Measurement, Classification and Conceptualisation of Atypical Handedness in Schizophrenia

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ABSTRACT

Atypical handedness is found to be more prevalent in schizophrenia patients than in psychiatric and normal controls, suggesting atypical brain lateralisation, particularly of regions associated with language. This 'behavioural aberration' is commonly considered as a marker of disturbed neurodevelopment, which is usually indexed by minor physical abnormalities. A prevailing view in the literature is that the atypical lateralisation of hand preference provides an additional index for the neurodevelopmental hypothesis of schizophrenia. Consistent with this hypothesis, an atypical lateralisation of hand preferences can also be considered as a consequence of environmental agents that might have interfered with early embryonic development. Notwithstanding the above, an atypical lateralisation of hand preferences can occur as a result of genetic factors as well as an interaction between genetic and environmental factors.

The overall objective of this thesis was to advance existing knowledge on atypical laterality in schizophrenia by addressing its various (though related) aspects, including measurement, classification and conceptualisation. Atypical lateralisation of hand preferences in schizophrenia patients was approached by five separate studies.

The aim of the first study was to provide a new insight in the prevalence of various atypical handedness categories in patients suffering from schizophrenia. A critical review of existing empirical data suggests that, in contrast to the prevailing view of increased mixed-handedness in schizophrenia patients, the shift in the handedness distribution is leftward, including an increased prevalence of left-handedness. A clear leftward shift implies either unilateral cerebral insult or disrupted genetic mechanism for development of cerebral asymmetry. The findings from this study are at variance with an extended concept of pathological left-handedness (early developmental and

bilateral cerebral insult), which has been proposed as the casual mechanism for atypical handedness in schizophrenia.

The second study addressed an overarching issue in laterality research in schizophrenia, namely the classification of handedness and the definition of cut-off points for defining different handedness categories. Due to the lack of clear and uniform handedness categorisation, many studies in laterality research have depended on *ad hoc* and non-standardised cut-offs, thus generating considerable inconsistency between studies. In contrast to the over-categorisation of hand preferences (eg. eight handedness categories), this study found that a three-way classification of handedness (left-, mixed-, and right-handedness) is sufficient to describe the variety of manifest handedness patterns. In addition, this study investigated which cut-offs 'best' separate mixed-handedness from clear left- and right-handedness.

The third study investigated the relationship between atypical lateralisation of hand preferences and schizotypal personality structure (hereafter schizotypy). Study results indicated that these two phenomena are independent in the general population, but not in the population of schizophrenia patients. As expected, there was a small but statistically significant association between mixed-handedness and the schizotypy factor of Cognitive Perceptual Dysfunction in schizophrenia patients.

The fourth study of this thesis was a multivariate modelling of several laterality indices in patients with schizophrenia, their unaffected and biologically unrelated siblings, and unaffected and unrelated controls. The laterality phenotypes derived in all groups were also investigated with regard to multiple cognitive measures, personality traits, and, for patients only, clinical variables such as number of admissions and length of stay in hospital. The results of this study showed a weak but consistent association between the two laterality subtypes ('left' and 'mixed') and poorer cognitive performance in schizophrenia patients. These two laterality phenotypes in schizophrenia patients were differently associated with parental left-handedness, ‘left’ with mothers’ left-handedness and ‘mixed’ with fathers’ left-handedness. These findings indicate that a multivariate integration of laterality measures and familial cofactors into complex laterality phenotypes might increase the likelihood of discovering the genetic, developmental, and environmental basis of cerebral and behavioural lateralisation.

The fifth and final study was concerned with the measurement of handedness by the most widely used instrument for the assessment of handedness, the Edinburgh Handedness Inventory. The specific objective of this study was to emphasise the importance of measurement issues in this area of research and to provide an improved measurement model. With regard to the latter, this study provided a psychometrically improved alternative to the standard form of the Edinburgh Handedness Inventory.

Overall, this thesis argues that the causes of atypical lateralisation of hand preferences are due to combined genetic and environmental factors and that its use as a marker of vulnerability to schizophrenia is limited. A cautious interpretation of various associations between the laterality and other measures, particularly cognitive measures, is advised until a broad agreement on the true nature of handedness is reached.

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Preface

This thesis is organised in the *series-of-papers* fashion, and comprises five related studies bounded by General Introduction and General Conclusions sections. This choice of the thesis organisation was driven by the following reasons: (a) to enable a quicker communication of results within the research community, (b) to avoid the "conflict between preparing the thesis for examination and preparing papers for publication" (UWA, Submission of a Thesis as a Series of Papers, 2004), (c) to use the feedback from reviewers (of published papers) to strengthen the quality of the thesis, and (d) to ease the process of thesis examination.

The thesis is divided into three parts. Part I is made of two sections, each containing a review of the pertinent literature, and ending with the rationale for the thesis and the specific objectives of the five studies included within it. The first section is concerned with handedness in the normal population, and provides the background knowledge on the phenomenon of hand dominance in humans and its relation to cerebral lateralisation. This literature review elaborates extensively on all relevant issues such as epidemiological information, theoretical concepts of handedness, neuropsychology, and measurement of hand dominance. The second section contains a review of the literature on handedness in schizophrenia and builds the case for five specific studies presented in Part II.

Part II of the manuscript comprises five scientific papers which have arisen from this thesis, and are at various stages of the publication process. One of the papers is already published ("Towards an improved measure of the Edinburgh Handedness Inventory: A one-factor congeneric measurement model using confirmatory factor analysis", in *Laterality*), and one is in press ("Categorisation and validation of handedness using Latent Class Analysis", in *Acta Neuropsychiatrica*). The two papers have been resubmitted after revision ("Handedness in schizophrenia: a quantitative review of evidence", to *Acta Psychiatrica Scandinavica*, and "Laterality phenotypes in schizophrenia patients, their siblings and control subjects: associations with clinical and cognitive variables", to *British Journal of Psychiatry*). The last paper ("Schizotypy and mixed-handedness revisited", in *Psychiatry Research*) is currently under review.

It should be noted that the first study presented in this thesis represents a quantitative and comprehensive review of the literature, presenting the most extensive examination of empirical evidence on this subject to date. For that reason, it has been separated from the overall literature review.

Finally, Part III of this thesis integrates the results and findings from all five separate studies and places them in a broader research perspective on schizophrenia and laterality, including an outlook for future work in this field.

PART I

Introduction and Literature Review

1. Handedness

1.1 Definition, measurement, classification and incidence

Handedness is usually defined as a tendency to use one hand rather than the other to perform most activities and is often considered as the most easily observed aspect of cerebral lateralisation (Peters, 1995) and as an exclusively human feature (Annett, 1985; Corballis, 1991). A similar lateral bias has been occasionally reported in few species such as chimpanzees (Hopkins, Dahl, & Pilcher, 2001), birds (Hunt, Corballis & Grey, 2001), rats (Elalmis, et al., 2003) or even domestic dogs (Wells, 2002). However, a prevailing view is that behavioural lateralisation in non-human species is influenced rather by chance (see Annett, 1985, 2002) and, if it exists, is well below the population bias as in humans (Corballis 1999), where 9 out of 10 people display apparent strong right hand dominance. Human hands are architecturally symmetrical, but they markedly differ in functional asymmetries such as the tendency to perform various manual activities more frequently with one (in the majority of people the right hand) than the other hand, and a greater motor proficiency of dominant hand over another. As these two aspects of hand dominance (preference and proficiency) significantly but imperfectly correlate (the preferred hand is usually more skilful than the non-preferred), a few researchers (Porac & Coren, 1981; Provins & Magliaro, 1993) concluded that these aspects are relatively independent phenomena. In addition, large intra-individual variations in hand preferences make a popular dichotomous distinction on left- and right-handers insufficient for a clearer understanding of this phenomenon. Some people are inconsistent in hand preferences, using a preferred hand for one and non-preferred hand for another manual activity. Such an inconsistency in hand preferences is usually described as mixed-handedness, in contrast to ambiguous handedness, where inconsistent use of hand for the same manual activity. Another relevant distinction is related to degree of hand preferences. Two right-handers (i.e. identical direction of hand preference) may differ in the degree of preference – one uses *always* the preferred hand for most activities, whereas the other (although right-handed) *sometimes* uses the non-preferred hand for certain activities. The complexity of this particular behavioural asymmetry can be metaphorically described as, to paraphrase a popular Churchill's description of Russia, 'a riddle wrapped in a mystery inside an enigma'. No wonder that the search for causes of this trait still echoes an ancient debate between Plato, a right-handed Greek philosopher who argued that handedness is learned, and his left-handed student Aristotle who, in his *Metaphysics,* claimed that people are right- or left-handed by nature. Pure phenotypic expression of handedness is further clouded by cultural pressures, affecting thus the validity of handedness measurement. Left-handers are forced to live in a world designed for the right-handed majority (shaking hands, scissors, music instruments, can openers, etc), with both left- and right-handers over-practicing their inherent preferences, such as exclusive use of preferred hand for writing. It has been shown (Coren, 1992) that the incidence of left-handedness is remarkably stable over time, suggesting that the small minority of left-handed individuals has been present since prehistoric times. The degree of cultural contribution is very hard to estimate, because the dominant majority (right-handers) has already shaped their environment according to their requirements. As Peters (1990) noted, cultural norms modify the inherent lateralisation of hand preferences, making thus the relationship between a particular phenotype and a particular genotype unclear.

In addition, it is not clear why only the phenotype for handedness should be considered as sufficient to represent a variety of other behavioural lateralities in humans. Handedness may not be fully representative of all other behavioural asymmetries, since (even within the handedness domain) preference imperfectly correlates with hand strength and hand skill. Inconsistencies between hand (for example) and other lateralities such as foot or eye dominance are even higher.

Two common methods for the assessment of handedness include self-reported measures of handedness (assessed by hand preference questionnaires) and hand performance measures (assessed by manual tasks such as tapping and peg moving), which are more time consuming. The use of various questionnaires is more common then performance tasks, as they have the advantages of being easy to administer and suitable for group testing. However, questionnaires are usually criticised due to bias in their choice of typical activities (Rigal, 1992), and a lack of factor clarity (Bryden, 1977), both of which may affect the validity of findings. It has been recommended (Bryden, 1977) that an unidimensional (one factor) handedness assessment is more reliable, and that items such as using a broom, which is a bimanual activity, and opening a box-lid, should be discarded. Internal consistency (i.e. that all items measure the same aspect of handedness) is a desirable property of any scale. Interestingly enough, development of psychometrically sound handedness scales has almost ceased since the introduction and widespread use of two questionnaires, the Edinburgh Handedness Inventory (Oldfield, 1971) and Annett's handedness scale (Annett, 1970). An overwhelming use of these scales in laterality research may lead to the conclusion that psychometric aspects of handedness measurement have reached their peak. Other scales such as Waterloo handedness questionnaire (Steenhius & Bryden, 1989), Shimizu handedness scale (Shimizu & Endo,1983), hand preference demonstration tests (Soper et al., 1986) are scarcely used in psychiatric research. Hand performance measurement, as an alternative approach to handedness assessment, is considerably less practical due to individual testing, but it provides valuable additional information. There have been many debates over which measure of handedness is more suitable – preference or performance. For some authors (Annett, 1972) hand preferences depend on underlying differences in hand skill. This means that performance tests can give us an objective and reliable measure of handedness. However, there are opposite views, which treat hand preference and hand performance as *separable* aspects of behaviour which could be mediated by separate mechanisms (Porac & Coren, 1981). Moreover, they have suggested that hand skill and preference might be orthogonal dimensions. The lack of both significant and high magnitude correlation between performance and preference is used repeatedly to argue that these two measures are relatively independent (Bishop, 1990a). Recently, Brown et al. (2004) have shown that a modest prediction of hand preference could be improved by using simultaneously several proficiency measures. Finally, Rigal (1992) recommended a unification of these measures, arguing that 'handedness should be established simultaneously through preference questionnaires and performance tests and that only subjects falling simultaneously into the same category on both measures be kept'. This recommendation has rarely been practised.

The most conventional classification (usually based on writing hand) is a simple dichotomy, with people classified as either left- or right-handed. While many authors see handedness as a dichotomy, some prefer other classifications. There are several classifications of handedness in the literature, the most common of which are described in Table 1.1.

The specificity of the ambiguous-handedness (AH) category has been advocated by Satz and Green (1999), who argued that this handedness subtype may have a specific aetiology compared to other handedness subtypes. In contrast to mixed-handed individuals, who are variable in hand preferences between manual tasks but consistent within particular task, ambiguous-handers are characterised by within-task inconsistency

Table 1.1 Description of the most common classifications of handedness in the literature

Classification	*Description*	*Common assessment*
Left or right	Common and convenient classification which assumes that handedness can best be understood as a dichotomous phenomenon	Writing hand or handedness questionnaire which splits individual responses into two, a left and right group
Left-, weak-left, weak-right, or right	Although this classification contains four categories, it essentially considers handedness as dichotomous entity.	Various handedness questionnaires, either self-report scales or sets of demonstration tasks
Left, mixed, and right	Increasingly used classification in medical research, which assumes that beside left- and right-handedness there are individuals without strong behavioural lateralisation in either direction. The mixed-handedness category comprises individuals with both weak left- and right-handedness.	Various handedness questionnaires, either self-report scales or collections of assorted demonstration tasks
Ambiguous or non-ambiguous	The concept of ambiguous handedness is introduced to highlight the difference between *within*- and *between*-task variability. Contrary to the mixed-handed individual who prefers one hand for one task and the other for another task, an individual with ambiguous handedness changes hand preference for a single task (i.e. within task inconsistency).	Soper et al. 1986. Hand Preference Demonstration Task
Non-right versus Right	This classification separates strong or consistent right-handers from weak right-, mixed-, and left-handers together. It is common in medical research, where is often assumed that right-handedness is a standard for of lateralisation and non-right handedness is 'anomalous' lateralisation.	Various handedness questionnaires, either self-report scales or sets of demonstration tasks
8 handedness classes	This classification is based on Annett's work (1970) and comprises two fully lateralised categories (left and right), and a number of handedness patterns, which combined provide a broadly defined mixed-handedness category	Annett's Handedness Inventory only

There have been several attempts to introduce other handedness classifications. The one that has received the most attention is division of the handedness distribution into two categories: (a) strong right-handedness, and (b) non-right-handedness. This categorisation originates from the work of Geschwind and Galaburda (1985) and reflects clearly their theoretical standpoint in which non-right-handedness is a behavioural index of *anomalous* dominance. Schachter, Ransil, and Geschwind (1987) have suggested as a method for non-right-handedness a cut-off of +70 on the Edinburgh Handedness Inventory. That is, subjects with laterality quotient of +70 and higher on this scale would be classified as strong right-handers, with all others in range from –100 to +69 classified as non-right-handers. In practice, this classification pools mixed- and left-handers together to form an *anomalous*, non-right-handedness subtype. However, some authors consider that handedness should not be simply lumped into categories, but rather be measured as an authentically continuous dimension. Annett (2000, p. 501), representing the latter, has throughout her work held that "confusions in the literature arose from attempts to impose a typology on the variable expression of handedness". Notwithstanding its continuous quality, a categorical approach to handedness still dominates current research practice in psychiatry. The issue of cut-offs for handedness classification will be specifically addressed in the second study of this thesis.

Despite a common belief that the distribution of handedness in general population can be approximated by the 9:1 ratio (i.e., in ten people there are nine right- and one left-hander) as well as its similarity across diverse cultures, races, and geographic regions, such a simplification has been seriously challenged (Singh & Bryden, 1994; McManus, 2002; Raymond & Pontier, 2004). However, reporting different proportions of left handed-subjects is not unusual. Hardyck and Petrinovich (1977), for example, reported that indices of left-handedness vary in range from low of 1% to a high of 30%, and conclude that this was due to different methods for determination of the handedness. In their earlier study (1975), Hardyck, Goldman and Petrinovich found a statistically significant, but with weak effect size, association between races and handedness in a large sample of school children (N = 7,688). They concluded, however, that differences in the prevalence of handedness subtypes are primarily culturally determined.

The first study investigating specifically the incidence of right- and left-handedness in different cultures was conducted by Perelle and Ehrman a decade ago. The handedness survey was administered to 12,000 subjects from 32 countries. This study (Perelle & Erhman, 1994) showed that the incidence of right-handedness (defined by writing hand) significantly varies over different cultures (Figure 1.1).

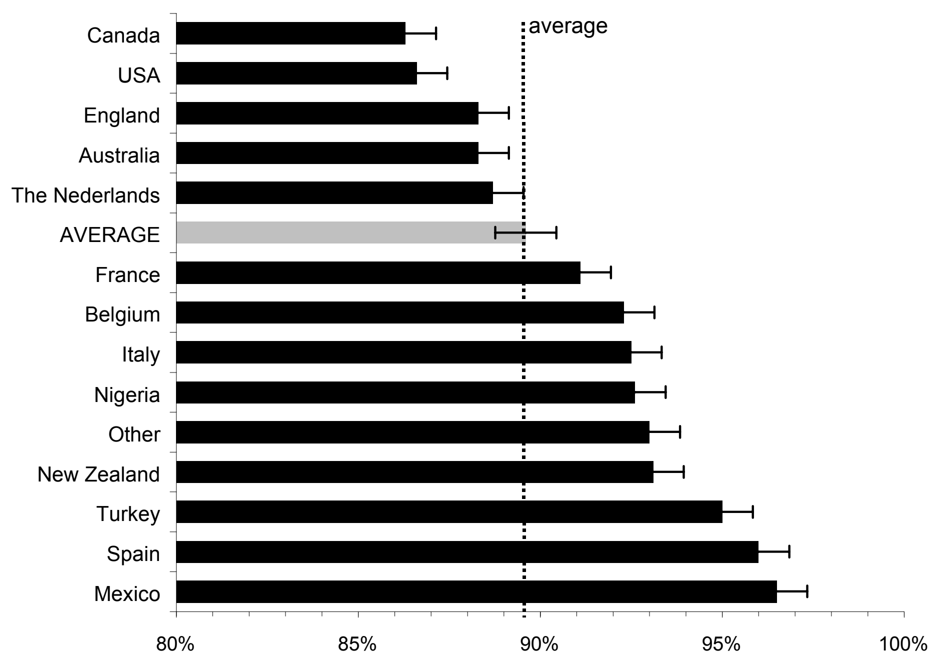

Figure 1.1 Percentages of right-handed individuals in 13 countries. Solid black bar and vertical dashed line indicate the average number of right handers in the sample. Several countries with small national samples are combined as other.

Although the observed discrepant incidence rates across various countries are usually interpreted in terms of the cultural tolerance towards left-handedness, a closer examination of the findings from this study suggest that differences in the preponderance of left-handedness between various countries can not be easily attributed to cultural tolerance. A distinction on developed and undeveloped countries is not of use, as developed countries feature contrasting percentages of right-handedness – 86.3% right-handers in Canada versus 93.1% in New Zealand and 92.5% in Italy.

To date the most ambitious study (Raymond & Pontier, 2004) addressing specifically the geographical variation of handedness by pooling 81 samples from 14 countries (over 1.2 million of individuals studied between 1922 and 1998) confirmed a significant cross-cultural variation of left-handedness. The potentially confounding variables such as sex, age of respondents and date of the study were controlled. A cross-cultural investigation of hand preferences was conducted using throwing and hammering as indicators of behavioural lateralisation. Observed geographical differences in this study were explained in terms of handedness polymorphism, by suggesting (Raymond & Pontier, 2004) that the dominance of each hand is associated with certain benefits and disadvantages for tool and weapon manipulation in particular. A specific benefit of left-handedness, as proposed by Raymond and Pointer (2004), is superiority when fighting against right-handers, which varies across various cultures. However, if cultural and geographical variations appear to be significant, it is not likely that the prevalence of left-handedness reflects benefits associated with fighting. Overall, the interpretation of the handedness polymorphism in various countries, anchored on weapon manipulation, should be considered as a weak attempt to revamp the old 'shield-and-sword' theory of left-handedness. Firstly, it is hard to explain why women have the same prevalence of left-handedness as men, despite the fact that throughout the history men fight overwhelmingly more frequently than women. Secondly, there are cultures in which fighting is a very sporadic or even unknown as a way of social interaction (e.g. Australian Aborigines), which nevertheless show the same prevalence of left-handedness as socially aggressive cultures.

Another common finding in the handedness literature is that in males there is a slight but consistent preponderance of left-handedness compared to females, and that the prevalence of left-handedness decreases with age. However, some researchers have argued that sex-differences in handedness do not exists (Silverberg, Obler, & Gordon, 1979) or that they are results of the bias in reporting (Bryden, 1977). To discern the effects of age, sex, cultures and races, very large samples are required. The largest popular study of this kind was conducted in 1986. Over one million of the National Geographic magazine readers responded to a survey in which they indicated their writing hand, showing changes in the proportion of left-handedness in the United States population during the last century and consistent sex differences. This study has clearly shown an increase of left-handedness during the first half of the 20th century with more left-handed males than females. The rise of left-handedness within the US was interpreted in terms of a greater social tolerance toward left-handed individuals. A similar trend has been observed in the Australasian population (Brackenridge, 1981). It appears that the process of social tolerance towards left-handedness within Australasia parallels (see Figure 1.2) that in the US.

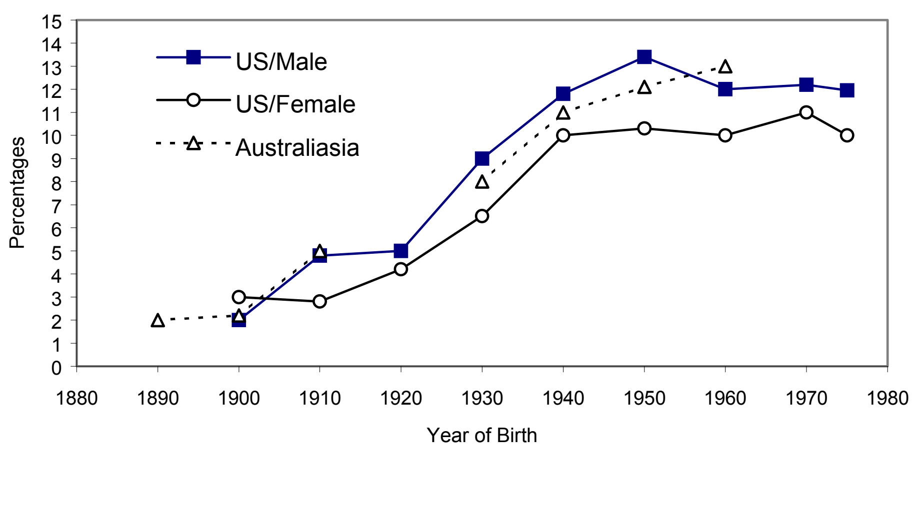

Figure 1.2 Distribution of left-handedness in US for males and females and in Australasia during the 20th century (adapted from original sources)

In summary, lateralisation of hand preference at the population level is the most obvious behavioural asymmetry and unique to humans. It has incorrectly been considered to be easy to measure and classify. Slight but consistent cultural and sex differences in lateralisation of hand preferences are commonly observed. Despite these differences, the presence of right hand dominance in all cultures and geographical regions suggest that this trait is not a result of learning. To date, no society that shows a leftward asymmetry has been identified.

1.2 Inheritance of handedness

Inheritance of handedness has been acknowledged firmly in the 20th century. One of the first models of inheritance of left-handedness was published in *The American Naturalist* at the beginning of the last century, where Ramaley (1913, p.738), studying a sample of 610 parents and 1,130 children, concluded that “left-handedness is a Mendelian recessive” trait. The observation that the left-handedness ‘runs in families’, however, is not conclusive evidence for genetic transmission; many other things run in families such as wealth and furniture. The indication that suggests a genetic effect, though inconclusive, is the fact that left-handed parents are more likely to produce left-handed offspring than right-handed parents (Rife, 1940; Annett, 1972; Coren & Porac 1980a; McKeveer, 2000b). However, intrafamilial correlations on a certain trait may be interpreted as a purely environmental effect. A parent-child similarity could also be explained in terms of learning. Although data from family studies do not provide a straightforward evidence of genetic effects, the observed frequencies are reasonably consistent showing that parents’ handedness has strong impact on the handedness of their offspring. Data from several large studies (Table 1.2), including the data from the Western Australian Family Study of Schizophrenia (WAFSS) support this hypothesis.

Table 1.2 Percentage of left-handed children as a function of parents' handedness

Study	Both parents right-handed	Left-handed parent	
		Mother %	Father %
Rife, (1940)	7.7	21.3	18.2
Annett, (1973)	9.7	28.5	14.0
Coren & Porac (1980a)	17.6[§]	30.6	13.6
Ashton, (1982)	9.4	18.2	10.5
McKeever, (2000b)	16.7*	23.3	18.1
WAFSS, (2004)	9.9[¥]	26.3	15.8
Mean		24.7	15.0

** High proportion of LH is result of 'extra' recruitment of LH student*

§ *Left- and ambiguous handers pooled together*

¥ *Unpublished data from the Western Australian Family Study of Schizophrenia (WAFSS)*

Table 1.2 clearly shows that left-handed parents are more likely to have left-handed offspring than right right-handed parents. Moreover, left-handedness of the mother has a greater influence, as the percentage of left-handed offspring is consistently higher when mother is left-handed. This particular effect of mother's handedness on handedness of offspring, the so-called 'maternal effect', has been observed in many studies (McGee & Cozad, 1980; Harkins & Michel, 1988; McKeever, 2000b).

Much stronger evidence for genetic transmission of handedness comes from adoption studies. One such study (Carter-Saltzman, 1980), demonstrated that in biologically related families the proportion of left-handed offspring reflected the handedness of the parents, whereas for adoptive families there was no increase of left-handedness in offspring with increasing left-handedness of parents. Thus, without the suspected environmental effect (i.e. being parented by left-handers) the genetic contribution to this trait was demonstrated. Further support for a genetic effect can be found in twin studies. Handedness in monozygotic twins has often been seen (McManus, 1985c; Corballis, 1991; Coren, 1992) as the Achilles's heel of genetic theories on the basis that monozygotic and dizygotic twins are concordant for handedness at an identical level to singletons. Bishop (2001) argued that family resemblance in twins and their parents could be efficiently accounted by a cultural rather than a genetic model. However, a recent meta-analysis on handedness in twins (Sicotte, Woods, & Mazziotta, 1999), comprising the empirical evidence from a large number of the twin studies, has confirmed that (a) frequency of left-handedness is similar in monozygotic and dizygotic twins, and (b) monozygotic twins are more likely to be concordant for handedness than dizygotic twins. A greater concordance for handedness in genetically identical monozygotic than in dizygotic twins is therefore supportive of genetic models of handedness inheritance.

During the last several decades several genetic theories on handedness have been proposed (Levy & Nagylaki, 1972; McManus, 1985c; Annett, 1985; Klar, 1999), among which the Right-Shift theory (Annett, 1985, 2002) has repeatedly been recognised (Corballis, 1983; Corballis, 1991; Crow, 2004) as the most plausible model of genetic transmission of handedness. Other genetic models are more or less variations of the theme proposed by Annett. Essentially, all models assume that the random asymmetry for hand preferences in the majority of people is shifted in the rightward direction due to a specific genetic influence, while in a certain proportion of individuals direction of handedness in determined by chance due to lack of a genetic contribution. It is important to stress, however, that the gene responsible for handedness is yet to be identified, so this theory (as well as any other) remains as a genetic model pursuing its final and full confirmation. The Right-Shift theory will be described in more details in the following section.

Whilst the majority of researchers agree that handedness is an hereditary trait, possibly under specific genetic control, some researchers (Collins, 1975; Provins, 1997) criticise the prevailing view. Collins (1975), on the basis of animal studies, argued that the directional asymmetry (e.g., paw dominance) is distributed by chance or ”asymmetry lottery” (p. 184), and that it could be substantially modified as a result of environmental biases. Without either right- or left biased environment (feeding tube placed in the middle of the cage), the distribution of paw preferences in mice was U-shaped. Introduction of the "bias defined environment" (feeding tube placed in the right or left corner, p. 184) resulted in J-shaped distribution of paw preferences. Both left or right paw preferences from this and previous experiments (Collins, 1968, 1969) were interpreted by Provins as a consequence of learning. A capacity to change paw preference due to environmental challenges in mice is considered as determinant of lateralisation. In addition, it has been argued (Provins, 1997) that inherited functional plasticity or capacity of learning is equal in both brain hemispheres, making possible that direction of hand preferences can go in either direction. The relative hand proficiency (skill), and thus hand dominance, are essentially determined by a learning process, including "chance or the opportunity for use in a laterality biased environment" (Provins, 1997, p.560). Nevertheless, a large body of evidence, including family, twin, and adoption studies, suggests that "our 'right-handed' world is rather a consequence of biological right-handedness" (Corballis, 1983, p.20), than the opposite. A few facts appear to contravene a purely environmental concept. Firstly, the occurrence of right-hand preponderance for manual activities such as thumb sucking and arm movements in foetuses at 10-18 weeks of gestational age (Hepper, Shahidullah, & White, 1991; Hepper, McCartney and Shannon, 1998; McCartney & Hepper, 1999) suggests rather its genetic origin than result of learning. Secondly, people with congenital malformations (or congenital absence) of the right hand are able to demonstrate their inborn hand dominance. Brugger, Kollias, Muri, Crelier, and Hepp-Reymond (2000) described a study subject, a woman born without arms and legs, but able to write with her mouth. She considered herself as being right-hand dominant, though her arms were not physically developed. McManus (2002) has described a very similar example. These examples clearly demonstrate that there is an inborn dominance in hand preferences, determined prior to birth and in the absence of learning experience.

1.2.1 The Right-Shift Theory

According to Annett (1985), the shift toward dextrality in humans is due to a genetic factor, described as the right-shift gene (RS+) and considered to be uniquely human. In contrast to humans, where the hypothesised RS+ gene *shifts* the distribution of handedness in the rightward direction, hand preferences in primates other than humans (or paw preferences in other species) are symmetrically distributed around the point of no clear left or right preference, i.e., being determined completely by chance. The Right Shift theory postulates a pair of alleles (RS+ and RS-) of a single autosomal gene as a mediator of the genetic effect. The hypothesised function of this genetic effect is to induce lateralisation of language to the left-hemisphere by delaying the growth of the right hemisphere during early development. According to Annett (1985), right-hand dominance in humans for both skill and preference is secondary to this process. The postulate that the RS+ gene is not 'for' handedness is a commonly misunderstood aspect of the Right Shift theory.

The RS+ gene is not present in all individuals. Annett (1985) claimed that approximately 20% of people do not have it. For individuals without the RS+ gene cerebral dominance for language is determined by chance. In the absence of cultural pressure, hand dominance in individuals without the RS+ gene would also follow a 50:50 distribution. However, due to cultural pressure, a majority of these individuals will be right-handed. An important step in development of the Right Shift theory was to determine the proportion of people without the RS+ gene. It is crucial to understand how Annett determined this proportion, because the estimate of its size was used to derive the proportion of the various genotypes. This was done by using samples of subjects with dysphasia following right hemispheric brain damage. According to a chance distribution (50:50), the proportion of individuals lacking the RS+ gene was determined as twice the proportion of individuals who became dysphasic following right hemispheric damage, and hence appeared to have language localised in the right hemisphere. The proportion of individuals with right hemisphere speech, irrespective of handedness, was deduced from diverse sources, including the World War 2 head injury archive (Conrad, 1949; Newcombe & Ratcliff, 1973) and other samples (Bingley, 1958; Hécaen & de Ajuriaguerra, 1964), in which there were about 10% of cases with dysphasia after right hemispheric damage. Four series differed substantially in sample characteristics; while the World War 2 data comprised young male soldiers, selected for service possibly on the basis of physical fitness, two other samples comprised cases with dysphasia (Hécaen & de Ajuriaguerra, 1964) and temporal lobe tumours (Bingley, 1958). A more exact estimate of 9.27% of the people with right hemispheric speech, or 18.54% of those who appear to lack the RS+, was based on these samples comprising 647 cases with dysphasia following right hemispheric lesion. Accordingly, the percentage of people with the RS+, either two or one RS+ allele, is 81.46% (100 – 18.54). The frequency of the two other genotypes (RS++ and RS+-) was inferred from the RS-- genotype (18.54%). Consistent with the Hardy-Weinberg equilibrium formulae, where genes are supposed to distribute in binomial proportions, i.e. ($(a + b)^2 = a^2 + 2ab + b^2$), Annett (1985) estimated the proportion of each genotype in the population to be: RS++ = 32.42%, RS -- = 18.54%, and RS+- = 49.04%.

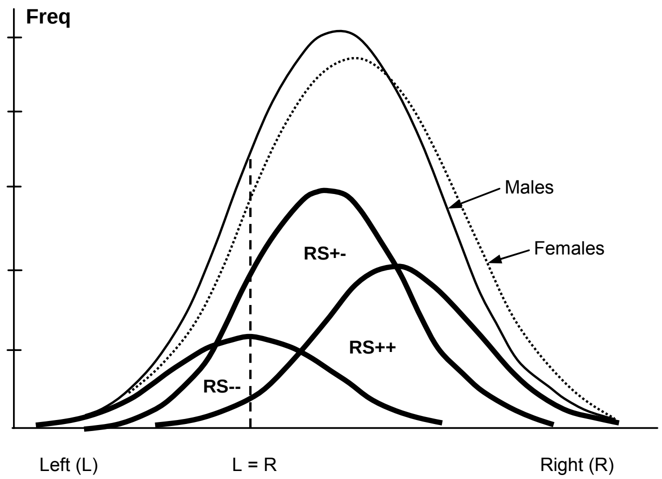

Figure 1.3 A simplified distribution of the relative hand skill in the three genotypes and in the total population for males and females (adapted from Annett, 2000, p. 123)

Figure 1.3 shows how each genotype is associated with its most visible phenotypic characteristic, a hand skill. As can be seen in Figure 1.3, a half of the RS-- homozygous individuals, with two recessive RS- alleles, would show the *absence* of the bias to either side. On the basis of chance they would develop either right or left hemispheric dominance for language and (accordingly) left- or right-hand dominance. RS++ homozygous individuals are expected to display a left hemispheric dominance for language with a strong right-handedness, while RS+- heterozygous individuals are expected to have a moderate rightward shift in hand dominance. Figure 1.3 also shows that two sexes differ in the expression of the RS+ gene, which is more strongly expressed in females than males.

Annett (1985) has adopted the *balanced polymorphism hypothesis* to describe the relationship between handedness and abilities. Homozygous genotypes (RS++ and RS--) are accordingly disadvantageous since they can impair hemispheric functions: (a) two RS+ alleles resulting potentially in deficient mathematical ability and reducing efficiency of the non-preferred, left hand due to impeded growth of the right hemisphere, and (b) two RS- alleles resulting in dysfunction of left-hemispheric capacities (e.g. language). The idea that the RS+ factor *handicaps* the right hemisphere rather than *enhancing* the left-hemisphere was supported (Kilshaw & Annett, 1983) by analysing hand performance of each hand in left- and right-handers. Right-handers showed a markedly slower performance with the non-preferred (left) hand, in contrast to right-handers who did not show such inferiority of the non-preferred (right) hand. In other words, the left hand of the right-handed is less skilled than the right hand of the left-handed individual. The findings from this study were supported in a following study (Annett & Manning, 1989), where it was observed again that strong right-handedness was associated with a weak left-hand skill on peg-moving task. In contrast, having two RS- alleles is supposed to lead to deficient left hemispheric function which may impair language and lead to reading disability. In contrast, the heterozygous genotype is advantageous since it minimises the risks while maximising the benefits; provides left hemispheric speech but does not have the adverse effect of suppressing right hemispheric growth. It is believed that in heterozygous individuals, due to the presence of more than a single molecular form of the gene, the ability to buffer or compensate for varying environmental stressors is greater than in homozygous individuals. However, the balanced polymorphism hypothesis is well documented only for the commonly cited example of sickle-cell anaemia in parts of Africa. What is specific to Annett's balanced polymorphism hypothesis is that each genotype may be predictively associated with cognitive abilities. However, the empirical evidence for the association between cognitive abilities and RS genotypes is weak and has been questioned (McManus, Shergill & Bryden, 1993). The major problem is that this hypothesis can be tested only indirectly because the RS+ gene, if it exists, is yet to be identified. As this gene affects cerebral lateralisation, and lateralisation of hand skills as a by-product, investigations of whether these behavioural manifestations (phenotypes) of the RS+ gene are associated with cognitive abilities have no alternative at present. In several studies Annett provided some evidence which appears to support the balanced polymorphism hypothesis. However, there are also studies which have challenged this hypothesis. Both sides of the evidence will be reviewed in more detail in the following section.

