Review of Psychology,
2008, Vol. 15, No. 1-2, 45-56 UDC 159.9

A joint occurrence of atypical behavioral lateralization and schizophrenia: coincidental or causative?

MILAN DRAGOVIC and GEOFF HAMMOND

The association between atypical lateralization of hand preferences (still a stigmatized behavioral trait in some cultures) with schizophrenia has been studied over the four last decades, repeatedly showing an increased incidence of atypical lateralization of hand dominance in this population. However, no final verdict on the causal direction between these two phenomena has been given. Atypical hand preferences, at the phenotypic level, have been subject to diverse classifications – commonly as left-handedness, but increasingly often as 'non-right-handedness', a 'pooled handedness' category made of two more homogeneous classes, and finally 'left- and mixed-handedness'. Research has identified many associations of atypical lateralization of hand preferences with structural and functional brain asymmetries, cognitive performance, and clinical features in the population of schizophrenia patients. In this article, we critically appraise this work and suggest that both complex phenotypes, atypical lateralization of hand dominance and schizophrenia, most likely have common neurodevelopmental and genetic origin.

Key words: schizophrenia, laterality, handedness, left-handedness, mixed-handedness

Human hands are architecturally symmetrical, yet distinctly different in their functional abilities. This seemingly unique human tendency to use the right hand rather than the left for fine motor function is observed in ~90% of the human population. The remaining ~10% are atypical (i.e. left-handers). In addition to clearly visible hand dominance in humans, there are other behavioural lateralities such as foot or eye dominance, but these have not attracted as much scientific scrutiny as hand dominance. Left-handedness is commonly associated with reduction of brain asymmetries, most notably in brain areas related to language. The general finding, irrespective of the technique used (invasive, such as the intracarotid sodium amytal test; non-invasive, such as transcranial Doppler sonography), is that a large proportion of right-handed individuals have language localised in the left hemisphere, with only a small proportion having the same faculty ipsilateral to the dominant hand. Although the majority of left-handers have language localised in the left hemisphere, just as right-handers, a much larger proportion of left-handers display either bilateral or right hemispheric representation of language. This association of handedness and brain asymmetries for language is likely to have genetic aetiology (Geschwind, Miller, DeCarli, & Carmelli, 2002). Although genetic factors, modified by environmental influences, are most likely involved in the inheritance of handedness, the gene for handedness is yet to be identified (Agtmael, Forrest, & Williamson, 2001, 2002).

In addition to genetic models, several other theories have been proposed to explain the origin of handedness and the mechanism of inheritance. Roughly, those theories can be divided into two groups: first, those which consider both left- and right-handedness as neutral and benign variations (e.g., Annett's Right Shift theory, 1985; McManus, 1985), and second, those which consider that right-handedness is the norm, with departure from the norm due to some pathology (e.g. Bakan's Birth Stress model, 1973). In these two groups of theories, the former usually try to explain the distribution of handedness in families and likely mode of inheritance, whereas the latter aim to describe the risk factors 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.

The distribution of hand preferences appears to be truly taxonic (McManus, 1985; Dragovic, Milenkovic, & Hammond, 2008), with a tripartite structure made up of two major classes of hand preference (left- and right-handedness), and a smaller class made up of individuals showing mixed handedness.

Milan Dragović, Centre for Clinical Research in Neuropsychiatry; School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Private Mail Bag No. 1, Claremont, WA 6910, Australia. E-mail: milan.dragovic@uwa.edu.au (the address for correspondence);

Geoff Hamond, School of Psychology, The University of Western Australia.

The elevated incidence of atypical lateralization of hand preferences (left-handedness, mixed-handedness, or both classes combined as non-right-handedness) in some clinical conditions such as autism (Hauck & Dewey, 2001) and dyslexia (Richardson, 1994) suggests that non-genetic as well as genetic factors act to determine handedness, and that non-genetic factors might interfere with neurodevelopment and cognition. An increased incidence of left-handedness above the population rate is also found in epilepsy (e.g. Lewin, Kohen, & Mathew, 1993), low birth weight infants (O'Callaghan, Burn, Mohay, Rogers, & Tudehope, 1993), Rett syndrome (Umansky et al., 2003), and even in those exposed to prenatal ultrasound (Kieler, Cnattingius, Haglund, Palmgren, & Axelsson, 2001). Among the clinical groups, schizophrenia patients are also consistently characterised with a high incidence of atypical hand dominance (Dragovic & Hammond, 2005). Although left- and mixed-handedness are clearly a hallmark of many neurodevelopmental disorders, they are not pathognomonic.

In this article we will review the literature on atypical behavioural lateralization in schizophrenia. We will start from epidemiological perspective to quantify the extent of this phenomenon in this population. We will then go on to explore whether this phenomenon is associated with particular neuroanatomical structures and with particular brain functions. Finally, we will examine the links of this atypical lateralization with clinical features and demographic variables in the population of schizophrenia patients.

Atypical lateralization in schizophrenia

Does the prevalence of atypical lateralization in patients differ from that in healthy people?

Quinan (1930) was the first to point out the potential importance of the relationship between of atypical lateralization (at that time labeled usually as sinistrality) and psychosis (dementia praecox), but his research effort was ignored over the next four decades. Research on psychopathology and laterality was restarted by Flor-Henry's (1969) seminal study of epileptic psychosis which showed a left-hemispheric dysfunction in schizophrenia and right-hemispheric dysfunction in affective psychosis. Oddy and Lobstein (1972) were the first to revisit Quinan's ideas and re-explore if the distribution of handedness in schizophrenia patients was atypical. Interestingly, their study coincided with both the revival of interest in structural brain changes in patients with schizophrenia (Johnstone and colleagues published the first study on ventricular dilatation in schizophrenia patients using CT scan technology in 1976) 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 showed that hand and eye dominance distributions measured separately resembled those of control subjects. However, when these two factors were combined and considered for crossed dominance (e.g., right hand but left eye dominance) the schizophrenia patients showed significantly higher incidence of crossed dominance. In retrospect, one could conclude that this particular study triggered laterality research in schizophrenia, particularly that on handedness. 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 lateralization with psychosis was summarized in the book Hemisphere Asymmetries of Function and Psychopathology (1979; edited by Gruzelier & Flor-Henry), specifying that there were distinct differences between schizophrenia (characterized by left-hemispheric dysfunction) and bipolar disorder (characterized by 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 were not included in this review.

