

STUDIES OF CEREBRAL LATERALITY IN EARLY ONSET SCHIZOPHRENIA

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ABSTRACT

Accumulating evidence suggests that schizophrenia is associated with altered cerebral laterality secondary to a deviation from normal brain development. A number of findings suggest that age of onset of psychosis and gender may have a significant bearing on the nature and extent of the deviation. In order to examine this, early onset patients (12-19 years of age) were compared to healthy controls and later onset patients in a series of studies using standard neuropsychological techniques, experimental divided visual field (DVF) measures and magnetic resonance imaging (MRI). Specific attention was directed to examining the influence of sex and age of onset on hemispheric specialisation.

In the neuropsychological studies, early onset patients (n=35) demonstrated significant impairment of intellectual functioning relative to normal adolescents (n=35) but no significant VIQ-PIQ discrepancy. Earlier age of onset was significantly correlated with reduced VIQ and FSIQ. Early onset patients showed significant reduction in hand skill, increased incidence of non-right eye preference and crossed hand-eye dominance. In addition, patients demonstrated reduced right ear advantage (REA) in dichotic listening and inability to modulate ear advantage by directing attention.

In the DVF experiments, early onset patients (n=20) demonstrated normal lateralisation in phonological word recognition but sexually dimorphic anomalies in lexico-semantic processing relative to normal controls (n=20). Males showed impairment in imageable word recognition whereas females were more impaired in emotional word recognition. In both cases, the observed anomalies implicated a disturbance in the semantic network subserved by left hemisphere ventromedial and superior temporal heteromodal cortex.

In MRI investigations, early onset patients (n=33) had smaller cerebral hemispheres and larger lateral ventricles than controls (n=32). Male patients showed reduction of leftward asymmetry in temporal lobe volume and female patients showed reversal of rightward asymmetry. Significant correlations were found between left ventricular brain ratio and reaction time to phonological word processing. Together, the combined results indicate that early onset schizophrenia is associated with a significant but selective alteration of cerebral laterality, that age of onset is likely to be a determinant of this alteration and that, to some extent, these changes are mediated by gender. The results are discussed within the context of neurodevelopmental aetiology

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This thesis is approximately 45,300 words

LIST OF ABBREVIATIONS

A	Accuracy
DL	Dichotic listening
DVF	Divided visual field
E	Emotional (stimuli)
EN	Emotionally neutral (stimuli)
FMRI	Functional magnetic resonance imaging
FSIQ	Full Scale Intelligence Quotient
HI	High imageability (stimuli)
KSADS	Schedule for affective disorders and schizophrenia – Child version
LEA	Left ear advantage
LH	Left hemisphere
LI	Low Imageability (stimuli)
LVF/RH	Left visual field/Right hemisphere
MRI	Magnetic resonance imaging
Ms	Milliseconds
PET	Positron emission tomography
PIQ	Performance Intelligence Quotient
RVF/LH	Right visual field/Left hemisphere
RH	Right hemisphere
REA	Right ear advantage
RT	Reaction time
VIQ	Verbal Intelligence Quotient

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STUDIES OF CEREBRAL LATERALITY IN EARLY ONSET SCHIZOPHRENIA

Thesis Overview

The aim of this thesis was to perform a comprehensive examination of cerebral laterality in early (adolescent) onset schizophrenia. Chapter one reviews the epidemiological, clinical, and neuropathological features of schizophrenia with particular emphasis on adolescent onset. A brief review of the current aetiology is also provided as well as a summary of Crow's theory as a rationale for investigating sex and age of onset in adolescent patients. In Chapter two, a series of neuropsychological investigations of functional laterality are presented. These investigations deal with the broad indicators of cerebral dominance including IQ, handedness and dichotic listening and examine the influence of age of onset and sex in relation to the severity of altered asymmetry. Chapter three examines lexical and lexico-semantic processing in three divided visual field experiments that were designed for more detailed examination of sex differences in laterality. Chapter four examines structural change in adolescent onset patients using magnetic resonance imaging in order to examine sex and age of onset effects in asymmetry as well as structure-function correlations. Finally, chapter five provides a summary of the findings and their relevance to the putative developmental aetiology of schizophrenia as well as suggestions for future research.

CHAPTER 1 INTRODUCTION TO EARLY ONSET SCHIZOPHRENIA

1.0.1 Background

Schizophrenia is a disabling mental illness characterised by psychosis, structural brain changes and impaired cognitive and psychosocial functioning. It is a widespread disorder, affecting approximately 1 per cent of the world's population, and can occur at any point in the lifespan. The social consequences of schizophrenia are immense. Patients suffer from chronic illness, with periods of exacerbation and remission of psychosis, poor social and vocational outcome and a high rate of suicide. As such, schizophrenia is a major mental health issue requiring ongoing research.

From the time that it was first delineated from other forms of mental illness (Kraepelin, 1896), the cause of schizophrenia has remained elusive. A range of hypotheses have been proposed to account for its occurrence, but accumulating evidence suggest that the disorder originates from a deviation in normal brain development. One clue to developmental basis of the illness lies in the distribution in the age at which symptoms first occur. Epidemiological studies consistently identify two important points: firstly, there is a peak in symptom onset in the late teens to mid twenties, and secondly, this peak is on average five years earlier in males than females (Hafner & Nowotny, 1995; Hafner et al, 1998). These factors suggest that the illness may be critically dependent upon the timing of brain development that is known to differ between men and women. Neurodevelopmental theories have been proposed that emphasise aberration of neural changes that normally occur from the time of early childhood to late adolescence, but research into the exact aetiology of these changes and their relationship to age of onset is at an early stage.

In recent years, the rise of the neurodevelopmental model of schizophrenia has lead to growing interest in people who first develop psychotic symptoms in *childhood* (i.e. pre-puberty) or *adolescence* (post-puberty). These atypical onsets provide an opportunity to examine a potentially more insidious form of the illness, and could reveal important insights into the neurodevelopmental changes underlying the disorder. An evolving literature has begun to detail the principal clinical, neuropathological and neuropsychological features of childhood onset disorders, but relatively little

is known about adolescent onset schizophrenia. This thesis is an examination of adolescent onset schizophrenia.

1.0.2 Clinical Epidemiology

Relatively few epidemiological studies of early onset schizophrenia exist and estimates vary according to diagnostic criteria, population sampled and definition of first onset. Blueier (1972) estimated that 4 - 5 percent of schizophrenic illnesses begin before the age of 15. Loranger (1984) examined 100 case notes retrospectively and found 39% of males and 23% of females developed psychotic symptoms before the age of 19. Hafner and Nowotny (1995) reported even greater numbers of males than females with onsets before 21 years of age (57% and 43% respectively). The apparent age-related change in prevalence is supported by Gillberg et al (1986) who reported an increase in undifferentiated psychosis from 0.9/10,000 population in 13 year olds to 17.6/10,000 population by 18 years. Remschmidt et al (1994) reported the results of three large-scale studies of varied onsets from 7 to 21 years of age and found that the greatest increase in prevalence occurred after the age of thirteen. Despite the apparent incongruity between studies, two salient points are revealed by these figures; first is the apparent increase in prevalence in the adolescent years, and second the preponderance of males in early onset samples. Together, they suggest that events in the second decade of life may be of great significance and that sex is likely to be an important mediating factor.

1.0.3 Clinical features

The clinical features of adolescent schizophrenia are comparable to those of adult onset schizophrenia (Carlson et al, 1994; Werry et al, 1994; Makowski et al, 1997; Schulz et al, 1998) and the disorder can be reliably diagnosed using adult criteria (Schulz et al, 1998). These include 'positive' symptoms such as; pressure, poverty or a blocking of the stream of thought; loosening of association. Changes in mood state such as anxiety, depression, euphoria, emotional flattening or incongruity are also apparent as well as auditory, visual or olfactory hallucinations and delusions (thought insertion, withdrawal or transmission). Negative symptoms include volitional disturbances (reduced spontaneity and drive), impairments in social behaviour (social withdrawal, poor self-care)

and a range of catatonic symptoms. Abnormalities of speech are common and cognitive deterioration is prominent. In most cases negative symptoms have a highly detrimental effect on education, employment and relationships and thus are associated with an increased risk of suicide (Oxford Textbook of Psychiatry, 1996). In order to meet criteria for schizophrenia according to the standard diagnostic reference DSM-IV (American Psychiatric Association, 1994), patients must exhibit at least two of the main symptoms continuously for at least one month; the disturbance must be present for at least 6 months; must not be secondary to another disorder and must impair social functioning.

There is considerable variability in symptomatology between schizophrenic patients. Various authors from the time of Bleuler have attempted to identify the primary symptoms underlying the disorder. Schnieder's 'nuclear' symptoms are probably the most influential to date (see table 1). Dimensional approaches have attempted to identify subtypes of the disorder based on aggregates of symptoms. Crow (1980) identified two syndromes (Type I and II) reflecting a positive/negative dichotomy. More recently, Liddle (1987) has employed a factor analytic approach to identify three syndromes - disorganisation, reality distortion and psychomotor poverty. However, thus far, taxonomies have been limited in their ability to link syndromes to other brain and neuropsychological markers of the disorder. Moreover, a clear relationship between symptoms and a potential aetiology has yet to be established.

Table 1: Kurt Schnieder's (1887-1967) symptoms of the first rank

Symptom	
Hearing thoughts spoken aloud	Third person hallucinations
Running commentary hallucinations	Somatic hallucination
Thought withdrawal/insertion	Thought broadcasting
Delusional perception	Feelings/actions are experienced/ influenced by external agents

1.0.4 Course & Outcome

Despite the apparent symptomatological continuity between adolescent and adult onset schizophrenia, earlier onset is generally associated with poorer outcome (Johnstone et al, 1989; Gillberg et al, 1993). Follow-up studies of adolescent patients report high rates of continuous illness, dependency and relapse associated with poor recovery and greater suicidality (Krauss and Thomsen 1991; Werry et al 1994). Correspondingly, social and vocational functioning are profoundly disturbed in adolescence and beyond (Welner et al, 1979; Werry et al, 1994; Cawthron et al, 1994; Remschmidt, et al 1994; Hollis, 1995; Smith et al, 1998; Schulz et al; 1998). At present, it is unclear if these problems reflect an underlying biological substrate or whether they are the consequence of developing a major mental illness at a critical time in social and educational development.

1.0.5 Cerebral Morphology: Principal findings

A plethora of CT, MRI and post-mortem studies have identified three more or less robust brain structural changes associated with schizophrenia. First, it is clear that most patients demonstrate *ventricular enlargement*. On average, there is a 20-40% increase in volume of the lateral and third ventricles relative to normal controls that appears to be present from the first episode (Lawrie and Abukmeil 1998; Weinberger et al, 1980; Delisi et al, 1991). Second, there is an overall *reduction in brain size and volume* averaging approximately 3% (Brown et al, 1986; Pakkenberg, 1987; Bruton et al, 1990). At the cellular level, abnormalities in arrangement and density of neurons in neocortical and subcortical sites are found. Reductions in the number, size and density of neurons are also found in subcortical (striatum and thalamus) and limbic (hippocampus and parahippocampal) areas (Harrison, 1999). However, consistent with an abnormality of neural development, there is no evidence that cellular changes are associated with gliosis –a reaction normally associated with acquired pathogenesis (Keshaven, 1997). Third, there is evidence for *reduction or alteration of cerebral asymmetry* (i.e. normal morphological differences between the right and left cerebral hemispheres and structures contained therein) (Petty, 1999).

Few studies have examined brain changes associated with early onset schizophrenia, but the available evidence suggests concordance with the adult literature. These include, increased ventricular volume (Reiss, et al; 1983; Schulz et al, 1983; Frazier et al, 1996; Jacobsen et al 1998; Smith et al, 1998), comparable 3-6% reduction in intracranial volume mostly localised the frontal and temporal lobes, and continued decline from childhood to adolescence (Rappaport et 1999). Studies of cerebral asymmetry report reductions in frontal and temporal asymmetry in earlier onset patients (age < 25 years) (Crow et al, 1989; Maher et al, 1999), but presently there are no studies that directly examine asymmetry in adolescent patients. In section 1.2, the evidence for loss of cerebral asymmetry will be examined in greater detail.

1.0.6 Neuropsychology: Principal findings

Patients with schizophrenia exhibit heterogeneous cognitive impairments. These include deficits of *intellectual function* (Payne et al, 1973; Taylor and Abrams 1980; Braff et al, 1991), *executive function* (planning, mental flexibility, abstract concept formation) (Weinberger, 1998; Elliott et al, 1995), *working memory* (short-term/immediate memory span) (Park and Holzman 1995); *episodic memory* (memory for daily events, recently acquired information) (McKenna et al 1990; Tamlyn et al 1992) and *semantic memory* (acquired, declarative knowledge of the world, word meaning) (Tamlyn et al, 1992; Chen and McKenna, 1994; McKay et al, 1996). Some exhibit impairments in *receptive and expressive language* including *reduced complexity* (less use of imbedded clauses), *poor integrity* (semantic, syntactic and omission errors) and *dysfluency* (poor output, increased use of pause fillers and perseveration) (Morice and Ingram, 1982; Morice and McNicol, 1985; Hoffman et al, 1985; Thomas et al, 1987; Hoffman and Sledge, 1988; Allen et al, 1993; Crawford et al, 1993; Allen and Frith, 1988; Rossell et al 1999). Finally, there is evidence of altered *functional laterality* on a range of tasks.

In adolescent patients, comparable reductions in IQ are reported (Goldberg et al, 1988; Kenny et al 1997; Oie & Rund, 1999). Similar impairment in executive functions are found (Goldberg and Weinberger, 1988; Gottschalk and Selin, 1991; Kenny et al 1997; Basso et al, 1997) and impairment of working and episodic memory is reported (Kenny et al, 1997; Oie & Rund 1999).

Hoff et al (1996) used a comprehensive neuropsychological battery including language measures in a group of adolescent (onset <15 years) and adult patients (onset >18years) and found prominent anomalies in expressive and receptive speech in the context of generalised impairment. Presently, only one study has addressed cerebral laterality using a dichotic listening task and found no difference between adolescent onset patients to normal controls (Oie and Rund 1999). The evidence for altered functional laterality will be reviewed in detail in section 1.3.

1.0.7 Aetiology

At the present time, the cause of schizophrenia is unknown. Over the last century a range of theories were proposed to account for the widespread occurrence of the illness, but as yet no clear explanation has been achieved. Broadly, these explanations fall into two categories – firstly those which pertain exogenous influences or environmental causes and secondly, those which invoke genetic explanations. These are summarised individually below.

1.0.6.1 Environmental

A number of environmental theories have been proposed on the basis of an observed excess of winter births in schizophrenic samples (Gupta & Murray, 1992; Boyd et al, 1986; Bradbury & Miller, 1985). From this, a range of potential pathogens have been proposed including; seasonal differences in temperature, photoperiod and nutrition during pregnancy. Viral hypotheses have been suggested which implicate prenatal exposure to infectious agents such as influenza. Another range of environmental theories implicate obstetric and other peri-natal complications including anoxia, forcep delivery and caesarean section (McNeil & Kaij, 1973; 1987; O' Callaghan et al, 1992).

Environmental explanations have been influential over the last thirty years but have so far failed to provide a consistent disease marker that would explain the majority of schizophrenic cases. This may be because many studies suffer from methodological limitations that have proven difficult to address. For example, seasonal differences in birth rate may be a statistical artefact as those born earlier in the year (i.e. northern hemisphere winter months) have a greater length of time to develop

the illness (Dalen, 1990). Viral hypotheses have failed to demonstrate a clear relationship between influenza and the disorder and there is a lack of replication and consistency between influenza epidemics and schizophrenic births (Crow & Done, 1992, Crow, 1994). Similarly, whilst evidence continues to support the high prevalence of obstetric complications in people who go on to develop schizophrenia, studies differ widely in terms of diagnostic criteria, assessment techniques and definition of what constitutes an adverse complication (Lewis, 1989). Methodologically, the general criticism of these studies is that they are retrospective and therefore susceptible to observer bias. For example, a recent prospective analysis failed to find any significant excess in peri-natal complications in patients compared to unaffected controls suggesting that the problem may be an artefact of under-reporting in control populations (Sacker et al, 1995). Thus far, environmental explanations have failed to provide a unified theory that would account for the evidence and presently the importance of environmental precipitants in the aetiology of schizophrenia is unknown.

1.0.6.2 Genetic

A substantial proportion of schizophrenia is explainable in terms of family hereditary and so the other major class of theories relates to genetic influences. Most studies of familial inheritance show elevated risk for the disorder in first-degree relatives (approx. 5%) compared to normal controls (approx. 0.2 - 0.6%) (Weissman et al, 1986). Higher than average rates are observed in siblings, nephews, nieces and other lesser degree relatives (McGuffin et al, 1994). The highest risk is identified in children whose parents are both schizophrenic (46%), and in twins where one twin is affected (48%)(Gottesman, 1991). Recent evidence suggests that adolescent onset cases lie at the extreme of familial liability. Hollis (2000) reported that adolescents were twice as likely to have a first degree with relative with schizophrenia (20% vs 13%) or psychosis (46% vs 23%) than their adult onset counterparts.

The above findings strongly implicate a genetic causality for schizophrenia but it is clear that the disorder does not conform to a simple pattern of inheritance. To date, molecular genetics has failed to identify a consistent locus, mechanism of transmission and/or expression. Moreover, a number of studies have failed to find elevated risk in first-degree relatives (Abrams and Taylor, 1983;

Coryell & Zimmerman, 1988) and elevated risk in itself does not rule out the possible influence of shared environmental precipitants. However, this appears to be unlikely as studies that have examined patients raised outside of schizophrenic families (i.e. adoptees) find comparable incidence rates to those raised within schizophrenic families (McGuffin, 1994; Kety et al, 1994). In sum, , it is presently unclear if schizophrenia is the consequence of purely genetic, environmental, or a combination of environmental and genetic influences. As yet, there is no unified theory that can account for these disparate findings.

1.0.8 Schizophrenia as a disorder of cerebral asymmetry

In two respects, schizophrenia differs from all other common environmental and genetic diseases. Firstly, it shows little regional variation - the World Health Organisation has established that when narrowly defined, schizophrenia is broadly similar in terms of symptomatology and occurs in approximately the same rate regardless of climate, culture or industrial development (Jablensky et al, 1992). Secondly, the disorder remains constant within the population despite the fact that affected individuals are less likely to marry and/or have offspring.

Crow (1989; 1995; 1996) has argued that the invariability and persistence of schizophrenia suggests that it is in some way intrinsic to humanity. As language is the primary capacity that separates humans from other species and is central to hominid sexual selection and evolution, the gene or genes responsible for the disorder must be intimately related to language capacity. In evolution, in order to accommodate the adaptation of language, it was necessary that a degree of independence be established between the cerebral hemispheres. Such independence is reflected in the uniquely human characteristics of cortical asymmetry; language 'dominance' in one or other hemisphere, hemispheric specialisation of cognitive function, and handedness. Crow has argued that a single genetic mechanism determines all of these characteristics and that in schizophrenia this is compromised. Thus, areas of the brain that are normally the most asymmetrical are expected to be anomalous in patients with schizophrenia and functions that are highly lateralised to one or other hemisphere are expected to be disturbed.

Crow's theory has been contested on a number of grounds. In particular, an ongoing issue is whether laterality exists in other realms of the animal kingdom and whether the evolution of lateralisation was necessarily driven by language (Bradshaw, 1998). Another point at issue is that defective cerebral dominance may not always lead to schizophrenia as in the case of language related disorders such as dyslexia and autism. Such arguments are difficult to resolve in the absence of strong genetic evidence. Notwithstanding, a substantial body of evidence clearly points to loss of cortical asymmetry and dominance in schizophrenia despite the fact the aetiology of disorder is unclear. In the next sections, this evidence will be reviewed with particular emphasis on the mediating influence of individual differences and its significance as a marker of developmental disorder.

1.1 STUDIES OF CEREBRAL ASYMMETRY IN NORMALS AND SCHIZOPHRENIA

1.1.1 Introduction to cerebral asymmetry

Cerebral asymmetry refers to the naturally occurring difference in the size and shape of the cerebral hemispheres. It is present from early in development but changes over the course of the lifespan and varies from individual to individual on the basis of handedness, sex and age. A significant body of evidence suggests that schizophrenia is associated with deviation from normal cerebral asymmetry that appears vary on the basis of individual differences such as age and sex. In this section, a brief review of studies of normal cerebral asymmetry and normal sexual and age-related dimorphism is provided. The evidence for altered asymmetry in schizophrenia follows this, including the evidence for sex and age of onset related dimorphism.

1.1.2 Cerebral asymmetry I: Normal Studies

Over the last 30 years, a vast literature relating to human cerebral asymmetry has evolved from post-mortem, CT, MRI and functional imaging studies. Seminal studies in the 1960's found that areas of the temporal lobe, known to be important in language, are disproportionately large in the left hemisphere. Most notably, the planum temporale, a triangular area of heteromodal cortex, was found to be larger on the left than the right in 65% of post-mortem brains (Geschwind and Levitsky, 1968). Such asymmetry has since been associated with right-handedness and left sided language representation (Foundas, et al, 1995; see also chapter 1.3) Other anatomically related language areas of the superior temporal gyrus, including Heschl's gyrus and the Sylvian fissure, are also larger on the left (Steinmetz et al, 1991; Witelson and Kigar, 1992; Rademacher et al, 1993; Galaburda, 1995). In addition, rightward hemispheric asymmetry is observed in occipito-parietal and sensory-motor regions of the cortex and the opposite leftward asymmetry is seen in prefrontal and premotor areas. These 'petalias' are reflected in relative differences in the overall length of the frontal and occipital poles and are believed to derive from an ongoing process of counter-clockwise 'torque' in normal development (Le May and Kido, 1978; Bear et al, 1986; Kertesz et al, 1992).

1.1.3 Individual differences in development: Normal Studies

Cerebral asymmetry can be seen in the brain from before birth. In utero and early infancy, asymmetries in the planum temporale, Sylvian fissure and fronto-occipital torque have been reported that appear to reflect differences in dimorphic brain growth (Wada et al, 1975; Le May, 1976; Chi et al, 1977). In infancy, right hemisphere size is reportedly larger in males compared to females (Chi et al, 1977; de Lacoste, et al 1991). Histologically, the right hemisphere develops precociously from birth but is gradually surpassed by the left hemisphere with the further development of language by around six years of age (Scheibel, 1993). Changes in asymmetry are more subtle in late childhood and are characterised by growth in limbic and diencephalic structures. There are some sexually dimorphic reductions in superior and lateral cortex (Jernigan et al, 1991; Sowell and Jernigan, 1998) and changes in the corpus striatum (Giedd, et al, 1996).

Adolescence marks a period of considerable brain change during which synapses are refined or 'pruned'. There is a steady decrease in grey matter between 11 to 18 years and an increase in white matter (Reiss et al, 1996; Courchesne et al, 2000) that appears to be synchronous to increases in lateral ventricle size (Giedd et al, 1996; 1997). In the late teens, this is followed by selective reduction in the volume of left fronto-temporal structures (Paus et al, 1999; Giedd et al, 1996) but no change in planum asymmetry (Priess et al, 1999). Such changes show a degree of sexual dimorphism from infancy into childhood and adolescence (e.g. Lange et al, 1997; Murphy et al, 1996; Giedd et al, 1997; Cowell et al, 1994; Pfefferbaum et al, 1994). In general, the female brain develops more quickly (Kretchmann et al, 1979) and is more symmetric than that of males (De Lacoste et al, 1991; Giedd et al, 1996). In normal males, specific left hemisphere language structures such as the arcuate fasciculus appear to continue growth throughout early adolescence whereas in females development in similar sites appears to be complete (Giedd et al, 1996).

In adulthood, sexually dimorphic asymmetries appear to become more fixed. Right-handed males show larger leftward asymmetry in the size of the planum and more pronounced petalial asymmetries (Kertesz, 1992; Karbe et al, 1995). Females are more likely to show greater variability in planum size and length as well as reduced torque asymmetry (Wada et al, 1975; LeMay and

Kido, 1978; Kertesz, 1992; Karbe et al, 1995; Shapleske et al, 1999). However, while certain language structures are larger in *area or size* in males (probably as a consequence of larger brain size), the same structures, particularly Broca's area, planum temporale and the superior temporal gyrus, are greater in *density and volume* in females (Fillipek et al, 1994; Schlaepfer et al, 1995; Reiss et al, 1996; Harasty et al, 1997; Gur et al, 1999). This suggests that females may have less functionally specialised brains than males possibly requiring greater inter-hemispheric connectivity. This is supported by evidence of larger corpus callosum in females (Witelson, 1989; Steinmetz et al, 1995).

In conclusion, although the study of individual differences in brain development is still at an early stage, it is already clear that ratios in asymmetry of many structures appear to differ depending upon age, sex and hand preference. These differences appear to reflect in the dimorphism in the rate and timing of normal development and are likely to be reflected in individual differences in functional specialisation. It is also apparent that adolescence is an important time in development in which growth plateaus and final maturation occurs. At present, the exact nature remains to be elucidated but they may be of considerable importance in respect to the structural changes observed in schizophrenia.

1.1.4 Cerebral asymmetry II: Schizophrenia

There has been interest in the relationship between cerebral asymmetry and mental illness for over a hundred years (Chrichton-Browne, 1879; Southard, 1915) but it is only recently that post-mortem, CT and MRI studies of schizophrenia have identified alterations of normal asymmetry. Foremost is the evidence relating to alterations in temporal lobe asymmetry. These include; enlargement of the left compared right lateral ventricle (Crow et al, 1989; Bogerts et al 1990) extending to the left temporal horn (Brown et al, 1986) as well as reduction in left relative to right temporal lobe size and volume (Johnstone et al 1989; Turetsky 1989; Highley et al 1999). Volume reduction appears also to be related to shortening of temporal poles that again is more pronounced on the left (Highley et al 1998).

In addition to changes in temporal lobe asymmetry, a series of studies show that normal torque asymmetry is reduced or reversed in both frontal (right > left) and occipital (right < left) regions when examined in CT (Luchins et al, 1982; Lee et al, 1985), MRI (Bilder et al, 1994; Turetsky et al; 1995; Delisi et al, 1997) or in post-mortem investigations (Falkai et al 1995b; Highley et al 1998). However, the precise demarcation of the frontal lobes complicates matters and not all studies of torque asymmetry have reported an overall difference between patients and controls (Guerguerian & Lewine, 1998). It therefore seems that changes in the ratio of fronto-occipital asymmetry are less consistently identified than temporal lobe asymmetry.

A third finding relates to asymmetrical reductions in key language areas of superior temporal gyrus including the planum temporale, Sylvian fissure and Heschl's gyrus - a subdivision of the superior temporal gyrus, that is part of the primary auditory cortex, and sends projections to other cortical areas, including those concerned with language (Crow et al, 1992; Falkai et al, 1992a; 1995; Shapleske et al, 1999; Petty et al, 1995; Harayasu, 2000). Asymmetrical loss of tissue volume is observed in heteromodal inferior/medial (fusiform, parahippocampal gyrus) segments of the temporal lobe (Barta et al, 1990; Petty et al, 1995; Highley et al 1998; 1999). These changes may in part be attributable to an asymmetric abnormality in the pattern of gyrification, possibly as a consequence of temporal lobe shortening, although further work is required before this is established (Crow, personal communication). Thus, there appears to be a complex relationship between reduced asymmetry and specific temporal anomalies but the exact nature of this relationship and the sequence underlying these changes requires further investigation. Longitudinal studies would therefore be of particular relevance.

1.1.5 Individual differences and altered asymmetry in schizophrenia

One problem of previous studies of cerebral asymmetry in schizophrenia is that only selected populations, typically chronic male patients, have been examined. When individual differences such as sex, handedness and age of onset are taken into account, the pattern of anomalous asymmetry appears to change. Earlier age of onset has been associated with greater overall reduction in temporal lobe length (Bogerts et al 1991; Bartzokis et al 1996), and reductions in

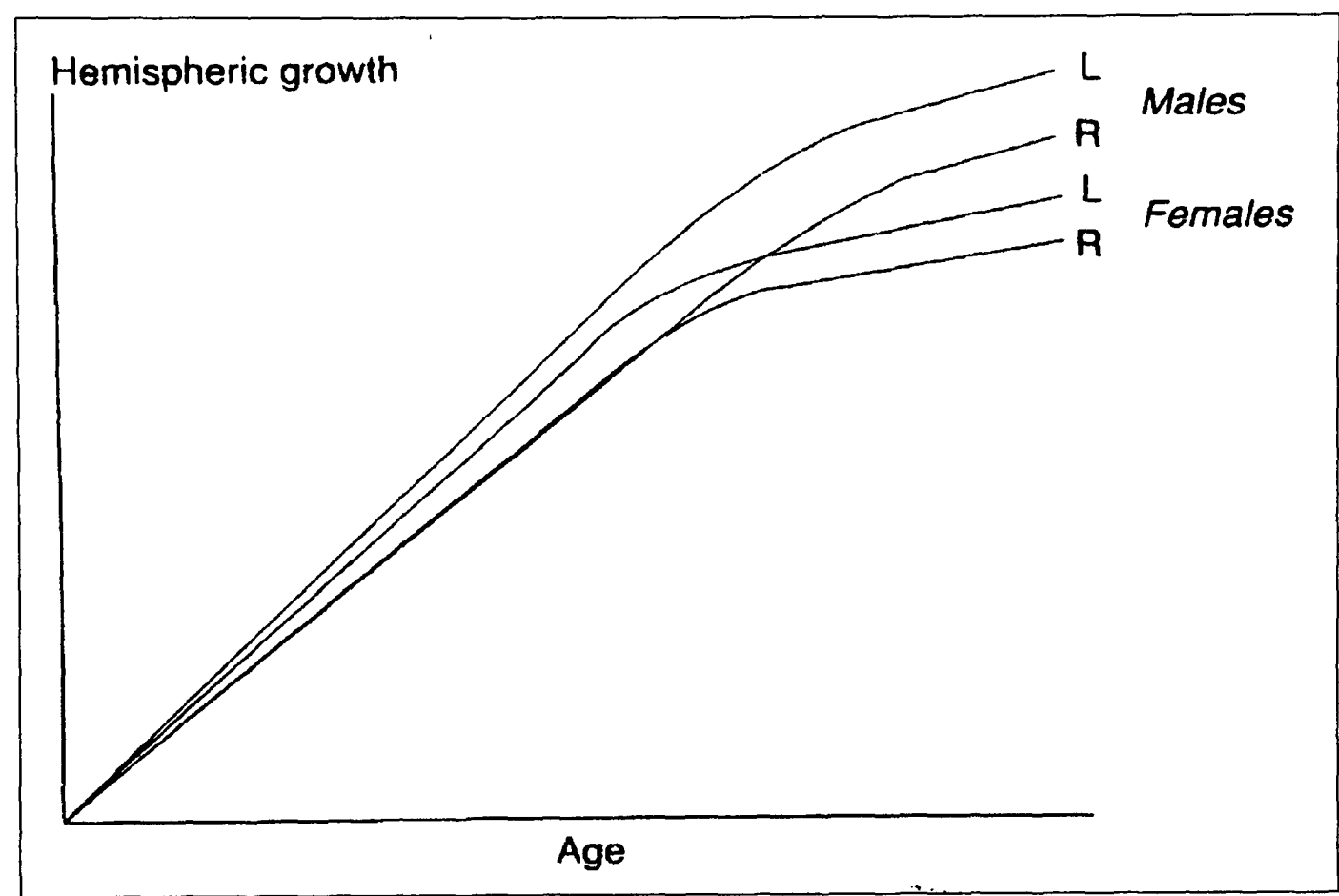
frontal *and* temporal volume asymmetries (Maher et al 1998). Several reports show that volume and length reductions in the left temporal lobe and superior temporal gyrus are greater in males (Ron et al, 1992; Cowell, et al, 1996; Bryant et al 1999; Rojas et al 1997; Reite et al; 1997; Hajek et al, 1997). Although there is no evidence for a sexual dimorphism in planum asymmetry (Shapleske et al, 1999), at least two studies have found significant reduction in asymmetry of the Sylvian fissure and posterior temporal lobes in females but not males (Hoff et al, 1992; Delisi et al, 1994). More recently, post mortem studies have shown reduction of asymmetry in areas of the inferior temporal cortex (parahippocampal and fusiform gyrus) in males that is more marked with earlier age of onset (Highley et al, 1999).

Interestingly, diagnosis $\times$ sex effects have not been reported when overall brain volume and lateral ventricular volumes are examined (Nasrallah et al, 1990; Wright et al, 2000). This finding is difficult to reconcile with the literature showing asymmetrical increases in ventricular volume but may suggest that some asymmetric effects are lost when sexes are examined separately. Alternately, it may be that asymmetric changes in tissue volume are not related to ventricular volume in the same way between the sexes. It is noteworthy, however, that when torque asymmetries are examined by sex, greater reduction in rightward torque is observed in male compared to female patients (Bilder et al, 1994; Highley et al 1998) which interacts with age of onset (Highley et al 1998; Guerguerian & Lewine, 1998). Thus, there appears to be a complex interaction of asymmetry sex and age of onset, but presently it is unclear why this relationship does not hold for ventricular asymmetry.