Although the Right Shift theory is recognised as the most likely model of handedness inheritance (Corballis, 1991), at least two key postulates deserve a closer scrutiny. First, the assumption that the RS+ is uniquely human, appears to be in conflict with a growing but still controversial body of evidence that a similar, though less prominent, bias toward dextrality is present in chimpanzees and other non-human primates (Hopkins & Leavens, 1998; Hopkins & Wesley, 2002). Lateralised behaviour at the population level has also been observed in non-primates such as domestic dogs (Wells, 2002), crows (Hunt, Corballis, & Gray, 2001), and female rats (Elalmis et al., 2003). Gannon, Halloway, Braodfield, and Braun (1998) showed that temporal planum, a brain region that hosts language, was larger in the left than the right hemisphere in chimpanzees in the majority of the studied animals. This structural brain asymmetry, due to its relationship with language, is considered as typically human (Geschwind & Galaburda, 1987). The presence of a lateral bias in primates which lack language capacity, though not to as great an extent as in humans, suggests that two separate but possibly overlapping processes operate; one for acquisition of language, and second for initiation of behavioural lateralisation. Second, Right Shift theory is heavily reliant on hand skill and ignores the relevance of hand preferences, as indices and quotients of hand preferences are considered by Annett (2002a) as “pseudo-science” (p.26). It is not difficult to agree with Annett that the measurement of hand preferences is not perfect and, by the same token, measurement of hand skill by pegboard does not provide a complete assessment of the hand skill. In addition, Annett’s view that hand preferences correlate nearly perfectly with hand skill is questionable, since handedness most likely cannot be precisely predicted using an isolated performance measure (Corey, Hurley, & Foundas, 2001; Brown, Roy, Rohr, Snider, & Bryden, 2004). In my view, measurement of hand preferences is seriously neglected in the laterality research, which is unnecessarily over-dependent on two handedness scales, the Edinburgh Handedness Inventory and Annett's scale. On the positive side, it seems that researchers increasingly recognise the complexity of the handedness assessment, by urging development of new handedness scales (McManus & Drury, 2004). Since two papers of this thesis address specifically the issue of handedness measurement and classification, further discussion on this point will be left to the general conclusions.

1.3 Handedness and cerebral lateralisation

The interest in functional brain asymmetries has risen since Broca's discovery that left-hemispheric lesions lead to language disorders. The common milestone in the area of brain lateralisation is the work of French surgeon, Paul Broca (Broca, 1865; in Harris, 1980), who examined a number of hemiplegic patients with loss of speech. Because all of his patients had left hemispheric brain damage (identified post-mortem), he concluded that the left hemisphere contained the faculty of the uniquely human function – of language. As some of his left-handed patients displayed hemiplegia of the right side, this inevitably led to, at that time revolutionary conclusion, that right-handers have language localised in the left hemisphere while left-handers mirrored them by having language localised in the right hemisphere. Very soon this oversimplified relationship between handedness and cerebral lateralisation proved to be imperfect by identifying aphasic right-handed patients with left hemiplegia (i.e., with the language capacity localised in the right hemisphere).

Progress in the study of brain lateralisation took place during the second half of 20th century by introducing non-invasive techniques such as the dichotic listening test (DLT) and tachistoscopic stimulus presentation. During the last quarter of the last century new powerful and non-invasive physiological technologies such DLT, functional transcranial Doppler sonography (fTCD), computerised axial tomography (CAT), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET), have been developed. These techniques have been developed to capture functional brain lateralisation in normal subjects.

A few invasive procedures have also been developed to identify cerebral dominance for language. A young Japanese neurosurgeon, Juhn Wada, developed a procedure which is considered as the gold standard – the sodium amytal test, a test in which first one and then the other cerebral hemisphere is temporarily anaesthetised through direct intracarotid application of sodium amytal. This procedure, also known as the Wada test, is still used for pre- and postsurgical evaluation of patients with epilepsy, despite the new and noninvasive techniques such as fMRI (Baxendale, 2002). Another invasive procedure for the determination of cerebral dominance employs the controlled current machines used in electroconvulsive therapy (ECT). However, none of these invasive procedures is suitable for use in healthy normal population.

The general finding, irrespective of the technique used, is that a large proportion of right-handed individuals have language localised in the left hemisphere. A small percentage of right-handed individuals have the same faculty ipsilateral to the dominant hand (see Table 1.3). The majority of left-handers have language localised in the left-hemisphere, just as right-handers. However, compared to right-handers, a much larger proportion of left-handers display either bilateral or right hemispheric representation of language. Cerebral dominance for language has frequently been examined in left- and right-handers using various techniques. Although these techniques are not always entirely consistent in determining the side of language lateralisation, they provide similar results (Table 1.3).

Table 1.3 Percentages of right- and left-handers with language presented in the left-, bilaterally, or right hemisphere

Study	Right-handers			Left-handers		
	Left	Bilateral	Right	Left	Bilateral	Right
Milner, 1975*	96	0	4	70	15	15
Rossi & Rosadini, 1967*	99	1	0	40	10	50
Pratt & Warrington, 1972#	99	0	1	-	-	-
Warrington & Pratt, 1973#	-	-	-	70	7	23
Geffen et al., 1978#	92	0	8	67	0	33
Geffen & Traub, 1979‡	84	9	7	61	15	24
Khedr et al., 2002^	88	8	4	74	16	10
Springer et al. 1999&	94	6	0	-	-	-
Pujol et al. 1999&	96	4	0	76	14	10
Szaflarski et al. 2002&	-	-	-	78	14	8
Hund-Georgiadis et al. 2002&	94	0	6	47	12	41
Knecht et al. 2000a†	-	-	4	-	-	27

* intracarotid sodium amytal test
# ECT
‡ dichotic listening test
^ repetitive transcranial magnetic stimulation (rTMS)
& fMRI
† fTCD

In a recent study Hund-Georgiadis, Lex, Friederici, and von Cramon (2002) reported a good overall agreement of lateralisation assessment between DLT and fMRI of 97.1%. Knecht and his coworkers (1998) validated fTDU against the Wada test and have found a significant correlation between the measures of lateralisation from both procedures.

The functional lateralisation and organisation of the human motor system has also been a subject of numerous investigations, showing that various brain structures are involved during motor actions including their planning, preparation and execution. It might be expected that capacity of the human brain to generate diverse and intricate manual activities is associated with the direction and possibly degree of lateralisation of handedness. The dominant hand is capable of performing more complex and refined manual activities than the non-dominant hand, and its behavioural superiority might be a result of additional cerebral support. Is the functional activation of the motor cortex identical in left- and right-handers during performance of motor task with both dominant and non-dominant hand? Kim et al. (1993) were among the first to explore this hypothesis with fMRI. In a study on right- and left-handed subjects they found the left motor cortex had a greater the surface area of activation in right- than left-handers during performance of a motor task with the dominant hand. Dassonville, Zhu, Ugurbil, Kim, and Ashe (1997) measured the volume of functional activation in cortical motor areas in seven right- and six left-handed subjects and observed a greater activation in the contralateral motor cortex of both the right- and left-handed subjects during movements of the dominant than the non-dominant hand. Furthermore a volume of functional activation of the motor cortex paralleled the degree of handedness in both left- and right-handers. Based on these findings they concluded that handedness, as far as functional activation of motor cortex is concerned, is a continuous trait, a conclusion consistent with one of Annett's core postulates. This study is important since schizophrenia appears to be characterised by diminished activity in the cortical motor regions (Guenther et al., 1994; Mattay et al., 1997) as well as an absence of typically lateralised patterns of cortical responses to various cognitive task in the cortical regions (Kircher et al., 2002; Sommer, Ramsey, Mandl, & Kahn, 2003; Walter et al., 2003).

In addition to functional brain asymmetries, handedness appears to be complemented by structural brain asymmetries. Earlier post-mortem studies of human brain provided the initial evidence for a structural substrate of functional asymmetries. Geschwind and Levicky (1968), analysing post-mortem human brains, showed that the human brain features an anatomical asymmetry particularly in areas involved in linguistic processes, namely the length of the planum temporalis. Their observation of a higher degree of asymmetry of the length of the planum temporalis in right-handers than in left-handers was further confirmed by *in vivo* morphometry (Steinmetz, Voklman, Jäncke, & Freund, 1991; Jäncke, Schlaug, Huang, & Steinmetz, 1994). Using the same technique, an additional anatomical asymmetry related to handedness was observed by Amunts et al. (1996); left- and right-handers differed in the depth of central sulcus. In a recent study by Amunts, Jäncke, Mohlberg, Steinmetz, and Zilles (2000) on 103 subjects, anatomical asymmetry of the central sulcus was found in males but not in females. In contrast, post-mortem studies (White et al., 1997) failed to show any systematic relationship between handedness and the depth of central sulcus of the motor cortex. Handedness is also associated with the size of the corpus callosum, a brain structure responsible for functional communication between the two cerebral hemispheres. Several studies (Witelson, 1980; Habib et al., 1991; Driesen & Raz, 1995; Moffat, Hampson, & Lee, 1998) reported evidence that left-handed individuals have a larger corpus callosum than those with consistent right hand dominance. However, Preuss et al. (2002) investigated also the relationship between handedness and corpus callosum size in healthy subjects, but failed to find a significant association. One possible explanation of the negative finding in this study is that subjects differed in the consistency of right-handedness, i.e. subjects were consistent and non-consistent right-handers.

In summary, lateralisation of hand preferences is associated firmly with structural and functional characteristics of the brain, suggesting that handedness is "fundamentally a manifestation of cerebral rather than bodily asymmetry" (Corballis, 1991, p. 105). The most striking structural brain feature that shows an association with handedness is the size of planum temporale. Evidence for the structural asymmetry of the central sulcus is mixed. The most prominent functional asymmetries of the human brain, which are related to handedness, are: lateralisation of language and lateralisation of functional activation in motor cortex.

1.4 Handedness and cognition

The relationship between cognitive abilities and behavioural lateralisation is elusive and results describing it are inconclusive. Views on this controversial issue range from the earlier (Levy, 1969; Miller, 1971; McManus & Mascie-Taylor, 1983) speculation that sinistrality is associated with lower IQ, over the Hardyck, Petrinovich, and Goldman's (1976, p. 277) famous statement that "there is no difference in performance that can be attributed to any deficit linked to handedness", to the popular notion that left-handers are particularly good mathematicians, sculptors, and architects. In contrast, Noroozian, Lotfi, Gassemzadeh, Emami, and Mehrabiet (2002) reported that left-handed students performed slightly better on university entrance exams than right-handed students, but the difference was significant only for the Art subject. Instead of reviewing sporadic studies, the review of the literature on this relationship will be focused on the three dominant hypotheses. The first hypothesis, deduced from the Right Shift theory, proposes that abilities are dependent on the laterality genotype ('balanced polymorphism'), the second argues that cognitive ability is lowest at the point of equivalent hand skills ('hemispheric indecision'). In contrast, the third hypothesis claims, on the basis of direct investigation, that cognitive abilities are independent for cerebral lateralisation for language and therefore independent of handedness. These hypotheses will be briefly reviewed in following sections.

1.4.1 Balanced polymorphism hypothesis

Relationship between the lateralisation of hand skills and cognitive abilities within the context of the Right Shift theory was explained in terms of balanced polymorphism (Annett, 1985, 1993a). The fact that left-handedness is present in the human population over time with a consistent prevalence of approximately 10% (Coren, 1992; Faurie & Raymond, 2003), has led Annett to conclude that this must be due to certain advantages associated with left-handedness. An implication of the balanced polymorphism hypothesis is that the heterozygous genotype would be superior to both homozygous genotypes. Balanced polymorphism for cerebral lateralisation, and subsequently for lateralisation of hand skill, was introduced to explain the fact that the RS+ gene is not universally present, leading Annett (2002) to question why everyone does not carry the RS+ gene if it is so beneficial for humans. Annett (1985) speculated that we are not all right-handed because the RS+ gene carriers, despite enjoying the benefits conferred by the RS+ gene are offset by certain disadvantages. The balance of advantages and disadvantages associated with the RS+ is explained using a classical example of balanced polymorphism, i.e. a sickle-cell anaemia. Hypothetically, the RS+ gene does not enhance the functional capacity of the dominant hemisphere but rather suppresses development of the non-dominant hemisphere, resulting thus in left hemispheric language and right-hand dominance. Therefore, the benefits of left hemispheric language and right-hand dominance are achieved at the cost of the right hemispheric functions. In other words, strong dextrality is associated with certain individual risks.

Annett (1985) and Annett and Manning (1989) have proposed that each of the three hypothetical genotypes – homozygous (RS ++), homozygous (RS --), and heterozygous (RS +-) with respective frequencies of 32%, 19%, and 49%, are associated with specific cerebral and cognitive risks. As this speculation cannot be tested directly, since the locus of hypothetical RS+ is unknown, the only option is to investigate whether phenotypic features of these genotypes such as hand skills and hand preferences are associated with cognitive abilities. And this is where difficulties of this speculative interpretation begin. A crucial limitation is the substantial overlap between the genotypes (see Figure 1.3), so the associations between the measures of laterality are expected to be subtle. By hypothesis, the homozygous (RS++) genotype is supposed to confer a marked left hemispheric advantage but also a marked right hemispheric disadvantage, resulting (a) behaviourally, in a strong bias to dextrality, but weak left-hand performance, and (b) cognitively, in weaker right hemispheric functions. The homozygous (RS--) genotype is supposed to have neither left hemispheric advantage nor right hemispheric disadvantage, as behavioural bias to either side is lacking. A risk for various developmental language problems such as dyslexia is greater in the RS-- genotype as compared to other genotypes, because it lacks the benefits associated with left hemispheric localisation of language. As the RS-- genotype is supposed produce an excess of non-right-handers this, according to Annett, would explain the preponderance of atypical lateralisation in children with early language difficulties (Annett, 1985, 1996). In contrast to both homozygous genotypes, the heterozygous (RS+-) genotype is considered advantageous, as it supposedly minimises risks and maximises benefits. As a behavioural consequence, this genotype produces moderate bias to dextrality. Annett conducted many studies investigating the balanced polymorphism hypothesis by using relative hand skill and her own classification of hand preferences. Specific advantages of the heterozygous genotype over the two homozygous genotypes, as indexed indirectly by their phenotypic feature, hand skill, have been identified in vocabulary IQ measure (Peabody Picture Vocabulary Test), performance on the Raven's coloured Progressive Matrices (Annett, 1995), educational attainment (Annett, 1993a, 1993b), and various measures of verbal processing interpreted in as a Spearman's general factor of intelligence (Annett, 2002). Both homozygous genotypes, RS++ and RS-- are associated with poor reading (Annett & Kilshaw, 1984).

The general problem with these studies and the balanced polymorphism hypothesis is an indirect and insufficient characterisation of the hypothetical genotypes, with the two laterality measures (hand skill and, secondary to hand skill, hand preferences) only considered as sufficient for the full characterisation of genotypes. To be fair to Annett, there is nothing wrong in using what is available in order to support the model, but incidentally these genotypes are considered to be 'for' different patterns of cerebral specialisation and not 'for' handedness; handedness itself is a mere by-product of the more fundamental process of cerebral lateralisation. Dependency of a single but insufficient phenotypic feature was followed by ignorance of all other laterality measures such as foot, eye, and ear dominance were largely ignored, despite suggestions, for example, that cerebral lateralisation might be related more to footedness than to other lateral preferences (Elias & Bryden, 1998; Elias, Bryden, & Bulman-Fleming, 1998). However, other laterality measures were considered by Annett, but only to show how they were related to the model, during origination of which they were omitted.

Characterisation of behavioural laterality as a relative hand skill creates another difficulty for the posited relationship between handedness and cognitive abilities (see Nettle, 2003). A measure of relative hand skill is calculated as the difference in performance between two hands (R – L), but it should be independent of overall hand skill. If the overall level of task performance correlates with cognitive measures, this association needs to be controlled, if not removed, when examining the relationship between relative hand skill and cognitive abilities. For example, in the National Child Development sample (see Nettle, 2003), the correlation coefficients between overall hand skill and verbal abilities were significant, though of small magnitude ($r = 0.18$ for boys and $r = 0.17$ for girls). An uncorrected measure of lateralisation which, when contrasted with measures of cognitive ability, could create results in which "an effect of general hand skill will appear to be an effect of lateralisation" (Nettle, 2003, p. 394). For example, in Annett's and Manning study (1989) the overall hand skill in weak dextrals is higher than in strong dextrals (see Annett & Manning, 1989, Table 2), and IQ advantage of moderate compared to strong right-handedness may reflect the correlation between cognition and overall hand skill rather than cognition and lateralisation of hand skill. Thus, weaker cognitive abilities of strong right-handers, defined as the R-L difference in skills, might be simply because of subjects with very poor left-hand skill in the presence of the average hand skill. A clumsiness of the non-preferred hand may be an indication of pathological right-handedness, a rare but logical counterpart of Bishop's (1984) 'pathological' left-handedness (see section 1.5.2).

The speculation of heterozygote advantage for cognitive abilities, based on indirect evaluation of the hypothetical genotypes, has not obtained much empirical support from studies other than Annett's. Several studies (Palmer & Corballis, 1996; Resch et al., 1997; Crow, T., Crow, L., Done, & Leask, 1998b; Cerone & McKeever, 1999; De Agostini & Dellatolas, 2001; Natsopoulos, Koutselini, Kiosseoglou, & Koundouris, 2002), have challenged this hypothesis by providing evidence contrary to the predictions based on Right Shift theory. The balanced polymorphism hypothesis has also been questioned from evolutionary perspective. Corballis (1991) raised the question how mathematical and reading ability, as very recent skills in human evolution, could be related to a genetic process that could have happened 40,000 or more years ago. Indeed, it is puzzling how an advantage for mathematical or reading ability developed in humans, if those abilities, reading in particular, were largely irrelevant for human kind for the most of its history.

The Right Shift theory's perspective on the intricate link between cognition and behavioural lateralisation, although speculative and providing indirect evidence, is not an isolated effort aiming to describe this association. In contrast to the previous, the following hypothesis posits that extremes of the distribution of hand skill and hand preferences are associated with cognitive advantages.

1.4.2 Crow's hypothesis

Another description of the relationship between handedness and cognitive abilities has been put forward by Crow et al. (1998b) and Leask and Crow (2001a), suggesting that variation in hand skills, indirectly indicating the degree of the cerebral lateralisation, is related to variation in human ability. The nature of this association obviously contrasts with Annett's balanced polymorphism hypothesis. It has been suggested (Crow et al., 1998b) that cognitive impairment is associated with the point of equal hand skill, referred to the point of 'hemispheric indecision'. Contrary to Annett's hypothesis, where strong biases to either side were associated with cognitive disadvantages, the 'hemispheric indecision' hypothesis argues that cognitive *disadvantage* is at the point of equality in hand skill. This hypothesis was supported in a study (Crow et al., 1998b), which used the National Child Development sample, a large cohort of individuals (N = 12,627) born in March 1958. At the age of 11 years, all subjects were assessed by a series of tests of cognitive abilities, while hand skill was assessed by the box-ticking task. Subjects were divided into 20 5-percentile categories of relative hand skill and plotted against the distribution of scores on each cognitive measure. Results showed that deficits in academic abilities (verbal, non-verbal skills, reading comprehension, and mathematical ability) were pronounced in subjects whose hand performance was symmetrical, that is, where the both left and right hand performed equally. Cognitive deficit at the point of 'hemispheric indecision' was interpreted as a consequence of an unestablished cerebral asymmetry (Crow et al., 1998b). An identical conclusion was made by Leask and Crow (2001a) after reanalysing the data from the National Child Development sample. Nettle (2003), using the identical data set and a more refined statistical analysis, generally repeated Crow's findings, though after adjustment for overall hand skill the results were less impressive than those of Crow et al. (1998b) and Leask and Crow (2001a). This specific association of behavioural lateralisation and cognitive ability is incorporated into a greater theoretical framework – Crow's theory of human evolution (2000), in which the loss of brain asymmetry, an evolutionary product associated with language acquisition, is associated with cognitive impairment.

The 'hemispheric indecision' hypothesis has been challenged by several studies. Mayringer and Wimmer (2002), aiming to replicate findings form Crow et al's study (1998b), used a sample of 350 boys, who were assessed by Annett's peg-moving task and tests for non-verbal intelligence and reading and spelling accuracy, failed to find a deficit on these measures at the point of equal hand skill. However, differences in the assessment of hand skill limit the comparability between these studies. While Crow et al. (1998b) used a box-ticking task, where writing experience could have an impact on hand performance, Mayringer and Wimmer (2002) used the peg-moving task, a task presumably less influenced by writing experience. It has been noted (McManus, 1985a, 1985b) that the peg-moving task gives a less clear differentiation of hand skill differences than tasks heavily influenced by writing experience. Subjects in Mayringer and Wimmer's study (2002) were also younger (6.9 years) than in the study of Crow et al. (1998b). Francks et al. (2003a), in a large study on 641 siblings from 265 families, examined also the relationship between hand skill and cognitive abilities. In this study, correlation coefficients between performance on Annett's peg-moving task, and reading and reading-related cognitive ability, were nonsignificant. Cognitive ability was slightly associated with overall manual skill, but was not associated with relative hand skill or with the overall degree of lateralisation of hand skill. An obvious inconsistency of these studies with both Crow's and Annett's hypotheses is partly explained by Nettle (2003), who showed that discrepancies between these studies could arise as a function of the statistical procedures for measuring laterality and a confounding association between overall hand skill and IQ. By using both overall and relative hand skill as independent predictors in a stepwise regression analysis, their independent effects were discerned. In my view, the 'hemispheric indecision' hypothesis was not seriously damaged by Mayringer and Wimmer (2002) and Francks et al's (2003a) findings. In both studies samples were of insufficient size to detect a relatively small effect, and in both studies the measure of hand skill differed from that in Crow's study. Nettle (2003), however, supported Crow's original conclusion that laterality affects cognitive abilities, as well as understated the extent of the hypothesised relationship – 1% of the variance in IQ was accounted by the relative had skill after adjustment for the overall motor skill. The impressive size of the National Child Development sample and subsequent support from a conservative statistical analysis on the same sample suggests that cerebral lateralisation is associated with cognition and that "lateralisation is fundamental to an understanding of human brain" (Crow, 2004, p.123). However, a full recognition of the hypothesised relationship between the laterality and cognition depends on replication in independent samples.

1.4.3 Knecht's hypothesis

The association of cerebral lateralisation of language and cognitive abilities can be investigated more directly by identifying cerebral lateralisation of language directly and not relying on lateralisation of hand preferences. The results from direct investigations appear to contradict both Annett's and Crow's models. Knecht et al (2001), using functional transcranial Doppler sonography (fTCD) [1] to determine

[1] The transcranial Doppler sonography technique is increasingly used in both clinical and research settings and is a new and robust technique based on the same principles as the fMRI. Subjects in studies using this method to localise language in the brain are asked to generate as many words as possible within a 5-second period after the letter presented on the computer screen cues the word generation. The fTCD measures cerebral blood flow velocity that corresponds to brain activity. The physical foundation for this technique is quite old and is based on the work of the Austrian mathematician and physicist, Christian Doppler (1803-1853), who discovered that the perceived change in the frequency of the signal is affected by the relative magnitude of the relative velocity between the transmitter and the receiver or observer.

language lateralisation, investigated various cognitive correlates of language lateralisation (left- and right-hemispheric, and bilateral). A total of 326 subjects (61% females) were included in the study, in which non-right-handed subjects were encouraged to participate. All of them were assessed by the Edinburgh Handedness Inventory and classified into three handedness categories; left (laterality quotient from -100 to -75), mixed (from -75 to +75), and right (+75 to +100). Various cognitive abilities were quantified: number of spoken languages, academic achievement, and involvement in any artistic activity such as music, painting or sculpture, verbal fluency, and speed of linguistic processing. A small group of subjects (n = 21) were additionally assessed by the German version of the Wechsler Adults Intelligence Scale. The fTCD revealed that a large majority of the study sample (264 or 81%) had language lateralised in the left, 31 (9.5%) in the right hemisphere, and 31 (9.5%) had bilateral presentation of language. Subjects who differed in language lateralisation (left, right, or bilateral) had nearly identical percentages of university qualifications, participation in artistic activities, and number of languages spoken. The correlation coefficient between verbal fluency and language lateralisation was not significant, nor was it significant between the IQ measures and language lateralisation in the small subgroup of subjects. Overall, the results show that atypical language lateralisation, i.e. left or bilateral, was not associated with lower cognitive abilities. However, the sample was not representative of the general population and included an exceptionally large proportion of highly educated subjects. More than 70% of the sample comprised subjects with a university degree. Nevertheless, results from this study are apparently at variance with both Annett's and Crow's predictions about the association of handedness and cognitive abilities in the general population. Knecht's conclusion that cognitive abilities are possibly independent of cerebral lateralisation of language is consistent with the study of Francks et al (2003), who also found that lateralisation of hand skill was not associated with reading related cognitive measures.

1.4.4 Intermediate summary

Several competing hypotheses, reviewed briefly on previous pages, advocate contradicting views about how lateralisation of hand preferences is associated with cognitive abilities. While Annett explains the variation of cognitive abilities in terms of balanced polymorphism, where deficits in cognitive abilities are thought to lie at the extremes of the handedness distribution, Crow maintains a view that symmetry (no differences in hand skill) results in cognitive deficit. Knecht, however, maintains a view that these two phenomena are not related. The proposed hypotheses have, however, their own proponents and critiques. A commonality in Annett's and Crow's hypotheses is that the association of handedness and cognition is of modest size.

An absolute independence of cognitive abilities from behavioural lateralisation however may not be the case in populations characterised by a significant departure from a (normal) distribution of hand preferences. The possibility that Knecht's findings may not be simply transposed to the population of schizophrenia patients, characterised by disturbances during neurodevelopment including micro and macroscopic brain changes, and a significant shift in behavioural lateralisation as compared to healthy people will be further explored in this thesis.

Figure 1.4 shows simplified associations between the handedness lateralisation and cognitive abilities as predicted by Annett, Crow and Knecht. Annett's model is much more complex, but for the purpose of this illustration is important to highlight that strong right handers as well as some left handers show underperformance on various cognitive measures as compared to moderate right handers (i.e. heterozygous).

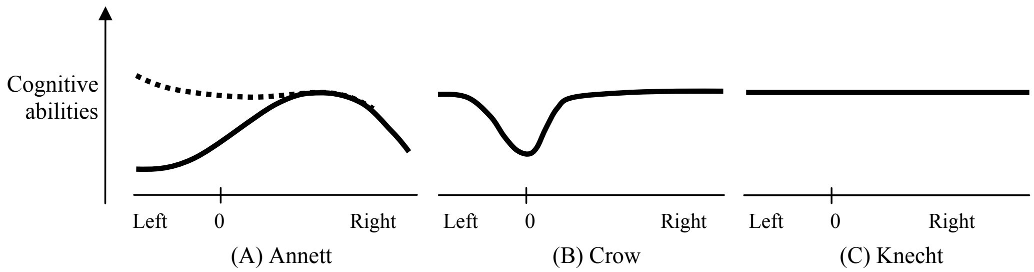

Figure 1.4 Predicted relationship between lateralisation of hand preferences and cognitive abilities in the three competing models

1.5 Departures from the typical handedness distribution – how to explain it?

Scientific interest in atypical lateralisation of hand preferences had taken place at the beginning of the 20th century, including pioneering attempts to describe the inheritance of handedness (Ramaley, 1913) and relating left-handedness to various developmental difficulties (Travis, 1931; Orton, 1937). Orton, an influential psychiatrist and paediatrician, argued that reading problems and stuttering result from a poorly established cerebral dominance. At that time cerebral dominance was ‘assessed’ by hand dominance, due to lack of direct measures such as the Wada test or fMRI. Many of his dyslexic patients were non-right dominant in hand preferences or came from families with a high incidence of sinistrality (Orton, 1937). Since then, atypical handedness has increasingly been linked to a number of conditions such as mental retardation (Gordon, 1921), ‘psychopathy ‘ (Quinan, 1930),‘general maladjustment’

(Palmer, 1963), delinquency (Fitzhugh, 1973), 'emotional instability' (Orme, 1970), and alcoholism (Bakan, Dibb, & Reed 1973), and 'criminal behaviour' (Boagert, 2001).

In the second half of the 20th century it was widely accepted that the distribution of handedness in some clinical populations differed from the general, healthy population, mostly by displaying a leftward shift in hand preferences characterised by an excess of left- and/or mixed-handedness as compared to normal controls. It was also believed that the excess of left-handedness was due to some pathology (Brain, 1945). The overall shift away from right-handedness has been labelled as 'anomalous' (Geschwind & Galaburda, 1985), 'alinormal' (Coren, 1992), or 'atypical' (Satz & Green, 1999). The excess of atypical handedness in such samples is believed to originate from some pathological processes, which either overpower or disrupt the genetics of hand preference. The reasoning was that genetic models might accommodate the observed frequencies of left- and right-handedness in the general population, but they cannot sufficiently explain why, for example, the prevalence of left-handedness is twofold in subjects with mental retardation (Satz, Orsini, Saslow, & Henry, 1985). Apparently, the excess of left-handedness that is above the population rate required the supplemental elaboration by distinguishing two sub-populations within left-handers; a natural from a pathological sub-population. A number of specific pathologies have been proposed to explain atypical handedness distribution. The list of various conditions other than schizophrenia associated with the left-handedness is long (Table 1.4), and many of the reported associations rarely replicated.

Table 1.4 List of various conditions (other than schizophrenia) with an increased prevalence of atypical handedness compared to normals

Conditions	Studies
autism	Gillberg, 1983; Laxer, Rey, & Ritvo, 1988; Lewin, Kohen, & Mathew, 1993; Soper et al., 1986; Hauck & Dewey, 2001.
low birth weight and premature birth	O'Callaghan, Burn, Mohay, Rogers, & Tudehope, 1993; O'Callaghan, 1993;ross Powls, Botting, Cooke, & Marlow, 1996; Saigal, Rosenbaum, Szatmari, & Hoult, 1992; Segal, 1989; Ross, Lipper, & Auld, 1987, 1992.
mental retardation	Pipe, 1990.
breast cancer	Kramer, Albrecht, & Miller, 1985; London & Albrecht, 1991.
strabismus	Lessell, 1986.
dyslexia	Eglinton & Annett, 1994; Tonnessen, Lokken, Hoien, & Lundberg, 1993; Orton, 1937.
epilepsy	Lewin, et al., 1993; Dellatolas, et al., 1993; Springer, et al., 1999; Knake et al., 2003.
maternal smoking	Little, 1999; Bakan, 1991.
prenatal ultrasound	Kieler, 2001.
psychopathy	Bogaert, 2001
posttraumatic stress disorder	Chemtob & Taylor 2003.
ulcerative colitis	Bryden et al., 1994; Geschwind & Behan, 1982.
alcoholism	Bakan, et al., 1973; London, 1990; London, Kibbee, & Holt, 1985; McNamara, Blum, O'Quin, & Schachter, 1994.
stuttering	Orton, 1937; Greiner, Fitzgerald, & Cooke, 1986; Dellatolas, et al. 1990

Apart from genetic models, which consider handedness in humans as the result of genetic influences, there are several biological models proposed to account for atypical variation in handedness distribution. Four such models will be briefly reviewed: (a) developmental instability, (b) pathological left-handedness, (c) the effect of testosterone on hand dominance, also know as Geschwind-Behan-Galaburda (GBG) model, and (d) birth-stress model (perinatal anoxic damage).

1.5.1 Developmental instability model

Developmental stability is the “ability of an organism properly to execute its ontogenetic program despite adverse environmental conditions” (Wadington, 1957, cited by Markow, 1992, p. 296). A failure to execute an ontogenetic program is often visible in both major and minor physical anomalies, which provide an indication of disruptive influences during neurodevelopment. In addition to minor physical anomalies (MPAs), there are another indicators of disturbed process of neurodevelopment, such as preterm birth and low birth weight (Saigal, Rosenbaum, Szatmari, & Hoult, 1992; O'Callaghan et al., 1993; O'Callaghan, Burn, Mohay, Rogers, & Tudehop, 1993; Powls et al., 1996). The first suggestion that non-right-handedness can result from developmental instability came from Van Valen (1962, 1978), who argued that directional asymmetries such as handedness might be a result of fluctuating asymmetry, which can be influenced by genetic and environmental factors. Fluctuating asymmetry is usually defined as a random non-directional deviation from perfect symmetry in bilaterally symmetrical traits. Fluctuating asymmetry, measured as the difference between the left and right sides for a particular trait (e.g. dermatoglyphic abnormalities), is a sensitive indicator of the ability to cope with various environmental stresses during early neurodevelopment. This idea was further expanded by Markow (1992) who suggested that *all* deviations from *modal* handedness might be the result of developmental instability. In her view, moderate right-handedness is the norm, while the extremes, strong left-handedness and strong right-handedness, are markers of developmental instability. Yeo, Gangsted, and Daniel (1993b) have provided some evidence for such a view by analysing the relation of MPAs and laterality measures (handedness measured by Annett’s questionnaire, and motor skill assessed by a peg-moving task). The authors reported that the relationship between MPAs and handedness (both preference and performance) is a U-shaped function, indicating that the number of MPAs increases at both sides of handedness continuum. In addition, a peculiar hypothesis has been put forward by Yeo and Gangestad (1993a). They proposed, citing earlier studies (Rife, 1940; and Boklage, 1987), that left-handed parents will show a lesser level of biological fitness (e.g. as measured by the number of produced offspring) than right-handed parents, and that left-handed mothers will be more prone to miscarriages than right-handed. However, very little has been done to test this theory, and the few replications that have been carried out provide no support for this model. It is not clear why would, if both extremes of the handedness distribution represent the shift from the modal, developmental instability yield unfitness in left-handed parents only but not, by the same token, in strongly right-lateralised parents. In a recent study on a large sample of 2,585 families, McKeever, Cerone, and Chase-Carmichael (2000a), and McKeever, Cerone, Suter, and Wu (2000c) failed to confirm the developmental instability hypothesis, which predicts that left-handed couples are less biologically fit, as manifested by smaller families and a greater risk of miscarriage. A link between left-handedness and autoimmune diseases is also problematic. An association between non-right-handedness and immune diseases was originally proposed by Geschwind and Galaburda (1985), and since then has been tested a number of times. The majority of these studies (Berenbaum, & Denburg, 1994; Elkadi, Nicholls, & Clode, 1999; Mathews et al., 2004) failed to confirm this association. As mentioned above, Yeo et al. (1993b) have argued that an increase of MPAs is significantly associated with both left and right departure from modal handedness. Reasoning that strong right-handedness may also be the result of disturbed development is consistent with Annett's balanced polymorphism hypothesis that strong right-handedness possesses certain disadvantages.

1.5.2 Pathological left-handedness (PLH)

The notion that left-handedness is a result of some pathology is not a recent concept. Gordon (1921) was among the first to observe an increase of left-handedness in the mentally retarded. Brain (1945) introduced an important distinction between what may be termed natural and pathological left-handedness. However, this concept was rejuvenated by Satz (1972) and Satz et al. (1985), who emphasised the distinction between natural and pathological left-handedness, and described its features, highlighting the claim that PLH is a result of early brain injury to the left cerebral hemisphere.

Pathological left-handers are by definition those who were genetically programmed to be right-handers, but who switched hand dominance due to early brain injuries. It is equally possible, however, that natural left-handed individuals become pathological right-handers (PRH), but due to the low incidence of left-handedness in the general population, PRH would occur less frequently. This subtype, compared with PLH, takes place rarely with approximate ratio of 1:11 (Satz, 1972). Recently, Satz and Green (1999, p. 66) restated that pathological left-handedness refers to a ”subset of natural right-handers who, because of early brain injury to the left hemisphere (before age 6), suffer a hypofunction of the right hand (often transient), which in turn causes a shift to preference for the left-hand”.

The features of the PLH syndrome (Satz et al., 1985) include several biological markers, which enable researchers and practitioners to differentiate two groups of left-handers. These features include the following markers: (1) displacement of speech and language to the right hemisphere, (2) impaired nonverbal spatial functions, (3) hemihypoplasia (underdevelopment of limbs), and (4) the lack of positive family history for left-handedness. The last marker, familial sinistrality, is not considered to be a reliable index of PLH (Bishop, 1990b). To the list of biological markers, Bishop (1984) has also added the clumsiness of the non-preferred hand as a 'unilateral soft neurological sign' of PLH.

Some authors strongly oppose the pathological handedness concept (see McManus, 1983a), primarily because of the elusiveness of the biological markers for identification of PLH. For example, localisation of language in the right hemisphere in left-handed individuals may represent a simple developmental variation based on chance (Annett, 1985). In addition, a certain proportion of left-handed individuals have language presented bilaterally (see Table 1.3). It is therefore unclear whether PLH should include left-handers with language localised in the right hemisphere only or left-handers with non-left hemispheric language, that is including those with language presented bilaterally. Impaired nonverbal function in PLH subjects results hypothetically from crowding of functions in one (in this case the right) hemisphere. The major weakness of the PLH model comes from the fact that there are certain conditions with a significant excess of non-right-handedness, but without specific cortical pathology (e.g. strabismus, deafness, and developmental dyslexia), or without a clear left-hemispheric pathology (autism, mental retardation). It appears that the PLH model is applicable as an explanation of the occurrence of left-handedness due to obvious damage of the left hemisphere. From this perspective, the PLH model is a weak model for the explanation of a much broader relationship between NRH and psychopathology (Previc, 1996).

