those with the congenital subtype of illness would be male. Therefore, if MPAs were biological markers for the congenital subtype of schizophrenia, we would expect that the preponderance of individuals with schizophrenia having an increased incidence of MPAs would be male. Very few studies have examined the relationship between gender and MPAs, and these have yielded inconclusive results (Akabaliev et al., 1998; Alexander et al., 1994; Green et al., 1989). In a high risk study that examined children of schizophrenic parents, males demonstrated more severe and numerous MPAs than females (Marcus et al., 1985). In another study that examined the difference between individuals with schizophrenia and gender matched controls, there was a trend for females with schizophrenia to have greater MPAs than female healthy controls. However, the authors did not compare MPAs between gender groups (O'Callaghan et al., 1995). In another study finding no differences in MPAs between male and females with schizophrenia, the sample was overwhelmingly male (Akabaliev et al., 1998). Perhaps, the failure to find a relationship in this study had to do with the sample having too few females, thus reducing the power of the study. Finally, one study that found a relationship between MPAs and early age of onset, found this relationship in males only (Green et al., 1989).

Relationship between MPAs and negative symptoms

Although negative symptoms are not specific to the proposed congenital subtype of schizophrenia, it is expected that the preponderance of individuals with this subtype would have negative symptoms. Therefore, if MPAs were markers for the congenital subtype, we would expect negative symptoms to be related to high MPA scores. Very few studies examined this relationship. Three studies found no relationship between MPAs and negative symptoms (Lohr et al., 1993, 1997; McGrath et al., 1995). O'Callaghan and coworkers (1995), however, found a relationship between negative symptoms and greater number and severity of MPAs in males only (O'Callaghan et al., 1995).

MPAs as assessed by the Waldrop scale and characteristics of the congenital subtype of schizophrenia

Over the past two decades, researchers attempted to validate a neurodevelopmental or congenital subtype of schizophrenia by evaluating relationships between MPAs and characteristics of the proposed congenital subtype (for example, Akabaliev et al., 1998; Alexander et al., 1994; Green et al., 1989; Guy et al., 1983; Lohr et al., 1993) McGrath et al, 1995 (O'Callaghan et al., 1995). However, findingsof relationships between MPAs and these characteristics are inconclusive. Despite its popularity, many researchers criticized the Waldrop and Halverson Scale for several reasons, including its limited usefulness across different racial groups, its inability to assess all of the MPAs which may be present in schizophrenia, and because of the inherent difficulties in making objective ratings of such subtle anomalies when informed of diagnosis (Lane et al., 1997). Perhaps the reason why no relationships were found between MPAs and characteristics of the congenital subtype is because of the limitations of the Waldrop and Halverson Scale. Other methods may yield results that are clearer.

Anthropometric methods to assess physical anomalies

The anthropometric method of assessing physical deviance involves taking measurements of features of the head and face using calipers, angle finders and tape measures. These methods have been used extensively in reconstructive surgery (Cutting & Dayan, 2003; Tiwari et. al., 2003) and anthropology (Dean et. al, 1998). These measurements are then compared to published normative values. While anthropometric methods are rather common in physical anthropology, only three studies to date have been published in detail that used anthropometric assessment in individuals with schizophrenia.

Lane and coworkers published the first study in 1997. In this study (Lane et al., 1997), a detailed set of craniofacial measurements and anthroscopic rating items were compiled and applied to one hundred and seventy-four individuals with schizophrenia and eighty demographically matched controls. All of the subjects were Caucasian, were of Irish descent and lived in the same region in Ireland. Compared to the Waldrop and Halverson Scale, the extended scale, which included anthropometric measurements, was able to better distinguish between healthy individuals and those with schizophrenia. These authors reported an overall elongation and narrowing of the lower and midfacial regions in patients with schizophrenia. Specific abnormalities of the head and face were reported as well and included high palate ($p<.001$), smaller mouth width ($p=.005$), greater ear protrusion ($p<.001$) and larger skull base width ($p<.0007$). This study demonstrated that anthropometric methods are superior to traditional anthroscopic methods such as the Waldrop and Halverson scale in detecting physical anomalies in individuals with schizophrenia.

The second study was published in December 2000 by Deutsch and coworkers (Deutsch et al., 2000). This group assessed craniofacial dysmorphology in ten subjects with schizophrenia, nine unaffected siblings of the patient probands, and ten normal control subjects. In addition, MRI studies were conducted on all of these subjects to assess deviations in the brain midline. The projected midline extended from the most anterior point of the interhemispheric fissure and the midpoint of the frontal horns through the third ventricle. In healthy controls, this midline was straight, but in individuals with schizophrenia, the posterior portion (posterior to mesencephalic structures) of the line was skewed.

All of the subjects were Caucasian, between ages 25 and 45, and right handed. In those with schizophrenia, morphological deviations were found in measurements related to frontonasal and maxillary processes. Specifically, subjects had anomalies of the eyes including length and inclination of the palpebral fissures and deviations in the mouth and upper palate. On MRI studies, the midline was delineated from the most anterior point of the interhemispheric fissure and the midpoint of the frontal horn. The line intersected the midline structures from the anterior pole of the longitudinal fissure and the third ventricle and projected through the posterior portions of the brain. These authors found that upon inspection, subjects with schizophrenia had greater deviations in posterior aspects if the brain midline (the degree to which the posterior aspects of the interhemispheric fissure deviated from the projected midline). Midline deviation scores were calculated for all of the subjects (for details see Deutsch et al., 2000). Subjects with schizophrenia had significantly greater midline deviation scores than normal controls. Siblings of schizophrenic probands had midline deviation scores between the probands and normal controls. However, the difference between siblings and normal controls on midline deviations scores was at the trend level. In the subjects with schizophrenia, correlations of moderate size were found between craniofacial deviation scores and midline interhemispheric deviation scores. The authors concluded that aberrant frontomaxillary development is related to deviations in midline brain development at the diencephalic -mesencephalic juncture. They postulated that these deviations occur early in prenatal development and can be due to genetic or intrauterine disruptions. These findings made a great contribution to the literature by providing further support for the neurodevelopmental model in schizophrenia. However, the authors themselves indicated that further studies must be conducted in larger samples (Deutsch et al., 2000).

The last study published to date was conducted by McGrath and coworkers (2002). As part of a large epidemiological study in Australia, this group collected individual minor physical anomalies and quantitative measurements of the head and face in 310 individuals with psychosis and 303 nonpsychotic control subjects. From these 180 matched pairs were derived (matched by age and gender). The entire sample consisted of Caucasians and aboriginals of Australia between the ages of eighteen to sixty-four. Only Caucasian subjects were used for the matched pairs analyses because, better normative data was available for this group. These authors found that specific measurements and physical anomalies could predict the presence of a psychiatric disorder (using odds ratio for the matched pairs) including wider skull base width (a finding similar to that of Lane and coworkers), smaller facial height, protruding ears, and wider palates. Principal components analysis of the entire sample revealed two factors: 1) an overall craniofacial size factor for which all of the measurements were positively loaded and 2) a craniofacial shape factor with positive loadings for face length measurements and negative loadings for skull base width and length. These authors concluded that individuals with psychosis have brachycephalic skulls (shorter and wider) and shortened lower thirds of the face. They projected that these findings may also be related to early development of the middle cranial fossa and abnormalities in the development of the temporal lobes (McGrath et al., 2002).

Hypotheses

The purpose of this study is to determine whether there is support for a congenital subtype of schizophrenia using an anthropometric scale to assess minor physical anomalies. No published study to date assessed the relationship between characteristics of the proposed congenital subtype of schizophrenia and MPAs using anthropometric methods.

The first hypothesis of the present study is that measures from the anthropometric scale and minor physical anomalies would reflect early prenatal maldevelopment. Therefore, it was expected that anthropometric measures and minor physical anomalies would be related to each other. Finding such a relationship would support the idea that both types of methods assess the same physical deviance. Failure to find such a relationship may indicate that one or both of these methods are not valid methods of assessing physical deviance. Alternatively, failure to find this relationship may indicate that these two methods assess physical deviance in difference ways. Perhaps the MPA scale assesses physical deviation related to the epidermis whereas the anthropometric scale assesses physical deviation related to the skull. In tis case, further tests of validity would need to be conducted.

Next it was hypothesized that individuals with schizophrenia and schizoaffective disorder have greater physical deviance relative to healthy adults. Therefore, it was expected that both MPAs and anthropometric measures would distinguish between patients and healthy controls. Specifically, it was expected that patients will have an excess of minor physical anomalies and deviant craniofacial measurements relative to healthy controls. Because previous studies generally find an excess of physical anomalies and craniofacial differences in individuals with schizophrenia, failure to find similar differences in this study may indicate poor validity of these methods as indicators of physical deviance.

Next it was hypothesized that a subgroup of patients have a neurodevelopmental subtype of schizophrenia. In order to test this hypothesis, statistical analyses would be used to examine whether MPAs and anthropometric measurements can distinguish a neurodevelopmental subtype of the illness. Three possible indicators of a neurodevelopmental subtype could be used: cognitive functioning, life functioning and age of onset. It was expected that MPAs and anthropometric measures would be related to a pattern of performance on neuropsychological tests consistent with early cognitive difficulties. Finding such a relationship would support the concept that individuals with schizophrenia and schizoaffective disorder with greater physical deviation also have poor early cognitive dysfunction, consistent with the neurodevelopmental hypothesis. It was also expected that MPAs and anthropometric measurements would be related to poor life functioning. Finding such a relationship would also support the neurodevelopmental subtype; those with the neurodevelopmental subtype are thought to have poor illness outcome. Finally, it was expected that increased physical deviance using MPA and anthropometric measurement instruments would be related to earlier age of illness onset. Those with the neurodevelopmental subtype are proposed to have an earlier age of illness onset. Therefore, finding this relationship would support the presence of a neurodevelopmental subtype.

Methods

A multidimensional cross-sectional design was employed to determine the degree to which assessment using the extended Waldrop and Halverson Scale and the Anthropometric scale could distinguish individuals with schizophrenia and schizoaffective disorder from healthy adults matched according to age, race and gender. Next, composite scores from the anthropometric scales and minor physical anomalies were used to determine the degree to which anthropometric measures were associated with putative indicators of a congenital subtype including earlier age of illness onset, low performance on tests of cognitive functioning and poor ratings of independent functioning in a sample of outpatients with schizophrenia or schizoaffective disorder.

Subjects

Subjects in schizophrenia and schizoaffective disorder group (SZ/SA)

Subjects in the schizophrenia/ schizoaffective disorder group (SZ/SA) were 61 consenting patients randomly selected from a longitudinal study examining the relationship between cognitive functioning and functional outcome, already being conducted at the Zucker Hillside Hospital. At the time subjects began the longitudinal study, they met the inclusion criteria of: (1) age between 18 and 56; (2) history of a severe psychiatric disorder for at least 5 years; (3) confirmation of schizophrenia or schizoaffective disorder diagnosis using the Structured Clinical Interview for the DSM IV (SCID) (First et al., 1995); (4) fluency in English; (5) no history of a primary neurological disorder. In addition, (6) subjects had to be of either Caucasian or African-American decent because normative data was only available for these groups in North

America. Finally, (7) subjects were eligible only if they had never undergone any cosmetic or reconstructive surgery to the head or face or if they had suffered a fractured bone in the head or face. Such surgeries and injuries are likely to be reflected in the measurements. During follow-up assessments in the longitudinal study, individuals who could be assessed in person at Zucker Hillside Hospital were asked to participate, so that they may be assessed in a dental chair to ease the process of measurement for both subject and experimenter. As patients were encountered who refused to participate, the process was repeated until at least 60 patients consented to the study.

Normal control subjects

Fifty-eight control subjects were recruited from the community. They had to be (1) between ages 18 and 60 (similar in age to the subjects with schizophrenia/ schizoaffective subjects) 2) no history of psychiatric hospitalization, 3) no history of learning disability or mental retardation, and 4) no history of cosmetic surgery or bone fracture to the head or face. The subjects were recruited by three methods: fliers posted in the community, the Zucker Hillside Hospital normal control subject pool, and the Queens College subject pool.

Thirty-nine of the subjects in the healthy control group responded to flyers posted in the community. Fliers were posted in Nassau County and Queens at local businesses including supermarkets, restaurants, colleges, laundromats, hair salons and other local businesses. The flyer asked for healthy adults who have not had cosmetic surgery or history of psychiatric hospitalization to participate in a research study. The flyer indicated that subjects would be reimbursed for their time (See Appendix 2 Healthy Control Flyer).

Eighteen subjects were recruited from the Normal Control Project at Zucker Hillside Hospital. These subjects previously responded to newspaper advertisements and flyers within the community and participated in research projects at Zucker Hillside Hospital as healthy controls in studies of mental illness. A recruiter from the Normal Control Project contacted them by phone and gave them information about this present study. The recruiter asked their permission to give contact information to the investigator. If such permission was granted, the investigator contacted them, described the study and invited them to participate.

One subject was recruited from the Queens College Subject pool. Students taking introductory psychology courses at Queens College are required to complete a research requirement by either reviewing current articles in psychology or by participating as research subjects for three hours in total. Experimenters post a flyer on a designated bulletin board for students to respond to. Students are given a voucher for their participation to indicate to their instructors that they completed the requirement. The subject responded to a flyer posted by the investigator.

All healthy control subjects were reimbursed for their participation and transportation.

Procedure

Subjects with schizophrenia or schizoaffective disorder who were participants in a longitudinal study at Zucker Hillside Hospital and were able to travel to this location were selected and recruited for this study. The longitudinal study examined the relationship between performance on neuropsychological tests and independent functioning as assessed using the Multidimensional Scale of Independent Functioning (work, education and residential functioning). In order to participate in the longitudinal study, all subjects had to meet criteria for a diagnosis for schizophrenia or schizoaffective disorder using the Structured Clinical Interview for DSM-IV (SCID) Mood and Psychosis Modules (First et al., 1995). In addition, they were administered the Zucker Hillside Hospital History interview which asks about demographic information and personal history (age, gender, education, work history, age of first symptoms, age of first treatment). In addition, these individuals were administered a series of neuropsychological tests including the Wechsler Adult Intelligence Scale – Revised Edition. (WAIS-R).

Healthy subjects were recruited from the community, the Zucker Hillside Hospital Normal Control project and the Queens College subject pool, as described above. Written consent was obtained from all subjects participating in this study (See Appendices 3 and 4). They were then asked questions to determine their eligibility to participate. Next, subjects were interviewed regarding their racial and ethnic background, and dental history (specifically if they worse dentures or partials, and if they had any teeth pulled or lost any teeth). The purpose of assessing dental work is that it may impact upon measurements of the lower face. According to Farkas (personal communication, 2000), the mandible and maxillare may diminish in size after teeth are removed. In order to assess body mass index, height and weight were measured for each subject.

According to Farkas (personal communication, 2000), individuals with deviant body mass (e.g. extreme obesity) tend to have deviant craniofacial measurements. Finally subjects were rated for the presence of physical anomalies using an extended version of the Waldrop and Halverson Scale and measurements of the subjects' head and face were taken. These procedures and training for these procedures are described below.

The Extended Waldrop and Halverson Scale

Subjects were examined for the presence of minor physical anomalies using an extended version of the Waldrop and Halverson Scale. The Waldrop and Halverson scale is an anthroscopic tool assessing the presence and at times severity of minor physical anomalies of the head, face, hands and feet. Although originally created for children, this scale is the most widely used instrument for assessing minor physical anomalies in adult schizophrenia.

Development of the extended version of the Waldrop and Halverson Scale.

The original Waldrop and Halverson scale consists of 18 items. For most of the items, the presence or absence of physical anomalies is noted by assigning a rating of one if the item is present or zero if it is absent. Some of the items have an additional severity rating (zero for absent, one for mild and two for severe). Some items from the scale, such as hair whorls and fine electric hair were omitted because these would never be present in African-American subjects. The items from the original Waldrop and Halverson scale are listed in Table 1.

Table 1: Description of original Waldrop and Halverson Scale items

Items	Definition	Rating
Fine Electric Hair*	Fine hair that stands on end and cannot be combed down easily	2= very fine 1= fine 0 = absent
Hair whorls*	A tuft of hair usually near the crown of the head that turns in a particular direction. It is usually not in midline and it typical for an individual to have one hair whorl.	1 = 2+ whorls 0 = 1 whorl
Head circumference**	Distance around the head.	2 = > 2 s.d. from mean 1 = $\geq$1 s.d. from mean 0 = <1 s.d. from mean
Epicanthus	A fold of skin near the inner corner of the eye that at least partially covers the lacrimal caruncle	2 = covering whole lacrimal caruncle 1 = partial covering 0 =absent
Hyperteliorism**	Abnormally large distance between the eyes	2 = > 2 s.d. more than mean 1 = $\geq$1 s.d. more than mean 0 = <1 s.d. more then mean
Low set ears ***	Ear sitting too low on the side of the head	2 = severe, 1 = mild 0 = absent
Adherent ear lobes	The ear lobe does not extend beyond the lower attachment of the front of the ear to the head	2 = lower edge upward and backwards 1 = horizontal lower edge 0 = absent
Malformed ears		1= yes, 0 = no
Asymmetric ears	Ears are visible different by sight not just by measurement	1= yes, 0 = no
Soft ears	The helix of the ear is soft and pliable to the touch and does not spring backward readily when pushed forward.	1= yes 0 = no
Palate	The palate, instead of being wide and round is narrow and flat at the top or narrow and pointed at the top	2 = clearly "steepled" 1= narrow and flat 0 = normal
Furrowed tongue ***	A line or grease running down the length of the tongue but not at the midline	1= yes 0 = no
Tongue with smooth rough spots	Tongue has raised flat patches.	1= yes 0 = no
Curved fifth finger	Fifth finger curves inward.	2 = markedly curved 1= slightly curved 0 = curve not present
Single transverse or abnormal palmar crease		1= yes 0 = no
Third toe longer than second toe ***		2 = clearly longer 1 = same length 0= no
Syndactyly	Webbing between toes	2= halfway to the distal interphalangeal joint 1= partial to the proximal interphalangeal joint 0 = no
Big gap between first and second toes		1= yes 0 = no

* This item was excluded because it does not generalize to this multiracial sample
** This item was assessed using measurement and training occurred as part of the measurement scale.
*** Because adequate agreement was not attained between two raters prior to collecting data for subjects used in this study, this item was not used

The Waldrop and Halverson scale has been criticized because it consists of few items and does not capture all of the anomalies thought to occur in schizophrenia (Ismail et al., 1998b; Trixler et al., 2001). In 1998, Ismail and coworkers developed an extended version of the Waldrop and Halverson scale including many more items. Based on photos of these anomalies, they rated the presence or absence of these anomalies in individuals with schizophrenia (Ismail et al., 1998b). For this study, additional items were added based on this group's modification of the Waldrop and Halverson Scale. The presence or absence of these features is rated in a manner similar to that used for the Waldrop and Halverson Scale (a rating of zero for absent and one for present).

In addition, several papers have been published describing the features of individuals with 22q11 deletion syndrome (also called velo-cardiofacial syndrome), a chromosomal abnormality resulting in specific differences in facial features, as well as cognitive difficulties and heart abnormalities (Holder et al., 1993; Usiskin et al., 1999). Approximately fifteen percent of individuals with 22q11 deletion syndrome have schizophrenia as well (Bassett et al., 1998, 1999). Several facial anomalies typically found in 22q11 deletion syndrome were added to the extended Waldrop and Halverson scale. Although the percentage of individuals with schizophrenia having this chromosomal deletion is small, some individuals with schizophrenia have anomalous facial features similar to 22q11 deletion syndrome, even though they do not have the chromosomal abnormality. Both the Ismail group items and the items from 22q11 deletion syndrome are listed in Table 2.

Table 2: List of items added to the original Waldrop and Halverson Scale items

Region	List of added items from Ismail's group (1998)	22q11 deletion syndrome items added
Face	Fused eyebrows	Retrognathia
	Anteverted nostrils	Narrow elongated face
	Micrognathia	Bulbous nasal tip
		Flattened nasal tip
		Narrow alar bases
		Squared nasal root
Eyes	Heterochromia	Shortened eye fissure
	Colombata	Long narrow palpebral fissures
Ears	Preauricular skin tag	Outstanding ears
	Ear lobe skin tag	
	Sinus before or behind the ear	
Mouth	Cleft uvula	
	Cleft lip microform	
	Thin upper lip	
Hands	Fifth finger one or three creases	Long fingers
	Retarded fingers	Slender hands
	Overlapping fingers	
	Small fingernails	
	Hyperconvex fingernails	
Feet	Deep crease or grooves on soles of foot	
	Overlapping toes	
	Retarded toes	
	Hyperconvex toenails	

All of the items listed on Table 2 were combined to create a new extended Waldrop and Halverson Scale for the purpose of the present investigation.

Rater training and reliability on the Extended Waldrop and Halverson Scale.

In order to establish the reliability of the investigator's ratings on the Extended Waldrop and Halverson Scale, a second rater underwent the same training. The two raters studied the items of the Waldrop and Halverson Scale, the additional items on McNeil's version of the scale and items associated with 22q11 deletion syndrome. After practice and discussion of item ratings, the two raters examined ten individuals at Zucker Hillside Hospital with a dual diagnosis of mental retardation and mental illness. This sample was selected because individuals with mental retardation typically have more physical anomalies than healthy individuals and those with purely psychiatric diagnoses. Therefore, the raters were more likely to see and rate the presence of anomalies in this population. Ismail reported that raters in his study learned the scale by rating individuals with mental retardation (Ismail et al., 1998b).

Because there was such little variation in the ratings, inter-rater reliability was determined by percent agreement between the two raters. Items with at least an 80% agreement were used in the study. Failure of just one rater to rate an item was counted as a disagreement. Of the total number of forty-two items that were rated in the pilot subjects having mental retardation, the raters attained at least 80% agreement for thirty-five of the items. The percent agreement for each of the items is listed in the Tables 3a to 3f. For two items, adherent earlobes and high palate, while the raters had high agreement for the presence of the anomalies, they had some disagreement regarding the severity of the anomalies. For these two items the number of subjects for which the raters agreed and disagreed on the presence of the anomalies is listed on the table in parenthesis.

Table 3a: Extended Waldrop and Halverson ratings for ten pilot subjects with mental retardation. – Head region

Region	Measure	% Agreement	Used for composite score
Head/face	Fused eyebrows	90%	Yes
Head/face	Frontal bossing	100%	Yes
Head/ face	Anteverted nostrils	60%	No
Head/ face	Micrognathia	100%	Yes
Head/ face	Retrognathia	90%	Yes
Head/ face	Narrow face	100%	Yes
Head/ face	Bulbous nasal tip	100%	Yes

Table 3b: Extended Waldrop and Halverson ratings for ten pilot subjects with mental retardation. – Eye region

Region	Measure	% Agreement	Used for composite score
Eyes	Epicanthus	90%	Yes
Eyes	Heterochromia	100%	Yes
Eyes	Ptosis	100%	Yes
Eyes	Colombata	100%	Yes
Eyes	Shortened eye fissure	80%	No
Eyes	Long narrow palpebral fissures	100%	Yes

Table 3c: Extended Waldrop and Halverson ratings for ten pilot subjects with mental retardation. – Ear region

Region	Measure	% Agreement	Used for composite score
Ears	Adherent ear lobes	60% (90% presence)	Yes*
Ears	Malformed ears	90%	Yes
Ears	Outstanding ears	90%	Yes
Ears	Low set ears	40%	No
Ears	Asymmetrical ears	90%	Yes
Ears	Soft ears	100	Yes
Ear	Earlobe skin tag		Yes
Ears	Preauricular skin tag	100	Yes
Ears	Sinus in anterior to the ear	100	Yes

*** The two raters agreed about the presence of the adherent earlobes with 90% accuracy, but disagreed about the severity of the anomaly in three subjects.**

Table 3d: Extended Waldrop and Halverson ratings for ten pilot subjects with mental retardation. – Mouth region

Region	Measure	% Agreement	Used for composite score
Mouth	High narrow palate (1=mild, 2 = steepled)	70 (90% for presence)	Yes **
Mouth	Furrowed tongue	50%	No
Mouth	Tongue with smooth rough spots	100%	Yes
Mouth	Cleft lip	100%	Yes
Mouth	Thin upper lip	100%	Yes

**** The raters agreed to the presence of the anomaly in nine subjects that were rated.**

Table 3e: Extended Waldrop and Halverson ratings for ten pilot subjects with mental retardation. – Hand Region

Region	Measure	% Agreement	Used for composite score
Hands	Curved firth finger	90%	Yes
Hands	Abnormal palm crease	100%	Yes
Hands	One or three creases on fifth finger	100%	Yes
Hands	Retarded finger	100%	Yes
Hands	Tapered fingers	70%	No
Hands	Long fingers	70%	No
Hands	Slender hands	100%	Yes
Hands	Overlapping fingers	100	Yes
Hands	Hyperconvex finger nails	100	Yes

Table 3f: Extended Waldrop and Halverson ratings for ten pilot subjects with mental retardation. – Foot region

Region	Measure	% Agreement	Used for composite score
Feet	Third toe longer than second	70%	No
Feet	Syndactily	100	Yes
Feet	Gap between first and second toe	100	Yes
Feet	Overlapping toes	90	Yes
Feet	Retarded toe	100%	Yes
Feet	Hyperconvex toenails	100%	Yes
Feet	Crease or grooves on soles of feet	77%	No

Only the items for which at least 80% agreement was achieved in the test sample were used for the subjects in the main study (schizophrenia/ schizoaffective disorder group and healthy control group). The scores for each item were added together to obtain two summary scores: 1) a sum of the items from the original Waldrop and Halverson Scale (ORIG-WAL) and the sum of all of the anthroscopic scores (EXTEND-WAL), including those from Ismail's group and those found in 22q1 deletion syndrome. It is expected that some individuals who are healthy may have a few minor physical anomalies. In order to determine if there is an excess of minor physical anomalies the composite score is used. Unlike anthropometric measurements, which are related to each other, minor physical anomalies are thought to be unrelated, therefore it is acceptable and standard practice to use a summary score (for example, Akabaliev & Sivkov, 1998; Green et. al, 1989, 1995; Marcus et. al, 1985; O'Callaghan et. al, 1991, 1995; Waddington et al, 1995).