Crow et al (1989) has argued that asymmetry, particularly in the temporal lobes, is of critical importance to understanding the deviation from normal development in schizophrenia. The hypothesis suggests that, as frontal and temporal growth occurs relatively late in the sequence of normal brain development (and therefore shows the greatest asymmetry), a deviation or lag in this pattern will result in reduced asymmetry and functional impairment. Given the differing rates of cognitive and structural development in males and females (figure 1), the effect of early onset psychosis on this process is likely to be reflected in altered sexual dimorphisms in cerebral structure and function. Moreover, as the regions that show the greatest degree of asymmetrical difference in males and females are those subserving dominant (particularly language related)

functions, alteration of normal sexual dimorphism in language laterality is expected. In the next section, the evidence for altered functional laterality is reviewed.

Figure 1: Proposed trajectories of hemispheric growth (adapted from Crow, 1995)



1.2 STUDIES OF FUNCTIONAL LATERALITY IN NORMALS AND SCHIZOPHRENIA

1.2.1 Functional Laterality I: Normal Studies

Functional laterality refers to relative specialisation of a hemisphere in performing certain cognitive and motor operations relative to other. The study of functional asymmetry has a long history from which a vast literature has developed. The aim of this chapter is to provide an overview of the main findings relating to schizophrenia and how individual differences in lateralisation may account for some of the disparate and conflicting findings. In order to do so, a summary of the literature relating to functional laterality in normal individuals is warranted including relevant evidence from functional imaging.

1.2.1.1 Language

Language is the best-characterised functional asymmetry within the brain. Traditionally the left hemisphere is considered 'dominant' in the production and perception of speech and many verbal aspects of intellectual function. Divided field and dichotic listening experiments find left hemisphere superiority in reaction time or accuracy when verbal material is presented to the right visual field or right ear (Zaidel 1985; Hugdahl 1995). There is evidence that the left hemisphere is primarily responsible for phonological, syntactic and semantic processes which underlie spoken and written language that, in turn, underlie higher level processes of logical and propositional thinking (Hellige, 1993; Springer & Deutsch, 1998). However, over recent years the assumption of left hemisphere 'dominance' in language has been revised as the important role of right hemisphere in speech production and perception has become increasingly recognised (Joanette et al, 1990; Beeman & Chiarello, 1994). It is now clear that the right hemisphere is particularly involved in holistic processing of language such the understanding of pragmatics, prosody and intonation. The right hemisphere is also involved in highly specific aspects lexico-semantic processing. Some of these aspects will be examined experimentally in following chapters.

1.2.1.2 Visuo-spatial processing

In contrast to the predominance of verbal processing in the left hemisphere, the right hemisphere principally subserves aspects of visuo-spatial processing. In normal subjects these include fundamental abilities such as judgement of size and distance, determining orientation of lines or other spatial objects, mental rotation and recognising perceptually degraded information (Hellige, 1993). The right hemisphere also appears to mediate in sub-processes involved in face recognition. Right-sided parieto-occipital lesions can result in prosopagnosia (inability to recognise familiar faces), hemineglect (attentional failure to perceive extracorporeal space to the left) and anomalies in the expression and perception of emotion (Hellige, 1993; Davidson & Hugdahl, 1995).

1.2.1.3 Handedness

The most immediately obvious functional asymmetry is hand preference. Around 90% of the population are considered right-handed. Given that the motor centres of the cortex are contralaterally organised for movement, strong right hand preference indicates left hemisphere dominance. The pattern of handedness in the population is continuous rather than dichotomous in that differing degrees of strength and direction exist between individuals. More recent classifications suggest that there are in fact three broad categories of handedness rather than two; consistent right handedness (CRH) consistent left handedness (CLH) and mixed handedness (MH). The distribution of these subtypes within the population is uneven (64%, 4% and 33% respectively) although the majority show a pattern of CRH (Annett, 1996). In general, consistent right-handers show a pattern of stronger and more consistent use of the right hand than non-right handers. The implication is that non-right handedness is a product of a less lateralised or more diffusely lateralised brain, for which there is considerable evidence (Springer & Deutsch, 1998).

1.2.2 Individual differences in laterality

Like structural asymmetry, functional lateralisation appears to be mediated by handedness and sex. Evidence from sodium amytal (Wada) testing suggests that 70-95% of right-handers are speech dominant in the left hemisphere compared to only 15% of mixed and left handers (Rasmussen & Milner, 1977). Left-handers also show smaller laterality effects on divided field and dichotic listening tasks (Segalowitz & Bryden, 1983). Lesion studies show that left handers are less likely to suffer from aphasia following either left or right damage, that initial aphasia is less severe, and may recover more quickly (Curtiss, 1985). From these studies it appears largely accepted that, in the case of language, left-handers are less strongly lateralised.

Sex differences in language and cognitive ability are controversial due to the inherent nature-nurture arguments that arise (Kimura, 1999). However, there is evidence that males are more strongly lateralised than females. Hiscock and colleagues (1994: 1995) conducted exhaustive reviews of the dichotic and divided visual field literature and concluded that, despite being highly variable, females generally demonstrate weaker laterality effects than males. Moreover, females are more likely to be either bilateral or right dominant for certain language tasks. For example, functional imaging studies have shown that phonological tasks activate bilateral areas of the frontal cortex in right handed females whereas right handed males show only unilateral (left) activation (Shaywitz et al 1995; Pugh et al 1996; Overmeyer et al 1999). Semantic language tasks activate widespread areas of the inferior middle and superior temporal gyrus in females, whereas males show more restricted left-sided activation (Pugh et al 1996; Rossell et al 2000; Wise et al 2000). Vikingstad et al (2000) found that right handed males are generally left lateralised on semantic tasks, females fall into two groups, left lateralised and bilateral.

Individual differences in laterality for visuo-spatial functions come from studies of sex. In general these show that males are more adept on visuo-spatial tasks than women when presented to the left visual field/right hemisphere, particularly when they involve mental rotation or discrimination of an image from a complex visual array (Kimura, 1992). In keeping with the supposition that females are less strongly lateralised, there is evidence that right hemisphere damage lowers performance

IQ relative to verbal IQ in males but does not differentially affect females (McGlone et al 1980). It is noteworthy, however, that despite weaker lateralisation of language and spatial skills, women demonstrate stronger hand preference than men and perform better on tasks requiring fine motor skills, such as in pegboard tasks (Kimura, 1999).

1.2.3 Does lateralisation develop?

The subject of developmental change in laterality is contentious. On the basis of Lenenberg (1967), the view that cerebral hemispheres are equipotential from birth and gradually become asymmetrically organised by adolescence, was widely accepted. This assumption was originally supported by the observation that right or left hemisphere damage in childhood can interrupt language development (Dennis & Whittaker, 1976). More recent evidence shows that aphasia is less severe and recovers quicker in children even after complete left hemispherectomy (Bishop, 1993) and in vivo measures (e.g. EEG, fMRI) suggest that the functional organisation of the cortex develops in a cyclical right followed by left pattern that presumably leads to functional asymmetry (Thatcher 1986; 1996; 2000; Chiron, 1997).

Notwithstanding, the argument for equipotentiality and the associated assumption that laterality develops has become less accepted in recent years. In infancy, stable functional laterality is detectable in hand preference and discrimination of speech sounds (Bertoncini et al, 1989). In early childhood, right ear advantage is found on dichotic listening and some visuo-perceptual measures, but does not appear to increase with age (Lokker & Morais, 1985; Sininger, et al, 1998). Moreover, while plasticity is greater in childhood this in itself does not mean that lateralisation is incomplete. Bradshaw (1989) has suggested that language laterality is firmly established by adolescence not as a product of a development but rather lost plasticity. Thus, specialisation is increased only with respect to the repertoire of asymmetrically organised functions emerging at different time points and not a product of increasing specialisation.

One exception to the above conclusion is in respect to attentional asymmetries. There is strong evidence that the ability to direct attention to one or other hemisphere is a skill acquired only in late

childhood or adolescence and is directly related to some aspects of language development (reading in particular). Dichotic listening studies show that the ability to re-direct attention from the preferred right ear to the left is only possible after approximately nine years of age (Bradshaw, 1989; Hugdahl 1995). Merola and Liederman (1985) and Liederman et al (1986) have shown that aspects of hemispheric co-operation (i.e. ability to inhibit one hemisphere relative to the other) increase substantially in adolescence.

1.2.4 Functional Lateralisation II: Schizophrenia

As mentioned in the introduction, a large number of studies laterality in schizophrenia has been conducted over the years. From these, a pattern of findings has emerged which implicate three, more or less separable categories of explanation for the disorder. These are reviewed individually.

1.2.4.1 Evidence for Left Hemisphere dysfunction

Flor-Henry (1969; 1983) first suggested that schizophrenia is a disorder of left temporal lobe. Following a series of DVF studies showing loss of right visual field/left hemisphere advantage and rightward eye movement, Gur (1978) first proposed that schizophrenia was associated with a disturbance of left hemisphere information processing secondary to overactivation. Surprisingly few studies supported this conclusion in subsequent years (Walker & Maquire, 1982) but more recent reviews of divided field (Ragland et al, 1999) dichotic listening (Walker and Green, 1982; Wexler et al, 1991) and functional imaging studies (Gur & Chin, 1999) suggest that the weight of evidence favours a disturbance of left rather than right hemisphere function.

The other major source of evidence for left hemisphere dysfunction comes from the observed increase in left and mixed handedness amongst schizophrenic samples (Nasrallah et al, 1982; Nelson et al, 1993; Cannon et al, 1997). Although a number of large studies have failed to find evidence for reduced dextrality (Taylor et al, 1982), when sample sizes are sufficiently large, the weight of evidence points to a measurable deviation in the normal distribution (Satz & Green, 1999). In support of the genetic argument, increased mixed handedness is found in unaffected monozygotic twins of patients with schizophrenia (Boklage 1977), children who later go on to

develop the disorder (Crow et al 1996) and first-degree relatives (Orr et al 1999). In view of the aforementioned evidence, it appears that lateralisation (particularly in respect to language and handedness) is atypical in schizophrenia secondary to left hemisphere anomaly.

1.2.4.2 Evidence for Right Hemisphere dysfunction

Cutting (1994) has put forth an argument for right hemisphere deficit in schizophrenia on the basis of neuropsychological test results and neuropsychiatric analogies. Evidence of impaired perception of emotion in speech (Murphy and Cutting, 1990) facial expression (Cutting 1981), and other linguistic tasks (Brownell et al 1984), which are known to rely heavily on right hemisphere processing, have been found in patients with schizophrenia. In line with these studies, Oepen et al (1987) reported hypersensitivity to emotional stimuli in a DVF experiment in 35 acute patients. DVF studies of schizotypal subjects also suggest the presence of right hemisphere overactivation and/or increased RH specialisation (Broks, 1984; Rawlings & Claridge 1984; Leonhard & Brugger, 1998). Furthermore, there is some evidence to suggest that patients with schizophrenia have subtle forms of hemineglect on haptic extinction tasks (Scarone et al 1981; 1987), cancellation tests (Tomer & Flor-Henry, 1989) and measures of tactile-kinethesis (Harvey et al 1993). While, Gur et al, (1985) and White et al (1998) have found evidence left hemisphere advantage on a spatial tasks suggesting possible reversal of normal specialisation.

1.2.4.3 Evidence for a dysfunction interhemispheric transmission

The case for a disturbance in interhemispheric communication derives from apparently normal laterality effects on some haptic, DVF and dichotic tasks in which stimuli are presented unilaterally, in the context of poor discrimination of bilaterally presented stimuli (Beaumont and Dimond, 1973; Hallett & Green, 1983; David, 1993). Some authors have suggested that patients with schizophrenia are not abnormally lateralised and attribute previous findings to methodological and sampling shortcomings (Rockstroh et al, 1998; Mohr et al, 1999). This is odds with the aforementioned functional and structural evidence for altered asymmetry and it is noteworthy that abnormalities in interhemispheric transfer are not always present (Ditchfield & Hemsley 1990; Kwapil et al, 1992). Moreover, disturbances in interhemispheric transfer are interpreted in terms of functional hypoconnection (Mohr et al, 1999) or hyperconnection and accelerated transfer (David,

1993). Both of these conclusions entail the supposition that the main route of transfer, the corpus callosum, is abnormal in schizophrenia. At present, the evidence for altered corpus callosum morphology in schizophrenia is conflicting and inconclusive (Woodruff et al, 1998).

1.2.4.4 Left, right or both?

The abovementioned findings do provide unequivocal evidence of a preferential disturbance of the left hemisphere, right hemisphere or interhemispheric transmission. However, as Richardson et al (1997) have pointed out, there seems no specific reason why a neurodevelopmental disturbance of lateralisation should preferentially affect one hemisphere and not affect the other. This argument would also apply to the case of interhemispheric transmission. In seeking an explanation for these apparently incongruous findings, it is worth noting that DVF and dichotic studies of schizophrenia usually employ tasks that are suited to either the right *or* left hemisphere but rarely use tasks that both hemispheres are capable of performing efficiently. This could explain the mixture of findings but does not necessarily rule out a predominant disturbance in one or other hemisphere and it is also possible that subsets of patients exhibit impairments that predominantly affect either left or right hemisphere (Magaro & Chamrad, 1983; Overby et al, 1989). Another possibility is that because patients are often studied in the acute stage of the illness, the observed effects may be a lateralised state, rather than trait, effect. At least one study has found that disturbances of perceptuo-spatial function reversed with chronicity and medication (Tomer & Flor-Henry 1989). Thus, some right hemisphere deficits could simply reflect uncontrolled processing secondary to loss of the inhibitory function of the left hemisphere rather than a primary deficit (Nasrallah, 1985). These issues are addressed experimentally in subsequent chapters of the thesis.

1.2.5 Individual differences in functional laterality: schizophrenia

A number of studies have examined cognitive function in schizophrenia in relation to gender. Although not all have found significant differences when the sexes are directly compared on large batteries of tests (Andia et al 1995), a number have reported proportionally greater impairment on language compared to spatial ability in males (Ragland et al, 1999; Golstein, 1994; 1998). These findings are supported by a recent MEG study showing that schizophrenic males demonstrated significantly greater reduction of asymmetry than females in M100 auditory evoked responses located within the transverse the superior temporal gyrus (Heschl's gyrus) (Reite et al, 1997)

Sexual dimorphic disturbances in laterality have also been inferred from IQ results. Lewine et al (1996) showed female patients were more impaired in PIQ relative to VIQ suggesting greater right hemisphere impairment whereas males were equally impaired on both. A subsequent study by Purcell et al (1998) indicated that males more frequently showed greater VIQ-PIQ discrepancy consistent with greater left hemisphere impairment. In contrast, Hoff et al (1992) could find no differences between the sexes on a large battery of neuropsychological tests in first episode patients, although it is noteworthy that the sample contained relatively few women. In a subsequent study, Hoff and colleagues (1992) could find no sex difference in performance in a group of first episode and chronic patients after symptom severity was controlled for. Instead the authors suggested that sex-differences may be a reflection of age of symptom onset and severity.

Lewine et al (1997) examined the relationship between age of onset and sex in a comprehensive neuropsychological study of nearly 200 patients. They found evidence of consistent and significant age of onset x sex interactions on a range of laterality measures including dichotic listening, judgement of line orientation, and hand skill. In every case, early onset men (onset <25) had lower scores than late onset men (onset >25), and early onset women had higher scores than late onset women. They interpreted these findings as being consistent with "hypolateralisation" in early onset men/late onset women, and "hyperlateralisation" in late onset men/early onset women. Unfortunately, Lewine and colleagues could not provide a plausible model for this dissociation, but it nevertheless suggests that individual differences in lateralisation may be an important component

in understanding loss of asymmetry in schizophrenia. Whether these are related to gender dimorphisms in structural laterality remains to be seen.

1.3.1 Summary & Aims

The purpose of chapter 1 was to provide an overview of the problem of schizophrenia, the main findings relating to early onset, and the evidence supporting loss of cerebral dominance as an explanation for the disorder. Evidence from the adult literature points to anomalous cerebral asymmetry that is most marked in structures associated with key cognitive processes, particularly language. Functional laterality studies show that normal asymmetries are often reduced, reversed or absent. A number of lines of evidence suggest that these disturbances stem from a developmental alteration in the normal trajectory of hemispheric growth; the lack of evidence of gliosis in the cortex; interactions with mediating variables – sex, handedness and age of onset; and the fact that anomalous laterality is also found in developmental disorders.

Crow has proposed that schizophrenia arises from an abnormality in the genetic control of brain growth leading to cerebral asymmetry. Adolescence marks an important period in the final maturation of the brain and the consolidation of asymmetry. Individual differences in both cerebral asymmetry and functional laterality are likely to reflect differing rates of cognitive and structural development of males and females in this age range. If growth is delayed in psychosis, as Crow suggests, sexually dimorphic anomalies of both cerebral asymmetry and functional laterality should be detectable in early onset patients who may lie at the extreme end of the severity continuum relative to later onset patients.

Studies reviewed in the introduction show that adolescent onset schizophrenia is broadly comparable to that of adult onset in terms of symptomatology, morphological changes and neuropsychological deficits. Moreover, there is evidence that earlier onset is associated with an over-representation of males, poorer outcome and possibly more severe structural and cognitive abnormalities. Thus far, few studies have directly examined functional laterality or structural asymmetry in this patient group. Given that early onset patients may provide an important source of information about the relationship of lateralisation to schizophrenia, the aim of this thesis was to determine the status of functional laterality and cerebral asymmetry in a comprehensive sample of adolescent onset patients. The secondary aim was to examine the influence of mediating variables,

such as sex and age of onset, upon functional laterality and asymmetry. The rationale for investigating these alterations is derived from Crow's theory of dominance suggesting that age of onset and sex are likely to be important determinants of the extent of altered asymmetry. On this basis, the following general predictions/hypotheses were made:

- ❖ Early onset patients would demonstrate reduction or loss functional laterality when compared to normal controls.
- ❖ Cerebral asymmetry would be reduced or reversed in patients with early onset schizophrenia.
- ❖ Performance on laterality tasks would be mediated by sex as a consequence of alteration to normal sex and handedness related differences in laterality.
- ❖ There would be a significant relationship between age of onset and the extent of reduced functional laterality and cerebral asymmetry (i.e. earlier onset patients would show greater reductions than later onset patients).
- ❖ Loss of structural cerebral asymmetry will be correlated with reduction in functional laterality.

CHAPTER 2 FUNCTIONAL LATERALITY IN EARLY ONSET SCHIZOPHRENIA

Overview

In this chapter, a broad battery of tests of functional laterality was administered to adolescents with schizophrenia. The aim was to make clear the status of functional laterality in early onset patients in comparison to both healthy adolescents and patients who develop schizophrenia later in life. In order to do so, a multi-task approach was designed in order to provide coverage of the main domains of laterality. Thus, generally accepted measures were employed; 1) general intellect in the form of verbal and performance IQ, 2) motoric laterality in terms of hand preference and skill, 3) ocular dominance and eye-hand consistency, and 4) language dominance as measured by dichotic listening. Each of these measures is examined in relation to the key variables of investigation – sex and age of onset.

2.0 Introduction

The studies described in this chapter are presented in three separate sections that individually examined IQ, hand and eye preference and dichotic listening. Each section begins with a literature review of studies relevant to domain under investigation, this is followed by a description of the sample, methods results and discussion. Before turning to the studies, a more general description of the participants, procedures and data analysis relevant to all of the studies is presented.

2.0.1 Subjects

The subjects in this study were recruited from adolescent psychiatric units across the south of England (see appendix for list of participating units) and the Warneford Hospital. All patients were diagnosed as having either schizophrenia or schizophreniform disorder according to the DSM-IV criteria (American Psychiatric Association, 1990) following a semi-structured interview using the Schedule for affective disorders and schizophrenia [KSADS] (Kaufman et al, 1997) administered by a trained psychiatrist. Exclusion criteria were: history of traumatic brain injury, epilepsy, dyslexia and other neurological or psychiatric conditions. It was not possible to completely exclude subjects on the basis of substance abuse, although subjects with a clear history of drug and alcohol abuse were excluded.

A total of 85 patients with schizophrenia or suspected schizophrenia were assessed in this study. Of these, 65 were defined as being of early onset if psychosis first appeared after the age of 12 but before 19. Thus, 55 subjects met diagnostic criteria for early onset schizophrenia or schizophreniform disorder, most had experienced only one psychotic episode, and all were clinically remitted. The remaining 10 were an assortment of other psychiatric illnesses including bipolar affective disorder, learning disorders, and non-specific psychoses. These subjects were not included in the analysis.

The remaining 20 patients comprised a sample of generally older individuals recruited from the wards and outpatients at the Warneford and Littlemore Hospitals. These subjects represented a broader range of onsets for comparison to the early onset group. All patients were 18 years or

older, met diagnostic criteria for schizophrenia or schizophreniform disorder and were clinically remitted. Most had experienced only one psychotic episode (see individual sections for details of age and sex breakdowns). When combined, the resulting sample of 75 patients meeting criteria for inclusion had data that could be used in subsequent analysis, however, as not all subjects possessed a complete dataset, the numbers included in each analysis differ from subset to subset.

The control groups for this study were acquired from two different sources. First, 35 adolescent control subjects were recruited from local general practitioners within the Oxford area. Exclusion criteria included: history of traumatic brain injury, epilepsy, dyslexia and neurological or psychiatric illness. Subjects completed all parts of the assessment and were paid for participation. They were later matched for age, sex and handedness in subsequent analyses. Subjects were not specifically matched on years of education but as the majority were still in full time education, matching on age was considered to be sufficient. The second source of controls was selected from unpublished normative data on 120 adults tested in our laboratory. All were volunteers from the Department of Experimental Psychology. The same exclusion criteria were applied and they were later matched for age, sex, education and handedness.

2.0.2 Procedure

The data was collected in a series of steps that varied in order of collection from patient to patient. First, after written consent was obtained, basic demographic data including handedness, age, height and weight was collected. Usually, patients (but not controls) were then assessed with the KSADS in order to determine the clearest possible diagnosis. Subjects then performed a battery of standard neuropsychological tests and experimental tasks. Together, the entire battery took approximately 2½ to 3 hours to complete per subject but the number of sessions taken to acquire each measure varied from subject to subject. This was done to avoid problems related to motivation, fatigue and compliance. Subjects also underwent MRI scanning at the Radcliffe Infirmary (see Chapter 4 for full description).

It is important to reiterate that not all subjects completed the entire neuropsychological battery. First, according to the ethical principals of the study, subjects were permitted to withdraw from the study at any point without explanation. A number of patients exercised this right. Second, subjects were also closely monitored throughout testing for state effects (e.g. fatigue, poor motivation, and inattention) that could affect the quality of the acquired data. If such effects were observed, testing was discontinued on that day and attempts were made to complete the assessment at a later date. In some cases, patients refused or were unable to complete the assessment. Finally, when examining laterality effects it was considered important to account for inter-individual differences that could affect performance. As one of the principal aims of this study was to examine the influence of sex and age of onset on laterality, only nominally right-handed subjects were included in some analyses. Although comparisons to left handed subjects would provide more information, the number of these subjects in each group was insufficient to warrant separate analyses. Thus, in the following chapters, the number of subjects completing each test or experiment is stated in table form.

2.0.3 Design and analyses

Both between (patients versus controls) and within subjects comparisons (early versus late onset; male versus female; pure versus mixed handed) were performed on each test. In most cases, multiple ANOVA design is employed but in response to the problem of unequal sample sizes and the problem of inhomogeneity of variance, an increased alpha level of .10 was permitted in post hoc testing of interaction effects (Winer, 1971). Simple main effects analyses were conducted with either paired or independent variables t-test – Bonferroni corrected. In the case of multiple means, Tukey's HSD test was the preferred method.

Studies of cognition in schizophrenia are affected by the almost universal problem of neuroleptic treatment effects. There are both positive and negative side effects of such treatment. In general, the newer atypical medications such as clozapine, olanzapine and risperidol appear to have some enhancing effects on cognitive function whereas the traditional neuroleptics such as haloperidol have either no affect or a worsening effect on cognitive abilities (Blyler & Gold, 2000). The majority of patients in this thesis were treated with atypical medications. Studies of atypical effects find

improvement of attentional functions (Spohn & Strauss, 1989; Serper et al, 1990) and some evidence of mild decrements in motor functions (Sweeney et al, 1990; Cutmore & Benninger, 1989). In order to account for these effects, correlations between neuroleptic dose and performance are examined in both paper & pencil and divided field experiments. In the latter, baseline reaction time is assessed in both patients and controls to identify psychomotor retardation.

2.1 GENERAL INTELLIGENCE

2.1.1 Background & Aims

It is well established that patients with schizophrenia demonstrate reduced IQ. Comprehensive reviews show that up to 75% of adult patients show intellectual decline in the order of 4 to 20 points depending upon clinical severity (Payne 1973; Taylor et al, 1980; Nelson et al 1990; Braff et al, 1991). From a laterality point of view it is significant that, in most cases, non-verbal intelligence (performance IQ) is reduced relative to verbal intelligence (verbal IQ) (Flor-Henry et al, 1981; Kolb & Whishaw, 1983; Goldberg and Weinberger, 1988). Relatively few studies have examined general intellectual ability in early onset patients in relation to normal controls or later onset patients. Goldberg et al (1988) reported significantly reduced performance IQ (72 v 93) but no difference in verbal IQ (75 v 83) in 41 DSM-III adolescent patients relative to normal controls. Kenny et al (1997) examined general cognitive function in 17 patients and found deficits in 10 of 13 neuropsychological measures. Oie & Rund (1999) examined 19 adolescent patients with a large battery of tests in the areas of abstraction-flexibility, visual memory and learning, spatial organisation, visual motor skills, motor function, auditory processing, selective/sustained attention, and span of apprehension. Overall, the adolescent group performed close to or greater than 2 standard deviations below normal in every domain except sustained attention. Taken together, these findings do not point to a consistent deficit or area of disturbance in adolescent patients. Instead, it would appear that patients exhibit diffuse impairment of cognitive function.

When early onset patients have been compared to later onset counterparts, mixed findings have emerged. Johnstone et al (1989) used a small clinical battery and found poorer remote memory and language problems in patients with adolescent compared to adult onset schizophrenia. More recently, Yang et al (1995) examined a small group of patients with onsets before or after the age of 15 and found significantly reduced PIQ in the early onset group. Similarly, Basso et al (1998) examined a group of chronic patients with either adolescent (before 21) or adult onset (after 25) schizophrenia on a range of tasks. They found greater impairment on tests of executive function and memory in the adolescent group but did not perform an IQ comparison. In contrast, Heaton et al (1994) examined 142 chronic patients and found no significant difference in cognitive ability

between early, adult, and late onset groups on the Halstead-Reitan battery or Wechsler Intelligence Scales. It is noteworthy, however, that in this study the 'early' group were included on the basis of onset before the age of 45 and are therefore difficult to compare to early onset patients in previous studies.

This highlights one of a number of methodological problems associated with studies examining age of onset effects on neuropsychological function. Differences in classifications of onset vary from study to study and thereby limit the generalisability of the results and patients are often drawn from adult, chronic and/or long-term hospitalised cohorts which introduce confounding effects of institutionalisation, long-term medication and chronic disease. Another problem is the failure to control for sex. A number of studies have shown greater IQ reduction and larger VIQ-PIQ discrepancy in early onset males when compared to females and/or later onset patients (Offord, 1974; Purcell et al, 1998; Lewine et al, 1996; 1997) Given that age of onset and sex may interact, it is necessary to take account of these factors independently.

Taken together, the above results suggest that decline in general intellectual function occurs in adolescent onset patients and is broadly comparable to that of adult schizophrenia. Comparisons on the basis of onset provide some support for the assumption that earlier onset is associated with diffuse impairment but presently the literature is small and there are some methodological problems. Presently, there are no studies have directly compared intellectual function in an early onset sample in relation to age of onset and sex. The present study was performed in order to address the following research questions;

- ◆ Do adolescent onset patients demonstrate impaired IQ relative to normal adolescents?
- ◆ Are there are any clear effects in IQ that might suggest anomalous lateralisation?
- ◆ Does age of onset or sex has any mediating effect on IQ?

2.1.2 Subjects

As a consequence of the drop out of some subjects in the study, IQ data was not available for the total pool of 75 early and later onset patients. In addition, comparable normal control IQ data was not available for the later onset patients. As such, two samples were created from the available pool of 60 schizophrenic subjects with IQ data and 35 adolescent controls:

Sample 1:

The first sample comprised a group of patients classified as adolescent onset (onset 19 years or younger) in relation to normal adolescent controls who were closely matched for age as well as sex. This created equally sized groups of 35 adolescent patients with schizophrenia and 35 matched normal controls (see Table 2). In the patients, there were no significant differences between the sexes in terms of age, age of onset, length of illness or current medication (chlorpromazine equivalent). There were no significant differences between patients and controls in age or sex. In general, education levels were comparable – although this was not examined explicitly.

TABLE 2: Sample 1 subject characteristics

	Patient s			Controls		
	Male	Female	Total	Male	Female	Total
N	21	14	35	21	14	35
Age (years)						
M	15.81	15.84	15.82	15.11	15.69	15.34
SD	1.07	1.41	1.20	1.72	2.16	1.90
Age of Onset (years)						
M	14.84	15.10	14.94			
SD	1.21	1.47	1.31			
Dur illness (months)						
M	12.55	10.92	11.88			
SD	8.41	10.47	9.17			
Chlorpromazine Eqv						
M	389.37	628.57	487.86			
SD	242.84	818.68	558.80			

Sample 2:

The second sample constituted a within subjects examination of all 60 schizophrenic patients regardless of age (range 13.2yrs – 42.2yrs). Thus, the original 35 patients from sample 1 were combined with the remaining patients with complete IQ results in order to examine the effect of age of onset on IQ. In order to generate a statistically valid between groups comparison, a median split

was performed and two groups were derived: onset <16.3 years [n = 30] and >16.3 years [n = 30]. In the following analysis these groups are arbitrarily termed “early and “peak” onset respectively. Median split was chosen as a consequence of the skewness of the distribution of IQ variance in the adult group from the Warneford Hospital as these were quite high functioning ‘mild’ cases (many were still students of the University with high IQ’s). Also, this breakdown would have created unequal sample sizes that would adversely affect the ANOVA design. There were no significant differences between onset groups in terms of duration of illness or current medication but the expected differences in age and age of onset of illness were significant. Approximate proportions of right and left-handers were included in each study.

TABLE 3: Sample 2 subject characteristics

	Early Onset Mean (SD)	Range (Min-Max)	Peak Onset Mean (SD)	Range (Min-Max)	Total
N (M/F)	30 19/11		30 20/10		60 39/21
Age (years)	15.6 (1.2)	13.2 - 19.7	21.2* (5.6)	16.0 - 42.2	18.4 (4.9)
Age of Onset (years)	14.4 (1.1)	12.02 – 16.03	19.5* (4.3)	16.04 - 34.06	17.0 (4.0)
Dur illness (months)	15.5 (11.3)	1.0 – 48.2	21.3 (28.4)	1.2 - 119.0	18.2 (21.7)
Chlorpromazine Eqv	359.7 (238.6)	60.3 – 1067.7	510.0 (594.9)	0 – 3300.1	436.5 (458.5)

*P<0.05, **P<0.01, ***P<0.001

2.1.3 Method

All subjects performed either the full version of the Wechsler Intelligence Test for Children - III (Wechsler, 1992) or, in the event that the subject was over the age of 16, the Wechsler Adult Intelligence Test – Revised (Wechsler, 1981). Whenever possible, testing was performed in one uninterrupted session. However, as some patients found it difficult to maintain concentration over long periods, it was necessary to perform several testing sessions over a number of days or weeks. Following testing, all subscale scores were transformed into age scaled scores in order to be equivalent. Standard IQ indices were calculated.