Studies which specifically investigated handedness in the population of schizophrenia patients can be divided in two main groups: (i) studies of prevalence of atypical lateralization and hand preference in schizophrenia patients; and (ii) studies exploring neuroanatomical, cognitive, and clinical correlates of anomalous handedness in schizophrenia.

Reviews of the empirical evidence of atypical hand preference lateralization in schizophrenia patients are relatively infrequent compared to reviews of other research domains in schizophrenia such as neuroimaging and neurocognitive studies. To date four reviews of the evidence have been conducted; two qualitative reviews by the same authors (Green, Satz, Smith, & Nelson, 1989; Satz & Green, 1999), and two quantitative (Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001; Dragovic & Hammond, 2005). 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, relative to healthy controls, schizophrenia patients are characterized by an increase in mixed-handedness, i.e., an attenuation of clear hand dominance. A similar conclusion was drawn ten years later by Satz and Green (1999), after reviewing 23 studies (16 of which were included in the previous review with 7 new studies) and counting again the overall box score outcomes (i.e. significant versus non-significant studies). The fact that diverse findings have been reported without rigorous quantitative evaluation of the evidence has led some researchers to conclude that laterality

studies themselves do not provide sufficient evidence for a significant shift in direction of hand preference in schizophrenia patients (Gruzelier, 1981; Flor-Henry, 1983; Gruzelier, 1999). In contrast to qualitative reviews, Sommer et al. (2001) concluded (based on meta-analysis) that schizophrenia patients are more frequently non-right-handed than healthy individuals. Although the authors used an adequate statistical procedure to assess the empirical evidence, their interpretation of the results is limited since they have conceptually equated two distinct handedness classes by pooling exclusive left-handed and exclusive mixed-handed individuals in the non-right-handed category. Dragovic and Hammond (2005) have conducted the most comprehensive review of empirical evidence. They analysed empirical evidence from 40 different studies published in the period from 1965 to 2004 and showed, similar to the conclusions of Sommer et al. (2001) that membership of each atypical handedness subtype identified, exclusive left-handedness, mixed-handedness, was in significant excess in schizophrenia patients compared to control subjects. In this report, the authors also argued that the methods of assessing handedness are an important source of heterogeneity of results in the published surveys, and that the two major questionnaires (the Edinburgh Handedness Inventory and Annett's handedness questionnaire) generated incongruous findings.

'Atypical' lateralization and brain structures in schizophrenia patients

There are a number of studies which have reported on structural macroscopic and morphological deviations of the brain in schizophrenia patients, consistently indicating departures from the 'normal' brain including: (1) ventricular dilatation (Wright et al., 2000); (2) reduced brain size and cortical mass (Lawrie & Abukmeil, 1998; Harrison, 1999; Wright et al., 2000; Collinson et al., 2003); and (3) reduced or reversed anatomical asymmetry of the planum temporale, Sylvian fissure, superior temporal gyrus, and temporal horn of the lateral ventricle (often described as a 'counterclockwise torque'; Crow, 1990; Berlim, Mattevi, Belmonte-de-Abreu, & Crow, 2003). This last finding, accompanied by a failure to establish lateralized language dominance, is considered by Crow (1990, 1993, 1997a, 1997b) to be 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 argued that this abnormality is not specific to schizophrenia as it has also been identified in patients suffering from other mental disorders, and it is sometimes present in normal comparison subjects. It is unlikely that schizophrenia is a "disorder of cerebral ventricles" (Jones, 1997, p. 144), and the exact neurobiological meaning of ventricular dilatation for either the aetiology or the consequences of schizophrenia remains unclear. Whereas some researchers such as Crow et al., (1989), 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 hand dominance in schizophrenia patients. Importantly, all of them (Andreasen, Dennert, Scott, & Damasio, 1982; Katsanis & Iacono, 1989; Satz, Green, Bartzokis, Bledin, & Vaclav, 1990; Clementz et al., 1994; O'Callaghan et al., 1995) came to the conclusion that left- and mixed-handed schizophrenia patients tend to have larger ventricular-to-brain ratios than the right-handed patients. In the first study of this type, Andreasen and colleagues (1982) used computerized tomography (CT) scans and found that a sample of left-handed schizophrenia patients had a significantly larger ventricular-brain ratio than a sample of 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 than 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. On the basis of hand preferences, twenty-five schizophrenia patients were divided into non-lateralized (i.e. switching preferred hands for the same item) and lateralized (i.e. 'consistent' right hand preferences) groups and compared with age-, gender-, and race-matched controls on several brain measures. Results revealed that both lateralized and non-lateralized patients had a significantly smaller left hemispheric volume than controls, and that non-lateralized patients had a significantly larger left than right ventricular-brain ratio. Lateralized patients and controls were similar in this regard. Since non-lateralized patients did not differ from normal controls on the size of lateral ventricles and the size of brain hemispheres,

but showed significant bilateral asymmetry (left > right), a bilateral neuroanatomical substrate was proposed as responsible for the leftward shift in the handedness distribution. 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. Clementz et al. (1994), which investigated the relationship between handedness and bilateral ventricular enlargement, 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, but not the females, had enlargement of both left and right ventricles.