Anthropometry scale

Rater training and reliability on the Anthropometric Scale. The anthropometric scale consists of measurements of the head and face, using sliding calipers, spreading calipers, and tape measures. These measurements are described in greater detail in the appendix. (See Appendix 5).

Dr. Leslie Farkas, of the Hopsital for Sick Children in Toronto and the creator of the Anthropometric Scale, trained the investigator over a five-day period. The investigator studied these measurements independently, prior to the formal training by studying Farkas' published methods (Farkas et. al, 1994) and practicing the measurements. Dr. Farkas identified eighteen items, which he deemed the most challenging measurements on the scale and collected these measurements from ten healthy adults. Every type of measurement was represented. The investigator took the same measurements from those ten individuals. Intra-class correlation coefficients

(ICCs) comparing the measurements of Dr. Farkas and those of this investigator were calculated and are listed in the Table 4.

Table 4: Intra-class correlation coefficients achieved for each of the eighteen measurements on ten healthy pilot subjects

Measurement	Landmarks used	ICCs
Length of the head	g-op	.98
Width of the head	Eu-eu	.87
Width of the face	Zy-zy	.94
Width of the mandible	Go-go	.65
Width of the forehead	Ft-ft	.81
Width of the maxillare	mx-mx	.22
Anterior height of the head	v-n	-.16
Craniofacial height	v-gn	.68
Auricular height of the head	v-po	.16
Morphological height of the face	n-gn	.90
Height of the lower face	Sn-gn	.97
Height of the mandible	Sto-gn	.84
Length of eye fissure (right eye)	Ex-en	.88
Height of the eye fissure	Ps-pi	.47
Width between the facial insertion points of the alar base	Ac-ac	.83
Width of the nose	Al-al	.89
Width of the mouth	Ch-ch	.64
Inclination of the upper face profile	Inclin g-sn	-.17

Those measurements with an ICC below .80 were omitted from analyses in the main study samples. Similarly, measurements from the original scale had not been selected for inter-rater reliability testing but were similar (using similar instruments and methods) to those measurements having ICCs below .80, were also eliminated from analyses. As a result, the Anthropometry scale used for the analyses in this study consisted of 33 measurements. The measurements in the final scale included those measurements for which an ICC of at least .80 was attained and those measurements that were similar to them (using similar instruments and methods).

Anthropometric measurements and Extended Waldrop and Halverson scale ratings were obtained for 61 patients with a diagnosis of schizophrenia or schizoaffective disorder and 58 control subjects who were similar to the patient group on gender, race (Caucasian or African-American) and age (within five years.) As the patient recruitment proceded, normal control subjects were recruited based on whether or not they were the same gender and race as a subject in the patient sample. In addition, they had to be within five years of age from another subject in the patient group.

Data reduction was achieved for each of these scales. For the Waldrop and Halverson scale, overall scores were obtained by adding the scores on this scale resulting in a ORIG-WAL score (sum of all of the items from the original Waldrop and Halverson scale), and EXTEND-WAL (sum of all of the original and added items). Data reduction for the Anthropometry Scale was achieved using Principal Components Analysis.

It was first hypothesized that ratings of both minor physical anomalies and anthropometry measurements would both reflect early developmental deviation. Therefore, it was expected that both measures would be related to each other. Based on published cut off scores for the original Waldrop and Halverson Scale, subjects were divided into those with an excess of minor physical anomalies and those without an excess of anomalies. It was hypothesized that individuals rated as having an excess of minor physical anomalies would also differ from those without anomalies on Anthropometry factor scores. Next, it was predicted that individuals in the schizophrenia/ schizoaffective disorder group would have higher ratings on the Waldrop and Halverson Scale and would differ from normal controls on scores derived from the Anthropometry Scale. Analysis of Variance and the General Linear Model were used in order to examine this relationship. The Westfall approach was used to correct for test multiplicity. Finally it was hypothesized that indicators of deviance on these craniofacial indices can distinguish a neurodevelopmental subtype among the patients. In order to test this hypothesis, the relationships between the Waldrop and Halverson and Anthropometry scores and measures thought to be related to a neurodevelopmental subtype (cognitive, clinical and functional history) were examined. The relationship between performance on cognitive tests and minor physical anomaly and anthropometry scores was examined using t-tests Pearson Correlation and Spearman Rank Order Correlation. Similarly, the relationship between age of onset and minor physical anomaly scores and anthropometry scores was examined using Pearson and Spearman Rank order correlations. Finally, the relationship between ratings of life functioning disability and minor physical anomaly and anthropometry scores was examined using Chi-Square and t-tests.

Results

Characteristics of subjects

Of the individuals with schizophrenia/ schizoaffective disorder (SZ/SA group) who participated in the study, 31 (50.8%) of the subjects had a diagnosis of schizoaffective disorder, 27 (44.3%) had a diagnosis of schizophrenia, paranoid subtype and three (5.9%) subjects had a diagnosis of schizophrenia, undifferentiated type.

Table 5: Diagnoses in sample with mental illness

	Schizoaffective disorder	Schizophrenia, paranoid subtype	Schizophrenia undifferentiated subtype
SZ/SA group	31	27	3
% of patient sample	50.8%	44.3%	5.9%

The average age of individuals in the SZ/SA group was 39.58 years (standard deviation = 9.4) with age ranging from 19.94 years to 53.81 years. Thirty-eight (62.3%) of the subjects were male and 23 (37.7%) of these subjects were female. Thirty-four individuals were Caucasian (55.7%) and 27 (44.3%) were African-American. Average age of symptoms onset was 18.57 years (standard deviation = 8.14 years, range 5 years to 40 years) and average age of first treatment for psychiatric illness was 20.61 years (SD=7.34 years, range 7 years to 40 years).

Table 6: Gender and race of SZ/SA group and healthy control group

	# Male	# Female	# Caucasian	# African-American
Number of patients (percentage)	38 (62.3%)	23 (37.7%)	34 (55.7%)	27 (44.3%)
Number of healthy control subjects (percentage)	31 (53.4%)	27 (46.6%)	37 (63.8%)	21 (36.2%)

In the healthy control sample, the average age was 37.96 years (standard deviation = 10.8 years, ranging from 19 years to 59 years). Thirty-one (53.4%) of the subjects were male and 27 (46.6%) were female. Thirty-seven of the control subjects (63.8%) were Caucasian and 21 (36.2%) were African-American. Healthy control subjects did not differ significantly from the SZ/SA group in age, (F (1, 117) = .75, p = .390), nor did these groups differ in height (F (1, 116) = .82, p=.68). However, individuals with schizophrenia and schizoaffective disorder weighed significantly more than healthy control subjects, (F (1,117)= 11.92, p =.001).

Table 7: Age, weight and height of SZ/SA group and healthy control group

	Schizophrenia/ schizoaffective sample	Normal control sample	Difference between patient sample and normal control sample
Age (years)	M = 39.57 Range 19.94 – 53.84	M= 37.97 Range 19.00- 59.00	F (1, 117)= .75 p= .390
Weight (lbs.)	M = 211.39 Range= 138-320	M = 182.45 Range = 103- 280	F (1, 117) = 11.92 p= .001
Height (inches)	M = 67.63 Range = 59 -76	M = 67.94 Range = 59 - 78	F (1, 116) = .82 p=.677

Calculating Extended Waldrop and Halverson Scale scores.

Due to the low occurrence rate of some of the physical anomalies, intraclass correlation coefficients could not be calculated. As described previously, composite scores were obtained by adding together all of the scores for which two raters achieved at least 80% agreement when rating pilot subjects with mental retardation. This level of agreement is an accepted standard (Nunnally, 1978). Separate scores were attained for those items that were from the original Waldrop and Halverson scale (ORIG-WAL). While the original Waldrop and Halverson scale consists of eighteen items, two of the items (fine electric hair and hair whorls) were not used because they were not applicable to some of the individuals in this multi-racial sample. Furthermore three additional items from the Waldrop and Halverson Scale (low set ears, furrowed tongue, and third toe longer than second toe) were omitted because raters could not agree on their presence in the pilot subjects. As a result, ORIG-WAL consisted of thirteen items from the Waldrop and Halverson Scale. The extended Waldrop and Halverson Scale (EXTEND RATE) consisted of the thirteen items of the ORIG-WAL scale, eighteen items from McNeil's scale and six items from the literature on 22q11 deletion syndrome. The items are listed in the Table 8.

Table 8: Extended Waldrop and Halverson Scale used in healthy control subjects and subjects with schizophrenia and schizoaffective disorder.

Region	Waldrop and Halverson items	Ismail group's items	22q11 deletion syndrome items
Head/Face	Head circumference	Frontal bossing Micrognathia	Retrognathia Narrow elongated face Bulbous nasal tip
Eyes	Epicanthus	Fused eyebrows	Long narrow palpebral fissures
	Telecanthus	Heterochromia Ptosis Colombata	
Ears	Adherent ear lobes Malformed ears Asymmetric ears	Pre-auricular skin tag Ear lobe skin tag Preauricular skin tag or skin tag behind the helix	Outstanding ears
	Soft ears		
Mouth	High palate Tongue with smooth rough spots	Cleft lip Thin upper lip	
Hands	Curved fifth finger	Fifth finger – one or three creases	Slender hands
	Single transverse or abnormal palm crease	Retarded finger	
		Overlapping fingers Hyperconvex fingernails	
Feet	Syndactyly Big gap between first and second toe	Overlapping toes Retarded toe	
		Hyperconvex toenails	

Calculating Anthropometry Scale scores.

Intraclass correlation coefficients were calculated to determine inter-rater reliability. This method is superior to using correlation to calculate inter-rater reliability (Bartko & Carpenter, 1976). Only measurements with ICCs of at least 80% (in pilot subjects) were used. This is a generally accepted standard of agreement (Nunnally, 1978). In each subject, for each of the 33 head and face regions measured, two to four actual measurements were taken. At least two of these trials were required to yield measurement values within one millimeter of each other. Only those values within one millimeter of each other were used for further analyses; the rest were discarded. This was to further ensure a high standard of reliability.

Averages for each measure were then calculated, resulting in 33 measurement averages for each subject. In order to analyze possible relationships between the anthropometry data and putative indicators of a neurodevelopmental subtype, the anthropometry data had to be further compressed using principal components analysis. In addition, conducting principle components analysis on the combined sample of healthy control and patient subjects has the potential to act as a discriminant functions analysis by elucidating differences between the two groups.

Two possible methods were considered. One was to conduct a principal components analysis on the average measurements themselves. However, the original patient (n=61) and normal control (n=58) samples were dissimilar in terms of gender and race. In order to eliminate race and gender differences between the patient sample and the normal control sample, only 52 subjects from each sample were used. Each subject in the patient sample had an age- (within five years), gender- and race- matched counterpart in the normal control sample thus eliminating racial and gender differences between the two groups. For these 104 subjects, 33 measurement averages were entered into a principal components analysis, which yielded six factors. They are listed in Table 9.

Table 9: The Six Head Measurement Factors.

Component number	Component title	Eigenvalue	Variance accounted for *	Measurements correlated with component	Loading
1	HEAD SIZE MEAS	14.49	43.91	All measurements have a loading of at least .5 except for those related to lip size.	
2	LIP SIZE MEAS	4.50	13.64	Vermillion height of upper lip Vermillion height of lower lip *Length of right ear* *Length of left ear* Width between facial insert points of the alar base Intercanthal width Width of nose	.72 .70 *-.66* *-.63* .59 .58 .50
3	FACE HEIGHT MEAS	2.70	8.20	Height of the lower face Morphological height of the face Height of cutaneous upper lip Physiognomic height of the upper face	.65 .56 .54 .49
4	EYE LENGTH MEAS	2.03	6.14	Length of eye fissure Right eye Left eye	 .52 .48
5	NOSE SIZE MEAS	1.54	4.66	Width of nose Width between facial insertion points of the ala base Width of auricle Left ear Right ear Length of ala Right side Left side	.53 .50 .44 .41 .32 .31
6	EAR SIZE MEAS	1.41	4.26	*Length of ala, right size* Width of ear Right side Left side *Length of ala, left size =*	*-.42* .41 .41 *-.35*

Measurements with negative loadings for factors are italicized.

* The total variance accounted for by these six factors is 80.81%.

While this method yielded information regarding patterns of craniofacial measurements, it did not yield information regarding patterns of craniofacial deviance. In order to determine patterns of craniofacial deviance, a second principal components analysis was conducted. For this principal components analysis, Z scores were calculated for each measurement based on already published normative data (means and standard deviations of specific measurements in Caucasian and African-American individuals between the ages of eighteen and twenty-four). This normative data set provides separate means and standard deviation for African-American females, African-American males, Caucasian males and Caucasian females. These Z scores yielded information regarding the deviance of patient scores from gender and race matched normal (in the published sample. Then, the Z scores were entered into a principal components analysis using varimax rotation to maximize the orthogonality among the factors. Eight factors were derived. They are listed in Table 10.

Table 10: The eight factors derived from principal components analysis of the measurement Z scores.

Component number	Component title	Eigen-value	Variance accounted for*	Measurements correlated with component	Loading
1	DEPTH OF LOWER 2/3 OF FACE Z	5.63	17.05	Depth of the maxillary region	
				Right side	.81
				Left side	.85
				Depth of the mandible	
				Right side	.82
				Left side	.83
				Labio-aural distance	
				Right side	.89
				Left side	.89
2	WIDTH OF UPPER FACE AND HEAD Z	4.22	12.79	Width of head	.81
				Width of face	.78
				Width of forehead	.78
				Intercanthal width	.68
				Depth of supraorbital rim	
				Right side	.51
				Left side	.53
				Head circumference	.52
3	FACE LENGTH Z	3.63	10.99	Morphological height of the face	.87
				Height of the lower face	.80
				Physiognomical height of the upper face	.80
				Height of upper lip	.76
4	EAR SIZE Z	3.02	9.15	Width of auricle	
				Right side	.84
				Left side	.81
				Length of auricle	
				Right side	.76
				Left side	.83
5	EYE LENGTH Z	2.77	8.41	Length of eye fissure	
				Right eye	.86
				Left eye	.91
				Biocular width	.73
6	NOSE SIZE Z	2.64	8.01	Width between facial insertion points of the alar base	.82
				Width of nose	.86
				Length of ala	
				Right	.73
				Left	.68
7	VERMILLION LIP SIZE Z	2.21	6.70	Vermillion height of the upper lip	.88
				Vermillion height of the lower lip	.87
8	HEAD LENGTH Z	1.74	5.27	Length of head	.86

* The total variance accounted for by these eight factors is 78.37%

In summary, two principal components analyses were conducted. The first principal components analysis was conducted using average measurements and only subjects that had gender, age and race matched counterparts were used in order to minimize the effect of age and race. This principal components analysis yielded six measurement factors. The second principal components analysis was conducted for Z scores were computed for the measurements. This analysis revealed eight Z score factors. The Z scores entered into this principal components analysis were computed using published normative data (means and standard deviations) with separate norms for gender and race group combinations (i.e., African-American males, African- American females, Caucasian males, and Caucasian females). Therefore, the effect of race and gender on these Z scores was thought to be reduced. All of the subjects were used in this analysis because race and gender differences between the SZ/SA group and the healthy control group were no longer a concern.

Next, the two sets of factors were compared based on composition and loading magnitude. Because the number of factors for each set was different (six MEAS factors and eight Z factors) and the factor loadings were different, these two sets of factors were concluded to be dissimilar.

The next set of analyses was conducted in order to determine which set of factors would be best suited to measure differences between patients and healthy controls without the confounding effects of gender and race.

First, potential differences due to gender and race in the six average measurement factor scores were examined using Analysis of variance. This method was chosen in order to reduce the chance of Type I error and to examine the potential interaction of gender and race. Significant differences between males and females were observed for the HEAD SIZE factor $F\,(1, 93) = 123.47, p <.001$ and lip size $F(1, 93) = 4.55, p =.04$. Therefore women had smaller head size factor scores and larger lip size factor scores than men. The results are shown in Figure 1 and Table 11.

Race differences were found for LIP SIZE $F\,(1, 93) = 126.36, p <.001$ and NOSE SIZE Z $F(1,93) = 7.30, p <.01$. Caucasian individuals had smaller lips than African-American participants. Similarly, nose size was narrower for Caucasian individuals compared to African-American participants. These results are shown in Table 11 and illustrated in Figure 2.

When gender and race interactions were examined for these measurement factors, differences were found for Eyelength $F\,(1, 93) = 9.62, p =.003$. Caucasian females had the greatest EYE LENGTH/ NARROW FACE factor scores (M=.36), whereas African-American females had the lowest (M=-.70), as demonstrated on Table 11 and Figure 3.

Table 11: Gender and Race differences for the six MEAS factors

Factor score	Gender	Race	Race X Gender	Means (SD)
HEAD SIZE MEAS	**F (1, 93) = 123.47 p <.001**	F (1, 93) = 3.23 p =.NS	F (1, 93) = .35 p =.NS	CM = .58 (.65) AM = .75 (.64) CF = -1.03 (.53) AF = -.70 (.76)
LIP SIZE MEAS	**F (1, 93) = 4.54 p =.04**	**F (1, 93) = 126.36 p <.001**	F (1, 93) = .09 p =.NS	CM = -.70 (.71) AM = .92 (.66) CF = -.36 .(60) AF = 1.18 .50)
FACE HEIGHT MEAS	F (1, 93) = .07 p =.NS	F (1, 93) = 3.04 p =.NS	F (1, 93) = .69 p =.NS	CM = -.02 (1.01) AM = .18 (1.05) CF = -.26 (.97) AF = .30 (.90)
EYE LENGTH MEAS	F (1, 93) = .77 p =.NS	F (1, 93) = 3.83 p =.NS	**F (1, 93) = 9.62 p =.003**	CM = -.10 (1.14) AM = .14(.94) CF = .36 (.82) AF = -.69 (.62)
NOSE SIZE MEAS	F (1, 93) = 2.00 p =.NS	**F (1, 93) = 7.30 p =.008**	F (1, 93) = 1.29 p =.NS	CM = -.19 (.97) AM = .61(1.28) CF = -.25 (.70) AF = .07(.76)
EAR SIZE MEAS	F (1, 93) = 1.97 p =.NS	F (1, 93) = .17 p =.NS	F (1, 93) = .001 p =.NS	CM = -.09 (.95) AM = -.19 (1.29) CF = .21 (.73) AF = .13 (1.10)

Similarly, analysis of variance was conducted to order to determine gender and race differences among subjects for the eight Z score factors. Because race and gender was corrected for by obtaining Z scores relative to published normative data, all of the subjects in the patient sample (n=61) and normal control sample (n= 58) were used for this analysis. It was predicted that, because race and gender differences were controlled for by obtaining Z scores, there would be fewer differences due to gender and race. However, significant gender differences were found for the DEPTH LOWER TWO

THIRDS FACE Z factor (F (1, 106) = 11.66, p =.003), .such that females had greater DEPTH OF LOWER TWO THIRDS OF FACE Z factor scores than males. These results are shown in Table 12 and Figure 4.

Numerous differences were found between race groups including DEPTH OF LOWER TWO THIRDS OF FACE Z (F (1, 106) = 5.07, p =.03), WIDTH OF UPPER FACE AND HEAD Z (F (1, 106) = 10.58 , p =.002), FACE LENGTH Z (F (1, 106) = 4.61 , p =.03), EAR SIZE Z (F (1, 106) = 4.04 , p =.05), NOSE SIZE Z (F (1, 106) = 7.44 , p =.007), and HEAD LENGTH Z (F (1, 106) = 15.62 , p =.003). These results are shown in Figure 5 and Table 12.

Finally, when gender and race were examined for interactions significant differences were found for VERMILLION LIP SIZE Z (F (1, 106) = 5.53, p =.02). These results are illustrated in Figure 6 and Table 12.

Considering the fact that gender differences should have been reduced when calculating Z scores based on gender matched normative data, it is surprising to find more differences between genders among the Z score factors. These results can be explained if the normative data used to obtain the Z scores are not representative.

Table 12: Gender and Race differences on 8 Z score factors.

Factor score	Gender	Race	Race X Gender	Means (SD)
DEPTH OF LOWER TWO THIRDS FACE Z	***F* (1, 106) = 11.67 *p* =.001**	***F* (1, 106) = 5.07 *p* =.03**	*F* (1, 106) = .34 *p* =.NS	CM = -.16 (1.05) AM = -.48 (.84) CF = .59 (.90) AF = .06 (.06)
WIDTH UPPER FACE AND HEAD Z	*F* (1, 106) = 3.50 *p* =.NS	***F* (1, 106) = 10.58 *p* =.002**	*F* (1, 106) = .03 *p* =.NS	CM = -.07 (.93) AM = .52 (.98) CF = -.46 (.93) AF = .20 (.92)
FACE LENGTH Z	*F* (1, 106) = .69 *p* =.NS	***F* (1, 106) = 4.61 *p* =.03**	*F* (1, 106) = 1.76 *p* =.NS	CM = .09 (1.03) AM = -.08 (1.04) CF = .19 (.86) AF = -.51 (.97)
EAR SIZE Z	*F* (1, 106) = 3.13 *p* =.NS	***F* (1, 106) = 4.04 *p* =.05**	*F* (1, 106) = .14 *p* =.NS	CM = .33 (1.03) AM = -.14 (1.04) CF = -.10 (.86) AF = -.50 (.97)
EYE LENGTH Z	*F* (1, 106) = .59 *p* =.NS	***F* (1, 106) = 5.13 *p* =.03**	*F* (1, 106) = 1.36 *p* =.NS	CM = .11 (1.11) AM = -.11 (.76) CF = .19 (1.11) AF = -.50 (.68)
NOSE SIZE Z	*F* (1, 106) = 3.82 *p* =.NS	***F* (1, 106) = 7.44 *p* =.007**	*F* (1, 106) = .03 *p* =.NS	CM = .37 (1.12) AM = -.19 (.87) CF = -.04 (.89) AF = -.31 (.79)
VERMILLION LIP SIZE Z	*F* (1, 106) = 3.52 *p* =.NS	*F* (1, 106) = .20 *p* =.NS	***F* (1, 106) = 5.53 *p* =.02**	CM = .42 (1.01) AM = -12 (1.10) CF = -.40 (.77) AF = -.03(.86)
HEAD LENGTH Z	F(1, 106) = .41 *p* =.NS	**F(1, 106) = 15.62 *p* <.001**	F(1, 106) = 1.88 *p* =.NS	CM = -.20 (1.10) AM = .30 (.86) CF = -.34 (.78) AF = .70 (.97)

CM= Caucasian males, AM= African American males, CF= Caucasian females, AF= African-American females

There were more differences due to gender and race in the factor scores based on the Z scores corrected for race and gender. One would expect that for these factors fewer differences would be found between race and gender groups. These differences, in theory, should have been eliminated by using the normative data to calculate Z scores. One possible reason could be the age differences between the subjects in this study (age 18-59) and the subjects in the normative sample from which these Z scores were calculated (age 19-25) (Farkas et al, 1994). Perhaps there are maturational differences among different race and gender groups. For example, if forty-year old African-American women have more similar craniofacial measurements to younger African-American women, compared to forty-year old Caucasian women relative to their younger counterparts, then there will be greater error in Z scores for Caucasian relative to African-American women. Another potential source of differences in Z score factors between age and gender groups may result from flaws in the normative sample. For example there are an unequal numbers of individuals in each cell and cell sizes in the African-American samples are modest (200 Caucasian women, 109 Caucasian males, 50 African-American females and 50 African American males).

Therefore the factor scores derived from actual measurements were used for all further analyses. Because HEAD SIZE MEAS & LIP SIZE MEAS scores reflected variance due to gender and LIP SIZE MEAS and NOSE SIZE MEAS scores reflected race, the remaining factors (FACE HEIGHT MEAS, EYE LENGTH MEAS and EAR SIZE MEAS) were thought to reflect developmental morphology that were common to both genders and racial groups. Larger head size in males and fuller lip size in females is consistent with a recent anthropometric study (Waddington et al, 2002). Differences in

Lip size and Nose size are also consistent with a study examining anthropometric racial differences (Farkas, 1994).

In order to determine if normal theory based parametric tests could be conducted using these factor scores, Shapiro- Wilks tests were conducted to test for normality. The results from these analyses are listed in Table 13.

Table 13. Shapiro-Wilks tests for six measurement factor scores

Factor scores	Test statistic (*W*)	*p*
HEAD SIZE MEAS	.98	.08
LIP SIZE MEAS	.98	.14
FACE HEIGHT MEAS	.99	.65
EYE LENGTH MEAS	.99	.76
NOSE SIZE MEAS	.96	.006
EAR SIZE MEAS	.99	.36

Five of the measures, HEAD SIZE MEAS, LIP SIZE MEAS, FACE HEIGHT MEAS, EYE LENGTH MEAS, and EAR SIZE MEAS, did not deviate from normal distribution. Therefore parametric tests will be used for these factors. However, one factor score, NOSE SIZE MEAS was not normally distributed. Therefore, further analyses for this measure will be conducted using nonparametric tests.