1.5.3 Birth stress model

The birth stress model is the most controversial explanation of the origin of left-handedness, which radicalises the previous, pathologic left-handedness, model by claiming that every single case of not-clear right-hand dominance is pathological. It suggests (Bakan, 1971) that non-right-handedness originates from birth stress, presumably greater for first and fourth and later births, and that *all* non-right-handedness should be considered as a pathologic side effect of such events. This model has evolved from a short letter to the editor of Nature (Bakan, 1971), in which the author postulated that pregnancy and birth complications are the major causal factor for non-right-handedness. Being the first and fourth and later born baby, and therefore more likely to experience traumatic birth, is considered as a risk factor for non-right-handedness. Bakan (1971) explained the tendency of left-handedness to 'run in families', as familial vulnerability to birth complications. Essentially, genetic factors involved in the inheritance of handedness were completely dismissed. The birth stress model has been revived on several occasions (Bakan, et al.,1973; Bakan, 1975, 1990, 1991), but response from the research community has been largely unsupportive. This radical approach to the origin of left-handedness in humans has frequently been debated, mostly to dispute its simplistic view on the origin of handedness. In line with this model, a less radical approach has been introduced by Coren (1992, 1998; also see Coren & Porac, 1980a; Coren & Searleman, 1990; Coren & Halpern1991), who has considered birth stress as one of a number of plausible pathological factors. In his view there are other unspecified factors associated with a number of conditions that exhibit a greater prevalence of non-right-handedness. As a consequence of these pathologies, left-handed individuals, as Coren (1992) has argued, are less fit, more prone to accidents than right-handers, and thus have a shorter life expectancy than right-handers.

The major problem with the birth stress model is the lack of empirical support. Dusek and Hicks (1980), using a sample of 600 elementary school children, found that none of the three birth-risk variables (sex, parity, maternal age) or relevant combinations of them were significantly related to handedness. Dellatolas, Curt and Lellouch (1991), in a large and representative sample of young men (n = 7,300) have also failed to find a clear and significant relationship between handedness and birth order; moreover, the trend was opposite to that claimed by Bakan (1971) and Badian (1983). Many other studies (Hicks, Elliott, Garbesi, & Martin, 1979; Hubbard, 1971; Coren & Porac, 1980b; Leiber & Axelrod, 1981; Perelle & Ehrman, 1994; Searleman, Porac & Coren., 1989; Medland et al., 2003) have also failed to confirm the effect of birth order on increased prevalence of left-handedness.

1.5.4 Geschwind-Behan-Galaburda (GBG) model

A few preliminary studies (Geschwind & Behan, 1982; Geschwind & Behan, 1984) preceded the full elaboration of this model, fully presented in three simultaneously published papers (Geschwind & Galaburda, 1985) and then recapitulated in a book *Cerebral Lateralization* (Geschwind & Galaburda, 1987). The GBG model is a comprehensive attempt to explain the biological mechanism and pathology of cerebral lateralisation in humans and its cognitive and behavioural consequences. At the root of this model lays the sex hormone testosterone, an excess of which is postulated to delay development of the left cerebral hemisphere. Geschwind and Galaburda (1985; p. 429) emphasised that "lateralization is a central theme in biology and medicine and not simply the esoteric concern of a small number of investigators". The notion of hand dominance is one of the essential parts of this theory and a unique biological mechanism responsible for its distribution has been proposed. A primary biological mechanism is believed to be the retardation of the growth of certain left-hemispheric regions, the language areas in particular. Slower maturation of the left-hemisphere supposedly increases the window of vulnerability, making possible that various pre-natal insults affect the left more than the right hemisphere (Bracha, 1991). Delayed left-hemispheric development, observable as a reduction of the size of planum temporale, is also meant to predispose to: (a) various developmental disorders such as autism, developmental dyslexia, stuttering, delayed speech, and hyperactivity, (b) cognition, (c) 'anomalous' cerebral dominance including 'anomalous' handedness, and (d) risk for immune disorders. This original concept of the role of testosterone in delaying the growth of certain brain regions was slightly modified (Galaburda, Corsiglia, Rosen, & Sherman, 1987) by suggesting that the testosterone interferes with the process of neuronal loss. The absence or reduction of neuronal loss would therefore lead to a symmetrical brain with a large planum temporale on each side. The 'anomalous' dominance in the GBG model is an umbrella term used to describe several 'anomalous' deviations from the norm such as reversal or reduction of degree of hand dominance, reversal or reduction of cerebral language representation, and reduction of right hemisphere functions. The norm, however, is defined on a statistical basis; any deviation from the majority of people is considered as anomalous. This concept has been identified as the one of weak point in this theory (McManus & Bryden, 1991), on the basis of its over-inclusiveness. According to McManus and Bryden's estimate (1991; p. 246) "it may be as many as 60% to 70% of the population would be showing anomalous dominance", which "does not seem pragmatically useful or biologically realistic".

Although this theory is considered to be controversial and unfalsifiable (e.g. McManus & Bryden, 1991; Bryden, McManus, & Bulman-Fleming, 1994), and has been strongly criticized (Bishop, 1990a), it is rich in that it has provided a plethora of new hypotheses to be tested. It should be noted that the model was originally presented as a “hypothesis and a program for research” (Geschwind & Galaburda, 1985; p. 428). McManus and Bryden (1991) have argued that this model belongs to the category of “grand” theories, which “gathers together a wide range of previously intractable neuropsychological phenomena under a single theoretical umbrella” (p. 237), and may not be falsifiable as “theories that integrate too many phenomena run the risk of explaining everything, and hence say nothing and becoming untestable and vacuous” (p. 238).

Apart from the concept of anomalous hand dominance, several other associations suggested by the GBG model have been questioned. Bishop (1990a) argued that the authors ignored the extensive literature on the relationship between handedness and developmental language disorders, which showed the association lacking or only weak. She also argued (p. 162) that the hypothesised associations such as that between foetal testosterone and development of the thymus, the level of testosterone and the development of the left hemisphere, and left-handedness and superior right-hemispheric skills (e.g . visuo-spatial abilities) are based on a highly selective review of the literature. Berenbaum and Denburg (1994) have concluded that little empirical evidence has been provided in support of the hypothesised link between testosterone and autoimmune disorders. They pointed out (p. 81) that immune-related disorders, including a prototypic systemic *lupus erythematosus* (chronic autoimmune disease primarily characterised by skin rashes), are more prevalent in women, which is entirely contrary to the suggested effect. Very recently, Mathews et al. (2004) tested the hypothesis that prenatal androgen levels influence hand preference and language lateralisation by analysing 69 individuals with congenital adrenal hyperplasia (a genetic disorder characterised by excessive production of androgenic hormone) and 59 unaffected relatives. The results, which showed a slight decrease of right-hand dominance in males relative to unaffected relatives, were inconsistent with the GBG theory. It has been argued (Mathews et al., 2004) that a slightly reduced right-handedness in male patients represents an enhanced male-typical pattern, with males showing a greater prevalence of left-handedness than females (Hicks & Kinsbourne. 1981; Gilbert & Wysocki, 1992; Perelle & Ehrman, 1994).

Although the GBG theory has many critics (Bishop, 1990a; McManus & Bryden, 1991; Bryden, et al., 1994; Segalowitz Berge, Lawson, & Brown, 1994; Grimshaw, Bryden, & Finegan, 1995; Annett, 2002), mainly due to its postulation of an inherent pathology responsible for non-right-handedness (or anomalous handedness in the GBG terms), many researchers (Hellige, 1994; Kaplan & Crawford, 1994; Previc, 1996) are rather cautious, proposing that it "would be unwise to throw out the baby with the bath water". Put differently, a developmental perspective about human handedness should not be completely abandoned because particular details of the GBG model are not correct.

1.6 Summary

Hand dominance is a uniquely human characteristic with the majority of people being right-handed (approximately 90% of the population). Despite growing evidence that the incidence of left-handedness is not independent of geographical variation, a popular 9:1 ratio describing the distribution of hand dominance persists in the current laterality literature. Handedness appears as a simple fact at the first glance, but no definite answers are known as to its origin. Genetic factors, modified by environmental influences, are most likely involved in the inheritance of handedness. Among several genetic models, the Right Shift theory of Annett (1985) is considered as the most plausible model of handedness inheritance. However, the gene for handedness is yet to be identified.

Hand dominance is associated with brain laterality, most notably with functional lateralisation of language. The impact of the functional organisation of the brain, as indexed by handedness, on cognitive abilities, is weak and possibly without practical importance. Several competing but conflicting models target this intriguing association, aiming to explain a potential association between the lateralisation of hand preferences and cognitive abilities.

It is not surprising that a number of theories have been proposed to explain the origin of handedness and the mechanism of inheritance. Roughly, theories about handedness can be divided into two groups: first, those which consider both left- and right-handedness as neutral and benign variations, and second, those which that right-handedness is the norm, with departure from the norm due to some pathology. In these two groups of theories, the former usually try to explain the distribution of handedness in families and likely mode of inheritance, while the latter aim to describe which risk factors are associated with the occurrence of non-right handedness. An implicit assumption contained in all the latter models is that left-handedness is a pathologic deviation from normality. One such model, the birth-stress model, offers an extreme view in which any departure from right-handedness is due to pathology. This extreme model, despite being unsupported with empirical evidence, was reviewed to illustrate that debate over the origin of handedness is enduring.

The incidence of atypical lateralisation of hand preferences (left-, mixed-, or combined as non-right-handedness) in some clinical populations suggests that, in addition to genetic determination of handedness, non-genetic factors might also be involved, and that they might interfere with neurodevelopment and cognition. Certain clinical populations display an excessive leftward shift in the handedness distribution. Among the clinical groups, schizophrenia patients are consistently characterised with a high incidence of 'atypical' hand dominance. In the next section will be reviewed a relevant literature concerning this issue.

2. Handedness and schizophrenia

2.1 Description of Schizophrenia

Schizophrenia is an umbrella term used to describe a psychotic condition often accompanied by various cognitive, emotional and behavioural abnormalities. Although current diagnostic and classification systems such as the International Classification of Diseases (ICD-10, World Health Organisation, 1993) and the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV, American Psychiatric Association, 1994) define schizophrenia as a *disorder*, a term such as *syndrome* appears to be a more suitable as descriptor of a great variety of clinical manifestations of this condition. The name and the definition of this condition has changed over time and what is called schizophrenia today used to be known as *dementia praecox.* The term was coined by Emil Kraepelin (1856-1926), a founder of modern psychiatry who also noted that symptoms of schizophrenia often result in severe incapacity of the patient. Kraepelin's diagnostic term for such a disabling condition was changed into *schizophrenia* by Eugene Bleuler (1857-1939) when his book *Dementia praecox oder Gruppe der Schizophrenien* (Bleuler, 1911) was published. While both Kraepelin's *dementia praecox* and Bleuler's schizophrenia are characterised by presence of similar types of negative and positive symptoms and signs, Kraepelin's concept of *dementia praecox* highlighted cognitive deficit as the core clinical feature of what is today defined as schizophrenia. Despite the fact that clinical description of schizophrenia might be a "surface feature, remote from the primary site of action of putative biological causes" (Jablensky, 2004, p. 308), the diagnosis of schizophrenia can only be given on the basis of its clinical symptoms and behavioural manifestations. An emphasis on clinical phenomenology of schizophrenia was placed by the introduction of Schneider's 'first rank symptoms' (FRS), which he believed were particularly important and specific for the diagnosis of schizophrenia. The list of Schneider's FRS included delusions and hallucinations as well as psychopathological phenomena such as thought insertion, thought broadcasting, delusions of control, and voices commenting. However, it should be noted that psychotic states which include FRS are not specific for schizophrenia, as they may also occur in other psychotic disorders (Peralta & Cuesta, 1998; Tsuang & Faraone, 2002a).

ICD-10 and DSM-IV differ in their specifications of diagnostic criteria for schizophrenia. For example, whilst the DSM-IV requires evidence that the symptoms of schizophrenia are accompanied with impairment in social and occupational functioning of the patient, the ICD-10 does not consider such evidence to be necessary for a positive diagnosis. Another difference is that the positive diagnosis of schizophrenia based on DSM-IV requires that continuous symptoms and signs of the disturbance persist for at least 6 months, whilst the ICD-10 duration requirement is only one month. Notwithstanding the differences in the operationalisation of diagnostic criteria, both classification systems consider presence of the following positive and negative clinical symptoms as a *conditio sine qua non* for the diagnosis of schizophrenia:

- *Delusions* of various types, which could briefly be described as fixed erroneous beliefs, maintained despite evidence to the contrary. The most common delusions in schizophrenia include delusional ideas of reference and persecutory delusions.
- *Hallucinations* are also relatively common clinical symptoms and can occur in any sensory modality, with auditory hallucinations being the most prevalent in schizophrenia. Visual and somatic hallucinations can also be present but are less common.
- *Disordered thinking* which is characterised by spontaneous changes of unrelated or only distantly related ideas. Presence of this symptom is generally observed in

disorganised speech or in idiosyncratic use of ordinary or made-up words called neologisms.

- *Reduced contact with reality,* resulting in the subjective experience that one's thoughts, feelings and experiences are known to, or manipulated by others (e.g., thought possession or thought withdrawal).
- *Grossly disturbed or catatonic behaviour* that includes a variety of motor disturbances, such as disorganised motor-coordination, hypoactivity (including its extreme modality known as stupor), unusual body posture and diminished facial expression.
- *Disturbed emotional control* resulting in the incongruence of thoughts and accompanying affects.
- *Affective flattening*, which refers to decreased responsiveness to emotions or the absence of any affective expression, commonly accompanied by motor hypoactivity including diminished facial expression and reduced vocal modulation (according to some authors, this symptom is one of the hallmarks of chronic schizophrenia).
- *Poverty of speech,* which is one of the most marked abnormalities of disordered thought process in schizophrenia patients, entailing reduced amount of speech production and poverty of speech content.
- *Loss of volition* or inability to maintain behaviour in pursuit of a goal. Severe disruption of motivation resulting in complete avolition is considered to be a particularly disabling clinical feature of schizophrenia.

The above-mentioned symptoms of schizophrenia are often being referred to as 'positive' (e.g. delusions, hallucinations) and 'negative' (the last three clinical symptoms of schizophrenia from the above list, which represent the absence or loss of normal behaviour.

Presence and intensity of positive and negative symptoms vary across schizophrenia patients, thus making it possible for a patient to receive this particular diagnosis without, for example, having hallucinations or being delusional. Depending on the combination of these symptoms, patients are placed in one of the following diagnostic subcategories of schizophrenia: paranoid, disorganised, catatonic, undifferentiated, residual, and simple schizophrenia.

Although aetiology of schizophrenia still remains only partially understood, research carried out in the course of last few decades suggests that it is a member of genetically complex diseases with a polygenic basis, such as diabetes, cancer and hypertension. All these complex diseases are genetically heterogeneous in the sense that different combinations of genes play a role in different populations or in different families within the same population and involve multiple environmental factors in the causal pathway. Other aspects of schizophrenia that potentially indicate its genetic aetiology include the following: (a) it is an illness that usually begins in the late teens and early twenties, (b) males are more frequently affected, and (c) persistence of illness in the human population despite the fact that the majority of individuals affected with schizophrenia do not marry or have children. In view of the above, it is expected that genetic and epidemiological studies will provide further valuable information on the aetiology of this condition in the years to come.

Schizophrenia is present in all populations and all cultures. A World Health Organisation (WHO) study on the cross-cultural prevalence of schizophrenia (defined by presence of the first rank or 'nuclear' symptoms) revealed that its prevalence rate is independent of geographic and social environments (Jablensky et al., 1992). This study, one of the largest epidemiological and cross-cultural investigations to date, was conducted in ten developed and developing countries with the aim of investigating incidence, clinical manifestations, and course of schizophrenia. It is widely accepted that the prevalence rate of schizophrenia is in the range 1.4 to 4.6 per 1000, an incidence rate is in the range 0.16 to 0.42 per 1000, and a lifetime risk at around 1 per cent (Jablensky, 2000a). The largest epidemiological study of psychotic disorders conducted in Australia, Jablensky et al. (2000b) found similar prevalence rate of psychotic disorders (ranging from 4 to 7 per 1000). Another important finding from this study was that, although assigned as 'low-prevalence', psychotic disorders (and in particular schizophrenia) were associated with a heavy burden including high social and personal costs thus constituting a huge and complex public health problem. For example, the direct cost treatment and services for schizophrenia patients in Australia is estimated at $1.5 billion per annum, the largest part of which is related to the cost of inpatient care. This cost is even higher when the lost productivity and impact on families are considered, and amounts to about 2.7 billion per annum (Carr, Neil, Halpin, & Holmes, 2001).

2.2 Review of the literature on handedness in schizophrenia

Quinan (1930) was the first to point out the potential importance of the relationship between sinistrality and psychosis (at that time called *dementia praecox*), but his research effort was ignored over the next four decades. Research on psychopathology and laterality was fully re-initiated by Flor-Henry's (1969) seminal study of epileptic psychosis showing a left hemispheric dysfunction in schizophrenia and right hemispheric dysfunction in affective psychosis. Oddy and Lobstein (1972) were the first to revisit Quinan' ideas and re-explore if there was an atypical distribution of handedness in schizophrenia patients. Interestingly, their study coincided with both the revival of interest in structural brain changes of patients with schizophrenia (e.g. in 1976, Johnstone and colleagues published the first study on ventricular dilatation in schizophrenia patients using the CT scan technology) and a pessimistic prophecy that schizophrenia is the 'graveyard of neuropathologists' (Plum, 1972). In the above-mentioned study, Oddy and Lobstein examined hand and eye dominance in 140 schizophrenia patients, and their results showed that when hand and eye dominance distributions were measured separately, they resembled control subjects. However, when these two factors were combined and considered for cross dominance (e.g. right-hand but left eye dominance) the schizophrenia patients differed significantly from normal controls. In retrospect, one could conclude that this particular study triggered the laterality research, particularly of handedness in schizophrenia. Since then, research papers addressing the issue of 'handedness' in schizophrenia have begun to appear regularly in various scientific journals. At the same time, the conceptual framework linking lateralisation with psychosis was summarised in the book *Hemisphere Asymmetries of Function and Psychopathology* (1979; edited by Gruzelier & Flor-Henry), specifying that there were distinct differences between schizophrenia (characterised by left hemispheric dysfunction) and bipolar disorder (characterised by due to right hemispheric dysfunction).

Notwithstanding the above, a review of the more recent literature (which was particularly focused on the issue of anomalous handedness in schizophrenia patients and covered the period from 1972 to early 2004) revealed that only about 40 research reports have been published on this topic, thus indicating an unimpressive scientific production of some two studies per year. However, it should be noted that studies which only briefly or superficially dealt with the phenomenon of handedness have not been included in this review.

Studies which specifically investigated handedness in the population of schizophrenia patients could be divided in two main groups: (i) studies on prevalence of atypical lateralisation and hand preference in schizophrenia patients; and (ii) studies exploring neuroanatomical and clinical correlates of anomalous handedness in schizophrenia. The latter group of studies could be divided further into: (a) neuroanatomical studies, (b) cognitive studies, and (c) clinical studies (figure 1.5).

A large number of the above-mentioned epidemiological studies published during the 70s and 80s were predominantly concerned with estimating the prevalence of atypical hand dominance in the population of schizophrenia patients (Oddy & Lobstein, 1972; Lishman & McMeekan, 1976; Wahl, 1976; Gur, 1977; Luchins, Weinberger, & Wyatt, 1979; Fleminger, Dalton, & Standage, 1977; Taylor, Dalton, & Fleminger, 1982a; Chaugule & Master, 1981; Nasrallah, McCalley-Whitters, & Kuperman, 1982; Piran, Bigler, & Cohen, 1982; Shimizu & Endo, 1985; Shan-Ming et al., 1985; Gureje, 1988; Green, Satz, Smith, & Nelson, 1989). In the course of the following decade, researchers began to explore the associations between abnormal functional lateralisation of hand preferences, and their neuroanatomical, cognitive and clinical correlates (Andreasen, Dennert, Scott, & Damasio, 1982; Merrin, 1984a; Manoach, Maher, & Manschreck, 1988; Katsanis & Iacono, 1989; Satz, Green, Bartzokis, Bledin, & Vaclav, 1990; Clementz, Iacono, & Beiser, 1994; Verdoux et al., 2004).

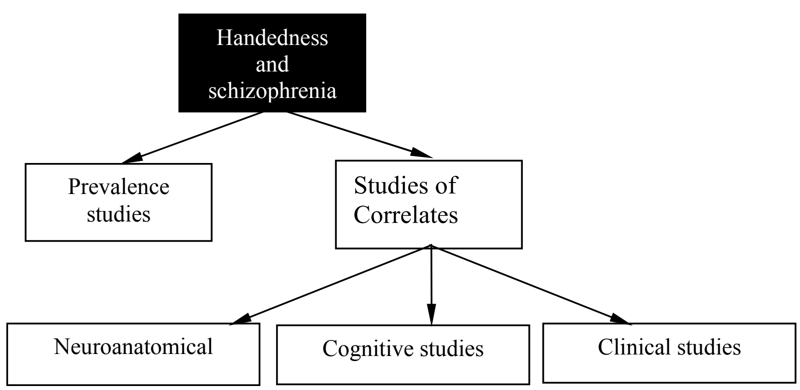

Figure 1.5 Classification of the literature on handedness in schizophrenia in the period 1972 to 2004

A brief summary of studies on prevalence rates and correlates of atypical handedness in patients affected with schizophrenia is given in Table 1.5. A critical evaluation of these studies, which have been divided in three groups according the above-mentioned categorisation, is discussed below. However, an initial observation of these studies leads to the conclusion that there is a leftward shift in handedness distribution in schizophrenia, which is associated with clinical, neurocognitive and neuroanatomical features of the patients suffering from this disorder.

Table 1.5 Review of the core papers

Author(s)	Sample(s)	Laterality assessment	*Findings*
Oddy & Lobstein, 1972	- Schizophrenia patients (n = 140) - Controls (497)	Annett's revised scale (5 items) Eye dominance	- Hand and eye dominance distribution similar in schizophrenia patients and controls. - Schizophrenia patients showed more crossed-dominance than controls - Mixed-handedness is more present in younger patients
Dvirskii, 1976	- schizophrenia patients (n = 1,270) - Controls (n=2,150)	Observation method	- the frequency of left-handedness was higher among men and women with schizophrenia than in the general population
Lishman & McMeekan, 1976	- Psychiatric patients (n = 130)	Annett's Handedness Questionnaire	- Young and male patients were more non-right-handed than female patients - Left-handed patients showed reduced incidence of familial sinistrality in relatives
Wahl, 1976	- Schizophrenia patients (n = 26) - Non-schizophrenia patients (n = 21) - Controls (n = 18)	Ad hoc 10 items and 5-point scale	- Schizophrenia patients were more confused about hand preference, but patterns of hand preference did not differ from controls and non-schizophrenic patients
Fleminger et al., 1977	- *Psychiatric patients (n = 800)* - Controls (n = 800)	Annett's Handedness Questionnaire	- Higher proportion of fully dextral subjects was found in both schizophrenics and affective groups compared with neurotics and controls
Gur, 1977	- Schizophrenia patients (n = 200) - Controls (n = 200)	23-item questionnaire (Rackowski et al., 1974); eye and foot dominance	- Schizophrenia patients manifest a higher degree of left-sidedness - Schizophrenia patients differed in handedness and footedness from controls, but not in eyedness - Schizophrenia patient and controls showed no significant association between handedness and eye dominance

Author(s)	Sample(s)	Laterality assessment	*Findings*
Luchins et al., 1979	- Schizophrenia patients or schizoaffective psychosis (n = 66)	- Edinburgh Handedness Inventory - Torque test	- Milder forms of schizophrenia were associated with anomalous lateralisation (severity of illness was indexed by chronicity, length of illness, and age at onset)
Taylor et al., 1980	- Schizophrenia patients (n = 272) - Controls (n = 800)	Annett's Handedness Questionnaire	- Schizophrenia patients differed significantly from controls in their handedness patterns, having a higher proportion of fully right-handed subjects
Chaugule & Master, 1981	- Schizophrenia patients (n = 93) - Affective psychosis (n = 25) - Neurotics (n = 23) - Controls (n = 150)	Annett's Handedness Questionnaire	- All psychiatric patients were more likely to be non-dextral than controls - Schizophrenia patients also displayed a significantly higher non-dextrality than controls
Taylor et al., 1982b	Existing samples: (a) Lishman & McMeekan (1976), and (b) Fleminger et al., (1977)	Annett's Handedness Questionnaire	- There was no significant excess of left-sidedness in either sample by either classification
Andreasen & Olsen, 1982	- Schizophrenia patients (n = 52)	Writing hand	- Patient with 'positive' schizophrenia were more likely to be right-handed than those with 'negative' schizophrenia (100% VS 69%)
Andreasen et al., 1982	- Schizophrenia patients (n = 52) - Controls (n = 47)	Writing hand	- Left-handed schizophrenia patients had significantly larger lateral ventricles than right-handed patients
Taylor et al., 1982a	- Schizophrenia patients (n = 232)	Annett's Handedness Questionnaire	- Thought disordered patients were more non-right-handed than those without formal thought disorder - Neither of remaining Schneiderian symptoms was related to handedness distribution
Nasrallah et al., 1982	- Schizophrenia patients (n = 80; all males) - Controls (n = 83)	13-item performance laterality scale	- Significant increase of left-handedness in the group of patients compared to controls - Significantly more mixed-footedness in schizophrenia patients compared to controls (86% VS 43%) - Leftward shift was the strongest in the paranoid subtype of schizophrenia
Piran et al., 1982	- Schizophrenia patients (n = 28) - Brain damage psychiatric patients (n = 24) - controls (n = 16) - students (n = 36)	Demonstration tests for hand (7 items), eye (3 items), and foot (3-items).	- Schizophrenia patients displayed a significantly higher leftward tendency on all measures - The incongruity in lateral preferences, in addition to the left-sidedness, was more typical for schizophrenia patients
Merrin, 1984a	- Schizophrenia patients (n = 52) - Affective disorder (n = 40) - Controls (n = 49)	Adapted 10-Item scale adapted; eye dominance	- No significant differences in handedness and sighting dominance between studied groups
Shimizu et al., 1985	- Schizophrenia in-patients from 24 hospitals (n = 1774) - University students (n = 4282)	13-item questionnaire (Shimizu, 1983)	- No statistically significant difference between schizophrenia patients and controls. - The incidence of converted handedness is higher in schizophrenia patients than in normal people (p=0.01) - Original non-right-handedness (present but converted right-handers plus present non-right-handers) in schizophrenia patients was significantly elevated compared to controls

Author(s)	Sample(s)	Laterality assessment	*Findings*
Shan-Ming, et al., 1985	- Schizophrenia patients (n = 225) - Bipolar disorder (n = 127) - Controls (n = 432	10-item ad hoc demonstration test	- Significant excess of non-dextrality in schizophrenia patients compared to controls. - A tendency for crossed-dominance in both schizophrenia and bipolar patients compared to controls
Gureje, 1988	- Schizophrenia patients (n = 70) - Controls (n = 40)	Demonstration tests for hand (5 items), eye (2 items), and foot (3-items).	- Two groups did not differ in the handedness distribution
Manoach & Maher, 1988	- Schizophrenia patients (n=58)	Writing hand	- All left- and only 70% of right-handed schizophrenia patients were thought disordered
Green et al., 1989	- Schizophrenia patients (n = 93) - Controls (n = 105)	Hand Preference Demonstration Test (Soper et al., 1986)	- Significant non-right shift in schizophrenia patients compared to controls. - This shift was due to increase of mixed-handedness
Katsanis & Iacono, 1989	- Schizophrenia patients (n = 63)	Writing hand; Tapping task	- Left-handed schizophrenia patients had larger lateral ventricles - Left-handed patients performed poorer on IQ (WAIS-R) and Wisconsin Card Sorting Test
Pearlson et al., 1989	- Schizophrenia patients (n = 50)	Annett's Handedness Questionnaire	- Left-handedness and history of abnormal delivery are significant predictors of the VBR
Oyebode & Davison, 1990	- 'Epileptic' schizophrenia patients (n = 32) - 'Functional' schizophrenia patients (n = 31 - neurological patients (n = 19)	Annett's Handedness Questionnaire	- Epileptics with psychiatric illness did not differ from the general population in handedness distribution - Male schizophrenia patients ('functional') were significantly more mixed-handed than epileptic patients with psychiatric illness. - Mixed- and left-handedness may be protective against the development of psychiatric illness
Satz et al., 1990	- Schizophrenia patients (n = 25) - Controls (n = 25)	Hand Preference Demonstration Test (Soper et al., 1986)	- Increased ventricular-brain ratio asymmetry was larger in non-lateralised than in lateralised patients
Faustman et al., 1991	- Schizophrenia patient (n =48), all male	Writing hand	- Left-handed patients showed a significantly poorer performance on several Luria-Nebraska Neuropsychological Battery measures compared to right-handed patients
Nelson et al., 1993	- Schizophrenia patients (n = 72) - Controls (n = 105)	8-item demonstration test (Soper et al., 1986)	- There was a significantly higher incidence of mixed-handedness in schizophrenia patients compared to controls irrespective of varying the task demand - Handedness responses of schizophrenia patients were stable over time
Torrey et al., 1993	- MZ twins discordant for schizophrenia (n = 27) - MZ twins concordant for schizophrenia (n = 13) - MZ twins unaffected	Edinburgh handedness Inventory	- Increase of non-right handedness in monozygotic twins with schizophrenia is unsupported

Author(s)	Sample(s)	Laterality assessment	*Findings*
Clementz et al., 1994	- Schizophrenia patients (n = 58) - Major depression (n = 23) - Bipolar disorder (n = 36) - Relatives (n = 117) - Controls (n = 119)	Edinburgh handedness Inventory	- Left-handed schizophrenia patients tended to have higher ventricle brain ratio - Schizophrenia patients were more left-handed than other psychiatric diagnoses - Relative of schizophrenia patients had handedness similar to control subjects
O'Callaghan et al., 1995	- Schizophrenia patients (n = 45)	Edinburgh handedness Inventory	- Left-handed male schizophrenia patients had larger left and right ventricle - This relationship was not confirmed for female patients - Female left-handed patients had poorer premorbid intelligence
Cannon et al., 1995	- Schizophrenia patients (n = 96) - Controls (n = 43)	Edinburgh handedness Inventory	- Significant increase of mixed-handedness in schizophrenia patients - Mixed-handedness in patients was associated with chronicity of illness
Taylor & Amir, 1995	- Core schizophrenia patients (n = 41) - Schizophrenia spectrum (n = 36) - Schizoaffective (n = 86) - Affective (n = 103) - Controls (n = 112)	Edinburgh handedness Inventory	- DSM-III schizophrenia patients were more mixed-handed than controls, but within this group only schizoaffective patients were significantly more mixed-handed than controls - There was no consistent relationship between handedness and psychopathology
David et al., 1995a	From a cohort of 50,000 male Swedish conscripts	Demonstration test (one item)	- Left-handedness was not associated with schizophrenia nor other psychoses - There was no evidence that left-handedness lead to an increased risk of schizophrenia
Tyler et al., 1995	- Schizophrenia patients (n = 686)	Postal questionnaire	- Left-handed patients had a more frequent history of difficult birth, more childhood cognitive and behavioural abnormalities and more persistent auditory hallucinations than did right-handed patients - The incidence of left-handedness in the sample of patients was 14%
Crow, Done & Sacker, 1996	UK National Child Development Study cohort (n = 16,980)	Parental report, writing, and hand skill	- Children who developed schizophrenia were more likely to be rated as ambidextrous (age 7) and as less right-handed (age 11) than those who did not
Malesu et al., 1996	- Schizophrenia patients (n = 96) - Schizoaffective (n = 41) - Affective (n = 55) - Controls (n = 89)	Annett's Handedness Questionnaire	- A nonsignificant excess of mixed-handedness in schizophrenia patients and other diagnostic groups
Cannon et al., 1997	- Schizophrenia patients (n = 24); out of random, epidemiological sample (n = 5362)	School doctors examination	- 'Pre-schizophrenic children showed a significant excess of left-eye dominance at age of 11 when compared with controls, but there was no significant difference in hand preference'
Hayden et al., 1997	Chronically mentally ill patients (n = 58), of whom 47 were schizophrenia patients	Hand Preference Demonstration Test (Soper et al., 1986)	- 32.8% of patients were ambiguous handers - Ambiguous patients showed significantly worse performance on verbal learning and manual dexterity tests compared to non-ambiguous patients.
Toomey et al., 1998	- Relatives of schizophrenia patients (n = 54) - Controls (n = 72)	Unreported	- Relatives of schizophrenia patients showed similar incidence of left-handedness to controls (90.7% vs 90.3%)

Author(s)	Sample(s)	Laterality assessment	*Findings*
Sperling et al., 1999	- Schizophrenia patients (n = 60) - Controls (n = 60)	Shimizu and Endo handedness questionnaire	- Non-right-handedness in schizophrenia patients was significantly elevated compared to controls - Pre-, peri, and postnatal obstetric complications were significantly higher in non-right-handed patients compared to right-handed. This has been confirmed in the male group only
Orr et al., 1999	- Schizophrenia patients (n=94) - Relatives (n=99) - Controls (n=85)	Annett's Handedness Questionnaire	- Significant excess of mixed-handedness in schizophrenia - No association between mixed-handedness and pregnancy and birth complications. - Excess of mixed-handedness in group of relatives
Norman, et al. 2001	- Untreated first episode psychosis (n = 113; 41% of those were patients with schizophrenia diagnosis)	Observation of the hand used for writing, throwing, and using scissors	- There was no excess of left-handedness in the sample (LH=10.6%; RH=89.4%; very close to the general population incidence). - Left-handers showed poorer performance on processing speed index, working memory, and all indices of visual and auditory memory (immediate and delayed)
Browne et al., 2000	- First episode of psychosis (n = 121)	Edinburgh handedness Inventory	- Mixed-handed patients with schizophrenia spent less years in education and had a poorer pre-morbid social adjustment, suggesting that this 'neurological dysfunction' is intrinsic to schizophrenia
Giotakos, 2001	- Schizophrenia patients (n = 68) - Controls (n = 944)	Annett's Handedness Questionnaire	- Schizophrenia patients were characterised by an excess of mixed-handedness irrespective of the definition of mixed-handedness
Egan et al., 2001	- Schizophrenia patients (n = 115) - Siblings (n=185) - Controls (n = 88)	Edinburgh Handedness Inventory	- Patients had the same incidence of of both left- and right-handedness as comparison subjects. Siblings of patients did not differ from controls on handedness
Reilly, et al., 2001	- Schizophrenia patients (n = 30) - Controls (n = 37)	Edinburgh handedness Inventory	- Schizophrenia patients were more likely to be classified as mixed-handers than controls (37% VS 16%) - Atypical hand skill and fluctuating asymmetry were significantly associated in schizophrenia patients
Buijsrogge, et al., 2002	- Schizophrenia patients (n = 73) - Controls (n = 81)	Edinburgh Handedness Inventory	- Male schizophrenia patients were significantly less right-handed than male controls - Sinistral shift in handedness was not found when sex was taken into account
DeLisi, et al., 2002	- Nuclear families with family member affected with schizophrenia (n = 259; with 905 individuals)	- Rackowski's questionnaire (Annett, 1985) - Tapping task	- Affected family members were less right-handed when compared to their well relatives. Handedness categories did reveal significant difference - Significant familiality of hand preference and hand skill was found in affected siblings
Tabares-Seisdedos, et al., 2003	- Schizophrenia patients (n = 84) - Controls (n = 31)	- Demonstration test - Motor dominance demonstration test	Right-handed schizophrenia patients showed reduced motor asymmetry only during bimanual tapping compared with controls due to reduction in right-hand performance
Verdoux et al., 2004	- Schizophrenia patients broadly defined (n = 20) - Psychotic mood disorder (n = 13)	Edinburgh Handedness Inventory	Greater left-handedness is associated with more intense Schneiderian first rank symptoms

Author(s)	Sample(s)	Laterality assessment	*Findings*
Collinson et al., 2004	- Schizophrenia patients (n = 44); early onset - Controls (n = 39)	Annett's Handedness Questionnaire and pegboard	-Significant excess of mixed-handedness in patients compared to controls - Crossed eye-hand and eye-foot preferences were not significantly increased in patients relative to controls
Byrne et al., 2004	- High risk for sz (n = 115) - Schizophrenia patients (n = 15) - Controls (n = 29)	Edinburgh Handedness Inventory and Annett's scale	- No sex differences - prevalence of handedness subtypes varied with changes in definition of handedness
Schiffman et al., 2004	- Schizophrenia spectrum (n = 26) - Others (n=226)	Annett's Handedness Questionnaire;	- No significant differences in handedness between children who developed schizophrenia and those who did not
Upadhyay et al., 2004	- Schizophrenia patients (n = 37) - Controls (n = 200)	Waterloo Handedness Questionnaire	- Schizophrenia patients were characterised by an excess of mixed-handedness, but it was evident more for unskilled than skilled activities

2.2.1 Prevalence studies of atypical handedness in schizophrenia

As already mentioned, early research in this area was primarily focused on the fact that in the population of schizophrenia patients there was an excess of non-right-handedness, which was higher than in normal controls or other psychiatric patients. Moreover, there were many other studies with a different focus that have also reported higher incidence rates of atypical behavioural lateralisation in schizophrenia patients. The literature search revealed that there were over 40 studies in which the higher prevalence rates of various handedness subtypes in schizophrenia patients were reported. A meta-analysis of these studies and a review of empirical evidence resulting from this laborious exercise are the subject of the first project carried out in the context of this thesis. In brief, this meta-analysis of the data aggregated from all available studies showed that each handedness subtype (i.e. exclusive left-handedness, mixed-handedness, and non-right-handedness) is in significant excess in schizophrenia patients compared to control subjects.