Although almost all studies have found that left-handed schizophrenia patients show a diffuse bilateral ventricular enlargement, the interpretation of such abnormalities as being causally and specifically associated to atypical handedness (as proposed by Satz et al., 1990) is difficult to accept because such an association does not necessarily assume causality. As mentioned previously, ventricular enlargement is not specific to schizophrenia and, importantly, is correlated with the number of demographic (socioeconomic status, diet, age, gender), clinical variables (negative symptoms, perinatal abnormalities, poor outcome, response to neuroleptic drugs), cognitive impairments, and (to complicate further) o handedness. From such situation, where everything-is-correlated-to-everything, it is difficult to select a single association and pronounce it a casual relationship, as in fact, Satz et al. did (1990). Although complicated, this association between hand dominance and this particular brain structure merits more further research.

Reduction of 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 that that the level of cerebrospinal fluid (CSF) is increased in schizophrenia patients, implying 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). The 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 than normals (a 2% decrease; Wright et al., 2000). Apart from these equivocal findings, which sometimes suggest a small 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 the 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 et al., 1997; Sommer et al., 2001), has been developed into a prominent theory by Timothy Crow, according to which schizophrenia, cerebral asymmetries, language lateralization, and handedness are linked to each other and to a single gene (Crow, 1989; Crow, 1997b; Crow, 2004a). In 1990, Crow elaborated this theory by providing various pieces of evidence supporting his view that schizophrenia results from an anomolous 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 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, morphologi-

cal 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 lateralization. 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 lateralization of handedness. Reduced functional lateralization of the motor cortex (Bertolino et al., 2004) and atypically lateralized patterns of cortical responses to cognitive tasks (Kircher et al., 2002; Sommer, et al., 2003; Walter et al., 2003) suggest a possible relationship between lateralization 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 first, that cerebral lateralization was delayed in children who later developed schizophrenia (Crow, Done, & Sacker), and second, that cognitive abilities were less developed in children who were less lateralized in hand skill (Crow, Crow, Done, & Leask, 1998).

Does 'atypical' lateralization affect cognition?

The association of cognitive performance and atypical behavioural lateralization in schizophrenia patients is less elusive than in healthy people. 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, found 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, & Newcomer (1991), a statistically significant association between cognitive deficit and left-handedness was 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 than right-handed patients. In many ways this study replicated and extended the results reported by Katsanis & Iacono (1989).

In a large study comprising data from 686 schizophrenia patients, Tyler, Diamond and Lewis (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 fewer years in education than left- and right-handed patients. Taken together, all these findings further indicate that atypical handedness is consistently associated with impaired cognitive and social functioning of schizophrenia patients.

Hayden, Kern, Burdick, and Green (1997) have found that people exhibiting another type of inconsistent hand preferences, either ambiguous handedness or a subtype of mixed-handedness characterized by within-task hand preference inconsistency, performed more poorly on the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) than consistent 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 also responsible for ambiguous handedness. Although this study can be criticised on the ground that a number of non-schizophrenic patients were included in the study, its results are nevertheless consistent with previous studies in showing a clear association between atypical handedness and neurocognitive profile.

More recently, Bilder at al. (2000) compared groups of right-hand dominant and non-right handed patients, with non-right-handedness 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 non-right patients. 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 lateralized hand preferences. In other words, the overall cognitive impairment of non-right handed patients as a group was due to poor performance of patients

who were consistently left-handed, but not due to performance of those who display inconsistent hand preferences. In line with previous studies, which examined the association between cognitive performance and atypical hand preferences, Norman, Townsend, and Malla (2001) reported that left-handed first-episode patients performed more poorly than right-handed patients on several neurocognitive measures such as speed of information processing and visual and auditory memory.

In conclusion, the evidence that 'atypical' lateralization of hand is associated with cognitive performance of schizophrenia patients is more or less consistently found, with non-right handed patients displaying 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 generalization. The studies reviewed differ in their 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) argue that left-handedness is associated with poorer cognition compared to right-handedness in schizophrenia patients. Nevertheless, all studies used only one behavioural index of lateralization – handedness, and none of them has investigated the effect of different manifestations of laterality on cognitive performance of schizophrenia patients.

Clinical and demographic characteristics

The associations of atypical behavioural lateralization 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 lateralization has not been firmly established in spite of the fact that it has been investigated over three decades.

Oddy and Lobstein (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 lateralization indexed by mixed-handedness. The examination of sex differences with regard to atypical lateralization followed shortly. Lishman & McMeekean (1976) in their study also found an increased shift towards 'atypical' hand preferences in young schizophrenia patients. Moreover, they found that left-handed schizophrenia patients have shown a reduce incidence of familial sinistrally compared to right-handed patients. This finding however, which can be interpreted as a strong possibility that, in some cases, left-handedness is more due to adverse environmental events and less due to genetic contribution, has been disputed by Chaugule and Master (1981). Similarly, Shan-Ming et al. (1985) did not find any sex differences, and the shift toward sinistrality was similar in both male and female patients. Oyebode and Davison (1990) 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 have not been consistently observed, e.g., Sperling, Martus and Barocka (1999) reported the opposite findings (i.e. male schizophrenia patients being more non-right-handed than female patients). However, many more studies have observed a trend of greater 'atypical' lateralization in males than in female schizophrenia patients, e.g., Manoach, Maher and Manschreck (1988), Manoach (1994), Manschreck and Ames (1984), Cannon et al. (1995). In a large group of schizophrenia patients (N = 367) from the Western Australia Study of Schizophrenia, male patients are significantly less right-handed than female patients (unpublished results).