2.1.4 Results

SAMPLE 1: Adolescent patients versus normal controls

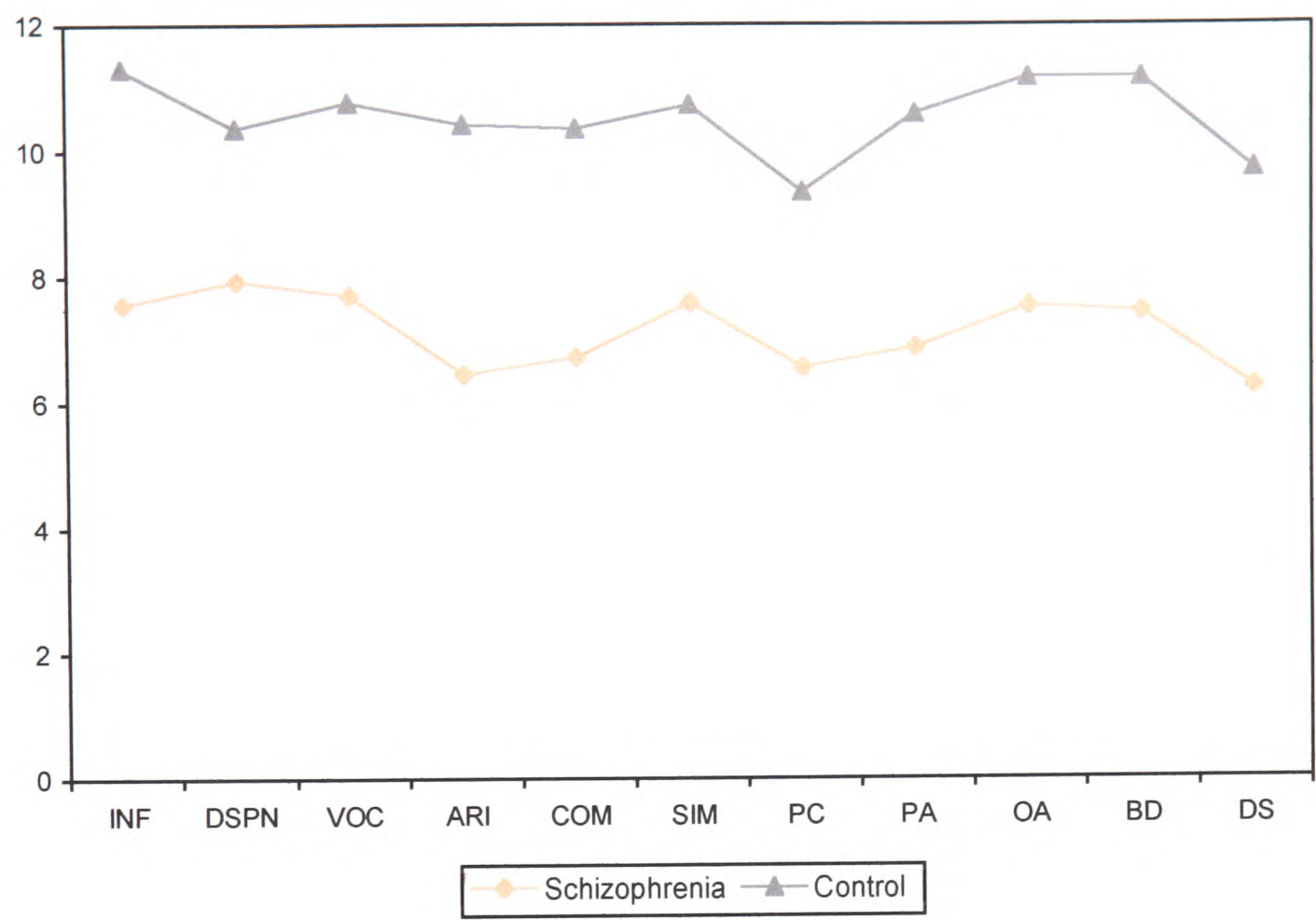
Mean VIQ and PIQ were examined by diagnosis and sex in separate multivariate two-way analysis of variance (ANOVA). FSIQ and VIQ-PIQ discrepancy were examined in univariate ANOVA by diagnosis and sex. Analysis of the full scale scores showed that the schizophrenic group had significantly reduced Full Scale IQ in relation to the normal controls $F [1, 70] = 41.09; p < 0.001$). The average IQ of the adolescent patients was 22 points below that of the normal control group (see table 4). There was no sex by diagnosis interaction. In total, 70.6% of patients fell below the standard cut-off for abnormality (FSIQ less than 85 or negative -1 standard deviation) whereas only 8.6% of the controls fell within this category. ($\chi^2 = 166.86 \text{ } p < 0.001$). Both verbal and performance IQ were also significantly below that of the normal controls (VIQ: $F [1, 70] = 29.63 \text{ } p < 0.001$; PIQ $F [1, 70] = 32.31 \text{ } p < 0.001$) However, neither the patient group nor the control group demonstrated a significant discrepancy between verbal and performance IQ.

In order to perform a profile analysis, individual subtests were then analysed in a multiple analysis of variance (MANOVA) design by diagnosis and sex. Multivariate Hotelling's T statistic indicated significant differences across subtests on the basis of group ($F [11, 53] = 4.16 \text{ } p < 0.001$) as well as a strong trend for sex differences ($F [11, 53] = 1.86 \text{ } p = 0.06$). The univariate analysis showed significantly impaired performance for the patient group across all subtests (see figure 3). No significant group by sex interactions were found.

Table 4: Sample 1: IQ by gender in early onset patients and controls

	Patients			Control		
	Male	Female	Total	Male	Female	Total
Verbal IQ						
M	85.04	82.79	84.25	100.67	106.29	102.91
SD	14.45	13.20	13.90	16.34	17.34	16.73
Performance IQ						
M	82.54	76.21	80.32	98.29	105.07	101.00
SD	14.53	16.12	15.21	14.86	17.00	15.87
Full Scale IQ						
M	82.73	77.71	80.97	99.81	106.67	102.31
SD	13.58	13.39	13.56	15.12	16.97	15.96

Figure 2: Profile of Wechsler IQ Performance (Age Scaled Scores)



INF = Information, DSPN = Digit Span, ARI = Arithmetic, COM = Comprehension, SIM = Similarities, PC = Picture Completion, PA = Picture Arrangement, OA = Object Assembly, BD = Block design, DS = Digit Symbol

SAMPLE 2: Early onset versus peak onset schizophrenia

Prior to performing ANOVA comparisons, correlational analyses were performed on the entire patient group (n=60) in order to establish if illness or treatment variables affected IQ performance. There was no significant correlation for duration of illness or current medication in relation to any of the IQ variables. However, a significant correlation was found between estimated age of onset and verbal IQ ($r = 0.26$, $p < 0.05$ two tailed) indicating that later onset was associated with greater VIQ. The Information subtest also correlated negatively with age of onset ($r = 0.33$, $p < 0.05$ two tailed) and age at testing ($r = 0.29$, $p < 0.05$ two tailed). In order to determine the individual contribution of each of these variables, a linear regression analysis was performed with VIQ as the dependent variable by age, age of onset, duration of illness and current medication. The stepwise regression equation showed that estimated age of onset predicted a small but significant amount of variance of VIQ ($R^2 [1,57] = 0.067$ $p < 0.05$). No other variable contributed significant variance.

Table 5: Sample 2: IQ in relation to age of onset and gender in early and peak onset schizophrenia

	Early Onset			Peak Onset		
	Male	Female	Total	Male	Female	Total
Verbal IQ						
M	81.32	83.55	82.14	89.75	87.50	89.00
SD	15.16	14.20	14.61	13.53	14.23	13.56
Performance IQ						
M	82.16	75.64	79.77	87.50	86.60	85.60
SD	14.47	16.83	15.42	14.23	14.59	15.46
Full Scale IQ						
M	80.21	77.11	79.30	89.00	86.47	86.47
SD	14.28	14.50	14.16	13.56	13.70	13.70

Multivariate ANOVA of FSIQ, VIQ and PIQ and VIQ-PIQ discrepancy by age of onset and sex were performed. This analysis revealed strong trends to significance for age of onset for VIQ ($p = 0.07$) and FSIQ ($p=0.05$) indicating inferior performance of the early onset group. This was reflected in the comparably greater number of early onset patients who fell below the cut-off of abnormality for VIQ (early = 70% versus peak = 30%) ($\chi^2 = 120.0$ $p < 0.001$) and FSIQ (early = 69% versus peak = 46%) ($\chi^2 = 4.80$ $p < 0.05$). In addition, there was a significant age of onset by sex interaction on

VIQ-PIQ discrepancy ($F [1, 60] = 5.13$ $p < 0.05$). This revealed that early onset females had significantly greater discrepancy than their age-onset/sex counterparts.

Individual subtest analysis was performed with a MANOVA design. Multivariate Hotellings T statistic revealed a significant gender main effect across all subtests ($F [11, 41] = 2.91$ $p < 0.01$) indicating that females were superior overall but there was no effect for age of onset. Univariate sex differences were present only on the digit symbol subtest ($F [1, 55] = 6.56$ $p < 0.05$; $F [1, 55] = 5.13$ $p < 0.05$) with females showing superiority. Digit symbol was also significantly poorer in early onset patients ($F [1, 54] = 5.26$ $p < 0.05$). Only picture completion showed a significant sex by age of onset interaction ($F [1, 55] = 4.19$ $p < 0.05$).

2.1.5 Discussion

Intellectual ability in adolescent onset schizophrenia

Do adolescent onset patients demonstrate impaired IQ relative to normal adolescents? The results of the first analysis confirmed that adolescents with schizophrenia have significantly lower verbal, performance and full scale IQ than normal adolescents who were matched for age and sex. In total, 70% of the patient group had full scale IQ's below the standard cut-off for abnormality. This cut off was used in on the basis of the expected frequencies of IQ under the normal curve. In cumulative percentage terms, IQ less than 85 occurs in less than 16% of the normal population, whereas IQ less than 70 (2 SD's) occurs in less than 3%. Thus, while descriptively 85 or less is 'low average', in accordance with previous adult studies examining schizophrenic patients (Purcell et al, 1998).

In general, these findings are consistent with previous studies of intellectual functioning in adolescent-onset schizophrenia and broadly consistent with those of chronic adult schizophrenia (Goldberg et al, 1988; Kenny et al, 1997; Oie & Rund 1999). However, unlike many studies of adult patients, mean VIQ-PIQ discrepancy was not significantly different from normal controls and there was no clear evidence of a sexual dimorphism in deficit. Typically (although not always) PIQ is more sensitive to decline than VIQ. This is generally due to the effect of schizophrenia on attention and aspects of 'fluid intelligence'. In sample 1 and 2, PIQ was marginally below that of VIQ.

However, this was not significantly greater than chance. Hence, strictly speaking it is not justifiable to conclude that PIQ was more sensitive. Instead, the most obvious explanation for this is that early onset patients suffer from a more diffuse rather than lateralised pattern of impairment. This highlights the importance of the next analysis and questions the validity of performing domain specific psychological testing in patients whose intellectual abilities are already severely compromised. It also argues in favour of a 'developmental' aetiology rather than a discrete, lesion like pathology.

Intellectual ability in relation to age of onset

Does age of onset have a mediating effect on IQ? A number of lines of evidence point to age of onset as a possible determinant of generalised intellectual decline. Age of onset correlated significantly with, and accounted for significant variance of, verbal IQ. There were also strong trends to significance for reduced VIQ and FSIQ in early compared to peak onset patients and greater numbers of early onset patients had abnormally reduced VIQ and FSIQ scores. Furthermore, the only significant subtest correlation was found between age of onset and performance on the information subtest - a measure of semantic knowledge. This suggests that patients are no longer acquiring new knowledge following the onset of illness possibly as a consequence of disturbance to the neural substrates underlying semantic memory and/or inability to maintain normal educational development. Taken together, these results confirm the hypothesis that early onset patients demonstrate greater impairment of general intellectual ability when compared to later onset patients of the same length of illness and current medication. That age of onset differentiates only VIQ performance suggests that verbal ability may lie closer than non-verbal ability to the underlying neurodevelopmental anomaly.

Intellectual ability in relation to sex

Does sex have any mediating effect on IQ? It was expected that early onset males would perform more poorly than later onset males and females. However, when sex was examined, early onset females demonstrated the largest decline in IQ as well as a marked VIQ-PIQ discrepancy (VIQ>PIQ). These findings do not agree with previous work showing reduced IQ and significant VIQ-PIQ discrepancies in male patients - particularly those with early onset (Purcell et al, 1998;

Lewine et al, 1996; 1997). Moreover, the findings contrast with the usual pattern observed in unilateral brain lesions as typically males demonstrate large (11-14 point) VIQ-PIQ discrepancies whereas females do not (Kaufman, 1990). The reasons for this difference are not clear, however, it is possible that sex-laterality effects are not as easily discernible in adolescent patients as a consequence of the diffuse nature of the neural changes and/or the age at which such changes become apparent (cf. Lewine, 1988). Also, it is possible that a larger sample size is required in order to detect sex and sex-onset discrepancies in IQ. Speculatively, it is possible that the disease “dose” may be higher in females at this early age and thus reduces intelligence more severely. Further work is therefore required in order to establish the contribution of gender to IQ differences in early onset schizophrenia. Another approach is to examine patients with more sensitive tests of laterality, this approach is taken in the followings sections.

Medication effects

The lack of correlation between duration of illness and medication effect with IQ variables was in line with the previous studies showing no effect of medication on WAIS performance (Seidman et al, 1993; Lee et al, 1994; Allen et al, 1997) but not with those showing enhanced performance (Gold and Hurt, 1990; Serper et al, 1994). This is due to two reasons. One is that correlational methods are more likely to show a zero order relationship between these factors if there is no ‘dose-effect’ relationship for cognition. In general, such effects are not consistently found in well-controlled studies (Blyler & Gold, 2000). Second, the average medication dose in this study was relatively high and thus the ‘saturation effect’ may obscure true treatment effects if they do indeed exist. Thus, caution is advisable as medication effects represent an unknown influence in this analysis.

2.2 HAND & EYE PREFERENCE

2.2.1 Background and aims

Handedness is an important correlate of cerebral dominance for language and its relationship to schizophrenia is an issue that has attracted considerable controversy. Studies that have examined this association report a mixture of findings including excess in atypical or mixed hand preference, left handedness, right-handedness or no difference from the normal distribution (Satz and Green, 1999). These discrepant findings have been attributed to differences in sample size, the measurement and definition of handedness and the complex relationship between handedness and sex. However, meta-analyses of hand preference studies concur that schizophrenia is generally characterised by a shift away from normal right hand preference and an excess in mixed handedness.

Atypical handedness is found in association with other putatively neurodevelopmental disorders such as dyslexia and autism (Richardson, 1994; Cornish & McManus, 1996; Satz and Green, 1999). In normals, ambidexterity has been associated with reduced left lateralisation of speech (Milner, 1974), and predicts poorer academic achievement (Leask & Crow, 1997; Crow et al, 1998). In relation to schizophrenia, Crow has argued that reduced hand preference and skill are indicators of the genetic failure to establish left hemisphere dominance in development. Presently, evidence for a direct association between altered brain structure and atypical handedness has been limited (Satz et al, 1990; Pearlson et al, 1989; and Clementz et al, 1994, see section 3.4) although associations between left-handedness and decreased intellectual ability (particularly on language measures) have been reported (Katsanis and Iacono, 1989; Hayden et al, 1997).

Handedness is clearly associated with another index of dominance – eyedness. In normals, up to 75% of left-handers show left eye eyedness and approximately 75% of right-handers show consistent right dominance (Mcmanus et al, 1999). Studies of adult patients with schizophrenia have shown increased incidence of left eyedness in association with increased left handedness (Gur, 1977) but it appears to be particularly associated with earlier age of onset and male sex. For example, Krynicki & Nahas (1979) and Piran et al (1982) have reported increased left eyedness,

left-handedness and incongruent hand-eye dominance in early-onset adolescents relative to psychiatric and normal controls. More recently, Seisdedos et al (1999) found earlier clinical onset and smaller brain size in 23 right-handed and non-right-eyed patients (crossed hand-eye dominant), compared to 38 right-handed and right-eyed patients with schizophrenia (consistent hand-eye dominance group). In adults, Oddy and Lobstein (1972) and Lishman and McMeekan (1976) found that mixed handed subjects were more likely to be younger and male but did not provide data on the estimated age of onset. In contrast, Merrin (1984) examined 52 chronic patients and did not find any evidence of an association between left eyedness or left-handedness and early-onset schizophrenia. Whereas Cannon et al (1995) found that mixed handedness was associated with negative family history and male gender but not age of onset.

Taken together, these findings suggest an association between altered hand and eye preference and earlier onset schizophrenia and implicate a relationship with altered brain development. If age of onset reflects differences in deviation from the normal trajectory of brain development, it is possible that this would be reflected in increased proportions anomalous hand preference in earlier relative to later onset patients. In light of the previous findings, the aims of this study were to answer the following questions:

- ◆ Is early onset associated with increased non-right handedness, eyedness or crossed hand-eye dominance relative to normal controls?
- ◆ Does age of onset or sex have any mediating effect on these variables?
- ◆ Is there any relationship between non-right handedness and intellectual functioning?

2.2.2 Subjects

59 of the pool of 75 schizophrenic patients had handedness data. These were all included in the analysis of handedness. In addition, the composition of the control group in this sample was bolstered by an additional 20 matched normal controls acquired from laboratory datasets (previously mentioned on page 29). Thus, combined with the original 35 adolescent controls, a control group of 55 age and sex matched controls was compared to the 59 schizophrenic patients. The same age of onset classification was used in this analysis (onset before/after the age of 16.3; see table 6). Equal proportions of nominally right and left-handed subjects were included on the basis of writing hand. Approximately equal proportions of males and females were included in all groups. There were no significant differences between groups or sexes with regard to duration of illness (months) or chlorpromazine equivalent dose. The expected differences in age and age of onset were present between the early and peak onset groups but neither was significantly different from the control group.

TABLE 6: Sample 3: Subject characteristics

	Patients		Controls	
	Mean (SD)	Range (Min-Max)	Mean (SD)	Range (Min-Max)
N (M/F)	59 38/21		55 34/21	
Age (Years)	18.4 (4.9)	13.2 – 42.2	18.2 (5.2)	12.0 – 39.0
Age of Onset (Years)	17.0 (4.1)	12.02 – 34.06		
Dur of illness (Months)	18.3 (21.9)	1.0 - 119.0		
Chlorpromazine Eqv	430.3 (460.0)	0 – 3300.1		

*P<0.05, **P<0.01, ***P<0.001

2.2.3 Method

Patients and controls performed two measures of handedness. Firstly, the Annett Handedness inventory (Annett, 1970). This is a widely used 12 item self-report questionnaire that assesses hand preference for various gross and fine motor activities. For example, the questionnaire asks for hand preference in writing, playing racquet sports, brushing teeth etc. Subjects can respond in five ways; always left, usually left, no preference, usually right, always right. Two measures were derived for analysis, first, a handedness quotient was calculated on the basis of the sum of responses across the entire handedness questionnaire (a score of -24 indicating maximum left hand preference and +24 indicating a maximum right hand preference). The second was a measure calculated on the basis of Annett's (1970,1985) primary actions (writing, throwing, hammering, brushing teeth, striking a match, holding a racquet) in order to identify and discriminate strong left or right-handedness from mixed handedness. Due to the relatively small size of the sample Annett's 8 categories were not employed, instead, subjects classified as either purely right or left handed or mixed handed if they did not show a consistent preference on any of the primary actions listed above.

The second task assessed relative hand skill. The Annett pegboard task involves the placement of ten pegs within a holed pegboard. The subject is instructed to place the pegs one at a time into the board as quickly as possible. In order to achieve optimal performance, subjects are encouraged to perform the task as quickly as possible and each hand is assessed five times. At the end of five trials, an average score is then derived for each hand. A laterality quotient is calculated according to equation 1:

Equation 1:

$$\frac{Right + Left}{Left - Right} \times 100$$

Eyedness was assessed by asking the subject which eye they would use to look through a telescope or by providing a cardboard inner tube and asking them to imagine themselves using it as a telescope.

Left and mixed handedness and left and mixed eyedness were combined in the following analysis for two reasons. Firstly, although previous studies show that mixed handedness is associated with schizophrenia, many also show that any shift from strong right preference may be important. Second, in view of the small sample size under investigation, the combined classification provides a more valid statistical comparison.

2.2.4 Results

Handedness

Before determining the proportion of mixed handedness within the schizophrenic sample, the proportion of pure and mixed handedness in the combined control group (N = 55) was examined. In total, 61% of this group were purely right or left-handed whereas 38% were classified as mixed handed. In relation to the population estimates of handedness provided by Annett (1996), this rate was somewhat above that of the general population (68% and 32% respectively). Table 7 shows that for the combined patient group the total proportion of right/left or mixed handedness was not significantly increased from that of the normal controls or Annett's population norms. When the sample was examined in relation to onset, proportionally more early onset patients demonstrated mixed over pure left/right handedness, although not significantly. Comparison to Annetts' population norms was also non-significant but there was a strong trend to significance for the early onset patients ($p = 0.07$). ANOVA on Annett hand preference score by group (early/ late/control) and sex (M/F) failed to show any significant main effects or interactions.

Performance in mean hand skill (in seconds) is presented in table 7a. This revealed that the schizophrenic subjects as a group were significantly slower in peg placement in both left and right hands relative to controls (Left: $F [1, 114] = 11.49$ $p = 0.001$; Right: $F [1, 114] = 14.01$ $p < 0.001$) and that early onset patients significantly worse than peak onset patients (Left: $F [1, 114] = 6.31$ $p = 0.05$; Right: $F [1, 114] = 9.73$ $p < 0.001$). When the ANOVA was performed on hand skill, a significant difference between groups was found ($F [1, 114] = 3.66$ $p < 0.05$). Post hoc Tukey HSD revealed that early onset patients had significantly reduced relative hand skill to later onset patients. No other main effects or interactions were present.

Table 7a: Mean hand skill performance (secs) in relation to group and onset

	Onset <16.03 years (n = 30)	Onset >16.03 years years (n=29)	Total (n=55)	Control (N=55)
Mean Hand Skill (secs)				
RIGHT (sd)	12.19 2.0	11.36 1.27	11.77 1.70	10.54 1.15
LEFT (Sd)	12.80 2.21	12.50 1.80	12.64 2.0	11.36 1.27

Eyedness and hand-eye dominance

For the combined patient group (regardless of onset) the total proportion of left eyedness as well as the proportion of crossed and consistent hand-eye dominance was not significantly different from controls. However when examined on the basis of onset, early onset patients demonstrated significantly higher proportion of left/either eyedness relative to normal controls ($\chi^2 = 30.0$ $p<0.001$) whereas peak onset patients did not. Early onset patients also demonstrated a higher proportion of crossed hand-eye dominance relative to controls that was not present in the later onset group ($\chi^2 = 6.11$ $p<0.05$).

Table 7b: Handedness, eyedness and hand-eye dominance in relation to onset

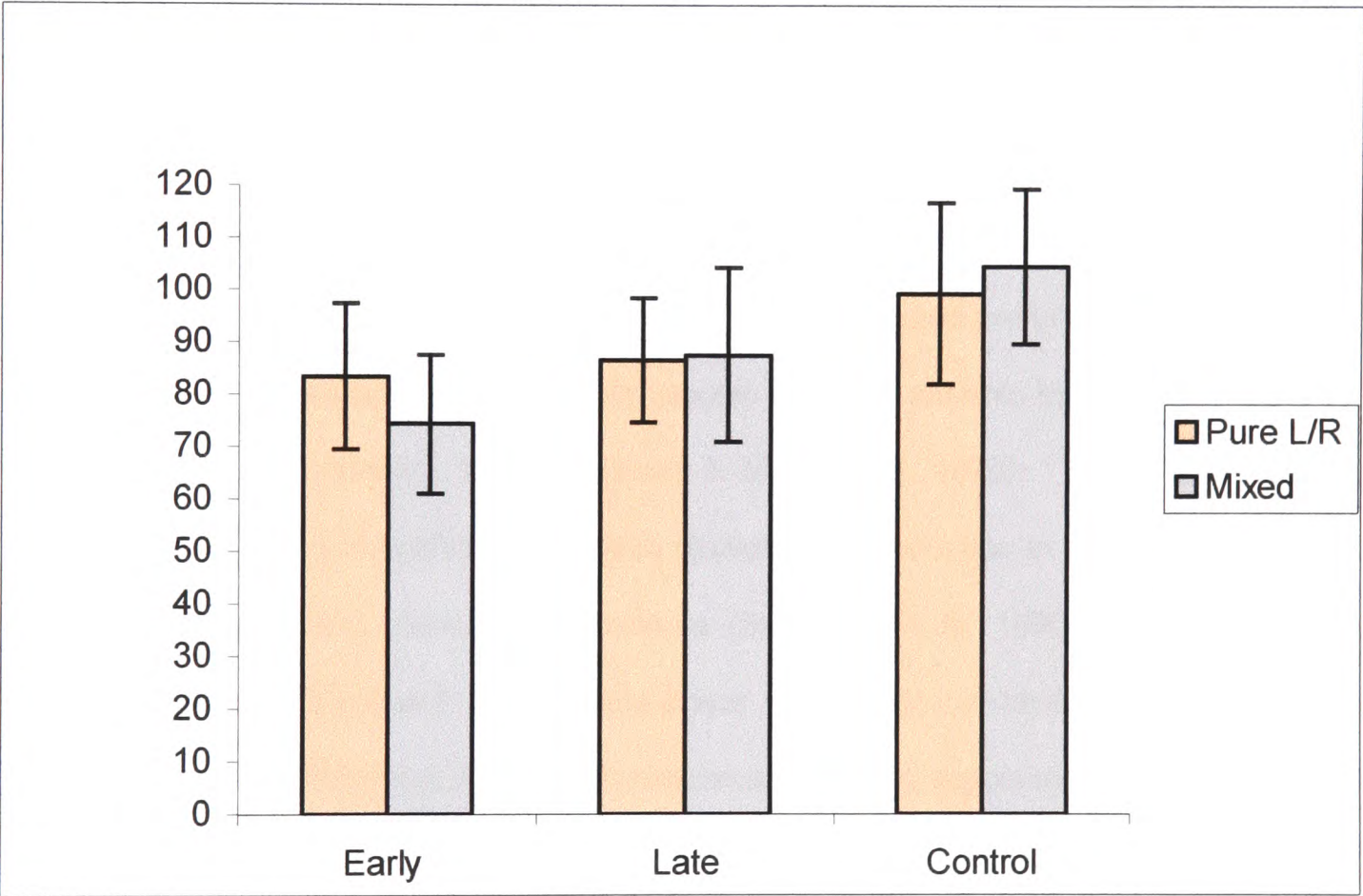
	Onset <16.03 years (n = 30)	Onset >16.03 years years (n=29)	Total (n=55)	Control (N=55)
% Hand Preference				
RIGHT/LEFT	53.3%	62.1%	57.6%	61.8%
MIXED	46.7%	37.9%	42.4%	38.2%
% Eye Preference				
RIGHT	60.0%	90.0%	75.0%	72.7%
LEFT/EITHER	46.4%*	10.3%	25.0%	27.3%
% Hand-Eye Preference				
CONSISTENT	70.0%	92.9%	81.0%	80.0%
CROSSED	30.0%*	7.1%	19.0%	20.0%

* $P<0.05$, ** $P<0.01$, *** $P<0.001$

Relationship of age of onset, handedness and IQ .

In order to ascertain the influence of handedness to IQ, univariate ANOVA was performed on IQ (FSIQ, VIQ, PIQ) in relation to hand preference (Pure R/L, Mixed) and age of onset (early, late, control). Group main effect revealed that patients were inferior to controls overall (FSIQ: $F [1, 92] = 20.55$ $p < 0.001$; VIQ: $F [1, 92] = 16.24$ $p < 0.001$ $F [1, 92] = 15.72$ $p < 0.001$) but no handedness by onset interaction. Mixed handed early onset patients demonstrated an FSIQ that was on average 9 points below that of pure R/L handed subjects but this failed to reach significance in post hoc testing (Figure 3)

Figure 3: Handedness & IQ by age of onset in patients and normal controls



2.2.4 Discussion

Hand/Eye preference in patients versus controls

Is early onset associated with increased non-right handedness, eyedness or crossed hand-eye dominance? The initial analysis of the combined group (n=59) revealed no significant difference from normal controls in terms of the proportion of pure and mixed handedness, strength of preference, or relative hand skill, although patients were significantly slower in motor speed relative to controls. Furthermore, the combined patient group failed to demonstrate excess in left eye or inconsistent hand-eye preference relative to the control group. These findings were inconsistent with the literature showing excess mixed handedness within the schizophrenic population and the smaller literature suggesting reduced right eye preference.

Hand preference and age of onset

Does age of onset moderate hand preference? Earlier onset patients demonstrated significant reductions in both raw motor speed in both left and right hands, reduction in the strength of relative hand skill, and a small (but non-significant) excess in mixed hand preference. Examining hand skill first, the present results agree with previous studies of young patients that find reduction in relative hand *skill* (Oddy & Lobstein, 1972; Lishman & McMeekan, 1976). This effect appears to be unrelated to medication as although previous studies show reduction in simple motor reaction time between medicated and unmedicated patients (Sweeney et al, 1990; Cutmore and Beninger, 1989), studies using pegboard tasks (Earle-Boyer et al, 1991) or tapping tasks (Cleghorn et al, 1990) do not find any medication effect on performance. If it is suggested that loss of relative hand skill may in part be attributable to overall slower speed, it is not immediately obvious why medication should reduce skill of the right hand relative to left hand or why younger patients with the disorder would be more susceptible to this. Thus, the present findings suggest that reduction in hand skill is a genuine effect of having schizophrenia and that is worse with earlier age of onset.

Looking at the preference data, it is clear that the results are not consistent with those that report an increase in atypical hand *preference* and left, rather than mixed, handedness (Krynicky & Nahas, 1979; Piran et al, 1982). This discrepancy may be attributable to the relatively small size of the

sample that would be expected to reduce the likelihood of detecting subtle anomalies in hand preference. However, in view of the fact that anomalous handedness was observed predominantly the early onset group, it is also possible that the failure to find reduced right-hand preference is attributable to the heterogeneity in onsets within the sample. Speculatively, this might explain previous inconsistency in the handedness literature as a consequence of the relative proportions of early and later onset patients within samples. Further large-scale studies would clarify this, but the present findings support a shift away from strong right skill in early onset patients.

Eye preference and age of onset

In the case of ocular dominance, there was evidence of excess left eyedness and crossed hand-eye dominance within the early onset sample. This partially agrees with previous studies that have found either increased left eyedness or crossed dominance in early onset patients (Krynicky & Nahas 1979; Piran et al, 1981) although it is noteworthy that the sex difference was not replicated (Oddy & Lobstien, 1979; Lishman & McKeekan, 1976). Additionally, whilst some have reported that 75% of early onset patients showed left eye preference (Piran et al, 1981), the present estimate of 46% was substantially less. It is therefore possible that differences in the assessment of eyedness (Pirans' used a three-point questionnaire to assess eye dominance) may explain the reduced incidence.

In this context, the significance of reduced right eye preference is unclear. It would be tempting to conclude that reduced eye preference is a further indicator of altered laterality but this is speculative for a number of reasons. First, hand and eye preference are usually closely associated suggesting that they are determined by an overall dominance factor or phenotype. Second, eye preference is usually considered to be secondary to hand preference as a marker of dominance (Mc'manus et al, 1999). Third, the neural substrates of ocular dominance are not well understood. Given that, in the present sample, the evidence for altered hand preference was not unequivocally established, it is difficult to interpret the evidence from eye-preference clearly. It is possible that reduced eye preference does reflect selective impairment of visual as opposed to motor circuitry involved in attentional preference. Alternatively, it may simply be a consequence of state effects during testing. The use of a multi-item measure may have reduced this possibility.

Relationship to IQ to handedness and age of onset

Is there any relationship between non-right handedness and intellectual functioning? The analysis revealed a strong trend to interaction between age of onset, hand preference and performance on IQ tests. Mixed-handed early onset patients demonstrated the poorest performance on IQ tests when compared to patients who showed stronger hand preference and normal controls. Leask & Crow (1997) and Crow et al (1998) have shown in large-scale population studies that healthy people who demonstrate reduced hand skill are more likely to demonstrate poorer academic skills when compared to those who show stronger hand preference and skill. This suggests that patients with schizophrenia may lie at one extreme of a laterality continuum that could explain the impairments observed in cognitive ability. This suggestion requires further study, preferably with larger samples.

2.3 AUDITORY LATERALITY

2.3.1 Background and Aims

Evidence for altered language laterality and cerebral dominance in schizophrenia has accumulated from studies using the dichotic listening task. In this technique, the subject hears pairs of linguistic stimuli (tones, phonemes, words, or stories) presented simultaneously, one stimuli per ear. Eighty to ninety percent of right-handed subjects achieve greater accuracy when stimuli are presented to the right ear relative to the left. Moreover, this right ear advantage (REA) appears also to be increased by attending to the right ear. Both of these findings may be explained by the fact that right-ear preference only occurs when there is conflict between the two inputs. The conflict presumably forces the language hemisphere to use the attention mechanism of the thalamus to suppress the left-ear input so that the interfering stimuli will be filtered out. It is likely that the left hemisphere can inhibit the left-ear input (ipsilateral input) better than it can inhibit the right-ear input because the contralateral projection is stronger. So the stronger pathway is better able to inhibit the weaker pathway than the weaker inhibit the stronger — hence, right-ear preference.

Studies of dichotic listening in schizophrenia have produced somewhat variable results including reduction in normal REA, increased REA, reversal to LEA and sometimes no difference from normal REA (Wexler & Heninger, 1979; Bruder et al, 1995; Green et al, 1994; Wexler et al, 1991). Some evidence suggests that REA improves with clinical remission suggesting that it may be a state rather than trait feature (Wexler & Heninger, 1980). Other possibilities include clinical heterogeneity, medication status and sex differences in laterality (Wexler et al, 1991; Green et al, 1994; Bruder et al, 1995). Another problem is that many studies have failed to account for attentional components of lateral processing. Green et al (1994) and Loberg et al (1999) have shown that, when separated, patients with schizophrenia show both a reduced REA *and* inability to modulate REA by shifting attention between ears.

To date, only one study has examined dichotic listening and selective attention in early onset patients. Oie et al (1998) examined a small group of 19 adolescent patients and normal controls and found no significant difference between groups in either measures of either REA or attentional modulation. The authors suggested that loss of REA may be secondary to long term illness and occur after maturational changes in adolescence. The following research questions were addresses in this study:

- ◆ Do early onset patients show absence or reduction of normal right ear advantage auditory compared to normal controls?
- ◆ Are reductions in auditory laterality mediated by sex or age of onset?
- ◆ Does reduced hand preference have any mediating effect on auditory laterality?