Reviews of the empirical evidence of atypical hand preference lateralisation in schizophrenia patients are relatively infrequent compared to research reviews of other domains in schizophrenia such as neuroimaging or neurocognitive studies. To date only three reviews of the evidence have been conducted; two qualitative reviews by the same authors (Green et al., 1989; Satz & Green, 1999), and one quantitative (Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001). In the first review article Green at al. (1989) reviewed 16 studies classifying them as those with 'positive' (9 studies), 'null' (5 studies), and 'paradoxical' (2 studies) results, and concluded that mixed-handedness was more prevalent in schizophrenia patients than in controls. A similar conclusion was drawn ten years later by Satz and Green (1999), after reviewing 23 studies and counting again the overall box score outcomes (i.e. significant versus non-significant studies). Reviews of the evidence by combining diverse studies on the basis of statistical significance into categories are further elaborated upon in the next two parts of the thesis.

The only quantitative review of the empirical evidence took place after thirty years of research (Sommer et al., 2001). In contrast to previous reviews, Sommer et al. concluded that non-right-handedness is more prevalent in schizophrenia patients compared to controls. The fact that diverse findings have been reported without rigorous quantitative evaluation of the evidence, led some researchers to conclude that laterality studies do not provide sufficient evidence that in schizophrenia patients there is a significant shift in direction of hand preferences (Gruzelier, 1981; Flor-Henry, 1983; Gruzelier, 1999).

2.2.2 Atypical handedness and schizotypy

Schizotypy can be described as a personality trait characterised by markedly eccentric and erratic thoughts, speech and behaviour and social isolation. A serious disturbance in these domains can also lead to a diagnosis of Schizotypal Personality Disorder (SPD), which is often described as similar to, but a less severe type of schizophrenia. As schizotypal personality traits are more common in biological relatives of schizophrenia patients than in the general population, investigations of such traits provide intermediate phenotypes that increase the power of genetic studies in schizophrenia research. It is widely believed that these endophenotypes show qualitatively similar, though quantitatively less marked, neurocognitive deficits as those identified in schizophrenia patients.

Investigations of the phenotypic markers as risk factors in schizophrenia are commonly conducted through the assessment of two groups of subjects which carry a greater risk for developing schizophrenia. These are namely first degree relatives of schizophrenia patients, and individuals described as being 'at-risk' to schizophrenia on the basis of high scores on various measures of schizotypy (psychosis-prone). Among the other phenotypic markers examined in these populations, atypical handedness has also been investigated in relationship to this concept of psychosis-proneness. A more detailed review of the literature on this topic is presented in the third study. Briefly, there is no convincing evidence that 'psychosis-proneness' is associated with anomalous lateral preferences typically found in the population of schizophrenia patients. The majority of empirical evidence related to the concept of proneness is based on student samples, while observed effect sizes in terms of Cohen's *d* are weak, and detectable as statistically significant in large samples only.

2.2.3 Relationship between atypical handedness and neuroanatomical, neurocognitive and clinical measures in schizophrenia

2.2.3.1 Atypical handedness and neuroanatomy of schizophrenia

There have been a number of studies which reported on structural macroscopic and morphological deviations of the brain in schizophrenia patients, indicating fairly consistently some relatively constant departures from the 'normal' brain including: (i) ventricular dilatation (Wright et al., 2000), (ii) reduced brain size and cortical mass (Lawrie & Abukmeil, 1998; Harrison, 1999; Wright et al., 2000; Collinson et al., 2003), and (iii) reduced or reversed cerebral asymmetry, described often as a 'counterclockwise torque' (Crow, 1990; Berlim, Mattevi, Belmonte-de-Abreu, & Crow, 2003). This last finding accompanied by a failure to establish lateralised language dominance is considered by Crow (1990, 1993, 1997a, 1997b) as a primary key for developing psychosis.

Enlarged brain ventricles are the most prominent and replicable macroscopic brain abnormality in schizophrenia patients (Wright et al., 2000). They are usually interpreted as indication of hypoplasia or cerebral atrophy which, along with other brain abnormalities, is considered to be a neuropathological substrate of schizophrenia. However, some researchers (Flaum et al., 1995) have interpreted this abnormality as non-specific to schizophrenia as it has also been identified in patients suffering from other mental disorders, and it is often present in normal comparison subjects. It is unlikely that schizophrenia is a "disorder of cerebral ventricles" (Jones, 1997, p. 144). The exact neurobiological meaning of ventricular dilatation in the context of schizophrenia remains unclear. Whereas some researchers such as Crow et al. (1989a), DeLisi et al. (1991), Buchsbaum et al. (1997), and Chance, Esiri, and Crow (2003) have reported that this specific brain abnormality in schizophrenia patients shows a laterality effect (i.e. abnormality of the left-hemisphere), other studies have found either bilateral (Weinberger, Suddath, Casanova, Torrey, & Kleinman, 1991; Flaum et al., 1995) or the opposite ventricular enlargement of some brain structures (e.g. temporal horns were found to be larger on the right side in the study of Flaum et al. 1995). Research in the area of this specific brain abnormality in schizophrenia patients is further complicated by the effects of many confounding variables such as gender, ageing, body mass, height, ethnicity, socioeconomic status, lifestyle (i.e. alcoholism, drug abuse, smoking) and handedness - all of which with an impact on brain development and its macroscopic characteristics.

Several studies have specifically explored the relationship between ventricular dilatation and handedness in schizophrenia patients. Importantly, all of them (Andreasen et al., 1982; Katsanis & Iacono, 1989; Satz et al., 1990; Clementz et al., 1994; O'Callaghan et al., 1995) came up with the identical conclusion that left- and mixed-handed schizophrenia patients tend to have a larger ventricular brain ratio than the right-handed patients. In the first study of this type, Andreasen and colleagues (1982) used computerised tomography (CT) scans and found that left-handed schizophrenia patients had significantly larger ventricular-brain ratio than right-handed patients. Several years later, this finding was corroborated by Katsanis and Iacono (1989), who reported that 12 (19 %) out of 63 left-handed schizophrenia patients showed both "neuropsychological and CT scan abnormalities" (p. 1057). Left-handed schizophrenia patients also had significantly larger lateral ventricles compared to right-handed patients. Similarly, Pearlson and colleagues (1989) found that left-handedness was a significant predictor of enlarged ventricle-brain ratio. A year later, Satz and colleagues (1990) conducted the first study which was specifically designed to address a neuroanatomical substrate of atypical hand preference in schizophrenia. Twenty-five schizophrenia patients were divided into non-lateralised (i.e. switching hands for the same item) and lateralised (i.e. consistent right hand preferences) groups on the basis of the Hand Preference Demonstration Test (Soper et al., 1986) and compared with age, gender- and race matched controls on several brain measures. Results revealed that both lateralised and non-lateralised patients had a significantly smaller volume of the left hemisphere compared to controls, and that non-lateralised patients had significantly larger left than right ventricular brain ratio. Lateralised patients and controls were similar in this regard. As non-lateralised patients could not be distinguished from normal controls (regardless of whether they had unusually larger left or small right ventricular brain ratio), a conclusion of a bilateral neuroanatomical substrate being responsible for the shift in handedness distribution was proposed. In contrast to all previous studies which examined bilateral ventricular brain ratio, this was the first study to focus on left and right hemispheric asymmetries regarding this anatomical feature. In a study by Clementz et al. (1994), which investigated the relationship between handedness and bilateral ventricular enlargement, it has also been found that patients with larger ventricles were significantly more left-handed. Finally, O'Callaghan and coworkers (1995) have also investigated this relationship and reported that the left-handed male schizophrenia patients had enlargement of both left and right ventricles, but not the females. However, left-handed female schizophrenia patients showed poorer premorbid intelligence compared to right-handed female patients.

Given that almost all studies have found that left-handed schizophrenia patients show a diffuse bilateral ventricular enlargement, the interpretation of such abnormalities as being causally related to atypical handedness (as proposed by Satz et al., 1990) remains dubious. Moreover, the observed relationship between ventricular dilatation and hand dominance is difficult to interpret in terms of causes and effects. For example, small sample sizes accompanied by unforeseen confounding factors could have resulted in an excessive amount of type II errors. In fact, it is more likely that handedness (or left hemispheric language dominance) may mediate and/or modulate ventricular dilatation and, as such, needs to be considered as an important confounder, along with gender, age and other factors. That left-handedness may be an important factor affecting the size of brain ventricles is shown in a study by Erdogan and colleagues (2004), who found that in left-handers, the lateral ventricle was larger in the left side, while in right-handers, the lateral ventricle was larger in the right side. This has been confirmed by several other studies (Crow et al., 1989a; Yotsutsuji et al., 2003), which also reported an asymmetric dilatation of the temporal ventricular horns (i.e. left larger than right). In a widely cited meta-analysis of regional brain volumes in schizophrenia (Wright et al., 2000), based on the data from 13 studies (including 424 schizophrenia patients and 367 comparative subjects), the left temporal horn was found to be 15% larger than the right.

Reduction of the overall brain mass was, historically speaking, the first morphological abnormality evidenced in the population of schizophrenia patients. In the first several decades of the last century, the use the pneumoencephalography (PEG) provided the first *in vivo* evidence showing that the level of cerebrospinal fluid (CSF) is increased in schizophrenia patients, which implied that patients had less brain tissue. Reduced overall brain size and smaller cortical mass in schizophrenia have later been confirmed by using modern radiological techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). Sophistication of PET and MRI techniques (the latter can differentiate gray and white matter) has enabled researchers to target and investigate more specific brain areas. After reviewing 31 MRI studies, McCarley et al. (1999) concluded that there was little evidence for whole brain differences between schizophrenia and control populations and that methodologically advanced studies tend to find less difference compared to previous studies. However, one other meta-analysis reported a 3% decrease of the overall brain size (Lawrie & Abukmeil, 1998), and another showed an absolute brain volume lower in patients compared to normals (98%), (Wright et al., 2000). Apart from these equivocal findings, which sometimes suggest reduction of brain size in schizophrenia patients and sometimes do not, it is not clear what the real meaning of such a subtle anomaly is and how it relates to clinical symptoms of schizophrenia. Exploration of asymmetrical changes in brain structure appears to be more promising in this regard. However, no study so far has examined the relationship between the overall brain size and hand dominance in a population of schizophrenia patients.

Despite immense research efforts aimed to explore the brain differences between schizophrenia patients and controls, structural brain changes in schizophrenia patients lack diagnostic specificity due to a significant overlap with control subjects on each and every brain measure. In a comprehensive review of the neuropathology of schizophrenia, Harrison (1999, p. 594) concluded that the neuropathology of schizophrenia remains unclear, pointing out a bold fact that "schizophrenia still cannot be diagnosed using either brain scan or a microscope".

From the above, one can see that the association between structural brain asymmetry and schizophrenia has long been the focus of researchers (Chichton-Browne, 1879, cited by Harrison, 1999). A growing body of evidence that the brain anomalies in schizophrenia patients are not symmetrical (Crow, 1990; Saugstad, 1998; DeLisi, Sakuma, Kushner, Finer, Hoff, & Crow, 1997; Sommer et al., 2001), is conveyed into a prominent theory developed by Timothy Crow, according to which schizophrenia, cerebral asymmetries, language lateralisation, and handedness are linked to each other and to a single gene (Crow, 1989b; Crow, 1997b; Crow, 2004a).

In 1990, Crow elaborated this theory by providing various pieces of evidence supporting his view that schizophrenia results from an anomaly of expression of the gene that determines the development of cerebral asymmetry. Several lines of empirical research were specifically addressed by Crow. First, it was the epidemiological evidence which suggested (perhaps somewhat exclusively) the genetic aetiology of the schizophrenia condition and ruled out environmental causes as scientifically unconvincing. The epidemiological evidence was particularly strengthened by the results of the seminal study by Jablensky et al. (1992) which reported a similar incidence of schizophrenia (defined by nuclear, Schneider's first-rank symptoms) across various geographical, climatic, and social environments. If schizophrenia occurs with a strikingly similar incidence and is independent of social, economic, climatic, and cultural factors, it could mean that genetic causality of this condition is more likely than environmental. Other epidemiological research facts are related to age of onset (coinciding with a reproductive phase in humans) and gender difference in the age at onset of illness (with males being affected a few years earlier than females). The second line of empirical evidence suggested that ventricular dilatation and reduction of brain volume predate the onset of schizophrenic illness and, hence, they are more likely to be an expression of a failure of development rather than a result of degeneration. Also, morphological brain changes in schizophrenia tend to be asymmetrical, including the reversal of cerebral asymmetry and such evidence has been supported by PEG, CT, MRI, and postmortem studies. The third and final piece of evidence comes from the studies on functional asymmetries in schizophrenia, by which a variety of cognitive dysfunctions in schizophrenia patients might be explained by disturbances of the process of cerebral lateralisation. Various abnormalities of functional brain asymmetries in patients with schizophrenia such as diminished activity in the cortical motor regions in particular (Guenther et al., 1994; Mattay et al., 1997) might be expressed phenotypically at the level of functional lateralisation of handedness. Reduced functional lateralisation of the motor cortex (Bertolino et al., 2004) and atypically lateralised patterns of cortical responses to cognitive tasks (Kircher et al., 2002; Sommer et al., 2003; Walter et al., 2003) suggest a possible relationship between lateralisation of hand preferences and cognition in schizophrenia. The association between cognitive deficit and lateral preferences has been articulated by Crow in the context of two studies based on the UK National Child Development Sample, which found that (a) cerebral lateralisation was delayed in children who later developed schizophrenia (Crow et al., 1996), and (b) cognitive abilities were less developed in children who were less lateralised in hand skill (Crow et al, 1998b).

2.2.3.2 Neurocognitive aspects of atypical handedness

The association of cognitive performance and atypical behavioural lateralisation in schizophrenia patients is less elusive than in healthy controls. Several studies have consistently implicated greater cognitive compromise in non-right-handed schizophrenia patients, suggesting that this association is more extreme in psychopathology.

In the first study which investigated the association between cerebral dysfunction and left-handedness, Katsanis and Iacono (1989), using a comprehensive neuropsychological assessment, have concluded that left-handed schizophrenia patients are neuropsychologically different form right-handed patients in that left-handed patients performed more poorly on a wide range of tasks than right-handed patients. The most pronounced differences between these two groups were in their performance on IQ tests (assessed by the WAIS-R, Wechsler, 1981) and Wisconsin Card Sorting Tests (WCST, Berg, 1948).

In a subsequent study by Faustman, Moses, Ringo, and Newcomer (1991), a statistically significant association between cognitive deficit and left-handedness has also been confirmed by comparing left- and right-handed schizophrenia patients and left-and right-handed controls. In all these groups the left- and right-handers were age- and education-matched and results showed that left- and right-handed control subjects did not differ on selected measures included in the Luria-Nebraska Neuropsychological Battery of tests (Golden, Hammeke, & Purisch, 1980). In contrast, left-handed schizophrenia patients showed significantly lower performance on attention, information encoding and processing, and memory measures compared to right-handed patients. It could be concluded that this study in many ways replicated and extended the above-mentioned results reported by Katsanis and Iacono (1989).

In a large study comprising data from 686 schizophrenia patients, Tyler et al (1995) revealed that left-handed patients (n = 94) experienced more serious reading problems than right-handed patients (n = 592). Left-handed patients were also more abnormally passive in their childhood compared to right-handed ones. Likewise, Orr, Cannon, Gilvarry, Jones, and Murray (1999) have reported impaired sociability in mixed-handed schizophrenia patients, but failed to find significant differences in their premorbid intellectual functioning assessed by the National Adult Reading Test (NART; Nelson & Willison, 1991). Browne et al. (2000) also found that mixed-handed patients diagnosed with first episode of schizophrenia had a poorer social adjustment and spent less years in education that lateralised patients. Taken together, all these findings further indicate that atypical handedness distribution is consistently associated with impaired cognitive and social functioning of schizophrenia patients.

Hayden, Kern, Burdick, and Green (1997) have found that ambiguous handers (a subtype of mixed-handedness characterised by within-task hand preference inconsistency) performed more poorly on the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) than non-ambiguous handers. In line with the neurodevelopmental model of schizophrenia, the authors concluded that impaired verbal learning might reflect the neurocognitive sequelae of abnormal development that is responsible for ambiguous handedness. Although this study could be criticised on the ground that a number of non-schizophrenic patients were included in the study, results are nevertheless consistent with previous studies by showing a clear association between atypical handedness and neurocognitive profile.

More recently, Bilder at al. (2000) compared a group of 67 right-handed with a group of 27 non-right handed patients. Non-right-handedness was defined as a laterality quotient less than +70 on the Edinburgh Handedness Inventory. The mean deficit score (in z score units) of right-handed patients based on several neurocognitive measures was –1.65 below the performance of comparison subjects. In contrast, non-right-handed patients had a mean score of –2.12, which was significantly lower than that of dextral patients. In addition, these authors failed to confirm the hypothesis that neurocognitive impairment was due to a subgroup of patients without clearly lateralised hand preferences. In other words, cognitive impairment of non-right handed patients in this study was due to under performance of patients who were consistently left-handed. In line with previous studies which have examined the association between cognitive performance and atypical hand preferences, Norman, Townsend, and Malla (2001) have reported that left-handed first-episode patients performed more poorly on several neurocognitive measures such as speed of information processing, and visual and auditory memory than right-handed patients.

In conclusion, the evidence that cognitive performance of schizophrenia patients is associated with atypical lateralisation of hand preferences is not overwhelming, although non-right handed patients display a mild cognitive deficit compared to right-handed. Interestingly enough, all studies reviewed in this section support this conclusion, and this has been confirmed in both first-episode schizophrenia patients (untreated with neuroleptics) and hospitalised patients, thus excluding an adverse effect that medication might have had on cognitive functions. Although the relationship between handedness and cognitive functioning is clearer than that in healthy controls, it still precludes a generalisation. Reviewed studies differ in assessment of handedness and classification of hand preferences as well as in assessment of cognitive functions. While some authors argue that ambiguous handedness in chronic psychiatric patients is likely to be linked to cognitive impairment (Hayden et al., 1997), others (Katsanis & Iacono, 1989; Faustman et al., 1991; Bilder et al., 2000) debate that left-handedness is associated with poorer cognition compared to right-handedness in schizophrenia patients. Nevertheless, all studies used only one behavioural index of lateralisation – handedness, and none of them has investigated the effect of multiple laterality measures on cognitive performance of schizophrenia patients. The lack of a multiple laterality assessment, including its relation to cognitive performance in schizophrenia patients, was considered as the specific impetus for the fourth study.

2.2.3.3 Associations with clinical measures

The associations of atypical behavioural lateralisation of schizophrenia patients and indices of clinical severity (number of admissions, length of hospitalisation, and types of medication), have also been investigated in the population of schizophrenia patients. A consistent pattern and direct evidence linking severity of the illness to atypical lateralisation has not been firmly established in spite of the fact that it has been investigated over three decades.

Oddy (1972) was the first to observe that mixed-handed patients included a disproportionate number of younger patients. This led him to suggest that earlier age at onset of psychosis is associated with the reduced cerebral lateralisation indexed by mixed-handedness. The examination of sex differences with regard to atypical lateralisation followed shortly. More left-handed male than female patients with schizophrenia have been found in a subsequent study (Lishman & McMeekean, 1976), together with a finding that there was a reduced incidence of familial sinistrality in their nuclear families. This finding, which can be interpreted as a strong possibility that left-handedness in schizophrenia patients is acquired rather than inherited, is disputed however by Chaugule and Master (1981). Similarly, Shan-Ming et al. (1985) did not find any sex differences, and the shift toward sinistrality was quite similar in both male and female patients. Oyebode and Davison (1990) have found that male epileptic patients with an additional diagnosis of schizophrenia were less likely to be left- or mixed-handed than the female patient comparison group. Gender inconsistencies were further clouded by Sperling, Martus ,and Barocka (1999), who have reported the opposite findings (i.e. male schizophrenia patients being more non-right-handed than female patients), and by Cannon et al. (1995), who observed a trend of greater mixed-handedness in males than in female schizophrenia patients.

Diagnostic relevance of schizophrenia subtypes and handedness was first addressed by Nasrallah et al. (1982), who stated that only paranoid schizophrenia, might be associated with disturbed brain lateralisation and loss of clear hand dominance. The results of an earlier study (Luchins et al., 1979) are also in line with this finding, suggesting that less severe cases of schizophrenia patients are more left-handed (i.e. more likely to display an anomalous brain lateralisation). A more recent study by Gureye (1988) also reported that paranoid cases were more likely to be mixed-handed than non-paranoid cases were. In contrast, Manschreck and Ames (1984) have reported the opposite: non-paranoid schizophrenia patients were more likely to display anomalous lateral preferences than paranoid patients.

Cannon et al. (1995) have specifically addressed several clinical correlates of mixed-handedness in schizophrenia. The major finding is that anomalous distribution of hand preferences (defined as mixed-handedness) in schizophrenia patients resembles a neurodevelopmental type of schizophrenia (Murray, O'Callaghan, Castle, & Lewis, 1992). Evidence supporting this hypothesis has been based on the facts that mixed-handed schizophrenia patients were more likely to be male (Cannon et al., 1995), to lack family history of schizophrenia (Nasrallah et al., 1982; Shimizu et al., 1985), and to have poor clinical course (Cannon et al., 1995). Clinical severity was determined as more than one year of continuous hospitalisation. However, in an earlier study by Merrin (1984a), no significant link was found between severity of schizophrenic illness (indexed by age at the first hospitalisation and total number of hospitalisations) and handedness.

Several studies have investigated whether specific clinical symptoms of schizophrenia and, in particular, formal thought disorder are associated with atypical handedness in schizophrenia patients. Results of such investigations are inconsistent, but at least one symptom, namely formal thought disorder, appeared to be more consistently linked with left- or mixed-handedness than the others. If formal thought disorder represents a disturbed language function, than it is likely it is associated with anomalous lateralisation. Indeed, Taylor et al. (1982a) have reported that mixed- and left-handed patients are more likely to be thought disordered. However, this finding was true for male patients only. Similar findings of male patient preponderance were reported in several subsequent studies by Manoach et al. (1988), Manoach (1994), and Manschreck et al. (1984). To the contrary, Taylor and Amir (1995) have found no significant relationship between handedness and numerous clinical symptoms of schizophrenia assessed using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen &

Olsen, 1982), and concluded that handedness may not be related to individual or grouped psychopathology. Dollfus, Buijsrogge, Benalli, Delamillieure, and Brazo (2002) have also found no association between hallucinations and non-right-handedness. Whether Schneider's first-rank symptoms are related to handedness in psychotic patients has recently been examined by Verdoux at al. (2004). Increased Schneiderian score (sum of 7 items on the Scale for the Assessment of positive Symptoms; SAPS, Andreasen, 1984) in 71 patients presenting with at least one positive psychotic symptom (hallucinations or delusions) were significantly associated with decreased right-hand lateral preferences. In particular, the laterality score was able to predict the following three specific symptoms of schizophrenia: (a) delusion of being controlled, (b) thought broadcasting, and (c) thought withdrawal. Concurrently, language disturbance (assessed by the Scale for the Assessment of Thought, Language and Communication Disorder; Andreasen, 1979) was negatively associated with the first rank symptoms. Irrespective of a specific neural mechanism underlying prominent clinical symptoms in schizophrenia, this study support a view that the agenesis of cerebral asymmetry, indexed by hand preference lateralisation, is involved in the occurrence of the hallmark schizophrenic symptoms.

In conclusion, it is hard to integrate diverse and conflicting findings on the relationship between atypical lateralisation of hand-preferences and clinical measures. Sex differences in atypical handedness are observed in some studies, but not in the others. The association between diagnostic schizophrenia subtypes and atypical handedness has not been established, as some studies link atypical handedness with non-paranoid schizophrenia subtype whilst other studies report the opposite. A similar inconsistency was observed for the association between various clinical symptoms in schizophrenia, although thought disorder appears to be more consistently linked to atypical handedness than other symptoms.

2.3 Conclusions

There are a number of conclusions that can be drawn from this review of the more recent literature on atypical handedness and schizophrenia.

Firstly, compared to the other research domains in schizophrenia, behavioural lateralisation studies are not adequately integrated and evaluated, and lacks a fine-grained quantitative analysis of empirical evidence. The two comprehensive review articles (Satz & Green, 1999; Sommer et al., 2001) addressing atypical handedness in schizophrenia patients have failed to provide a necessary quantitative evaluation of the literature. In addition, the only quantitative review of the evidence (Sommer et al., 2001) failed to provide the estimates on various handedness categories. Although it is widely accepted that in schizophrenia patients there is a significant leftward shift in distribution of hand preferences, its real nature is yet to be explained.

The second obvious conclusion is that the association of atypical lateralisation of hand preferences, namely mixed-handedness and schizotypal traits in those who are at-risk for schizophrenia appear to be overemphasised. The great amount of empirical evidence is based on student samples using various 'pen-and-paper' schizotypy questionnaires, while representative samples from the general community have rarely been investigated. In this regard, this literature review has also revealed that the effect size of the association of atypical behavioural lateralisation and schizotypal personality traits are weak, and statistical significance of this association can only be reached in very large samples.

Thirdly, classification of handedness appears to be arbitrary and represents an unresolved research problem. Current research on atypical handedness in schizophrenia is based on numerous and arbitrary classifications of hand preferences. This is an issue of particular concern, which significantly reduces the level of comparability between the laterality studies, and may be associated with a biased post-hoc classification of hand preferences. The Edinburgh Handedness Inventory, although a widely used instrument for the assessment of both direction and degree of hand preferences, is not evaluated for the purpose of handedness classification. Analyses of the latent structure of handedness are rarely conducted. The only two classification studies are conducted on other, less frequently used scales, but they have never been replicated.

Fourthly, the relationships between laterality and neuroanatomical, neurocognitive and clinical variables are numerous, conflicting, and hard to integrate. With regard to neuroanatomical measures, the most prominent finding is that left- and mixed-handed patients affected with schizophrenia have a larger ventricular brain ratio. Research on the association between neurocognitive performance and atypical lateralisation of hand preferences in schizophrenia has also provided some evidence that atypical handedness (left-handedness in particular) is associated with a poorer performance on various cognitive measures. Although it appears that there is consistent and solid association between behavioural lateralisation and cognitive performance, the evidence is not overwhelming and is scattered across several studies that can hardly be compared in terms of their methodology. In addition, the strength of associations between lateralisation and cognition in terms of Cohen's effect size is weak, suggesting that it is difficult to identify the effect in small samples.

The final conclusion of this review is that the current trend in the laterality research, focusing on single laterality measures while ignoring many others, does not seem to be an adequate research strategy. It is unlikely that the complexity of cerebral and behavioural lateralisation can be reduced, and therefore understood, by overemphasising a single, disjunct laterality measure. For example, majority of reviewed laterality studies in schizophrenia research used a single laterality measure, namely hand preference, seven studies assessed two laterality measures (hand preference and hand skill), while remaining six assessed three laterality measures (hand, eye, and foot dominance). Multivariate assessment of various laterality indices in schizophrenia research should be considered as a priority in this area of research.

3. Rationale for the study

The extensive review of the more recent literature on atypical handedness in schizophrenia suggests several outstanding research issues that need to be further investigated. They are as follows:

- There is a need for an exhaustive and quantitative evaluation of the relevant literature in order to achieve better understanding and facilitate further progress in this area of research.
- The laterality research lacks an evidence-based and widely accepted classification of hand preferences.
- As the association of atypical hand preferences in those who are at-risk for schizophrenia (i.e. 'psychosis-prone' endophenotypes) appears to be exaggerated, it needs to be re-investigated using a representative sample from the general community.
- A study based on the simultaneous examination of multiple laterality measures and the identification of complex laterality phenotypes and their relationship with cognitive, personality traits, and clinical variables has never been conducted.
- Many researchers agree that there is a need for the development and evaluation of reliable and valid measurement tools for the assessment of the direction and degree of hand preferences. The psychometric properties of the existing handedness questionnaires are rarely examined and reported in the literature and little has been done to improve their measurement properties.

4. Specific objectives

In view of the conclusions of the literature review done for this study and in accordance with the outstanding research issues summarised in its rationale, the specific objectives of this study have been assigned as follows:

1. To evaluate empirical evidence for atypical lateralisation of hand preferences by -

   Estimating the combined prevalence rates for the three most common handedness categories.

2. To facilitate development of a commonly accepted classification of hand preferences and limit arbitrariness for the definition of various handedness categories by -

   (i) Identifying the latent structure of handedness using latent class analysis; and

   (ii) Determining the cut-off points that would sensibly separate various handedness categories.

3. To address the relationship between schizophrenia endophenotypes and atypical lateralisation of hand preferences, by testing the following two hypotheses:

   (i) The psychosis-proneness, determined on the basis of schizotypy questionnaire, is associated with atypical lateralisation of hand preferences in the general community; and

   (ii) Genetic liability to schizophrenia is associated with atypical hand dominance.

4. To introduce a novel, multivariate approach to the research on laterality by:

(i) Identifying and describing the optimal number of laterality phenotypes in schizophrenia patients, their unaffected and unrelated siblings, and controls; and

(ii) Comparing the obtained laterality subtypes on the set of neurocognitive measures, personality traits, and (for patients only) measures of severity of illness

5. To enhance the quality of handedness measurement by -

Exploring the psychometric properties of the Edinburgh handedness Inventory using a congeneric measurement model.

Part II

Specific Studies

The second part of this thesis contains five studies which have been presented in a "thesis by series of papers" format. In order to be incorporated in the overall text of the thesis, the referencing system and the numbering of tables and figures for each of these five studies were given in the uniform fashion, and the paper abstracts which had to follow specific journal styles and requirements were omitted.

The first study delivers a quantitative review of empirical evidence on atypical handedness in schizophrenia and contrasts the findings with the two most recent review articles (Satz & Green, 1999; Sommer et al., 2001). A comprehensive re-examination of available empirical evidence also addresses a few serious weaknesses present in previous reviews.

The second study addresses the classification of handedness. The importance of this study is twofold: (a) it provides an answer as to the optimal number of handedness categories that can be derived from the Edinburgh Handedness Inventory, and (b) it suggests cut-offs for the classification of hand preferences. The results and theoretical implications are elaborated upon in the discussion section.

The third study re-evaluates the hypothesis that high schizotypy (i.e. psychosis-proneness) is associated with the biological marker of mixed-handedness, and examines whether a genetic liability to schizophrenia is related to this biological marker. In addition to a large sample of adults from the general community, this study included three supplementary samples: schizophrenia patients, their unaffected siblings, and controls screened for presence of psychiatric disorders.

The fourth study investigates complex laterality phenotypes by using various laterality measures and familial indices in the population of schizophrenia patients. In addition, this study presents an investigation of the relationship between various domains (cognition, personality, clinical measures) and composite laterality subtypes using Grade of Membership analysis.

Finally, the fifth study addresses the measurement of handedness. It is a neglected area in laterality research, with measurement properties of even widely used questionnaires often taken for granted. In the last study of this thesis, the measurement properties of the most commonly used instrument, the Edinburgh Handedness Inventory, are scrutinised by the means of confirmatory factor analysis.

3. Study 1: Examination of evidence: a new perspective

3.1 Introduction

Disturbed brain lateralisation, including structural and functional asymmetries, has long been one of the central points in schizophrenia research. Structural brain changes such as ventricular dilation (McCarley et al., 1999; Harrison, 1999; Wright et al., 2000; Gaser, Nenadic, Buchsbaum, Hazlett, & Buchsbaum, 2004), reduced cortical mass (Lawrie & Abukmeil, 1998; Harrison, 1999; Wright et al., 2000), and reversed or reduced cerebral asymmetry (Crow, 1990) have repeatedly been implicated. An indicator of disturbed cerebral lateralisation in schizophrenia patients is a significant leftward shift in the handedness distribution compared to both psychiatric and healthy controls. Two review articles (Satz & Green, 1999; Sommer et al., 2001) have confirmed this leftward shift.

It has been argued in the major review article (Satz & Green, 1999, p. 64) that the leftward shift in handedness distribution in schizophrenia patients is exclusively 'due to increase of mixed-handedness compared to normal or psychiatric controls'. This assertion was drawn after the qualitative review of the evidence reported in 23 examined articles, only two of which (Gur, 1977; Manoach et al., 1988) reported an increase in left-handedness. The impact of the major review article was immediate, and several studies (Orr et al., 1999; Browne et al., 2000; Reilly et al., 2001; Byrne et al., 2004; Collinson et al., 2004) have specifically investigated an increased prevalence of mixed-handedness in the population of schizophrenia patients.

A quantitative review of evidence on atypical handedness in schizophrenia patients was reported a few years later by Sommer et al. (2001), using the empirical evidence from sixteen studies. Sommer et al. (2001) concluded that there is an increase of non-right-handedness in schizophrenia patients. Only those studies that provided data on hand preference in both patients and controls were admitted to analysis. This approach, however, omitted studies that reported only prevalence data in patients. Another criticism of this meta-analysis is related to the definition of non-right-handedness. Originally, the term 'non-right handedness' was introduced by Geschwind and Galaburda (1985), to represent individuals without *strong* right hand preferences, including thus into a single, non-right handedness category all those who are left-handed, mixed-handed, or weakly right-handed. This definition of non-right handedness was not strictly followed in Sommer et al. (2001) report, where qualitative differences between various handedness subtypes were conceptually equalised. For example, left-handed writers (e.g. Nasralah et al., 1982; Clementz et al., 1994) were combined together with exclusive mixed-handers (e.g. Taylor & Amir, 1995; Orr et al., 1999) and non-right-handers (e.g. 20). Finally, the study of Manschreck and Ames (1984) was included in the meta-analysis, despite providing the prevalence rate for a composite index of sensorimotor anomalous laterality (a mixture of eye, foot, and hand preferences).

Nevertheless, there are discrepancies between the qualitative review (Satz & Green, 1999), which emphasise an increase of mixed-handedness, and the quantitative review of the literature (Sommer et al., 2001), which emphasises an increase of non-right-handedness. This divergence raises the question of whether the essence of such a shift is expressed as an increase of exclusive left-handedness, mixed-handedness, or non-right-handedness.

3.1.1 Aims of the study

The major objectives of the present study are to summarise empirical evidence from all available studies by taking into account the various classifications of handedness and to test the supposition that the leftward shift in the handedness distribution in schizophrenia patients relative to normal controls is principally due to an increase of mixed-handedness. In addition, this study also aims to extend a previous meta-analysis, which was first to integrate the empirical evidence and the first that has clearly signalled that an increase of mixed-handedness cannot explain the entire leftward shift in handedness distribution in the population of schizophrenia patients.

3. 2 Method

3.3.1 Studies

Studies included in the analyses were published in the period between 1972 and 2004. Unpublished data from a large Western Australia Family Study of Schizophrenia (WAFSS) are also included in the analysis. Relevant studies were identified by searching several electronic databases (MEDLINE, Science Direct, PsyINFO, and Ovid) using the following key words: left-handedness, mixed-handedness, right-handedness, and schizophrenia. Studies were also attained by examining the reference lists in the review. To include as much published data as possible, the following criteria were used: (a) studies had used various diagnostic criteria for schizophrenia, as they change over time. The restriction to modern DSM-III-R and DSM-IV diagnostic criteria for schizophrenia was considered as constraining; (b) studies had reported on assessment and prevalence of hand dominance in schizophrenia patients. For studies, which had not reported the prevalence rates of handedness for psychiatric and normal controls, adequate normative data were provided. This approach has allowed the inclusion of several studies published before the introduction of modern diagnostic systems.

Tables 2.6 and 2.7 list 42 studies admitted to the meta-analysis, and shows prevalence rates for each classification of handedness. As can be seen from Table 2.6, a large number of studies (n = 16) have reported on a dichotomous classification of handedness based on: (a) writing hand (10, 17, 23), (b) single demonstration task (David, Malmberg, Lewis, Brandt, & Allebeck, 1995), (c) school medical reports (Canon, Jones, Murray, & Wadsworth, 1997), and (d) various questionnaires (Gur, 1977; Clementz et al., 1994). An equally common classification of handedness was trichotomous (i.e. left – mixed – right, as in Table 2.7), being entirely based on assessment of multiple manual activities using either self-report or demonstration. Six studies (Chaugule & Master, 1981; Shan-Ming et al., 1985; Oyebode & Davison, 1990; Sperling et al., 1999; Schiffman et al., 2004) used the 'right' versus 'non-right' classification, (i.e. combining both left- and mixed-handers together), and six studies (Taylor & Amir, 1995; Hayden et al., 1997; Orr et al., 1999; Browne et al., 2000; Giotakos, 2001; Collinson et al., 2004) used the 'mixed' versus 'non-mixed' classification (i.e. strong left- and strong right-handers combined).

Comment [MD1]: Orr, Browne, Taylor&Amir, Collinson, and Hayden

Studies included in this review differed in the way in which samples were collected (in-patients, out-patients), in sample sizes (ranging from 24 to 1744, with a median of 76.5), diagnostic criteria for schizophrenia, and most markedly with regard to assessment of handedness (19 different assessments ranging from writing hand to a 32-item questionnaire) and – more importantly – their classification of handedness.