The diagnostic relevance of schizophrenia subtypes and handedness was first addressed by Nasrallah, McCalley-Whitters and Kuperman (1982), who stated that only paranoid schizophrenia might be associated with disturbed brain lateralization and loss of clear hand dominance. The results of an earlier study (Luchins, Weinberger, & Wyatt, 1979) are also in line with this finding, suggesting that schizophrenia patients with less severe symptomatology are more left-handed, that is, more likely to display an anomalous brain lateralization. A more recent study by Gureje (1988) also reported that paranoid cases were more likely than non-paranoid cases to be mixed-handed. In contrast, Manschreck and Ames (1984) have reported the opposite: non-paranoid schizophrenia patients were more likely than paranoid patients to display 'atypical' lateral preferences.

Cannon et al. (1995) specifically addressed several clinical correlates of mixed-handedness in schizophrenia. Their major finding is that anomalous of hand preference (defined as mixed-handedness) in schizophrenia patients resembles a neurodevelopmental type of schizophrenia. Evidence supporting this hypothesis is based on the findings that mixed-handed schizophrenia patients were more likely to be male (Cannon et al., 1995), to lack a family history of schizophrenia (Nasrallah et al., 1982; Shimizu & Endo 1985), and to have poor clinical course (Cannon et al., 1995). Clinical severity was determined as more than one year of continuous hospitalization. However, one earlier study (Merrin, 1984), found no significant link between severity of schizophrenic illness (indexed by age at the first hospitalization and total number of hospitalizations) 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, appears to be more consistently linked with left- or mixed-handedness than the others. In so far as formal thought disorder represents disturbed language function, it is likely to be associated with anomalous lateralization. Indeed, Taylor, Taylor, Dalton, and Fleminger (1982) reported that mixed- and left-handed patients are more likely to be thought disordered. However, this was found only for male patients. To the contrary, Taylor and Amir (1995) 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, & Brazo (2002) 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 scores (the sum of 7 items on the Scale for the Assessment of Positive Symptoms, Andreasen and Olsen, 1982) in 71 patients presenting with at least one positive psychotic symptom (hallucinations or delusions) were significantly associated with decreased right-hand preferences. In this study the authors found that decreased lateralization of hand preferences predicted the following three specific symptoms of schizophrenia: (a) the delusion of being controlled, (b) thought broadcasting, and (c) thought withdrawal; i.e, the more left-handed the patient, the higher Schneiderian scores. 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 the prominent clinical symptoms in schizophrenia, this study support a view that the abnormal development of cerebral asymmetry, indexed by hand preference, is part of the hallmark schizophrenic symptoms.

In conclusion, it is not easy to integrate diverse and sometimes conflicting findings on the relationship between atypical lateralization of hand preferences and clinical measures. Sex differences, with male patients displaying 'atypical' lateralization more frequently than female patients, appear to be a relatively stable finding. It is also relatively consistent finding that patients exhibiting decreased behavioural lateralization resemble a neurodevelopmental type of schizophrenia; i.e., displaying cognitive deficits, having a poor clinical course of illness, and being male. The association between diagnostic schizophrenia subtypes and atypical handedness has not been firmly established, as two 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 language related clinical symptoms appears to be more consistently linked to atypical handedness than other symptoms.

SUMMARY

The relationships between laterality and neuroanatomical, neurocognitive, and clinical variables are numerous, sometimes contradictory, and not always easy to integrate in both healthy and clinical populations. The lack of true replication studies, and myriads of sample characteristics (differing age, uneven sex distribution, various treatments, exposure to different medications, diverse clinical presentation, unequal length of illness, etc.) are just a few methodological obstacles that prevent any firm conclusion. Notwithstanding these impediments, 'atypical' lateralization appears to show some relatively consistent associations with neuroanatomy, cognitive performance, and, in particular, clinical variables in the population of schizophrenia patients.

With regard to neuroanatomical measures, the most prominent finding is that left- and mixed-handed patients affected with schizophrenia have larger ventricular-brain ratios. Research on the association between neurocognitive performance and atypical lateralization 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. It appears that there is consistent and solid association between behavioural lateralization and cognitive performance, but the evidence is not overwhelming and is scattered across several studies that can hardly be compared in terms of their methodology. Therefore, this appears as a promising stream in laterality research. The most consistent associations are found between 'atypical' lateralization and clinical presentations of illness. It seems that there is enough evidence to claim that 'atypical' lateralization is more prevalent in a so-called, 'neurodevelopmental type' of schizophrenia. That is, schizophrenia type characterised by impaired cerebral development, poor premorbid adjustment, abnormalities of early motor and cognitive development, and higher prevalence of obstetric adversities. Future studies aiming to test specifically this hypothesis would also appear promising.

Atypical behavioural lateralization in schizophrenia possesses some qualities as a candidate endophenotype in genetic research, it is far from being fully qualified as an intermediate phenotype. On the positive side that support this trait as a potential endophenotype are: its measurability, its independence of illness, and emergence earlier than schizophrenia symptoms. The real setback, however, is that atypical behavioural lateralization is not specific to schizophrenia; numerous studies have identified this abnormality in diverse conditions, making it unsuitable for genetic linkage and genetic association studies in schizophrenia research.

This trait also fails on a criterion which is useful for identifying endophenotypes of complex diseases; namely, that the endophenotype should be found in non-affected family members of patient at a higher rate than in the general population. So far, the laterality literature does not support this criterion.

Atypical behavioural lateralization is however an important factor in schizophrenia research because of its (although subtle and intricate) association with brain structures and functional brain lateralization. Thus, this factor should be regularly considered as a modifying or confounding factor that needs to be carefully controlled for by creating homogenous groups with regard to hand preference or by covarying this trait on dependent measures of interest. It is common practice that fMRI studies are regularly done using only right-handed subjects to avoid the confounding effect of handedness.