Determining "EXCESS" of Minor Physical Anomalies using the ORIG-WAL and EXTEN-WAL Rating Scales

In order to determine composite scores for scales of minor physical anomalies for both ORIG-WAL and EXTEN-WAL, the ratings for each of the individual items on each scale were added in order to yield composite scores. Therefore the 13 items of the original Waldrop and Halverson Scale were added in order to determine the composite ORIG-WAL score. The EXTEN-WAL scale consisted of 35 items including the same thirteen items from the original Waldrop and Halverson Scale. Each score from the individual items on this scale were added together to determine the composite EXTEN-WAL scale.

On the original 18 items on the Waldrop and Halverson scale, individuals with a composite score of "3" or more are considered to have an excess of minor physical anomalies; this is a standard used for this scale (for example, Green et al., 1989; Marcus et al, 1985). The same cut off score was used to determine an excess of minor physical anomalies on the ORIG-WAL scale. Using the original cut-off score for the eighteen item scale on this thirteen item scale yielded a more conservative standard for categorizing individuals as having an excess of minor physical anomalies.

Because the EXTEN-WAL scale is new, there are no standard methods for categorizing an individual as having an excess of minor physical anomalies. Therefore, a prorated cut off score based on the standard for the original Waldrop and Halverson scale was determined. The original Waldrop and Halverson Scale consists of eighteen items and has a cut-off score of "3". The EXTEN-WAL scale consisted of 41 items. Therefore, the ratio of the cut off score to the total number of items on the Waldrop and Halverson Scale was used to determine a cutoff score for the forty-one item scale. A cut off score of "6" was used. The reason for using a prorated score rather than the original score was to determine if the newer items on the EXTEN-WAL scale were useful in categorizing individuals as having an excess of MPAs. In addition, this cut off score was found to be optimal for distinguishing between healthy controls and individuals with schizophrenia on a forty-one item extended minor physical anomalies scale (Ismail et al, 1998).

Validity of the Anthropometric scale.

Taking measurements of the head and face to assess the presence of developmental anomalies is a relatively new procedure. The first two analyses were conducted for the purpose of assessing the validity of the Anthropometric scale as an instrument for assessing minor physical deviation. First, it was necessary to determine if there was a relationship between this instrument and the standard method of assessing minor physical anomalies (the Waldrop and Halverson Scale). Next it was important to establish whether or not the Anthropometric scale was able to distinguish the schizophrenic/ schizoaffective sample from the sample without mental illness.

Relationship between anthropometric measurements and the original Waldrop and Halverson scale items.

First, it was expected that individuals who have high ratings on the Waldrop and Halverson scale would have higher factor scores for those factors thought to reflect early developmental differences. Recall that Factor 1, HEAD SIZE MEAS generally reflects overall size. Factor 2, LIP SIZE MEAS reflected racial differences as did Factor 5, NOSE SIZE MEAS and for Factor 3, EYE LENGTH MEAS, a race and gender interaction was observed, reflecting an interaction of these two variables. Therefore, it was expected that individuals with higher ratings of physical anomalies would have greater factor scores for the FACE HEIGHT MEAS, and EAR SIZE variables.

Next, the relationships between ratings of minor physical anomalies and factor scores derived from head measurements were examined. In order to determine if subjects who were rated aberrantly high on items from the original Waldrop and Halverson Scale differed on measurement factor scores from those who were rated low on these MPA scales, t scores were calculated. The results are listed in Table 14. Those having an excess of MPAs, as assessed using ORIG-WAL do not differ from those without an excess of MPAs on ORIG-WAL. Therefore, minor physical anomalies and anthropometric factor scores are unrelated to each other. This could mean that they measure two different aspects of craniofacial development or perhaps, that at least one of the methods does not assess early development.

Table 14: t-tests comparing six factor scores between individuals rated low (less then three, N=58) and high (3 or more, N=36) on ORIG-WAL (N=94)

	Low ORIG-WAL M (SD)	High ORIG-WAL M (SD)	t	df	p
HEAD SIZE MEAS	-.09 (1.02)	.13 (.97)	-1.02	93	NS
LIP SIZE MEAS	-.09 (.97)	.21 (1.03)	-1.46	93	NS
FACE HEIGHT MEAS	- .01 (1.00)	- .05 (.96)	.285	93	NS
EYE LENGTH MEAS	.03 (.96)	.03 (1.08)	-.00	93	NS
NOSE SIZE MEAS	.08 (.75)	-.13 (1.28)	1.04	93	NS
EAR SIZE MEAS	- .09 (.98)	.09 (1.01)	-.92	93	NS

A similar exploratory analysis was conducted to determine if those rated high on ratings of MPAs on the extended Waldrop scale (EXTEN-WAL) differed on the measurement factor scores. A t test was conducted comparing those individuals who obtained a rating of six or more on the extended Waldrop and Halverson scale and those who were rated six or less. The results are listed in Table 15.

Table 15: t-tests comparing six factor scores between individuals rated low (less than 6, N=81) and high (6 or more, N=10) on EXTEN-WAL (N=92)

	Low EXTEN-WAL M (SD)	High EXTEN-WAL M (SD)	t	df	p
HEAD SIZE MEAS	-.02 (1.05)	-.04 (.64)	.06	91	NS
LIP SIZE MEAS	.04 (.98)	-.19 (1.14)	.69	91	NS
FACE HEIGHT MEAS	- .07 (.98)	-.2 (.97)	-.80	91	NS
EYE LENGTH MEAS	-.005 (.98)	-.11 (1.04)	.34	91	NS
NOSE SIZE MEAS	-.03 (.99)	.36 (1.04)	-1.170		NS
EAR SIZE MEAS	.004 (1.00)	-.23 (.96)	-.704		NS

Once again, the results from this exploratory study indicate no differences in anthropometric factor scores between those rated for high physical anomalies and those rated low for physical anomalies. These finding indicates that anthropometric measurements and ratings of minor physical anomalies are not reflecting the same sources of variance. Although no relationship was found between ratings of physical anomalies and head and face measurement factors, it still cannot be concluded that the anthropometry factor scores are not valid indicators of physical deviance. The original Waldrop and Halverson Scale was widely criticized for failing to account for all of the physical anomalies that can be seen in individuals with psychosis. In addition, the scale was created for children and may not be readily generalized to adults, despite the fact that many studies have assumed generalizability. While numerous items from the extended Waldrop and Halverson scale have been tested in healthy adults, they were never tested in a multiracial sample (Ismail et al., 1998a). Therefore, the degree to which these minor physical anomalies are valid indicators of early developmental anomalies in a multiracial sample of adults is questionable.

Another explanation for failing to find a relationship between MPAs and anthropometric measures may have to do with the type of early anomalous development that is reflected. Perhaps MPA scales capture variance due to hand and feet differences and to anomalous features on the skin surface (derived from the ectoderm), whereas, anthropometric measurements capture variance due to primarily to variability of underlying bone and cartilage of the craniofacial complex.

Do SZ/SA subjects differ from normal controls on ORIG-WAL, EXTEN-WAL, and HEAD MEASURE factors?

It was hypothesized that individuals with schizophrenia and schizoaffective disorder have physical deviance related to early maldevelopment, relative to healthy adults. The next set of analyses explored the relationship between MPAs and the Head Measure scores. It was expected that SZ/SA subjects would more frequently be categorized as having an excess of minor physical anomalies on both ORIG-WAL and EXTEN-WAL. The original Waldrop scale has been criticized for failing to capture all of the minor physical anomalies that are present in schizophrenia and schizoaffective disorder (Trixler, 2000; Trixler et al., 1997). The purpose of using the EXTEN-WAL and having a higher prorated score is to determine whether it is more sensitive to minor physical anomalies found in individuals with schizophrenia and schizoaffective disorder.

Figure 5 illustrates the number of subjects categorized as high or low on the original thirteen items from the original Waldrop and Halverson Scale. While the number of subjects categorized as having a significant number of physical anomalies varies from study to study, some authors estimate that approximately 33% of patients with psychosis have an excess of minor physical anomalies, defined by having a score of three or more on the Waldrop and Halverson scale. In this study, more than half of the patient sample was categorized as having an excess of minor physical anomalies (54%, n=33). In addition, 21% (n=12) of the normal control subjects were categorized as having an excess of minor physical anomalies. A Chi-Square test revealed that individuals in the SZ/SA group were more frequently rated as having an excess of minor physical anomalies on ORIG-WAL (χ^2 (1) = 9.46, p=.002).

In order to determine differences between the original Waldrop and Halverson scale and the extended Waldrop and Halverson Scale, a cut off score was determined for the extended scale. The cut off score was prorated based on the cut off score from the original Waldrop and Halverson scale. The original Waldrop and Halverson scale consists of eighteen items and the cut off score for having an excess of physical anomalies is three. Based on this ratio, it was determined that of the thirty-five items used for the extended Waldrop and Halverson scale, the prorated cut off score is 6. The number of subjects categorized as high on the extended Waldrop and Halverson Scale is illustrated in Figure 7.

The extended Waldrop and Halverson scale was able to discriminate SZ/SA subjects form healthy controls, despite the fact that it is less sensitive in categorizing individuals as having an excess of MPAs relative to the ORIG-WAL scale. Using this scale, 18% (n=11) of the patient sample was categorized as having an excess of minor physical anomalies, whereas only 10% (n=6) of the normal control sample was categorized as having an excess of minor physical anomalies. A Chi-Square test, revealed that significantly more individuals in the SZ/SA group were categorized as having an excess of MPAs relative to those in the normal control sample (χ^2 (1)= 5.65, p=.02). EXTEN-WAL scale is less sensitive to categorizing individuals as having an excess of minor physical anomalies in part because some of the anomalies on this scale, specifically those from Ismail's group (1997) were not present in any of the participants in this study. These include colombata, heterochromia, preauricular skin tag, cleft lip microform, overlapping fingers and retarded finger.

In order to explore the validity of the anthropometry scale as an index of physical deviance, differences had to be determined between the patient group and the normal control group on these factors. Specifically, it was expected that patients and normal controls would differ on the factor scores thought to reflect early developmental processes. These factors include FACE HEIGHT MEAS and EAR SIZE MEAS. It was previously established that the HEAD SIZE MEAS factor was related to gender (most likely because of difference in overall size), LIP SIZE MEAS and NOSE SIZE MEAS reflected structural differences across race in both samples, and there was a gender by race interaction for EYE LENGTH MEAS. Pairwise t-tests were conducted between each subject in the patient group and their age- gender- and race-matched counterparts in the normal control sample in order to determine differences between these SZ/SA and their race, gender and age-matched counterparts on FACE HEIGHT MEAS, EYE LENGTH MEAS and EAR SIZE MEAS. The results are illustrated in Table 16.

Table 16: Differences between schizophrenia/schizoaffective disorder subjects and healthy control subjects on composite scores derived from head and face measurements (N=45 for each group)

Factor scores	SZ/SA M (SD)	HC M (SD)	t	df	p
FACE HEIGHT MEAS	-.19 (1.00)	.14 (.96)	-1.931	44	.06
EAR SIZE MEAS	-.02 (.93)	-.01 (1.04)	-.05	44	NS

This analysis revealed a difference at the trend level between patients and normal controls on face height t (44)=-1.93, p=.06. Similarly a trend was observed for EYE LENGTH MEAS t (44)=-1.95, p=.08. No other difference in craniofacial factor scores emerged between these subjects. Patients appear to have greater FACE HEIGHT MEAS factor scores than healthy control subjects.

Table 17: Differences between SZ/SA group and healthy control group on composite scores related to race and gender

Factor scores reflecting size or race	SZ/SA M (SD)	HC M (SD)	t	df	p
HEAD SIZE MEAS	.09 (1.03)	- .08 (.96)	1.02	44	.NS
EYE LENGTH MEAS	- .02 (1.07)	.02 (.97)	**-1.95**	44	**.08**
LIP SIZE MEAS	- .002 (1.01)	.002 (1.01)	.122	44	.NS
NOSE SIZE MEAS	- .23 (1.02)	.11 (.94)	-1.59	44	.NS

Because the Anthropometry Scale is a relatively novel scale, some further exploratory analyses were conducted to determine if individual items were able to better distinguish patients from healthy control subjects. Patients and normal controls were matched according to gender, race, and age (within five years) resulting in 52 matched pairs. A hierarchical linear model analysis was used to assess differences between these pairs among the measures. This method was selected because it takes into account the potential correlations among the matched pairs. To control for Type I error, the Westfall approach was used (Westfall et al., 1998). This procedure is similar to the Bonferroni approach except it takes into account relatedness among the measures. Skull base width was significantly different between the matched pairs (F (1, 51)= 13.11, p=.0005), such that individuals with schizophrenia or schizoaffective disorder had greater skull base width. This finding is consistent with one published in a recent paper by McGrath's group (2002), in which he found brachyencephaly (wide skull base width) in patients with psychosis. Height of the cutaneous lower lip was also significantly greater in individuals with schizophrenia or schizoaffective disorder (F (1, 51) = 7.90, p= .0059). Other measurements demonstrated a trend for being larger in individuals with schizophrenia or schizoaffective disorder relative to their healthy counterparts. These included width of face (F (1, 51) = 3.84, p =.053) head circumference (F (1, 51) = 3.46, p = .066) and depth of the maxillary region (F (1, 51) = 3.05, p =.087), and width of the forehead (F (1, 51) =2.84, p =.095). These findings are listed in the Table 18.

Table 18: Differences in specific head and face measurements between mentally ill subjects and their healthy counterparts matched according to age, race and gender

Measurement	SZ/SA M (SD)	HC M (SD)	F	df num	df denom	p
Skull base width	**146.13 (7.12)**	**142.02 (8.13)**	**13.11***	**1**	**51**	**.0005***
Height of cutaneous lower lip	**13.20 (3.08)**	**11.63 (2.86)**	**7.90***	**1**	**51**	**.0059***
Width of face	138.16 (6.54)	136.00 (7.39)	3.84	1	51	.053
Head circumference	579.84 (21.43)	572.09 (20.95)	3.46	1	51	.066
Depth of maxillary region right side	131.25 (5.75)	129.94 (5.86)	3.05	1	51	.087
Width of forehead	111.58 (5.66)	109.94 (5.67)	2.84	1	51	.095

(N= 104, 52 matched pairs)

Because these measures may be confounded by weight and race, these two variables were introduced as covariates using a hierarchical linear model. The results are listed in Table 19. Although weight accounted for a significant portion of the variance for skull base width ($F\,(1, 101) = 34.06, p<.0001$), this measure was still significantly greater in patients compared to their healthy counterparts ($F\,(1, 55.9)=7.40, p = .0087$). Similarly, with weight and race as covariates, height of cutaneous lower lip was still significantly greater in patients compared to their healthy counterparts ($F\,(1, 57) =6.01$, p =.0174).

Table 19. Difference between patients and healthy controls on individual measurements with weight and gender as covariates.

Measurement	F	df numerator	df denominator	p
Skull base width				
SZ/SA vs. HC	**7.40**	**1**	**55.9**	**.0087**
Weight	**34.06**	**1**	**101**	**<.0001**
Race	.80	1	51.2	NS
Height of cutaneous lower lip				
SZ/SA vs. HC	**6.01**	**1**	**57**	**.0174**
Weight	1.33	1	97.2	NS
Race	.81	1	52.5	NS

Table 20. Skull base width and height of cutaneous lower lip: Means and standard deviations for Caucasian and African-American patient and healthy control participants.

Measurement	SZ/SA Caucasian M (SD)	SZ/SA African-American M (SD)	HC Caucasian M (SD)	HC African-American M (SD)
Skull base width	146.22 (7.42)	145.98 (6.79)	143.10 (8.68)	140.28 (8.68)
Height of cutaneous lower lip	13.06 (3.08)	13.44 (3.13)	12.03 (2.58)	10.95 (3.24)

In summary, the factors from two separate principal components analyses (factors derived from Z scores versus factors derived from measurements) were compared. There appeared to be very little overlap among these factors. Further analyses revealed more numerous differences between race and gender groups using the factor derived from the Z scores than factors obtained from raw measurements. This result was counterintuitive because racial differences were expected to be reduced by using gender and race matched norms. Therefore, the normative sample used did not adequately represent the samples used in this study. However, a principle components analysis of the raw (unstandardized) craniofacial measurements revealed six factors. Two of these factors were thought to be related to early development.

In addition, no relationships were found between ratings of minor physical anomalies (ORIG-WAL or EXTEND-WAL) and the two craniofacial factors thought to represent neurodevelopmental difficulties. More SZ/SA subjects compared to healthy control subjects had an excess of physical anomalies both on the ORIG-WAL and EXTEN-WAL scales. Although SZ/SA subjects and healthy control subjects did not differ significantly from each other on any of the craniofacial measurement factor scores, t-tests revealed a trend toward different FACE HEIGHT MEAS factor scores between SZ/SA subjects and normal control subjects ($t\ (44) = -1.93$, $p=.06$). Exploratory analyses were conducted examining possible differences between SZ/SA subjects and their age, race and age-matched counterparts in the healthy control group in the 33 measurements. Only two measurements were significantly different between these matched pairs. Skull base width ($F\ (1, 51) = 13.11$, $p=.0005$) and height of cutaneous lower lip ($F\ (1,51) = 7.90$, $p = .0059$), were both larger in patient sample than in normal control subjects.

ORIG-WAL, EXTEND-WAL and MEASURE FACTORS as indicators of a neurodevelopmental course of mental illness

Finally, it was hypothesized that a neurodevelopmental subtype exists within at least a subgoup of those with a diagnosis of schizophrenia and schizoaffective disorder; it was further hypothesized that measures of physical deviance can be used to distinguish individuals having this subtype. The next set of analyses explored the relationship between ratings of MPAs and anthropometry factor scores and putative indicators of a neurodevelopmental subtype. It was expected that those patients having an excess of minor physical anomalies would also demonstrate characteristics consistent with the neurodevelopmental subtype such as poor cognitive functioning, poor life functioning and early age of onset. Similarly, subjects with characteristics consistent with the neurodevelopmental subtype were predicted to differ from other subjects on FACE HEIGHT MEAS and EAR SIZE MEAS factor scores, thought to reflect early development. Patterns of measurements consistent with a neurodevelopmental subtype of illness are described below:

Cognitive Measures

"Hold" versus "Don't hold" Tests. On the WAIS-R the term "Hold" tests refers to those subtests that, relatively speaking, are expected to substantially withstand brain injury or other deteriorative changes. These tests include Vocabulary, Information, Object Assembly, and Picture Completion. "Don't hold" tests are those that are relatively more sensitive to brain injury or brain changes. These tests include Digit Span, Similarities, Digit Symbol, and Block Design. Wechsler assumed that deterioration on "Don't Hold" (compared to "Hold) tests that exceeds normal limits may reflect an abnormal organic process. He created a Deterioration Index to compare "Hold" tests with "Don't Hold" tests in the following formula (Lezak, 1995):

$$\text{Deterioration Index} = \frac{\text{Hold} - \text{Don't Hold}}{\text{Hold}}$$

Patients with an acute onset of schizophrenia are thought to have relatively intact cognitive functioning prior to illness and then experience a decline just preceding illness onset. These individuals would be expected to perform well on "Hold" tests, but have lower performance on "Don't hold" tests. In contrast, individuals with a (putative) neurodevelopmental form of the illness, characterized by an early onset and deteriorative course, are thought to have lower cognitive functioning even in childhood. These individuals would be expected to perform similarly poorly on both "hold" and "don't hold" tests. It is expected that those with the neurodevelopmental form will have more physical anomalies (higher composite scores on the Anthropometry scale and the Extended Waldrop and Halverson Scale) than those having an acute onset. Therefore, it is expected that higher composite scores on these two scales of physical anomalies would be related to poor performance on "hold" tests, but not on "don't hold" tests. That is, those patients with the congenital subtype (and more physical anomalies) are predicted to do poorly on both "hold" and "don't hold" tests, whereas, those with an acute onset (with fewer physical anomalies) are predicted to do poorly on just don't hold tests. As a result, patients with an acute onset (fewer physical anomalies) are expected to have a high deterioration index and patients with the congenital subtype (greater physical anomalies) will have a low deterioration index.

It was predicted that those individuals in the SZ/SA group having an excess of minor physical anomalies would also have poor performance on hold tests and low deterioration index. Independent t-tests were conducted to compare individuals having an excess of physical anomalies with those having few physical anomalies on cognitive test scores. When group membership was based on scores on the ORIG-WAL scale, there were no differences between these two groups for "hold" tests ($t= .05$, $p=.96$), "don't hold" tests ($t = -.9$, $p =.37$) or deterioration index ($t =1.05$, $p =.30$). Similarly, when classified based on scores from EXTEN-WAL, no differences were revealed between SZ/SA subjects with an excess of minor physical anomalies versus those without an excess of minor physical anomalies on hold tests (t=.07, p=.95), "don't hold" tests (t=.06, p=.95) and deterioration index (t=-.166, p=.87).

Table 21: High /Low groups classified according to ORIG-WAL scores compared on neurocognitive tests

	ORIG-WAL low (< 3) M (SD)	ORIG-WAL High(≥ 3) M (SD)	t	df	p
"Hold" tests	7.76 (SD=2.02)	7.73 (SD=2.07)	.05	43	NS
"Don't hold" tests	7.76 (SD=1.50)	8.24 (SD=1.99)	-.90	43	NS
Deterioration Index	-.03 (SD =.18)	-.09 (SD=.22)	1.049	43	NS

Table 22: High/ Low groups classified according toEXTEN-WAL scores on neurocognitive tests

	EXTEN-WAL low (<6) M (SD)	EXTEN-WAL high (> 6) M (SD)	t	df	p
"Hold" tests	7.77 (SD=2.08)	7.72 (SD=2.15)	.065	40	NS
"Don't hold" tests	8.07 (SD=1.79)	8.03 (SD=1.89)	.06	40	NS
Deterioration Index	-.07 (SD=.27)	-.06 (SD=.13)	-.166	40	NS

Next, correlations were computed to determine whether there were relationships between MEASUREMENT FACTORS and neurocognitive tests. Specifically, it was expected that FACE HEIGHT MEAS and EAR SIZE MEAS would be related to worse performance on "hold" tests, but unrelated to performance on "don't hold" tests and the deterioration index. Because HEAD SIZE MEAS, LIP SIZE MEAS, EYE LENGTH MEAS, and NOSE SIZE MEAS were correlated with gender and race, no relationship was predicted to emerge among these factors and performance on tests of neurocognitive functioning. Spearman Rank Order Correlations were conducted to examine the relationship between NOSE SIZE and neurocognitive tests, because NOSE SIZE factor scores were not normally distributed. Pearson correlations were used to examine the relationships between neurocognitive tests and craniofacial factor scores, because the remaining craniofacial scores were normally distributed.

Table 23: Results of correlations* between composite neurocognitive scores and composite head and face measurement scores

	Hold tests	Don't hold tests	Deterioration index
Neurodevelopmental factors			
FACE HEIGHT	r= .10 p=NS	r= -.01 p= NS	r= .20 p=NS
EAR SIZE MEAS	r=.005 p=NS	r=.16 p=NS	r= -.121 p= NS
Factors reflecting size and race			
HEAD SIZE MEAS	r= .16 p=NS	r= .02 p= NS	r= .20 p=NS
EYE LENGTH	r=.184 p=NS	r=.12 p= NS	r=.18 p= NS
LIP SIZE MEAS	r=-.40 **p=.005**	r= -.42 p= .004	r= -.04 p= NS
NOSE SIZE MEAS	rho=.02 p= NS	rho= .062 p= NS	rho= -.027 p= NS

* Pearson correlations and Spearman Rank Order correlations for NOSE SIZE MEAS data because distribution of data deviated from normal distribution.

Hold tests. In these exploratory analyses, no relationship emerged between performance on hold tests and any of the factors thought to be related to neurodevelopment. However, hold test scores were related to LIP SIZE MEAS, a factor score that was not thought to reflect developmental morphology.

Don't Hold Tests. No relationships were revealed between Don't hold test scores and any of the factors thought to be related to developmental morphology. However, LIP SIZE MEAS ($r = -.42$, $p=.004$) was inversely related to performance on Don't hold tests. Again, this factor was not thought to reflect developmental morphology.

Deterioration Index. No significant relationship was found between the Deterioration Index and any of the measurements. Therefore, minor physical anomalies and anthropometric measures are not related to a pattern of cognitive performance consistent with the presence of a neurodevelopmental subtype.

Multidimensional Scale of Independent Functioning (MSIF).

(Jaeger et al., 1995)

This scale rates level of functioning in three environments: work, education, and residential. Separate ratings are obtained for role position, level of support, and performance in all three environments. Individuals with a neurodevelopmental course of illness are thought to have worse functional ability because they have a more chronic onset and chronic course of illness and therefore, expected to have worse ratings on measures of independent functioning. Two MSIF ratings used to assess overall functioning are global role position (a composite role position score for all three environments) and overall global (a composite score of this scale which takes into account support and performance). Scale ratings range from one (most independent) to seven (completely dependent).

Because MSIF scores are not normally distributed, SZ/ SA subjects were classifed into two groups. One group consisted of individuals who were rated one to three, (considered to be within healthy limits or INDEPENDENT, N=10), and the other group consisted of individuals that had a score of 6 or 7 (most disabled or DEPENDENT, N=27) (Jaeger, personal communication 2003). These two groups were selected to reflect the two extremes of disability. It was predicted that more subjects with an excess of physical anomalies would receive global role position ratings in the impaired range.