2.3.2 Subjects

As language laterality differs on the basis of hand preference, only nominally right-handed subjects were examined in this analysis based on an arbitrary classification of right-handedness (preference for handwriting). In total, 57 of the original pool of 75 patients had available dichotic listening data and were classified as right-handed. From the available controls, only 49 subjects were classified as right handed, had dichotic data and could be matched for age and sex to the patient group. Subjects were classified as early onset if onset was before the age of 16 years, three months. This resulted in two groups (early $n=27$, peak $n=30$). There were no significant differences within the schizophrenic groups or between sexes with regard to duration of illness or chlorpromazine equivalent dose. The expected differences in age of onset ($p<0.001$) and age ($p<0.001$) were present between the schizophrenic groups, but in relation to age, neither schizophrenic group was significantly different from the control group (see Table 8).

TABLE 8: Sample 4: Subject characteristics

	Schizophrenia		Controls
	Onset < 16.03	Onset >16.03	
N (M/F)	27 15/12	30 20/10	49 25/24
Age (Years) M SD	15.68 1.64	20.89*** 5.50	18.26 5.33
Age of Onset (Years) M SD	14.45 1.38	19.18*** 4.10	
Duration of illness (months) M SD	17.60 19.89	21.4 28.35	
Chlorpromazine Eqv M SD	394.80 510.78	268.06 594.96	

***P<0.001

2.3.3 Method

Subjects were examined with consonant-vowel dichotic listening procedure (Hugdahl & Andersson, 1987). In this test, auditory stimuli were recorded on tape cassette, played via Marantz CP230 stereo cassette reorder via high quality Sennheiser HD420 headphones at 70 Db. Subjects were presented with combinations of six stop-consonant-vowel syllables (/ba/, /da/, /ga/, /pa/, /ta/, /ka/) which were presented simultaneously to each ear in three attentional conditions: Non-forced (NF), forced right (FR) and forced left (FL). In each case the subject was required to repeat the sound presented according to the attentional instruction. Two indexes of DL performance were derived for analysis. The first was the percentage of correct reports for each ear and condition (NF, FR, FL). Incorrect responses were not examined. Second, a laterality quotient was derived from the non-forced condition according to equation 2. According to the equation, a positive value indicates a right ear advantage whereas a negative value indicates a left ear advantage.

Equation 2:

Laterality Index =

RE correct – LE correct

RE correct + LE correct

X 100

2.3.4 Results

In order to establish the influence of sex and handedness upon dichotic listening performance, a preliminary ANOVA was conducted. Within subjects variables were attentional condition (non-forced, forced-right, forced-left) and ear (right, left), by group (early schizophrenia, peak schizophrenia, control), sex (male, female) and hand preference (right-pure, right-mixed). This analysis yielded significant main effects for group ($F [2, 92] = 9.13, p < 0.001$), condition ($F [2, 92] = 8.22, p < 0.01$), ear ($F [2, 92] = 18.90, p < 0.001$) and sex ($F [2, 92] = 4.98, p < 0.05$) as well as ear x condition interaction ($F [2, 92] = 24.32, p < 0.05$), and a strong trend to significance for condition x ear x group interaction ($p < 0.08$). There was no significant group x sex interaction. Simple main effects analysis revealed that all groups demonstrated a significant right ear advantage (REA) in the non-forced condition. However, in the early onset group, this did not withstand Bonferroni correction. Furthermore, early onset patients failed to modulate performance FR and FL attentional conditions, whereas the peak onset and comparison subjects significantly increased their REA in the FR attention condition, and switched to a left ear advantage (LEA) in the FL attention condition (see figure 4).

The preliminary analysis also revealed a significant group x handedness ($F [2, 92] = 6.72, p < 0.05$) and ear x group x handedness interactions ($F [2, 92] = 5.73, p < 0.01$). In order to examine the effects of condition more closely in relation to hand preference, a separate two-way analysis of variance (ANOVA) was performed according to a 3 (group) x 2 (hand preference) x 2 (ear) design, for the three attention conditions. Post hoc Tukey's (HSD) tests were performed for significant effects involving more than two means.

In the NF condition, there was a significant main effect of Group ($F [2, 104] = 3.77, p < 0.05$) and hand preference ($F [1, 104] = 5.33, p < 0.05$) on right ear performance. Overall, although all groups correctly reported more syllables from the right ear, thereby demonstrating normal right ear advantage, the early onset patients reported significantly fewer correct items than either later onset or control subjects. In the FR attention condition, there was a significant main effect of Group in relation to right ear stimuli ($F [2, 104] = 4.37, p < 0.05$). Despite identifying more syllables from the

right ear than the left, the early onset patients reported fewer correct items than the peak onset or control subjects.

The two-way interaction between Group and hand preference was significant but only in relation to left ear stimuli ($F [2, 104] = 4.47, p < 0.05$). Post hoc comparisons showed a significant difference between the pure and mixed handers only in the early onset group ($t [24] = 2.82, p < 0.01$). In the FL attention condition there was a strong trend toward main effect of Group for left ear stimuli ($p = 0.06$) but no other main effect or interactions.

In order to ascertain the relative proportions of patients demonstrating normal REA, groups were examined separately relation to the proportion of REA in the normal control sample and tested for significance with non-parametric Chi-square statistic. REA was determined on the basis of a positive score according to equation 2. In total, 74% of normal controls demonstrated REA. This figure is marginally below estimates of the normal population (80-90% Hugdahl, 1995). Comparatively, 63% of the early onset patients and 66% of the peak onset group demonstrated REA. There was no significant difference between groups in the relative proportion of REA. This was also the case when hand preference was examined, although the relative proportion of REA was (non-significantly) lower in mixed handed patients regardless of onset (see table 9).

Finally, in order to ascertain the influence of treatment related and illness related variables a series of correlations were performed between age, age of onset, duration of illness, and chlorpromazine equivalent dose in relation to dichotic performance. The results are shown in Table 10. As all of these variables were highly inter-correlated, a series of linear regression analysis were also conducted. These analyses revealed that age, age of onset, duration of illness all predicted some degree of performance. However, the strongest effects were seen in relation to age of onset. Most notably, age of onset significantly predicted non-forced right ear performance (see table 11).

Figure 4: Dichotic listening performance in by age of onset in early and peak onset patients and normal controls

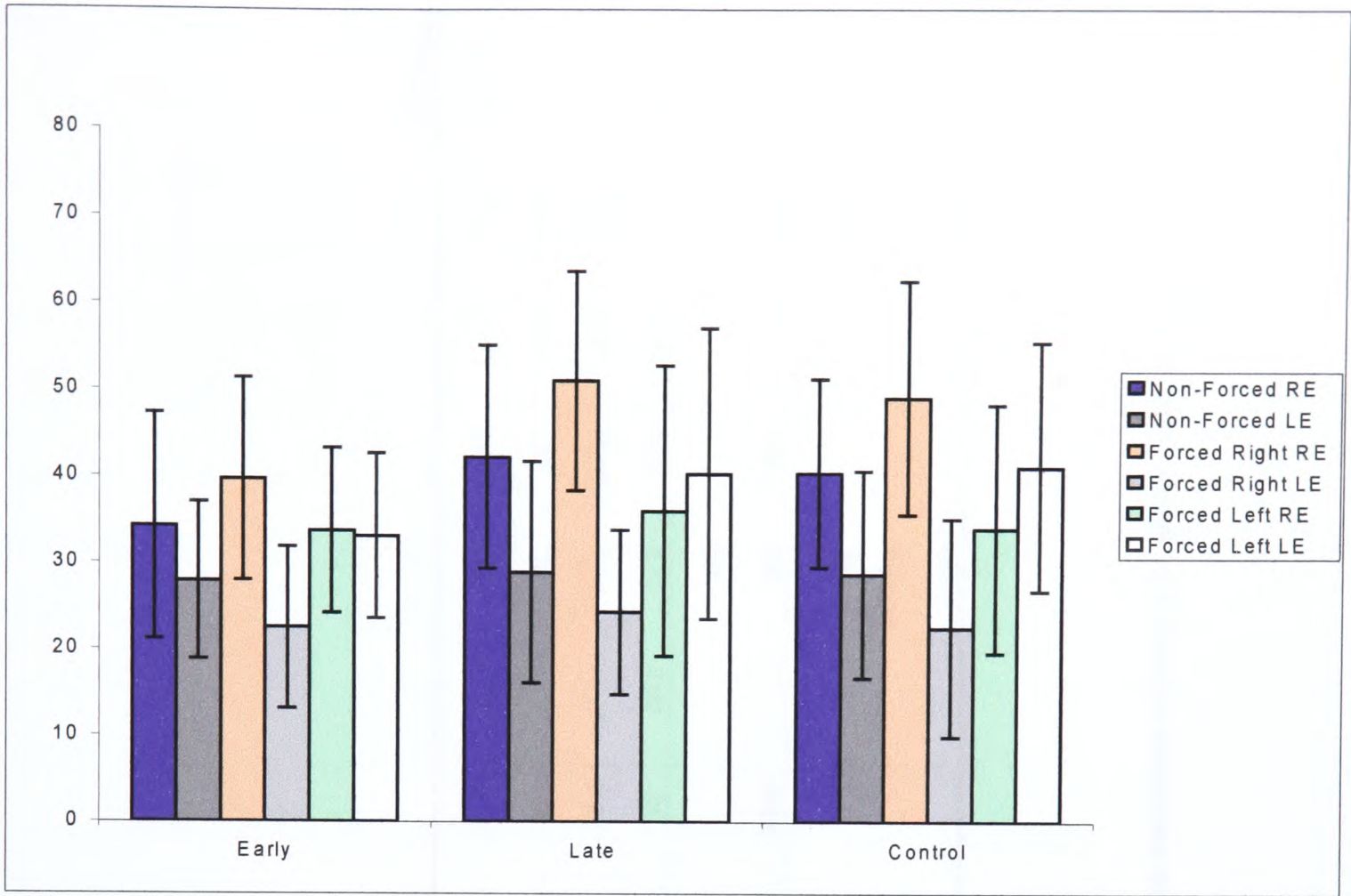


Table 9: Relative proportions of right ear advantage in relation to onset and hand preference

	Early Onset			Peak Onset			Control		
	Pure	Mixed	Total	Pure	Mixed	Total	Pure	Mixed	Total
REA	68.8%	50%	63%	73.3%	50%	66.7%	67.9%	81.0%	73.5%
LE / No Adv.	31.3%	50%	37%	26.3%	50%	33.3%	32.1%	19.0%	26.5%

Table 10: Correlation matrix of treatment and illness related variables in relation to dichotic measures.

	Age	Est Ons	Est Dur	CPZ eqv	Non- Forced Right	Left	Forced Right Right	Left	Forced Left Right	Left
Age	-	.92**	.63**	-.04	.14	-.04	.21	-.10	.13	.00
Est. Onset	-	-	.30*	-.05	.28*	-.02	.30*	-.06	.18	.11
Est Dur	-	-	-	-.00	-.17	-.12	-.11	-.15	.00	-.27*
CPZ EQ	-	-	-	-	-.15	.26*	-.30*	-.06	-.25	.30*

*P<0.05, **P<0.01, ***P<0.001

Figure 11 Results of individual entered linear regression analyses of dichotic listening performance in relation to treatment and illness related variables.

	Non- Forced Right			Non- Forced Left			Forced Right Right Ear			Forced Right Left Ear			Forced Left Right Ear			Forced Left Left Ear		
	Beta	Std Err.	T	Beta	Std Err.	T	Beta	Std Err.	T	Beta	Std Err.	T	Beta	Std Err.	T	Beta	Std Err.	T
Age	-9.38	4.44	-2.10*	8.23	4.10	2.00	.31	5.61	.05	-.22	4.35	-.05	-10.22	5.34	-1.91	5.16	5.59	.92
Est. Onset	10.63	4.48	2.37*	-8.16	4.14	-1.97	1.27	5.73	.22	.22	4.38	.05	11.00	5.38	2.04*	-4.20	5.64	-.74
Est Dur	.57	.35	1.61	-.70	.32	2.16*	-.18	.45	-.40	-5.95	-.11	-.17	.75	.42	1.79	-.64	.44	.15
CPZ EQ	-3.92	.04	-1.10	6.89	.003	2.09*	-1.05	.005	-2.31*	9.51	.35	2.71**	-8.23	.004	-1.92	1.12	.004	2.50*

*P <0.05, **P<0.01

2.3.5 Discussion

Right ear advantage in relation to early onset

Do early onset patients show absence or reduction of REA in early onset patients compared to normal controls? The adolescent patients in this sample did not perform normally on a DL task compared to later onset patients and age and sex matched controls. Although the majority of early onset patients showed evidence of a right ear advantage (REA) the magnitude of REA was reduced in relation to the other groups. This finding contradicts the only previous study of dichotic listening in adolescents in which no abnormality was detected 15 right-handed patients (Oie et al, 1999) and concurs with previous adult studies (Wexler et al, 1991; Bruder et al, 1995). Reduced REA could be a marker of left hemisphere disturbance. Studies of brain-damaged patients show that unilateral left disturbance can result in decreased REA, no ear advantage or a tendency to LEA (Walker & McGuire, 1980). Thus, *reduced* REA is consistent with a subtle dominant hemisphere disturbance and its presence in early onset patients suggests that it is not the consequence of long-term illness.

Modulation of ear advantage in relation to early onset

Compared with peak onset patients and controls, early onset patients' demonstrated inability to improve REA by focusing attention to or away from the dominant ear. This finding is in agreement with that of Green et al (1994) who found similar inability to modulate attention in adult patients and Loberg et al (1999) who found inability to shift to LEA using the same dichotic test. This deficit was not attributable to the effects of medication as increased medication significantly improved the ability to shift attention away from the dominant hemisphere. This is important in two ways; Developmentally, the ability to shift auditory attention away from REA has been linked to the maturation of language processing subsystems and the development of literacy. In normal children this ability is not present until at least 9 years of age, increases with the further development of reading skills, and may be delayed in developmental disorders of language (Hugdahl & Andersson, 1987; Lamm & Epstein, 1997). With respect to the schizophrenic sample, although it is difficult make conclusions on the basis of cross sectional data alone, the current anomalies may be interpreted as stemming from a failure of normal development that can be dated to before the onset

of the illness. Prospective and longitudinal studies would confirm this. Secondly, recent fMRI evidence has shown that the dominant hemisphere mediates both REA and forced attention. Shah et al, (2000) showed in normal subjects bilateral auditory cortex activation to dichotic stimuli but stronger left auditory cortex as well as left frontal and prefrontal activation when focussing attention. Thus, reduced REA and inability to shift attention are in line with lost dominance.

REA and REA modulation in peak onset

Are reductions in auditory laterality mediated by sex or age of onset? In this study, peak onset patients did not demonstrate a significant REA reduction or inability to modulate auditory attention when compared to normal, age and sex matched controls. This is at odds with the majority of literature relating to dichotic listening in adult schizophrenia. In examining the reasons for this incongruence, it is helpful to examine the handedness data. Normal studies show that right hand preference is associated with stronger language laterality and dominance (Milner, 1974; 1975). This is also true of this sample as, regardless of age of onset, mixed handed patients showed a tendency to loss of REA. Given that the later onset patients demonstrate a stronger hand preference overall, they are therefore less likely to show this effect. This last point suggests that reduced hand preference has a mediating effect on auditory laterality and indirectly supports the hypothesis that age of onset may predict the degree of ambilaterality in schizophrenia. Moreover, as with handedness, this may also suggest why there is considerable variability in findings within the literature.

Medication effects

It is noteworthy that a complex series of correlations were found between medication and chlorpromazine equivalent dose. These showed that increased medication dose increased left ear advantage as well as forced left performance but decreased performance in identifying stimuli in the right ear. One interpretation of this finding is that medication assists in suppression of competing contralateral and ipsilateral information processing from left hemisphere – in effect enhancing the ability of the right hemisphere to process information as David (1993) and others (Tomer & Flor-Henry, 1989) have suggested. This may also explain why right ear (left hemisphere) performance is reduced by increased medication.

Point summary of Chapter 2:

- The average IQ of early onset patients is 22 points below that of normal age and sex matched controls.
- 70% of early onset patients have full scale IQ's in the abnormal range but no significant VIQ-PIQ discrepancy in early onset patients.
- Greater reduction of verbal IQ is correlated with earlier age of onset.
- Early onset patients demonstrate significantly reduced relative hand skill in comparison to later onset patients. There was also a strong trend to reduced right hand preference in early onset patients relative to population norms.
- Early onset patients show an increase in the proportion of non-right eye preference and a significantly greater proportion demonstrate crossed hand-eye dominance in comparison to peak onset patients and normal controls.
- On average, mixed handed early onset patients showed an average but not significant FSIQ reduction of 9 points relative to purely right-handed early onset patients.
- Early onset patients showed reduced right ear advantage in dichotic listening relative to later onset patients and controls. Early onset patients did not significantly increase REA by attending focussing attention to that ear, whereas later onset patients and controls did.
- Greater reduction of REA and poorer performance when focussing attention to the right ear were significantly correlated with earlier age of onset.
- Mixed-handed patients demonstrate reduced REA relative to purely right-handed patients.

CHAPTER 3: DIVIDED VISUAL FIELD STUDIES OF LEXICO-SEMANTIC INFORMATION PROCESSING IN EARLY ONSET SCHIZOPHRENIA

Overview

In this chapter a series of divided visual field (DVF) experiments are described that were designed in order to examine hemispheric specialisation of word level language processing in early onset patients. The DVF approach was chosen for its ability to assess processing capacities of the hemispheres independently, to detect differences in laterality in small groups of subjects and for its' sensitivity to individual differences. In addition to the primary aim of examining laterality of language, each experiment was specifically designed in order to be sensitive to sex differences in lateralisation. The chapter begins with an introduction to word recognition studies in normal subjects and the DVF method for eliciting hemispheric specialisation. This is followed by a description of three separate experiments examining different aspects of lexical and lexico-semantic processing. The chapter ends with a general discussion. In order to ensure that each experiment was sensitive to sex differences and was appropriate for young patients with schizophrenia, pilot studies were performed prior to testing on patients. The results of these studies are also included.

3.0 General introduction

From the multitude of studies examining single word reading in both normal subjects and in defect states it appears that word recognition is multi-stage process involving a number of sub-processes. The dual route model of reading suggests that word-recognition can occur via two possible routes, the first, lexical route, gains access to word representations by translation of the orthographic forms of words directly to a visual lexicon leading to semantic access. The second, sub-lexical route, involves access via the phonological form through indirect grapheme-phoneme assembly (see figure 5) (Coltheart, Patterson, Marshall, 1987). This model suggests that word processing is performed in a fashion that adheres to the basic tenets of modularity as proposed by Fodor (1983). Modules are seen to possess a number of attributes. For example, they are considered to be innate, specific to a domain or function, neurally specific, and encapsulated such that each module can only perform functions for which they are specified. Specific aspects of modularity and the concept itself have been challenged, but the essential idea that word processing is performed in a distributed and modular fashion is supported by the weight of literature emanating from studies of selective cognitive impairments including dyslexia, agraphia, and semantic dementia.

Zaidel et al (1990), suggest that the various stages of the processing model can be examined in relation to laterality and cerebral specialisation of function (see figure 5). This is derived from divided visual field (DVF) of normal subjects that show relative specialisation of function for certain categories of word processing. The DVF technique involves the projection of stimuli to one or other visual hemi-field in order to ensure that information reaches the intended hemisphere independently and is (at least initially) processed therein (figure 6). For this to be achieved, the subject must maintain fixation on a central point while targets are presented to the left or right visual field at a rate faster than the eye can saccade (approx < 180 milliseconds). Responses are made via a button press and reaction time and accuracy data provide an index of each hemisphere's capacity to identify the presented stimulus set.

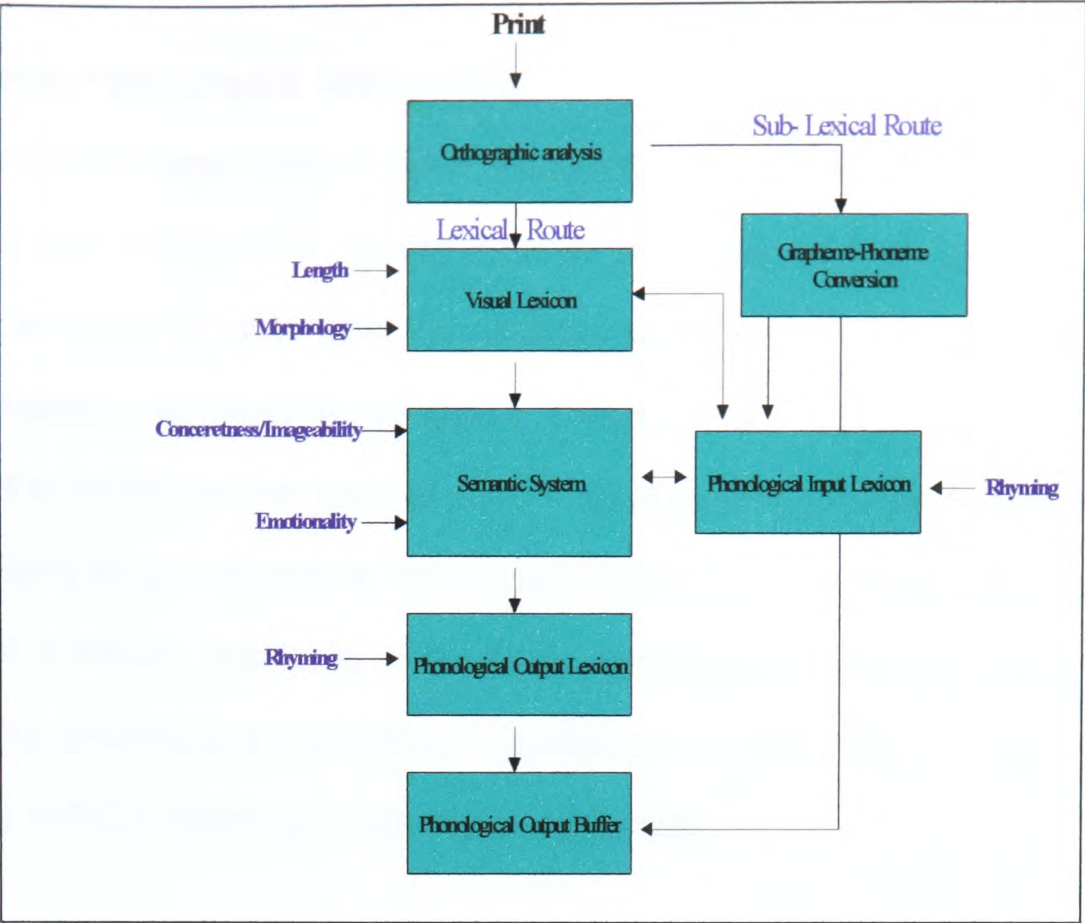


Figure 5: The dual route model of lexical access adapted from Zaidel et al (1990).

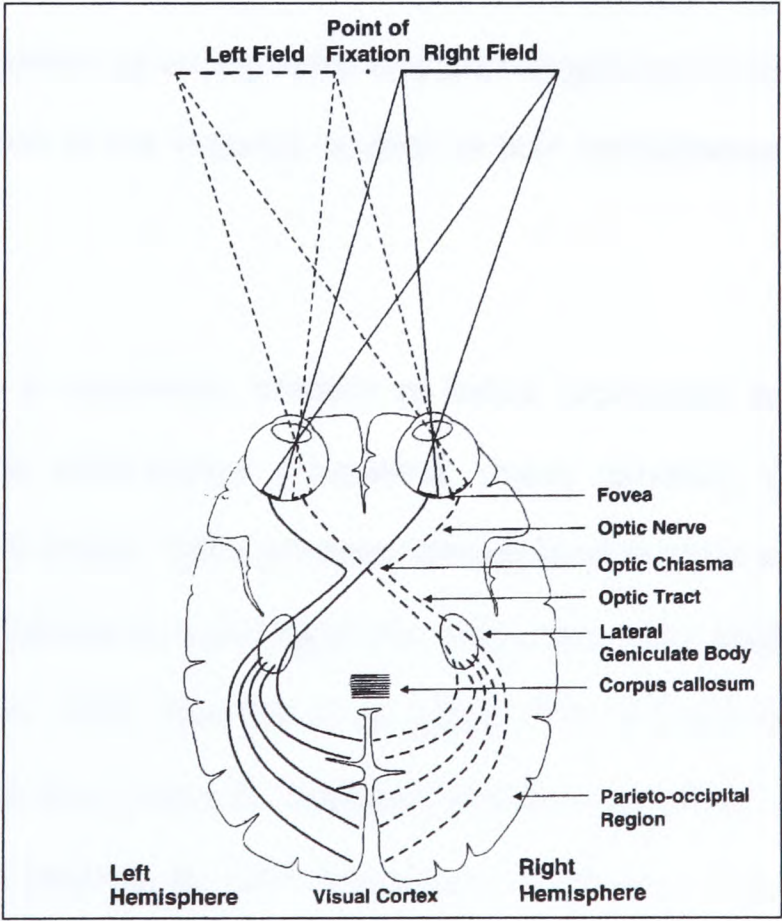


Figure 6: Schematic representation of the visual pathways involved in the divided visual field technique (Kimura,1992).

3.0.1 Lexicality, Phonology & Orthography

One distinction that has been made in terms of laterality is in the relative hemispheric specialisation of phonological and orthographic reading. Studies of normal subjects typically show a natural processing advantage in reaction time and accuracy when word recognition is compared to non-word (pronounceable pseudoword) recognition (Young et al, 1984, Koenig et al, 1992). This 'lexicality' effect is considered the result of a time limited process in which the orthographic lexicon is initially consulted for an appropriate lexical match based upon the visual features of a word, but in the event of a failure, resorts to a grapheme to phoneme conversion (Taft, 1991). When orthographic and phonological processing is examined in DVF studies of right-handed normal subjects, strong RVF/LH advantage is usually found for both.

While phonological processing appears to be especially dependent upon the left hemisphere¹(Young et al, 1984), accumulating evidence has shown that the right hemisphere is also capable of limited orthographic recognition when words are short, frequent, and concrete in nature (Joanette et al, 1990; Beeman & Chiarello, 1998). DVF studies employing such stimuli often report no hemi-field difference in reaction time or accuracy and, infrequently, show LVF/RH advantage. Thus, the comparison of orthographic and phonological processing provides a means of accessing the lateralisation of the linguistic abilities of both hemispheres and their respective dissociations.

An important consideration in examining laterality of lexical processing is the question of sex differences. With respect to phonological processing, males generally show strong RVF/LH laterality effects (Crossman & Polich, 1988) whereas females tend to show weaker or no laterality effect suggesting that the substrates subserving phonology are more bilaterally represented in females (Bradshaw & Gates, 1978; Weekes et al, 1999). This is supported by evidence that females are less susceptible than males to language problems following left hemisphere insult (McGlone, 1978) and, more recently, by fMRI investigations showing greater bilateral activation

¹ Although Chiarello et al, (1999) have argued that the right hemisphere also possesses some phonological abilities.

when performing phonological decomposition tasks in females, whereas in males this is more restricted to the left side (Shaywitz et al, 1995; Overmeyer et al, 1999).

With respect to orthographic processing, although females generally show greater right hemisphere proficiency than males (Majeres, 1999), the degree of right hemisphere involvement between the sexes appears to differ depending upon the semantic content of the words (e.g., concreteness, imageability, emotionality) (Joanette et al, 1990). Some functional imaging investigations (Pugh et al, 1996; Overmeyer et al, 1999) but not all (Frost et al, 1999) support the distinction of sex and lateral differences in semantic ability. Together, these findings suggest that when examining for lexicality effects, special attention should be paid to both the sample under investigation the and semantic composition of the stimuli as these appear have strong bearing on the degree of involvement of distributed lexical sub-processes.

3.0.2 Imageability

In language, semantics comprise the hierarchy of associations, word meanings and concepts underlying both expressive and receptive abilities. In early development, knowledge of the world and the material objects within it is acquired through direct sensory experience. Words intrinsically entail reference to these experiences but differ in the degree to which they evoke them (e.g. mouse – mammal). Additionally, many words are abstract, do not possess sensory attributes and are dependent upon the context in which they appear (e.g. there, them). In linguistics, the degree to which words differ in their relationship to sensory experience is referred to as word *imageability*.

Divided visual field studies of normal subjects show that highly imageable words are processed faster and more accurately than low imageability words - the so called 'imageability effect'. Although at least two DVF studies of normal subjects have failed to find this effect (Lambert & Beaumont 1983; Howell & Bryden, 1987), most find equal or LVF/RH superiority for highly imageable words in combination with a selective LVF/RH disadvantage for words of low imageability (Ellis & Shepherd, 1974; Hines et al, 1977; Day; 1977; Day 1979; Patterson & Marcel, 1977; Bruyer & Strypstein; 1985; Eviatar et al 1990). These studies suggest that the processing of

low imageability words is highly lateralised to the left hemisphere whereas highly imageable words may be processed in either hemisphere. This division of labour is supported by some (Wise et al, 2000) but not all (Beauregard et al, 1997; Kiehl et al, 1999) functional imaging studies.

Sex differences in imageable word recognition have been reported. Young & Ellis (1985) found a sex by VF interaction in imageable word recognition consistent with stronger laterality in males. In contrast, McMullen & Bryden (1987) failed to find LVF/RH advantage in highly imageable word recognition in females, but did not examine males within their sample. However, subsequently, Eviatar et al (1990) found opposite patterns of processing dissociation in males and females with respect to word concreteness. In this case, males showed a strong RVF/LH advantage for low imageability words whereas females showed an LVF/RH advantage for highly imageable words. So the bilateral distribution of lexical processing provides a means of accessing sex differences in laterality.

3.0.3 Emotionality

Emotionality refers to the degree to which a word represents or evokes an emotion or emotional response. Similar to imageability, emotionality is multimodal in nature and derives in part from sensory experience. In recent decades, the special role of the right hemisphere in processing lexical components of emotion has become recognised (Borod et al, 1992a; 1998). Studies of normal subjects show that emotionally negative words are processed faster and more accurately than emotionally neutral words if presented to the LVF/RH² and more accurately recalled when targets are preceded by LVF/RH prime (Brody et al, 1987; Van Strien & Morpurgo, 1992; Van Strien & Heijt, 1995; Richards et al, 1995). Studies of brain-damaged subjects show that right hemisphere damage impairs the discrimination and identification of emotional words (Semenza et al, 1986; Borod et al, 1992b; Cicero, 1997) whereas left hemisphere damage does not (Landis & Regard, 1990).

² Although one study has demonstrated a significant RVF/LH advantage for emotional words (Strauss 1983).

Like imageability, emotional word processing may be influenced by sex differences in laterality but few studies have directly examined this. Graves et al (1981) found a significant VF × emotionality × sex interaction indicating an overall LVF/RH advantage for emotional words in normal males whereas normal females showed an RVF/LH advantage. In another study, Eviatar & Zaidel (1988) reported the opposite pattern showing that females were faster and more accurate to LVF/RH decisions in short (4 letter) words whereas males showed RVF/LH superiority. Sex differences that favour females have been found in right hemisphere emotional perception within other modalities, including face and speech prosody, (Crucian and Berenbaum, 1998). These tend to correlate well with right hemisphere lexical emotionality in normal controls but not in brain damaged subjects (Borod et al, 1998).

3.0.4 Relevance of lexicality, imageability and emotionality to schizophrenia

DVF studies of lexico-semantics in schizophrenia differ markedly in terms of hypotheses, stimuli and sample composition. Nonetheless, it appears that basic level phonological and orthographic processing is intact in adults with schizophrenia. RVF/LH advantage has been reported in patients when tested with a letter identification tasks (Beaumont & Dimond, 1973), and phonological tasks decomposition (Colborn & Lishman, 1979; Mohr et al 1999). Such findings would appear to argue against a widespread disturbance of the dominant hemisphere, but conflict with the evidence from the dichotic literature suggesting loss of dominant hemisphere advantage in phonological processing.

A substantial body of evidence suggests that semantic memory is disturbed in schizophrenia. Firstly, semantic anomalies are consistently observed in verbal fluency (Joyce et al, 1996; Rossell, et al, 1999), confrontational naming (Barr et al, 1989; McKay et al, 1996) and possibly sentence level speech (Oh et al – unpublished manuscript). Additionally, semantic anomalies are observed in aspects of receptive language including reading comprehension (Silverberg-Shalev et al, 1981), categorisation (Chen et al, 1994) and (inconsistently) in semantic priming (Manschreck et al, 1988; Chapel et al, 1990). The possibility that these anomalies are somehow influenced by altered laterality is supported by the aforementioned paper by Weisbrod et al (1997) who found evidence of

RVF/LH indirect priming in patients with schizophrenia but not controls. This suggests that remote semantic associations may be disorganised in the left hemisphere and that loss of dominance may influence the ability to access left hemisphere word level semantic information. Given that post-mortem and neuroimaging studies of schizophrenia point to pathological changes in areas of heteromodal temporal cortex involved in lexical and semantic processing (Nobre et al, 1994; Nobre & McCarthy, 1995; Binder et al, 1997; Wise et al, 2000) and that imageability is often dissociably impaired in pathological states that affect the temporal neocortex (Warrington, 1981; Coltheart, et al 1980), it is important to examine this process in early onset patients.

There is some evidence to suggest that right hemisphere lexical processing could also be altered early onset patients. Oepen et al, (1987) performed a DVF experiment of acute patients in which unilateral emotional distractors or no distractors followed bilaterally presented words or faces. The authors found that performance was impaired in the patient group when emotional distractors were presented to the LVF/RH but not RVF/LH. This suggested RH hypersensitivity to emotional stimuli. In a related study, Leonhard and Brugger, (1998) demonstrated enhanced semantic overactivation of the right hemisphere for concrete words in schizotypal subjects with a high susceptibility to abnormal beliefs or experiences. This suggested that altered laterality may result in loss of normal inhibition over the right hemisphere thereby allowing RH semantic material gain access to consciousness (Nasrallah, 1985). In other work, Cutting & Murphy (1990) showed that patients with schizophrenia are poor at judgements of lexical similarity for emotional words and a range of studies show abnormalities in face-emotion and speech-emotion processing in patients with schizophrenia (Cutting, 1994).