Despite the aforementioned limitations and a variety of pitfalls which this trait experiences in schizophrenia research, further research on this intriguing phenomenon is needed. In our view, the most promising area for further development is in the conceptualisation of this trait and its measurement. At present, neither of these aspects is satisfactory. On the conceptual level, the advantages of using hand preference measures in place of hand proficiency measures of behavioural lateralization are uncertain. Teasing apart inherited components of handedness from environmental (cultural) effects on the inherent lateralization of hand preferences is paramount. Personally, we believe that the most intriguing and intuitive approach would be to abandon a single-measure approach to behavioural lateralization and an over-reliance on hand preference distribution based on writing hand. Instead, researchers should focus on biologically and theoretically more plausible distributions of hand preferences. For example, use of handedness classes determined by using various statistical techniques instead of simple classification based on writing hand might be more fruitful. Distributions determined using this taxometric approach show different distributions which are close to the distribution specified by the Geschwind & Galaburda (1985) biological model, and with the distribution of hand preferences specified by the Right Shift theory (Annett, 1985). In addition, instead of using single laterality measures, future research should further explore ways to integrate various laterality indices into single and potentially useful composite endophenotype. So far, only one study has addressed this possibility (Dragovic, Hammond, & Jablensky, 2005). The very poor measurement properties of a few dominant and somewhat obsolete handedness questionnaires has repeatedly been criticised (McFarland & Anderson, 1980; Williams, 1986; Dragovic & Hammond, 2007), but very little has also been done to improve the assessment of this conspicuous trait.

Finally, to answer the question posed in the title of this article, we would like to suggest that the link between schizophrenia and atypical lateralization is certainly causative. However, we also suggest that the increased atypical asymmetries in this population are secondary to the prima facie causes of schizophrenia. By 'causes of schizophrenia,' we mean all the genes involved in its aetiology, as well as complex epigenetic events and/or environmental contributors. The combination of these factors (genetic, epigenetic and environmental), triggers an inexorable cascade of events resulting in this disabling condition approximately two decades later. Instability of early neurodevelopment therefore is most likely to be responsible for increased phenotypic variation of behavioural lateralization in schizophrenia, probably in the exactly same way it is responsible for more pronounced variation of cognitive deficits (e.g. general intelligence, memory, executive functions, attention), or for increased frequency of neurological soft signs and minor physical abnormalities in this population.

REFERENCES

Agtmael, T., V, Forrest, S, M, & Williamson R. (2001). Genes for left-handedness: How to search for the needle in the haystack? *Laterality, 6*, 149-164.

Agtmael, T. V., Forrest, S.M., & Williamson, R. (2002). Parametric and non-parametric linkage analysis of several candidate regions for genes for human handedness. *European Journal of Human Genetics, 10,* 623-630.

Andreasen, N. C., Dennert, J.W., Scott, A.O., & Damasio, A.R. (1982). Hemispheric asymmetries and schizophrenia. *American Journal of Psychiatry, 139*, 427-430.

Andreasen, N. C. (1979). Thought, language, and communication disorders I: Clinical assssment, definition of terms, and evaluation of their reliability. *Archives of General Psychiatry, 36*, 1315-1321.

Andreasen, N. C., & Olsen, S. (1982). Negative vs. positive shizophrenia: Definition and validation. *Archive of General Psychiatry, 39,* 789-794.

Annett, M. (1985). Left, Right, Hand and Brain: The Right Shift Theory. Hillsdale, New Jersey: Lawrence Erlbaum Associates Ltd.

Bakan, P., Dibb, G., & Reed, P. (1973). Handedness and birth stress. *Neuropsychologia, 11,* 363-366.

Bakan, P. (1975). Are left-handers brain damaged? *New Scientist, 67*, 200-202.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *Journal of General Psychology, 39*, 15-22.

Berlim, M. T., Mattevi, B.S., Belmonte-de-Abreu, P., & Crow, T.J. (2003). The etiology of schizophrenia and the origin of language: Overview of a theory. *Comprehensive Psychiatry, 44*, 7-14.

Bertolino, A., Blasi, G., Caforio, G., Latorre, V., De Candia, M., Rubino, V., Callicott, J.H., Mattay, V.S., Bellomo, A., Scarabino, T., Weinberger, D.R., & Nardini,

M. (2004). Functional lateralization of the sensorimotor cortex in patients with schizophrenia: effects of treatment with olanzapine. *Biological Psychiatry, 56*, 190-197.

Bilder, R. M., Goldman, R.S., Robinson, D., Reiter, G., Bell L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M., Woerner, M.G., Geisler, S., Kane, J.M., & Lieberman, J.A. (2000). Neuropsychology of first-episode schizophrenia: Initial characterisation and clinical correlates. *American Journal of Psychiatry, 4,* 549-559.

Browne, S., Clarke, M., Gervin, M., Lane, A., Waddington, J.L., Larkin, C., & O'Callaghan, E. (2000). Determinants of neurological dysfunction in first episode schizophrenia. *Psychological Medicine, 30*, 1433-1441.

Buchsbaum, M. S., Yang, S., Hazlett, E., Siegel, B.V., Germans, M., Haznedar, M., O'Flaithbheartaigh, S., Wei, T., Silverman, J., & Siever, L.J. (1997). Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. *Schizophrenia Research, 27*, 45-53.

Cannon, M., Byrne, M., Cassidy, B., Larkin, C., Horgan, R., Sheppard, N.P., & O'Callaghan, E. (1995). Prevalence and correlates of mixed-handedness in schizophrenics. *Psychiatry Research, 59*, 119-125.

Collinson, S. L., Mackay, C.E., James, A.C., Quested, D.J., Phillips, N., & Crow, T. (2003). Brain volume, asymmetry and intellectual impariment in relation to sex in early-onset schizophrenia. *British Journal of Psychiatry, 183*, 114-120.