Table 2.6 Studies published in the period from 1972 to 2004 with prevalence rates for various dichotomous handedness classifications

Studies	Schizophrenia patients		Controls	
Left – Right	Total N	Left N (%)	Total N	Left N (%)
(33) Dvirskii, 1976	1270	93 (7.3)	4340	176 (4.1)
(9) Gur. 1977	200	32 (16.0)	200	22 (11.0)
(34) Piran et al., 1982	26	6 (23.1)	16	2 (11.1)
(17) Nasralah et al., 1982	80	15 (19.0)	83	5 (6.0)
(10) Manoach et al., 1988*	58	18 (31.0)	2321	255 (11.0)
(23) Katsanis & Iacono, 1989*	63	12 (19.0)	2321	255 (11.0)
(18) Clementz et al., 1994	117	22 (19.0)	119	12 (10.0)
(24) David et al., 1995	196	19 (9.7)	49711	4160 (8.4)
(35) Tyler et al., 1995	686	94 (13.7)	179	20 (11.2)
(19) Taylor & Amir, 1995	163	23 (14.0)	112	5 (4.5)
(36) O'Callaghan et al., 1995	45	9 (20.0)	24	5 (20.8)
(37) Crow et al., 1996	31	3 (9.7)	1484	140 (9.4)
(25) Cannon et al., 1997	24	4 (16.7)	3953	389 (9.6)
(38) Buijsroge et al., 2002	73	6 (8.2)	81	1 (1.3)
(39) Upadhyay et al., 2004	37	3 (8.1)	200	10 (5.0)
(22) WAFSS, 2004	165	27 (16.4)	140	11 (7.9)
Non-right – Right	N	Non-right N (%)	N	Non-right N (%)
(20) Chaugule & Master, 1981	93	63 (67.7)	150	76 (50.7)
(26) Shimizu et al., 1985	1744	232 (13.1)	4282	471 (11.0)
(27) Shan-Ming et al., 1985	225	45 (20.0)	432	30 (6.9)
(28) Oyebode & Davidson, 1990*	31	8 (25.8)	2321	325 (14.0)
(29) Sperling et al., 1999	60	19 (31.7)	60	5 (8.3)
(30) Schiffman et al., 2004	22	4 (15.4)	216	29 (13.4)
Mixed – Lateralised	N	Mixed N (%)	N	Mixed N (%)
(11) Orr et al., 1999	94	15 (16.0)	85	3 (3.5)
(31) Hayden et al., 1997†	58	19 (32.8)	105	15 (14.3)
(19) Taylor & Amir, 1995	163	42 (25.8)	112	17 (15.2)
(12) Browne et al., 2000‡	66	22 (33.3)	43	5 (11.6)
(32) Giotakos, 2001	68	10 (14.7)	944	97 (10.3)
(15) Collinson et al., 2004	44	9 (20.5)	785	67 (8.5)

* Annett's normative sample (54) was used as the baseline
† Green et al's (47) data were used as the baseline
‡ Cannon et al's (49) data were used as the baseline

Table 2.7 Studies published in the period from 1972 to 2004 with prevalence rates for three-way classification of handedness

Studies	Schizophrenia patients			Controls		
Left-mixed-right	N	Left N (%)	Mixed N (%)	N	Left N (%)	Mixed N (%)
(40) Oddy & Lobstein, 1972	140	1 (0.1)	13 (9.3)	497	17 (3.4)	84 (16.9)
(41) Wahl, 1976	26	1 (3.8)	1 (3.8)	18	1 (5.6)	0 (0.0)
(42) Fleminger et al., 1977	800	74 (9.2)	298 (37.2)	800	70 (8.8)	334 (41.8)
(43) Taylor et al., 1980a	165	15 (9.1)	49 (29.7)	800	70 (8.8)	334 (41.8)
(44) Kameyama et al., 1983	584	30 (5.1)	56 (9.6)	686	33 (4.8)	88 (12.8)
(45) Merrin, 1984b	52	4 (7.7)	5 (9.6)	49	1 (2.0)	10 (20.0)
(46) Gureye, 1988	70	0 (0.0)	8 (11.4)	40	0 (0.0)	8 (20.0)
(47) Green et al., 1989	93	2 (2.2)	36 (38.7)	105	4 (3.8)	15 (14.3)
(48) Nelson et al., 1993†	72	2 (2.8)	31 (43.1)	105	4 (3.8)	15 (14.3)
(49) Cannon et al., 1995	96	2 (5.2)	35 (36.4)	43	3 (7.0)	5 (11.6)
(50) Malesu et al., 1996	120	6 (5.0)	36 (30.0)	86	8 (9.3)	21 (24.4)
(37) Crow et al., 1996	31	3 (8.6)	8 (25.8)	1484	140 (9.4)	103 (6.9)
(51) Egan et al., 2001	115	8 (7.0)	42 (36.5)	88	3 (3.4)	21 (23.7)
(13) Reily et al., 2001	30	1 (3.3)	11 (36.7)	37	3 (8.1)	6 (16.2)
(52) DeLisi et al., 2002*	418	28 (6.7)	42 (10.0)	2321	57 (7.0)	151 (6.5)
(39) Upadhyay et al., 2004	37	2 (5.4)	5 (13.5)	200	6 (3.0)	14 (5.0)
(22) WAFSS, 2004	165	13 (7.9)	60 (36.4)	140	5 (3.6)	16 (11.4)

* Annett's normative sample (35) was used as the baseline
† Green et al's (47) data were used as the baseline

3.3.2 Statistical analyses

The StatsDirect software package (version 2.3.3) was used to estimate the prevalence of various atypical handedness subtypes in schizophrenia patients with each study weighted by its variance which is related to sample size. Due to few observations in some handedness categories, an exact likelihood method (Martin & Austin, 2000) was chosen to evaluate the combined odds ratio. For several studies where there were no data for control subjects we used normative control data. In addition, normative data had to use identical measure of handedness and identical classification criteria for categorisation of hand preferences. For example, studies which used hand preference demonstration tasks were provided by the normative data obtained on identical test. Thus, for the study of Hayden et al's (1997), normative data were provided using the data from Green et al. (1989), and for the study of Browne et al's (2000), normative data were provided using the data from Cannon et al. (1995). For all remaining studies not providing control data, Annett's large sample (1970; N = 2,321) was used as the normative data. The possible impact of the publication bias was addressed by examination of the funnel plots, conventional means of detecting the existence of publication bias in meta-analyses (Gilbody, Song, Eastwood, & Sutton, 2000), and using the test of asymmetry proposed by Egger et al. (1997). A statistical test of heterogeneity, Woolf Q-non-combinality (based on the $\chi 2$ distribution), was employed for all groups of studies. Where the assumption of homogeneity was violated, a random-effects model was used to derive pooled odds ratios.

3.3 Results

3.3.1 Odds for exclusive left-handedness

This estimate is based on 16 studies (see Table 2.6), which reported a dichotomous, left or right, classification of hand preferences, with a total of 3,175 schizophrenia patients and 65,284 control subjects. Examination of the funnel plots for these studies revealed that there was no asymmetry that would indicate a bias due to the absence of studies with negative findings, which remained unpublished. The forest plot suggested that the study results were homogenous, and formal testing of heterogeneity ($\chi^2 = 18.5$, df = 15, P = 0.24) supported this view. The formal test of bias (Egger et al., 1997) was not significant (p = 0.55). From the prevalence of left-handedness in schizophrenia patients and controls, odds ratios were calculated for each study, and then the odds ratio meta-analysis was conducted. A fixed-effects model produced a combined odds ratio of 1.81, with exact 95% confidence interval from 1.6 to 2.1, indicating that schizophrenia patients are significantly more left-handed than controls. As expected, a combined odds ratio by assuming a random-effects model was close at 1.85 (95% CI 1.5 – 2.2). In Figure 2.6 a solid black square represents the weight that each study exerts in the meta-analysis, while a horizontal line represents the confidence interval for the estimate from the study. The combined odds ratio is marked by unfilled diamond at the bottom of the figure.

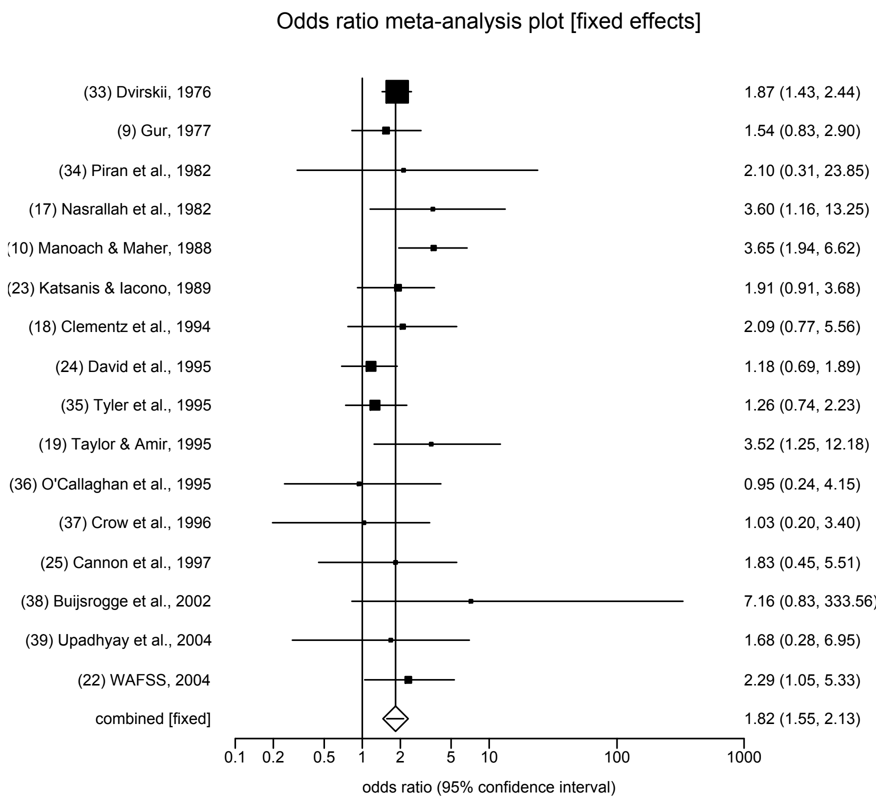

Figure 2.6 Odds ratios of left-handedness in schizophrenia patients. The vertical dashed line indicates the pooled odds ratio for the combined samples in analysis.

3.3.2 Odds for non-right-handedness

A likely population rate of non-right-handedness in schizophrenia patients was estimated from the raw data extracted from 23 independent studies. Studies are listed in Table 2.7, including 5 studies, which used right versus non-right classification of handedness from Table 2.6. The total of 5,223 schizophrenia patients and 14,960 controls were used in this analysis. Non-right-handedness was defined as the strong left- and mixed-handedness grouped together in contrast to a strong right-handedness. The funnel plot for these studies was fairly symmetrical indicating no significant publication bias. The formal test of heterogeneity, however, indicated (χ^2 = 133.6, df = 22, p =0.00) that the random-effects model was appropriate to derive the combined estimate. The test of bias (Egger et al., 1997) was significant ($p < 0.05$). The pooled odds ratio using a random-effects model for non-right-handedness in the schizophrenia patients compared to controls was 1.58, with 95% confidence interval ranging from 1.2-2.0, showing that patients are significantly more non-right-handed than controls. Estimates for each study and the combined odds ratio are presented in Figure 2.7.

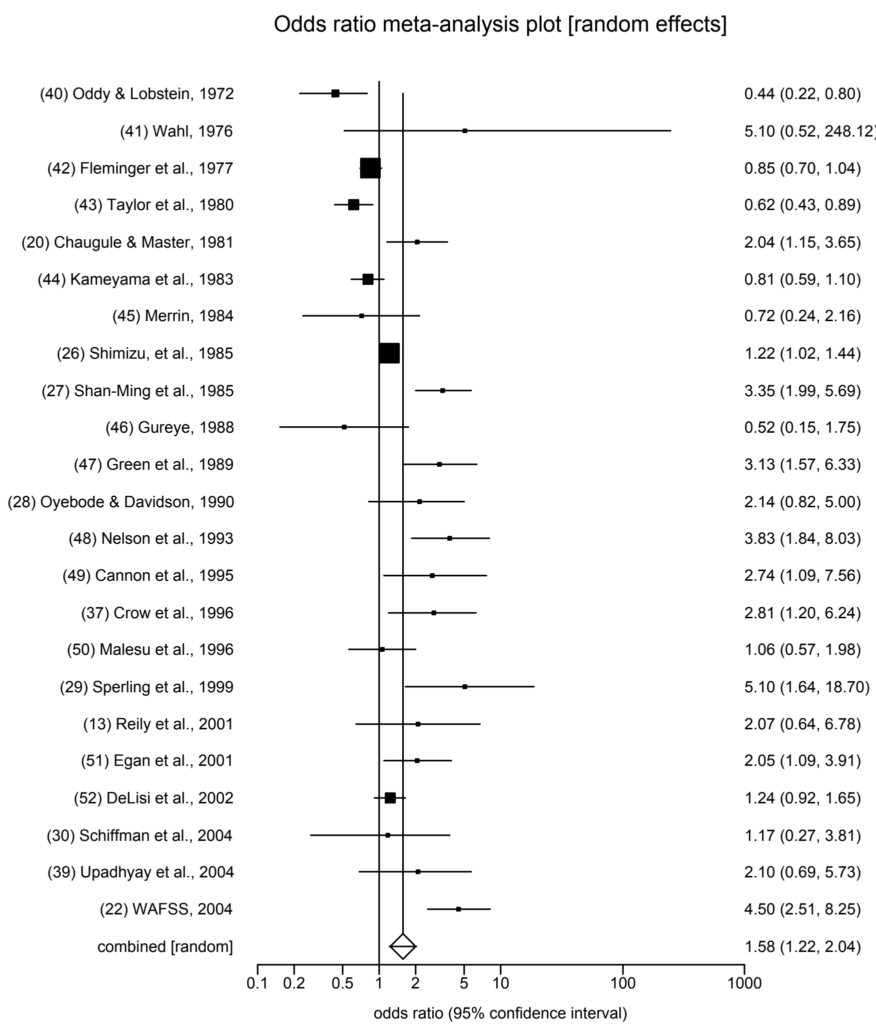

Figure 2.7 Odds ratios of non-right-handedness in schizophrenia patients.

3.3.3 Odds for mixed-handedness

Finally, an estimate of the population rate of mixed-handedness in schizophrenia patients was based on 23 studies with the total of 3,507 schizophrenia patients and 9,573 controls. To test the hypothesis that the shift in handedness distribution is due to an increase of mixed-handedness, the mixed-handed group was compared with the 'lateralised' group (i.e. left- and right-handers combined). Although the funnel plot for these studies showed no marked asymmetry that would indicate a significant publication bias, the more formal test suggested the presence of a possible bias. A random-effects model for the combined estimate was therefore indicated as appropriate on the basis of the formal test of heterogeneity ($\chi^2 = 137.3$, df = 22, $p < 0.0001$). The test of bias (Egger et al., 1997) was significant ($p < 0.01$). The estimate of pooled odds ratio was 1.77, with exact Fisher's 95% confidence interval from 1.3-2.4. Figure 2.8 shows the weights and confidence intervals of each study. The magnitude of the pooled odds ratio is intermediate between left- and non-right-handedness, indicating that mixed-handedness is more prevalent in schizophrenia patients than in healthy controls.

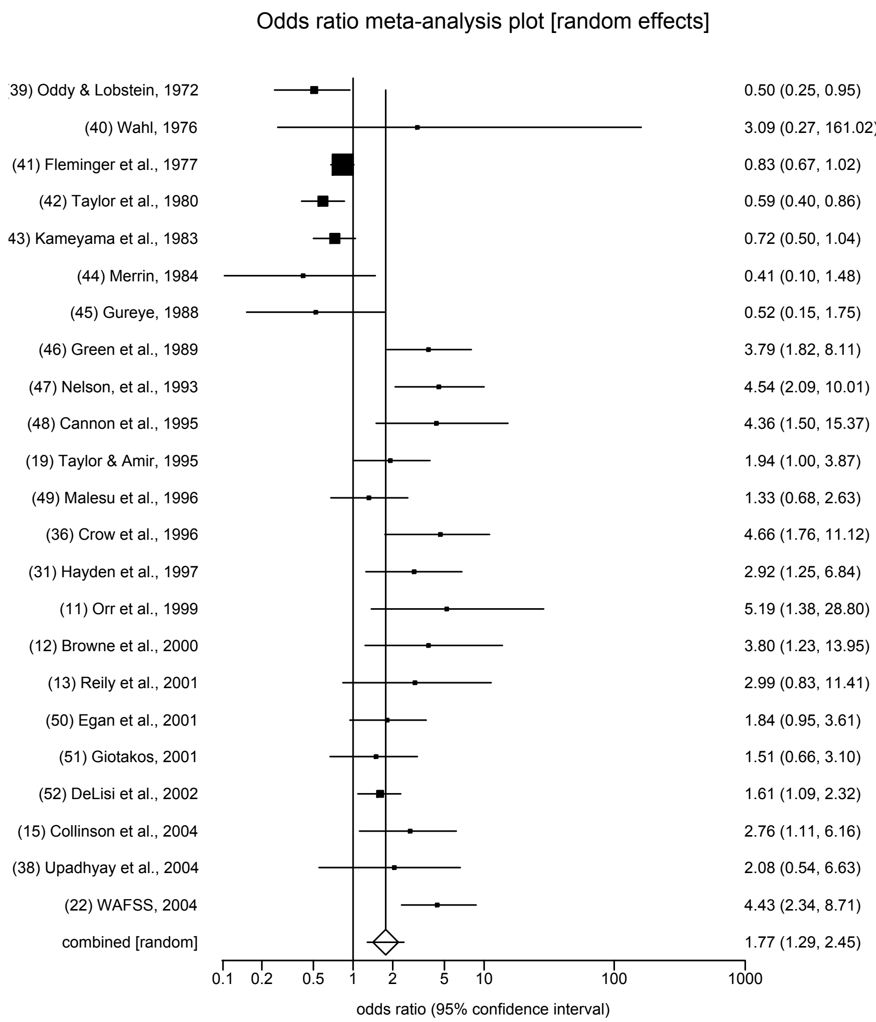

Figure 2.8 Odds ratios of mixed-handedness in schizophrenia patients

Taken together, these analyses showed that each of the atypical handedness subtypes is more prevalent in schizophrenia patients than in controls. To estimate the combined odds ratios the data obtained on 8,622 schizophrenia patients were examined, showing that the prevalence of each handedness subtype was significantly higher in schizophrenia patients than controls. However, the magnitude of the prevalence rates differed, being the highest for exclusive left-handedness, then for mixed-handedness, and then non-right-handedness.

The impact of the largest study (Fleminger et al., 1977), which reported that mixed-handedness was more prevalent in control than schizophrenia patients, on the combined odds ratio for mixed-handedness was investigated by taking into account the re-classification of the original data by Taylor et al, (1982b). Although the combined odds ratio was nearly identical (random-effects model; OR = 1.77) with 95% confidence intervals from 1.3-2.5), the overall results remained unchanged. The re-classification of the data did not alter the fact that there was a greater prevalence of mixed-handedness in controls than in schizophrenia patients.

Table 2.8 Summary of separate meta-analysis for studies showing a significant heterogeneity on the basis of the handedness assessment (preferred model in bold)

Categorisation of handedness	Assessment of handedness			
	Annett's Handedness Questionnaire	Edinburgh Handedness Inventory	Other assessments	Combined
Mixed	n = 8	n = 6	n = 9	n = 23
Pooled odds ratio	**1.19** ^{r}, 0.93 ^{f}	2.82 ^{r}, **2.84** ^{f}	**1.87** ^{r}, 1.45 ^{f}	**1.77** ^{r}, 1.21 ^{f}
q-test	37.61, p=0.00	6.35, p=0.274	51.46, p=0.00	137.27, p=0.00
Bias indicator (56)	p = 0.20	p = 0.48	p = 0.36	P = 0.00
Non-right	n = 8	n = 4	n = 11	n = 23
Pooled odds ratio	**1.00** ^{r}, 0.92 ^{f}	2.86 ^{r}, **2.95** ^{f}	**1.89** ^{r}, 1.37 ^{f}	**1.58** ^{r}, 1.20 ^{f}
q-test	25.85, p=0.000	4.09, p=0.25	57.74, p=0.000	133.63, p=0.00
Bias indicator (56)	p = 0.56	p = 0.58	p = 0.14	p = 0.03

^{r} … random-effects model
^{f} … fixed-effects model

The significant heterogeneity of the results that was observed in the collected studies for the prevalence assessment of mixed- and non-right-handedness was further examined to identify the major underlying source of heterogeneity. In each group, studies were divided into three subgroups on the basis of handedness assessment: the Edinburgh Handedness Inventory, Annett's Handedness Questionnaire, with remaining assessments grouped as 'other'. Table 2.8 presents the results of separate analyses performed within each subgroup, showing that the pooled estimates vary substantially as a function of handedness assessment, indicating that the assessment method used is an important source of heterogeneity.

3.4 Discussion

One of the main findings in the present meta-analyses on handedness from a large number of studies is that schizophrenia patients are significantly more left-handed than normal controls, a finding incompatible with an assertion from a major review of the literature (Satz & Green, 1999). The combined odds ratio for exclusive left-handedness, which is higher than the odds ratios for both mixed- and non-right handedness, rejects the hypothesis that the leftward shift in the handedness distribution is entirely due to an increase of mixed-handedness (Satz & Green, 1999). The estimated combined odds ratio for mixed- and non-right-handedness are also significant, and in a good agreement with Sommer et al's (2001) study, replicating the finding that the schizophrenia population is characterised by the leftward shift in handedness distribution. Given the magnitude of pooled odds ratios, this shift is due to combined effect of both exclusive left-handedness and mixed-handedness.

One possible explanation for the overemphasis on mixed-handedness in the literature may lie in the fact that many studies on handedness in schizophrenia patients were omitted from the major review article (Satz & Green, 1999). The authors listed only two studies with the prevalence rates of left-handedness (Gur, 1977; Manoach et al., 1988), and failed to include a number of studies which had reported on left-handedness. Many studies have reported prevalence rates of left-handedness, indicating a prevalence rate that is nearly two times higher in patients than in controls. Taken together and in contrast to the assertion that data on handedness are inconsistent (Gruzelier, 1981; Gruzelier, 1999) and conflicting (Annett, 2002), these meta-analyses provide evidence that in the population of schizophrenia patients there is a steady and significant leftward shift in direction of hand-preference. The fact that this shift features both increased exclusive left-handedness and mixed-handedness has theoretical implications.

The results presented in this study support the hypothesis that the failure to establish cerebral asymmetry (Crow et al., 1989; Crow 1990, 1997, 2004), reflected partially in atypical hand dominance, is central to schizophrenia. A number of anatomical post-mortem and functional imaging studies (for review see Sommer et al., 2001; Crow, 2004) have shown that schizophrenia is characterised by reduced cerebral asymmetry, most likely resulting from an anomaly of a genetic mechanism responsible for cerebral lateralisation. Indeed, Satz and Green (1999) have also argued that an increased incidence of left-handedness in schizophrenia would provide more credence to a left-hemispheric substrate of schizophrenia (p. 69). The perspective advocated by Annett (1985, 2002), in which hand dominance arises as a by-product of cerebral lateralisation of language and, in a sizeable minority of subjects, as a result of chance factors, is congruent with Crow's theory. It has been hypothesised (Annett, 1999, 2002) that in the schizophrenia population, the process of cerebral lateralisation could be disrupted due to mutation of the right shift gene, so the mutant, agnosic gene is likely to be responsible for an atypical shift in hand dominance. Findings from this study are not entirely consistent with hypothesised effect of the agnosic gene of handedness distribution. It has been argued (Annett, 2002, p. 274) that in schizophrenia population the handedness distribution 'should be without bias to either side'.

Brain lateralisation for language is significantly related to hand preferences in healthy population (Knecht et al., 2000) in a way that left-handed individuals less frequently display the left hemispheric dominance than right-handed. Using a large sample of healthy controls, Knecht et al. (2001) have also shown that atypical (bilateral or right-hemispheric) language lateralisation is not associated with behavioural deficits. Subjects with typical and atypical language lateralisation did not differ in cognitive performance, speed of linguistic processing, academic achievement, artistic talents, or verbal fluency. A significant shift suggest that this population is characterised with a significantly greater atypical hemispheric language lateralisation compared to normal controls, but it is unclear whether impairments stem from this atypical lateralisation or not. Several studies (Katsanis & Iacono, 1989; Faustman et al., 1991; Bilder et al., 2000) have reported that atypical handedness distribution is associated with a poorer cognitive performance. Consistent with these findings, an association of atypical cerebral lateralisation and clinical symptoms has also been reported. Using functional magnetic resonance imaging to establish language lateralisation in a small sample of male schizophrenia patients, Sommer et al. (2001) have observed that increased right hemispheric language lateralisation in male schizophrenia patients is associated with a greater severity of hallucinations. The advent of functional transcranial Doppler sonography (fTCD) has enabled a valid and cost effective way to investigate whether atypical language lateralisation is associated with behavioural changes in large groups of schizophrenia patients. To our knowledge, this noninvasive but reliable and valid procedure (Knecht et al., 1998; Rihs, Sturzenegger, Gutbrod, Schroth, & Mattle, 1999; Knake et al., 2003; Deppe et al., 2000; Deppe, Ringelstein, & Knecht, 2004) has rarely been used in the population of schizophrenia patients, with no study that involved behavioural laterality measures.

In contrast to genetic mechanism, Satz and Green (1999) argued that a prenatal hemispheric insult is responsible for the loss of hand preference direction, and is considered as bilateral and diffuse, thus unlikely to induce a complete change in hand dominance. A greater prevalence of left-handedness as well as mixed-handedness in schizophrenia patients than in normal controls suggests that any mechanism that causes a shift in hand dominance is neither necessarily symmetric nor bilateral. The hypothesis that there are two mechanisms involved in the shift of handedness distribution: (a) in mixed-handed patients ‘bilateral and diffuse’ insult, and (b) in left-handed a more severe insult, capable of producing ‘pathological left-handedness’, is not parsimonious.

However, this does not mean that in some instances a severe left-hemispheric trauma in early childhood cannot cause a complete change of hand dominance. However, consideration of early brain pathology as the only factor responsible for a change in hand preference implies that pathological left-handedness is a perfect explanatory model for any form of atypical handedness, which may not be the case. In line with the pathology model, the excess of left-handedness in schizophrenia patients, and by the same token the excess of any deviation from the right-handed norm, assumes the existence of a *normal* (inherited) and *pathological* (caused by early, left-hemispheric lesions). McManus (1983), on the basis of historical review and empirical data, rejected the concept of pathologic handedness, while Annett (2002a) argued that pathological left-handedness present in only a minority of left-handed subjects. It has also been claimed that the prevalence of left-handedness due to brain pathology is low, ranging from one in 250 individuals (Schilling, 1992) to no more than 5% (Bishop, 1990). On a more general note, the evidence for neurodevelopmental pathology indicated by minor physical anomalies, the cornerstone of the Satz and Green model (1999), is considered as weak and circumstantial (Weinberger, 1996) since it is based on indirect evidence which does not categorically implicate brain abnormality.

There are several limitations of this review that might affect the interpretation of the results. Firstly, although the majority of studies had control samples, most of these were samples of convenience and varied greatly in size, with about one third of them containing 100 or fewer control subjects. Only a few studies used sufficiently large and representative normative data from the general population. Secondly, the review of evidence gathered in different countries and published over a long period of time raises questions about the reliability of psychiatric diagnoses across culturally and economically different countries and different times. We believe, however, that differing diagnostic criteria for schizophrenia are likely to have had less of an effect on the results than differing methods of assessing handedness. Out of 42 reviewed studies only 6 were published prior to the inception of DSM-III. Instead, different measures of handedness appear to be the primary source of heterogeneity of the results. Indeed, a separate analysis of the two major handedness questionnaires (the Edinburgh Handedness Inventory and Annett's handedness questionnaire) showed that they generated incongruous results, and that all other handedness assessments produced results consistent with those obtained with the Edinburgh Handedness Inventory more often than with Annett's handedness questionnaire (see Table 3).

In summary, although meta-analyses are sometimes criticised on the basis that they: (a) select studies of variable quality, (b) aggregate incommensurable studies, (c) include selection and publication bias, and (d) are non-independent (i.e. each study is considered as a random sample from a common population), they are still a valuable technique for statistical integration of multiple empirical studies, capable of dealing with the noise associated with single studies. The present study identified the method of handedness assessment as an important source of heterogeneity of handedness classification in the reported studies. The lack of clear and agreed upon criteria for the classification of handedness for the two widely used questionnaires (Edinburgh Handedness Inventory and Annett's Handedness Questionnaire) most likely encourages researches to exercise their own, ad-hoc criteria. The pooled estimates for mixed- and non-right-handedness need therefore to be used with caution. This finding reinforces the need for uniformity in measurement of handedness and in the classification of handedness sub-types in research into functional lateralisation (Byrne et al., 2004; Collinson et al., 2004). More progress is unlikely until these issues are resolved.

4. Study 2: Classification of hand preferences

4.2 Introduction

There has been a growing interest in handedness during the last few decades due to a close relationship between this behavioural trait and the biological process of brain lateralisation in humans (Annett, 1985; McManus, 1985c, 2002; Corballis, 1991). Despite the continuous quality of handedness (Annett, 1985), a categorical approach still dominates current research practice in psychiatry. Most common is a three-way classification, where subjects are classified into left-, right-, and mixed-handed categories, although there are a few authors who consider handedness as a simple dichotomy (McManus, 1985c, 2002). The mixed-handed group comprises individuals without clear or consistent hand preference lateralisation. It is believed that mixed-handedness reflects left-hemispheric dysfunction that may result from early (pre- or perinatal) brain damage (Bakan, 1975, 1990; Schwartz, 1990) or other neurodevelopmental causes (Geschwind & Behan, 1984; Green et al., 1989; Satz & Green, 1999). Mixed-handedness, which is more prevalent in schizophrenia patients than in normal subjects, is even considered as a biological marker of schizophrenia (Satz & Green, 1999). Although mixed- rather than left-handedness is currently the focus of this area of research, little attention has been paid to cut-offs, which are supposed to provide a meaningful distinction between clear hand preference lateralisation and mixed-handedness.

The definition of the mixed-handedness category depends upon the choice of questionnaire and the choice of cut-off points, which divide the continuum of handedness quotients into a smaller number of handedness categories. With a few exceptions (Annett, 1970; Peters & Murphy, 1992), the majority of existing handedness questionnaires lack valid criteria for partitioning the continuous measure into a small number of handedness classes. The criteria for defining mixed-handedness in Annett's questionnaire (Annett, 1970) have been derived from a method known as association analysis, a technique developed by botanists. Using this technique, Annett (1970) postulated continuity of hand preferences in humans and argued that subdivisions on this continuum would be arbitrary. Notwithstanding the arbitrariness argument, further analyses revealed the existence of at least eight hand preference classes - two defined by a clear lateralisation in either left and right direction, and the remaining six representing various mixtures of hand preference. The latter are collectively referred to as mixed-handedness, although it has been suggested that more narrow criteria should be used (Lishman & McMeekan, 1976; Orr et al., 1999; Giotakos, 2001). In contrast, measures based on another widely used instrument, such as the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), have repeatedly been subject to arbitrary divisions of handedness classes.

The various arbitrary cut-off points that have been imposed on EHI responses in order to classify individuals into handedness categories, have resulted in considerable variation in the reported proportions of mixed-handed individuals. The cut-off points are usually supported by reference to previously published work, implying that they have been validated. However, such an arbitrary practice is not exclusive to the EHI. It is often exhibited in other, less frequently used handedness questionnaires, such as for example the Shimizu and Endo handedness questionnaire (Shimizu & Endo, 1983). Some authors in the field (Bishop, 1990a) have warned that in research on laterality there is a constant danger that the selection of cut-off points may succeed the examination of the data (ie. choosing the 'right' cut-offs that give a 'significant' association). The definition of mixed-handedness ranges from a broad (Green et al., 1989; Cannon et al., 1995) criterion, where individuals with any manifest inconsistency in hand preferences are categorised as mixed-handed, to the narrow criterion where only ‘the pure’ inconsistency occurs (Orr et al., 1999). Sometimes, researchers (Taylor et al., 1982a; Browne et al., 2000; Giotakos, 2001) exercise more than one criterion in order to test the stability of their findings or to allow comparability with similar studies.

The most widely used questionnaire, the EHI (Oldfield, 1972), has never been subjected to multivariate analysis aimed to explore the clustering of individuals into smaller homogenous groups on the basis of their responses to handedness items. Peters and Murphy (1992) conducted a study on the 60-item Waterloo questionnaire, and the short selection (14 items) from this questionnaire, which was considered as a modification of Oldfield’s questionnaire. Using the traditional k-MEANS cluster analysis, authors identified 5 clusters of subjects in the full version, and 3 clusters in the shortened version of the Waterloo questionnaire. As a result of using hand writing preference for the initial cluster indication, all derived clusters were related to that initial classification. The outcome was that all clusters constituted partitions of the initial bimodal classification. For example, in a 5-cluster solution, there were three groups of left-handers (consistent left, weak left, and inconsistent left), and two groups of right-handers (weak and consistent right). The outcome was similar in the shortened version, where the middle cluster has been described as inconsistent left.

In this study we used the LCA, a statistically sophisticated alternative to k-MEANS (Vermunt & Magidson, 2000a), which does not require an *a priori* initialisation and is sometimes described as a ‘categorical analog’ of factor analysis (McCutcheon, 1987). The first objective of this study was to determine the number of handedness categories and to validate this classification against the hand demonstration tests. The second objective was to examine the level of agreement between the LCA model of hand preferences and the range of arbitrary criteria for categorisation of individuals into handedness classes. Using statistical criteria, we also aimed to identify optimal cut-off points for EHI scores that will reliably select individuals with single hand preference lateralisation from other handedness classes.

4.3 Method

4.3.1 Subjects

Subjects in this study were randomly selected from metropolitan Perth, Western Australia. The study sample consisted of 167 men (mean age 40.0 years, range 18 - 79) and 187 women (mean age 39.8 years, range 18 - 56). The Survey Research Centre, the University of Western Australia, collected data for the present study. Out of 1172 individuals contacted, and who satisfied the inclusion criteria (not younger than 18 years and English language competency), 356 returned questionnaires. Two questionnaires were not useable due to incomplete data. The response rate, for this type of study, was relatively high, at 30.4%.

4.3.2 Assessment

The Edinburgh Handedness Inventory (EHI) consists of 10 items which assess hand preference. Additional (eye and foot) preferences were not considered in the present analysis. On each item participants indicated their hand preferences as *strong* (++), *less strong* (+), or *indifferent* (+/+). For the purpose of this study, responses for each item on the EHI were recoded as 1=left hand preference (ie. pooled strong and less strong left preference), 2=indifferent, and 3=right (pooled strong and less strong right preference). This approach only took into account the direction of hand preference, in line with Bishop's (1996) argument that laterality indices provide a more meaningful classification of individuals when self-reported strength of preference is ignored.

4.3.3 Statistics

The basic aim of the LCA is to detect a small number of discrete and unobserved classes from a number of observable variables. In this sense, LCA is similar to both factor and cluster analysis. In comparison to factor analysis which reduces a number of *items* into smaller number of factors, LCA derives the unobserved clusters of *individuals*. LCA differs from the standard cluster analysis in that it is model based. Whereas traditional clustering employs classification algorithms that cluster cases on *ad hoc* definitions of distance (24), a model-based approach utilises probability-based classification. The probabilistic approach also takes into account an uncertainty about class membership, which makes LCA conceptually similar to fuzzy clustering techniques. LCA was performed with LatentGOLD, version 2.0.11 (Vermunt & Magidson, 2000b).

A simple Chi-square test was used for the external validation of the derived handedness classification.

4.4 Results

4.4.1 Exploration and classification of hand preferences

The first aim was to determine the number of handedness categories that best describe the individual hand preferences. Table 2.9 provides a summary of five successive LCA analyses performed to determine the optimal number of latent classes in the sample, with a number of information criteria to evaluate the quality of the latent class solution. The L^2 statistic quantifies the maximum association between variables in the analysis. The baseline, 1-cluster, model assumes that variables in the analysis are unrelated (ie. all cases in the analysis are members of a single cluster). However, an underlying (latent) similarity between the cases can be modelled. The quality of the subsequent model can be judged on the basis of L^2 reduction from the baseline, and changes in the information criteria (lower values indicate better solutions). The 2-cluster solution revealed that classifying subjects into two classes gave a 60.7% reduction from this baseline. The next, 3-cluster, solution gained an additional 17.5%, while the gain of the two subsequent models (4- and 5-clusters) was marginal. All the information indexes (*BIC*, *CAIC* and *AWE*) including an increasing error of classification, commenced to rise after the 3-way classification indicating that the quality of further models deteriorated.