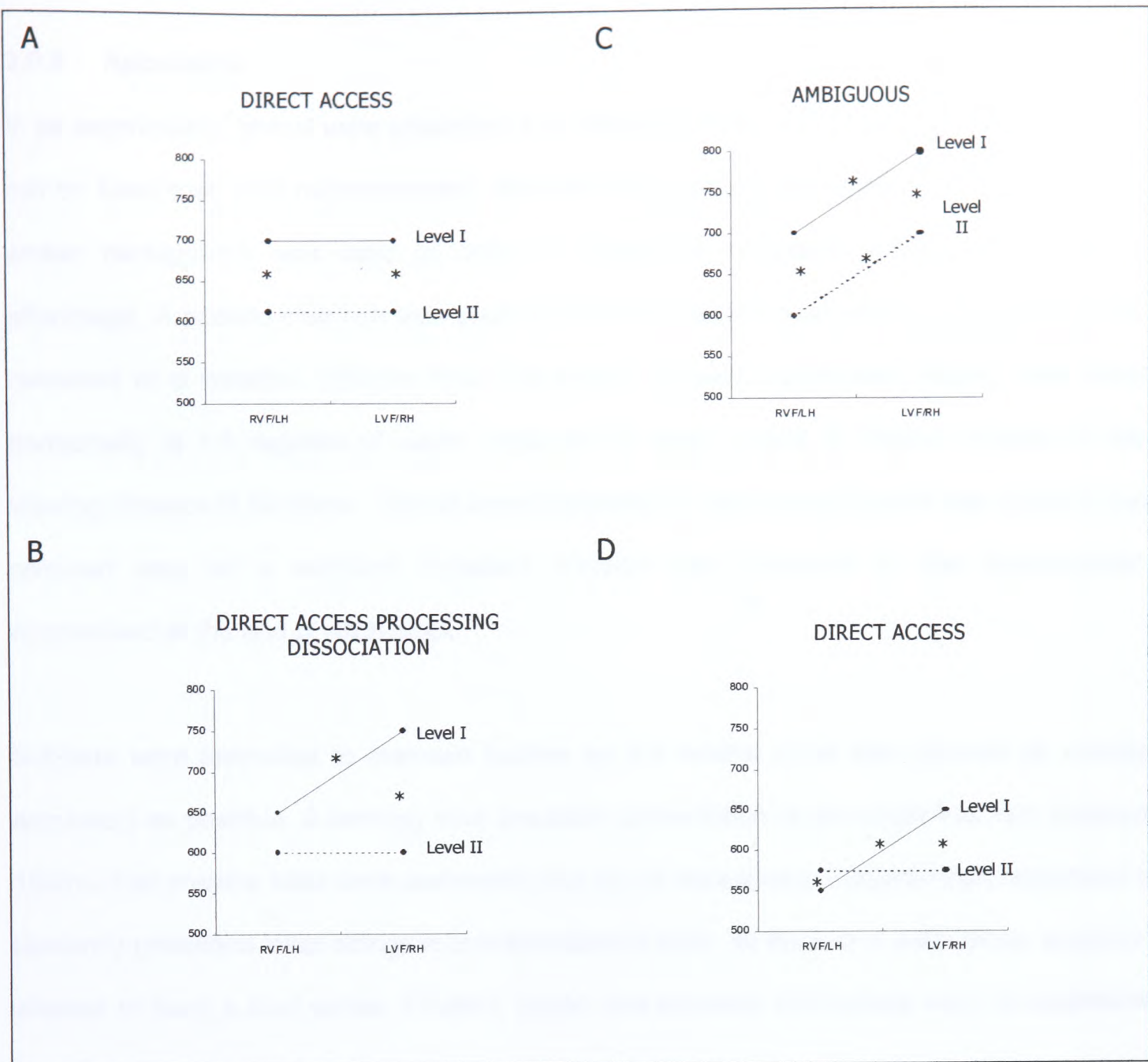
In the following experiments, lexicality, imageability and emotionality are examined separately in order to assess the relative linguistic competencies of *both* cerebral hemispheres in early onset patients. In order to be valid with children and adolescents each task was designed to be relatively simple to perform and matched as closely as possible for difficulty. The aim was to reduce the potentially confounding effects of higher-level abilities such as attention, episodic memory, and executive function. However, before turning to the individual experiments, a summary of methodology is necessary.

3.0.5 DVF Method

Differences in the relative speed and/or accuracy of responses to laterally presented stimuli are interpreted as evidence of the relative or absolute specialisation of one or other hemisphere. To some extent, this entails an assumption that both left and right cerebral hemispheres are independently capable of processing, interpreting and acting upon environmental or internally generated information (spatial, linguistic or mnemonic) and thus each hemisphere functions as a relatively independent information processor acting either alone, in parallel and/or in concert with the opposite hemisphere (Zaidel, 1985; 1990).

Zaidel (1990) has proposed a two limit case model to account for lateral differences in performance: Firstly, the assumption of *direct access* is that an incoming stimulus will be processed within whichever hemisphere it reaches regardless of differences in specialisation. In effect, this means that when a stimulus reaches the hemisphere specialised in processing that information, a performance advantage will occur. This also assumes that if the specialised hemisphere does not receive the information, inefficient processing will result in slower reaction time and/or error (see figure 6). Second, the assumption of *callosal transfer* is that the specialised hemisphere always processes information, but in the event that information is not received by the specialised hemisphere it will be projected via the cerebral commissures to the opposite hemisphere for processing. This transfer process results in a delay or degradation in the signal and is reflected in reduced reaction time and/or accuracy.

Theoretically, direct access and callosal transfer can be inferred on the pattern of response data and variable interactions. In the case of one experimental variable (Y) with two levels (I,II), direct access (i.e. equal competence) is assumed if there is no difference between visual hemifields as in the case with figure 7a. Where there is Y x VF interaction or processing dissociation such as in 7b, both direct access and callosal transfer are assumed. Figure 7c represents an ambiguous pattern in which the RVF/LH is superior at both levels but it is unclear if this is due to poor RH processing or callosal transfer. Figure d) shows direct access but a RVF/LH advantage at level I.



Figures 7a-d: Potential interactions of an experimental variable (Y) with two levels by hemifield (VF) in divided visual field experiment. Adapted from Zaidel, Clarke and Suyenobu (1990).

3.0.6 Apparatus

In all experiments, stimuli were presented and individual responses recorded using Superlab (v1.2) run on Macintosh LCII microcomputer. Reverse video Macintosh monitor (black stimulus against amber background) was used in order to counteract luminance effects and reduce retinal afterimage. A padded chin rest was used in order to maintain head position and ensure that eyes remained at a constant distance from the screen. In each experiment targets were presented horizontally at 1.5 degrees of visual angle at the edge closest to fixation creating a standard viewing distance of 59-60cm. Stimuli were responded to with the right index and middle fingers via coloured keys on a standard keyboard. Fixation was monitored by the experimenter and emphasised at the end of each block.

Subjects were instructed to maintain fixation on the central cross and respond as quickly and accurately as possible. A warning tone preceded presentation of the target that was displayed for 150ms. Ten practice trials were performed prior to the experiment. Subjects then responded to the randomly presented letter strings in counterbalanced trials. At the end of each block, subjects were allowed to have a brief pause. Fixation, speed and accuracy instructions were re-emphasised at each break

3.0.7 Stimuli

Word stimuli were selected from the MRC Psycholinguistic Database Version 2.0 (Coltheart, 1981, http://wapsy.psy.uwa.edu.au/uwa_mrc.htm). In each experiment, words were as closely as possible according to standard norms contained within the database (individual stimuli sets are described in the experiment sections). Words were randomly assigned to RVF and LVF presentations and there were no significant differences in ratings when examined by visual field of presentation. Regular non-words were constructed by altering one or two vowels of the target word. Each word-nonword pair was therefore matched on length number of phonemes and syllables.

3.0.8 Data Analysis

Reaction time (RT) was calculated for each variable-stimulus set on the basis of mean reaction times minus errors. The problem of long reaction time and outlier responses in both normal and schizophrenic studies remains unresolved (Ratcliffe et al, 1993). A number of statistical methods are used to overcome this problem including using median RT's, logarithmic transformation and data trimming (high-low reaction times). Review of this literature suggested that the best method for the current study was that of data trimming. So, in the following sections, analyses were conducted on the basis of data clipped below 200 milliseconds and above 2000 milliseconds. These reaction times were therefore considered as error data and excluded from mean calculations. Accuracy of response was examined as the mean percentage of correct responses according to the above criteria. All corrected means are examined using repeated measures analysis of variance (ANOVA). In each case, 2 x 2 ANOVA's are conducted with the experimental condition and visual field as within subjects variables, with sex and group as a the between groups variable. As the design involved only two variables, Tukey post hoc tests were not calculated. Instead, univariate effects were examined with independent or paired t tests.

3.0.9 Subjects

3.0.9.1 Pilot studies

For the preliminary validation studies, 40 undergraduate and postgraduate students were recruited from the Departments of Experimental Psychology and Psychiatry at the University of Oxford. Subjects had no history of neurological illness, head injury or psychiatric illness. Each was assessed for handedness with the Annett Handedness Inventory and estimated IQ was determined with the National Adult Reading Test (NART) (Nelson 1982).

Of the original 40 subjects, 32 were considered to be consistently right handed, the remaining 8 had a pattern of left or inconsistent handedness and were excluded. There were no significant differences in age or IQ (see table 11).

Table 11: Sample 5: Subject characteristics for DVF pilot studies

	N	Age (M/Sd)	Age Range (Min-Max)	NART-IQ (M/Sd)	IQ Range (Min-Max)
<i>Pilot Study</i>					
Males	13	21.8 (3.8)	19-31	117.5 (3.8)	110-124
Females	19	23.1 (4.2)	19-34	115.7 (23.1)	110-123
Total patients	32	22.6 (1.1)	19-34	116.4 (3.6)	110-124

3.0.9.2 Patient Studies

Data was acquired across the three experiments from 20 (10 male/10 female) early onset patients from the original subject pool described in chapter two. No significant within group sex differences were present in the following variables; age, age of illness onset, duration of illness or medication at the time of testing. Patients were compared to 20 normal control subjects selected from the original sample and closely matched for age, sex and education but not IQ (see table 12). As variability of lateralisation is increased significantly by the inclusion of left handed subjects and may interact with sex in potentially complex ways, only nominally right handed patients and controls were included in these studies.

Table 12: Sample 6: Characteristics of early onset patients and controls for DVF studies

	N	Age	FSIQ	Hand Pref	Age of onset	Duration (Y/M)	CPZ Eqv.
<i>Schizophrenia</i>							
Males	10	16.6 (.69)	83.2 (13.1)	22.9 (1.2)	15.8 (.65)	7.3 (4.0)	515.9 (295.8)
Females	10	15.7 (1.4)	84.0 (13.7)	19.7 (3.3)	15.2 (1.4)	9.7 (10.4)	410.0 (307.5)
Total patients	20	16.2 (1.1)	83.2 (10.9)	21.1 (2.9)	15.4 (1.1)	8.5 (7.6)	460.1 (298.5)
<i>Controls</i>							
Males	10	16.4 (1.1)	106.1 (14.5)	21.7 (2.7)			
Females	10	15.6 (1.6)	109.1 (12.7)	20 (3.3)			
Total controls	20	16.0 (1.4)	107.5*** (13.3)	20.9 (3.0)			

*P<0.05, **P<0.01, ***P<0.001

EXPERIMENT 1: LEXICALITY, PHONOLOGY & ORTHOGRAPHY

3.1.1 Aim & Hypotheses

This DVF task was performed in order to directly compare directional asymmetries in orthographic (lexical) and phonological (sub-lexical) word recognition in early onset patients. The general hypothesis for this experiment were:

- ◆ Early onset patients would show a reduction of normal lexicality effect relative to controls.
- ◆ Both male and female early onset patients would show reduction of RVF/LH processing advantage in both phonological and orthographic recognition relative to controls.
- ◆ As a consequence of normally greater lateralisation of these processes to the left hemisphere in males, RVF/LH processing would be more severely affected in early onset males.
- ◆ As a consequence of more bilateral (or right) representation of phonological processes in females, female patients would show faster/more accurate LVF/RH non-word recognition than RVF/LH non-word recognition.

3.1.2 Stimuli

30 frequently occurring, concrete four letter words were selected from the MRC Psycholinguistic Database Version 2.0 (Coltheart, 1981) and matched for length, number of phonemes, syllables and frequency of occurrence. Where norms were available, words were also matched closely on familiarity, meaningfulness and age of acquisition. Words were randomly assigned to RVF and LVF presentations and there were significant differences in ratings when examined by visual field of presentation. 30 regular non-words were constructed by altering one or two vowels of the target word. Each word-nonword pair was therefore matched on length number of phonemes and syllables. Targets were presented horizontally at 1.5 degrees of visual angle at the edge closest to fixation at a viewing distance of 60cm.

Subjects were instructed to maintain fixation on the central cross and respond to real words when recognised. A separate button press was required for non-words. A warning tone preceded presentation of the target that was displayed for 150ms. Ten practice trials were performed prior to the experiment. Subjects then responded to the 60 randomly presented letter strings in counterbalanced 2 x 30 trials (15/15 words/non-words). At the end of each block, subjects were allowed to have a brief pause. Fixation, speed and accuracy instructions were re-emphasised at each break.

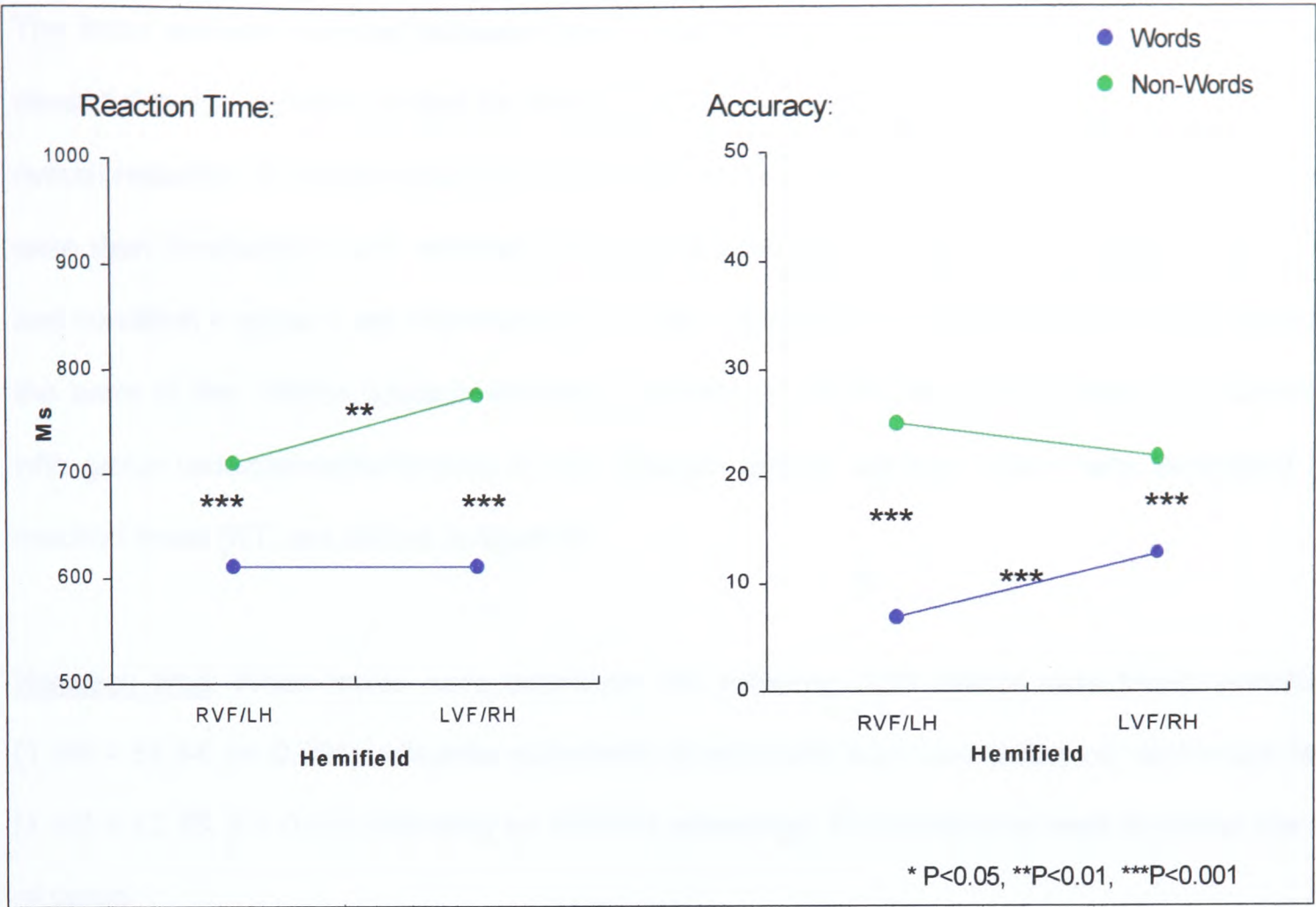
3.1.3 Results: Pilot study

Separate 2 x 2 repeated measures ANOVA were conducted. Within subjects variables included visual field (RVF/LVF) and condition (word/nonword) with sex as the between groups variable. Line charts illustrating mean reaction time (RT) and accuracy (A) are shown in figure 8.

Reaction time: The following significant main effects were present: VF ($F [1,30] = 5.74, p < 0.05$) indicating an overall RVF/LH advantage, condition ($F [1,30] = 124.4, p < 0.001$) indicating a word over non-word advantage, and sex ($F [1,30] = 6.55, p < 0.05$) indicating overall female superiority. As expected, a significant condition $\times$ VF processing dissociation was found ($F [1,30] = 9.05, p < 0.01$). Post hoc tests showed no hemifield difference in word processing, but a RVF/LH advantage in non-word processing ($t [31] = -3.60, p = 0.001$). The predicted VF $\times$ condition $\times$ sex interaction did not reach significance.

Accuracy: Only one main effect was detected in accuracy; Regardless of hemifield, subjects made significantly more errors in making non-word relative to word decisions ($F [1,30] = 63.45, p < 0.001$). A significant Condition $\times$ VF processing dissociation ($F [1,30] = 8.47, p < 0.01$) indicated that fewer errors were made to RVF/LH words ($t [31] = -2.79, p < 0.001$), but there was no hemifield difference non-word decisions. No sex interaction was observed.

Figure 8: Pilot data showing reaction time and accuracy for word/non-word lexical decisions.



3.1.4 Results: Patient Study

The initial analysis involved between groups one-way comparison of mean RT collapsed across visual fields and condition to test for medication induced slowing of reaction time. This revealed no overall reduction in baseline reaction time in the patient group. 2×2 repeated measures ANOVA were then conducted which revealed strong trends toward condition $\times$ visual field $\times$ sex ($p=0.08$) and condition $\times$ group $\times$ sex interactions ($p=0.08$). Separate 2×2 ANOVA's were then repeated on the basis of sex. Within subjects variables included VF (RVF/LVF) and Condition (word/nonword) with group (schizophrenia/control) as the between groups variable. Line charts illustrating mean reaction times (RT) are shown in figure 9.

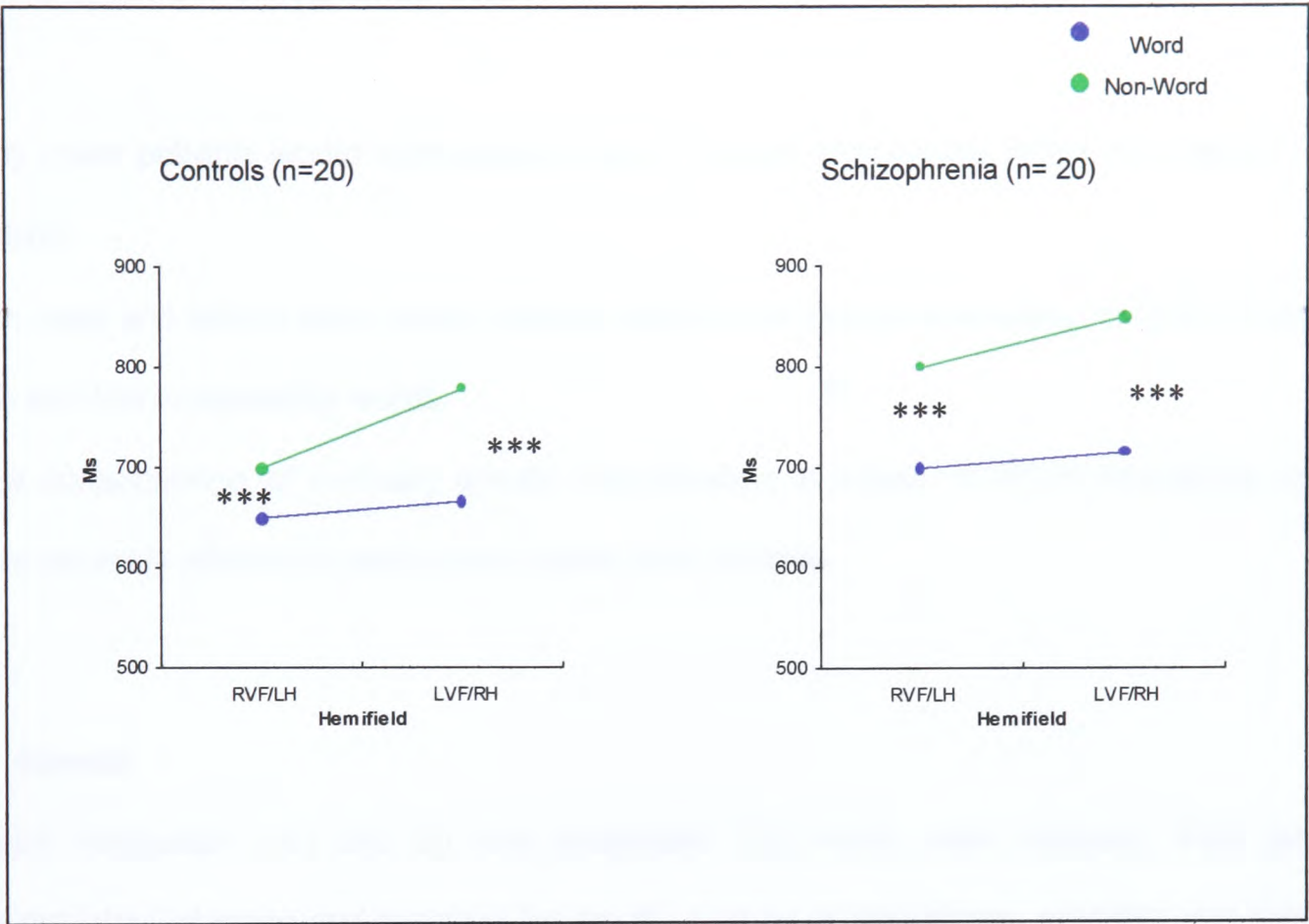
Reaction time: When males were examined, the following main effects were found; condition ($F [1,18] = 51.84, p < 0.001$) indicating superiority of word over non-word decisions, and visual field ($F [1,18] = 12.78, p < 0.01$) indicating an RVF/LH advantage. No interactions were found on the basis of group.

When the females were examined, a condition main effect was found ($F [1,18] = 47.03, p < 0.001$) but there was no main effect for visual field. A trend towards VF $\times$ condition $\times$ group interaction was observed ($p=0.10$). On the basis of combined groups three-way interaction, post hoc testing was permitted. This analysis revealed a strong pattern of lateralisation in both male controls and patients indicating superior RVF/LH processing of both words and non-words. Female controls and patients demonstrated a bilateral pattern showing no hemifield difference in either words or non-words. Thus, despite a trend to sex by group interaction effect there was no significant difference between the sexes or the groups with respect to overall pattern of performance.

Accuracy: The following main effects were found in males; condition ($F [1,18] = 22.05, p < 0.05$) [word < non-word]; visual field ($F [1,18] = 6.42, p < 0.05$) [RVF < LVF] and group ($F [1,18] = 9.21, p < 0.01$) [controls < patients]. A strong trend to VF $\times$ group interaction ($p = 0.08$) suggested that male patients tended to make more errors in recognising words in the LVF/RH ($t [9] = -2.31, p < 0.05$).

Females showed a significant main effect for condition ($F [1,18] = 47.03, p<0.001$) but no other main effect. There was a strong trend to $VF \times condition \times group$ effect ($p=0.06$).

Figure 9: Comparison of reaction time for word-nonword lexical decisions in early onset patients and normal controls.



EXPERIMENT 2: IMAGEABILITY

3.2.1 Aim & Hypotheses

The aim of this experiment was to investigate the integrity of lexico-semantic organisation in early onset patients using an imageability paradigm. The following predictions were made:

- ◆ Early onset patients would demonstrate loss of normal imageability effect compared to normal controls
- ◆ Both male and female early onset patients would show poorer processing in RVF/LH presented high and low imageability words.
- ◆ As a consequence of normally greater lateralisation in males, RVF/LH processing would be more severely affected in early onset males than females.

3.2.2 Stimuli

30 'highly imageable' (HI) and 30 'low imageable' (LI) words were selected from the MRC Psycholinguistic Database and matched for length, number of phonemes, syllables and frequency. Where possible, words were matched closely on familiarity, meaningfulness and age of acquisition. No significant differences were found in ratings between word groups except for imageability and concreteness. No significant differences in ratings were present by field of presentation. In addition, 60 regular non-words were constructed by altering one or two vowels of the target word. The 120 letter strings were presented in four counterbalanced blocks of 30 trials (15 words and 15 nonwords), randomly presented to the left or right of fixation.

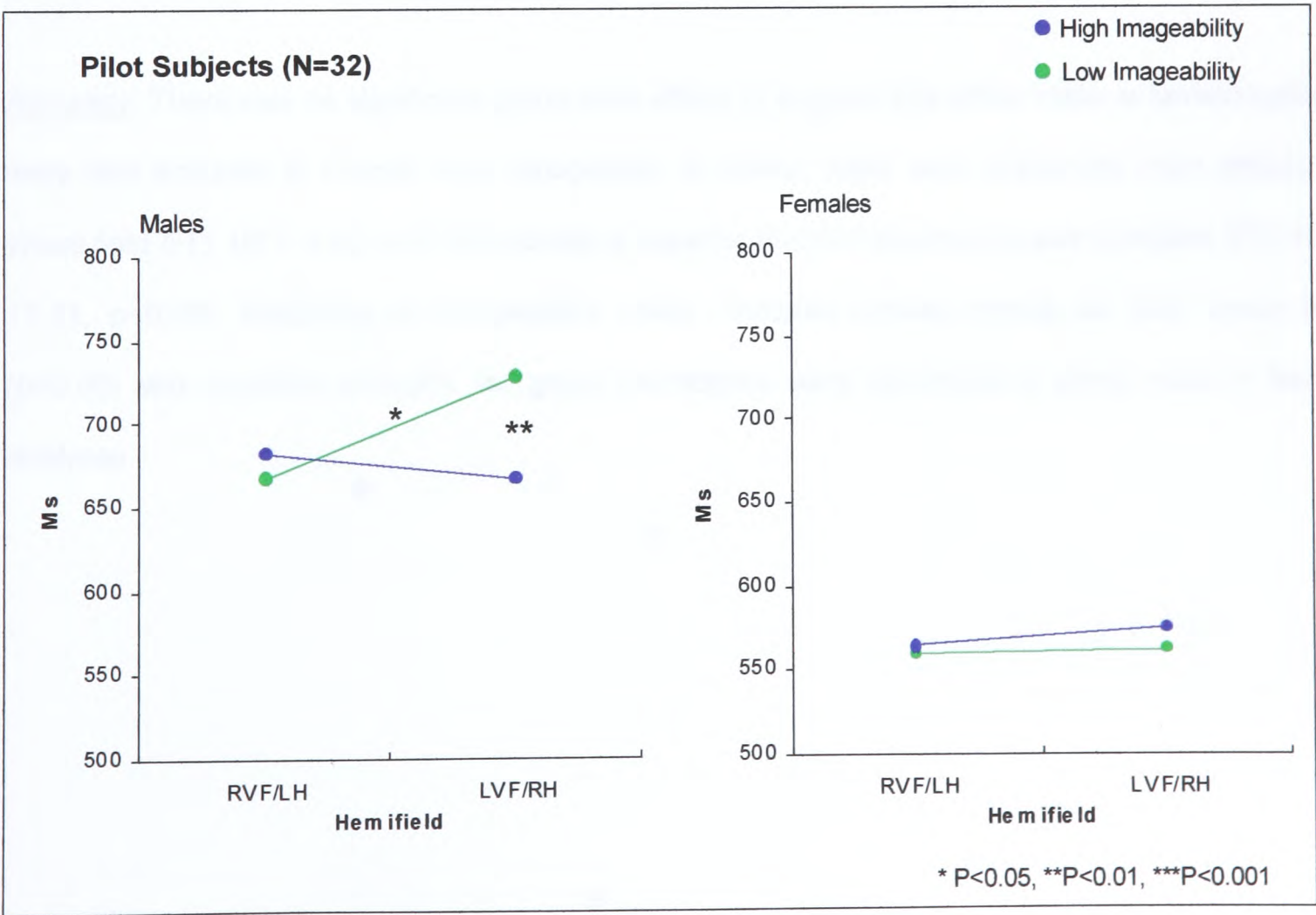
The same instructions and procedure were used as in the previous experiment. Ten practice trials were performed prior to the experiment. At the end of each block, subjects were allowed to have a brief pause when fixation, speed and accuracy instructions were re-iterated.

3.2.3 Results: Pilot study

Reaction time: Repeated measures ANOVA was performed with visual field (RVF, LVF), condition (High, Low imageability or HI LI) as within subjects variables, and sex (M,F) as the between subjects variable. There were no significant main effects but two strong trends to significance were found for condition × sex ($p=0.06$) and VF × condition × sex ($p=0.09$) interactions. Post hoc testing revealed that males (but not females) demonstrated a selective disadvantage in reaction time to LI words presented to the LVF/RH relative to RVF/LH presented words ($t [12] = -2.88, p<0.05$). Thus, male patients demonstrated the predicted laterality effect in low imageability words whereas the female performance indicated bilateral ability.

Accuracy: Repeated ANOVA examining of accuracy revealed a significant main effect for visual field ($F[1,30] = 11.81, p<0.01$) indicating that all subjects were more accurate in making lexical decisions to RVF/LH presentations. No other results attained significance.

Figure 10: Pilot data showing mean reaction time for high/low imageability lexical decisions by sex



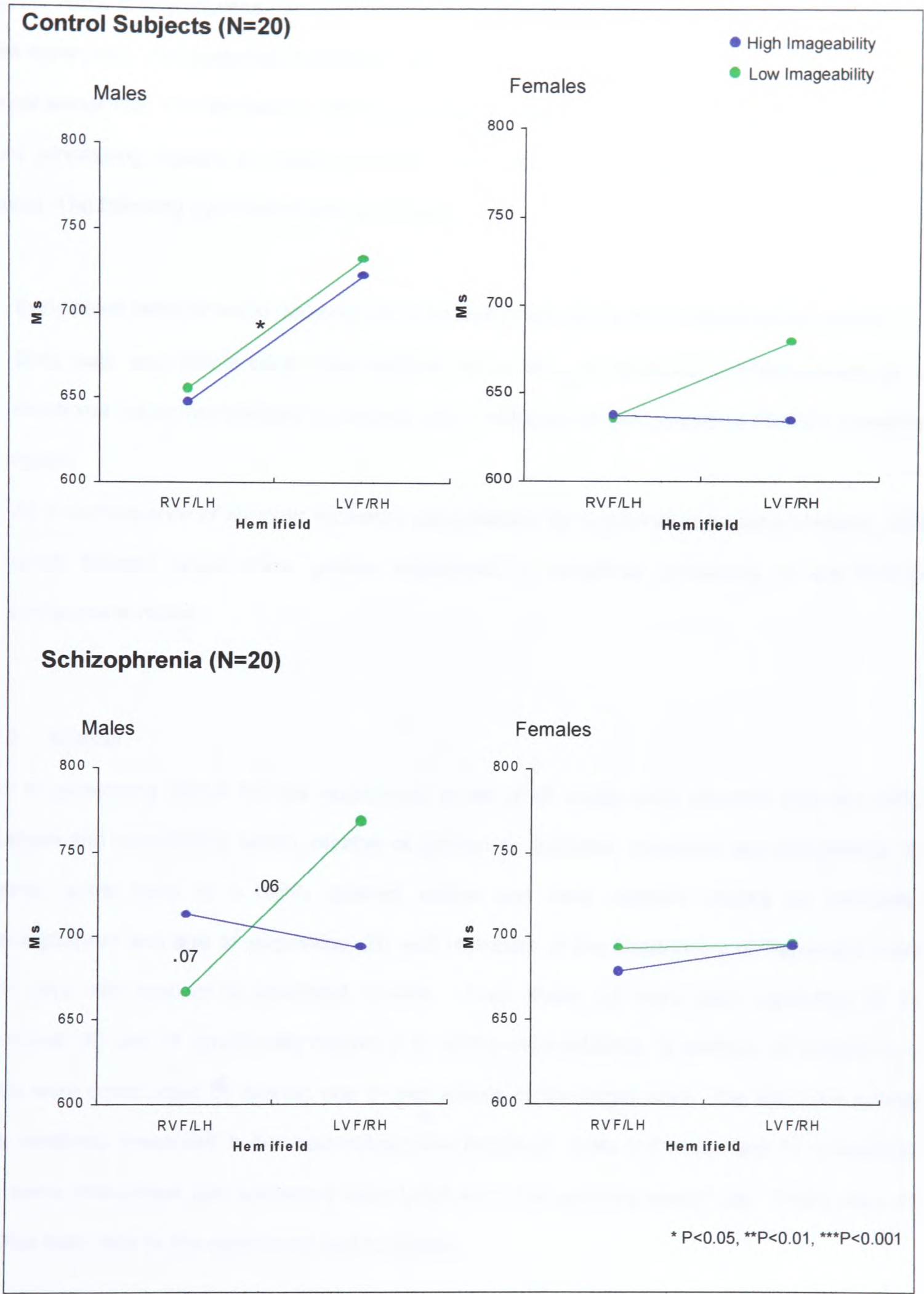
3.2.4 Results: Patient Study

Reaction time: As in the previous study, one-way comparison of mean RT collapsed across visual fields and condition between groups was conducted. This revealed no overall difference to suggest that groups were operating from a different baseline reaction time. Combined sexes repeated measures ANOVA of visual field (RVF, LVF), condition (HI, LI) by Group (Schizophrenia, Control) and sex (M, F) revealed a significant 4 way interaction (VF × condition × group × sex) ($F[1,36] = 4.40, p < 0.05$). As such, separate ANOVA's were repeated on the basis of sex.