Chance, S. A., Esiri, M.M., & Crow, T.J. (2003). Ventricular enlargement in schizophrenia: a primary change in the temporal lobe? *Schizophrenia Research, 62*, 123-131.

Chaugule, V. B., & Master, R.S. (1981). Impaired cerebral dominance and schizophrenia. *The British Journal of Psychiatry, 139*, 23-24.

Clementz, B. A., Iacono, W.G., & Beiser, M.,. (1994). Handedness in First-Episode Psychotic Patients and Their First-Degree Biological Relatives. *Journal of Abnormal Psychology, 103*, 400-403.

Crow, T. J., Ball, J., Bloom, S.R., Brown, R., Bruton, C.J., Colter, N., Frith, C.D., Johnstone, E.C., Owens, D.G.C., & Roberts, G.W. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry. *Archives of General Psychiatry, 46*, 1145-1150.

Crow, T. J. (1989). Developmental arrest of cerebral asymmetries in early onset schizophrenia. *Psychiatry Research, 29*, 247-253.

Crow, T. J. (1990). Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophrenia *Bulletin, 16*, 433-443.

Crow, T. J. (1993). Sexual selection, Machiavellian intelligence, and the origin of psychosis. *Lancet, 342*, 594-598.

Crow, T. J., Done, D.J., & Sacker, A. (1996). Cerebral lateralization is delayed in children who later develop schizophrenia. *Schizophrenia Research, 22*, 181-185.

Crow, T. J. (1997a). Is schizophrenia the price the *Homo sapiens* pays for language? *Schizophrenia Research, 28*, 127-141.

Crow, T. J. (1997b). Schizophrenia as failure of hemispheric dominance for language. *Trends in Neuroscience, 20*, 339-343.

Crow, T. J., Crow, L.R., Done, D.J., & Leask, S. (1998). Relative hand skill predicts academic ability: Global deficits at the point of hemispheric indecision. *Neuropsychologia, 36*, 1275-1282.

Crow, T. J. (2004). Cerebral asymmetry and the lateralization of language: Core deficits in schizophrenia as pointers to the gene. *Current Opinion in Psychiatry, 17*, 97-106.

DeLisi, L. E., Hoff, A.L., Schwartz, J.E., Shields, G.W., Halthore, S.N., Gupta, S.M., Henn, F.A., & Anand, A.K. (1991). Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. *Biological Psychiatry, 29*, 159-175.

Delis, D. C., Kramer, J.H., Kaplan, E., & Ober, B. (1987). *California Verbal Learning Test Manual* (Version 1). San Antonio, TX: Harcourt Brace Jovanovich.

DeLisi, L. E., Sakuma, M., Kushner, M., Finer, D.L., Hoff, A.L., & Crow, T.J. (1997). Anomalous cerebral asymmetry and language processing in schizophrenia. *Schizophrenia Bulletin, 23,* 255-271.

Dollfus, S., Buijsrogge, J.A., Benalli, K., Delamillieure, P., & Brazo, P. (2002). Sinistrality in subtypes of schizophrenia. *European Psychiatry, 17*, 272-277.

Dragovic, M. (2004). Towards an improved measure of the Edinburgh Handedness Inventory: A one-factor congeneric measurement model using confirmatory factor analysis. *Laterality, 9*, 411-419.

Dragovic, M., & Hammond, G. (2005). Handedness in schizophrenia: A quantitative review of evidence. *Acta Psychiatrica Scandinavica, 111*, 1-10.

Dragovic, M., Hammond, G., & Jablensky, A. (2005). Schizotypy and mixed-handedness revisited. *Psychiatry Research, 136*, 143-152.

Dragovic, M., & Hammond, G. (2007). A classification of handedness using Annett's Hand Preference Questionnaire. *British Journal of Psychology, 98*, 375–387.

Dragovic, M., Milenkovic, S., & Hammond, G. (2008). The distribution of hand preference is discrete: A taxometric examination. *British Journal of Psychology, 99,* 445–459.

Faustman, W. O., Moses, J.A., Ringo, D.L., & Newcomer, J.W. (1991). Left-handedness in male schizophrenic pa-

tients is associated with increased impairment on the Luria-Nebraska Neuropsychological battery. *Biological Psychiatry, 30,* 326-334.

Flaum, M., Swayze, V.W. 2nd., O'Leary, D.S., Yuh, W.T., Ehrhardt, J.C., Arndt, S.V., & Andreasen, N.C. (1995). Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. *American Journal of Psychiatry, 152*, 704-714.

Flor-Henry, P. (1969). Psychosis and temporal lobe epilepsy. *Epilepsia, 10,* 363-395.

Flor-Henry, P. (1983). *Commentary and synthesis*. In P. Flor-Henry, and Gruzelier, J. (Ed.), Laterality and Psychopathology (pp. 3-19). Amsterdam: Elsevier Science Publishers B.V.

Geschwind, N., & Galaburda, M.A. (1985). Cerebral lateralization: Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archives of Neurology, 42*, 428-459.

Geschwind, H. D., Miller, L.B., DeCarli, C., & Carmelli, D. (2002). Heritability of lobar brain volumes in twins supports genetic model of cerebral laterality and handedness. *Proceedings of the National Academy of Science, 99*, 3176-3181.

Golden, C. J., Hammeke, T. A., & Purisch, A. D. (1980). *The Luria-Nebraska Neuropsychological Battery: Manual*. Los Angeles: Western Psychological Services.

Green, M. F., Satz, P., Smith, C., & Nelson, L. (1989). Is There Atypical Handedness in Schizophrenia? *Journal of Abnormal Psychology, 98*, 57-61.