Chi-square tests were conducted in order to determine if individuals with poor role ratings of role positions also had an excess of physical anomalies. Chi-square tests were used because composite scores from the scales of MPAs are not normally distributed and require the use of nonparametric tests. Those individuals with an excess of MPAs based on ORIG-WAL were not more frequently categorized as having more impaired role position on the MSIF, (χ^2 (1) = .61, p=.NS). Similarly, no relationship was found between EXTEN-WAL and ratings of global role position, (χ^2 (1) = .62, p=.NS). These tests failed to demonstrate an excess of MPAs (using ORIG-WAL and EXTEN-WAL) in patients rated as most functionally disabled. These findings are illustrated in Figure 8.

Similarly, t tests were conducted comparing those individuals with good versus poor ratings on MSIF global role position to determine if there were differences in Head Measurement Factors: FACE LENGTH MEAS and EAR SIZE MEAS factors. No difference was expected in factor related to HEAD SIZE MEAS, EYE LENGTH, LIP SIZE MEAS, and NOSE SIZE MEAS factors. As shown in Table 26, no differences were found between any of the factors between individuals with good role position and those with poor role position ratings.

Table 24: Ratings and measures of physical anomalies – subjects were grouped according to global role position the MSIF.

Variable	Independent M (SD)	Dependent M (SD)	t	p	df
Factors thought to be related to early development					
FACE HEIGHT	-.35 (.74)	-.04 (1.03)	-.81	NS	28
EAR SIZE	-.02 (1.06)	.01 (.92)	-.05	NS	28
Factors related to general size and race					
HEAD SIZE	-.33 (.97)	.10 (.83)	-1.23	NS	28
LIP SIZE	-.34 (.93)	.14 (1.12)	-1.13	NS	28
EYE LENGTH	.33 (1.29)	-.12 (.95)	1.17	NS	28
NOSE SIZE	-.40 (1.06)	-.12 (1.23)	-.56	NS	28

For the next set of exploratory analyses, subjects were grouped by ratings on their MSIF overall global scores in a manner identical to that used for the global role position scores. The INDEPENDENT ROLE group consisted of individuals who were rated one to three (least impaired, N=10), and the DEPENDENT ROLE group was rated six or seven (most impaired, N=32), similar to the previous analysis. The characteristics of these subgroups are listed in Table 25.

Similarly patients were divided into INDEPENDENT and DEPENDENT groups based on overall independent function ratings on the MSIF. Chi-Square tests were conducted to determine if these groups differed with respect to excess of minor physical anomalies. As stated previously, the composite scores of MPAs are not normally distributed and necessitate the use of nonparametric tests, such as the Chi-Square test. These tests reveal no relationship between ratings of independent life functioning and ratings of MPAS on ORIG-WAL (χ^2 (1)= .26, p=.NS) and EXTEN-WAL (χ^2 (1)= .45, p= NS).

Similarly, t-tests were conducted between those individuals having good versus poor overall life functioning ratings on the MSIF to determine if there were differences on head measurement factors thought to be related to early development: FACE LENGTH MEAS and EAR SIZE MEAS factors. No difference was expected in factor related to HEAD SIZE MEAS, EYE LENGTH MEAS, LIPS SIZE MEAS and NOSE SIZE MEAS factors. However, no differences in any of the factor scores between any of the factors on individuals with good role position and those with poor ratings of role position. These results are shown in Table 25.

Table 25: Ratings and measures of physical anomalies – subjects were grouped into one of two groups according to overall life functioning MSIF measure

Variable	Independent M (SD)	Dependent M (SD)	t	p	df
Factors thought to be related to early development					
FACE HEIGHT	.33 (.74)	-.05 (1.01)	-.79	NS	29
EAR SIZE	-.02 (1.06)	-.06 (.94)	.10	NS	29
Factors related to general size and race					
HEAD SIZE	-.33 (.97)	.01 (.90)	-.93	NS	29
LIP SIZE	-.34 (.93)	.19 (1.12)	-1.25	NS	29
EYE LENGTH	.33 (1.29)	-.20 (.94)	1.27	NS	29
NOSE SIZE	-.37 (.80)	-.03 (1.26)	-.73	NS	29

In summary, no relationship was found between ratings of independent life functioning and composite scores on the original and extended versions of the Waldrop and Halverson Scale. Similarly, no differences were found between groups categorized as dependent versus independent on head measurement factor scores.

It is possible that level of independent functioning at the time of anthropometric examination might be subject to fluctuation (e.g. recent loss of a job). A more stable measure of independent functioning is overall best independent functioning. The highest overall independent functioning score over an extended period of time (the length of time subjects participated in the longitudinal study) was selected among the four possible timepoints over the three year longitudinal study. The highest independent functioning score was found to correlate highly with most recent role position (rho = .83, $p < .01$) and most recent overall functioning (rho = .80, $p < .01$) scores. These high correlations indicate the stability of the MSIF values for these subjects.

Age of illness onset.

Individuals with the neurodevelopmental form of illness are thought to develop the illness earlier than those with an acute onset. Thus it would be expected that those subjects with higher composite scores on the physical anomaly scales would have an earlier age of onset. Because, anecdotally, individuals report more certainty when they report age of first treatment for mental illness than age of first symptoms, this measure was used to estimate age of illness onset. t-tests were conducted in order to determine if individuals with higher ratings of minor physical anomalies also had an earlier age of onset. Two different cut off points were used. For the Original Waldrop and Halverson Scale those subjects with a rating of three or more were considered to have an excess of minor physical anomalies. This is the standard in the literature. For the extended Waldrop and Halverson Scale the cut off score is prorated; a score of six of more is considered to indicate an excess of minor physical anomalies. The results from these analyses are illustrated in Table 26.

Table 26: Relationship between MPAs and Age of First Treatment

	Low MPA M (SD) N	High MPA M (SD)	t	df	p
Orig WAL	18.81 (6.16) N=21	21.71 (8.88) N=24	-1.25	43	NS
EXTEN-WAL	18.71 (6.63) N=34	24.75 (10.42) N=8	-1.57	40	NS

Analyses failed to reveal any relationship between age of first treatment and ORIG-WAL, t (43)=-1.25, *p*=.22. Similarly no relationship emerged between age of first treatment and EXTEN-WAL t (40) = -1.57, *p*= -1.57. Although no significant differences were found, Figure 11 illustrates paradoxically that those with an excess of minor physical anomalies appear to have a later age of onset than those with fewer MPAs.

Next, Pearson correlations were computed to determine possible relationships between age of onset and three head measurement factor scores related to development (FACE HEIGHT MEAS and EAR SIZE MEAS). It was predicted that these measures would be related to earlier age of onset. The results of these analyses are listed in Table 27. No relationship was found between age of onset and FACE HEIGHT MEAS and EAR SIZE MEAS.

Table 27: Craniofacial factor scores and age of onset

Craniofacial factor scores	Pearson r	p
FACE HEIGHT MEAS	r= -.01	p= NS
EAR SIZE MEAS	R = -.13	p= NS

It was predicted that no such relationship would be found between age of onset and the factor scores related to race and gender. Pearson correlation was conducted between HEAD SIZE MEAS, EYE LENGTH MEAS and LIP SIZE MEAS. Because NOSE SIZE MEAS factor scores were not normally distributed, Spearman rank order correlation was used to compute the correlation between NOSE SIZE MEAS and age of onset. Results are shown in Table 28.

Table 28: Age of onset and craniofacial factor scores reflecting gender and race

Craniofacial factor scores	correlation	p
HEAD SIZE MEAS	r = .06	p= NS
LIP SIZE MEAS	r =-.27	p=NS
EYE LENGTH MEAS	**r= .31**	**p= .03**
NOSE SIZE MEAS (Spearman Rank Order Correlation)	rho=.03	p= NS

It was predicted that those factors thought to be related to early developmental difficulties (FACE HEIGHT MEAS and EAR SIZE MEAS) would relate to age of onset. However, no relationship was expected between head measurement factors related to general size and race (HEAD SIZE MEAS, LIP SIZE MEAS, EYE LENGTH MEAS and NOSE SIZE MEAS).

Another method to detect the presence of a neurodevelopmental subtype is to compare the differences in physical deviance (minor physical anomalies and craniofacial factor scores) between subjects with both an early age of onset and poor performance on hold and don't hold tests to all other subjects. Subjects who were first treated at age sixteen or younger were considered to have an early age of first treatment based on other studies (Hoff et al, 1996). Subjects with average scores on hold tests of 6 or less were considered to have poor performance on hold tests. This score is considered to be in the borderline range. Subjects having both early age of onset and low performance on hold tests (EARLY TX/ LOW HOLD) were compared to the other subjects on measures of physical deviance (NO EARLY TX/LOW HOLD).

First Chi square tests were conducted in to determine if those EARLY TX/LOW HOLD subjects (N=5) were more frequently categorized as having an excess of minor physical anomalies on the ORIG-WAL scale. This finding was negative (χ^2 (1)= 2.51, p=.11). A similar analysis was conducted to determine if EARLY TX/LOW HOLD subjects were more frequently categorized as having an excess of minor physical anomalies on EXTEN-WAL. They were not more frequently categorized as having an excess of minor physical anomalies (χ^2 (1)= 1.34, p=.25).

Next, EARLY TX/LOW HOLD subjects were compared to the others (NO EARLY TX/LOW HOLD) on craniofacial factor scores. It was predicted that those EARLY TX/ LOW HOLD subjects would differ from other subjects on Face Depth and ear size factors, but not on Head size Eye size, Lip size or Nose size factors. t tests were conducted to compare the EARLY TX /LOW HOLD subjects to the NO EARLY TX/ LOW HOLD subjects. As shown in Table 29, these two groups did not differ on any of the craniofacial factor scores. One explanation for the lack of differences between EARLY TX/ LOW HOLD subjects and NO EARLY TX/LOW HOLD subjects is that only five subjects in the whole sample met criteria for having both age of first treatment before the age of sixteen and hold test scores at 6 or below. There may not have been enough power to find differences between this small group and the other patients on measures of physical deviance. Individuals with an early age of first treatment and poor hold test performance may be rarw of may have been underrepresented in this sample.

Table 29: No differences in craniofacial factor scores between EARLYTX/ LOW HOLD SUBJECTS and NO EARLY TX/LOW HOLD SUBJECTS

Variable	EARLY TX/ LOW HOLD M (SD)	NO EARLY TX/ LOW HOLD M (SD)	t	p	df
Factors thought to be related to early development					
FACE HEIGHT	-. 43 (.86)	-.12 (1.04)	-.63	NS	44
EAR SIZE	-.14 (1.32)	-.02 (.89)	-.28	NS	44
Factors related to general size and race					
HEAD SIZE	-.15 (1.14)	.12 (1.02)	-.56	NS	44
LIP SIZE	.75 (.93)	-.09 (1.01)	1.76	NS	44
EYE LENGTH	-.69 (.77)	.04 (1.08)	-1.46	NS	44
NOSE SIZE	.19 (1.02)	-.25 (1.03)	.90	NS	44

In summary, Minor Physical Anomalies and Craniofacial Factor Scores were unrelated to neurocognitive performance, life functioning and age of onset. However, only five subjects were categorized as having both early age of onset and poor performance on neurocognitive test. Therefore, the failure to find a relationship between physical deviance and characteristics consistent with the neurodevelopmental hypothesis may be due to inadequate sampling of subjects with the neurodevelopmental subtype.

Summary of Results

Principal components analysis was conducted on the 33 of the head and face measurements for the purpose of data reduction and to reveal underlying relationships among the measurements, particularly those relationships that may be related to early development. Six factors were revealed: 1) HEAD SIZE MEAS, 2) LIP SIZE MEAS, 3) FACE HEIGHT MEAS, 4) EYE LENGTH MEAS, 5) NOSE SIZE MEAS, and 6) EAR SIZE MEAS. However four of these factors (HEAD SIZE MEAS, LIP SIZE MEAS, EYE LENGTH MEAS and NOSE SIZE MEAS) were significantly related to other characteristics such as gender and race. The remaining factors (FACE HEIGHT MEAS, and EAR SIZE MEAS factors) were thought to reflect early developmental differences.

It was hypothesized that individuals with schizophrenia and schizoaffective disorder have early maldevelopment and therefore, greater physical deviance relative to healthy adults. In order to test this hypothesis, the next set of analyses were conducted to determine if the SZ/SA group and normal control group differed in ratings of physical anomalies on the ORIG-WAL and EXTEN-WAL and if they differed on craniofacial measurement factor scores thought to be related to early development (FACE HEIGHT MEAS and NOSE SIZE MEAS). Both the original and extended Waldrop and Halverson Scales distinguished patients having schizophrenia or schizoaffective disorder from healthy control subjects. Chi-Square test revealed that significantly more individuals were characterized as having an excess of minor physical anomalies both for the ORIG-WAL scale and the EXTEN-WAL scale. Regarding the head and face measurement factors, there was a trend for differences between SZ/SA group and the normal control group on the FACE LENGTH factor ($t=-1.931$, $p=.06$). A matched subjects design using a general linear model approach revealed significant differences between these two groups on measures of skull base width ($F= 13.11$, $p=.0005$) and height of the cutaneous upper lip ($F= 7.90$, $p= .0059$).

Next t-tests were conducted to determine if ratings of physical anomalies were related to head and face measurement factors. However, ratings of minor physical anomalies were unrelated to craniofacial measurements.

Next, three variables were identified as likely indicators of a congenital subtype of schizophrenia: lower performance on cognitive tests, lower ratings on a scale of independent functioning, and earlier age of treatment for illness. It was predicted that individuals with an excess of minor physical anomalies would have lower scores on cognitive tests, poor ratings of independent life functioning and earlier age of first treatment. It was also predicted that these three characteristics would be related to craniofacial factor scores thought to reflect abnormal development. No relationship was found between any ratings or measures of physical deviation and any measurement of neurocognitive functioning, poor life functioning or early age of onset. Therefore, measures of physical deviance were unable to distinguish a neurodevelopmental subtype. When a subgroup of patients with both an early age of onset and poor neurocognitive functioning was identified, there were only five. Failure to find a relationship between co-occurring characteristics of the neurodevelopmental subtype and measures of physical deviance may be due to an inadequate representation of individuals with the neurodevelopmental subtype.

Discussion

Differences between patients and healthy controls on craniofacial measurements and ratings of physical anomalies

Proportionally, patients with schizophrenia and schizoaffective disorder had significantly more numerous and severe minor physical anomalies than normal control subjects, a finding that is consistent with the literature. Despite the fact that different groups use different versions of the Waldrop and Halverson scale, most studies find that individuals with schizophrenia or psychosis have significantly greater scores on the Waldrop and Halverson scale (Akabaliev et al., 1998; Alexander et al., 1994; Cantor-Graae, E. et al., 1994b; Green et al., 1989; 1994a; Guy et al., 1983; Lohr et al., 1993, 1997). When items that were added to the original Waldrop items were analyzed as a group, patients still had significantly more of these physical anomalies than normal control subjects. This is in agreement with the findings of Ismail (Ismail et al., 1998b) and is consistent with criticisms that the Waldrop and Halverson Scale does not adequately all of the minor physical anomalies found in individuals with schizophrenia and schizoaffective disorder (Trixler et al., 1997, 2001; Lane et al., 1997).

Although a handful of studies have examined Waldrop scores in a racially mixed sample such as this one (for example, Alexander et al., 1994), this is the first study to demonstrate an increase in physical anomalies beyond those on the Waldrop scale in a racially mixed sample. Even when race was a covariate, the findings remained the same.

Similarly, this was the first study to examine anthropometric data in Caucasian and African-American adults with schizophrenia and schizoaffective disorder. Although the patient sample appeared to have greater overall anthropometric deviation scores than normal controls, this difference was only at a trend level. In contrast, Lane's group found that individuals with schizophrenia had significantly different overall anthropometric scores than healthy adults. This discrepancy in findings may be due to the fact that Lane et al's sample is larger and ethnically more homogeneous than the sample used in this study. However the similar findings found in this racially mixed group indicates that anthropometric differences in schizophrenia and schizoaffective disorder are likely generalizable to racial groups other than Caucasian. This is a promising result, but further studies must be conducted in other racial groups to determine the generalizability of this finding.

A principal components analysis was conducted to determine which measurements were related to each other. Six factors were derived from the anthropometry scale: 1) HEAD SIZE MEAS, 2) LIP SIZE MEAS 3) FACE LENGTH MEAS 4) EYE SIZE MEAS, 5) NOSE SIZE MEAS, and 6) EAR SIZE MEAS. However, three of these factors (HEAD SIZE MEAS, LIP SIZE MEAS and NOSE SIZE) MEAS) appeared to reflect gender and racial differences within the sample. These results, at first glance, differ from those of McGrath's group (McGrath et al., 2002). In that study only two principal factors emerged, the craniofacial size factor (with positive loadings for all measurements of the head and face used in that study), similar to the HEAD SIZE MEAS factor in this study, and a craniofacial shape factor (with positive loadings for midline measurements of the face and negative loadings for skull width, skull length and head circumference). In their study (McGrath et al., 2002), only eleven measurements were entered into the PCA, three regarding the length, width and circumference of the head, five vertical lengths within the midline of the face, and three facial depth measurements. However, in this study, more comprehensive measurements were taken of the face and (ears, eyes, nose and mouth) which accounts for the discrepancy between this study and that of McGrath and coworkers (2002), both with respect to the factor structure observed, and with respect to group differences. Differences in the frontonasal and maxillary structures of the face were found in another study as well, and appeared to be related to differences in the brain midline of individuals with schizophrenia (Deutsch et al., 2000).

Of the six factors derived from the measurements, a trend was observed for differences in the FACE HEIGHT MEAS factor. Similarly, when individual measurements were compared between age, gender and race matched pairs, skull base width was significantly greater in patients with schizophrenia and schizoaffective disorder. Trends were found for increased width of the face, head circumference, and maxillary depth in the patient groups compared to matched healthy control subjects. These findings are consistent with the two major anthropometric studies in schizophrenia. In the McGrath et al 2002 study individuals with psychosis have brachycephalic (short and wide) skulls. Both McGrath's (McGrath et al., 2002) and Lane's (Lane et al., 1997) groups independently found increased skull base width in their patient samples.

A curious finding is that height of the cutaneous lower lip (distance between lower lip and the crease on the chin) was significantly larger in individuals with schizophrenia and schizoaffective disorder in the current study. This is the first study to demonstrate significant difference on this measure between individuals with psychiatric illness and healthy controls. This finding is consistent, however with Lane's group's finding that individuals with schizophrenia demonstrate elongation of the lower two thirds of face (1997).

Relationships between ratings of minor physical anomalies and measurements of the head and face.

No relationship was found between ratings of physical anomalies and measurements derived from the Anthropometry rating scale. It appears as though ratings of MPAs and anthropometric measurements are not reflecting the same aspects of physical deviance. Although both Lane's group (Lane et al., 1997) and McGrath's group (McGrath et al., 2002) analyzed anthropometric data and ratings of minor physical anomalies, these data were analyzed separately and the relationship between these two methods, while assumed to exist, was not demonstrated. This is the first study to analyze the relationship between ratings of physical anomalies and anthropometric measurements of the head and face in individuals with schizophrenia and schizoaffective disorder.

Relationship between ratings of physical anomalies and putative indices of a neurodevelopmental subtype

No relationship was found in this study between putative indices of a neurodevelopmental subtype of the illness and any version of the Waldrop and Halverson Scale. In particular, ratings of physical anomalies were unrelated to patterns of neuropsychological performance thought to reflect poor premorbid functioning (i.e. poor performance on hold tests) and a lack of decline from premorbid neurocognitive levels (i.e. low deterioration index). No other study has examined the relationship between MPAs and this pattern of neurocognitive scores. Two previous studies did, however, examine the relationship between performance on tests thought to reflect premorbid ability and ratings of minor physical anomalies. While O'Callaghan's group found that poor performance on the a test thought to measure premorbid functioning (O'Callaghan et al., 1995), another study found no relationship between Vocabulary scores and MPAs (Guy et al., 1983).

Several other studies that have attempted to find relationships between MPAs and neurocognitive functioning (Alexander et al., 1994; Green et al., 1989) not found such a relationship (Ismail et al., 2000). The present study replicates and extends this finding in schizophrenia using an extended version of the Waldrop and Halverson scale. However, some studies have found relationships between higher ratings of MPAs and both motor tasks (Green et al., 1994b;, McGrath et al., 1995) and a test of set shifting involving a motor component (Trail Making Test B) in females only (O'Callaghan et al., 1991).

No relationship was found in the present study between ratings of physical anomalies and independent life functioning. No other study has examined this relationship. However the current finding does not support the prediction that higher ratings of MPAs are related to a more disabling form of the illness.

Finally, no relationship was found between age of onset (first treatment) and minor physical anomalies as assessed by original and extended versions of the Waldrop and Halverson Scale. The findings of previous studies have been equivocal. Some authors report that increased rates of minor physical anomalies are related to age of first hospitalization (Green et al., 1989). Others have not found such a relationship using other indices of onset including age of first treatment, or first psychotic episode (Akabaliev et al., 1998 Lohr et al., 1993; McGrath, J. J. et al., 1995). Taken together, the majority of studies do not find this relationship.

Relationship between anthropometric measurements and putative markers of the neurodevelopmental subtype.

This is the first study attempting to distinguish subtypes of schizophrenia and schizoaffective disorder based on craniofacial measurements and ratings of minor physical anomalies. Although craniofacial measurements and minor physical anomalies did not distinguish among subtypes of patients, they did distinguish between individuals with psychosis and healthy individuals. This finding is consistent with those from previous studies that revealed wider skull base width in individuals with schizophrenia compared to healthy subjects.

No consistent relationships were found among putative markers of a neurodevelopmental subtype of schizophrenia and craniofacial morphological deviance. Specifically, it was expected that factors related to craniofacial deviance (FACE HEIGHT MEAS and EAR SIZE MEAS) would be related to poor scores on neurocognitive tests, particularly those tests that reflect premorbid functioning and are resistant to deterioration following onset of illness ("hold" tests). No relationship was found among cognitive measures and any of the three factors thought to reflect physical deviance. Similarly, no relationship was found between ratings of independent functioning (overall role position and overall life functioning) and any of the anthropometry factors. To date, no published study has examined the relationship between craniofacial measurements and neurocognitive functioning or ratings of life functioning.

Finally, it was expected that earlier age of first treatment for illness would be associated with increased physical anomalies. However, no relationship was found.

In summary, no relationships were found between deviant craniofacial measurements or minor physical anomalies and putative indices of a neurodevelopmental subtype of schizophrenia with the exception of craniofacial measurements related to eye size and age of onset. When a subgroup of patients having both an early age of onset and poor performance on neurocognitive tests was identified, only five of fifty-two patients had both of these characteristics. Therefore, one explanation for failing to find a relationship between measures of physical deviance and putative characteristics of the neurodevelopmental subtype is the under-representation of those with the neurodevelopmental subtype. Only those subjects who were able to travel to Zucker-Hillside Hospital could participate in this study. Those patients who were chronically ill and required long-term hospitalization were unable to participate in this study. Perhaps many of these individuals have the neurodevelopmental subtype but were not included in this study.

One possible explanation for why ratings of physical anomalies and craniofacial measurements were unrelated to putative indices of a neurodevelopmental subtype is that a neurodevelopmental subtype does not exist. That is, all patients with schizophrenia or schizoaffective disorder have some craniofacial anomalies, but no fundamentally distinct subgroup exists within these illnesses. This theory is supported by a study by Lane's group's (1997). This group found that composite anthropometric scores for both normal control subjects and patients were normally distributed, but the means of the groups were significantly different. Lane's group argued that if only a subgroup of schizophrenic patients had craniofacial anomalies, then the composite craniofacial morphology scores would be bimodally distributed (Lane et al., 1997) Thus there is not a subgroup of patients with schizophrenia having marked craniofacial abnormalities that accounts for the overall differences between individuals with schizophrenia and normal controls. Rather, craniofacial deviance seems to occur in patients with schizophrenia as a group, to varying degrees.

No consistent relationships emerged between putative indicators of a neurodevelopmental subtype and ratings of MPAs and anthropometry scores. Therefore results of this study do not support the presence of a neurodevelopmental subtype of schizophrenia or schizoaffective disorder. Further exploration of the possible relationships between specific regions of craniofacial deviance and other clinical characteristics are necessary to understand these relationships.

Methodological strengths and limitations of the Waldrop and Halverson scale and craniofacial measurements

Strengths of the Waldrop and Halverson Scale and other anthroscopic methods.

The Waldrop and Halverson Method has several advantages over the Anthropometric measurements. It is an easier examination to administer than the anthropometric exam. It requires just one instrument, a tape measure. Thus, it less expensive to use and it can be conducted comfortably in a variety of settings. In addition, it takes approximately fifteen minutes to administer. This makes studies easier to carry out and less burdensome for subjects. The presence of anomalies is not influenced by age, weight and height. In contrast, as described in greater detail below, the anthropometric measurements require numerous instruments, are time consuming and are influenced by height weight and age.

Limitations of the Waldrop and Halverson Scale and other anthroscopic methods.

The Waldrop and Halverson scale poses many methodological limitations. The original scale was created for Caucasian children and is not easily generalizable to adults, particularly of different racial and ethnic backgrounds. It does not encompass all of the anomalies found in schizophrenia (Ismail, B. et al., 1998b; Trixler et al., 1997, 2000) . While several other studies have used extended versions of the Waldrop and Halverson Scale (Ismail, B. et al., 1998b; Lane et al., 1997) or altogether different methods (Lane et al., 1997; McGrath, J. et al., 2002; Trixler et al., 1997), few have published manuals providing operational definitions for rating the presence or absence of such anomalies. In addition, there are variations in the items used and scoring methods among those studies using the Waldrop and Halverson method. All of these factors limit the ability to compare results across studies. Furthermore, very few studies have been conducted to assess the validity of characterizing these variations as anomalie. In a study by Farkas, mild epicanthus was found to be a normal variation of the eye in Caucasians (Farkas et al., 1979). More prevelance studies in healthy adults, such as this one, must be conducted to determine whether particular physical variations are truly anomalies.