Table 2.9 Testing five subsequent LCA models

	L^2	Reduction from the baseline	Gain	*BIC**	*CAIC**	AWE*	Classification error
1-cluster	2187.7	-		4126.8	4144.8	4286.4	0.00
2-clusters	860.6	60.7%	60.7%	2911.2	2948.2	3239.4	0.00
3-clusters	476.2	78.2%	17.5%	2638.3	2694.3	3192.6	0.04
4-clusters	405.3	81.5%	3.3%	2679.0	2754.0	3436.3	0.05
5-clusters	332.6	84.8%	3.3%	2717.8	2811.8	3641.6	0.05

* Information criteria to evaluate the quality of latent class solution: BIC (Bayes Information Criteria), CAIC (Consistent Akaike Information Criterion, which penalises for the sample size and complexity of the model), AWE (similar to BIC, but takes classification performance into account)

The optimal LCA solution, which partitioned the hand preference matrix into three latent classes, showed that most hand activities made a significant contribution to the overall solution (Table 2.10), which is indicated by the information content value (Wald statistics). However, some manual activities were more informative than others. Manual activities such as the use of a broom (Wald = 124.1; p = .00), or opening a box lid (Wald = 115.9; p = .00), carried greater information content for the three latent classes solution than activities which are highly influenced by excessive everyday practice, such as writing (Wald = 33.8; p = .00) and drawing (Wald = 39.6; p = .00). The item *striking matches* was not significantly informative (Wald = 8.7; p = .07).

Table 2.10 contains conditional cluster probabilities that sum to 1.0 across rows. For example, probability for right hand writers to be classified within the Cluster 1

(Right-handers) was 0.82, for Cluster 2 (Mixed-handers) 0.18, and for Cluster 3 (Left-handers) 0.0. All individuals were assigned to one of the three clusters on the basis of their individual handedness pattern.

Table 2.10 The conditional probabilities for the three cluster model of handedness

Indicants	Direction of preference	Wald statistic (p-value)	Right n=261	Mixed n=57	Left N=36
	Left		0.00	0.12	0.88
writing	Right	33.8 (0.00)	0.82	0.18	0.00
	Left		0.00	0.13	0.87
drawing	Right	39.6 (0.00)	0.81	0.18	0.01
	Left		0.10	0.00	0.90
throwing	Either	83.4 (0.00)	0.15	0.74	0.11
	Right		0.82	0.16	0.02
	Left		0.04	0.00	0.96
scissors	Either	49.9 (0.00)	0.11	0.83	0.06
	Right		0.81	0.16	0.04
	Left		0.00	0.03	0.97
tooth brush	Either	63.2 (0.00)	0.13	0.80	0.07
	Right		0.86	0.13	0.01
	Left		0.09	0.00	0.91
knife	Either	86.3 (0.00)	0.11	0.89	0.00
	Right		0.83	0.15	0.02
	Left		0.00	0.00	1.00
spoon	Either	31.8 (0.00)	0.08	0.92	0.00
	Right		0.89	0.11	0.00
	Left		0.31	0.04	0.65
broom	Either	124.1 (0.00)	0.35	0.59	0.06
	Right		0.93	0.06	0.01
	Left		0.00	0.00	1.00
striking matches	Either	8.7 (0.07)	0.00	0.96	0.04
	Right		0.86	0.13	0.01
	Left		0.38	0.00	0.62
opening box lid	Either	115.9 (0.00)	0.36	0.58	0.06
	Right		0.94	0.03	0.03

Latent class I: This class (see Table 2.10) comprised individuals with the rightward shift in hand preferences and includes a large portion (74%) of the study sample. Individuals within this class were characterised by consistent use of the right hand for most manual activities. However, members of this class sometimes also use the left or either hand for some activities. For example, there was 0.38 probability for those who open a box lid with the left hand, and 0.36 for those who use either hand to be a member of this cluster.

Latent class II: This class included 16% of the study sample. This type is characterised by mixed hand preferences for most manual activities. This type was also characterised by proportionate probability for left- (0.12) and right-handed writers (0.18).

Latent class III: This class included 10% of the study sample and was composed of individuals who displayed a clear leftward shift in hand preference.

4.4.2 External validation of statistical criteria

As a concurrent validation of the handedness classification obtained with the LCA, we used two external criteria sets. Firstly, we compared the LCA classification with those obtained by the hand demonstration tests, which are generally considered superior to the self-report measures. Secondly, we tested the level of agreement between the LCA classification and several arbitrary criteria which were or might be imposed to the EHI to classify individuals into handedness categories.

Two studies, which utilised the direct observation method, were selected (Table 1.11). The first study (Green et al., 1989) used the Hand Preference Demonstration Test, which comprises eight items that were randomly administered three times to a group of 105 control subjects. Proportions of right-, mixed-, and left-handers were similar to those derived from the LCA, i.e. the chi-square test was non-significant. The second study (Cannon et al., 1995), which may be considered even more relevant, asked the study subjects to demonstrate their preferences on the EHI items. Comparison of the handedness classifications between the two methods again revealed good agreement.

Table 1.11 Comparison between the LCA classification and classification of subjects on the basis of hand performance test

	Right (%)	Mixed (%)	Left (%)	χ^2	p-value
Current study	73.7	16.1	10.2	-	-
Green, et al. 1989	81.9	14.3	3.8	4.64	.10
Cannon, 1995*	81.4	11.6	7.0	1.19	.55

Secondly, we compared the LCA classification with a number of arbitrary criteria. In practice, a variety of arbitrary cut-off points on the laterality quotient scale from the EHI have been used to define the mixed-handedness category, from 0±10 to 0±90. The number of cases in the mixed-handedness category is a function of the size of the interval. Figure 2.9 demonstrates that the percentage of extracted mixed-handed individuals is a simple exponential function of the interval defined by arbitrary criteria. The broader the interval, the greater the number of selected mixed-handed individuals.

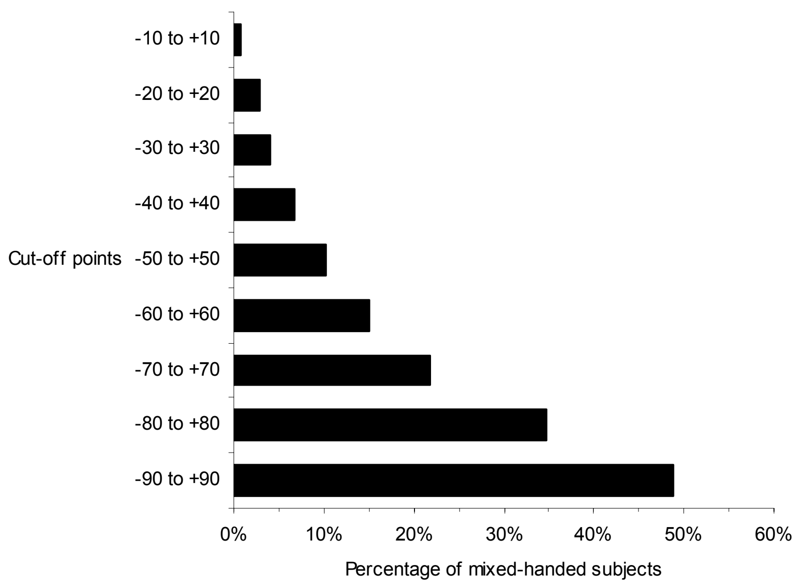

Figure 2.9 Percentages of mixed-handed individuals identified by using various cut-off points

The broad criteria (i.e. 0±90) yields nearly 50 percent of MH individuals in the study sample. Narrowing of the gap between the two handedness extremes decreases the number of MH individuals in both groups. Applying a set of extremely narrow criteria such as 0±10 almost eliminated mixed-handedness.

Table 2.12 Intraclass coefficients of correlation between arbitrary cut-off points and LCA classification

Cut-off points	Intraclass coefficient	95% CI
± 10	0.79	0.69 - 0.85
± 20	0.80	0.69 - 0.86
± 30	0.81	0.72 - 0.87
± 40	0.85	0.79 - 0.89
± 50	0.88	0.84 - 0.91
± 60	0.89	0.86 - 0.91
± 70	0.87	0.84 - 0.89
± 80	0.76	0.71 - 0.80
± 90	0.58	0.47 - 0.66

Finally, we examined which classification of cases based on arbitrary criteria in the range from 0±10 to 0±90, gives the best agreement with hand preference classification based on the statistical criteria. The agreement between the two classification methods was estimated by calculating intraclass coefficients of correlation (Table 2.12) for each level of arbitrary cut-off points. The best agreement between the LCA designation and the arbitrary criteria was achieved at the 0±60 range of the laterality quotient.

4.5 Discussion

This study is the third attempt in the last thirty years which grapples with the clustering of individuals into meaningful handedness categories, and the first one which has used LCA modelling for this purpose. The first two attempts (Annett, 1970; Peters & Murphy, 1992) reported different numbers of handedness classes compared to present study. Annett (1970), using the association analysis identified eight distinct classes, whereas Peters and Murphy (1992) using the traditional cluster analysis found at least three, but possibly five discrete handedness clusters.

Three latent classes of handedness extracted by the LCA analysis were accepted as statistically sufficient to accommodate the variety of response patterns. Each case was assigned on the basis of class membership to one of three clusters. Sixteen percent of all subjects in the study sample manifested a distinct handedness pattern, statistically and most likely aetiologically independent (Satz & Green, 1999) from the two evident, left- and right-handedness. This cluster of subjects was labelled as mixed-handers, as they were recruited from both the left and right side of the handedness continuum. Any further partitioning of handedness into a larger number of categories resulted in less parsimonious solutions. It is possible, indeed, to extract many more specific mixed-handedness patterns, as Annett postulated (Annett, 1970, 1985), but these would be more likely to represent individual variations in responses across a variety of manual activities. The definition of mixed-handedness on statistical ground justifies the extraction of mixed-handed individuals into separate groups to examine whether those individuals relate to other neuropsychological measures.

The LCA model allows an assessment of the contribution of each manual activity to the final classification, by using the information content index (Wald statistic). As expected, writing and drawing were less informative than the other items contained in the final solution, possibly due to clear dichotomous hand preference lateralisation for these activities. Conversely, items concerning the opening of a box lid and using a broom carried the highest information content. Annett (1970, 1985) also found that items other than writing were important for the definition of handedness classes by association analysis. The higher informativeness of these items is possibly related to increased variability in responses. Due to their ambiguity these items are often considered as problematic (McFarland & Anderson, 1980; Williams, 1986). To test the hypothesis that the 3-way classification was due to increased noise variability associated with these two items, we re-modelled the reduced, 8-item scale. However, the 3-way classification was confirmed again as the most parsimonious description of individual differences. We have also examined an alternative strategy to avoid the impact of increased variability related to these problematic manual activity items by eliminating them from measurement (Study 5).

An additional objective of this study was to determine the cut-off value which 'best' separated mixed-handedness from single left- and right-handedness. That value, for the Edinburgh Handedness Questionnaire, was somewhere between 0±50 and 0±70. For these arbitrary cut-offs we found the greatest agreement with classification based on statistical criteria. More importantly, arbitrary cut-off points lower than 0±50 and greater than 0±70 were in progressively lower agreement with statistical criteria, based on the LCA analysis, indicating a higher misclassification of cases. Cut-offs that are too narrow will exclude individuals who exhibit substantial inconsistency in hand preference, whereas cut-offs that are too broad will include clearly lateralised individuals who alter only marginally their otherwise very consistent hand preference lateralisation. From this perspective the LCA analysis confirmed that intervals that are either too narrow or too broad would increase the level of misclassification and might lead to entirely different conclusions (Giotakos, 2001; Taylor et al., 1982b). Proportions of mixed-handed individuals identified by the LCA are also in significant agreement with reported proportions based on hand preference demonstration tests (Green et al., 1989; Cannon et al., 1995). This agreement demonstrates the value of the convenient and less time-consuming data collection by handedness questionnaires.

In conclusion, we have demonstrated that handedness is probably not a dichotomous phenomenon, and that mixed-handedness exists as an autonomous handedness pattern entrenched along the continuum and between the two extremes of human handedness, i.e. left and right. External validation revealed a good agreement between statistically identified handedness classes and hand performance tests. This may further encourage the use of handedness questionnaires as an inexpensive and time efficient instrument that provides a valid measure of the direction of hand preferences. We have also shown the usefulness of LCA analysis, in determining the thresholds for mixed-handedness on the hand preference continuum. These thresholds are essential because intervals that are too broad or too narrow might lead to the severe misclassification of individuals. The definition of handedness classes in this study and the subsequent validation against external criteria will make future research less dependent on the arbitrariness in this domain.

5. Study 3: Schizotypy and mixed-handedness revisited

5.2 Introduction

The origin of the schizotypy concept can be traced down back to Kraepelin and Bleuler (Kendler, 1985) who were the first to observe that nonpsychotic relatives of schizophrenia patients display mild schizophrenia-like symptoms and signs including deficits in both cognitive and interpersonal domains. A serious dysfunction in these domains may lead today to a diagnosis of schizotypal personality disorder (SPD) based on criteria outlined in the American Psychiatric Association nomenclature of mental disorders (DSM-IV, 1994). According to Meehl (1962, 1990), schizotypy is an attenuated phenotype of schizophrenia. Whether the underlying genetic vulnerability ('schizotaxia') evolves into psychosis or remains expressed as schizotypal personality traits, depends on environmental conditions and additional background genetic factors. The lifetime risk of developing schizophrenia is about 1%, and the only well-established risk factor is being biologically related to a person with schizophrenia. Monozygotic twins who share 100% of their genes have a lifetime risk of 50%, whereas dizygotic twins and siblings show much lower risk. A variety of environmental risk factors, which interact with genetic vulnerability, make the aetiology of schizophrenia and schizotypy extremely complex and only partially understood.

During the last decades, a number of studies have attempted to identify those who are 'psychosis-prone' in the general population. For this purpose, scales have been developed to measure schizotypal features (Chapman, Chapman, & Raulin, 1976, 1978; Chapman et al., 1984; Eckbald & Chapman, 1983, 1986; Claridge & Broks, 1984; Venables, Wilkins, Mitchell, Raine, & Bailes, 1990; Raine, 1991). Amongst these, the Schizotypal Personality Questionnaire (SPQ, Raine, 1991), has been widely used due to its psychometric properties (Raine, 1991, 1994; Vollema & Hojitnik, 2000) and close correspondence to the DSM-III-R criteria. Factor analyses of the SPQ have identified a three-factor underlying structure that best describes individual variations in schizotypal personality (Raine et al., 1994; Chen, Hsiao & Lin, 1997; Vollema & Hojitnik, 2000; Reynolds, Raine, Mellingen, Venables, & Mednicket, 2000). The SPQ three-factor structure resembles the structure of schizophrenic symptoms: Cognitive/Perceptual Dysfunction (ideas of reference, magical thinking, unusual perceptual experiences, and paranoid ideation); Interpersonal Deficit (social anxiety, no close friends, constricted affect, and paranoid ideation); and Disorganisation (odd behaviour and odd speech).

A less frequently investigated biological marker related to schizotypy is hand dominance. Cerebral lateralisation of human brain functions, most notably left hemispheric linguistic processing, is related to behavioural dominance of hand (Annett, 1985; Corballis, 1991; Knecht, 2000a). It is generally thought that atypical hand preference lateralisation, (mixed-handedness) is significantly associated with schizotypy in the same manner as it is related to some clinical symptoms in schizophrenia patients (see Satz & Green, 1999). Several studies (Chapman & Chapman, 1987; Kim et al., 1992; Overby, 1993; Poreh, 1994; Poreh, Levin, Teves, & States, 1997; Claridge, Clark, Davis, & Mason, 1998; Shaw, Claridge, & Clark, 2001; Barnett & Corballis, 2002; Gregory, Claridge, Clark, & Taylor, 2003) on the handedness-schizotypy association found that mixed-handedness, but not left-handedness, is associated with high schizotypy scores. The absence of clear hand preference in those individuals is then explained analogous to schizophrenia patients, implying an identical aetiological mechanism (Chapman & Chapman, 1987; Kim et al., 1992; Gruzelier & Doig, 1996). Moreover, it has been claimed (Claridge et al., 1998), and recently reiterated (Gregory et al., 2003), that research in this area has generated more uniform results than that in schizophrenia research (for review see Satz & Green, 1999; and Sommer et al., 2001).

A critical review addressing all the relevant methodological issues should, however, precede such conclusions.

There are several reasons to be cautious in proposing such a generalisation. First, there is no unequivocal uniformity in the reported findings, nor in methodology. Three studies have failed to confirm the schizotypy-handedness relationship (Overby, 1993; Dinn, Harris, Aycicegi, Greene, & Andover, 2002; Gregory et al., 2003), though Overby's study (1993) has been challenged (Poreh, 1984; Claridge et al., 1998) on the ground of handedness assessment. A recent study (Gregory et al., 2003) also failed to find an association between mixed-handedness and schizotypy. Samples of students may be appropriate for investigating the factor structure of schizotypy scales or improving their psychometric properties, but generalisations from such a homogenous population is methodologically problematic. A highly selected sample (age, cognitive abilities, interests, academic achievement, social background) is far from being representative. To our knowledge, no study has been published on a large representative sample from the general community. Secondly, reported links between schizotypal traits and mixed-handedness in most studies represent weak effect sizes explaining a small amount of the variance in the dependent variables. Thirdly, schizotypy is a heterogenous condition that may not be validly assessed by 'paper-and-pencil' questionnaires (Kendler, Thacker, & Walsh, 1996). Schizotypy may have variable clinical characteristics and different aetiologies (Tsuang, Stone, Tarbox, & Faraone, 2002b; Tsuang et al., 2002c), and its expressions may change over time (Venables & Bailes, 1994; Peters, Joseph, & Garety 1999; Verdoux & van Os, 2002). Tsuang et al. (2002c) have recently stated that while schizotypy is a heterogeneous condition, *negative* schizotypy, rather than *positive*, presents with abnormalities similar to those in schizophrenia. A negative form of schizotypy may be the only phenotype predisposing to schizophrenia, whereas its positive presentation may be unrelated to psychosis.

Furthermore, phenotypic features of the schizotypal personality may be confused by their association with use of illicit drugs, particularly cannabis (Williams, Wellman, & Rawlins, 1996; Nunn, Riza, & Peters, 2001; Skosnik, Spatz-Glenn, & Park, 2001; Dumas et al., 2002), anxiety and depression (Braunstein-Bercovitz, 2000) and impaired neuropsychological performance (Mass, Bardong, Kindl, & Dahme, 2001). Finally, handedness classifications pose another problem, causing difficulties in comparisons between respective studies, even when identical measures of handedness are used. The impact of different classifications of handedness has not been systematically investigated, but it seems plausible that varying classifications of handedness may result in different conclusions.

There is, therefore, a good reason to justify a re-examination of the relationship between schizotypy and hand preference in a community based sample. In contrast to previous studies on homogenous samples of undergraduates, we randomly selected individuals from the general population. In addition, we performed the same analyses on three supplementary samples drawn from the Western Australian Family Study of Schizophrenia (Hallmayer et al., 2003): screened volunteers ('super healthy' control subjects), unaffected siblings of schizophrenia patients, and schizophrenia patients. Thus several different levels of genetic liability to schizophrenia were represented: 1) 'super healthy' screened volunteers (without history of psychiatric disorders in family), 2) participants drawn from the general population (risk of around 1%), 3) siblings of schizophrenia patients who are at a greater risk of developing schizophrenia than control subjects, and 4) schizophrenia patients. Utilising supplementary samples enables testing of the hypothesis as to whether the relationship between mixed-handedness and schizotypal traits shows a correspondence to the genetic liability to schizophrenia.

5.3 Methods

5.3.1 Participants

The community sample comprised 353 randomly selected participants from metropolitan Perth in Western Australia. It consisted of 168 males (mean age 40.0 years, range 18 - 79) and 185 females (mean age 39.8 years, range 18 - 56). Participants were recruited using the telephone directory and, after initial contact, each respondent was invited to participate in this study. After obtaining informed consent questionnaires were mailed to their residential address. The collection of data was carried out in collaboration with the Survey Research Centre of the University of Western Australia. Out of 1172 individuals contacted, and who satisfied the inclusion criteria (not younger than 18 yrs and English language competency), 356 returned questionnaires.

The supplementary samples comprised 131 ‘super healthy’ volunteers, 97 full siblings of schizophrenia patients, and 173 schizophrenia patients. The sample of screened volunteers consisted of 65 males (mean age 38.2, range 17 - 77) and 66 females (mean age 39.4, range 18 - 74). Each volunteer, recruited through a Red Cross blood donor agency and local newspapers, was screened for the presence of history of psychotic disorder, organic brain disease or substance use disorder. The sample of siblings consisted of 36 males (mean age 41.1 years, range 19 – 77) and 61 females (mean age 42.6 years, range 14 – 88). Patients (n = 176), who met both ICD-10 and DSM-IV criteria for a diagnosis of schizophrenia, were recruited from consecutive admissions to a psychiatric hospital. This sample consisted of 134 males (mean age 32.6, range 17 - 69) and 42 females (mean age 36.4, range 18 - 66). The participants in supplementary samples were drawn from the Western Australian Family Study of Schizophrenia (Hallmayer et al., 2003). Written informed consent was obtained from all participants and the study was approved by the Committee for Human Rights of the University of Western Australia and the Graylands Hospital Ethics Committee.

5.3.2 Measures

Schizotypy was assessed using the Schizotypal Personality Questionnaire (Raine, 1991). The SPQ comprises 74 items and nine subscales which correspond to the DSM III-R diagnostic criteria for Schizotypal Personality Disorder. For the purpose of investigating the relationship between various facets of schizotypal personality and mixed-handedness, three composite scores were computed as an unweighted linear combination, following Raine et al. (1994), to reflect the three factors (Cognitive/Perceptual, Interpersonal, and Disorganisation) which underlie individual differences. The total score on the SPQ scale was used as an global/general measure of schizotypy.

Handedness was assessed using the Edinburgh Handedness Inventory (EHI, Oldfield, 1971), which comprises 10 items for hand preference. On each item participants indicated their hand preference as *strong* (++), *less strong* (+), or *indifferent* (+/+). Using the standard expression EHI = ((R–L)/(R+L))*100, laterality quotients ranging from –100 (left-handedness) to +100 (right-handedness) were computed for each subject in the study. Subjects with laterality quotients ranging from -100 to -71 were classified as left-handers, those with laterality quotients from +71 to +100 as right-handers, and remaining subjects (from –70 to +70) were classified as mixed-handers. For the purpose of correlation analysis, another measure was derived - an index of hand inconsistency (IHI). This index quantifies the degree of inconsistency of hand preference irrespective of the direction. The IHI ranges from 0 to 1 and is calculated by a simple formula [$IHI = 1 - \text{sqrt}((EHI^2)/100))$]. Subjects with close to zero IHI scores display full hand preference lateralisation (either left or right), with a declining consistency as the IHI rises to the value of 1 (absolute inconsistency).

5.4. Results

The four samples differed in their mean scores on the Edinburgh laterality quotient. There was a trend (Figure 5.1) of a decreasing level of right-sidedness in the four groups. A series of Mann-Whitney tests, however, revealed that only the schizophrenia patients differed significantly in the laterality quotient mean score from all other groups. Screened volunteers, participants from the general community, and unaffected siblings of schizophrenia patients did not differ in this regard.

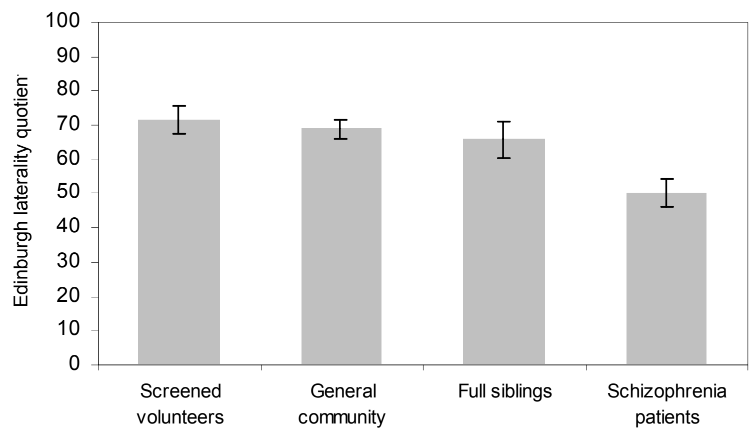

Figure 2.10 Mean scores of the Edinburgh laterality quotient four samples

As the distributions of scores on each schizotypy factor and total SPQ score were non-normal, a distribution-free non-parametric procedure, analogous to one-way analysis of variance, was chosen for analysis of between-group differences. Table 1 shows mean scores for three schizotypy factors and the total SPQ score for each hand preference category, and the results of the nonparametric (Kruskal-Wallis H) tests with estimated effect size (Cohen's *f*).

Table 2.13 Test of differences in mean scores by the three-way classification of handedness in four samples

Samples	Left	Mixed	Right	Asympt. Sig.	Cohen's *f*
	Mean (SD)	Mean (SD)	Mean (SD)		
General community (n = 353)	n = 21 (6%)	n = 76 (22%)	n = 256 (72%)		
Cognitive-perceptual	5.10 (5.1)	6.81 (5.6)	6.53 (6.2)	.435	.066
Interpersonal	8.29 (7.7)	7.22 (6.2)	7.73 (6.5)	.915	.038
Disorganisation	2.65 (2.6)	3.22 (3.2)	3.21 (3.2)	.856	.044
SPQ total score	12.95 (10.4)	15.68 (11.1)	15.52 (11.9)	.565	.006
Screened controls (n = 131)	n = 5 (4%)	n = 27 (21%)	n = 99 (75%)		
Cognitive-perceptual	2.20 (2.6)	3.33 (4.5)	3.47 (4.1)	.775	.074
Interpersonal	3.40 (3.6)	5.26 (5.2)	6.52 (6.2)	.409	.127
Disorganisation	1.20 (0.8)	2.70 (2.9)	2.77 (3.2)	.735	.119
SPQ total score	5.60 (4.7)	10.48 (9.4)	11.76 (10.5)	.417	.145
Siblings of schizophrenia patients (n = 96)	n = 5 (5%)	n = 25 (26%)	n = 66 (69%)		
Cognitive-perceptual	2.20 (2.3)	5.08 (4.7)	3.88 (4.8)	.315	.167
Interpersonal	6.20 (6.4)	6.88 (7.4)	5.50 (5.1)	.996	.095
Disorganisation	0.80 (0.8)	3.08 (3.5)	2.68 (3.1)	.342	.173
SPQ total score	8.00 (8.2)	13.64 (12.7)	11.06 (9.6)	.552	.135
Schizophrenia patients (n = 176)	n = 11 (6%)	n = 80 (46%)	n = 85 (48%)		
Cognitive-perceptual	10.00 (8.9)	16.68 (8.0)	14.09 (8.8)	.034	.210
Interpersonal	15.50 (7.9)	15.67 (8.3)	15.69 (7.9)	.989	.006
Disorganisation	5.60 (3.6)	7.55 (3.7)	7.33 (4.2)	.305	.119
SPQ total score	27.30(16.4)	35.45(16.2)	32.60(16.8)	.268	.129

The percentages of mixed-handed individuals were the lowest in the group of screened volunteers (21%), and participants from the general community (22%). It was higher in siblings (26%), and was at the highest in schizophrenia patients (46%). The trend of increase of mixed-handed individuals as a function of genetic liability to schizophrenia was significant (Chi-square = 31.48, *df* = 1, *P* = 0.000).

The non-parametric analysis performed on composite scores and total SPQ score, failed to show any significant differences between the three handedness categories in the community sample, and two subsamples from the Western Australian Family Study of Schizophrenia (controls, and siblings). However, there was a significant difference in the group of schizophrenia patients, where mixed-handed patients displayed higher scores on the Cognitive Perceptual factor, but not on the two other schizotypy factors and the total SPQ score. Mixed-handed siblings of schizophrenia patients displayed an elevated score on the Cognitive Perceptual factor, similar to their affected relatives, but this trend (although with an effect size similar to that in schizophrenia patients) was not significant.

The Kruskal-Wallis H test was carried out separately for male and female subjects in all samples. Results (available on request) revealed that the relationship between handedness and schizotypy factor was generally independent of gender in all samples. The only interaction was found for the Disorganisation factor in the sample of siblings: left-handed females had significantly higher score on this particular factor than right-handed females.

To address the issue that handedness categorisation might have concealed the true relationship between schizotypy and handedness, we calculated correlation coefficients (non-parametric Spearman's *rho*) between schizotypy factors and the total SPQ score, and two measures of hand preference lateralisation across all samples (Table 5.2 on the next page). A conservative two-tailed test was chosen to test significance of the hypothesised relationship

Table 2.14 Correlation coefficients (Spearman's r) between the three SPQ factors and two laterality measures (Edinburgh laterality index and Index of inconsistency) in four samples

Samples	Edinburgh Lat. index		Index of inconsistency	
	rho	*p*	*rho*	*p*
General community				
Cognitive/perceptual	.00	.961	.02	.731
Interpersonal	-.02	.706	.01	.802
Disorganisation	-.01	.811	.01	.833
Total SPQ score	-.01	.812	.04	.528
Screened volunteers				
Cognitive/perceptual	-.04	.682	.06	.529
Interpersonal	.07	.420	-.05	.569
Disorganisation	.01	.892	.03	.698
Total SPQ score	.03	.756	.01	.913
Siblings of schizophrenia patients				
Cognitive/perceptual	-.03	.804	.08	.420
Interpersonal	.05	.651	-.02	.874
Disorganisation	-.06	.530	.15	.156
Total SPQ score	.01	.956	.07	.519
Schizophrenia patients				
Cognitive/perceptual	-.15	.069*	.22	.009**
Interpersonal	-.12	.131	.07	.378
Disorganisation	-.05	.564	.12	.162
Total SPQ score	-.12	.162	.15	.077*

** Two-tailed significance
* One-tailed significance

Only one correlation coefficient was significant, and two approached the 0.05 level of significance. In the group of schizophrenia patient there was a significant positive association between the index of inconsistency and the Cognitive Perceptual schizotypy factor. Had we chosen a one-tailed test, two more correlation coefficients would have emerged as significant in the group of schizophrenia patients. First, where a greater score on Cognitive Perceptual factor is associated with a lower laterality index, and second, where a greater total SPQ score is associated with an increase of the index of inconsistency. The magnitude of significant correlation coefficients (either one- or two tailed) was mild, implying a modest amount of shared variance between two variables.

The last step in the analyses was to enlarge the sample size by combining the three samples of nonpsychotic individuals together (N = 580). This combination did not alter the results. The association between schizotypy factors and handedness in the pooled data was not significant (Cognitive/perceptual, Chi-square = 1.85, df = 2, p = 0.397; Interpersonal, Chi-square = 0.45, df = 2, p = 0.797; Chi-square = 1.71, df = 2, p = 0.426; Disorganisation, Chi-square = 2.23, df = 2. p = 0.328).

5.5 Discussion

The major objective of this study was to re-explore the relationship between schizotypal traits and attenuated hand preference (mixed-handedness) in a large community sample, since previous studies did not establish a clear-cut case for this association. Predominant use of student samples, small effect sizes, and the existence of studies which have already reported negative findings, are considered as a sufficient ground for re-investigation. In addition, using the three supplementary samples from the family study of schizophrenia, we tested the hypothesis whether this tentative relationship can be related to genetic liability to schizophrenia.

The results from a sample of 353 randomly selected adults from the general community suggest that schizotypy factors and mixed-handedness are unrelated in non-clinical samples. Importantly, this finding has been replicated in the two supplementary samples: screened volunteers and asymptomatic siblings of schizophrenia patients. In contrast, the relationship was confirmed for the Cognitive Perceptual Dysfunction factor in schizophrenia patients. Two important trends were also observed. First, a decrease of right-sidedness in four samples, which implies that the ascending proportion of mixed-handed individuals correspond to an increase in the genetic liability to schizophrenia. Second, mixed-handed siblings of schizophrenia patients showed higher scores on the Cognitive Perceptual factor in comparison to the both left- and right-handed siblings. We suggest that siblings display a milder form of the association observed in the affected members of the family, possibly due to a shared genotype. Although the effect size for this particular factor in siblings was similar to that in schizophrenia patients, this association remained statistically unsupported. It should be noted, however, that the sample of siblings was small compared to other samples in this study, and may lack statistical power to detect a modest effect size. The absence of the relationship between mixed-handedness and schizotypy traits in a large non-clinical sample is difficult to reconcile with the notion that 'psychosis-proneness', as determined solely on the basis of the 'paper-and pencil' questionnaire, is associated with a neurodevelopmental marker typical for schizophrenia patients (Poreh, 1994; Gruzelier, 1996; Poreh, Levin, Teves & States, 1997; Claridge et al., 1998; Shaw et al., 2001).

Historically, schizotypal traits were divergently approached by psychiatrists and psychologists (Kendler et al., 1996). While psychiatrists favour clinical observation and use of structured interview protocols to assess mild schizophrenia-like symptoms in unaffected relatives of schizophrenia patients, psychologists have developed a number of self-report scales aiming to identify 'psychosis-prone' individuals in the general community. The predictive validity of these scales is questionable on the grounds that they could not successfully identify those at risk for developing schizophrenia. In terms of the diagnostic accuracy, these scales are not sufficiently specific, yielding unacceptably high false-positive results. For example, in the 10-year follow-up study (Chapman L J, Chapman JP, Kwapil, Eckblad, & Zinser, 1994), of those who had a high score on the Magical Ideation scale, 98.3% did not develop schizophrenia over the 10 years of follow-up. Kendler et al. (1996) demonstrated that self-report questionnaires performed poorly in identifying the relatives of schizophrenia patients in comparison to the Structured Interview for Schizotypy (Kendler, Lieberman, & Walsh, 1989), while in a recent review of self-report and interview-based measures of schizotypy, Catts, Fox, Ward, and McConaghy (2000) argued that questionnaires are less efficient than interview-based assessments. A current conceptualisation of schizotypy acknowledges its heterogeneity, including specific pathophysiology, neuropshychological dysfunctions, and social concomitants (Tsuang, Stone, & Faraone, 2001; Tsuang et al., 2002b). Two distinct subtypes of schizotypy are now recognised: *negative* schizotypy, typically present in relatives of schizophrenia patients and reflecting vulnerability to schizophrenia, and *positive* schizotypy characterised by positive symptoms (e.g.

magical ideation). The latter subtype is a poor index of vulnerability, but much easier to assess by self-report scales (Kendler, McGuire, Gruenberg, & Walsh, 1995; Kendler et al., 1996). It may be interpreted as a 'healthy' schizotypy trait. This perspective accommodates the notion that schizotypal personality traits are not necessarily incomplete variants (*formes frustes*) of the disease process (Claridge, 1997; McCreery & Claridge, 2002).

Classification of hand preferences and its relationship to underlying neurodevelopmental processes remains problematic. The lack of valid classification of individuals into handedness categories is the Achilles' heel of this kind of research. In the laterality literature there is only one published method for classification of individuals into handedness categories (Annett, 1970), which, interestingly, has never been independently replicated. While this method has been used with one handedness questionnaire only, other questionnaires are often linked to arbitrary classifications of handedness. Another problem is associated with the neurobiology of handedness. There are several explanatory approaches to individual variations in human handedness: (a) genetic models (Annett, 1985; McManus, 1985a; Klar, 1999), (b) obstetric complications model (Bakan, 1973, 1990; Schwartz, 1990), (c) developmental instability model (Markow, 1992; Yeo & Gangestad, 1993a, 1993b; Yeo et al., 1999), (d) pathological left-handedness concept and/or mixed-handedness as a result of bilateral cerebral insult (Satz, 1972; Satz et al., 1985; Satz & Green, 1999), (e) a model linking testosterone to anomalous brain lateralisation (Gecshwind & Galaburda, 1985), and (f) vestibular model (Previc, 1991, 1996). In some of these models, both left- and mixed-handedness are benign variations (Annett, 1985; McManus, 1985a; Klar, 1999; Previc, 1991, 1996), while in other models any shift from right-handedness is thought to reflect an underlying pathology (eg. Bakan, 1973; Schwartz, 1990). Sometimes even strong right-handedness is considered to be a sign of developmental instability (Yeo &

Gangestad, 1993a, 1993b; Yeo et al., 1999). Which of the atypical handedness categories is likely to be associated with the hypothesised pathology: left-, mixed-, non-right-handedness, or any deviations from the modal hand dominance including a strong-right handedness? There is no simple answer to this question. If it is mixed-handedness, as claimed due to the handedness pattern in schizophrenia patients (Satz & Green, 1999; Sommer et al., 2001), then any interpretation of results should be related to this particular hypothesis.

There are several limitations in this study that have to be taken into account. Firstly, the response rate for the community sample was slightly over 30 percent, which may suggest a somewhat biased proportion of respondents who participated in the study. Secondly, the sample of siblings of schizophrenia patients was small compared to other samples in this study, with insufficient statistical power. The group of siblings, who accepted the participation in the family study, may also be biased, representing a selection of siblings with absent or minor psychological problems. It is also possible that siblings have developed a 'defensive' response set denying the presence of their symptoms. These possibilities cannot be simply ruled out nor confirmed and future studies should take it into account as a potential bias. Notwithstanding a few possible systematic biases, it is unlikely that they have had such a severe effect that would invalidate present findings.

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6. Study 4: Composite laterality phenotypes

6.2 Introduction

Atypical hand preference in schizophrenia patients has been described by numerous investigators. However, considering that most neurobehavioural and neurocognitive markers in schizophrenia are of modest effect size (Heinrichs, 2001), reliance on hand dominance may restrict the power of studies to detect consistent relationships among laterality measures, cognition and familial risks. The assumption that handedness is sufficiently representative of all other asymmetries is present in genetic models of handedness (Annett, 1985; McManus, 1985). This approach has recently been criticised on the basis that assessment of various asymmetries is necessary for complex genetic modelling (McManus, 1999). In the present study we employed a novel approach by integrating various behavioural asymmetries and familial indices. The model was tested in schizophrenia patients, their siblings, and controls – first in the pooled sample of all the three groups, and then separately in patients, siblings and controls. In each group, we examined the relationship between the obtained laterality phenotypes and a range of neurocognitive measures, personality traits, and (for schizophrenia patients only) clinical variables.