Gruzelier, J., & Flor-Henry, P. (Ed.). (1979). *Hemisphere Asymmetries of Function and Psychopathology*. Amsterdam: Elsevier/North-Holland Biomedical Press.

Gruzelier, J. H. (1981). Cerebral laterality and psychopathology: Fact or fiction. *Psychological medicine, 11*, 21-227.

Gruzelier, H. J. (1999). Functional neuropsychophysiological asymmetry in schizophrenia: A review and reorientation. *Schizophrenia Bulletin, 25*, 91-120.

Guenther, W., Brodie, J.D., Bartlett, E.J., Dewey, S.L., Henn, F.A., Volkow, N.D., Alper, K., Wolkin, A., Cancro, R., & Wolf, A.P. (1994). Dimished cerebral metabolic response to motor stimulation in schizophrenics: A PET study. *European Archive of Psychiatry and Clinical Neuroscience, 244*, 115-125.

Gureje, O. (1988). Sensorimotor laterality in schizophrenia: Which features transcend cultural influences? *Acta Psychiatrica Scandinavica, 77,* 188-193.

Harrison, P. J. (1999). The neuropathology of schizophrenia: A critical review of the data and their interpretation. *Brain, 122*, 593-624.

Hauck, J. A., & Dewey, D. (2001). Hand preference and motor functioning in children with autism. *Journal of Autism & Developmental Disorders, 31*, 265-277.

Hayden, J. L., Kern, R.S., Burdick, N.L, & Green, M.F. (1997). Neurocognitive impairments associated with ambiguous handedness in the chronically mentally ill. *Psychiatry Research, 72*, 9-16.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J.E., Day, R., & Bertelsen, A. (1992). Schizophrenia: Manifestations, incidence and course in different cultures. A World Health Organisation Ten-Country study. Psychological Medicine. *Monograph Supplement, 20*, 1-97.

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

Jones, P. (1997). The early origins of schizophrenia. *British Medical Bulletin, 53*, 135-155.

Katsanis, J. M. A., & Iacono, W.G. (1989). Association of left-handedness with ventricle size and neuropsychological performance in schizophrenia. *American Journal of Psychiatry, 146*, 1056-1058.

Kieler, H., Cnattingius, S., Haglund, B., Palmgren, J., & Axelsson, O. (2001). Sinistrality - a side-effect of prenatal sonography: A comparative study of young men. *Epidemiology, 12*, 618-623.

Kircher, T.T.J., Liddle, P.F., Brammer, M.J., Williams, S.C.R., Murray, R.M., & McGuire, P.K. (2002). Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia. *Psychological Medicine, 32*, 439-449.

Lawrie, S. M., & Abukmeil, S.S. (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *The British Journal of Psychiatry, 172,* 110-120.

Lewin, J., Kohen, D., & Mathew, G. (1993). Handedness in mental handicap: Investigation into populations of Down's syndrome, epilepsy and autism. *British Journal of Psychiatry, 163*, 674-676.

Lishman, W. A., & McMeekan, E.R.L. (1976). Hand preference patterns in psychiatric patients. *British Journal of Psychiatry, 129*, 158-166.

Luchins, D. J., Weinberger, D.R., & Wyatt, R.J. (1979). Anomalous lateralization associated with a milder form of schizophrenia. *American Journal of Psychiatry, 136*, 1598-1599.

Manoach, D. S., Maher, B.A., & Manschreck, T.C. (1988). Left-handedness and thought disorder in the schizophrenias. *Journal of Abnormal Psychology, 97*, 97-99.

Manoach, D., S. (1994). Handedness is related to formal thougth disorder and language dysfunction in schizophrenia. *Journal of Clinical and Experimental Neuropsychology, 16*, 2-14.

Manschreck, T. C., & Ames, D. (1984). Neurologic features and psychopathology in schizophrenic disorders. *Biological Psychiatry, 19*, 703-719.

Mattay, V. S., Callicott, J.H., Bertolino, A., Santha, A.K., Tallent, K.A., Goldberg, T.E., Frank, J.A., & Weinberger, D.R. (1997). Abnormal functional laterization of the senzorimotor cortex in patients with schizophrenia. *Neuroreport, 8*, 2977-2984.

McCarley, R. W., Wible, C.G., Frumin, M., Hirayasu, Y., Levitt, J.J., Fischer, I.A., & Shenton, M.E. (1999). MRI anatomy of schizophrenia. *Biological Psychiatry, 45*, 1099-1119.

McFarland, K., & Anderson, J. (1980). Factor stability of the Edinburgh Handedness Inventory as a function of test-retest performance, age, and sex. *British Journal of Psychology, 71*, 135-142.

McManus, I. C. (1985a). Handedness, language dominance and aphasia: A genetic model. *Psychological Medicine: Monograph Supplement, 8*, 1-40.

McManus, I. C. (1985b). Right- and left-hand skill: Failure of the right shift model. *British Journal of Psychology, 76*, 1-16.

Merrin, E. L. (1984). Motor and sighting dominance in chronic schizophrenics: Relationship to social competence, age at first admission, and clinical course. *British Journal of Psychiatry, 145*, 401-406.

Nasrallah, A. H., McCalley-Whitters, M., & Kuperman, S. (1982). Neurological differences between paranoid and nonparanoid schizophrenia: Part I. sensory-motor lateralization. *Journal of Clinical Psychiatry, 48*, 305-306.

Nelson, H. E., & Willison, J. (1991). *National Adult Reading Test Manual* (2nd edition). Windsor: NFER-Nelson.

Norman, M. G. R., Townsend, L., & Malla, K.A. (2001). Duration of untreated psychosis and cognitive functioning in first-episode patients. *British Journal of Psychiatry, 179*, 340-345.