Another limitation of the Waldrop and Halverson scale is its subjectivity. Although standard criteria are established to rate various items, these anomalies by their very nature (minor) often vary slightly from what is considered typical. In addition, very few examples are given in the Waldrop and Halverson manual. As a result, the rater may encounter many features for which the rating has not been operationally defined, forcing the rater to use his or her own judgment, rather than a standard for rating an item. Even if raters within groups decide on criteria for rating these features, different groups using the scale may have slightly different methods for rating. The result will make it difficult compare findings across studies.

Similarly, because observers are sometimes forced to use their judgment, the ratings may be influenced by the observer's expectations. While many authors have attempted to carry out anthroscopic assessment blind to diagnosis, this is difficult to do. Individuals with severe mental illness may reveal their illness via their behavior, presence of negative symptoms, motor difficulties or gestural and expressive peculiarities (such as maintaining eye contact for too long). Therefore, if the rater expects more anomalies in those with psychiatric illness, factors revealing the presence of psychiatric illness may influence ratings of physical anomalies. Improving the manual by providing more photographs with ratings will help alleviate this problem. Another strategy for reducing the influence of subject behavior on ratings is to have the observer rate photographs of individuals he has never met. The photographs would need to be clear and depict all of the features of interest.

Strengths of anthropometric measurement.

The anthropometric scale has several advantages. It is certainly more objective than rating methods. It has better normative data than anthroscopic methods. However, more normative data are needed, particularly in older adults. It more readily lends itself to comparison with healthy adults because there is published normative data from healthy adults when compared to ratings of physical anomalies.

Limitations of the anthropometric scale.

Anthropometric instruments are costly. In particular, some specialized instruments are very expensive. We have found that one of our specialized instruments (double sliding caliper) was not calibrated in the same manner as the expert's instrument was, making it difficult to establish inter-rater reliability and making it impossible to use the normative data to obtain standard scores for the subset of measurements that required this instrument.

In addition, craniofacial measurements are much more time consuming than ratings of physical anomalies. As a result, they are more costly assessments and may add to subject burden. In this study, a full craniofacial examination required two to three hours to complete, while ratings of physical anomalies typically required only fifteen minutes, even using an extended scale.

Training for craniofacial measurements is time consuming and requires supervision by an expert as well as inter rater reliability with an expert. One group helped to alleviate this problem by offering to mail to trainees "manikin heads" so that the trainees could measure various items and send their ratings to this group of experts for inter-rater reliability (Farkas, 1994). While this is a relatively inexpensive and convenient way to establish inter-rater reliability with established experts, it does not properly train some aspects of anthropometric measurements. Specifically it does not teach the measurer to set and keep the head at a particular angle in a live subject (necessary for inclination measurements and measurements using a double sliding caliper) or to negotiate the correct pressure to put on soft tissue with the instruments.

Although there are published methods to obtain anthropometric measurements, in this study, it appeared as though the published normative data did not seem representative of the individuals in this sample. It is most likely that one reason for this is the large overall difference in age between individuals in this study and the average age of individuals in the normative sample. However, this limitation can be corrected by extending the normative sample to include older individuals. In addition, there are few standard sets of measurements used across studies. This makes it difficult to make comparisons across studies.

It is difficult to determine the degree to which craniofacial measurements are related to prenatal influences. Craniofacial measurements are influenced by many factors other than prenatal development, such as age, ethic background, previous injury, weight (which is a problem in many individuals with mental illness due to weight gain side effects from many atypical neuroleptics). There is significant variability among healthy individuals for craniofacial measurements as indicated by the vast individual variability in the appearance of the head and face among healthy people. Systematic developmental differences may be relatively difficult to detect because of the numerous factors that can influence the measures (such as weight, size, race, ethnic differences and age). Therefore, large samples need to be used to detect developmental differences, which may be relatively subtle.

In addition, the normative data for craniofacial measurements, while superior to those rating scales, is limited. Adult norms are based on 309 Caucasian subjects (109 males and 200 females) and 100 African-American subjects (fifty males and fifty females) between the ages of 18 and 25 (Farkas, 1994). In the present study, the use of published data from the normative sample to determine Z scores was abandoned because this method appeared to introduce more differences among individuals in the study, which varied systematically with race. In addition, older individuals (patients and healthy control subjects) were not adequately represented by the sample. More normative data needs to be collected and published to reduce variation of scores due to age, race ethnic background, race and weight. Weight is of particular importance in studying craniofacial morphology in schizophrenia and schizoaffective disorder because atypical neuroleptics prescribed to these individuals often result in large weight gains.

Limitations of this study

Aside from some of the limitations inherent in the anthroscopic and anthropometric methods described previously, this study has several of its own limitations that must be considered when interpreting the results.

Relative to recent studies examining anthropometric measures in schizophrenia/ schizoaffective disorder, the sample size is small. Many variables (such as gender, race, ethnic background, age, height and weight) can influence craniofacial measurements of the head and face. The differences found between individuals with schizophrenia/ schizoaffective disorder and healthy controls are relatively subtle and large samples are necessary to find these differences, particularly because so many other variables cause differences in these measurements. If subtle craniofacial differences did exist among schizophrenic/schizoaffective subjects, this study may have failed to detect them; the small sample resulted in low power.

Another potential limitation of the study is that the patient sample may not adequately represent individuals with a neurodevelopmental subtype. Subjects in this group were selected from an ongoing longitudinal study based on their ability to travel to the hospital to undergo the craniofacial measurements. The reasoning for this was pragmatic; participants could sit in a dental chair for their comfort while the lengthy craniofacial examination was conducted. Therefore, those individuals who were hospitalized were not eligible to participate. When a subgroup of patients in this sample were selected based on having an early age of first treatment and poor performance on neurocognitive tests, only five of the fifty-two subjects had these characteristics. It is likely that if a neurodevelopmental subtype exists, they are either rare or were under represented in this study. This may explain why measures of physical deviance did not distinguish a neurodevelopmental subtype of illness. Had this study included chronically ill patients that were chronically hospitalized, perhaps a neurodevelopmental subtype could have been distinguished.

Another limitation is the fact that the rater was not blind to subject status, which may have impacted the physical anomalies rating portion of the study. Although the examiner used a conservative approach and tended not to rate an item if there was any uncertainty regarding its presence, the unusually large proportion of subjects with schizophrenia and schizoaffective disorder that were rated as having an excess of minor physical anomalies compared to other studies (Green et al., 1987), raises the possibility that the rater's knowledge of subject status influenced the ratings. It is unlikely that this interfered with the measurements, as they are less prone to bias.

While these factors provide some converging evidence that prenatal disruption can cause both brain and craniofacial dysmorphology, a recent study in nonhuman primates provides a model for how this may actually occur (Gelowitz et al., 2002). Two groups of monkeys were irradiated prenatally. One group was irradiated during the time of thalamic development whereas the other group was irradiated after thalamic development. Based loosely on anthropometric measures by Farkas, craniofacial dysmorphic assessments (including height weight, head circumference, middle head width, biocular distance, nasal base width ear height and ear width) were completed when monkeys reached adulthood. For those monkeys receiving early prenatal radiation (during the time of thalamic development) all measurements appeared lower than the control group without prenatal radiation. Only three of these measurements, biocular width, head width and ear width were significantly smaller than the control group. In the group that received later prenatal radiation, six of the measures were smaller than the control group; however only ear width was significantly lower than the control group. Although the differences observed in the monkeys were not identical to those found in humans with schizophrenia, these findings support a model of prenatal disruption leading to craniofacial and brain dysmorphogenesis in schizophrenia.

It appears as though disruption can occur in a variety of times and anatomic areas and via numerous mechanisms and can result in brain and craniofacial anomalies. Most studies, however discuss neurodevelopmental disruption as though it is a unitary construct. Instead, it is more likely that there is a range of events that can occur prenatally to result in schizophrenia. This is supported by the fact numerous epidemiological studies examining the relationship between schizophrenia and sources of prenatal insult such as prenatal infection (Barr et al., 1990; Brown et al., 1999; Mednick et al.,1988, 1994; Murray et al., 1992c; Pandurangi et al., 1994; Selten et al., 2002; Suvisaari et al., 1999; Wright et al., 1999) or RhD incompatibility (Hollister et al., 1996 1999), link the teratogenic insult to different periods of development (typically first trimester or second trimester).

Some aspects of neurodevelopmental disruption may be heterogeneous among individuals with schizophrenia and schizoaffective disorder. Perhaps all individuals with schizophrenia and schizoaffective disorder sustain some event (teratogenic or genetic) that results in anomalous development of a wider skull base width. Later insult may be the source of heterogeneity in other features of the illness such as symptom presentation and type and degree of neurocognitive functioning. For example, two preschizophrenic fetuses may both have wider skull base width occurring likely in the first trimester of development. One fetus further experiences prenatal infection during the second trimester but the other one does not. The infected fetus is likely to be different from the uninfected fetus in terms of clinical presentation.

Another explanation is that there are pre-existing differences among preschizophrenic fetuses such that when the putative insult occurs resulting in wider skull base widths, the fetuses respond differently to it. For example, one fetus that is relatively unaffected my have developed a wider skull base width and a few other anomalous features, but the development of this fetus' head and face was relatively resistant to this insult. In another more susceptible fetus, the insult resulting in wider skull base width may have interrupted the normal pattern of development resulting in further maldevelopment of the brain and craniofacial structures. These two fetuses would also be likely to have different clinical presentations of the same illness.

Therefore, it is important examine the potential heterogeneity in neurodevelopment among individuals with schizophrenia and schizoaffective disorder. While there are some aspects of craniofacial development that appear to deviate consistently (such as an increase in skull base width) across individuals with psychosis and suggest a unitary prenatal disruption, there may be considerable heterogeneity in craniofacial morphological deviation as well as deviation in brain differences, neurocognitive functioning, psychiatric symptoms and course of illness. While no clear support for this theory was found in the present study, it may explain timing differences in epidemiological studies linking schizophrenia to teratogenic insult (first versus second trimester). Although it is important to establish origins common to all individuals with psychosis, the potential heterogeneity in neurodevelopment must still be addressed.

Future directions of research

One source of focus for future research is to improve the methods of collecting ratings of minor physical anomalies and craniofacial measurements. Specifically, the prevalence of these physical anomalies must be examined in healthy adults in order to determine whether they are truly anomalous or just normal variations. Manuals for anomaly rating scales should include operational definition and include numerous photos of examples so that less is left to the judgment of the rater, resulting in better-standardized scales. Regarding anthropometric measurements, more comprehensive normative data (using individuals of different ages, races, ethic background and body mass) needs to be collected. These developments can improve understanding of minor physical anomalies and craniofacial morphology in general, and provide a stronger foundation on which to base findings from studies in schizophrenia and schizoaffective disorder.

This is the first study to examine craniofacial deviance in Caucasian and African-American individuals with schizophrenia or schizoaffective disorder. Future research should examine these features in individuals of other racial and ethnic backgrounds to develop a more thorough understanding of the extent to which these results generalize across gender and race.

Future studies must examine the validity of inferences made about relationships between the craniofacial measurements and the skull. For example, it has been suggested here and previously (McGrath et al., 2002) that increased skull base width is related to development of the middle cranial fossa. Future research should investigate the validity of this prediction by comparing measurements of skull base widths to actual measurements of the middle cranial fossa, perhaps based on imaging studies of the skull. For example, Farkas studied the relationship between the external endocanthion to the bony endocanthion by attaching a metallic sticker to the external landmark and determining the degree to which the two corresponded (Farkas, personal communication 2000). A similar study could be conducted by taking X-rays of the skull while a metallic sticker is placed on the tragus of the subject. Such a study may reveal that the increase in skull base width in psychosis found in this and other studies is actually related to deviation in the development of a different craniofacial anomaly. The tragus is found on the most anterior portion of the ear. Therefore, if the ear is displaced on the head the skull base width as well as facial depth measurements can be affected. This would not refute the findings thus far, but would point to a different aspect of prenatal development that should be studied to further understand anomalous prenatal development in schizophrenia and schizoaffective disorder.

One must understand the prenatal interactions between brain and craniofacial development in the healthy fetus before one can understand how pathological development of the brain can negatively impact craniofacial development (and vice versa). However, to date, there has been little exploration of how the brain and craniofacial structures interact during development. Exploring this relationship may provide a foundation for understanding potential mechanisms of prenatal maldevelopment in individuals with schizophrenia and schizoaffective disorder.

To date, all studies of craniofacial measurement in schizophrenia have examined single measurements. However, as demonstrated in this study, overall size of a feature is related to the overall size of the person, rather than some neurodevelopmental event. Future research should explore the relationships among specific measurements because these may be more informative regarding early craniofacial development. One way to explore this relationship is via 3-D lazar surface imagery (Hennessy et. al, 2002). This technology can calculate numerous measurements quickly and may have the potential to quickly examine numerous relationships among these measurements.

Exploration of the relationships between physical deviance and other illness characteristics is in its infancy. This is fertile ground for future research. Such studies may examine the relationship between craniofacial morphology and prenatal and obstetric complications, brain structure, response to medication, chronicity of illness, symptoms presentation, symptoms found in studies and the degree to which particular craniofacial deviations predict development of illness later in life. Studying craniofacial differences within individuals with severe mental illness may lead to a better understanding of the heterogeneity of the illness and its etiology.

Appendix 1: Glossary

Glossary

Adherent ear lobes – when the entire front of the earlobe is attached to the head. This is an item from the Waldrop and Halverson scale. This item is not rated if there is any portion of the ear lobe that extends beyond the lowest point of where the ear attaches to the head. This item is rated "2" if the lower edge extends upward toward the crown of the head (Waldrop and Halverson, 1971).

Ala – the curved areas of the nose lateral to the nostrils (Farkas, 1994).

Alar curvature of alar crest (ac) – This is the anthropometric landmark of the nose. According to Farkas, it "is the most lateral point in the curved base line of each ala, indicating the facial insertion of the nasal wingbase" (Farkas, 1994 p. 24).

Alare (al) A landmark of the ala (portion of the nose) used for craniofacial measurement. It "is the most lateral point on each alar contour" or the most lateral portion of the side of the nose nearest the nostril (Farkas, 1994, p. 23).

Anteverted nostrils – the base of the nose is malformed allowing the observer to see the entire nostrils when looking at the front view of the face (Chow et al., 1999).

Anthropometric – related to measurement of the human form (Farkas, 1994).

Anthroscopic – related to a means of assessing physical anomalies based on rating the presence absence and sometimes the severity of a physical anomaly, based on observation alone, not measurement (Farkas, 1994).

Biocular width – This is a measurement of the eye region, specifically, the distance across both eyes. According to Farkas, this is the "distance between the exocanthions (most lateral aspects of the palpebral fissures). This biocular width is shorter than the external orbital breadth." When taking the measurement, the subject should gaze upward so that the upper lid does not obscure the exocanthions. The sliding caliper should be under the eyes with the arms of the sliding caliper at the exocanthions (Farkas, 1994, p. 35).

Chelion (ch) – This is an anthropometric landmark of the mouth corresponding to "the point located at each labial commissure". It corresponds to the lateral corners of the labial fissure (mouth opening) (Farkas, 1994 p. 25).

Cleft lip microform – a minor physical anomaly in which the upper lip is malformed so that there is a cleft present. In its microform, this may appear as a crease (Ismail et al., 1998a).

Cleft Uvula – The uvula is malformed such that the bulbous portion of the uvula is bifid. It may appear as though there are two bulbous portions side by side. (Ismail et al., 1998a)

Colombata – a physical anomaly of the eye, a gross defect to the fissure or lid of the eye (Ismail et al., 1998a).

Curved fifth finger - This is an anomaly on the Waldrop and Halverson scale and is rated when the fifth finger (commonly called the "pinky") curves inward toward the other fingers (Waldrop & Halverson 1971).

Depth of the mandibular region (t-gn) - This is the "depth of the lower third of the face" and is "measured between the tragion (t) and the gnathion (gn)" (Farkas, 1994, p. 34). With the subject's head tilted back, one arm of the spreading caliper is steadied at the tragion and the other arm is brought to the gnathion. Measurements are taken on the left and right sides (Farkas, 1994, p. 34).

Depth of the maxillary region (t-sn) - This is "the depth of the middle third of the face" which is "measured between the tragion (t) and the subnasale (sn)" (Farkas, 1994, p. 34). With the subject's head tilted back, one arm of the spreading caliper is steadied at the right tragion and the other is brought to the subnasale. Measurements are taken on the left and right sides (Farkas, 1994, p. 34).

Depth of the supraorbital rim (t-g) - This is " the depth of the upper third of the face which is measured between the tragion (t)(portion of the ear) and glabella (g) (midpoint of forehead)" (Farkas, 1994 p. 34). With the subject's head tilted upward, one arm of the spreading caliper is held steady at the tragion as the other arm goes to the glabella. Measurements are taken for the right and left side (Farkas, 1994 p. 34).

Ear lobe skin tag – an outgrowth of skin on the ear lobe (Ismail et al., 1998a).

Endocanthion (en) - It is a landmark of the eye used for craniofacial measurement and is in the innermost corner of the eye. Farkas defines it as "the point of the inner commisure of the eye fissure. The soft endocanthion is located lateral to the bony landmark (MO) that is used in cephalometry" (Farkas, 1994, p.22.)

Epicanthus - a fold of skin covering or partially covering the lacrimal caruncle (inner corner of the eye). This is frequently found in children and according to Farkas (personal communication, 2000), and often becomes absent as the nasal bridge develops. It is rated as "1" if, with the subject looking forward or straight ahead, there is any vertical skin partially covering the lacrimal caruncle (inner corner of the eye) on either or both eyes.

If there is full coverage of the lacrimal caruncle, it is rated as "2" (Waldrop & Halverson, 1971).

Eurion (eu) "is the most prominent lateral point on each side of the skull in the area of the parietal and temporal bones" (Farkas, 1994, p. 21). These landmarks are found when taking the measurement of the width of the head. The arms of the spreading caliper are places on the sides of the head and are slid until the greatest width is achieved on the caliper. The eurions are those points on the head that the arms of the spreading calipers are touching to achieve this widest measure (Farkas, 1994, p.21).

Exocanthion (ex) (or ectocanthion) - a craniofacial landmark corresponding to the outermost corner of the eye. According to Farkas it "is the point at the outer commisure of the eye fissure. The soft exocanthion is slightly medial to the bony exocanthion" (Farkas, 1994, p.22).

Facial depth measurements – linear measurements of the face taken using a spreading caliper. They are taken from a point of the ear (tragion) to a midpoint in the face. There were three facial depth measurements used in this study for each side of the face: (1) the depth of supraorbital ridge taken from the tragion to a midpoint on the forehead (glabella), (2) the depth of the mandible taken from the region to the midpoint of the face just underneath the nose (subnasale) and (3) the maxillary depth, taken from the tragion to a midpoint just under the chin (Farkas, 1994).

Fifth finger one or three creases – instead of two creases on the palmar side of the fifth finger, there is either one or three creases (Ismail et al., 1998a).

Fine electric hair – very fine, usually blonde hair, which won't comb down easily or becomes awry after having been combed down. On the Waldrop and Halverson scale, if the hair cannot be combed down at all it is rated “2”. If it becomes awry shortly after it is combed it is given a rating of “1” (Waldrop & Halverson, 1971). This is the first item on the Waldrop and Halverson scale. Because fine electric hair is not found in African-American individuals, it was not used in this study.

Frontal bossing – When examining an individual’s profile, the forehead typically slopes backward, such that the supraorbital portion of the forehead is more anterior to the portion of the forehead near the hairline. When frontal bossing occurs, the portion of the forehead near the hairline is more anterior to the supraorbital portion of the forehead and the angle within the profile is in the opposite direction of what is typically seen (Ismail et al., 1998a).

Frontotemporale (ft) - Farkas defines this as “the point on each side of the forehead, laterally from the derivation of the linea temporalis. This location was chosen due to difficulties of finding the linea temporalis in children with disfigurements of the head. The position of the landmark approximately corresponds with the level of the terminal points of the tail of the eyebrow.” (Farkas, 1994, p.21).

Frontozygion (fz) – This landmark is defined as the depressed region on the lateral aspect of the forehead between the frontotemporale and the zygomatic arch (Farkas, 2000, personal communication).

Furrowed tongue groove or grooves on the tongue – This physical anomaly is defined as any groove or grooves on the tongue EXCLUDING the groove that is often seen in the middle of the tongue (Waldrop & Halverson, 1971)

Fused eyebrows – a minor physical anomaly from Ismail's extended scale. The medial aspects of the eyebrows grow in such a way as to connect above the nose (Ismail et al, 1998a).

Glabella – (g) According to Farkas, this craniofacial landmark is "the most prominent midline point between the eyebrows and is identical to the bony glabella on the frontal bone" (Farkas, 1994, p. 21).

Gnathion (gn) - This craniofacial landmark, according to Farkas "is the lowest median landmark on the lower border of the mandible. It is identified by palpation and is identical to the bony gnathion. This point is the lowest point used in measuring facial height." (Farkas, 1994, p. 22). Upon palpation it is the lowest portion of the front of the mandible, where one typically feels a ridge (Farkas, 2000, personal communication).

Gothic Palate - When during prenatal development, the two plates that ultimately form the palate (roof of the mouth) do not fuse properly. The result can be a palate that is triangular in shape, meeting at a point where the plates fused. The normal palate is rounded in shape (Farkas, L.G., 2000, personal communication).

Hair whorl – This is a point near the crown of the head where the hair grows in a circular pattern, usually around a point. According to Waldrop and Halverson, this typically occurs on either the right or left hemisphere. This is the second item on the Waldrop and Halverson scale and an individual is rated if there are two or more hair whorls or if a hair whorl grows around a line at least an inch in length (instead of growing around a point). This item was omitted because it was not applicable to a multiracial sample (Waldrop & Halverson, 1971).

Head circumference – This is the length around the head. More specifically, Farkas defines this as "measured in the horizontal plane around the head through the glabella (a midpoint on the forehead) and opisthocranion (most posterior point on the head)" (Farkas, 1994, p. 27). The tape must be held tightly around the head" to minimize the increase in the measure due to hair (Farkas, 1994, p. 28).

Height of cutaneous lower lip (li-sl) - This is the "height of the skin portion of the lower lip between the labiale inferious (li) (midpoint of the lowermost line of the lower lip) and the sublabiale (sl) (mentolabiale ridge) " measured using the sliding caliper (Farkas, 1994, p. 44).

Height of the lower face (sn-gn) – According to Farkas, "it is the distance between the subnasale (sn) (the point just under the nose) and the gnathion (gn) (the point just under the chin") (Farkas, 1994 p. 30). The sliding caliper is held parallel to the face. One arm of the caliper is fixed on the bony gnathion and while the other is brought to the subnasale. The subject's head should be tilted backward (Farkas, personal communication, 2000).

Heterochromia – Heterochromia is unmatched eye color in both eyes within the same individual. (For example having a blue eye and a brown eye.) This was an item from the Ismail extended physical anomaly scale (Ismail et al., 1998a).

Height of the cutaneous upper lip (sn- sto) - This is not to be confused with vermillion height of upper lip, which is the thickness of what is commonly thought of as upper lip. The cutaneous upper lip extends from where the lips meet to just under the nose. According to Farkas, it is "the height of upper lip between the subnasale (right below the nose) and the stomion (midpoint of the labiale fissure)" (Farkas, 1994 p.44) and is measured using the sliding calipers.

Hyperteliorism – Hyperteliorism is unusually wide set eyes. Waldrop and Halverson indicate that in children, this length had to be estimated because they could not get it in their sample without restraining them. In this study, the actual measure was taken using a sliding caliper to measure the endocanthions or most inner points of the eye. If epicanthis was present, the extra fold of skin was moved away from the lacrimal caruncle by pulling the skin toward the top of the nasal bridge and measuring the distance between the most interior portions of the palpebral fissures (Waldrop & Halverson, 1971).

Hyperconvex nails – When looking at the nailbed, most individuals have nails that are somewhat curved, rather than flat. Nails that curve excessively are considered hyperconvex nails (Ismail et al., 1998a).

Intercanthal width (en-en) – According to Farkas, this is the measurement "between the endocanthions (en) (innermost corners of the eye)" (Farkas, 1994 p. 35). The sliding caliper should be steadied against the forehead and the tips should be brought close to the endocanthions (Farkas, 1994 p. 35).

Labiale inferious (li) - This craniofacial landmark of the mouth is defined by Farkas as "the midpoint of the lower vermillion line" (midpoint of lower border of what is commonly thought of as the lower lip)." (Farkas, 1994, p. 24).

Labiale superious (ls) - This craniofacial landmark of the mouth is defined by Farkas as "the midpoint of the upper vermillion line" (midpoint of the upper border of what is commonly thought of as the upper lip) (Farkas, 1994 p. 24).

Labio-aural distance (t-ch) -This is the distance between the tragus of the ear and the chelion (side of the mouth) using the spreading caliper (Farkas, 1994).

Lacrimnal caruncle – This is the inner portion of the eye from which one can see muscles to the side of the orbit (Waldrop & Halverson, 1971).

Length of ala (ac-prn) - According to Farkas this craniofacial measurement is "the distance between each facial insertion point of the alar base (where the side of the structure around the nostril meets the face) and the pronasale (tip of the nose)" (Farkas, 1994 p. 42). This is measured using the sliding caliper by placing one of the arms on each of the landmarks (Farkas, personal communication, 2000).