In the ANOVA for males, there was a strong trend for VF main effect ($p = 0.05$), VF × condition ($p = 0.08$) and for the VF × condition × group interaction ($p = 0.08$). Post hoc testing revealed a stronger pattern of lateralisation in males showing inferior processing of low imageability words in the LVF/RH relative to the RVF/LH ($t[9] = -2.39, p < 0.05$). The source of the strong trend to group interaction was attributable to poor processing of high relative to low imageability words in the RVF/LH. This effect failed to reach significance, but showed a strong trend ($t[9] = -1.97, p = 0.07$). The ANOVA of female reaction time revealed no significant main effects or interactions to suggest a difference between patients and controls.

Accuracy: There was no significant group main effect to suggest that either male or female patients were less accurate in overall word recognition. In males, there were significant main effects for visual field ($F[1,18] = 4.40, p < 0.05$) indicating superior RVF/LH processing and condition ($F[1,18] = 17.11, p < 0.05$), indicating an imageability effect. Females showed trends for both visual field ($p = 0.06$) and condition ($p = 0.06$). No group interactions were significant in either male or female analyses.

Figure 11: Comparison of reaction time for high/low imageability lexical decisions in early onset patients and normal controls by sex.



EXPERIMENT 3: EMOTIONALITY

3.3.1 Aims & Hypotheses

This experiment was designed in order to examine the integrity of right lateralised components of lexical semantics. The aim was to determine if early onset patients showed laterality in emotional word processing relative to normal controls and whether sexual dimorphism in laterality was altered. The following hypotheses were proposed:

- ◆ Early onset patients would demonstrate increased emotionality effect compared to controls.
- ◆ Both male and female early onset patients would show a increased LVF/RH advantage for emotional nouns comparable to controls but a reduction in processing to RVF/LH presented nouns.
- ◆ As a consequence of stronger rightward specialisation for emotional processing in males, early onset females would show greater impairment in emotional processing in the RVF/LH compared to males.

3.3.2 Stimuli

Prior to generating stimuli for this experiment, a set of 40 words were selected from the MRC Database and matched for length, number of phonemes, syllables, frequency and imageability. In general, words were of a highly abstract nature and were matched closely on familiarity, meaningfulness and age of acquisition. 20 staff members at the Department of Psychiatry rated each word with respect to emotional content. From these, 28 word pairs consisting of 14 'emotional' (E) and 14 'emotionally neutral' (EN) words were selected. In addition, 28 regular non-words were constructed by altering one or two vowels of the target word. The 120 letter strings were randomly presented in two counterbalanced blocks of trials (14 words and 14 nonwords). The same instructions and procedure were used as in the previous experiment. There were no practice trials prior to the experiment and no breaks.

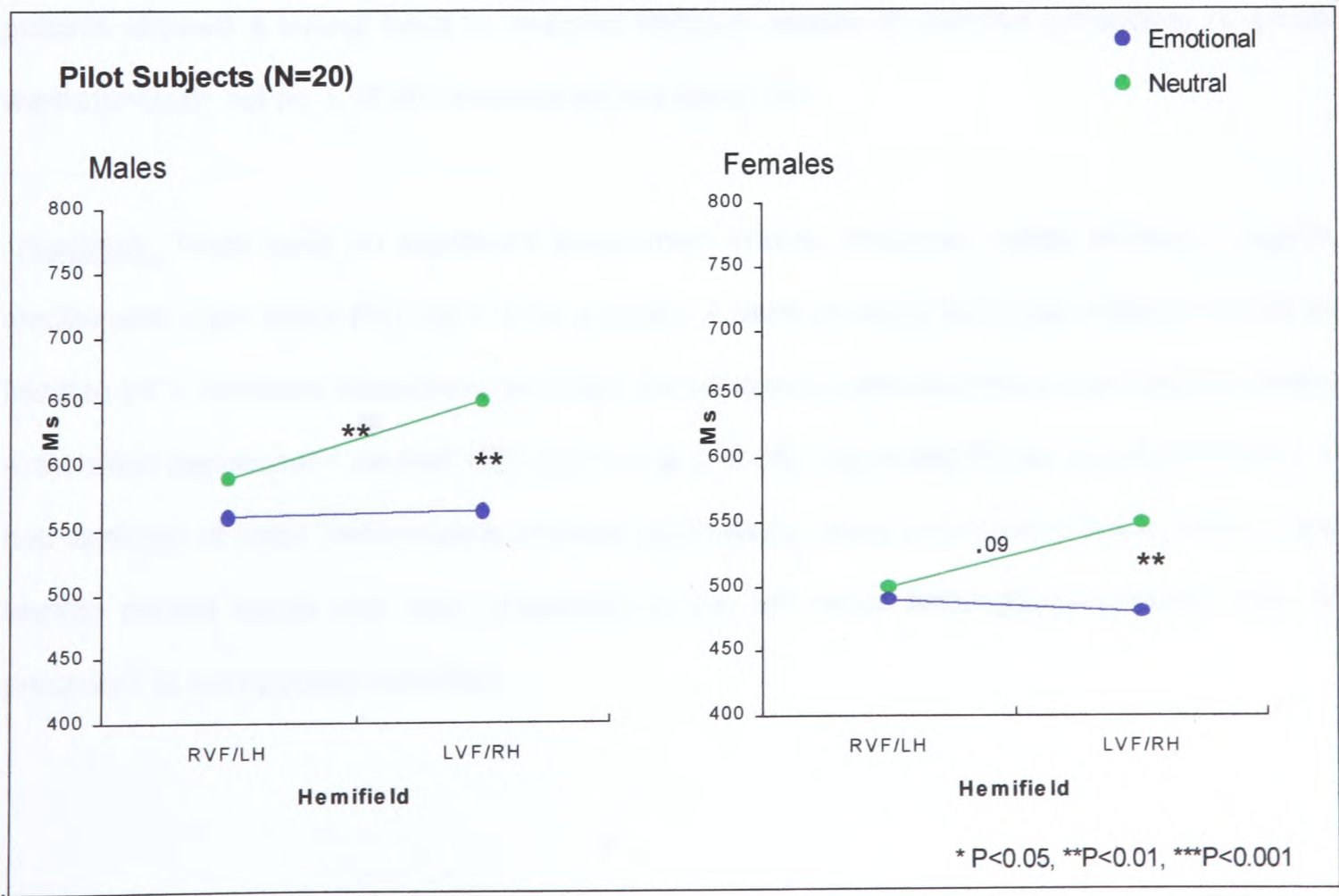
3.3.4 Results: Pilot Study

20 (10 males/10 females) of the original 32 pilot subjects completed this experiment. When they were compared on the basis of sex, there were no significant differences in age (males = 19.7 [sd .65]; females 20.3 [sd 1.05]) or estimated IQ (males = 112.8 [sd 11.04]; females 114.8 [sd 2.14]).

Reaction time: Repeated measures ANOVA was performed and revealed a significant main effect for visual field [LVF<RVF] ($F[1,18] = 4.83, p<0.05$) and emotionality [emotional < neutral] ($F[1,18] = 19.32, p<0.001$) as well as a strong trend to sex main effect ($p=0.05$). The VF × condition interaction was found ($F[1,18] = 7.40, p<0.05$) attributable to inferior processing of neutral (EN) words in the RVF/LH (see figure 12). In line with expectations, females showed superior LVF/RH processing of emotional words when compared to males ($t [18] = 2.42 p<0.05$).

Accuracy: There was a significant main effect for emotionality ($F[1,18] = 19.76, p<0.001$). There was a strong trend to interaction for VF × condition ($p=0.08$). Significant interactions were found for sex × condition ($F[1,18] = 8.57, p<0.01$), VF × sex × condition ($F[1,18] = 4.47, p<0.05$). Post hoc tests showed LVF/RH accuracy to neutral stimuli was inferior in males.

Figure 12: Pilot study comparison of reaction time in emotional word processing by sex



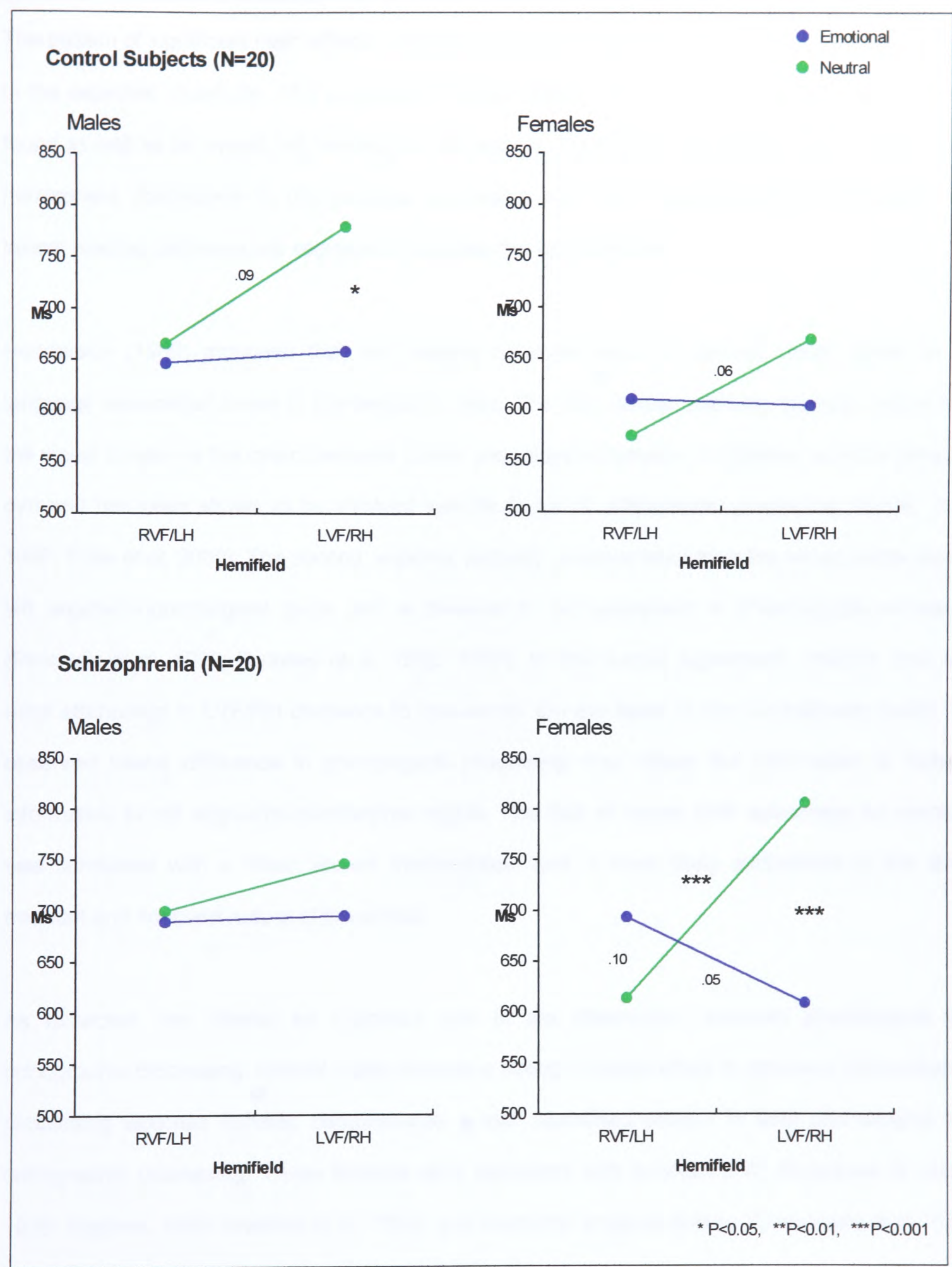
3.3.4 Results: Patient Study

Reaction time: Baseline reaction time was the same for patients and controls. Combined sexes ANOVA revealed significant main effects for VF [right<left] ($F[1, 36] = 8.54$ $p < 0.01$) and emotionality [emotional<neutral] ($F[1, 36] = 5.6$ $p < 0.05$) as well as significant interactions for VF $\times$ condition ($F[1, 36] = 21.64$ $p < 0.001$), VF $\times$ condition $\times$ sex ($F[1, 36] = 4.40$ $p < 0.05$) and VF $\times$ condition $\times$ sex $\times$ group ($F[1, 36] = 4.64$ $p < 0.05$). Thus, repeated measures ANOVA's were re-run on the basis of sex.

In the ANOVA analysis on males, trends to visual field ($p = 0.08$) and condition ($p = 0.07$) main effect were found, but no other effects or interactions indicated a difference between patients and controls. In females ANOVA, there was a significant main effect for visual field ($F[1, 18] = 5.45$ $p < 0.05$) as well as significant VF $\times$ condition ($F[1, 18] = 37.19$ $p < 0.001$) and VF $\times$ condition $\times$ group ($F[1, 18] = 8.27$ $p = 0.01$) interactions. The post hoc analysis showed the following effects: In male and female controls there were strong trends to superior RVF/LH processing of neutral words relative to a selective disadvantage in LVF/RH neutral word processing. This trend was significant in female patients ($t[9] = -5.08$ $p = 0.001$) but not in male patients. In the case of emotional words, both patients and controls showed no significant hemi-field difference in reaction time. Female patients showed a strong trend to reduced RVF/LH relative to LVF/RH processing of emotional words ($p = 0.05$) but no LVF/RH advantage (see figure 13).

Accuracy: There were no significant group main effects. However, males showed a significant emotionality main effect ($F[1, 18] = 5.18$, $p < 0.05$), a trend to visual field main effect ($p = 0.05$) and a trend to VF $\times$ condition interaction ($p < 0.06$). Females also demonstrated a significant emotionality main effect [emotional < neutral] ($F[1, 18] = 4.74$, $p < 0.05$), but no significant visual field effect. Post hoc analysis of male performance showed significantly more errors were made when trying to identify neutral words that were presented to the left visual field/right hemisphere than when presented to the opposite hemifield.

Figure 13: Comparison of reaction time for emotional and neutral word decisions in early onset patients and normal controls by sex.



3.4.1 Discussion

Lexicality, orthography and phonology in normal subjects

The pattern of significant main effects and interactions for normal subjects in the pilot study were all in the expected directions. The predicted lexicality effect in both reaction time and accuracy was found as well as an overall left hemisphere advantage. This finding supports the assumption of left hemisphere dominance in phonological processing and the suggestion that orthographic and lexical reading pathways are segregated between the hemispheres.

Henderson (1986) proposed that two reading networks exist to connect visual cortex to the language association areas in the temporal lobes. The first, ventral pathway receives output from the visual cortex via the infero-temporal cortex and relays information to bilateral superior temporal gyri and has been shown to be involved specific forms of orthographic processing (Binder et al, 1997; Wise et al, 2000). The second, superior pathway receives input from the visual cortex via the left angular/supramarginal gyrus and is believed to be specialised in phonological processing (Petersen et al, 1990; Rumsey et al, 1992; 1997). In the current experiment, reaction time was most attenuated to LVF/RH decisions to non-words. On the basis of the two-pathway model, the observed lateral difference in phonological processing may reflect the time taken to transfer information to left angular/supramarginal region. The lack of strong RVF advantage for words in was consistent with a direct access interpretation and is most likely attributable to the short, frequent and concrete nature of the stimuli.

As expected, sex played an important role in the dissociation between phonological and orthographic processing. Normal males showed a strong laterality effect in non-word (phonological) processing whereas females demonstrated a less lateralised pattern in both phonological and orthographic processing. These findings were consistent with previous DVF (Bradshaw & Gates, 1978; Majeres, 1999; Weekes et al, 1999) and functional imaging studies (Overmeyer et al, 1999; Shaywitz et al, 1995) that suggest that, females are generally less strongly lateralised for phonology than males. In sum, these results showed that the paradigm was sensitive to both lateral

and individual differences in lexical abilities. The results also support the putative sex difference in lateralisation of phonology.

Lexicality, orthography and phonology in early onset schizophrenia

Patients with schizophrenia showed no significant difference from normal controls in baseline reaction time or accuracy that might suggest extraneous mediation effects and/or psychomotor retardation. In line with the original predictions, early onset patients showed a normal lexicality effect, normal RVF/LH advantage in phonological processing and a normal bilateral effect in orthographic processing. This pattern was essentially the same as in the normal controls and suggests that basic lexical processing is intact in early patients with early onset schizophrenia. Furthermore, the sex effects for word processing were the same in both patients and controls suggesting that this basic sexual dimorphism is not altered. These findings do not agree with the hypothesis of a generalized left hemisphere impairment of language, but it is important to note that concrete stimuli are unlikely to reveal lateral differences between the hemispheres. However, contrary to expectations, the predicted loss of laterality effect was not found in non-word (phonological processing) in the early onset group. This was consistent with a previous study by Mohr et al, (1999) which showed that phonological abilities are normally lateralised in adult patients with schizophrenia.

In view of the fact that early onset patients demonstrated loss of REA in auditory laterality and that many of the same patients were involved in both dichotic and the present study, the finding of normal laterality effect is unexpected. The most obvious explanation for the discrepancy is that reductions are modality specific, and reflect selective disturbance to the segregated pathways that subserve auditory but not visual phonology (Rockstroh et al, 1998). Another possibility is that the attentional demands of dichotic listening are greater as a consequence of bilateral stimulation and therefore affect processing more than unilateral visual activation. Another possibility is that graphemic non-word stimuli do not require the same degree of auditory processing as purely phonemic auditory stimuli. In PET studies, activation of the left superior temporal gyrus during visual lexical decisions is significantly increased when also required to pronounce words (Price et al, 1994; Rumsey et al, 1997). Thus, despite the likelihood of a shared processing network

involving the left superior temporal gyrus, it seems that phonology is not a unitary process. Hence, the results of this and previous experiments suggests that dichotic and DVF tasks are not comparable. If future, studies can match these tasks in terms of attentional requirements and overall difficulty they may be able to discriminate between disturbances in visual and auditory pathways.

Imageability in normal subjects

The results of the pilot experiment confirmed those of previous DVF studies that have examined imageability/concreteness in lexical processing (Ellis & Shepard, 1974; Hines et al, 1977; Day; 1977; Day 1979; Patterson & Marcel 1977; Bruyer & Strypstein; 1985). Firstly, highly imageable stimuli were processed faster than stimuli of low imageability. This suggests that the semantic content or associated representations of words influence the efficiency of processing. Second, highly imageable stimuli are processed efficiently by both cerebral hemispheres whereas low imageability words were efficiently processed only in the right visual field/left hemisphere. Third, males demonstrate evidence of a laterality effect for low imageability stimuli but females did not, thus supporting the assumption of stronger lateralisation in this aspect of lexico-semantic processing. This is consistent with Eviatar et al (1990) and Young & Ellis (1985) who also examined sex separately.

Pavio (1971; 1986) has previously explained imageability effects in normals in terms of a dual coding theory. According to the model, highly imageable words are represented by both their verbal and imaginal referents and are available to both cerebral hemispheres whereas low imageability words are represented by their verbal code and available to only the left hemisphere. A number of studies support the notion of separable neural substrates involved in imageable word reading. A recent PET study by Wise et al (2000) showed increasing imageability resulted in increased activity in the left fusiform, lateral parahippocampal gyrus and bilateral medial temporal lobes within the perirhinal cortex. The authors proposed that the fusiform gyrus is amodal in nature and links words from various input modalities to higher order episodic and semantic memory located in the heteromodal temporal cortices. This explanation is supported by some ERP and fMRI studies (Nobre et al, 1994; Binder et al, 1997) but not by others who have reported *right rather than left*

anterior-superior temporal gyrus activation when normal subjects view low imageability/abstract words (Beauregard et al, 1997; Kiehl et al, 1999). At present, the neural substrates require further elucidation, but notwithstanding, the visual field and task differences observed in the present study support the notion of bilateral ability in imageable word reading and lateralised processing in low imageable word reading.

Imageability in schizophrenia

When patients with schizophrenia were examined, the pattern of mean reaction times was significantly different from controls but not as predicted in the original hypothesis. There was no significant overriding imageability effect but some laterality effects in processing low imageability words were present. The four-way interaction revealed a complex relationship between sex and diagnosis in the pattern of reaction time data. In general, schizophrenic females showed a non-lateralised pattern that suggested direct access for both high and low imageable words. This was similar to that of the control females and consistent with the general assumption that lateralisation is more bilateral in females. Male patients, on the other hand, showed a strong trend to reduced processing of high imageability stimuli in the left hemisphere despite a normal laterality effect for low imageability words. This reduction was not explainable by differences in current medication, age, age of onset or length of illness and suggests that there is a disturbance in left hemisphere lexical processing in males with early onset schizophrenia.

Contrary to the original prediction that reaction time would be reduced to RVF/LH presentations regardless of word type, no decrement was observed to low imageability/abstract stimuli. This suggests that the impairment is not simply one of altered laterality but rather the type of processing that is undertaken in left hemisphere. Hence, if it is true that the left fusiform connects word forms to heteromodal associations (Binder et al, 1997; Wise et al, 2000), altered asymmetry in the superior temporal gyrus, parahippocampal and fusiform gyri suggests a possible explanation for this selective impairment. If there is a disruption or disconnection between the amodal infero-temporal areas and heteromodal temporal areas involved in semantic memory, this may suggest a common route for many language impairments observed in schizophrenia. A point that is further reinforced by the fact that lesions in the fusiform gyrus can result in semantically incoherent speech

and impaired comprehension similar to that observed in psychosis (Alexander et al, 1989). In view of the normally greater reliance of males on left hemisphere substrates, it is more likely that the altered asymmetry would affect male patients more profoundly.

Emotionality in normal subjects

The pilot study supported the findings of previous DVF studies examining hemispheric asymmetry in emotional word recognition (Brody et al, 1987; Van Strien & Morpugo, 1992; Van Strien & Heijt, 1995; Richards et al, 1995). There was a strong laterality effect for emotionally neutral words in both RT and accuracy compared with bilaterality (direct access) for emotional words. With respect to emotionally neutral (EN) words, a laterality effect comparable to the previous study was found that was most likely attributable to the high abstractness of the stimuli. In the case of the emotional stimuli, the lack of laterality effect is consistent with the literature suggesting a special role of the right hemisphere in emotion (Liotti & Tucker, 1995).

Although the three-way interaction involving sex was not significant, a gender main effect showed that normal females were faster and more accurate in processing emotional and neutral stimuli than males. When RT's were compared individually, females showed a significant advantage in right hemisphere processing of highly emotional words. Sex effects in accuracy were also found, showing better performance in LVF/RH recognition in females. These findings agree with those of Eviatar & Zaidel (1988), but not those of Graves et al (1981) and suggest that there may be greater specialisation of emotion in the right hemisphere in females compared to males.

Unfortunately, despite a general correspondence in the pattern of findings in normals between this and the patient study, the right hemisphere advantage in females was not replicated. This suggests that there may be marked individual differences in right hemisphere specialisation of emotional perception. A potential reason may be that normal subjects differ in their sensitivity to the valence of the stimuli used. One line of evidence suggests that the right hemisphere is particularly sensitive to negatively (withdrawal – avoidant) valenced stimuli (e.g. kill) whilst the left hemisphere is sensitive to positive (approach-related) stimuli (e.g. love) (Liotti & Tucker, 1995). Another line of evidence suggests that right hemisphere is primary in emotional processing regardless of valence

(Borod, 1992). Recent fMRI data favours the valence hypothesis. Canli et al (1998) has shown significant activation in left middle frontal, middle and superior temporal gyrus in response to positively valenced stimuli whereas negative valence was associated with right inferior frontal and angular gyrus activation. In the study, both positive *and* negative valenced stimuli were used but unfortunately differences in the proportions of each type of stimulus prohibited a statistically valid comparison of valence on the basis of visual field. Future studies may be able to separate these effects.

Emotionality in schizophrenia

When patients with schizophrenia were examined, the expected main effects for visual field and emotionality, as well as significant interactions with sex and group were found, but not in the expected directions. When separated on the basis of sex, despite a reduction in RVF/LH advantage to neutral words, the pattern in male patients was basically the same as in normal males. However, female patients were markedly different from the female controls. Normal females showed direct access in both emotional and neutral words, whereas schizophrenic females showed a strong laterality effect for neutral words and a strong trend to reversal of the normal pattern for emotional words. This effect may be plausibly interpreted in two ways; first, it may be an unusually strong LVF/RH advantage for emotional words, possibly reflecting right hemisphere hypersensitivity, second, it may reflect a significant reduction in RVF/LH processing of emotional words. Two points suggest that the latter explanation is more appropriate; first, the usually close association of emotional and neutral word processing in the RVF/LH in normal females is not apparent in the female patients and second, LVF/RH emotional word processing is not different from controls. So the present results do not support those of Oepen et al (1987) who suggested an RH hypersensitivity to emotional material in acute adults schizophrenia. However, it is worth noting that all patients in this study were clinical remitted rather than acutely psychotic, and Oepen et al did not examine any female patients in their study. Hence, the current findings are not strictly comparable.

Finally, as a consequence of the relatively restricted processing demands of the present experiment, the present findings do not rule out an abnormality of emotional processing when there

are higher level interactions with other cognitive processes. For example, Oepen et al's experiment is likely to have required greater attentional demands than the present study and may therefore reflect the impairment of contralateral attentional processes (Tomer & Flor-Henry, 1989). Moreover, these findings do not rule out the possibility that normal inhibition of the right hemisphere is lost (Leonhard and Brugger, 1998). Hence, further studies are needed in order to establish the relative contribution of higher order processes (see discussion Chapter 5).

3.4.2 Point Summary of Chapter 3:

- Normal subjects demonstrate a strong laterality effect in phonological reading but show evidence of direct access in orthographic reading.
- Normal males demonstrated stronger laterality effects than normal females in lexical and orthographic processing.
- Early onset patients demonstrated normal lexical and non-word processing effects compared to normal controls consistent with hemispheric independence in basic orthographic processing and left hemisphere dominance in phonological processing.
- Early onset patients failed to show a normal imageability effect compared to normal controls. Male patients showed a normal laterality effect in low imageability processing but impaired processing of highly imageable words in the RVF/left hemisphere. This suggests disturbances may be specific to the left heteromodal areas involved in semantic memory
- Female early onset patients show a trend to reduced processing of highly emotional words in the left hemisphere. Male early onset patients demonstrated a reduction in laterality effect in relation to emotionally neutral word processing.

CHAPTER 4: CEREBRAL ASYMMETRY AND STRUCTURE-FUNCTION RELATIONSHIPS*

Overview

The evidence for altered cerebral asymmetry in schizophrenia was reviewed in chapter 1. This review showed that asymmetries in the temporal lobes and fronto-occipital torque are reduced or reversed in adults with schizophrenia and that sex and age of onset may influence the extent of this reduction. Presently there are no studies that have examined asymmetry in early onset patients close to the time of first onset. In addition, while the functional correlates of structural asymmetries have received some attention in the adult literature, there are no corresponding studies of early onset patients. This chapter reports the preliminary results of MRI investigations of cerebral asymmetry in the early onset group and the relationship of structural asymmetry to functional laterality. As the evidence for altered asymmetry was previously reviewed, this chapter begins with a review of structure-functional correlations

*Manuscript submitted – see appendix

4.1 Introduction

Computer tomography (CT) and magnetic resonance (MRI) investigations show that brain structure and cerebral asymmetry are altered in schizophrenia but only a limited number of studies have examined their relation to altered cognitive functioning. Notably, reduced volume of the prefrontal (dorso-lateral and orbital) cortex is correlated with poor performance on tests of executive function (Seidman et al, 1994; Gur et al, 2000a) and impairments of episodic memory have been found to correlate with reduced volume of the temporal (hippocampal and parahippocampal gyrus) cortex (Delisi et al, 1991; Baare et al, 1999; Gur et al, 2000b). A number of studies have found significant correlations between reduced overall volume and ventricular enlargement with reduced IQ (Flaum et al, 1994; Zipursky et al, 1998) as well as impaired performance on batteries of cognitive tests (Bornstein et al, 1992; Sullivan et al, 1996; 1998; Gur et al, 1999).

The relationship between altered cerebral asymmetry and neuropsychological impairments has not been addressed in detail. Seidman et al (1994) reported that the correlations between impaired executive functions and prefrontal cortex volume were strongest in relation to the left hemisphere and Satz et al (1990) found an association between larger leftward ventricular brain ratio asymmetry and increased mixed handedness. Degreeef et al (1992) found significant correlations between severity of symptoms and temporal lobe enlargement (particularly on the left). However, in a well controlled study, Gur et al (2000b) failed to find any laterality differences in relation to temporal volume or asymmetric structure-function correlations. Similarly, Delisi et al (1991) found no evidence for a relationship between altered asymmetry and cognitive function in either first-episode or chronic patients, although they did find that reduced verbal memory impairment was associated with reduced left-sided parahippocampal size. So, thus far, the evidence for a general association between altered asymmetry and cognitive impairment is equivocal.

When sex, age of onset and handedness are taken into account, the relationship between structure and function becomes more complex. For example, Pearlson et al, (1989) and Clementz et al, (1994) both showed an association between increased ventricular brain ratio and left-handedness. Hollinger and colleagues (1999) showed that reduction in left superior temporal gyrus was

associated with thought disorder in right-handed schizophrenic males, whereas the association was significant for the right side in left-handers. Gur et al (2000a,b) showed that the correlations between reduced prefrontal cortex and executive function were sex-specific and that temporo-limbic correlations with memory were present in men but not in women. Age of onset appears to have been addressed in only two studies. Johnstone et al (1989) reported poorer general cognitive function and semantic memory performance was associated with ventricular size in early onset (<25 years) but not later onset (>25 years) patients. Jeste et al (1998) examined 82 patients with schizophrenia in a comprehensive MRI - neuropsychological study and found that earlier age of onset was correlated with poorer performance on tests of learning/abstraction and cognitive flexibility, as well as larger volumes of the caudate and lentiform nucleus but smaller thalamic volume.

Taken together, the general findings suggest some association between altered brain structure and functional deficits, but the literature is small and few studies have directly examined asymmetry. There is some evidence that individual differences may influence the degree of alteration but asymmetry has not been examined explicitly. As such, the aim of this study was to examine structural asymmetry in early onset patients and its relationship to the alterations in functional asymmetry reported in chapters 2 and 3. The following predictions were made:

- ◆ Early onset patients would demonstrate reduction of total and regional brain volume compared to normal adolescent controls
- ◆ Early onset patients would show reduction of normal structural asymmetries in the hemispheres and temporal lobes
- ◆ Reduced volumes and altered asymmetry would be mediated by sex. In particular, males would demonstrate greater volume reduction and loss of asymmetry compared to female patients
- ◆ Reduced volume and asymmetry would correlate with decrements observed in performance measures.

4.2 Subjects

The majority of subjects in this group were the same subjects denoted as 'early onset' in the previous analyses. The same adolescent controls were used as in previous studies.. In total, the scans of 33 patients (20 males, 13 females) and 32 (19 males, 13 females) adolescent control subjects matched for age and sex were examined in both the structural analysis and the structure-function analysis with IQ, handedness and dichotic listening performance (see Table 12). However, in the case of the DVF correlations, scans were available for only 17 (8 males, 9 females) of 20 patients and 17 of the 20 controls (9 males, 8 females). There were no significant differences between groups or sexes in terms of age, age of onset, length of illness or current medication (chlorpromazine equivalent).