6.2 Methods

6.2.1 Participants

Participants were drawn from the Western Australian Family Study of Schizophrenia (Jablensky, 2004; Hallmayer et al., 2003). The patient group included 157 (34 females) biologically unrelated individuals aged 17 to 69 years who met both ICD-10 and DSM-IV criteria for a lifetime diagnosis of schizophrenia disorder and had been recruited from consecutive admissions to a psychiatric hospital. Patients with comorbid organic brain disease or substance abuse disorder that could account for the psychotic symptoms, or with language difficulties were excluded. The comparison sample consisted of 74 (50 females) clinically unaffected siblings of schizophrenia patients (14 to 63 years of age) and 77 (34 females) unrelated community control subjects (19 to 74 years of age). Controls were excluded if they had a history of a psychotic disorder, organic brain disease or substance use disorder. Written informed consent was obtained from all participants. The study was approved by the Committee for Human Rights at The University of Western Australia and the Graylands Hospital Ethics Committee.

6.2.2 Clinical assessment

All patients, siblings and controls were interviewed by a psychiatrist or other trained mental health professional using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, Wing et al., 1990). In addition, all participants filled in the self-administered Schizotypal Personality Questionnaire, SPQ (Raine, 1991). The World Health Organisation Psychiatric and Personal History Schedule, PPHS (Jablensky et al., 1992), was used to collect information on the patients from key family members. Case notes were consulted to extract data on number and duration of hospitalisations, and dosage of antipsychotic medication prescribed.

6.2.3 Laterality measures

The Edinburgh Handedness Inventory (EHI; Oldfield, 1971) was used to assess hand preference in the study subjects and to record the reported handedness of their parents. Eye and foot preferences were included as independent items in the analysis. On the basis of EHI, each subject was classified into left-, mixed-, or right-handedness category before statistical analysis. Subjects with laterality quotients ranging from -100 to -71 were classified as left-handers, those with laterality quotients from +71 to +100 as right-handers, and the remaining subjects (from –70 to +70) as mixed-handers. These cut-offs for the EHI, determined on the basis of statistical criteria, were found to be in good agreement with handedness categorisation based on hand demonstration tasks (Dragovic, 2004). Writing hand and familial sinistrality (FS) variables were also extracted from the EHI responses.

Motor proficiency of each hand was assessed by the finger-tapping task (Reitan, 1969) with tapping speed and inter-tap interval variability as measures yielding a tapping laterality quotient (TQ). On the basis of the TQ, all subjects were assigned to motor skill lateralisation categories: (a) left dominant; (b) mixed (no clear dominance); and (c) right dominant.

6.3.4 Neurocognitive assessment

Each subject was assessed using a neurocognitive battery administered by a trained research psychologist. Current intellectual functioning was assessed by the

Shipley Institute of Living Scale (SILS; Zachary, 1986) which comprises two subtests: a vocabulary and an abstraction subtest, and yields a reliable estimation of WAIS-R Full Scale IQ (Zachary et al., 1985; Phay, 1990). Premorbid intellectual functioning was estimated by the revised National Adult Reading Test (NART; Nelson & Willison, 1991). Sustained attention was assessed with two forms of the Continuous Performance Tasks (CPT) – (i) identical pairs (Cornblatt et al., 1988), which measures the effects of an increased processing load on working memory, and (ii) degraded stimuli version (Rosvold et al., 1956) which measures the effects of an increased processing load on visual encoding. For each CPT version we use the discrimination index, d_L (Snodgrass & Corwin, 1988), which indicates ability to discriminate signal from noise, as a measure of processing sensitivity. Verbal learning was assessed by the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964). Speed of information processing was assessed by the Inspection Time task (IT; White, 1996; Stough et al., 1996), which produces a more accurate assessment of an individual's speed of processing than traditional reaction time measures. Verbal Fluency, FAS version (Benton et al., 1994) was used as a measure of executive lexical retrieval.

6.2.5 Statistical analyses

To identify complex patterns of laterality and their distribution within the study population, we used a version of latent class analysis known as grade of membership, or GoM (Woodbury et al., 1978; Woodbury & Manton, 1982; Manton et al., 1994). It estimates multivariate regression relationships between sets of discrete or continuous variables, and partitions the data into several analytically derived latent classes or 'pure types', identified by conditional maximum likelihood. The number of pure types providing optimal partitioning of the data is determined by a formal criterion, based on changes in the significance of the likelihood ratio chi-square in successive iterations of the model with increasing (or decreasing) numbers of pure types. Pure types estimate the probabilities of joint occurrence of variables and are described by profiles of attributes where the probability (λ_{kj}) is estimated of each attribute being manifested by an individual (j) belonging entirely to a given pure type (k). Simultaneously, GoM quantifies the degree (grade of membership score, or g_{ik}) to which an individual belongs to any of the identified (k) pure types (g_{ik} are constrained to add up to 1, so that a person may belong exclusively to one pure type or partially to several). GoM represents the set of attributes characterising an individual as a weighted linear combination of pure type coefficients (λ_{kj}) and grade of membership scores (g_{ik}), where all individual heterogeneity of the data is accounted for by the g_{ik} scores. The input data for GoM include (i) internal variables, used to identify pure types; and (ii) external variables, estimated conditional on the identified pure types and placing the latter in a context, without affecting their definition. The level of correspondence of each variable to the final pure type definition is assessed by the information content statistic (H), which can be interpreted as effect size indicating the level of contribution of each variable to the model likelihood (values of H less than 0.10 suggest a nonsignificant contribution). GoM operates with both continuous and categorical data, and requires no assumptions about the distributions of the dependent variables. It has been utilised in both psychiatry research (Manton et al., 1994; Jablensky & Woodbury, 1995; Nurnberg et al., 1999; Cassidy, Pieper, & Carrol, 2001; Szádóczky et al., 2003), and genetic studies (Corder & Woodburry, 1993; Corder et al., 2001; Hallmayer et al., 2003), including a new multivariate test for genetic linkage (Kaabi & Elston, 2003).

The pure types in this analysis were derived from two sets of internal variables: (i) behavioural lateralities (writing hand, handedness category, motor proficiency, and foot and eye dominance), and (ii) familial indices (parents' and sibling's handedness, and familial sinistrality).

As each individual may approximate to varying degrees (quantified by grade of membership score), more than one pure type, GoM allows subjects to be uniquely assigned to discrete groups, based on the pure type for which they exhibited the highest g_{ik}. Further characterisation of such groups can then be obtained by performing conventional statistical analyses for relevant external variables, including, in this study, neurocognitive performance (scores on each neurocognitive task), personality traits (three schizotypy factors derived from the SPQ (Raine et al., 1994), and several clinical measures (for schizophrenia patients only).

6.3 Results

Several behavioural asymmetries (writing hand, handedness, footedness, eyedness, and motor lateralisation) and familial cofactors (familial sinistrality and parents' handedness) were used as internal variables to delineate latent laterality subtypes in the three samples.

The first stage of GoM analysis, which explored the data for latent patterns of lateralisation in the pooled sample of patients, siblings and controls, resulted in 3 ideal pure types (labelled 'left', 'mixed', and 'right' respectively), as the most parsimonious solution, integrating all of the measures into a left, a mixed, and a right composite patterns that were uncorrelated with one another. Each pure type was expressed, to a varying degree, in patients, siblings and controls, with a moderately increased probability (lambda = 64.9%) for an individual expressing fully the left pure type to be a patient.

In the second stage we investigated whether a comparable latent structure, using the identical set of internal variables, is present in separate samples. The results showed that the best GoM model for schizophrenia patients consisted of three composite pure types, whereas two pure types ('left' and 'right') provided the best description of the data in siblings of schizophrenia patients and in the controls. After obtaining the three pure type solution in the group of schizophrenia patients, and the two pure type solution in the groups of siblings and controls, further modelling of the data failed to produce significant improvement in goodness-of-fit. In the group of patients, a change in the chi-square was significant for the 2-type solution (p = 0.000), and for the 3-type solution (p = 0.005), but not for the 4-type (p = 0.920). In the samples of siblings and controls a change in the chi-square was significant for the 2 pure type solution (siblings p = 0.001; controls p = 0.003), but was not for the 3-type solution (siblings p = 0.119; controls p = 0.117).

6.3.1 Laterality pure types and their expression in patients, siblings and controls

Table 2.15 describes the internal variables defining each laterality pure type in the three groups of subjects in terms of probabilities (λ_{kj}).

Pure Type 'left': characterised by a leftward lateralisation on the majority of behavioural and familial indices. This pure type, expressed in schizophrenia patients, siblings and controls, describes individuals with high probability of leftward ('left' or 'mixed') lateralisation on all behavioural indices. In contrast to other pure types, this type was characterised by preference of left-hand for writing, left- or mixed-footedness, and greater motor proficiency of the left hand. Individuals expressing fully this type are more likely to have at least one left-handed first-degree relative, compared to the 'right' pure type in patients, siblings, and controls.

Table 2.15 Pure types of lateralisation in the 3 samples, defined by lambda (λ_{kj}) probabilities (shown as percentages) of internal variables. Numbers and proportions of subjects assigned to each type are shown at the bottom of the table

		Schizophrenia patients				Siblings			Controls		
PURE TYPES (PT)[a)]			'Left'	'Mixed'	'Right'		'Left'	'Right'		'Left'	'Right'
Internal variables	Level	H[b)]	λ_{kj}	λ_{kj}	λ_{kj}	H[b)]	λ_{kj}	λ_{kj}	H[b)]	λ_{kj}	λ_{kj}
Writing hand	Left	0.54	100.0	0.0	0.0	0.75	100.0	0.0	0.60	100.0	0.0
	Right		0.0	100.0	100.0		0.0	100.0		0.0	100.0
Handedness category (EHI)[c)]	Left		25.2	0.0	0.0		20.0	0.0		33.3	0.0
	Mixed	0.48	74.5	34.4	0.0	0.64	80.0	0.0	0.52	66.7	0.0
	Right		0.0	65.6	100.0		0.0	100.0		0.0	100.0
Footedness	Left		77.9	0.0	0.0		28.2	0.0		50.0	0.0
	Mixed	0.58	22.1	45.3	0.0	0.22	22.5	0.0	0.51	50.0	0.0
	Right		0.0	54.7	100.0		49.3	100.0		0.0	100.0
Eyedness	Left		79.1	0.0	0.0		34.4	27.4		8.5	30.6
	Mixed	0.89	0.0	100.0	0.0	0.01	24.1	18.6	0.30	67.6	0.0
	Right		20.9	0.0	100.0		41.5	54.1		23.9	69.4
Motor skill lateralisation	Left		100.0	0.0	27.8		67.3	0.0		53.1	17.2
	Mixed	0.80	0.0	100.0	2.8	0.48	32.7	47.5	0.15	46.9	26.2
	Right		0.0	0.0	72.2		0.0	52.5		0.0	56.6
Parental handedness	LxL		12.4	0.0	0.0		5.1	2.4		15.8	0.0
(mother X father)	LxR	0.35	37.2	0.0	0.0	0.23	15.2	0.0	0.54	44.4	0.0
	RxL		0.0	42.5	0.0		35.6	0.0		55.6	0.0
	RxR		50.4	57.5	100.0		44.1	97.6		0.0	100.0
Familial sinistrality (FS)[d)]	FS-	0.69	0.0	0.0	100.0	0.08	23.9	65.2	0.53	0.0	100.0
	FS+		100.0	100.0	0.0		76.1	34.8		100.0	0.0
SUBJECTS ASSIGNED TO PT BY DEGREE	Number		33	56	68		27	47		27	50
OF SIMILARITY (grade of membership)	Percent		21	36	43		36	64		35	65

a) The optimal (most parsimonious) number of pure types partitioning the data matrix is indicated by the changes in the log likelihood ratio for consecutive potential solutions. Chi-square values (being twice the difference of the log likelihood ratio for subsequent pure types) were significant for the 2 and 3 type solution in the group of schizophrenia patients, but were non-significant after 4 PT solution onwards. In the groups of siblings and controls only 2 PT solution yielded a significant change.
b) Information content index; estimates the contribution of each variable to the likelihood ratio.
c) Mixed = ranging from –70 to +70 of the laterality quotient (LQ); Right = greater than +70 of the LQ; Left = less than -70 of the LQ.
d) FS- no left-handed first-degree relatives; FS+ at least one first-degree relative is left-handed.

Log likelihood ratios were obtained for a series of potential solutions (up to 5 pure types) in each group. Chi-square values (being twice the difference of the log likelihood ratio for subsequent pure types) were significant for the 2 and 3 type solution in the group of schizophrenia patients, but were non-significant after 4 PT solution onwards. In the groups of siblings and controls only the 2 PT solution yielded a significant change.

Pure Type 'mixed': identified in schizophrenia patients, but not in siblings or controls. Its main feature is lack of a clear preference in overall handedness, footedness, eye dominance and motor proficiency, despite a right-hand dominance for writing. This type was associated with positive familial sinistrality and parental left-handedness, in which the father was more likely to be left-handed. Although the distributions of handedness categories and foot dominance in this pure type were in a rightward direction, individuals fully expressing this type show absence of clear eye and motor dominance.

Pure Type 'right': expressed in the majority of subjects in all three samples. It is characterised by a rightward lateralisation in all domains (hand, foot, eye, and motor proficiency) and matching right-handedness in the first-degree relatives.

6.3.2 External variables associated with pure types

The pure types described by lambda (λ_{kj}) probabilities represent extreme profiles, expressed in their entirety (grade of membership, $g_{ik} = 1.0$) by only a minority of individuals in the sample, while the majority approximate any such profile to a varying, quantifiable degree. In order to compare the lateralisation patterns identified by GoM pure types in terms of conventional descriptive statistics, patients, siblings and controls were grouped into discrete clusters, based on each individual's highest grade of membership for any laterality pure type. Within the group of schizophrenia patients, 33 (21%) were classified as 'left'; 56 (36%) as 'mixed'; and 68 (43%) as 'right'. Within the two comparison groups, 27 (36%) of the siblings and 27 (35%) of the controls were classified as 'left', while 47 (64%) of the siblings and 50 (65%) of the controls were assigned to the 'right' phenotype category.

Further characterisation (Table 2.16) of the pure types was achieved by performing analysis of variance and Kruskal-Wallis test (for schizophrenia patients), using pure type assignments as the main factor and Student t-tests (for siblings and controls subjects) for external variables that had not been used in the identification of laterality pure type. Since schizophrenia patients assigned to the three pure types did not differ in age ($F_{[2,154]} = 0.496$, $p = 0.610$) and education ($F_{[2,153]} = 0.016$, $p = 0.984$), these variables were not used as covariates.

The comparison of clinical measures, schizotypy scores (based on the SPQ factors, Raine 1994), and neurocognitive performance revealed that members of pure types, schizophrenia patients in particular, differ on these measures.

Within the patient group, a consistent (non-significant) trend of differences between the three pure types emerged on several clinical measures. The ‘left’ patients had the greatest total number of hospitalisations, the highest total length of stay in psychiatric hospital, and the highest duration of the single longest in-patient admission. There was a nonsignificant increase in the median number of hospitalisations in the ‘mixed’ and ‘left’ patients combined, relative to the group of ‘right’ patients. No difference was found across the three groups with regard to the median daily dosage of anitpsychotic medication (converted into chlorpromazine equivalents). All schizophrenia patients had higher scores on the SPQ schizotypy traits than their siblings and the controls (the latter two groups did not differ consistently from one another on these measures). Within the schizophrenia group, schizophrenia patients assigned to the ‘left’ pure type displayed significantly higher scores ($F_{[2,124]} = 3.66$, $p = 0.029$) on the cognitive-perceptual dysfunction factor (ideas of reference, magical thinking, unusual perceptual experiences and paranoid ideation) than patients assigned to the ‘right’ and ‘mixed’ pure types. There was a nearly significant ($F_{[2,124]} = 2.89$, $p = 0.059$) increase on the SPQ interpersonal factor (social anxiety, no close friends, constricted affect). The three schizophrenia groups did not differ on the SPQ disorganisation factor (odd behaviour, odd speech).

Table 2.16 External evaluation of pure types in the three samples by comparing mean scores on the three sets of measures

External variables	Schizophrenia patients			Siblings		Controls	
	'Left'	'Mixed'	'Right'	'Left'	'Right'	'Left'	'Right'
Neurocognitive performance – Mean (SD)							
NART	97.8 (11.0)	96.8 (10.0)	98.9 (11.5)	104.6 (6.4)	105.7(10.1)	106.8 (7.5)	106.5 (7.1)
Current IQ	88.8 (12.5)	88.7 (13.5)	93.2 (14.4)	105.4 (7.5)	103.7 (8.9)	108.5 (7.8)	109.1 (8.0)
Verbal fluency	26.8 (8.2)	28.4 (10.0)	30.6 (10.7)	35.7 (9.2)	36.1 (10.5)	39.7 (13.5)	38.6 (8.3)
CPT-DS/dL	4.236 (1.8)	4.520 (1.6)	4.634 (1.4)	5.766 (1.0)	5.724 (1.2)	6.032 (1.1)	5.895 (1.0)
CPT-IP/dL	2.950 (1.8)	2.774 (1.6)	3.147 (1.9)	4.630 (1.5)	4.461 (1.4)	4.449 (1.3)	5.086 (1.8)
Inspection time	42.9 (15.0)	41.3 (15.0)	38.7 (12.4)	32.8 (10.7)	36.3 (14.7)	37.4 (16.2)	37.0 (11.4)
RAVLT immediate recall	21.3 (7.1)	20.3 (6.2)	20.5 (6.5)	27.8 (6.3)	28.9 (5.6)	28.7 (6.1)	28.7 (5.9)
RAVLT delayed recall	5.8 (3.2)	5.4 (2.8)	5.9 (3.2)	8.8 (3.0)	10.0 (3.0)	9.2 (3.6)	9.8 (2.8)
Schizotypal personality – Mean (SD)							
Cognitive and perceptual dysfunction ‡	20.2 (9.5)	14.6 (7.2)	16.5 (8.9)	3.4 (4.0)	4.5 (5.2)	3.9 (3.2)	3.3 (3.9)
Interpersonal deficit †	20.4 (6.6)	15.7 (8.3)	16.4 (8.8)	4.9 (5.4)	6.8 (6.9)	6.0 (5.1)	6.3 (6.8)
Disorganisation	8.7 (3.9)	7.3 (4.1)	7.9 (3.9)	2.2 (3.3)	2.9 (3.0)	3.4 (3.1)	2.7 (3.0)
Clinical measures – Median (interquartile range)							
Total length of stay in days	354 (207-874)	235 (90-450)	243 (103-758)	-	-	-	-
Longest length of stay in days*	138 (74-211)	70 (43-128)	76 (48-252)	-	-	-	-
Number of hospitalisations	12 (12-32)	10 (10-22.5)	11 (11-21)	-	-	-	-
Medication (mg/day)	600 (300-625)	375 (250-600)	675 (375-1025)	-	-	-	-
Age at onset £	20.5 (17-25)	21.0 (18-24)	23.0 (18-27)	-	-	-	-
Paranoid Sz vs other Sz (n/%) ¶	9 (14.8) 24 (25.0)	22 (36.1) 34 (35.4)	20 (49.2) 27 (39.6)		-	-	-

‡ $F_{[2,123]} = 3.66$, $p = 0.029$, $\eta^2 = 0.06$; † $F_{[2,123]} = 2.89$, $p = 0.059$, $\eta^2 = 0.04$; * Kruskal-Wallis chi-square = 4.78, df = 2, p = 0.092; £ Kruskal-Wallis chi-square = 2.86, df = 2, p = 0.2; ¶ Chi-square = 2.66, df = 2, p = 0.264

Schizophrenia patients assigned to the 'left' and 'mixed' pure types tended to have poorer performance than patients assigned to the 'right' type, on premorbid and current IQ, verbal fluency, and the two versions of the Continuous Performance Task, and to be slower on the Inspection Time task. Although the differences in mean scores were not statistically significant, the trend (Figure 2.11) of greater impairment in performance on tasks involving effortful lexical retrieval, sustained attention and working memory in patients assigned to the two 'non-right' types was consistent.

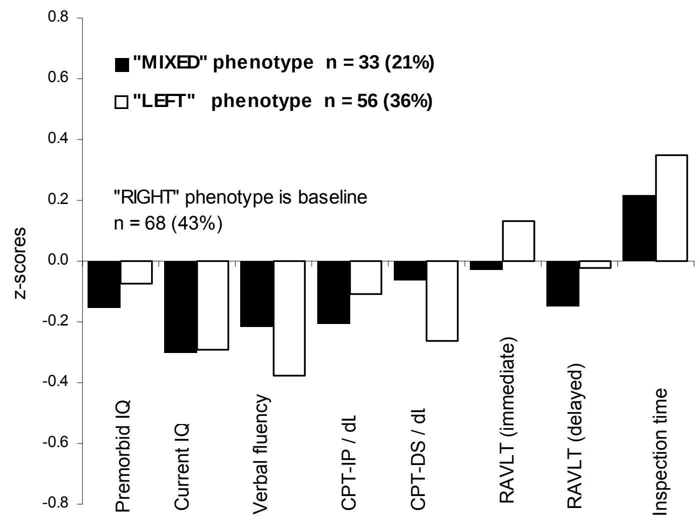

Figure 2.11 Neurocognitive profiles of the three laterality subtypes in schizophrenia patients (performance of subjects assigned to the 'right' subtype provides the baseline)

In the group of siblings and controls, the tests for between group differences revealed that members of the two laterality subtypes performed almost equally on all neurocognitive tasks.

Finally, in the group of patients we examined whether left-handedness of each parent was specifically associated with patient's assignment to a composite laterality subtype. Of the 19 schizophrenia patients who reported having a left-handed mother, 14 were assigned by GoM to the 'left' laterality subtype, 1 to the 'right', and 4 to the 'mixed'. In contrast, of 18 patients with left-handed fathers, 13 were assigned to the 'mixed' subtype, 1 to the 'right' and 3 to the 'mixed. The differential association between fathers' or mothers' left-handedness and patient's assignment to a laterality subtype was statistically significant ($\chi^2 = 10.30$, $df = 2$, $p < 0.01$).

6.4 Discussion

6.4.1 Main findings

This study explored the presence of latent, composite laterality phenotypes, defined by probabilities of joint occurrence of multiple measures of behavioural asymmetries in patients with schizophrenia, their unaffected siblings, and healthy controls. Three composite subtypes ('left', 'right' and 'mixed' latent pure types) provided an optimal partitioning of the patient sample. In contrast, only two laterality subtypes characterised the sibling and control groups, where a 'mixed' subtype did not improve the fit of the model to the data. While the majority of both sibling and control samples were assigned to the 'right' composite laterality type, over 50% of schizophrenia patients expressed atypical or attenuated behavioural lateralisation (21% with high grades of membership in the 'left' and 35.7% with high grades of membership in the 'mixed' subtype). The frequencies of atypical composite laterality phenotypes in unaffected subjects (36% in siblings and 35% in controls) are nearly identical to the proportion of individuals (approximately 35%) in the general population, estimated by Geschwind and Galaburda (1985) as having 'anomalous' dominance. Similarly, Annett's 'right shift' theory (Annett, 1985) predicts that 37% of people should be classified as non-right hand dominant. Notably, our latent class grade of membership model classified both left- and mixed-handedness among the siblings and controls as part of the composite 'left' pure type. The closeness of our empirical findings to those estimates and predictions provides indirect support to the validity of the GoM modelling of multiple laterality measures.

The lack of clear behavioural lateralisation in schizophrenia patients is best illustrated by the 'mixed' subtype, which represents a close approximation to the 'mixed-handedness' construct. In contrast to previous studies, where reduced functional lateralisation has been restricted to hand preference (Cannon et al., 1995; Malesu et al., 1996; Orr et al., 1999; Collinson et al., 2004), our model broadens this construct by including multiple measures of behavioural asymmetries. Furthermore, our finding of two 'non-right' patterns ('left' and 'mixed') of anomalous lateralisation in schizophrenia implicates both reductions of lateral preferences and increases in left-sidedness, rather than merely an increase of mixed-handedness (Satz and Green, 1999). This is consistent with a number of studies (Katsanis & Iacono; 1989; Clementz et al., 1994; Tyler et al., 1995), which have reported an excess of left-handedness in schizophrenia patients compared to healthy controls.

Our finding that schizophrenia patients assigned to the 'left' phenotype were more likely to have a left-handed mother (but not a left-handed father), while patients assigned to the 'mixed' phenotype were more likely to have a left-handed father (but not a left-handed mother), suggests a familial effect that might be either genetic or environmental. However, the clear absence of an excess of atypical lateralisation in the unaffected siblings of schizophrenia patients is in line with the findings of several other studies (Clementz et al., 1995; Toommey et al., 1998; Byrne et al., 2004) and suggests that atypical lateralisation is unlikely to be a robust phenotypic marker of the genetic vulnerability to schizophrenia.

6.4.2 Neurocognitive and clinical correlates

The associations between the laterality phenotypes identified in this study and selected clinical, personality traits, and neurocognitive variables implicated in the vulnerability to schizophrenia do not provide unequivocal support to the hypothesis (Crow et al., 1998; Leask & Crow, 2001; Nettle, 2003) that cognitive performance increases with increasing lateralisation of hand preferences in either direction, and that cognitive abilities are lowest around the point of equal hand skills - 'point of interhemispheric indecision' (Crow et al., 1998). In schizophrenia patients, greater clinical severity (as reflected in more frequent and longer hospitalisations), earlier age at onset, and higher scores on self-assessed cognitive-perceptual dysfunction and interpersonal deficit, characterised the 'left' subgroup of patients showing a nearly complete reversal of lateralisation (assessed on multiple indices), and not the 'mixed' subgroup, which did not differ on these measures from the patients with complete 'right' lateralisation. On the other hand, the 'left' and 'mixed' subgroups combined showed a consistent trend of poorer cognitive performance than the 'right' subgroup, but did not differ from one another on these measures. Thus, our data suggest that some degree of cognitive deficit is associated with a leftward laterality shift, rather than with a mere reduction of behavioural asymmetry. However, since the effect size of this association (Cohen's *d* for neurocognitive measures in this data set was in range from 0.08 to 0.16) is small, it is likely that behavioural asymmetries explain only a small proportion of the variance in cognitive performance in schizophrenia patients.

6.4.3 Limitations

The study has several limitations. First, the sample of unaffected siblings is relatively small and may represent a biased proportion of the sibling population (it might have been the case that mainly ‘healthy’, high-functioning siblings have participated). Inclusion of all siblings might reveal differences from the controls in both laterality subtypes and neurocognitive profiles. Secondly, several of the laterality measures (including parental handedness) are based on self-reports, which may not be entirely reliable. However, the EHI is the most widely used questionnaire and is widely accepted as the standard in eliciting handedness data (Ransil & Schachter, 1994).

6.4.4 Conclusions

Notwithstanding such caveats, the present study demonstrates that the complexity of behavioural lateralisation can be effectively partitioned into distinct latent types using a multivariate analysis, such as GoM. An important finding is that, within individuals, the probabilities of association between different measures are not uniformly distributed, e.g. left or right writing hand can be associated with varying probabilities for other behavioural preferences, suggesting that the writing hand is a poor predictor of other laterality measures. We suggest that the multivariate integration of laterality measures and other relevant cofactors into composite laterality traits may provide a more refined tool for further research into the genetic, developmental and environmental underpinnings of behavioural and cerebral lateralisation.

Clinical implications

- A leftward shift in behavioural lateralisation in schizophrenia patients is associated with greater clinical severity, higher schizotypy factors scores and poorer cognitive performance.
- The integration of laterality measures into a multivariate composite trait provides a potential tool for clinical and genetic research into cerebral and behavioural lateralisation.
- Atypical lateralisation is unlikely to be a reliable marker of vulnerability to schizophrenia.

Limitations

- High functioning, healthy individuals may be over-represented in the sample of unaffected siblings of schizophrenia patients.
- Several of the laterality measures are based on self-report.
- The number of maternal reports on obstetric complications is small.

7. Study 5: Improved measurement of handedness

7.2 Introduction

Assessment of handedness is a standard procedure in any investigation of human behavioural asymmetries and in many neuropsychological investigations. Numerous 'handedness questionnaires' have been designed, all with the intention to quantify the direction and degree of handedness. Amongst them, two appear to be the most prominent in current research: the Edinburgh Handedness Inventory (EHI), Oldfield (1971), and Annett's handedness questionnaire (Annett, 1970). The EHI is by far the most commonly used of the two (Bishop, 1996).

Although the EHI is widely used, only a few studies have examined its psychometric properties. Bryden (1977) recommended that items that do not conform to the unidimensional construct of handedness (e.g. using a broom, which is basically a bimanual activity) should be discarded. Williams (1986) argued that the EHI should be shortened by eliminating items with a weak contribution to the 'handedness' factor. McFarland and Anderson (1980) demonstrated that the EHI possesses a stable factor structure across both age and gender, but noted the presence of some troublesome items. To overcome their weak contribution to the handedness factor, McFarland and Anderson (1980) suggested a weighting procedure to augment the overall validity of the EHI. They (1980) suggested that derived factor scores, which represent the hypothetical score of each individual on an extracted factor, should be allocated to the items with poor loading onto handedness factor. It appears that this suggestion has not been followed up. These criticisms of the original EHI deserve to be re-examined using a stronger statistical procedure, which is able to validate the latent handedness construct by dissecting the measurement properties of each handedness item.

To address the validity of the EHI, researchers have usually employed exploratory factor analysis (principal components) to examine its latent structure without imposing a preconceived underlying structure. This technique is possibly more useful in the early stages of research (Tabachnick & Fidell, 1996, p. 637), where the relationship between latent constructs and indicator items is unknown. In this regard, a theory-testing procedure, such as confirmatory factor analysis (CFA), is a more rigorous statistical technique as compared to exploratory factor analysis (Jöreskog, Sörbom, du Toit, & du Toit, 1999), because indicator items are specified a priori to load on given theoretical construct.

This study reports the results of the congeneric measurement model (Jöreskog, 1971), using Lisrel (version 8.52) on a sample of EHI scores collected from mentally well adults (N = 203) recruited as part of the Western Australian Family Study of Schizophrenia. The congeneric measurement model assumes that items are not equally accurate indicators of the latent construct. In this paper I argue that the EHI requires a dissection of its psychometric properties. I propose that a simple exclusion of one redundant and two ambiguous items, which presumably measure something other than handedness, would significantly enhance the validity and internal consistency of the handedness construct. This proposal will be addressed after confirming that a simple sum (or its algebraic variation – laterality quotient, where the difference between left and right side responses is divided by their sum) of all items is not a statistically sound index of the handedness construct.

7.2 Method

7.2.1 Participants

The complete EHI was administered individually to a sample of 203 participants from metropolitan Perth. This sample comprised 90 men (mean age 47.4, 95%CI 43.2 – 51.4) and 113 women (mean age 44.8, 95%CI 41.8 – 47.7). Subjects in this study are part of the Western Australian Family Study of Schizophrenia. All participants in this study were screened for the absence of psychiatric disorder.

7.2.2 Instrument

The Edinburgh Handedness Inventory consists of 10 items indexing hand preference (writing, drawing, throwing, using scissors, a toothbrush, a knife without a fork, using spoon, the upper hand when using a broom, striking a match, and opening the lid of the box). For each item, participants indicated their hand preference in the following range: *strong* (++), *less strong* (+), to *indifferent* (+/+). In order to perform the CFA under normal distribution requirements the responses were recoded into a five-point Lickert-type scale (1-5). Strong left-handedness was given a score of 1 and strong right-handedness a score of 5.

7.2.3 Statistical analysis

In many areas of research, a composite score for some instrument is a simple sum of the scores of individual items, being based on the a priori assumption that each item carries an equal weight and contributes equally to the overall score. In the EHI, for example, by summing scores for 10 items (or calculating a laterality quotient from them), the same weight is assigned to each item. The first task in this study was to investigate whether all items contribute equally or not to the composite measure of handedness. This issue was addressed by testing three measurement models on the full 10-item scale: (1) a parallel model (which assumes that each item carries an equal prediction of the composite score), (2) a tau-equivalent model (which assumes that each items is an equally accurate indicator of the composite score, but allows error variances to differ), and (3) a congeneric model, in which each item is assumed to indicate the same generic true score, but with a unique contribution to the composite score and an item-specific error variance. However, if measures of handedness prove to be congeneric in their nature, this allowed further fitting of the model in order to achieve a more reliable and valid scale. These measurement models are tested again after the last modification of the EHI.

Since the data were not normally distributed, they were analysed in PRELIS, where polychoric coefficients and an asymptotic covariance matrix were generated for analysis in a LISREL. Because of the relatively small sample size, maximum likelihood (ML) estimation was used. A scaled chi-square statistic (Satorra & Bentler, 1988) was used to assess the fit of various measurement models as well as for modifications of the congeneric model. This statistic corrects an inflated chi-square value due to non-normality, and is recommended for use in small samples (Curran, West, & Finch, 1996).

Apart from the chi-square statistic, which is sensitive to sample size, the fit of all subsequent scale modifications is assessed by a number of other fit indices, such as RMSEA (root mean square error of approximation), SRMR (standardised root mean-square residual), GFI (goodness of fit index), AGFI (adjusted goodness of fit index) and CFI (comparative fit index). Scale reliability was assessed by the measure of variance extracted (Fornell & Larcker, 1981).

7.3. Results

Table 2.17 presents chi-square measures-of-fit for three measurement models: parallel, tau-equivalent, and congeneric model for the full, 10-item scale. The parallel model of measurement, which assumes that each item contributes equally to the composite score, including an identical measurement error for each item, showed a significantly poorer fit than two other models. A second, tau-equivalent model, which also assumes that each item is equally good indicator of the latent (handedness) construct, but which allows differences in error variances across all items, was significantly better than the parallel model. Although the last, congeneric model was superior to the other two models, the absolute fit of this model indicates that it might be enhanced by scale modification.

Table 2.17 Chi-square measures of fit for three measurement models for the Edinburgh Handedness Inventory

Model	S-B χ^2	df	χ^2_{diff}	Δ df
Parallel	161.1	53	-	-
Tau-equivalent	128.1	44	33.0*	9
Congeneric	98.6	35	29.5*	9

S-B χ^2 = Satorra-Bentler Scaled Chi-square
* $p < .05$.

The next step was to fully assess the goodness of fit of the full, 10-item scale, and to determine how well each item predicts the construct. On the basis of this modifications of the full scale (baseline model) were possible.

Table 2.18 presents the parameter estimates (squared multiple correlations for observed variables and factor regression scores) and fit statistics for the original 10-item scale and two modifications (9- and 7-item scale). The 10-item scale failed on several grounds. Squared multiple correlation for the two items (using a broom and opening a box-lid) were below 0.50, indicating that, for these observed variables, there was more error variance (1 minus proportion of explained variance) than variance attributable to the latent construct. These items are, therefore, unlikely to be valid and reliable predictors of the construct because of the large measurement error associated with them (Kline, 1998). Other items of concern in the 10-item scale were writing and drawing. The almost perfect correlation (0.98) between these two items suggests that only one of them is sufficient for the prediction of the construct. This scale also failed on all fit indices (S-B χ^2, RMSEA, GFI, AGFI, CFI), while factor score regressions (Table 2.18) suggest that items other than writing and drawing contributed little to the handedness latent trait.

By eliminating the drawing item (9-item model), most, but not all, fit indices improved substantially. Both chi-square ($\chi^2 = 29.1$ with 27 *df* and $p = 0.35$) and RMSEA index (0.2) indicate a good absolute fit to the data (Browne & Cudeck, 1993). The comparative fit index (CFI) was also acceptable (0.98). However, goodness-of-fit (GFI = 0.89) and adjusted-goodness-of-fit (AGFI = 0.82) for this modification were well below the recommended value of 0.90. More importantly, the contribution of the items ‘using a broom’ and ‘opening a box-lid’ to the common latent construct remained unacceptably low. They both have unacceptably large level of error variance (both 0.54) and low factor score regressions (both 0.04) that indicate a marginal contribution to the latent construct.