O'Callaghan, M. J., Burn, Y.R., Mohay, H.A., Rogers, Y., & Tudehope, D.I. (1993). Handedness in extremely low birth weight infants: Aetiology and relationship to intellectual abilities, motor performance and behaviour at four and six years. *Cortex, 29*, 629-637.

O'Callaghan, E., Buckley, P., Madigan, C., Redmond, O., Stack, J.P., Kinsella, A., Larkin, C., Ennis, J.T., & Waddington, J.L. (1995). The relationship of minor physical anomalies and other putative indices of developmental disturbance in schizophrenia to abnormalities of cerebral structure on magnetic resonance imaging. *Biological Psychiatry, 38*, 516-524.

Oddy, H. C., & Lobstein, T.J. (1972). Hand and eye dominance in schizophrenia. *British Journal of Psychiatry, 120*, 331-332.

Orr, K. G. D., Cannon, M., Gilvarry, M., Jones, P.B., & Murray, R.M. (1999). Schizophrenic patients and their first-degree relatives show an excess of mixed-handedness. *Schizophrenia Research, 39*, 167-176.

Oyebode, F., & Davison, K. (1990). Handedness and epileptic schizophrenia. *British Journal of Psychiatry, 156*, 228-230.

Pearlson, D. G., Kim, W.S., Kubos, K.L., Moberg, P.J., Jayaram, G., Bascom, M.J., Chase, G.A., Goldfinger, A.D., & Tune. L.E. (1989). Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. *Archives of General Psychiatry, 46*, 690-697.

Plum, F. (1972). Prospects for research on schizophrenia. 3. Neuropsychology. Neuropathological findings. *Neurosciences Research Program Bulletin, 10,* 384-388.

Quinan, C. (1930). The principal sinistral types: An experimental study, particulalrly as regards their relation to the so-called psychopathic states. *Archives of Neurology and Psychiatry, 24*, 35-47.

Richardson, A. J. (1994). Dyslexia, handedness and syndromes of psychosis-proneness. *International Journal of Psychophysiology, 18*, 251-263.

Satz, P., Green, M.F., Bartzokis, G., Bledin, A., & Vaclav, J.F. (1990). *The neuroanatomy of atypical handedness in schizophrenia*. In S. Coren (Ed.), Left-Handedness; Behavioural Implications and Anomalies (pp. 153-166). North-Holland: Elsevier Science Publishers B.V.

Satz, P., & Green, M.F. (1999). Atypical handedness in shchizophrenia: Some methodological and theoretical issues. *Schizophrenia Bulletin, 25*, 63-78.

Saugstad, L. F. (1998). Cerebral lateralization and rate of maturation. *International Journal of Psychophysiology, 28*, 37-62.

Shan-Ming, Y., Flor-Henry, P., Dayi, C., Tiangi, L., Shuguang, Q., & Zenxiang, M. (1985). Imbalance of hemispheric function in the major psychoses: A study of handedness in the people's Republic of China. *Biological Psychiatry, 20*, 906-917.

Shimizu, A., & Endo, M. (1985). Hand preference in schizophrenics and handedness conversion in their childhood. *Acta Psychiatrica Scandinavica, 72*, 259-265.

Sommer, I., Aleman, A., Ramsey, N., Bouma, A., & Kahn, R. (2001). Handedness, language lateralization and anatomical asymmetry in schizophrenia. *British Journal of Psychiatry, 178*, 344-351.

Sommer, I. E. C., Ramsey, N.F., Mandl R.C.W., & Kahn, R.S. (2003). Language lateralization in female patients with schizophrenia: an fMRI study. *Schizophrenia Research, 60*, 183-190.

Sperling, W., Martus, P., & Barocka, A. (1999). Non-right-handedness and obstetrical complications in paranoid

hallucinatory schizophrenics. *Psychopathology, 32*, 267-276.

Taylor, P. J., Dalton, R., & Fleminger, J.J. (1982). Handedness and schizophrenic symptoms. *British Journal of Medical Psychology, 55*, 287-291.

Taylor, M. A., & Amir, N.A. (1995). Sinister psychotics: Left-handedness in schizophrenia and affective disorder. *The Journal of Nervous and Mental Disorder, 183*, 3-9.

Tyler, M., Diamond, J., & Lewis, S. (1995). Correlates of left-handedness in a large sample of schizophrenic patients. *Schizophrenia Research, 18*, 37-41.

Umansky, R., Watson, J.S., Colvin, L., Fyfe, S., Leonard, S., de Clerk, N., & Leonard, H. (2003). Hand preference, extent of laterality, and functional hand use in Rett syndrome. *Journal of Child Neurology, 18*, 481-487.

Verdoux, H., Liraud, F., Droulout, T., Theillay, G., Parrot, M., & Franck, N. (2004). Is the intensity of Schneiderian symptoms related to handedness and speech disorder in subjects with psychosis? *Schizophrenia Research, 67*, 167-173.

Walter, H., Wunderlich, A.P., Blankenhorn, M., Schäfer, S., Tomczak, R., Spitzer, M., & Grön, G. (2003). No hypofrontality, but absence of prefrontal lateralization comparing verbal and spatial working memory in schizophrenia. *Schizophrenia Research, 61*, 175-184.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale - Revised*. New York: Psychological Corporation.

Weinberger, D. R., Suddath, R.L., Casanova, M.F., Torrey, E.F., & Kleinman, J.E. (1991). Crow's 'lateralization hypothesis' for schizophrenia. *Archives of General Psychiatry, 48,* 85-87.

Williams, M. S. (1986). Factor analysis of the Edinburgh Handedness Inventory. *Cortex, 22*, 325-326.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P.W., David, A.S., Murray, R.M., & Bullmore, E.T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry, 157*, 16-25.