Length of the auricle (sa-sba) – This is the length of the ear or, more specifically, the "maximum length of the long axis of the pinna between the superaurale and subaurale of the right ear"(Farkas, 1994, p. 48). It is measured using the sliding caliper.

Length of eye fissure (ex-en) - "The distance between the endocanthion (en) (inner corner of the eye) and the exocanthion (ex) (outer corner of the eye)" (Farkas, 1994, p.34). The subject should gaze upward so that the upper lid does not obscure the endocanthion. The sliding caliper should be under the eye, with one arm directly under the endocanthion and one arm under the exocanthion. The sliding caliper should be steadied on the subject's cheek (Farkas, 2000, personal communication).

Length of head (g-op) - This is defined by Farkas (1994, p. 27) as "the distance between the glabella (g) (a midpoint on the forehead) and the opisthocranion (op) (the most posterior point of the head)." One arm of the spreading calipers is laid on the gnathion. The second arm slides up and down the back of the head until the maximum distance is achieved. This point at the maximum distance is by definition the opisthocranion.

Low set ears – ears that are lower on the head than usual. This is an item on the Waldrop and Halverson Scale. A pencil or straight edge is held next to the subject's head. The rater lines the straight edge up with the bridge of the nose and the outer corner of the eye, keeping the stright edge perpendicular to the floor. If the line falls lower than ¾'s of the ear, a rating of 0 is given. If the line falls though the upper ¼ of the ear, a rating of 1 is given. If the ear falls below the line, then a rating of 2 is given (Waldrop & Halverson, 1971).

Malformed ears – this is an item from the Waldrop and Halverson scale and encompasses any grossly misshapen ear (Waldrop & Halverson, 1971).

Micrognathia – This minor physical anomaly is defined as an abnormally small mandible, from the Ismail et al scale (Ismail et al., 1998a)

Morphological height of the face (ngn) - "The distance between the nasion (n) and the gnathion (gn) (midpoint underneath the chin)" (Farkas, 1994, p. 30). The sliding caliper is held so that the blades are horizontal to the face. One arm is fixed on snugly on the bony gnathion and the other arm is raised to the nasion. The subject should close his or her teeth for this measurement (Farkas, personal communication, 2000).

Narrow alar bases – the base of the nose near the nostrils is unusually narrow.

Nasion (n) - This is defined by Farkas as "the point in the midline of both the nasal root and nasofrontal suture" (Farkas, 1994 p. 23). The slight ridge on which it is situated can be felt by the observer's fingernail. This point is always above the line that connects the two inner canthi. The soft nasion and the bony nasion are identical (Farkas, personal communication, 2000).

Opisthocranion (op) - This is the most posterior point on the head, or "the point situated on the occipital region of the head and is most distant from the glabella; that is, it is the most posterior point of the line of the greatest head length. It is close to the midline on the posterior rim of the foramen magnum. The location of this landmark depends on the shape of the occipitale" (Farkas, 1994 p. 21).

Outstanding ears – the ears protrude outward from the head.

Physiognomical height of the upper face (n-sto) -The distance between the nasion (n) and the stomion (sto). With the subject's head tilted backward, one arm of the sliding caliper is fixed to the nasion. The other arm of the sliding caliper is brought down to the stomion, the midpoint of the labial fissure. The subject's lips should be gently closed (Farkas, 1994).

Postaurale (pa) -This is " the most posterior point on the free margin of the ear'. (Farkas, 1994, p. 25).

Preaurale (pra) – This is "the most anterior point of the ear, located just in front of the helix attachment to the head" (Farkas, 1994 p. 25).

Preauricular skin tag – This is an outgrowth of skin just anterior to the ear (Ismail et al., 1998a).

Ptosis – The eyelids droop so that the pupil is at least partially covered (Ismail et al., 1998a).

Retarded fingers/ toes – The proximal phalynx grows from a portion of the hand or foot lower than the other fingers and/or toes (Ismail et al., 1998a).

Retrognathia – Rerognathia is defined as a chin that angles backward. This occurs frequently when the mandible is usually small. However, micrognathia is not a requirement for this item to be rated (Ismail et al., 1998a).

Single transverse palmar crease – an umbroken line going straight across the palm of the hand. This item is from the Waldrop and Halverson scale (Waldrop & Halverson, 1971).

Sinus before or behind the helix – a crevice or pit on the skin just anterior to or posterior to the ear (Ismail et al., 1998a).

Skull base width (t-t) - Farkas defines this craniofacial measure as "the distance between the tragions" (Farkas, 1994, p. 26). The spreading caliper ends are laid on these points and the examiner's forefingers support the calipers behind the traguses (Farkas, 2000, personal communication).

Soft ears – Ears with this anomaly are jelly-like and soft. They do not spring back into place quickly as do ears with strong cartilage (Ismail et al., 1998a).

Squared nasal root – the upper portion of the nose just inferior to the nasal suture is square-like in shape (Chow et al., 1999).

Steepled palate (see also Gothic Palate) - When during prenatal development, the two plates that ultimately form the palate (roof of the mouth) do not fuse properly, the result can be a palate that is triangular in shape, meeting at a point where the plates fused. The normal palate is typically rounded in shape (Waldrop & Halverson, 1971).

Subaurale (sb) - Farkas defines this craniofacial landmark as "the lowest point of the free margin of the ear lobe" (Farkas, 1994, p. 25).

Sublabiale (sl) -This craniofacial landmark is defined as the point that "determines the lower border of the lower lip and the upper border of the chin. It corresponds with the mentolabiale ridge of anatomists, a point in the midline of the nasolabial sulcus or the point marked as the inferior labial point or labiomentale. The identification of this landmark on the lower face with deep and indented mental sulcus is easy. In shallow ridges and flat surfaces of the receding chins the landmark on the surface was determined with the help of the level of the bottom of the lower lip, by intraoral examination." (Farkas, 1994, pp. 21-22). That is, a tongue depressor is inserted vertically along the inside of the lower lip. The sublabiale will correspond roughly to the lowest point that the tongue depressor can go (Farkas, 2000, personal communication).

Subnasale (sn) - A landmark used for craniofacial measurement. It defined as "the midpoint of the angle of the columnella base where the lower border of the nasal septum and the surface of the upper lip meet" (Farkas, 1994, p. 23). "The landmark is identified in the base view of the nose, or from the side, where the nasolabiale angles are found with curved contours" (Farkas, 1994, p. 24).

Superaurale (sa) – This landmark is defined as "the highest point on the free margin of the auricle" (Farkas, 1994 p, 25).

Syndactyly – webbing between fingers and toes. However the specific anomaly for the purpose of this study is webbing between the toes. If there is webbing to the proximal interphalangeal joint, a rating of one is given. However, if there is webbing to the distal phalange, then a weight of two is given. This is an item from the original Waldrop and Halverson Scale (Waldrop & Halverson, 1971).

Tongue with smooth rough spots – tongue with thickened epithelium that appears to look like smooth-rough spots. This anomaly is from the Waldrop and Halverson Scale and must not be confuse with raised palpillae, which can occur after eating certain foods (Waldrop & Halverson, 1971).

Tragion (t) "is the notch on the upper margin of the tragus" (Farkas, 1994. p. 25) or the most anterior part of the ear; anterior to the ear canal (Farkas, 2000, personal communication).

Vermillion height of the upper lip (ls-sto) - This craniofacial measurement is defined as the "thickness of the vermillion in the facial midline between the labiale superius and the stomion" (Farkas, 1994, p. 44). It is measured using the sliding caliper.

Width of the auricle (pra-par) - This measurement is "the maximum distance between the prearale and the postaurale" (Farkas, 1994, p. 48) of the ear measured using the sliding caliper (Farkas, 1994, p. 48).

Width between facial insertion points of the alar base (ac-ac) – This craniofacial measurement as "the width of the facial insertion points of the alar base (and is measured between) the most lateral points of the curved base lines of alae oriented toward the face (alar crests or ac)" (Farkas, 1994, p. 38). The pointed ends of the sliding caliper should be used for a more accurate measure (Farkas, 2000, personal communication).

Width of face (zy-zy) - According to Farkas this is "measured at the widest part of the face, between the zygions. The tips of the (spreading) caliper are pressed over the zygomatic arch until the maximal breadth is determined" (Farkas, 1994, p. 29).

Width of forehead (ft-ft) -This craniofacial measurement is defined by Farkas as the "distance between the frontotemporale points, points lateral to the temporal lines. The spreading calipers are used for this measure and should be pressed inward to the bony points."(Farkas, 1994, p. 27)

Width of head (eu-eu) – This craniofacial measurement is defined as "the distance between the eurions" (Farkas, 1994, p. 26). Using the spreading calipers, fixate them on the sides of the head. Slide the spreading calipers around until the maximal distance is attained. Calipers should be pressed in to touch the bone, but not to cause discomfort (Farkas, 2000, personal communication).

Width of nose (al-al) – This craniofacial measurement is defined as "the distance between the most lateral points on the alae. The arms of the (sliding) caliper only touch the skin." (Farkas, 1994, p. 38). The arms of the caliper must not press the alae because this will change the measure (Farkas, 2000, personal communication).

Zygion (zy) – This craniofacial landmark is defined this as "the most lateral point of each zygomatic arch. It is identified by trial measurement, not by anatomical relationship. It is identical to the boney zygion of the malar bones" (Farkas, 1994, p. 21).

Appendix 2: Healthy Control Flyer

Healthy Adults Needed

For a Research Project That May Benefit People With Serious Disabling Mental Illness

In some people with serious mental illness, subtle differences in features of the head, face, hands and feet may give clues about how they developed their illness. To learn more about these physical features in healthy people, we need adults who are similar to our mentally ill participants in terms of age, gender and racial background.

You may be eligible to participate if you:

- Are between the ages of 18 and 55
- Have not been hospitalized for psychiatric reasons
- Have not had plastic surgery to your face

At this time, only individuals who are of African –American or Caucasian decent are needed.

You will be reimbursed for your time.

Your help may give us a better understanding about how some mentally ill people developed their illness. In the future, this may lead to better detection, diagnosis, and more effective treatment for people who suffer from these disabling illnesses.

For further information, contact:

Anne-Marie Donovan, Ph.D. candidate, Hillside Hospital
718 470-8739

Appendix 3: Patient Participant Consent form

Informed Consent to Participate in:

Neuropsychology of Psychiatric Disability and Service Needs: Cohort 2

(version 12/27/99)

Investigators:

Principal Investigator: Judith Jaeger, Ph.D., M.P.A.

Co-Investigators: Stefanie Berns, Ph.D.

Research Assistants: Anne-Marie Donovan, M.A., Sara Conway, Stephen Panopoulos, M.A., Cristina Gomes, Sherif Abdelmessih

Purpose of this Project:

This study is being done to learn more about the characteristics of people who suffer from serious mental illness. These illnesses can often last a long time and interfere with many parts of living - many people with this illness have trouble holding a job, making friends, having a family and even just enjoying life. This purpose of this study is to better understand the degree to which this difficulty in living independent lives is a result of impaired cognitive skills (which includes memory, attention, and problem solving) in patients with certain mental illnesses. In order to do this, we will be focusing on people between the ages of 18 and 54 who have recently been discharged from the hospital.

Expected Duration of the Subjects Participation:

If you agree to take part in the study, we will need to see you for up to three separate days sometime within the next week or two for the baseline assessment. In 6, 18, and 36 months from now, we will need to see you again for a followup assessment that takes about two days. . It is possible we will also need to see you for up to two additional followup assessments depending on the course of your illness. Also, you will be called once each month and asked some questions by phone which will take approximately 30 minutes each time.

Description of Procedures:

During your visits, you will be administered tests that involve puzzles, computer tasks, and pencil and paper tests that assess skills such as memory, attention and problem solving. During some of these tasks you will be timed. You also will be asked questions about any symptoms you may have experienced during the past week as well as questions about work, education and living arrangements. If you become tired you may ask for a break or request that it be continued on another day. Measurements will also be taken of your face, head, hands and feet. When we see you again in six months and also in eighteen months, we will administer many of the same tests and questionnaires. Also, you will be asked to keep a diary of your doctor and therapy visits and other mental health services that you use on a weekly basis. When we call you each month, we will ask you to tell us about the services you have used and also about changes in your work, education, living arrangements.

You will be reimbursed for transportation and given lunch for every visit. You will be paid by check after the completion of all of the tasks at each of the timepoints (baseline and followup assessments). You will also be reimbursed by check for completing the diaries and monthly telephone interviews.

In order to ensure the accurate transcription of the information you provide, it can be very useful to us if we video-tape or audio-tape portions of the sessions. Your name will not be on the tape and it will be kept in a locked file cabinet. Only staff involved in this project would have access to the tape. If you choose not to be taped, you can still participate in the study and no portion will be taped. Please initial below if you do **not** want to be audio- or video-taped.

_______I do **not** want to be audio-taped. ______I do **not** want to be video-taped.

If in the course of this research, information relevant to my protection or the protection of others is learned, it will be released. Any other information about me obtained from this research including answers to questionnaires, history, or audio or videotapes be kept confidential. However, if I agree, information from clinical interviews may be shared with my treatment team. Please initial below if you do **not** want such information shared with your treatment team.

_______ I do **not** want information shared with my treatment team.

<u>Possible Discomforts and/or Risks:</u>

Potential risks of participating in this study are extremely minimal but may include fatigue and test anxiety.

<u>Possible Benefits of Participation:</u>

Potential benefits of participating in this study may include the advantage of careful monitoring of your condition and circumstances.

<u>Alternative Treatment</u>

Although this study does not involve a treatment, you have the alternative of not taking part in the study.

Confidentiality

Your decision to participate is voluntary. Your identity and participation are confidential to the extent permitted by law. Your test results will not be identified with your name, but by a number code to maintain your confidentiality and all results will be stored in locked areas. If you decide not to participate or if you choose to withdraw after beginning the study, you will not lose any benefits associated with your medical care.

<u>Costs</u>

There will be no costs to you for your participation in this study.

Compensation for Injury

In the case of physical injury resulting from participation in the study, only immediate, essential, short-term treatment determined by a physician will be made available to you without charge. There will be no monetary compensation or non-emergency care provided by the Long Island Jewish Medical Center. In the event that medical assistance is required, you are instructed to call your doctor or 911.

Contact Questions

You are encouraged to ask questions before deciding whether you wish to participate and any time during the course of the project by contacting Stefanie Berns at 718-470-8436 or Dr. Jaeger, the Director of the Center for Neuropsychiatric Outcome and Rehabilitation Research at 718-470-8342. For questions concerning this research project and/or research subjects' rights, you should call the Office of the Institutional Review Board at 516-470-6400. The IRB is the committee that oversees research at this institution. A copy of this consent will be given to you.

INFORMED CONSENT QUESTIONNAIRE

It is important that you understand the contents of this consent form. Below are some true/false questions about the consent form.

Circle One:

True False 1. Participating in this study requires a change in my medication.

True False 2. I will receive transportation reimbursement each visit but only the study participation reimbursement when I complete all the tasks required for each timepoint even if it takes several days.

True False 3. I can ask to take a break at any time.

True False 4. This is a type of day treatment program.

True False 5. Once I agree to participate I can't change my mind.

True False 6. Results of the tests are kept confidential.

True False 7. I can choose not to be video- or audio-taped.

True False 8. I will be asked to return for followup sessions.

I have offered an opportunity for further explanation of the risks and discomforts which are, or may be associated with this study and to answer any further questions relating to it. I also verify the subject's ability to provide informed consent:

Signature of clinician obtaining consent ____________ Date ____________

I hereby consent to participate.

Subject's Name (print) ____________

Witness Signature (someone with no connection to this research project) ____________

Subject's Signature ____________

Witness Identification (e.g. nurse, friend, receptionist, etc.) ____________

Date ____________

Appendix 4: Normal Control Participant Consent Form

Queens College/CUNY
65-30 Kissena Blvd.
Flushing NY 11367

CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

Project Title: Minor Physical Anomalies and Neuropsychological Functioning in Schizophrenia

Project Director/ Investigator: Judith Jaeger, Ph.D., Adjunct Professor, Neuropsychology Subprogram, CUNY,
Queens College, (718) 470-8342.

Research Study Investigator: Anne-Marie Donovan, MA, Ph.D. Candidate, Neuropsychology Subprogram, CUNY
(718) 470-8739.

You are being asked to participate in a research project conducted through Queens College CUNY. Queens College requires that you give your signed authorization to participate in this research project.

A basic explanation is written below. Please read this explanation and discuss it with the research investigator. If you then decide to participate in the research project, please sign the last page of this form.

Nature and Purpose of this Project

Patients with schizophrenia vary widely in their symptom presentation, course of illness, cognitive ability (performance on tests of memory, attention, and problem solving ability). It is known that some patients have minor physical anomalies; minor physical anomalies are subtle differences in the structure of the face, hands and feet which are thought to reflect a disturbance in prenatal development. The same prenatal disturbance related to the development of these features is thought to be related to abnormal brain development. The purpose of this study is to measure these features in patients with schizophrenia and to compare them to the features of healthy subjects. The degree to which these physical anomalies can predict performance on tests of cognitive functioning (e.g. attention, memory, problem-solving ability) in patients with schizophrenia will be determined. Your participation will help provide the information about structure of the head, face, hands and feet in healthy adults. In addition, previous research has revealed a higher incidence of non-righthandedness (left-handedness or ambidextrousness) in patients with schizophrenia compared to the general population. Some researchers believe that this higher instance in non-righthandedness in schizophrenia is due to differences in early brain development in schizophrenia. Your participation will also provide information about handedness and fine motor skill in healthy adults.

Explanation of Procedures

You will be interviewed regarding possible history of psychiatric illness, developmental disorders, serious physical injury, and cosmetic/ reconstructive surgery. This will determine whether you are eligible to participate in this study. You will also be asked to provide basic demographic information, including you age and gender. Provided that you are eligible to participate, measurements will be taken of your head, face, hands and feet, as well as height and weight. Some of the measurements require the use of calipers, angle finders, and tape measures. You will also be given a brief assessment of handedness including a test assessing fine motor skill. Your entire participation is expected to take approximately three hours.

Potential Discomfort and Risks:

The potential risks associated with your participation are minimal. However, some individuals may experience mild anxiety upon being examined. Your comfort is important and you are free to request a break at any point during the study.

Potential Benefits

You will receive $25 to reimburse you for your time. If you are part of the Queens College subject pool you will also receive credit for participating in a three hour experiment. While you will not benefit directly in any other way from participation in this project, your involvement may help further knowledge about different causes and types of schizophrenia. Better understanding of the illness may lead to more effective means of treatment.

Alternatives to Participation:

You have the alternative of choosing not to participate at any point during the study. Choosing not to participate will not effect any services you may receive in the future from Queens College.

Withdrawal from Participation for Queens College Psychology Subject Pool Students

If you choose to withdraw from this experiment, you understand that you will not receive credits toward the Psychology 101 research requirement, but that you may participate in other studies or write a research report to fulfill the requirement.

Termination of Participation

Your participation may be terminated if it is determined that you are ineligible to participate. Subjects in this comparison group are required to have no current experience of, or history of serious psychiatric symptoms, cosmetic/reconstructive surgery of or serious injury to the head, face, hands or feet, or a history of developmental disorder.

Confidentiality

The results of your participation will be kept confidential to the fullest extent permitted by law. To ensure confidentiality, a code number, rather than your name , will identify your records. This means that only project staff will know about your specific results. Only information that cannot be traced to you will be used in reports or manuscripts published by project staff.

Withdrawal from this Project

Your participation in this research project is completely voluntary. You may decide to stop participating in this project at any time without penalty. You are free to leave at any time.

Who to call if you have any Questions:

The approval stamp on this consent form indicates that the project has been reviewed and approved by the Queens College (CUNY) Institutional Review Board for the Protection of Human Subjects in Research and Research Related Activities.

If you have any questions about your rights as a research participant, or to report a research related injury, you may call the Office of Research and Sponsored Programs, Queens College (CUNY) at (718) 997- 5400.

If you have concerns or questions about the conduct of this research project, you may call Dr. Judith Jaeger
Adjunct Professor, Neuropsychology Subprogram CUNY, Queens College, (718) 470-8342

What signing this Form Means:

By signing this consent form, you agree to participate in this research project. The purpose, procedures to be used, as well as the potential risks and benefits of your participation have been explained to you in detail. You can refuse to participate or withdraw from this research at any time and without penalty. Refusal to participate in this study or withdrawal from this study will have no effect on any services you may otherwise be entitled to from Queens College (CUNY). You will be given a copy of this consent form.

____
Printed name of participant

____
Printed name of Research/ Study Investigator

____
Signature of participant

____
Signature of Research /Study Investigator

____
Today's Date

____
Today's date

Appendix 5: Anthropometric landmark definitions (from Farkas, 1997)

Head

Glabella – (g) "the most prominent midline point between the eyebrows and is identical to the bony glabella on the frontal bone". p. 21

Opisthocranion (op)"is the point situated in the occipital region of the head and is most distant from the glabella; that is, it is the most posterior point of the line of the greatest head length. It is close to the midline on the posterior rim of the foramen magnum. The location of this landmark depends on the shape of the occipitale" p. 21

Eurion (eu) "is the most prominent lateral point on each side of the skull in the area of the parietal and temporal bones". P. 21

Frontotemporale (ft) "is the point on each side of the forehead, laterally from the derivation of the linea temporalis. This location was chosen due to difficulties of finding the linea temporalis in children with disfigurements of the head. The position of the landmark approximately corresponds with the level of the terminal points of the tail of the eyebrow." P.21

Face

Zygion (zy) "is the most lateral point of each zygomatic arch. It is identified by trial measurement, not by anatomical relationship. It is identical to the boney zygion of the malar bones" p. 21

Sublabiale (sl) "determines the lower border of the lower lip and the upper border of the chin. It corresponds with the mentolabiale ridge of anatomists, a point in the midline of the nasolabial sulcus or the point marked as the inferior labial point or labiomentale. The identification of this landmark on the lower face with deep and indented mental sulcus is easy. In shallow ridges and flat surfaces of the receding chins the landmark on the surface was determined with the help of the level of the bottom of the lower lip, by intraoral examination." P. 21-22 That is, a tongue depressor is inserted vertically along the inside of the lower lip. The sublabiale will correspond roughly to the lowest point the tongue depressor can go (personal communication with Farkas, 2000).

Gnathion (gn) "is the lowest median landmark on the lower border of the mandible. It is identified by palpation and is identical to the bony gnathion. This point is the lowest point used in measuring facial height." P.22 Upon palpation it is the lowest portion of the front of the mandible, where one typically feels a ridge (Farkas, 2000, personal communication).

Orbits

Endocanthion (en)" is the point of the inner commisure of the eye fissure. The soft endocanthion is located lateral to the bony landmark (MO) that is used in cephalometry" p.22.

Exocanthion (ex) (or ectocanthion) "is the point at the out commisure of the eye fissure. The soft exocanthion is slightly medial to the bony exocanthion". P.22.

Nose

Nasion (n) "is the point in the midline of both the nasal root and nasofrontal suture. The slight ridge on which it is situated can be felt by the observer's fingernail. This point is always above the line that connects the two inner canthi. The soft nasion and the bony nasion are identical." P. 23

Alare (al) "is the most lateral point on each alar contour" p. 23 or the most lateral portion of the side of the nose near the nostril.

Subnasale (sn) "is the midpoint of the angle of the columnella base where the lower border of the nasal septum and the surface of the upper lip meet. This point is not identical to the bony subnasion or nasospinale which is the 'midpoint of the anterior margin of the apertura piroformis at the base of the spina nasalis anterior'. The landmark is identified in the base view of the nose, or from the side. Where the nasolabiale angles are found with curved contours." P. 23 & 24.

Alar curvature of alar crest (ac) "is the most lateral point in the curved base line of eah ala, indicating the facial insertion of the nasal wingbase". P. 24.

Lips and Mouth

Labiale superious (ls) "is the midpoint of the upper vermillion line". P. 24.

Labiale inferious (li) is the midpoint of the lower vermillion line." P. 24

Chelion (ch) is the point located at each labial commissure " p. 24 – 25.

Ears

Superaurale (sa) "is the highest point on the free margin of the auricle" p. 25

Subaurale (sb) "is the lowest point of the free margin of the ear lobe" p. 25

Preaurale (pra) "is the most anterior point of the ear, located just in front of the helix attachment to the head'. P. 25.

Postaurale (pa) “is the most posterior point on the free margin of the ear’. P. 25

Tragion (t) “is the notch on the upper margin of the tragus” p. 25 (most anterior part of the ear; anterior to the ear canal)

Appendix 5: Definitions of anthropometric measurements

Name of measure	abbreviation	Definition
Morphological height of the face	ngn	This is "the distance between the nasion and the gnathion". P. 30. The sliding caliper is held so that the plades are horizontal to the face. One arm is fixed on snugly on the bony gnathion and the other arm is raised to the nasion. The subject should close his or her teeth for this measurement.
Height of the Lower Face	sngn	This "is the distance between the subnasale and the gnathion". P. 30. The sliding caliper is held parallel to the face. One arm of the caliper is fixed on the bony gnathion and while the other is brought to the subnasale. The subject's head should be tilted backward.
Physiognomical height of the upper face	nsto	The distance between the nasion and the stomion. With the subject's head tilted backward, one arm of the sliding caliper is fixed to the nasion. The other arm of the sliding caliper is brought down to the stomion, the midpoint of the labial fissure. The subject's lips should be gently closed.
Depth of the supraorbital rim right side	Tgrt	This is " the depth of the upper third of the face which is measured between the right tragion and glabella". P.34 With the subject's head tilted upward. One arm of the spreading caliper is held steady at the tragion as the other arm goes to the glabella.
Depth of the supraorbital rim left side	tglt	Same as above but for the left side.
Depth of the right Maxillary region	tsnrt	This is "the depth of the middle third of the face" which is "measured between the tragion and the subnasale". With the subject's head tilted back, one arm of the spreading caliper is steadied at the right tragion and the other is brought to the subnasale.
Depth of the left Maxillary region	tsnlt	Same as above but for the left side.