Table 13: Sample 7: Characteristics of early onset patients and controls for MRI study

	N	Age	FSIQ	Age of onset	Duration (Y/M)	CPZ eqv.
Schizophrenia						
Males	20	16.2 (0.9)	83.2 (13.1)	13.5 (4.9)	12.6 (8.2)	395.4 233.8
Females	13	16.0 (1.4)	79.5 (13.4)	12.9 (5.9)	10.9 (10.4)	630.0 803.3
Total patients	33	16.1 (1.1)	81.8 (13.2)	13.3 (5.2)	11.8 (9.0)	485.1 (550.9)
Controls						
Males	19	15.2 (1.7)	98.4 (14.8)			
Females	13	15.7 (2.2)	108.4 (15.2)			
Total controls	32	15.4 (1.9)	102.5 (15.5)			

4.3 MR image acquisition and analysis

MR scanning was performed at the Radcliffe Infirmary MR department and the protocol was administered by a trained radiographer. Scans were then analysed by Dr Clare MacKay in the department of Psychiatry.

MR images were acquired using a 1.5T Magnetom Vision whole body system (Siemens Medical System Inc., Erlangen, Germany). One hundred and sixty coronal T1-weighted images were obtained using a 3D spoiled gradient echo (SPGR) pulse sequence (TR of 35ms, TE of 5ms and flip angle of 35°). The Field of View (FOV) of the images was 20cm, and each image refers to a contiguous section of tissue of 1.5mm thickness. The volume acquired MR images possess minimal partial voluming artefact and exhibit good contrast between grey matter, white matter and CSF.

The left and right temporal lobe were optimally visualised, and their volumes best measured, on image sections oriented perpendicular to the long axis of the hippocampus (Mackay et al, 1998). These sections were obtained by reformatting oblique sections through the acquired 3D data using NRIA software (Brain Behaviour Laboratory, University of Pennsylvania, USA). Analyses were run on a ULTRA 10 workstation (SUN Microsystems, CA, USA), where the 256 x 256 x 160 acquired voxels of side 0.78mm x 0.78mm x 1.5mm were linearly interpolated to 256 x 256 x 256 cubic voxels of side 0.78mm. The resulting 0.78mm thick contiguous coronal sections lie approximately perpendicular to the mean direction of the long axis of the hippocampus in the left and right cerebral hemispheres. This was also a convenient sectioning direction for volume estimation of the left and right cerebral hemisphere and lateral ventricles.

Unbiased estimates of structure volume were obtained within EasyMeasure software (www.easymeasure.co.uk) using the stereological method of point counting (Roberts et al, 1994). An illustration of the application of the stereological point counting technique is given in Figure 16. The posterior limit of the temporal lobe is defined as the point where the lateral ventricles divide into the frontal and temporal horns. The cerebral hemispheres were separated from the brain stem

at the superior limit of the pons. A more detailed description of the definitions is given in Mackay et al (1998).

For estimating the volume of each structure of interest, a series of equally spaced MR images were sampled in a direction parallel to the long axis of the hippocampus, beginning from a random starting position. Each image was overlaid with a test system comprising a regular array of test points and the number of points lying within the transect through the structure of interest recorded. The volumes of the hemisphere, temporal lobe and lateral ventricles were measured using a grid spacing of 1.17cm (15 pixels), 0.781cm (10 pixels), and 0.234cm (3 pixels), and a slice interval of 1.17cm, 0.469cm and 0.391cm respectively. Unbiased estimates of the transect area were obtained by multiplying the total number of points recorded by the area corresponding to each test point. An unbiased estimate of structure volume was obtained as the sum of the area of the consecutive systematic sections multiplied by the distance between sections.

An asymmetry index was computed for each structure by subtracting the volume of the left from the volume of the right and expressing this difference as a percentage of their mean volume, i.e. $(R-L)/((R+L)/2)$. The proportion of lateral ventricle and temporal lobe volume to hemisphere volume were calculated for the left, right structures.

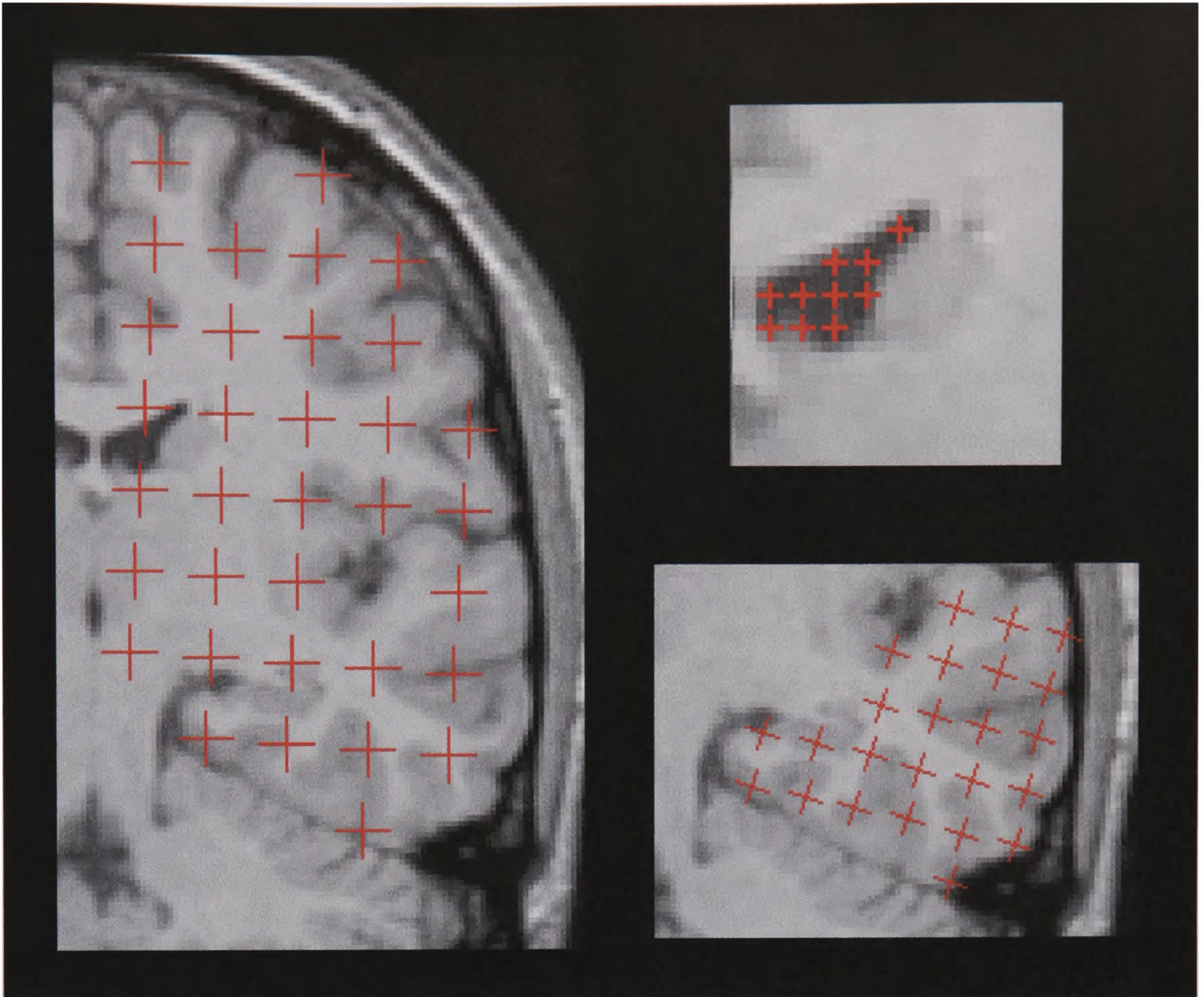


Figure 16. Example of design based stereology in conjunction with the Cavalieri method of unbiased volume estimation for the hemisphere (left panel), lateral ventricle (top right panel) and the temporal lobe (bottom right panel).

4.4 Results

Male and female patients and controls were examined separately. There are no significant differences in mean age between any of the groups but as age influences the size the brain, it was entered as a covariate in a general linear model. Main effects and interactions between diagnosis and sex were examined in relation to the volumes of the left and right hemispheres, lateral ventricles and temporal lobes. Mean volumes and standard deviations for the volumes of the left and right hemisphere, lateral ventricle and temporal lobes (ml), and the asymmetry index for the male and female patients and controls are shown in Table 13.

Volumes of left and right hemispheres and temporal lobes were significantly reduced in patients relative to controls. Hemisphere volumes are reduced by 6.9% in males, 3.8% in females that equated to an overall reduction of 5.6%. The patients had a significantly larger left and total (left + right) ventricle to brain ratio. There were significant main effects of sex in the volume of the left and right hemispheres and temporal lobes with males being larger than females in all cases. There was a significant interaction between diagnosis and sex in temporal lobe asymmetry (see Figure 1). Male patients exhibit reduced leftward asymmetry compared with male controls, whereas female patients exhibit leftward asymmetry compared to rightward asymmetry in female controls. The left temporal lobe volume also tends towards significance with the difference in volume between male patients and controls being much larger than the difference between female patients and controls.

Table 14: Analyses of variance of structure volumes and asymmetry. Results are shown for the main effects of sex and diagnosis, and for sex*diagnosis interactions. Results for the lateral ventricles and temporal lobes are shown both raw and as a proportion of hemisphere volume (Prop).

Dependent variable			Sex			Diagnosis			Sex * Diagnosis		
			F	df	p	F	df	P	F	df	P
Hemisphere	Left		18.20	1:66	<0.001	7.95	1:66	0.00	1.5	1:66	0.21
	Right		17.58	1:66	<0.001	7.16	1:66	0.01	0.4	1:66	0.49
Temporal lobe	Left	Raw	11.39	1:66	0.001	4.29	1:66	0.04	3.9	1:66	0.05
		Prop	0.01	1:66	0.906	0.03	1:66	0.85	1.1	1:66	0.28
	Right	Raw	7.95	1:66	0.006	4.18	1:66	0.04	0.5	1:66	0.46
		Prop	0.23	1:66	0.634	0.01	1:66	0.90	0.0	1:66	0.85
Lateral ventricle	Left	Raw	2.63	1:66	0.110	2.53	1:66	0.11	0.8	1:66	0.36
		Prop	1.32	1:66	0.255	4.37	1:66	0.04	1.0	1:66	0.31
	Right	Raw	3.16	1:66	0.081	1.93	1:66	0.17	0.1	1:66	0.73
		Prop	2.22	1:66	0.142	2.95	1:66	0.09	0.1	1:66	0.71
Hemisphere asymmetry			0.02	1:66	0.887	0.12	1:66	0.73	2.0	1:66	0.15
Temp lobe asymmetry			0.41	1:66	0.526	0.02	1:66	0.89	4.1	1:66	0.04
Lat ventricle asymmetry			0.87	1:66	0.355	0.34	1:66	0.56	3.0	1:66	0.08

Table 15: Mean volumes of the left and right hemisphere, lateral ventricle and temporal lobe and mean asymmetry indices for each structure in the male and female patients and controls. Standard deviations are shown in parentheses.

	Hemisphere		Lateral ventricle		Temporal lobe		Asymmetry		
	left	right	left	right	left	right	H'sphere	Lateral ventricle	T' lobe
Male patients	536.3 (36.5)	539.1 (37.6)	8.2 (4.9)	8.2 (7.7)	76.8 (6.7)	76.3 (6.8)	0.48 (3.4)	-8.73 (27.3)	-0.15 (8.1)
Male controls	574.7 (40.3)	572.6 (43.1)	5.8 (3.1)	6.0 (3.1)	84.9 (7.4)	82.5 (6.3)	-0.40 (2.5)	3.11 (42.4)	-2.82 (5.9)
Female patients	499.5 (33.7)	496.4 (34.6)	5.7 (3.9)	5.5 (3.5)	73.7 (9.5)	72.1 (9.8)	-0.52 (3.3)	-2.50 (32.5)	-2.48 (4.4)
Female controls	516.5 (55.5)	518.9 (53.3)	5.1 (1.7)	4.2 (1.5)	73.9 (8.3)	75.0 (9.6)	0.53 (1.7)	-19.32 (22.2)	1.25 (6.3)
Total patients	521.8 (39.4)	522.3 (41.7)	7.3 (4.7)	7.1 (6.5)	75.5 (7.9)	74.7 (8.2)	0.09 (3.6)	-6.32 (29.1)	-1.05 (6.9)
Total controls	551.1 (54.6)	550.8 (53.8)	5.5 (2.7)	5.2 (2.7)	80.5 (9.4)	79.4 (8.5)	-0.02 (2.2)	-6.01 (36.9)	-1.17 (6.3)

Figure 17. Asymmetry volumes hemisphere, ventricles and temporal lobes in male and female patients and controls (see figure 18 For key).

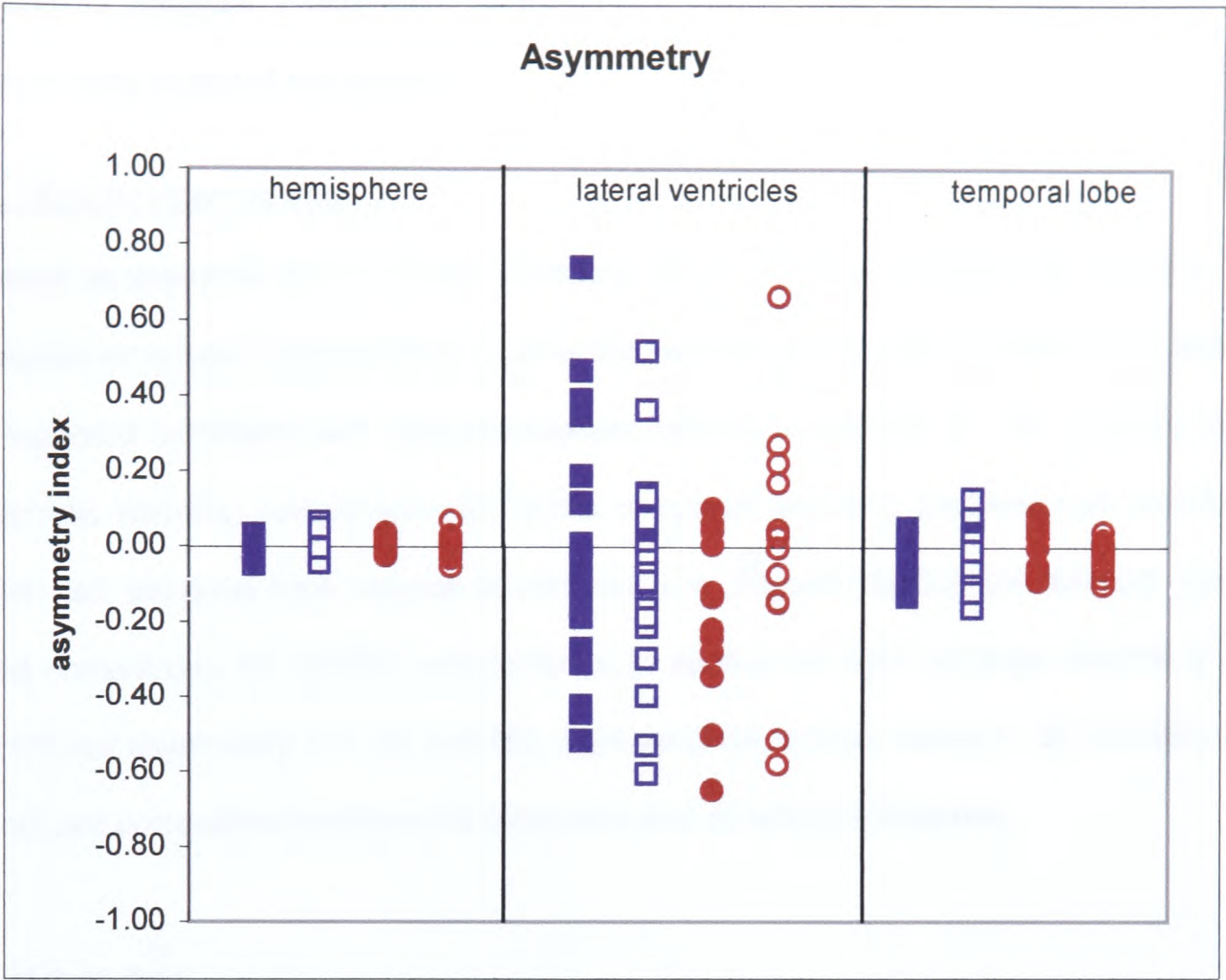
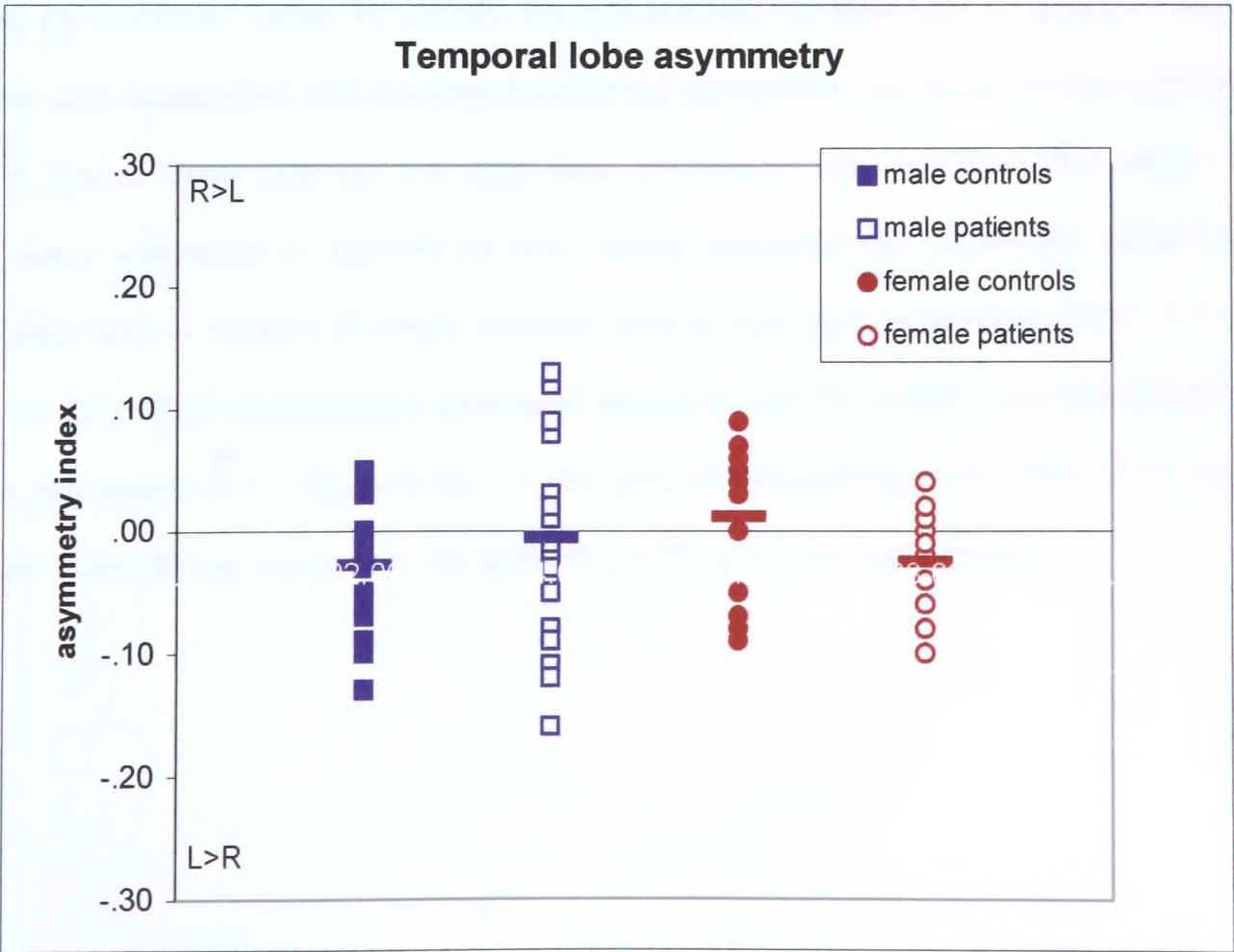


Figure 18. Enlarged figure of temporal lobe asymmetry for the male and female patients and controls



Correlational analysis

The relationships between structure volume and cognitive function were assessed separately in the 33 patients and 32 controls. There were no significant correlations between age and structure volume or asymmetry in any of the groups.

Handedness, dichotic listening and IQ

Hand preference as assessed by the Annett Inventory did not correlate significantly with any of the structural volumes or volume asymmetries in either the patients or controls. Relative hand skill from the Annett Pegboard correlated with right hemisphere volume in patients ($r = .36$, $p < 0.05$) but not controls. Dichotic listening performance (in terms of overall laterality quotient) was significantly correlated with left temporal lobe volume in patients ($r = .39$, $p < 0.05$) but not controls. Controls demonstrated correlations for dichotic performance in relation to right ventricle volume ($r = .35$, $p < 0.05$), ventricular asymmetry ($r = .43$, $p < 0.05$), right ventricle to brain ratio ($r = .35$, $p < 0.05$). There were no significant correlations between IQ measures and structural measures.

Divided visual field data

Structure volumes and DVF reaction times were correlated separately in the 17 patients and 17 controls. There were no significant correlations or strong trends between any of the DVF measures and volumes for controls. Table 15 shows the correlations for patients. In general, increased reaction times were associated with increased rightward asymmetry and temporal lobe volume as a proportion of overall brain size on the right was associated with poorer performance. When correlations were examined in relation to sex, males demonstrated significant effects in left ventricular brain ratio in relation to better reaction time to non-word processing (RVF: $r = -.65$, $p = .07$; LVF: $r = -.72$, $p < 0.05$ respectively); increased temporal lobe asymmetry was associated faster neutral word processing ($r = -.73$, $p < 0.05$; $r = -.64$, $p = 0.08$ respectively) but slower RVF and LVF reaction times to emotional words ($r = .75$, $p < 0.05$; $r = .70$, $p = 0.05$ respectively).

Table 16: Mean asymmetry indices and temporal lobe to brain ratios in relation to RVF/LVF reaction time in male and female early onset patients.

	Asymmetry			Temporal Lobe to brain ratio		
	Hem'phere	Lateral ventricle	T' lobe	Right	Left	Total
Lexicality						
RVF/LH Word	.28	-.05	.43 (.08)	.48*	.32	.43 (.08)
Non-Word	.36	.05	.12	.35	.48*	.44 (.07)
LVF/RH Word	.11	.13	.13	.32	.28	.32
Non-Word	.14	.09	.09	.33	.37	.37
Imageability						
RVF/LH High	.29	-.05	.35	.47*	.37	.45 (.06)
Low	.16	-.09	.49*	.41	.16	.41
LVF/RH High	.12	.34	.02	.27	.33	.27
Low	.06	-.01	.23	.23	.15	.23
Emotionality						
RVF/LH Emotional	.08	-.15	.45 (.06)	.37	.15	.28
Neutral	.12	.00	.57**	.40	.10	.27
LVF/RH Emotional	.15	-.01	.51*	.46 (.06)	.24	.38
Neutral	.09	.16	.46 (.06)	.06	-.18	.05

*P<0.05, **P<0.01, ***P<0.001

4.5 Discussion

Structural asymmetry in early onset patients and controls

In normal controls and early onset patients there was a significant sex difference in the overall volume and asymmetry of the brain. In males, the brain is larger in volume and more leftwardly asymmetrical in the temporal lobes, whereas in females it is smaller in volume and more rightwardly asymmetrical in the temporal lobes. For controls, these findings are in line with previous studies of normal adults showing sex differences in overall volume and asymmetry (Wada et al, 1975; LeMay and Kido, 1978; Kertesz, 1992; Karbe et al, 1995; Shapleske et al, 1999).

When examined in relation to diagnosis, although the results could not be compared to later onset patients, the general trend of findings was in keeping with studies of adult patients that suggest that earlier onset is associated with reduced brain volume and altered asymmetry (Bogerts et al 1991; Bartozokis et al 1996; Maher et al 1999). Volumes of left and right hemispheres and temporal lobes were significantly reduced in patients relative to controls. Hemisphere volumes are reduced by 6.9% in males, 3.8% in females that equated to an overall reduction of 5.6%. This reduction is comparable to studies of adult patients that typically find reductions of 3-6%. In addition, lateral ventricle volume as a proportion of brain volume was increased, particularly on the left. Consistent with other imaging (Johnstone et al 1989; Rossi et al 1990) and post-mortem (Brown et al 1986; Crow et al 1989; Highley et al 1999) studies of adults, there was evidence for alterations in temporal lobe asymmetry. In male patients, leftward asymmetry was reduced in comparison to male controls, whereas a slight rightward bias in normal females was reversed to a leftward bias in female patients. Furthermore, reduced temporal lobe volume was correlated with earlier onset in males but not females.

These findings are consistent with the second hypothesis and Crow's suggestion that late developing, normally asymmetric, areas of the cortex are most affected in schizophrenia. Moreover, these disturbances are in line with the overall hypothesis of this thesis that sex is an important determinant of altered asymmetry, particularly in relation to the temporal lobes. This dimorphism in asymmetry suggests that the rate and timing of dimorphic brain development may

be important in the aberrant growth processes that putatively underlie schizophrenia. Moreover, its presence in early onset patients, close to the time of onset and without long-term illness, hospitalisation and/or neuroleptic exposure suggests that aberrant growth is intimately involved in schizophrenia and perhaps the process leading to onset. Thus, longitudinal studies are required in order to establish the exact time course of these changes and their relationship to other indices of brain change.

Structure-function correlations

There were some significant correlations between functional measures and structural asymmetry in the patient group but no significant correlations within the controls. These findings differ from previous studies of brain structure and IQ in both normal and schizophrenic adults (Willerman et al, 1991; Andreasen et al, 1993, Flaum et al 1996). In normal subjects, Andreasen et al (1993) found that IQ correlated significantly with the volume of the hemispheres, temporal lobe, cerebellum and hippocampus in both males and females. In a subsequent study of schizophrenic adults, Flaum et al (1996) reported that the pattern of structure-function correlations in female patients were similar to those of female controls, but male patients demonstrated no significant structure/function correlations. In the present study, there were no significant structure-IQ correlations in male subjects.

However, increased left and right temporal lobe to brain ratio was associated with poorer performance on some of the DVF language measures. This supports the assertion that aspects of verbal processing that are subserved by heteromodal areas of the temporal lobe are affected in early onset patients. However, paradoxically, direct correlations were also observed between better lexical, imageable and emotional word processing and indices of rightward asymmetry. Similar findings were observed in dichotic listening performance and right hand skill. Such findings are difficult to reconcile with the expectation of a relationship between reduced overall brain volume and reduced right hand preference (Satz et al, 1990; Pearlson et al, 1989; Clementz et al, 1994), and the idea that increased leftward asymmetry (as a marker of increased functional laterality) should be correlated with performance on language measures. Although, in the case of DVF experiments, it is important to note that loss of asymmetry went in opposite directions in males and

females and this would explain the incongruity in structure/function correlations. When examined by sex, males showed general trend to poorer processing in association with markers of reduced asymmetry and increased ventricular brain ratio. These findings suggest that left hemisphere indices are representative of the pathological changes underlying motor and cognitive impairments in schizophrenia. However, given the very small sample sizes and the fact that relatively few studies have performed similar analyses, caution is required in accepting these findings until there is further replication.

4.6 Point summary of chapter 4:

- ◆ Normal adolescent males demonstrate significantly larger brain volume and temporal lobes than normal adolescent females. Adolescent patients showed a reduction of 5.6% in cerebral volume comparable with studies of adult patients.
- ◆ Early onset (adolescent) patients' show reduced left and right hemisphere and temporal lobe volumes and increased left lateral ventricle volumes relative to normal adolescents.
- ◆ Sex × diagnosis interactions in temporal lobe asymmetry indicated reduced leftward asymmetry in male patients, whereas female patients exhibit reversal of the normal rightward asymmetry. The reduction was more pronounced for males than females.
- ◆ No sex × diagnosis effects are present in overall hemisphere asymmetry, however a trend in relation to lateral ventricle asymmetry was also found.
- ◆ Decreased left temporal lobe volume was correlated with greater right ear advantage on a dichotic listening task in patients but not controls.
- ◆ Increased left ventricle to brain ratio was associated with decreased reaction time to non-word processing in both RVF and LVF but not emotional word processing in males but not females.

CHAPTER 5: CEREBRAL LATERALITY IN EARLY ONSET PSYCHOSIS: CONCLUSIONS.

5.1 Summary & General conclusions

Laterality in early onset schizophrenia

The primary aim of this thesis was to determine the status of cerebral laterality in patients with early onset schizophrenia. The first hypothesis was that early onset patients would demonstrate a reduction or loss of functional laterality when compared to healthy controls. In a series of neuropsychological and experimental divided visual field studies, patients demonstrated anomalous laterality in the form of reduced right hand skill and right eye preference as well as increased crossed hand-eye dominance. In addition, early onset patients showed reduced right ear advantage in auditory processing, as well as inability to modulate attention to, or away from, the dominant hemisphere. Finally, early onset patients showed abnormalities in lateralised components of lexico-semantic processing but not basic phonological processing. These anomalies occurred within the context of a general impairment of intellectual functioning suggestive of diffuse brain disturbance. In sum, the findings provide the first evidence that functional laterality is altered in early onset schizophrenia, and thereby support the first hypothesis.

The second hypothesis of this thesis was that cerebral asymmetry would be reduced or reversed in early onset patients. In MRI investigations, early onset patients revealed anomalous temporal lobe asymmetry in association with a general reduction of temporal lobe size, overall brain size, and increased lateral ventricle volume. These abnormalities provide the first clear evidence that cerebral asymmetry is altered in early onset patients, and provide broad support for the neuropsychological and DVF evidence. Furthermore, it was also predicted that reduction of cerebral asymmetry would be correlated with performance on laterality measures. Some support for this prediction was found; reduced IQ correlated with reduced left and right hemisphere volume; reduced REA in dichotic listening was associated with reduced left temporal lobe volume; and increased temporal lobe to brain ratio was associated with reduced efficiency in some aspects of lexico-semantic processing. These correlations were generally in line with predictions, and suggest a direct relationship between structure and function, however, given that the associations were

modest and some were opposite to expectations, the findings should be accepted with a degree of caution.

The significance of age of onset and sex

The secondary aim of this thesis was to examine the influence of individual differences in relation to laterality in schizophrenic patients. Firstly, it was hypothesised that age of onset would be related to the severity of the alteration in functional asymmetry. When earlier onset patients are compared to an arbitrarily defined later onset sample, they showed greater reduction of right ear advantage in dichotic listening as well as reduced hand and eye preference. Earlier onset was also significantly correlated with the severity of verbal IQ deficit as well as reduced right ear advantage on a dichotic listening task. In keeping with the suggestion that shift away from strong hand preference is detrimental to intellectual ability (Leask & Crow, 1997; Crow et al, 1998), a strong trend suggested that reduction in IQ was greater in mixed handed early onset patients than in those with stronger hand preference. These results agreed with the hypothesis that age of onset influences the degree of anomalous laterality, particularly in relation to language.

Second, it was hypothesised that sex would have a mediating affect on performance asymmetries and cerebral asymmetry. A number of findings in the present study point to an interaction between sex and laterality. In the DVF studies, males performed more poorly in relation to imageable word processing whereas females performed poorly in relation to emotional word processing. In addition, significant correlations between temporal structure, asymmetry and verbal IQ were only in significant in males. Such disturbances suggest that left lateralised components of language processes are affected in both males and females (although perhaps more profoundly in males) but the precise relationship between specific aspects of language processing sex and lateralisation remains to be determined.

In the MRI analysis, structural dimorphism was reflected in reduction of leftward asymmetry of the temporal lobes in males and reversal in rightward asymmetry in females. This agrees with the previously mentioned studies of that show specific alterations of asymmetry that relate to sex and age of onset (Highley et al 1998; 1999; McDonald, et al 2000). Highley et al's studies showed that

temporal lobe and fronto-occipital torque asymmetries go in opposite directions between the sexes in patients with schizophrenia. In the later study, Highley et al and McDonald et al showed that the relationship between anomalous asymmetry and age of onset was different between the sexes. Thus, taken together, these findings support a growing literature in adult patients that implicates age of onset and sex as important determinants of altered temporal lobe asymmetry (Bogerts, et al 1991) functional laterality (Lewine et al, 1997) and generalised cognitive deficits (Purcell et al, 1998). More specifically, the findings offer qualified support the assumption that early onset and male sex are particular risk factors in determining the severity of this alteration. Close inspection of specific temporal substrates (i.e. fusiform, parahippocampal and superior temporal gyri) involved in semantic memory would be a logical next step.

5.2 Relevance to the neurodevelopmental hypothesis of schizophrenia

The present findings are relevant to the neurodevelopmental explanation of schizophrenia in a number of ways. It is important to re-emphasise that altered functional and structural asymmetry was found in patients who were close to the time of first onset, with little exposure to medication or long-term hospitalisation. This suggests that these changes are unlikely to be related to antipsychotic exposure, institutionalisation or a protracted illness following onset. In addition, the findings are consistent with the majority of neuropsychological (Wexler et al, 1991; Ragland, et al 1999) post mortem (Brown et al 1986; Crow et al 1989; Highley et al 1999) and structural imaging studies of laterality in adult patients (Johnstone et al 1989; Rossi et al 1990). As such, their presence at this early age suggests that anomalous asymmetry it is characteristic of the illness and probably exists prior to the onset of symptoms.