Table 2.18 One-factor congeneric measurement models for the EHI and the two modifications, including squared multiple correlations (proportion of variance explained by the construct), factor score regressions (specific weight of each item), and goodness-of-fit measures

Observed variables	Baseline 10-items		1st modification 9-items		2nd modification 7-items	
	Squared multiple correlations	Factor scores	Squared multiple correlations	Factor score	Squared multiple correlations	Factor scores
Writing	.98	.56	.87	.22	.88	.23
Drawing	.96	.24	-	-	-	-
Throwing	.64	.02	.66	.07	.66	.07
Scissors	.76	.04	.82	.14	.82	.16
Toothbrush	.73	.04	.81	.14	.81	.15
Knife	.70	.03	.80	.13	.80	.14
Spoon	.74	.04	.81	.14	.82	.15
Broom	.43	.01	.46	.04	-	-
Matches	.80	.05	.85	.18	.84	.17
Opening box-lid	.35	.01	.46	.04	-	-
Goodness-of-fit measures						
No of iterations	13		9		8	
S-B χ^2	98.6		$30.0^{\S}$		$11.6^{\#}$	
Degrees of freedom df	35		27		14	
Probability p	.00		.27		.65	
RMSEA	.10		.02		.00	
Standardised RMR	.06		.03		.02	
GFI	.62		.89		.93	
AGFI	.45		.82		.87	
CFI	.92		.98		.99	
Variance extracted estimate	.53		.53		.61	

S-B χ^2 = Satorra-Bentler scaled chi-square;
RMSEA = Root Mean Square Error of Approximation;
Standardised RMR = Standardised Root Mean-square Residual;
GFI = Goodness-of-Fit Index;
AGFI = Adjusted Goodness-of-Fit Index;
CFI = Comparative fit index;
§ = difference in chi-square between baseline and 1st modification ($\Delta\chi^2 = 68.6$) is significant ($p<.05$)
# = difference in chi-square between 1st and 2nd modification ($\Delta\chi^2 = 18.4$) is significant ($p<.05$)

A second scale modification in which two less valid predictors of the latent construct (using a broom and opening a box-lid) were excluded, resulting in a 7-item scale that considerably improved the estimation of the handedness construct. In this modification all fit indices were acceptable. More importantly, the modified, 7-item, scale had a more balanced contribution from all items, as indicated by factor regression scores. A measure of the scale reliability (Fornell & Larcker, 1981) which is the measure of variance extracted, showed that this revision performed extremely well (0.61), in contrast to the 10-item scale and 9-item revision, where it was just over 0.50. Changes in the chi-square statistics from the original, 10-item scale to the final revision were significant (Table 2.18), indicating that each modification improved significantly the validity of the latent (handedness) construct.

Table 2.19 Chi-square measures of fit for three measurement models for the 7-item scale

Model	S-B χ^2	*df*	$\Delta\chi^2$	Δdf
Parallel	19.5	26	-	-
Tau-equivalent	17.4	20	2.1*	6
Congeneric	11.6	14	5.8*	6

S-B χ^2 = Satorra-Bentler Scaled Chi-square
* $p > .05$

On the second scale modification, tests of differences between parallel, tau-equivalent, and congeneric model (Table 2.19) were performed. Differences in chi-square measures of fit between three measurement models were not significant indicating that simple aggregation of the item scores and its alternative (the laterality quotient) is an acceptable composite score for the EHI.

Table 2.20 A comparison between the full and revised EHI scale

	EHI 10-items			EHI 7-items		
	Mean score*	Laterality Quotient	% left-handed	Mean score**	Laterality Quotient	% left-handed
Male	41.5	66.9	13.3	29.7	72.0	13.3
Female	42.1	71.0	9.7	29.9	74.6	9.7

* Scores are in range from 10 (left-handedness) to 50 (right-handedness)
** Scores are in range from 10 (left-handedness) to 35 (right-handedness)

Finally, the comparison of descriptive statistics (Table 2.20) on both the original and the shortened scale, revealed that modification of the original scale did not affect major parameters, such as the mean score or the average laterality quotient. Both versions produced identical proportions of left-handed individuals with expected sex differences on both measures.

7.4 Discussion

Confirmatory factor analysis of the EHI has shown that the internal consistency of the handedness construct could be substantially improved by simply eliminating three unreliable items. The removal of these items resulted in a considerably improved unidimensional measurement model. Both revisions demonstrated statistically significant improvement in chi-square goodness-of-fit. Thus, the laterality quotient based on seven selected items from the EHI suggests a more valid quantification of the direction and degree of hand preference than that of the full 10-item version.

The rationale for the exclusion of particular items from the EHI is twofold. The first problem with some items is a straightforward redundancy. For example, two items - writing and drawing - are almost perfectly collinear. Therefore, keeping both items in the measurement model is, at least statistically, unnecessary. This redundancy was deliberately built into the EHI (Oldfield, 1971), since it was argued that the case when a person writes with left hand, but draws with right, is a clinically useful distinction. Although this may be true, the presence of a psychometrically redundant item can inflate the laterality score in either direction, and might affect the categorisation of subjects into smaller number of handedness classes. In order to accommodate these considerations I suggest that the EHI might be administered fully, in its original form, if identification of clinical rarities is required. However, for the purpose of quantifying the level of lateralisation, especially in large samples, this particular item, can be safely discarded. The second problem stems from the fact that the scores on two items (using a broom and opening a box-lid) appear to be sensitive to ambiguity of interpretation and seem to be driven by a factor other than handedness. Williams (1986), using principal component analysis, demonstrated that these two items had the lowest loading on a handedness factor. Their error variances are greater than the variance influenced by hand preferences. Therefore, a weak gain in validity of the handedness construct with these items cannot justify their inclusion on the ground that they would be important to capture an underlying biologically determined continuum (Bishop, 1996, pp. 283). The marginal contribution of these items to the phenotype of handedness has been emphasised by Peters (1990, pp. 174), who argued that such items simply *do not matter,* since preferences on these items are more likely to reflect the environment than pure handedness. It has been also shown (Ransil & Schachter, 1994) that scores on these items are unstable over time, and that test-retest agreement was poorest for bimanual activities (using a broom and opening a box lid). Thus, the inclusion items that *do not matter* can obscure the estimate of hand preference lateralisation.

As traditional laterality quotients contain information about the direction of hand preference, but not the strength (i.e. do not differentiate weak from strong handedness), the mean score, either the sum or Schachter's variation (2002), for the shortened version of the EHI should also be calculated. Schachter (2002) exposed this weakness of the laterality quotient, since such a measure cannot clearly differentiate the degree of lateralisation. For example, it may happen that two subjects manifest an identical direction of lateralisation, indexed by the laterality quotient, but with a dissimilar degree of lateralisation. It should be noted however, that calculating only the total score is also problematic, because an equal weight is given to each scale point, on the assumption that the EHI contains interval scales. Unless the interval nature of measurement is proven, it is preferable to consider the EHI scales as genuinely ordinal, retaining simultaneously both measures of direction and degree. Therefore I suggest that the shortened scale should be used in two ways, one to calculate the traditional laterality quotient (direction) and the other to calculate the total score (strength and direction of hand preference).

Overall, both the original and the revised EHI scale provide similar outcomes (mean scores, laterality quotients, and proportion of left- and right-handed individuals) at the group level. The most important changes, however, happened at the individual level. On the original EHI, subjects who display a *weak* lateralisation due to preferences with the opposite hand on uninformative items (broom and opening the box lid) may loosely be classified as inconsistent in their hand preferences. However, using the shortened version will eliminate such a possibility, most likely providing a better approximation of the true direction and strength of hand preference lateralisation.

To summarise, a revived interest in handedness during the last several decades, and an increasing body of literature on behavioural asymmetries in non-human species that indicates presence of a rightward bias similar to the one in humans (Corballis, 1998) highlights the need for a more accurate measurement of the hand preference asymmetry. It is time perhaps for a revision or modernisation of the existing questionnaires. Outdated items such as use of broom or matches may no longer be relevant, whilst some modern unimanual activities, such as use of computer mouse, may be more powerful predictors of hand preference asymmetry in humans.

PART III

8. General Conclusions

The results of the five studies comprising this thesis have addressed several core issues in current laterality research in schizophrenia. The main findings of these studies will be discussed in this section, and directions for further research indicated.

The lack of a reliable summary of the evidence on atypical handedness in schizophrenia was the specific stimulus for the first study. Traditional reviews of the literature are often insufficiently systematic in summarising the diverse and extensive evidence published usually over several decades, as they bear several weaknesses such as the failure to include substantial numbers of published studies and the lack of precise quantification of available evidence. In addition, traditional reviews allow subjective judgments, which might influence the selection of studies, thus leading to a biased interpretation of the evidence. In contrast, meta-analysis is an unbiased way for quantification of available evidence which usually requires an extensive search for all published work. It is not a perfect tool for summarising the evidence of course, but it is still better than a casual tally of significant and non-significant results (Meehl, 1978; Wolf, 1986).

The results of the first study provided a much stronger quantitative review of the literature than was available previously and highlighted the question as to the true shift in lateral preferences in schizophrenia patients. An increase in exclusive left-handedness in schizophrenia patients compared to healthy controls is a finding of great theoretical importance. Firstly, a view of an exclusive increase of mixed-handedness in the schizophrenia population cannot be further sustained. In contrast to the prevailing opinion in the literature, this shift includes an increase of exclusive left-handedness as well as mixed-handedness. Secondly, the hypothesised causal mechanism responsible for mixed-handedness needs to be revised accordingly, if not rejected completely. Satz and Green (1999) have proposed that bilateral and diffuse impairment of the brain is the most likely mechanism that would explain an increase of mixed-handedness in schizophrenia patients. Since the shift in the handedness distribution of schizophrenia patients is characterised by an excess of left-handedness as well as mixed-handedness compared to normal controls, bilateral cerebral insult would not obviously suffice to explain a unidirectional change. Unilateral insult, left hemispheric in right-handers but right hemispheric in left-handers, that leads to mixed-hand preferences, is a more plausible account and it is consistent with the view that anomalous brain asymmetry is specific to schizophrenia (Crow, 1989b). Severe unilateral insult may therefore result in complete change of hand dominance, i.e., pathologic left- or right-handedness. However, consideration of early brain pathology as the only factor responsible for a change in hand preference implies that pathological left-handedness is a perfect explanatory model for any form of atypical handedness, which may not be the case. In line with the pathology model, the excess of left-handedness in schizophrenia patients, and by the same token the excess of any deviation from the right-handed norm, assumes the existence of a *normal* (genetically driven) and *pathological* (caused by early, not bilateral but left-hemispheric lesions). McManus (1983), on the basis of historical review and empirical data, rejected the concept of pathologic handedness, while Annett (2002) argued that pathological left-handedness occurs in the minority of left-handed subjects. It has also been argued that the prevalence of left-handedness due to brain pathology is low, ranging from one in 250 individuals (Schilling, 1992) to no more than 5% (Bishop, 1990b). On the more general note, the evidence for neurodevelopmental pathology indicated by minor physical anomalies, the cornerstone of Satz and Green model (1999), is considered as weak and circumstantial (Weinberger, 1996) since it is based on indirect evidence which does not categorically implicate brain abnormality. It also has been claimed (McGrath et al., 1995) that minor physical anomalies, indicating a range of subtle alterations in development, provide limited information to the understanding of functional psychoses such as schizophrenia. Like atypical handedness, minor physical anomalies are not specific to schizophrenia as they have been found to be more prevalent in various neurodevelopmental disorders such as mental retardation, attention deficit disorder, autism and cerebral palsy (McGrath et al., 1995).

Another difficulty for the bilateral-and-diffuse-insult hypothesis, according to the data presented in fourth study, lies in the fact that mixed-handedness in schizophrenia patients is associated with familial sinistrality and parents' handedness. Mixed-handed patients are more likely to have a left-handed member of the nuclear family, the mother in particular. This however suggests that a causative function of familial factors cannot be excluded.

In conclusion, Satz and Green's (1999) model is essentially an extension of the pathologic left-handedness concept, in which the excess of any atypical lateralisation of hand preferences (mixed and ambiguous handedness) is conceived as being primarily due to adverse brain insults during early prenatal development. As such, mixed-handedness in schizophrenia patients is understood as a biological marker of abnormal intrauterine development indicating a non-genetic, neurodevelopmental type of schizophrenia (Murray et al., 1992). However, an interpretation of causal mechanisms restricted to hypothetical early brain lesions, without recognising the contribution of familial (most likely genetic factors) is not sufficient. The more convincing account is that the degree of manifestation of this marker can be influence jointly by exogenous and genetic factors.

One important characteristic of the research on atypical lateralisation of hand preferences in schizophrenia is that the overwhelming majority of studies used a categorical approach to describing the handedness distribution in schizophrenia patients. Although handedness can be considered as a continuous trait, and in some studies was used as a continuous variable (Buijsrogge et al., 2002), its distribution, the so-called J-distribution, can hardly be normalised to perform parametric analyses. This might be the reason why categorisation of handedness prevails in laterality research. However, Annett (2002a) has argued against the categorisation of handedness, pointing out that discrete handedness subtypes such as left, right, or mixed are misleading, since their description varies across the studies as a result of variable assessments and criteria. Categorisation of handedness is not a problem on its own; continuous traits such as intelligence are often described in categorical terms. What appears problematic is the lack of clear and widely accepted criteria for classification. This problem was emphasised by Bishop (1990a, p. 165), who noted that "failure to recognise this (post hoc classification procedures determined by trial and error) is probably the single most important source of non-replicable findings in this field". The overwhelming use of various and arbitrary cut-off points for the classification of handedness is frequently blamed as the primary cause of between-studies inconsistencies (Satz & Green, 1999; Byrne et al., 2004; Nettle, 2003), but little has been done to overcome this problem. A doubt that the handedness distribution cannot be decomposed into smaller number of operational categories was further enhanced by the notion that the distribution is exclusively continuous, and therefore admissible only to ad hoc and subjective partitioning (Annett, 1985).

A few attempts to introduce a valid categorisation of hand preferences have failed to provide a clear, simple and uniform classification criterion that could be used in a standardised manner to increase the comparability between various studies.

Annett's classification system, which is restricted to scores derived from her own handedness questionnaire, includes eight handedness classes (recently reduced to seven; Annett, 2002a), six of which are considered as distinct mixed-handedness patterns. Annett's categorisation of hand preferences, with six mixed-handedness classes, has caused considerable confusion in the laterality literature. A perfect illustration of this disorientation in schizophrenia research are studies of Lishman and McMeekan (1976) and Fleminger Dalton and Standage (1977), which used different combinations of mixed-handedness categories. An odd definition of mixed-handedness in the latter study led to a ridiculous categorisation of control subjects; less than 50% of them were categorised as right-handed. These studies however had to be reanalysed (Taylor et al., 1982b) to assess the impact of essentially arbitrary definitions of mixed-handedness. Another problem associated with Annett's handedness classification is the effect of post-hoc classification (Bishop, 1990a,c) of study outcomes. If a broad classification does not provide a significant result (e.g. prevalence of mixed-handedness in patients as compared to controls), someone might be tempted to adjust criteria for the classification of handedness by using a narrow definition (Orr et al., 1999; Browne et al., 2000). Finally, Annett's classification of handedness lacks an independent validation, possibly due to use of the little-known association analysis. Association analysis was among the first statistical classification techniques developed by botanists (Williams & Lambert, 1959) as a method for classification of vegetation. On one occasion, Williams and Ferguson (1982) acknowledged that the first variant of the model "was not quite accurate", that explanations for the model were "unsound" (p. 16), and that the chi-square model should be replaced. The choice of this analysis, in spite of several other well-developed clustering procedures, is a likely reason why Annett's classification study has never been replicated. The introduction of another classification system, a four-way statistically based classification of hand preferences (Peters & Murphy, 1992), failed to attract investigators in schizophrenia research.

One of the most appropriate statistical analyses for dealing with multiple and discrete manual activity responses to identify an optimal number of handedness subtypes is the analysis of latent structures[1] (Lazarsfeld, 1950), which evolved later into latent class analysis. The essence of latent class analysis is a reduction of a manifest heterogeneity in the observed data to a smaller number of latent structures.

Latent class analysis was used for the second study of this thesis (Dragovic, 2004a) to examine the latent structure of handedness and to determine cut-offs for the Edinburgh Handedness Inventory on the basis of statistical criterion. The latent structure of handedness included only one mixed-handed subtype in addition to the left and right subtypes, which is in contrast to Annett's classification of handedness. No more than one intermediate handedness category was required statistically to accommodate the various mixed-handedness patterns. The cut-offs for classification of handedness which 'best' separate mixed-handers from those who are consistently lateralised are neither narrow nor broad, reducing thus a misclassification of cases. The problem with narrow criteria for mixed-handedness is exclusion of individuals with marked inconsistency in hand preferences, while the problem with criteria for mixed-handedness that are too broad is inclusion of individuals with only slight inconsistency in hand preference. This is exactly where the problem with Annett's classification of handedness occurs. In practice, researchers (see Figure 3.12) use criteria that are either too narrow or stringent for classification of mixed-handedness (Annett's classes 5 and 6) or too broad and over inclusive (Annett's classes from 2 to 7).

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[1] Interestingly, the analysis of latent structures originates from attempts to assess attitudes of the USA military personnel during WW II. Paul F. Lazarsfeld demonstrated and formulated a theory of latent structure models in Volume 4 of *The American Soldier* (1950). However, his refined textbook *Latent Structure Analysis* (1968) has become a standard reference.

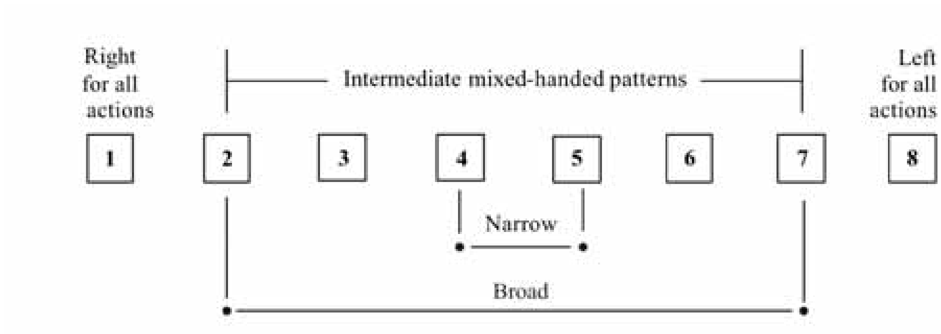

Figure 3.12 Annett's classification of handedness based on association analysis

An additional confirmation for the proposed cut-offs for the Edinburgh Handedness Inventory in the second study was obtained by comparison of proportions of mixed-handed individuals using this cut-off with proportions provided by studies which used hand preference demonstration tasks. Demonstration tasks are widely believed to be more valid assessments of hand preferences than self-report. More importantly, a good agreement was observed between the self-report and demonstration tasks assessment using the same instrument, the Edinburgh Handedness Inventory. This finding supports the validity of the Edinburgh Handedness Inventory. Eliciting hand preference responses by using the Edinburgh Handedness Inventory is sufficiently reliable and provides estimates consistent with the time-consuming demonstration tasks. The Study 2 clearly illustrates that the Edinburgh Handedness Inventory can be safely used for collecting hand preference data and classifying them into handedness categories.

Another important question raised by this thesis is the existence of a meaningful relationship between diminished hand dominance and schizotypy as an attenuated phenotype of schizophrenia. For the purpose of this study, a sample of 353 randomly selected participants from the general community was obtained in addition to subjects from the Western Australian Family Study of Schizophrenia. Schizotypy was assessed using the Schizotypal Personality questionnaire (Raine, 1991), whereas handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Thus, we were able to concurrently investigate the relationship between schizotypal personality traits and mixed-handedness in four samples: three samples comprising unaffected individuals, and a sample of schizophrenia patients. It is believed that mixed-handedness is associated with schizotypal personality in the same way as it is associated with some clinical symptoms in schizophrenia (for review see Satz & Green, 1999). This question was specifically addressed by using a large sample (N = 353) of randomly selected individuals from the general community. In addition, several complementary samples were drawn from the WAFFS to test the hypothesis that this association is related to genetic liability to schizophrenia: (a) screened volunteers for the presence of history of psychiatric disorders, organic brain disease or substance use disorder ('super healthy' control subjects), (b) schizophrenia patients, and (c) their first-degree biological relatives. The major finding in this study was the lack of association of mixed-handedness and psychosis-proneness, which is in sharp contrast with both findings and interpretations of this relationship in the literature.

The general rationale provided in the literature is that schizotypy, as an attenuated schizophrenia phenotype, should be associated, though mildly, with various cognitive deficits and other abnormalities as in overt schizophrenia (Chapman & Chapman, 1987; Kim et al., 1992). Furthermore, it has been claimed (Claridge et al., 1998; Gregory et al., 2003) that the handedness-schizotypy association is clearer and more consistent in those who are prone to psychosis than in those who are already psychotic. However, there are several problems with this uncritical claim and they are discussed in details in the third study. The major problem stems from the psychosis proneness concept, which takes a high score on a paper-and-pencil schizotypy questionnaire as sufficient to identify those with an increased liability to schizophrenia.

In third study we have argued that such a relationship is unlikely unless several core issues are solved. Firstly, a hard-and-fast proclamation of individuals as prone to psychosis cannot be justified by using a single self-administered questionnaire, as it appears invalid (Kendler et al., 1989; Catts et al., 2000). Secondly, little research has been done to corroborate or to refute this hypothesis by using randomly selected samples from the general community instead of convenient student samples. Raine (1991) himself, the author of the Schizotypy Personality Questionnaire, noted that the student population usually gives results incompatible with the general population. Thirdly, the use of various definitions for mixed-handedness can be questioned, as there is no wide agreement as to its boundaries. For example, by varying the cutoffs along the handedness distribution continuum it is possible to extract different subsets of 'mixed-handed' individuals. Finally and most importantly, schizotypy is unlikely to be a homogenous condition with invariable clinical characteristics, single aetiology, and stable over time. There are at least two broad schizotypy syndromes (Tsuang et al., 2002b), labelled as negative and positive to parallel distinct sets of clinical symptoms in schizophrenia. Whereas negative schizotypy shares abnormalities similar to those in schizophrenia and is more frequently observed in biological relatives of schizophrenia patients, positive schizotypy may be unrelated to psychosis. However, positive schizotypy (e.g. magical ideation) is much easier to detect by self-administered questionnaires (Kendler et al., 1995; Kendler et al., 1996). In conclusion, research on atypical handedness-schizotypy relationship is based on two premises which may not be true. First, the claim that a high score on paper-and-pencil questionnaire warrants proneness-to-psychosis status, and second, that atypical lateralisation of hand preferences is necessarily a symptom of neurodevelopmental pathology.

To investigate additionally the handedness-schizotypy hypothesis, a simple yet potentially useful index indicating the level of inconsistency of hand preferences was developed (See study 3). This index ranges from 0, when participants display consistent preferences for all items on the Edinburgh Handedness Inventory, to 1 when participants indicate equal preferences for each item. The later possibility is however highly unlikely though possible, describing an individual who shows equal preferences for both left and right hand for writing, drawing or throwing. In the study presented in third study we found that correlation between cognitive-perceptual schizotypy factor and index of inconsistency was in range from 0.02 (in the sample of screened, 'healthy' volunteers) to 0.22 (in the sample of schizophrenia patients). The results from this study suggest that this association (if present at all) in the general population is trivial.

Several collateral findings of the third study are of interest. Firstly, the relationship between mixed-handedness and schizotypy was not found in controls, but was in the group of schizophrenia patients. Mixed-handed schizophrenia patients had significantly higher scores on the cognitive-perceptual factor than left- and right-handed patients with a modest effect size. Interestingly, mixed-handed siblings of schizophrenia patients also had increased scores on this factor. Although the effect size was similar to that in their affected family members, the difference in mean scores was not big enough to reach statistical significance, perhaps due to the relatively small sample of siblings. The sample of unaffected siblings might have represented a biased selection of the sibling population, comprising mainly siblings with minor psychiatric problems. It is also possible that siblings have developed a 'defensive' response set, denying the presence of 'odd' symptoms that characterise their affected family member. Inclusion of more siblings from the available sibling population and use of comprehensive, an interview-based assessment of schizotypal personality would certainly provide an additional insight on a delicate relationship between lateralisation of hand preferences and liability to schizophrenia.

The second important finding was that the prevalence of mixed-handedness in four samples (screened volunteers, randomly selected participants from the general community, unaffected siblings, and schizophrenia patients) parallels an increase in the genetic liability to schizophrenia. The lowest prevalence of mixed-handedness was observed in screened, 'super healthy' controls, followed by a slight increase in the community sample, then in unaffected siblings of schizophrenia patients, being the highest in affected family members.

To conclude, proneness to psychosis, determined on the basis of self-administered questionnaires in the general population, is a weak indicator of liability to schizophrenia and unlikely to be associated with atypical lateralisation of hand preferences. An impression is that a benign variation of hand preferences in the general population such as left- or mixed-handedness is too readily interpreted as a clear pathological sign or neurodevelopmental abnormality. In addition, mixed-handedness is considered to be associated with schizotypal personality in the general population in the same manner (e.g. Kim et al., 1992) as the relationship between mixed-handedness and 'positive' symptoms such as thought disorder in schizophrenia patients (see Manoach, et al., 1988; and Manoach, 1994). The acceptance of these premises and exploiting a simple analogy with schizophrenia, however, might have resulted in discovery of, most likely, a spurious and inconclusive association between mixed-handedness and scores on schizotypal personality questionnaires.

In a recent study, analysing the handedness of Leonardo da Vinci (famous renaissance artist, also known as the most renowned left-handed individual to date), McManus and Drury (2004) have suggested that handedness can not be fully grasped by measuring direction or degree of *handedness* only. They concluded that, after drawing a complex path-analysis like diagram comprising regression coefficients between various items from a newly developed handedness questionnaire, that responses on various preference items cannot be simply “lumped together into a single laterality index” (p. 7). If inter-relationships between presumably valid measures of someone’s handedness are so complex, then the inter-relationships between all other behavioural laterality measures combined into a composite phenotype are even more intricate. It would be wrong to assume that popular laterality measures such as handedness fully represent all other behavioural asymmetries. As behavioural asymmetries are interrelated (Gur, 1977; Bryden, 1997; Papousek & Schulter, 1999; Corballis, 1997) and sometimes claimed to be associated with specific cognitive processing, we performed multivariate data analysis as a part of a model-building process. The primary objectives of the study presented in Study 4 were to identify laterality phenotypes in schizophrenia patients by using some methodological refinements and to assess cognitive and clinical measures in different phenotypes.

Is atypical behavioural lateralisation, indexed by several laterality measures, associated with cognitive dysfunction? In contrast to studies using samples of healthy people, which generated a mixed evidence for this relationship, studies on patients with schizophrenia are far more consistent in this regard. Five investigations reviewed in Introduction (Katsanis & Iacono, 1989; Faustman et al., 1991; Tyler et al., 1995; Hayden et al., 1997; Bilder at al., 2000) were consistent by showing that left-handed patients generally under-perform on various cognitive measures compared to right-handed patients. This suggests that the pathology of brain asymmetry is related to cognitive dysfunction in schizophrenia. In the fourth study of this thesis a weak cognitive deficit was also observed in the two non-right laterality phenotypes, being somewhat more prominent in the ‘left’ subtype. The effect size of the cognitive deficit in the ‘left’ subtype is small however, but the direction of association was consistent with other studies. It does not seem unreasonable to conclude that a nontrivial proportion of schizophrenia patients owe their condition to a atypical lateralisation of brain functions. In addition to a slight cognitive deficit, the ‘left’ and ‘mixed’ subtypes were characterised by a more severe course of illness than the ‘right’ subtype. In contrast, atypical handedness subtypes in their siblings and controls showed no systematic relationships with cognitive performance.

Frequencies of subjects unaffected with schizophrenia assigned to each laterality subtype (Table 3.21) are nearly identical to percentages of individuals with ‘anomalous’ dominance (Geschwind & Galaburda, 1985) and percentages of consistent right-handed individuals according to the Right Shift Theory (Annett, 1985, 2002a). This is also remarkably consistent with a reported distribution of handedness in primates (Hopkins & Leavens 1999), suggesting that GoM modelling reveals a underlying bias inherent to a wide range of asymmetries, including nonhuman species. In contrast to healthy controls and unaffected siblings, more than half of the schizophrenia patients (57%) were not consistently right sided, supporting the suggestion that “phenotypic variation in behavioural lateralisation is more extreme in psychopathology” (Markow, 1992, p. 303).

Table 3.21 Comparisons of distributions in siblings and controls versus distributions based on two theoretical models were non significant

Model	Classification	%
Annett, 1985	Non-right	37
	Right	63
Geschwind & Galaburda, 1985	Anomalous	35
	Standard	65
GoM, *siblings*	Non-right	36
	Right	64
GoM, *controls*	Non-right	35
	Right	65
GoM, *patients*	Non-right	57
	Right	43

Inadequate characterisation of the laterality phenotypes may be the most important limitation in the identification of genes causing left-right asymmetry in humans. All genetic studies to date (Francks et al., 2002, 2003a, 2003b; Agtmael, Forrest, & Williamson, 2001, 2002) have used hand skills as a description of the phenotype. Restriction of the laterality phenotype to a single and isolated measure such as hand dominance results in its incomplete characterisation, and may be enriched by inclusion of other related laterality measures including various familial cofactors.

One additional issue that has to be considered is the heterogeneity of the schizophrenia syndrome. A theoretical perspective maintained since Bleuler coined the term schizophrenia is that this syndrome is more likely a group of various and heterogeneous conditions than a single entity (Andreasen, 1997). Individual differences in lateralisation among schizophrenia patients might eventually help in distinguishing various schizophrenia subtypes. The two complex schizophrenia phenotypes identified in the Western Australia Family Study of Schizophrenia were not equally associated with laterality measures (Hallmayer et al., 2003); schizophrenia patients assigned to the deficit schizophrenia syndrome were more non-right-handed than patients assigned to the non-deficit syndrome. Since the first report from the WAFFS on distinct schizophrenia phenotypes was published, a number of new families have been obtained and future work will examine a generalisibility of this finding. The most current state of the available evidence (Jablensky et al., 2004), including 112 families (number of individuals = 388) with one or more family members affected with schizophrenia, also suggests that non-right-handedness in schizophrenia patients is even more solidly associated with the deficit type of schizophrenia than previously thought.

At present, a firm conclusion as to genetic and environmental causation of atypical handedness in schizophrenia patients cannot be made. It appears that both factors are implicated. The 'left' laterality phenotype was characterised by a greater clinical severity (earlier age at onset and longer hospitalisation) and more obstetric complications than the 'right' phenotype. However, gender differences in the age at onset of schizophrenia are disputed (Jablensky & Cole, 1997) on the basis that the gender effect is confounded by marital status. The clinical profile of the 'left' subtype is consistent with neurodevelopmental hypothesis of schizophrenia (Weinberger, 1995) and resembles the 'neurodevelopmental' type of schizophrenia (Murray et al., 1992), while the associations of mother's left-handedness with the 'left' phenotype and father's left-handedness with the 'mixed' indicate a specific familial effect, which might be either genetic or environmental.

Several outstanding issues will be specifically addressed in future research. Firstly, inclusion of as many siblings as possible in the WAFFS will help to assess a likely bias associated with the current small sample of siblings. Secondly, further collection of information on obstetric complications from key informants will help to evaluate the hypothesised association of pregnancy and birth complications with a greater confidence. Finally, new statistical procedures such as the mixed-models technique will be used to avoid a possible impact of intrafamilial covariation in various laterality measures. Statistically, mixed models are an extension of ordinary linear models by adding random effects, which can account for subject heterogeneity, sample clustering or intrafamilial covariation, omitted explanatory variables, and measurement error. Intrafamilial covariation was the rationale for using only one patient, one sibling, and one control subject per family for the grade of membership modelling.

The last study in this thesis was purely psychometric and aimed to illustrate that the measurement of hand preferences can be substantially improved and to highlight an additional direction for the future work (Dragovic, 2004b). The association of handedness with cerebral lateralisation can be investigated appropriately if problems with measurement and classification of handedness are resolved, and if the relationship between observed preference and performance is determined. Although handedness appears dichotomous at the first glance, it cannot be simply classified and the prevalence of left- and right-handed individuals cannot be easily estimated since there is no widely accepted consensus as to its measurement. Even the most common, though insufficient classification on the basis of writing hand, yields various prevalence rates across various populations and over time. Using only one item such as writing hand can pose a problem for classification since some individuals who write with right hand throw with the left hand and vice versa (Gilbert & Wysocki, 1992; Perelle & Ehrman, 1994). Inclusion of more than one item in measurement of handedness can certainly resolve the dilemma of how to classify handedness in individuals discordant for manual preferences, but it is not without problems as various items contribute unequally to the construct of handedness. It has been demonstrated in the last study of this thesis that the original, 10-item version of the Edinburgh Handedness Inventory comprises a few items which are a poor indication of the latent construct. The measurement properties of this instrument were substantially enhanced by their exclusion. The use of less commonly used hand preference items today such as use of broom or striking matches is no longer justified. New items such as the use of a computer mouse should be considered for inclusion in any standard handedness inventory. One of advantages of the using-computer-mouse item over some rarely exercised manual activities such as striking matches is that manipulating a computer mouse is becoming a widespread manual activity in the general population. Everyday observation suggests that people use computer mouse more frequently than they hold a hammer, or tennis racket. A revised version of the Edinburgh Handedness Inventory should be used instead of its original form, if not replaced with an entirely new handedness inventory.

8.1 Concluding comments

Advances in measurement, classification, and conceptualisation of handedness are prerequisites for further progresses in laterality research. Until these issues are solved and conclusions accepted by the research community, the relationships between handedness and other neuropsychological variables need to be cautiously considered and interpreted. The association between mixed-handedness and schizotypal personality is perhaps the best illustration how the two disparate phenomena can unexpectedly converge. One reason for caution is the potential impact of cultural factors on phenotypic expression of handedness, and in turn on handedness classification. Apart from the cultural factors there are some other outstanding theoretical issues which, when answered, might have an immense effect on future laterality research. Is a single laterality measure such as handedness a sufficient substitute for all other indices of lateralisation? During the last three decades the majority of laterality studies in schizophrenia were concerned with investigation of single laterality measure, handedness in particular. At present, there is no definite answer to this question, although the fourth study presented in this thesis showed that the complex modelling of multiple and various indices of lateralisation provides new and meaningful insights. Firstly, it has been demonstrated that the leftward shift in schizophrenia involves both reductions of lateral preferences and increases in left-sidedness, rather than merely an increase of mixed-handedness (Satz & Green, 1999). The finding from this study is consistent with previously discussed conclusions based on quantitative review of evidence. Secondly, the multivariate integration of laterality measures and familial cofactors into composite laterality traits may provide a more refined tool for further research into the genetic, developmental and environmental underpinnings of behavioural and cerebral lateralisation.

Another and perhaps heretic question concerns the real nature of handedness. Is handedness a continuous trait or not? The two leading authors in laterality research still fiercely defend contrasting perspectives. Whereas Annett (1985) believes in the handedness continuity, McManus (2002) postulates the opposite position, maintaining a view much closer to the conventional wisdom, where people are usually unmistakably either left- or right-handed. At present, there is no definite answer to this question, although the most of work presented in this thesis used handedness as a qualitative entity. Ironically, the vast majority of laterality researchers first tend to acknowledge the continuous nature of handedness, and then treat it exclusively in categorical terms.

Can handedness serve as a robust vulnerability marker to schizophrenia? A view presented in this thesis is that it currently cannot, at least with the present small subset of siblings included in this investigation. The primary requirement of a genuine marker for any disease is its high prevalence in affected individuals and low prevalence in people with other disorders, and in healthy people (Heinrichs, 2001). Its specificity to schizophrenia relative to other disorders and presence in biologically related but unaffected relatives would make a vulnerability marker additionally useful. By the same token, occurrence of the same marker in other illnesses makes such a marker less specific to schizophrenia. At present, two factors act against handedness as a robust marker: (a) long list of various conditions other than schizophrenia which are associated with atypical handedness (see Table 1.4), and (b) atypical handedness is weakly present the first-degree relatives of schizophrenia patients. Several studies (Clementz et al., 1995; Cannon et al., 1997; Toommey et al., 1998; Bryne et al., 1999, 2004) have failed to detect a significant increase in either left- or mixed-handedness in biological relatives of schizophrenia patients. Thus, the majority of available evidence does not support a few sporadic claims (Orr, 1999; Crow, 1999) that a similar shift in the handedness distribution is present in unaffected and biologically related individuals. As both current and future recruitment of the first-degree relatives of schizophrenia patients within the Western Australia Family Study of Schizophrenia may potentially increase the proportion of atypically lateralised yet unaffected family members, this exciting hypothesis will be carefully pursued. The current state of the available evidence certainly warrants a large-scale epidemiological research on this topic.

Direct investigation of functional brain lateralisation in relation to the manifest behavioural asymmetries in schizophrenia patients will provide more definite answers as to specific patterns of cerebral functional organisation in left-, mixed-, and right-handed patients. Currently, there are no such studies on the population of schizophrenia patients. Numerous fMRI studies conducted on schizophrenia patients are concerned with handedness only as a secondary, nuisance, variable that has to be controlled. The advent of sophisticated and non-invasive technologies during the 1980s and 1990s has enabled a non-invasive approach to the assessment of language dominance and its relationship with handedness. One of the most elegant and cost effective methods for determining cerebral dominance for language is functional transcranial Doppler sonography (fTCD) which is increasingly used in both clinical and research settings, and appears as the promising way for future studies of anomalous language dominance in schizophrenia patients.

Finally, the accumulation of detailed laterality data from schizophrenia samples across different cultures will allow powerful and fine-grained analyses addressing various issues such as sex differences, ageing and laterality, and genetics of handedness. These will provide additional clues to the aetiology of schizophrenia (eg. the putative role of the process of establishing cerebral asymmetry) and may serve as co-indicators of severity of illness or indicators of risk (with other measures such as questionnaires of mental states) to develop psychosis. An international collaboration and data sharing appears as necessity for the full progress in laterality research.

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