Definitions of anthropometric measurements (continued)

Name of measure	abbreviation	Definition
Depth of the mandibular region right side	Tgnrt	This is the "depth of the lower third of the face" and is "measured between the tragion and the gnathion". With the subject's head tilted back, one arm of the spreading caliper is steadied at the tragion and the other arm is brought to the gnathion.
Depth of the mandibular region left side	tgnlt	Same as above but for the left side.
Width of face	zyzy	It is "measured at the widest part of the face, between the zygions. The tips of the calipers are pressed over the zygomatic arch until the maximal breadth is determined" using the spreading caliper. p. 29.
Width of forehead	Ftft	The distance between the frontotemporale points, points lateral to the temporal lines. The spreading calipers are used for this measure and should be pressed inward to the bony points.
Length of head	Gop	"The distance between the glabella and the opisthocranion." P. 27. One arm of the spreading calipers is laid on the gnathion. The second arm slides up and down the back of the head until the maximum distance is achieved. This point at the maximum distance is by definition the opisthocranion.
Width of head	Eueu	"The distance between the eurions." P. 26. Using the spreading calipers, fixate them on the sides of the head. Slide the spreading calipers around until the maximal distance is attained. Calipers should be pressed in to touch the bone, but not to cause discomfort.
Skull base width	Tt	"The distance between the tragions." P. 26 The spreading caliper ends are laid on these points and the examiner's forefingers support the calipers behind the traguses.

Definition of anthropometric measurements (continued)

Name of measure	abbreviation	Definition
Head circumference		This is "measured in the horizontal plane around the head through the glabella and opisthocranion." P. 27. The tape must be held tightly around the head" p. 28.
Length of eye fissure right	Exenrt	This is "the distance between the endocanthion and the exocanthion". The subject should gaze upward so that the upper lid does not obscure the endocanthion. The sliding caliper should be under the eye, with one arm directly under the endocanthion and one arm under the exocanthion. The sliding caliper should be steadied on the subject's cheek.
Length of eye fissure left	Exenlt	The same as above but for the left eye.
Biocular width	Exex	This is the "distance between the exocanthions. This biocular width is shorter than the external orbital breadth." P. 35. The subject should gaze upward so that the upper lid does not obscure the endocanthions. The sliding caliper should be under the eyes.
Intercanthal width	Enen	This is the measurement "between the endocanthions". P. 35. The sliding caliper should be steadied against the forehead and the tips should be brought close to the endocanthions.
Length of ala right	Acprnr	This is "the distance between each facial insertion point of the alar base and the pronasale"p.42. This is measured using the sliding caliper.
Length of ala left	Acprnl	The same as above but for the left side.
Width between facial insertion points of the alar base	Acac	This is "the width of the facial insertion points of the alar base" and is measured between the most lateral points of the curved base lines of alae oriented toward the face" p. 38. The pointed ends of the sliding caliper should be used for a more accurate measure.

Definition of anthropometric measurements (continued)

Name of measure	abbreviation	Definition
Width of nose	Alal	This is "the distance between the most lateral points on the alae. The arms of the (sliding) caliper only touch the skin." P. 38. The arms of the caliper must not press the alae because this will change the measure.
Height of the cutaneous upper lip	Snsto	This is "the height of upper lip between the subnasale and the stomion." P. 44 using the sliding calipers.
Vermillion height of the upper lip	Lssto	This is the "thickness of the vermillion in the facial midline between the labiale superius and the stomion" p. 44. measured using the sliding caliper.
Vermillion height of the lower lip	Stoli	This is" thickness of the vermillion in the facial midline between the labiale inferius and the stomion" p.44 measured using the sliding caliper.
Height of cutaneous lower lip	Lisl	This is the "height of the skin portion of the lower lip between the labiale inferious and the sublabiale" (p. 44) measured using the sliding caliper.
Labio-aural distance right side	Tchrt	This is the distance between the tragus of the ear and the chelion (side of the mouth) using the spreading caliper.
Labio-aural distance left side	tchlt	
Width of the auricle right side	prapar	This is "the maximum distance between the prearale and the postaurale" (p.48) of the right ear measured using the sliding caliper.
Width of the auricle left side	prapal	
Length of the auricle right side	sasbar	This is the "maximum length of the Long axis of the pinna between the supoeraaurale and subaurale of the right ear". P. 48 It is measured using the sliding caliper
Length of the auricle left side	sasbal	

Appendix 6: Normative data for craniofacial measurements

Name of measure	regions	abbreviation	Male Caucasian norms	Female Caucasian norms	Male African American norms	Female African American norms
Morphological height of the face	Face	Ngn	M=124.7 SD=5.7 N=109	M=111.4 SD=4.8 N=200	M=125.9 SD=8.2 N=50	M=116.5 SD=6.1 N=50
Height of the Lower Face	Face	sngn	M=72.6 SD=4.5 N=109	M=64.3 SD=4.0 N=200	M=78.9 SD=6.7 N=50	M=71.5 SD=5.2 N=50
Physiognomical height of the upper face	Face	nsto	M= 76.6 SD=4.0 N=109	M=69.4 SD=3.2 N=200	M=78.0 SD=4.8 N=50	M=72.7 SD=4.5 N=50
Depth of the supraorbital rim right side	Face	Tgrt	M=129.5 SD=5.8 N=109	M=119.7 SD=4.2 N=193	M=128.9 SD=5.0 N=50	M=121.9 SD=4.6 N=50
Depth of the supraorbital rim left side	Face	Tglt	M=129.3 SD=5.7 N=109	M=118.9 SD=5.6 N=193	M=128.3 SD=4.5 N=50	M=120.8 SD=4.8 N=50
Depth of the Maxillary region right side	Face	tsnrt	M=133.0 SD=4.6 N=109	M=120.5 SD=3.8 N=200	M=132.6 SD=5.8 N=50	M=125 SD=4.9 N=50
Depth of the Maxillary region left side	Face	tsnlt	M=131.8 SD=4.3 N=109	M=119.3 SD=4.0 N=200	M=132.6 SD=5.6 N=50	M=124.8 SD=4.5 N=50
Depth of the mandibular region right side	Face	Tgnrt	M=148.5 SD=5.0 N=109	M=134.0 SD=5.0 N=200	M=149.5 SD=7.3 N=50	M=138.1 SD=6.0 N=50
Depth of the mandibular region left side	Face	tgnlt	M=148.2 SD=5.2 N=109	M=133.9 SD=5.1 N=200	M=150.2 SD=6.9 N=50	M=138.8 SD=5.6 N=50
Width of face	Face	zyzy	M=139.1 SD=5.3 N=109	M=130 SD=4.6 N=200	M=138.7 SD=5.6 N=50	M=130.5 SD=4.8 N=50
Width of forehead	head	Ftft	M=115.9 SD= 5.2 N=109	M= 111.5 SD= 4.4 N=199	M=116.3 SD=5.6 N=50	M=111.4 SD=5.2 N=50
Length of head	head	Gop	M=197.4 SD=6.7 N=109	M=186.8 SD=6.8 N=199	M=199.2 SD=6.0 N=50	M=186.6 SD=6.5 N=50

Normative data for craniofacial measurements (continued)

Name of measure	regions	abbreviation	Male Caucasian norms	Female Caucasian norms	Male African American norms	Female African American norms
Width of head	head	Eueu	M=151.1 SD= 5.7 N=109	M= 144.1 SD = 5.1 N=200	M=148.8 SD=6.7 N=50	M=141.4 SD=6.0 N=50
Skull base width	head	Tt	M=146.8 SD= 5.6 N=109	M= 138.3 SD = 4.9 N=200	M=143.4 SD=6.1 N=50	N=136.1 SD=4.7 N=50
Head circumference	head	Head circumference	M=579.0 SD=14.4 N=109	M=549.0 SD= 14.8 N=200	M=573.6 SD=15.8 N=50	M=547 SD=16.2 N=50
Length of eye fissure right	eye	Exenrt	M=31.3 SD=1.2 N=109	M=30.7 SD=1.2 N=200	M=32.9 SD=1.7 N=50	M=32.4 SD=2.4 N=50
Length of eye fissure left	eye	Exenlt	M=31.3 SD=1.2 N=109	M=30.7 SD=1.2 N=200	M=32.9 SD=1.6 N=50	M=32.2 SD=2.0 N=50
Biocular width	eye	Exex	M=91.2 SD=3.0 N=109	M=87.8 SD=3.2 N=200	M=96.8 SD=4.6 N=50	M=92.9 SD=5.3 N=50
Intercanthal width	eye	Enen	M=33.3 SD=2.7 N=109	M=31.8 SD=2.3 N=200	M=35.8 SD=2.8 N=50	M=34.4 SD=3.4 N=50
Length of ala right	nose	Acprnr	M=35.0 SD=1.6 N=109	M=31.5 SD=1.8 N=199	M=34.0 SD=2.2 N=50	M=31.5 SD=1.8 N=50
Length of ala left	nose	Acprnl	M=35.0 SD=1.7 N=109	M=31.4 SD=1.8 N=198	M=34.0 SD=2.2 N=50	M=31.6 SD=1.8 N=50
Width between facial insertion points of the alar base	nose	Acac	M=32.8 SD=2.3 N=86	M=30.5 SD=2.2 N=45	M=40.0 SD=4.5 N=50	M=37.7 SD=3.5 N=50
Width of nose	nose	Alal	M=34.9 SD=2.1 N=109	M=31.4 SD=2.0 N=200	M=44.1 SD=3.4 N=50	M=40.1 SD=3.2 N=50
Height of the upper lip	mouth	Snsto	M=22.3 SD=2.1 N=109	M=20.1 SD=2.0 N=200	M=26.1 SD=2.5 N=50	M=24.5 SD=3.0 N=50

Normative data for craniofacial measurements (continued)

Name of measure	regions	abbreviation	Male Caucasian norms	Female Caucasian norms	Male African American norms	Female African American norms
Vermillion height of the upper lip	mouth	Lssto	M=8.0 SD=1.4 N=109	M=8.7 SD=1.3 N=200	M=13.6 SD=2.1 N=50	M=13.3 SD=1.9 N=50
Vermillion height of the lower lip	mouth	Stoli	M=9.3 SD=1.6 N=109	M=9.4 SD=1.5 N=200	M=13.8 SD=2.1 N=50	M=13.2 SD=1.9 N=50
Height of cutaneous lower lip	mouth	Lisl	M=11.9 SD=2.2 N=109	M=10.7 SD=2.1 N=200	M=11.8 SD=2.5 N=50	M=10.7 SD=2.4 N=50
Labio-aural distance right side	mouth	Tchrt	M=114.5 SD=5.0 N=109	M=104.1 SD=4.6 N=194	M=121.3 SD=5.7 N=50	M=113.4 SD=5.2 N=50
Labio-aural distance left side	mouth	tchlt	M=113.6 SD=4.8 N=109	M=103.5 SD=4.9 N=194	M=121.3 SD=5.4 N=50	M=112.8 SD=4.9 N=50
Width of the auricle right side	ear	prapar	M=36.9 SD=2.5 N=109	M=33.5 SD=2.3 N=200	M=36.7 SD=3.5 N=50	M=34.6 SD=2.9 N=50
Width of the auricle left side	ear	prapal	M=36.4 SD=2.4 N=109	M=33.7 SD=2.2 N=200	M=36.2 SD=3.2 N=50	M=34.2 SD=2.9 N=50
Length of the auricle right side	ear	sasbar	M=62.7 SD=3.6 N=109	M=59.6 SD=3.4 N=200	M=60.5 SD=4.1 N=50	M=57.2 SD=3.5 N=50
Length of the auricle left side	ear	sasbal	M=62.9 SD=3.5 N=109	M=59.9 SD=3.5 N=200	M=59.8 SD=4.0 N=50	M=57.0 SD=3.3 N=50

Appendix 7: Figures

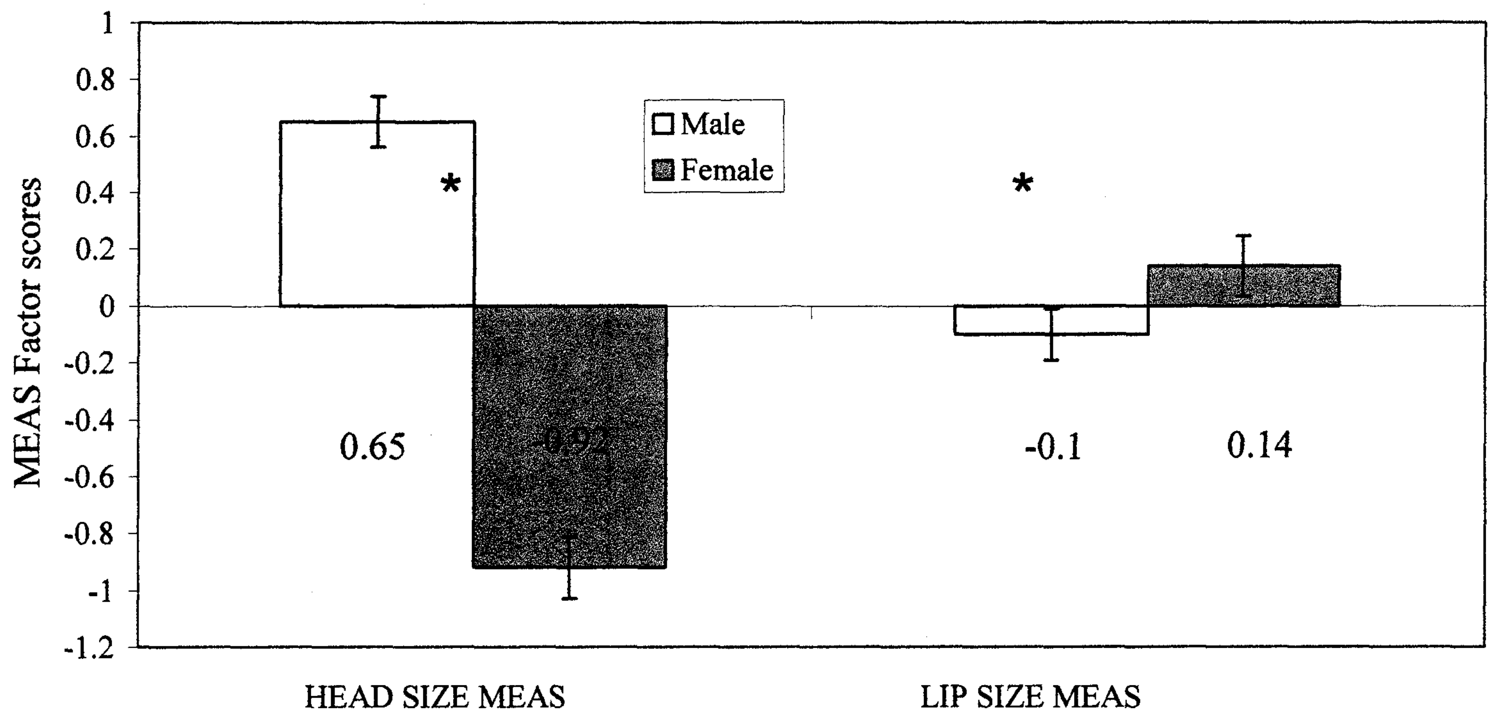

Figure 1: Gender differences on MEAS Factor scores
HEAD SIZE MEAS ($F(1, 93) = 123.47$, $p < .001$) LIP SIZE MEAS ($F(1, 93) = 4.54$, $p = .04$).

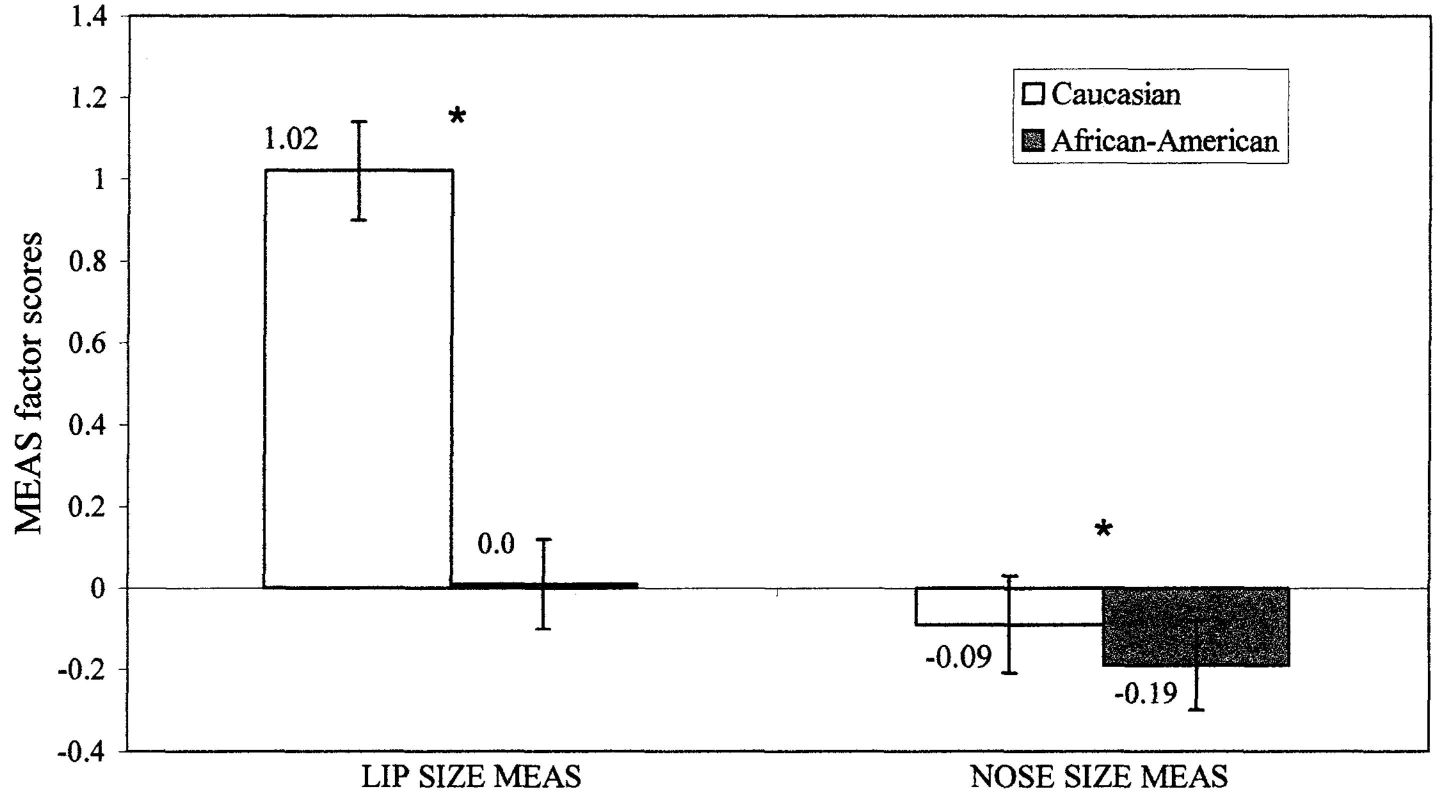

Figure 2: Differences between race groups on MEAS factor scores
LIP SIZE MEAS ($F(1, 93) = 126.36$, $p<.001$) NOSE SIZE MEAS ($F(1, 93) = 7.30$, $p = .008$).

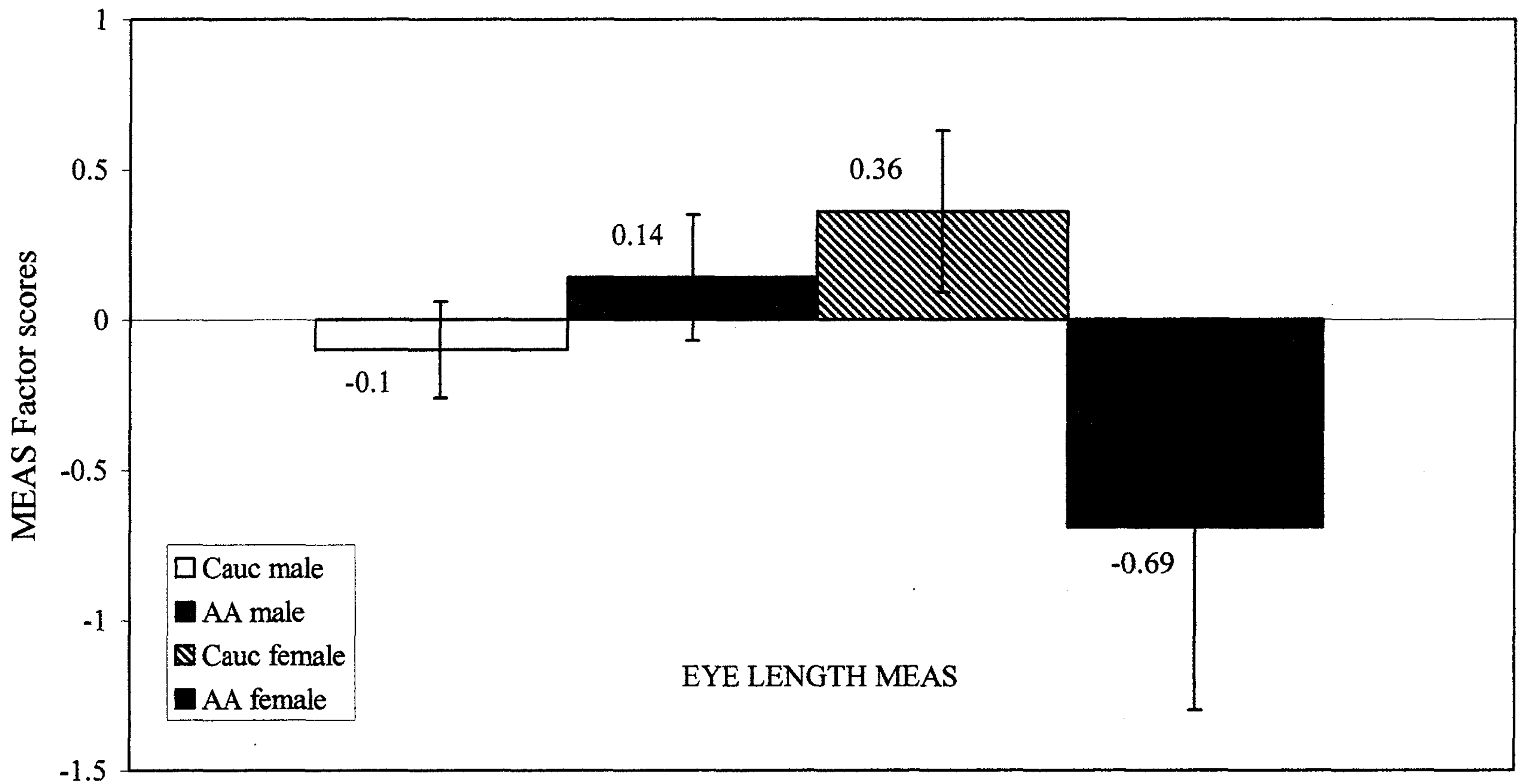

Figure 3: Gender and race interactions for MEAS Factor scores.
Eye Length MEAS: $F\ (1, 93) = 9.62, p = .003$.

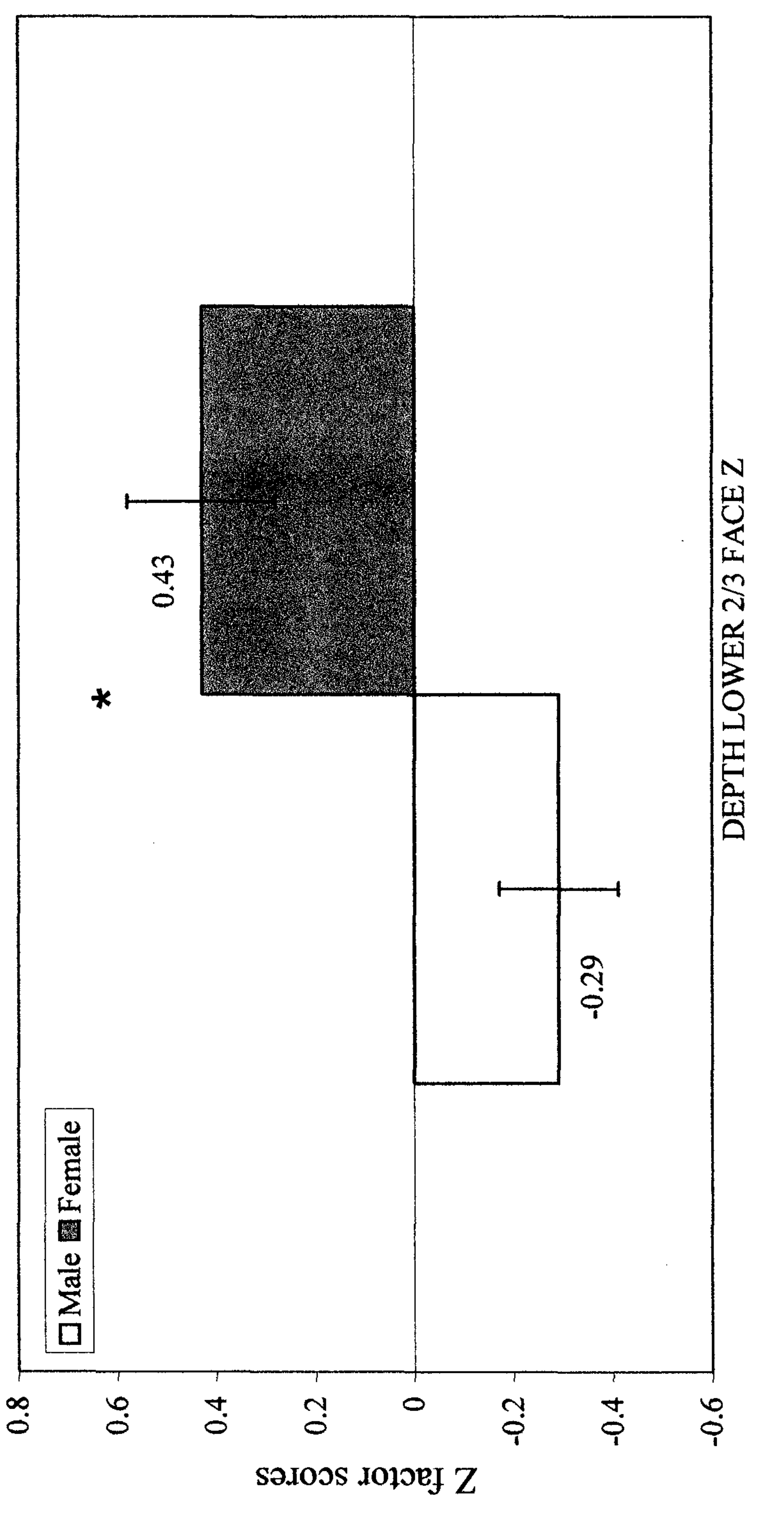

Figure 4: Gender differences for craniofacial Z factor scores: DEPTH LOWER 2/3 FACE Z: F (1, 106) = 11.66, p =.003.