Furthermore, the general characteristics of the early onset sample were in keeping with the characteristics of neurodevelopmental disorders including male predominance, subtle brain abnormalities, increased non-right handedness, and language impairments. Early onset patients in the present study demonstrated all of these characteristics to a greater or lesser extent. Thus findings support the contention that cortical development in later maturing temporal cortex is altered in schizophrenia (Crow et al, 1989). In particular, the MRI evidence of reversal of temporal

asymmetry suggests that the underlying disturbances may be intimately related to brain development. The specific assertion that sex differences in rates of development should be reflected in altered asymmetry was also supported, as reversal of asymmetry was sexually dimorphic in the early onset group. Moreover, the strongest associations between age of onset, structure and function were observed in males. If it is assumed that these findings reflect differing rates of cognitive and structural development of males and females in this age range, and the effect of early onset psychosis on this process, it is plausible that brain development is more delayed in males relative to females.

More generally, that altered structural asymmetry is found in association with basic, word level language disturbance provides some support for the hypothesis that asymmetry and language are integral in psychotic illness. The observed impairment was not consistent with a disturbance in the articulatory processes involved in addressed phonology but does implicate the semantic components involved in normal word recognition. This disturbance may underlie the modest reading delay observed in children who later go on to develop schizophrenia (Crow et al, 1995) and could explain some of the abnormalities observed at both sentence and discourse level speech. Further work is required in order to elucidate the relationship between word and higher-level reading and speech processes (see next section), but it is tempting to ascribe developmental significance to these results. That the dimorphic impairments appear to particularly affect semantic processes implicates medial and superior temporal, substrates that underlie lexical representation and semantic memory that are likely to form the basis of wider-level semantic impairments observed in schizophrenia (Chen and McKenna, 1994; McKay et al, 1996; Rossell, 1998). So, in view of the triad of association between language measures, temporal lobe anomalies and age of onset (albeit in males only) the pattern of positive results suggests that disturbances in asymmetry, language and cognitive ability are linked to alteration in the normal trajectory of hemispheric development as Crow has suggested. At this stage, it is not possible to invoke a causal connection but future studies would benefit from examining these factors together.

5.3 Methodological considerations

A number of methodological and theoretical issues need to be addressed before turning to directions for future research. Firstly, in chapters 2 and 3 of this thesis, the literature relating to cerebral asymmetry and functional laterality in neurologically normal subjects was reviewed prior to examining laterality in early onset patients. Such studies differ markedly in terms of method, stimuli and findings, and do always provide replicable evidence of lateral specialisation. Furthermore, performance asymmetries in normal subjects are potentially influenced by a range of factors other than innate specialisation including differences in stimulus luminance, arousal and attentional strategies (Beaumont, 1997; Richardson et al, 1997). Moreover, lateral asymmetries (specifically attentional ones) can change over the time course of development (Merola and Liederman, 1985; 1986; Hugdahl, 1987) a point that which may be of particular relevance when studying dichotic listening early onset patients. These problems are difficult to resolve and remain a general criticism of laterality research. In this thesis, considerable effort was expended in order to ensure that laterality effects were present in normal subjects (and to some degree replicable) before investigating them in patients with schizophrenia. In addition, attention was given to matching tasks in terms of difficulty and to control and account for individual differences. These precautions go some way in addressing the above concerns, but it is not always possible to account for extraneous variables.

Another general criticism of laterality studies is that performance asymmetries *infer* cerebral specialisation but they are not directly observed. With the increasing application of functional imaging such as PET, fMRI and MEG, it is becoming clear that processes previously believed to be unique to one or other hemisphere clearly involve both cerebral hemispheres and a degree of interhemispheric interaction. Thus, traditional notions of absolute hemispheric specialisation are being superseded by evidence for relative or complimentary specialisation. As Richardson et al (1997) point out and the present studies show, the relative involvement of each hemisphere is likely to differ according to the nature of the stimulus, the type of processing required and the stage of processing accessed. The current DVF experiments and the interpretation of hemispheric independence and/or callosal transfer are based upon a model that *infers* callosal transfer occurs

in the absence of specialisation, but it is equally possible that asymmetry results from poor or inefficient processing in the supposedly non-specialised hemisphere. This somewhat 'black box' approach is appropriate for unilateral experiments and provides useful information if combined with paradigms that are sensitive to both cerebral hemispheres, but provides limited information about the mechanics of interhemispheric transmission which may be a source of impairment (see chapter 2). As such, two potential improvements are suggested for future DVF studies in this area. Firstly, the use of bilateral conditions in order to better ascertain the possible effects of interhemispheric transfer (see next section), and secondly, co-registration with either fMRI and/or MEG in order to determine the spatial and temporal aspects of performance asymmetries.

Finally, it is worth considering that schizophrenia is unlikely to be a unitary disorder. Although some evidence in this thesis suggests that early onset patients are a relatively homogeneous group compared to adults, it remains that there is still considerable heterogeneity within schizophrenic samples in terms of symptomatology, cognitive impairment and structural anomalies. With regard to lateralisation, it appears that anomalies are more pronounced in individuals who would normally possess stronger laterality effects (i.e. males compared to females, right handers compared to left handers) and age of onset appears to be of considerable importance, it is also possible that disturbances influence, or are influenced by, other factors. Speculatively, complex interactions between proposed subtypes such as Crow's type I and II (Crow, 1980), Liddle's three syndromes (Liddle, 1996), or Gruzeller's (1996) active-withdrawn dichotomy may hold the key to understanding heterogeneity of schizophrenia. Thus, one drawback of the present study was that detailed assessment of symptomatology was not performed. In view of the fact that early onset is associated with greater symptom severity, poorer treatment response and worse social outcome (Lewine, 1981; Goldstein, 1988; 1997; Angermeyer et al, 1990; Lewis, 1992; Tamminga, 1997), the relationship between clinical symptomatology and altered asymmetry is an important area of future of investigations.

5.4 Future directions

Hemispheric independence and inhibition

In the previous section, the issue of interhemispheric interaction was alluded to as a direction for future research. A relevant question that emerges from the current study relates to how loss of cerebral dominance in adolescence influences interhemispheric processing and control. Several DVF studies of normal subjects suggest that there is a change in the relative involvement of the hemispheres in late childhood/early adolescence. In short, two developmental changes seem to occur around 10 to 12 years of age. First, there is increased information exchange between the hemispheres (i.e. information *sharing*), and second there is a consolidation of hemispheric independence as a consequence of lost plasticity (i.e. information *shielding*) (Merola and Liederman, 1985; 1986; Hugdahl, 1987). This developmental transition allows the hemispheres to operate as relatively independent processors and, at the same time, exchange information when required. The emergence of these abilities may be governed by the rate of myelination in the corpus callosum that is not complete until early adolescence (Yakovlev & Lecours, 1967). This is supported by recent evidence suggesting that callosal relay is acquired only in early adolescence (Waldie & Mosely, 2000).

David (1993) has made the case that schizophrenia is characterised by callosal hyperconnection and excessive callosal transfer. If this is true, two key questions are relevant to future studies of adolescent onset patients. First, it would be necessary to determine if the normal developmental transition to hemispheric independence has occurred and, if not, it is important to determine whether the anomaly is traceable to hemispheric sharing, hemispheric shielding or a combination of both. Speculatively, a lag or delay in the relative development of the hemispheres and loss of dominance could prevent establishment of hemispheric shielding and thereby prevent the inhibition of interhemispheric transfer. This is further supported by evidence suggesting that the normal age related decrease in corpus callosum size is not present in patients with schizophrenia (Woodruff et al, 1997). Thus, As Nasrallah (1985) has suggested, the intrusion of non-dominant hemisphere information upon thought and language processes could explain the often bizarre and semantically incoherent language of patients in the acute phase of the illness. In order to investigate this, closer

examination of the semantic abilities of the left and right hemisphere are required, as well as the mechanics of interhemispheric transmission and exchange in relation to semantic information. Finally, future studies should also take into account the role of sex and dimorphic brain growth in relation to the corpus callosum.

Lexico-semantics and the laterality of meaning

A number of important questions arise from the observation that semantic functions are abnormally lateralised in early onset patients. Foremost is the question of how far these impairments extend and what their relationship is to the observed impairments in higher-level semantic memory and language. In order to answer this, one must refer to the functions of each hemisphere. For example, Beeman (1998) has proposed the left hemisphere is specialised in the use of a relatively fine or focused semantic code that gains access a single relevant meaning or relevant feature associated with a word. The right hemisphere, on the other hand, employs a relatively coarse, broadly based code that activates a number of alternative features or meanings. This explains why the left hemisphere uses context more efficiently and is a more adept language processor, and might explain why the right hemisphere is more limited in relation to language abilities. In support of this concept, Coney and Evans (2000) have empirically demonstrated that the left hemisphere better processes dominant meanings of words whereas various subordinate meanings appear to be better processed by the right.

Patients with schizophrenia demonstrate anomalies of thought and speech in the selection and understanding of appropriate words and meanings. If language problems are secondary to a developmental failure of hemispheric dominance, this may be reflected in the regulation of dominant and subordinate meaning within the cortex. For example, at the single word level, intrusion of subordinate over dominant words or meanings might explain poor output and paralexias in semantic fluency tasks. At the sentence level, semantic misattribution or inability to place semantic constructs within a sentence frame could explain common symptoms such as 'loosening of association' and 'word salad'. At the level of discourse, misattribution of meaning extends to both input and output, and may have implications for attribution of intention and delusion. Thus, a number of research questions can be addressed in future studies; 1) are

appropriate meanings accessed through lexico-semantic processing? 2) are impairments attributable to intrusions from subordinate meanings and/or failure to appreciate context? And 3) what is the relationship between brain development (and delay) and the processes involved in establishing hemispheric independence? Potentially, the study of semantics processing within the context of laterality could provide a rare glimpse into the neural changes underlying the disorder and their functional outcome. Given that adolescence is an important juncture in both neural development and the establishment of hemispheric independence, early onset patients are the most appropriate group to examine these changes in.

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APPENDIX:

1. Participating units
2. Submitted manuscript - *American Journal of Psychiatry*, 2001
3. Submitted abstracts - *International Congress of Schizophrenia Research*, 2001

Temporal lobe asymmetry as the key to understanding sex differences in schizophrenia.

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ABSTRACT

Objective: The sex difference in age of onset and outcome of psychosis (earlier and worse respectively in males) is unexplained. We present here results from the Oxford Early Psychosis Project in which we investigated sex differences in brain structure, cerebral asymmetry and structure function relationships in adolescent onset patients with schizophrenia. **Method:** Intellectual function of 33 adolescent schizophrenic patients (20 males, 13 females, mean age = 16.1) and 32 controls (19 males, 13 females, mean age = 15.4) was assessed using the WAIS-R or the WISC-III, and all subjects were scanned using a 3D T1 weighted MPRAGE sequence on a 1.5T Magnetic Resonance (MR) system. The volumes of the left and right cerebral hemisphere, temporal lobe and lateral ventricle were estimated using the Cavalieri method in combination with point counting. **Results:** Patients demonstrated significantly lower IQ, smaller cerebral hemispheres and temporal lobes than controls, as well as larger lateral ventricles ($p < 0.05$). Significant sex x diagnosis interactions revealed a reduction of leftward asymmetry in temporal lobe volume in males with schizophrenia and reversal of rightward asymmetry in females with schizophrenia when compared to their age and sex matched controls. Significant correlations were found between verbal and full-scale IQ and cerebral hemisphere volume in male patients ($r > 0.47$, $p < 0.05$), but in no other group. **Conclusions:** An interaction between sex and diagnosis in both brain asymmetry and structure-function relationships is relevant to onset of psychosis and outcome in adolescence. Sex differences in temporal lobe asymmetry may be the key to understanding sex differences in age of onset and outcome in schizophrenia.

INTRODUCTION

Early onset of schizophrenia is associated with worse outcome; i.e. high rates of continuous illness, relapse and suicide as well as poor social and vocational functioning (1,2). Early onset is more common in males than females (3-5) but this finding is unexplained. In a retrospective study, 39% of males and 23% of female patients were reported as having experienced psychotic symptoms before the age of 19 (6). Age of onset and sex interact to determine outcome (7), and this interaction may reflect the operation of a single underlying variable.

Adolescent onset is associated with diffuse impairments on cognitive tests relative to both normal controls (8-10), and adult onset patients (11,12). Structural imaging studies show reductions in brain volume (13,14) and ventricular enlargement (15,16) in adolescent patients that are similar to those of adult onset patients. Earlier onset is associated with comparably greater reduction in temporal lobe measures (17,18) and asymmetry (19,20). Structure-function correlations have been found in early but not late onset patients (21) Johnstone et al 1989), and, more recently, interactions between age of onset and sex have been found on measures of functional laterality (22) Thus, early onset holds clues to the process underlying anomalies of development of the brain in schizophrenia.

Crow (23) argued that timing of onset is an index of a failure to establish dominance secondary to a genetically determined deviation in the trajectory of sexually dimorphic brain development. In support, some studies have reported lateralised changes that are present in male but not female adults with schizophrenia (21, 24, 25), while others have shown either lateralised differences in both sexes (26) or bilateral differences that differ between the sexes (25). Some studies (eg 26, 28, 20) have found that greater reduction of asymmetry is

associated with earlier age of onset but have not examined sex. The relationship between asymmetry, sex and onset of psychosis is therefore unclear.

We present here the first results from the Oxford Early Psychosis Project in which we measured verbal, performance and full-scale IQ in 33 adolescent patients who met the diagnostic criteria for schizophrenia and 32 age and sex matched controls. The Cavalieri method was used in combination with point counting in order to estimate the volumes of the left and right cerebral hemisphere, temporal lobe and lateral ventricles. In particular, we investigated sex differences in brain structure volume asymmetry, and in the relationship between brain structure volume and IQ.

Method

Subjects were recruited from adolescent psychiatric units across the south of England and the Warneford Hospital. All patients were diagnosed with schizophrenia according to the DSM-IV criteria (American Psychiatric Association, 1990) following a semi-structured interview using the Schedule for affective disorders and schizophrenia [KSADS] (29) administered by a trained psychiatrist. In total, 33 patients (20 males, 13 females, mean age = 16.1) met diagnostic criteria, most had experienced only one psychotic episode, and all were clinically remitted. The mean age of the subjects and estimated age of onset of schizophrenia are shown in Table 1). Exclusion criteria were: history of significant substance abuse, traumatic brain injury, epilepsy, or other neurological or psychiatric disorder. In addition 32 (19 males, 13 females, mean age = 15.4) age matched adolescent control subjects were recruited from local general medical practitioners within the Oxford area. The same exclusion criteria were applied. After a complete description of the study to the subjects and parents, written informed consent was obtained from both.

IQ Assessment

Patients and controls under 16 years were assessed by a trained clinical neuropsychologist (SLC) with the full version of the Wechsler Intelligence Scale for Children – III [WISC-III-UK Version] (30). Those over the age of 16 years were assessed using the full version of the Wechsler Adult Intelligence Scale–Revised [WAIS-R- UK Version] (31). Whenever possible, testing was performed in one uninterrupted session, however, in order to reduce potential fatigue and maintain concentration, some patients were tested over multiple sessions. Standard verbal, performance and full-scale intelligence quotients were calculated.

MR image acquisition and analysis

MR images were acquired using a 1.5T Magnetom Vision whole body system (Siemens Medical System Inc., Erlangen, Germany). One hundred and sixty coronal T1-weighted images were obtained with a 3D spoiled gradient echo (SPGR) pulse sequence (TR of 35ms, TE of 5ms and flip angle of 35°). The Field of View (FOV) of the images is 20 cm, and each image refers to a contiguous section of tissue of 1.5 mm thickness.

The left and right temporal lobe were optimally visualised, and their volumes best measured, on image sections oriented perpendicular to the long axis of the hippocampus (32, 33). These sections were obtained by reformatting oblique sections through the acquired 3D data using NRIA software (Brain Behaviour Laboratory, University of Pennsylvania, USA) running on a ULTRA 10 workstation (SUN Microsystems, CA, USA), where the 256 x 256 x160 acquired voxels of side 0.78mm x 0.78mm x 1.5mm were linearly interpolated to 256 x 256 x 256 cubic voxels of side 0.78mm. The resulting 0.78mm thick contiguous coronal sections lie approximately perpendicular to the mean direction of the long axis of the hippocampus in the

left and right cerebral hemispheres. This was also a convenient sectioning direction for volume estimation of the left and right cerebral hemisphere and lateral ventricles.

Unbiased estimates of brain structure volume were obtained within EasyMeasure software (www.easymeasure.co.uk, see 34) by using the stereological method of point counting (35). The posterior limit of the temporal lobe is defined as the point where the lateral ventricles divide into the frontal and temporal horns. The cerebral hemispheres were separated from the brain stem at the superior limit of the pons. A more detailed description of the definitions has been given previously (33).

For estimating the volume of each structure of interest, a series of equally spaced MR images were sampled in a direction parallel to the long axis of the hippocampus, beginning from a random starting position. Each image was overlain with a test system comprising a regular array of test points and the number of points lying within the transect through the structure of interest recorded. The volumes of the cerebral hemisphere, temporal lobe and lateral ventricles were measured with a grid spacing of 1.17cm (15 pixels), 0.781cm (10 pixels), and 0.234cm (3 pixels), and a slice interval of 1.17cm, 0.469cm and 0.391cm respectively. Unbiased estimates of transect area were obtained by multiplying total number of points recorded by the area corresponding to each test point. An unbiased estimate of structure volume was obtained as the sum of the area of the consecutive systematic sections multiplied by the distance between sections. Sectioning and point counting intensities were optimised to achieve a coefficient of error (CE) on the Cavalieri estimates of volume of between 3 and 5 %, as previously described (35). All estimates were obtained by a single rater (CEM) who had previously carried out an inter/intra rater reliability study with two other raters. Intra-class correlation coefficients (ICC) were greater than 0.9 for the lateral ventricles, and 0.8 for the temporal lobe and cerebral hemisphere

An asymmetry index was computed for each structure by subtracting the volume of the left from the volume of the right and expressing this difference as a percentage of their mean volume, i.e. $(R-L)/((R+L)/2)$. The proportion of lateral ventricle and temporal lobe volume to cerebral hemisphere volume were calculated for the left, right structures.

Results

Means and standard deviations for age, age of onset in patients, and verbal (VIQ), performance (PIQ) and full-scale IQ (FSIQ) are presented in Table 1. Means and standard deviations of volumes of left and right cerebral hemisphere, lateral ventricle and temporal lobes (ml) and asymmetry indexes of each structure for the male and female patients and controls are shown in Table 2. There are no significant differences in mean age between any of the groups of male and female patients and controls but in order to control for normal development, age was entered as a covariate in a general linear model. Main effects and interactions between diagnosis and sex were examined in relation to IQ and volumes of the left and right cerebral hemisphere, temporal lobe and lateral ventricle. Statistical results are shown in Table 3.

Patients had significantly lower verbal, performance and full-scale IQ than controls, but there were no effects of sex or sex*diagnosis interaction. Volumes of left and right cerebral hemispheres and temporal lobes were significantly reduced in patients relative to controls. Patients also had a significantly larger left and total (left + right) ventricle volume to brain volume ratio. There were significant main effects of sex in volume of the left and right cerebral hemispheres and temporal lobes with males larger than females in all cases. There was a significant interaction between diagnosis and sex in temporal lobe asymmetry (see Figure 1). Male patients exhibited reduced leftward asymmetry compared with male controls,

whereas female patients exhibited leftward asymmetry compared to rightward asymmetry in female controls. There was a strong trend to significance in left temporal lobe volume as the difference between male patients and controls was larger than the difference between female patients and controls.

Correlational analysis

The relationships between brain structure volume and cognitive function were assessed separately in male and female patients and controls. There were no significant correlations between age and structure volume or asymmetry in any of the groups. The estimated age of onset of psychosis was negatively correlated with left temporal lobe volume in the male, but not the female patients ($r = -0.47$, $p = 0.04$). Both verbal and full-scale IQ were significantly correlated with left ($r=0.47$, $p=0.042$ and $r=0.50$, $p=0.03$ respectively) and right ($r=0.56$, $p=0.013$ and $r=0.55$, $p=0.015$ respectively) cerebral hemisphere volume in male patients. There was a similar non-significant trend in the female controls, but no such relationship in the male controls or female patients. These correlations are not significant after Bonferroni correction for multiple comparisons.

Discussion

The main finding is that adolescent onset is associated with significant reduction in IQ and brain volume as well as significant alteration in cerebral asymmetry. In particular, consistent with other imaging (21, 36) and post-mortem (37, 26, 38) studies, we found evidence for alterations in temporal lobe asymmetry. In male patients, leftward asymmetry was reduced in comparison to male controls, whereas a slight rightward bias in normal females was reversed to a leftward bias in female patients. Crow (26, 23) has proposed that schizophrenia arises from an abnormality in the genetic control of cerebral asymmetry, and several imaging studies

are consistent with this general view (39-45). The present findings support the more specific assertion that this developmental anomaly is sexually dimorphic. Such a conclusion is consistent with the findings of several other imaging studies (21, 24, 25) and particularly with findings of recent post-mortem studies of asymmetries across the superior cortical surface (19) and the relationship between temporal lobe asymmetry and age of onset (35, 46). In each case an interaction between psychosis, sex and cerebral hemisphere points to lateralization as the variable that can explain the sex differences in schizophrenia.

The sex difference applies also to the relationship between brain structure and function. In particular, we observed significant correlations between verbal, full-scale IQ and cerebral hemisphere volume in male patients but not in female patients or controls. These findings differ from previous studies relating brain structure and IQ in both controls and adults with schizophrenia (47-49). In a study of 67 normal subjects, Andreasen et al (48) found that IQ correlated significantly with the volume of the cerebral hemispheres, temporal lobe, cerebellum and hippocampus in both males and females. In a subsequent study of adults with schizophrenia, Flaum et al (49) reported that the pattern of structure-function correlations in female patients were similar to those of female controls, but male patients demonstrated no significant structure-function correlations. We suggest that the present findings reveal the sex difference more clearly as a consequence of the age and developmental stage of our sample. In normal subjects, the male brain develops more slowly (50) and is more asymmetric than that of females (51, 52). Adolescence is a critical stage in development in which there is an increase in the proportion of white matter relative to a reduction in the proportion of grey matter (52-54). Moreover, the volume of the lateral ventricles increases significantly in adolescence but only in males (52, 55). Thus, some aspects of normal brain development

appear to be delayed in males relative to females, and early onset of psychosis may reflect an anomaly of growth resulting in altered brain morphology and cognitive function.

If rates of cognitive and structural development differ in males and females in adolescence, and these differences relate to the onset of psychosis, lateralization could hold the key to understanding the relationship. As noted above, the female brain grows faster and is more symmetrical than that of the male but mean age of onset of psychosis is earlier in males than females. Moreover, females as a group are more strongly right-handed and less likely to be left-handed than males (56, 57). Thus, if females are lateralizing more strongly and reach the plateau of brain development earlier than males, it appears to follow that risk of psychosis is associated with failure to achieve adequate cerebral lateralisation (58). This explanation of the sex difference is supported by others who have found evidence that early onset and male sex are associated with performance decrements on specific laterality measures (22) and greater VIQ-PIQ discrepancy (59) consistent with hypolateralisation. Our results provide further support for the hypothesis but it remains to be determined whether the underlying mechanism is the same in the two sexes or in some significant way different. Notwithstanding, the present results draw attention to the importance of studying males and females separately, and to the temporal lobes as the locus of lateralisation.

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Table 1. Mean age, age of onset and IQ scores (verbal [VIQ], performance [PIQ] and full scale [FSIQ]) for the male and female patients and controls. Standard deviations are shown in parentheses.

	N	Age (years)	Age of onset	VIQ	PIQ	FSIQ
Male patients	20	16.2 (0.9)	13.5 (4.9)	86.5 (13.5)	81.8 (13.7)	83.2 (13.1)
Male controls	19	15.2 (1.7)		99.3 (16.0)	97.2 (15.2)	98.4 (14.8)
Female patients	13	16.0 (1.4)	12.9 (5.9)	84.5 (13.4)	77.8 (16.6)	79.5 (13.4)
Female controls	13	15.7 (2.2)		107.8 (16.9)	107.7 (14.4)	108.4 (15.2)
Total patients	33	16.1 (1.1)	13.3 (5.2)	85.7 (13.3)	80.3 (14.8)	81.8 (13.2)
Total controls	32	15.4 (1.9)		102.8 (16.7)	101.4 (15.5)	102.5 (15.5)

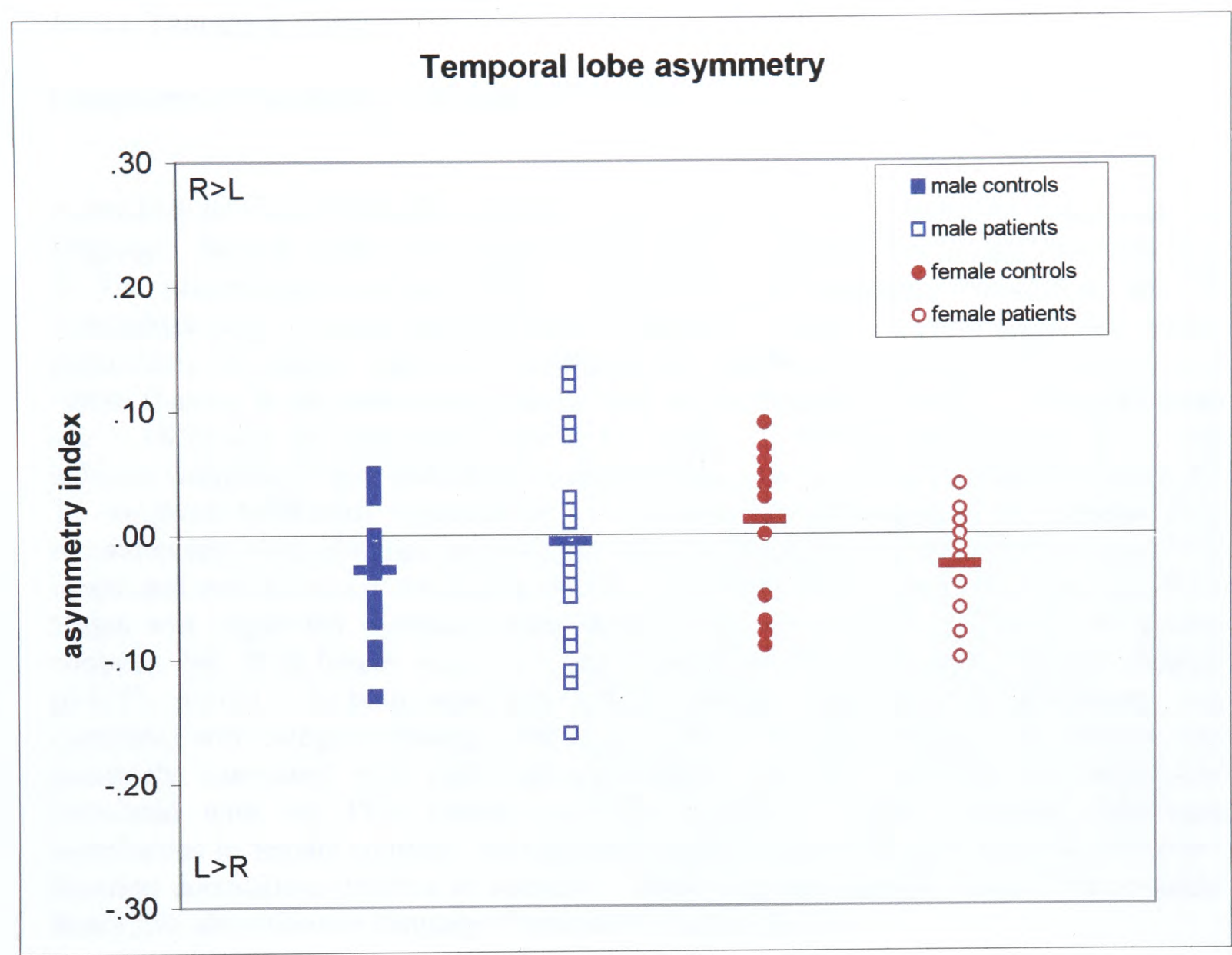
Table 2. Mean volumes (ml) of the left and right cerebral hemisphere, lateral ventricle and temporal lobe and mean asymmetry indices for each structure in the male and female patients and controls. Standard deviations are shown in parentheses.

	Cerebral hemisphere		Lateral ventricle		Temporal lobe		Asymmetry		
	left	right	left	right	left	right	H'sphere	Lateral ventricle	T' lobe
Male patients	536.3 (36.5)	539.1 (37.6)	8.2 (4.9)	8.2 (7.7)	76.8 (6.7)	76.3 (6.8)	0.48 (3.4)	-8.73 (27.3)	-0.15 (8.1)
Male controls	574.7 (40.3)	572.6 (43.1)	5.8 (3.1)	6.0 (3.1)	84.9 (7.4)	82.5 (6.3)	-0.40 (2.5)	3.11 (42.4)	-2.82 (5.9)
Female patients	499.5 (33.7)	496.4 (34.6)	5.7 (3.9)	5.5 (3.5)	73.7 (9.5)	72.1 (9.8)	-0.52 (3.3)	-2.50 (32.5)	-2.48 (4.4)
Female controls	516.5 (55.5)	518.9 (53.3)	5.1 (1.7)	4.2 (1.5)	73.9 (8.3)	75.0 (9.6)	0.53 (1.7)	-19.32 (22.2)	1.25 (6.3)
Total patients	521.8 (39.4)	522.3 (41.7)	7.3 (4.7)	7.1 (6.5)	75.5 (7.9)	74.7 (8.2)	0.09 (3.6)	-6.32 (29.1)	-1.05 (6.9)
Total controls	551.1 (54.6)	550.8 (53.8)	5.5 (2.7)	5.2 (2.7)	80.5 (9.4)	79.4 (8.5)	-0.02 (2.2)	-6.01 (36.9)	-1.17 (6.3)

Table 3. Analyses of variance for IQ and structure volumes and asymmetry. Results are shown for the main effects of sex and diagnosis, and for sex*diagnosis interactions. Results for the lateral ventricles and temporal lobes are shown both raw and as a proportion of cerebral hemisphere volume (Prop).

Dependent variable			Sex			Diagnosis			Sex * Diagnosis		
			F	df	p	F	df	p	F	df	p
Verbal IQ			0.80	1:66	0.375	19.99	1:66	0.000	2.03	1:66	0.160
Performance IQ			0.94	1:66	0.336	32.78	1:66	0.000	3.32	1:66	0.074
Full scale IQ			0.88	1:66	0.352	34.57	1:66	0.000	3.46	1:66	0.068
Cerebral hemisphere	Left		18.20	1:66	<0.001	7.95	1:66	0.006	1.57	1:66	0.215
	Right		17.58	1:66	<0.001	7.16	1:66	0.010	0.47	1:66	0.497
Temporal lobe	Left	Raw	11.39	1:66	0.001	4.29	1:66	0.043	3.97	1:66	0.051
		Prop	0.01	1:66	0.906	0.03	1:66	0.859	1.18	1:66	0.281
	Right	Raw	7.95	1:66	0.006	4.18	1:66	0.045	0.54	1:66	0.466
		Prop	0.23	1:66	0.634	0.01	1:66	0.906	0.03	1:66	0.856
Lateral ventricle	Left	Raw	2.63	1:66	0.110	2.53	1:66	0.117	0.82	1:66	0.367
		Prop	1.32	1:66	0.255	4.37	1:66	0.041	1.03	1:66	0.313
	Right	Raw	3.16	1:66	0.081	1.93	1:66	0.170	0.11	1:66	0.738
		Prop	2.22	1:66	0.142	2.95	1:66	0.091	0.13	1:66	0.718
Cereb. hemisphere asymmetry			0.02	1:66	0.887	0.12	1:66	0.733	2.09	1:66	0.153
Temp. lobe asymmetry			0.41	1:66	0.526	0.02	1:66	0.893	4.19	1:66	0.045
Lat. ventricle asymmetry			0.87	1:66	0.355	0.34	1:66	0.563	3.00	1:66	0.088

Figure 1. Temporal lobe asymmetry for the male and female patients and controls. The interaction between sex and diagnosis is significant.



Verbal fluency and the paracingulate sulcus in adolescent onset schizophrenia: Evidence for altered of lateralisation

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According to Crow [1], schizophrenia results from a lack of cerebral dominance for language. Several studies have found verbal fluency impairments in schizophrenia [e.g. 2]. The paracingulate sulcus (PCS) is associated with language function in the left hemisphere [e.g. 3], and Yucel [4] found leftward asymmetry in PCS length in controls, particularly in males. Here we investigate the relationship between PCS length and verbal fluency in 26 adolescent patients with schizophrenia (14 male, 12 female, mean age = 16.2) and 29 adolescent controls (17 male, 12 female, mean age = 15.3). All subjects completed letter and category verbal fluency tests and were scanned using a 3D T1 weighted MPRAGE sequence on a 1.5T Magnetic Resonance (MR) system. PCS measurements were obtained according to Yucel's [4] criteria. Correlations between PCS length and verbal fluency revealed group and sex differences. In male controls, right PCS length was negatively correlated with category fluency ($r=-0.76$, $p<0.001$). In female controls, left PCS length was positively correlated with letter and category fluency ($r>0.71$, $p<0.01$). In both male and female controls, leftward PCS asymmetry was correlated with category fluency ($r>0.64$, $p<0.026$). In male patients, letter fluency was positively correlated with rightward asymmetry ($r=0.726$, $p<0.003$) and negatively correlated with left PCS length ($r=-0.556$, $p<0.039$). There were no significant correlations in female controls. In summary, patients had reduced or reversed structure-function correlations relative to controls. These findings provide support for sexually dimorphic alterations in language dominance in schizophrenia.

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Priory Hospital, Southgate.