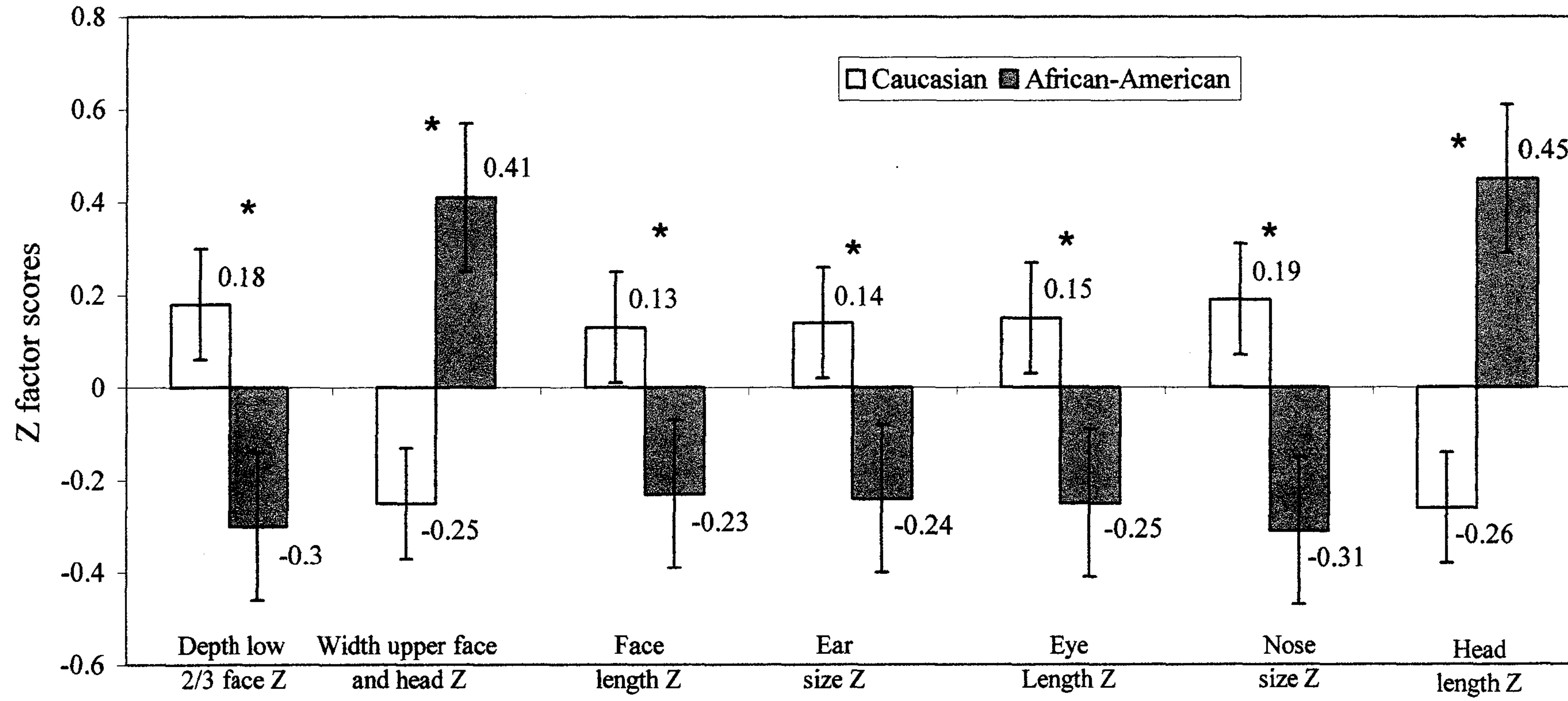

Figure 5: Race differences for craniofacial Z factor scores: DEPTH OF LOWER TWO THIRDS OF FACE Z ($F\ (1, 106) = 5.07$, $p = .03$), WIDTH OF UPPER FACE AND HEAD Z ($F\ (1, 106) = 10.58$, $p = .002$), FACE LENGTH Z ($F\ (1, 106) = 4.61$, $p = .03$), EAR SIZE Z ($F\ (1, 106) = 4.04$, $p = .05$), NOSE SIZE Z ($F\ (1, 106) = 7.44$, $p < .007$), HEAD LENGTH Z ($F\ (1, 106) = 15.62$, $p = .003$).

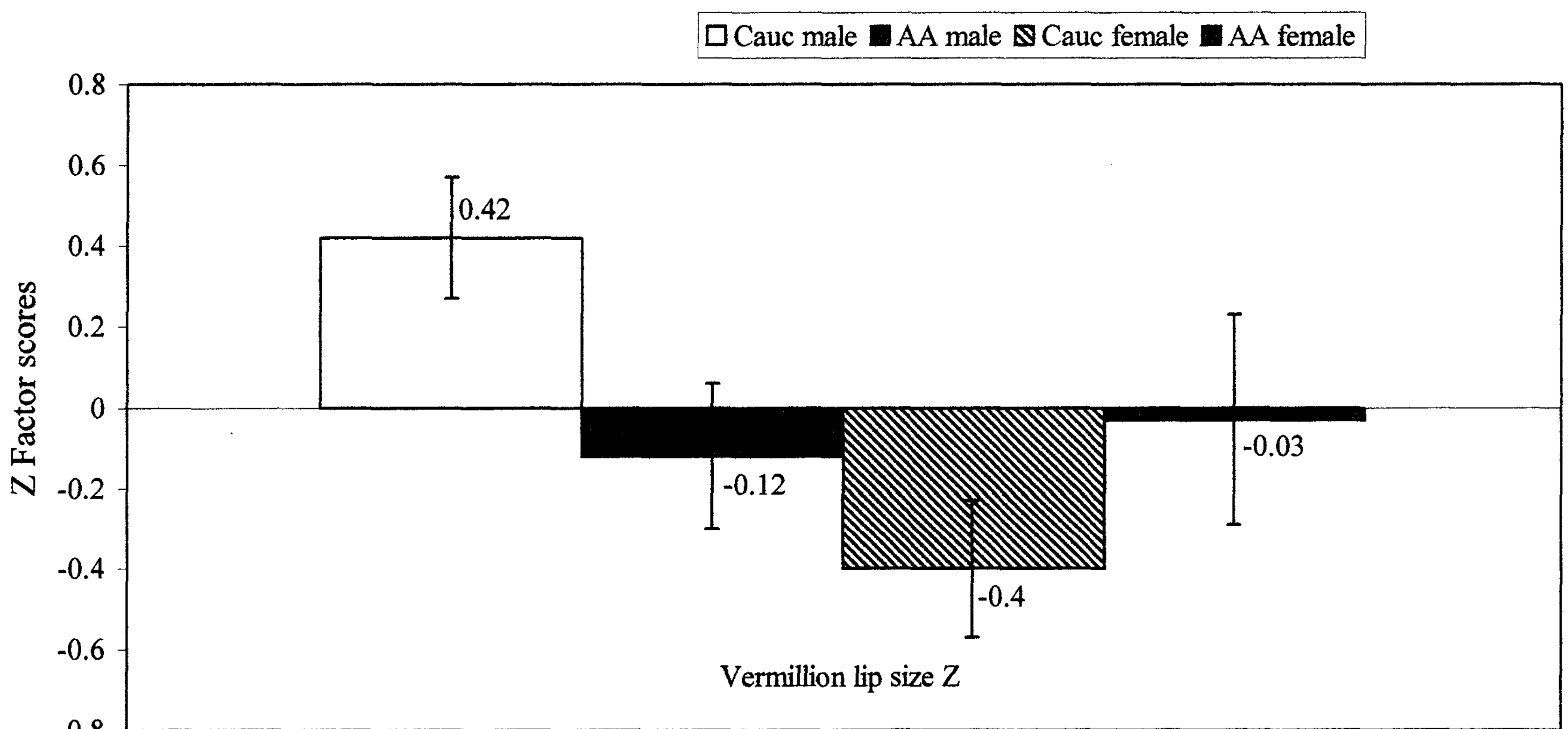

Figure 6: Race and gender interaction for craniofacial Z factor scores VERMILLION LIP SIZE Z ($F(1, 106) = 5.53$, $p = .02$).

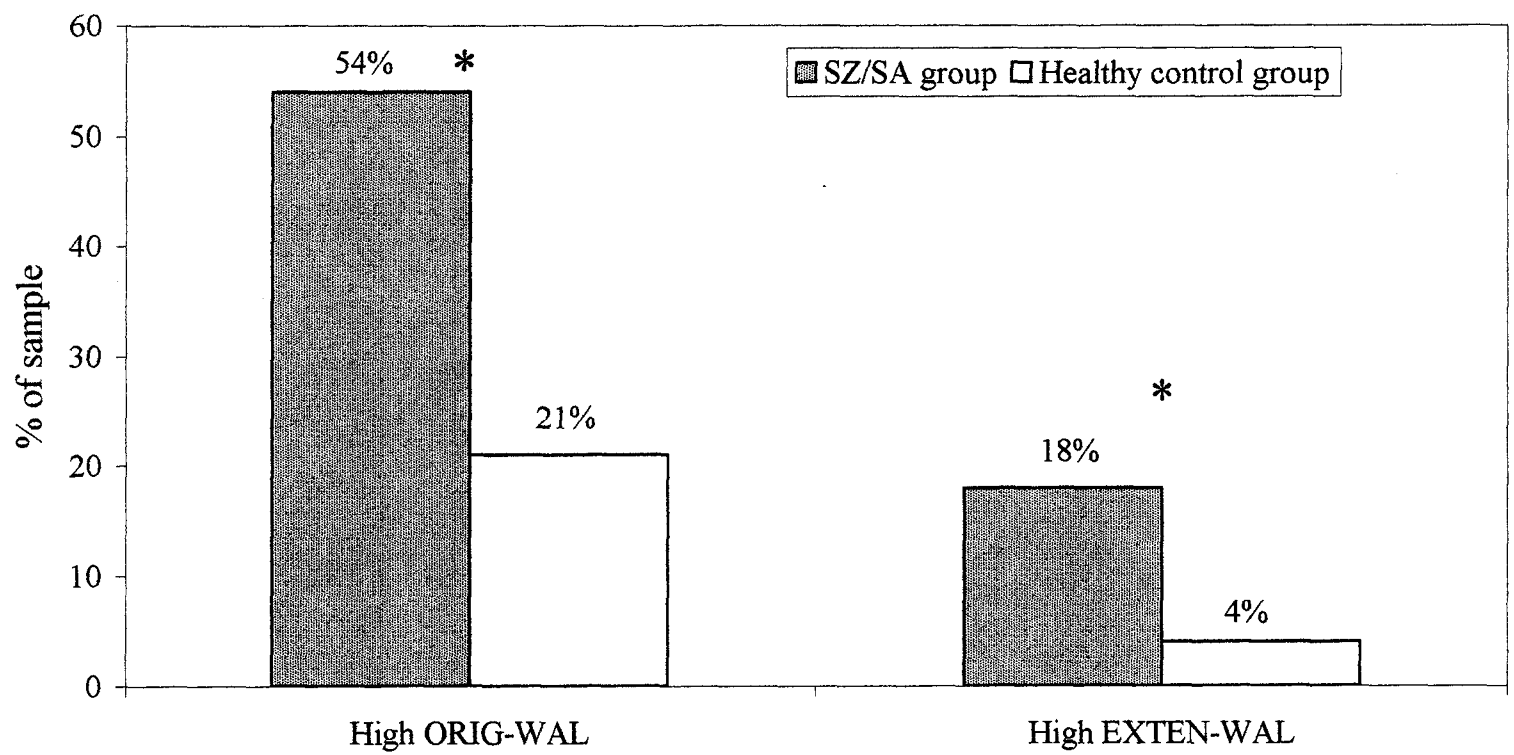

Figure 7: Excess of MPAs in SZ/SA relative to healthy control subjects.
ORIG-WAL (χ^2 (1) = 9.46, p=.002). EXTEN-WAL (χ^2 (1)= 5.65, p=.02).

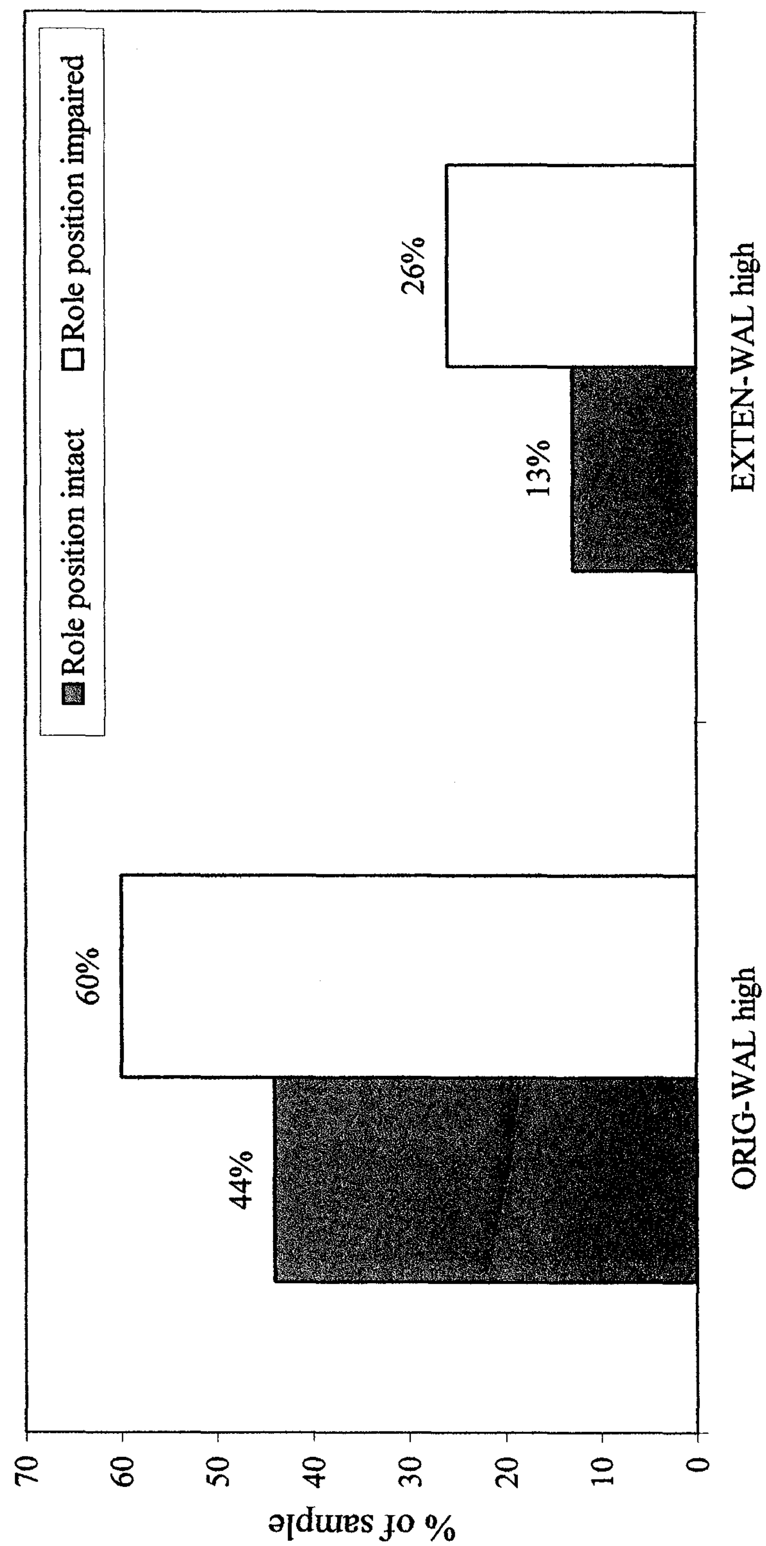

Figure 8: No relationship between MPAs and role position: For ORIG-WAL (χ^2 (1) = .607, p=.44), For EXTEN-WAL (χ^2 (1) = .622, p=.43).

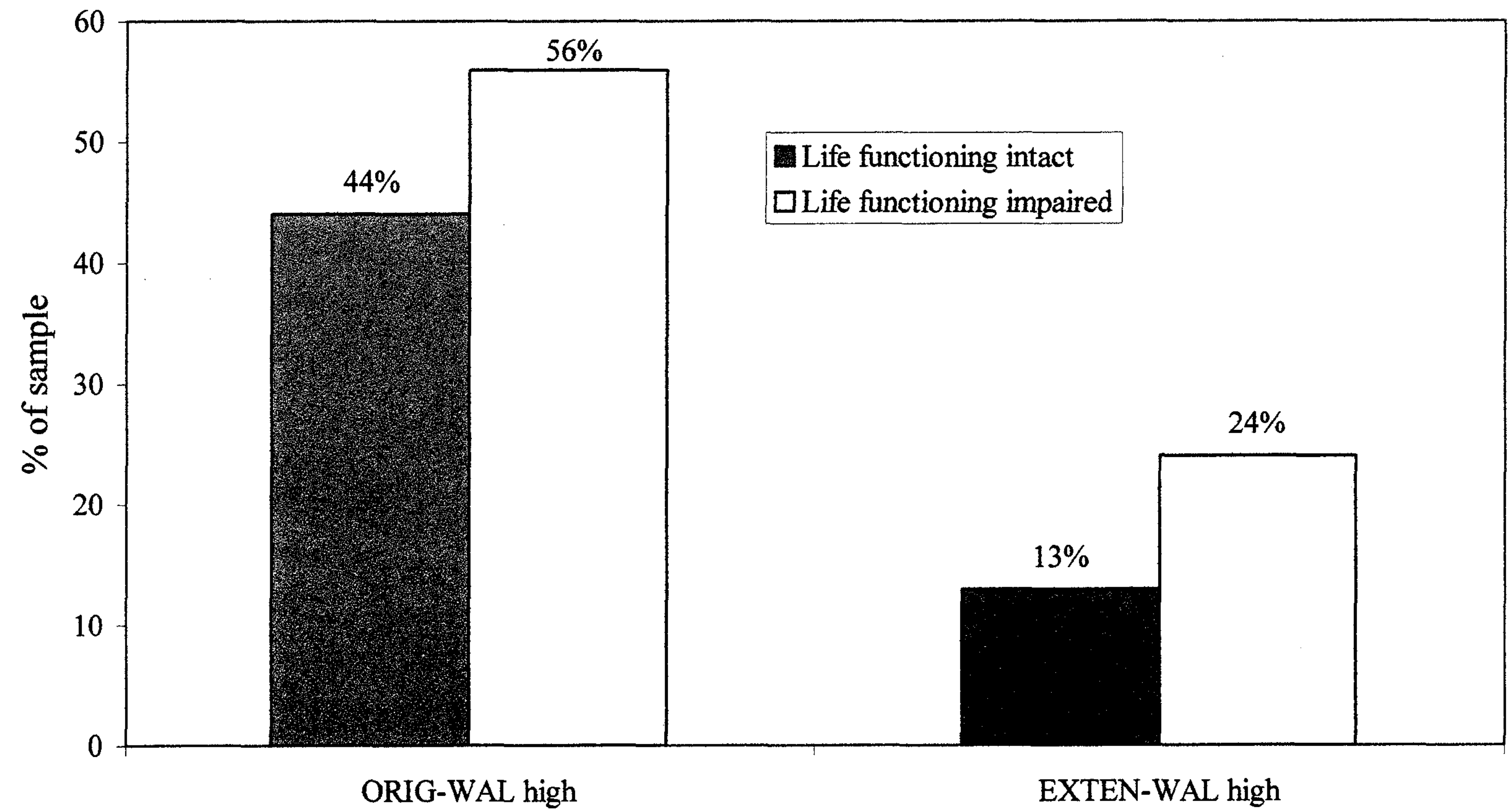

Figure 9: No relationship between MPAs and life functioning: ORIG-WAL (χ^2 (1)= .26, p=.60) and EXTEN-WAL (χ^2 (1)= .45, p=.50).

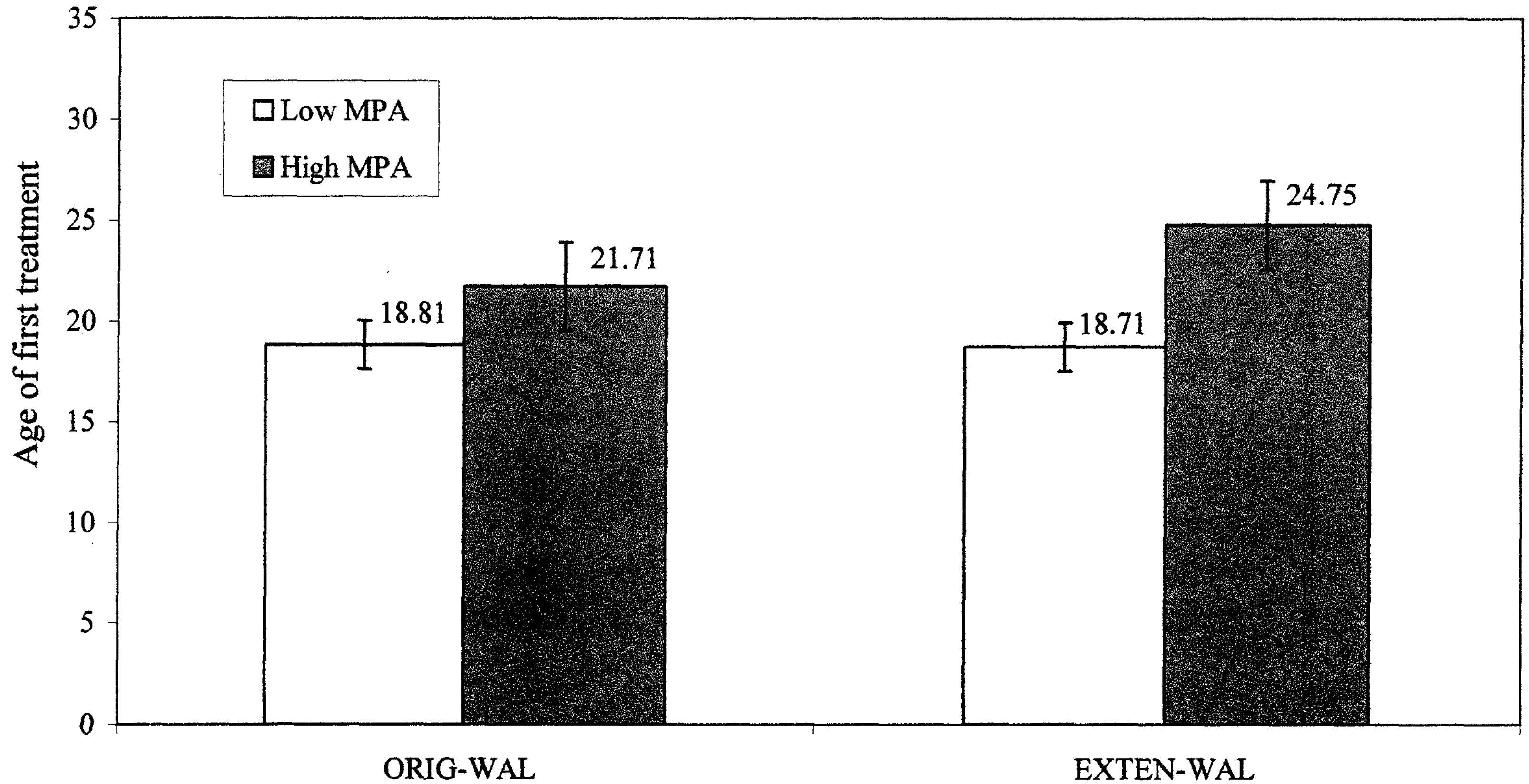

Figure 10: No relationship between age of first treatment and ratings of MPA: ORIG-WAL, (t (43)=-1.25, p=.22) EXTEN-WAL (t(40) = -1.57, p= .15).

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