Introduction and Review of Literature

Asymmetrical hand preference is species-specific characteristic of humans and it is present for a long time. In human beings, some people are left handed and ambidextrous, however, most are right-handed. This dominance of the right hand is universal, independent of race and culture (Porac & Coren 1981). Dennis (1958) found that the people represented in the paintings in Egyptian tombs were usually engaged in right-handed activities. Wilson (1885) reported that most paleolithic tools, weapons, and ornaments were apparently made with the right hand. Uhrbrock (1970) concluded that many prehistoric hand prints came from right-handers.

Despite universal favor of right hand use in populations across space and time among human beings studies have reported that there are differences in incidence of handedness in different societies. Large number of studies, using similar assessment procedure, showed that incidence of handedness varies from 10-15% in western countries and 2-4% in oriental countries (Briggs & Nebes, 1975; Gilbert & Wysocki, 1992; Hatta & Nakatsuka, 1976; Singh, Manjary & Dellatolas, 2001; Shimizu & Endo, 1983;

Dawson (1977) after a series of cross cultural studies (Dawson, 1972; 1977) done on liberal hunting and gathering societies like Alaskan *Eskimo*, Australian *Arunta* and Hong-Kong *Boat People*, and on conservative agricultural societies like *Hakka* and *Katanganese* of Hong-Kong and *Temne* of Sierra Leone showed that social pressure can have profound influence on handedness.

However, differences in gene frequency in societies have also been forwarded as an explanation of differences in incidence of handedness (McManus, Amir, Singh & Ida, 1999).

Handedness is one of the variables, which has been found to be related with cerebral lateralization of function. The important insight concerning functional asymmetry was first clearly communicated by Paul Broca in 1863. On the basis of the study of some patients who got brain damage at specific locations in frontal cortex of left hemisphere Broca for the first time enunciated that ‘we speak with our left brain’. Broca (1865) also speculated that right-handed people are likely to be left hemisphere dominant for speech and left-handed people right dominance. Later studies, however, showed that no one-to-one relationship exit between language lateralization and handedness (Porac & Coren, 1981;
Rasmussen & Milner, 1977; Sagalowitz & Bryden, 1983; Kimura, 1983). It was found that while right-handers have predominantly left-brain speech dominance, the left-handers were more heterogeneous in language lateralization (Rasmussen & Milner, 1977; Sagalowitz & Bryden, 1983). Porac and Coren (1981) in a large study showed that 97% of right-handers have left brain language dominance, whereas only 69% of left-handers have left-hemisphere language representation.

One of the major problems in relating handedness to other variables is that different investigators used different means of assessing handedness. In investigating the relationship between language representation and handedness Rasmussen and Milner (1977) have combined ‘mixed’ and ‘left handed’ people in to a single group of ‘non right-handers’. In contrast, Geffen and Cauderey (1981) distinguished clearly between strong left handers and people of mixed handedness. Recently it has been shown that the distribution of hand preferences is taxonic (McManus, 1985; Dragovic, Milenkovic, & Hammond, 2008). There is 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. Although left- and mixed-handedness
are clearly a hallmark of many neurodevelopmental disorders, they are not pathognomonic (Dragovic & Hammond, 2005).

**Theories of handedness.** A number of theories of causation of handedness have been proposed. The evidence favors a genetic basis, but existing genetic models are all limited by the fact that data on the incidence of handedness are extremely variable (Hardyck and Petrinovich, 1977).

Explanations for the preference habits of man are extensive in that any detailed account is impractical. However, these theories commonly emphasize that handedness was entirely a matter of habits or adaptation (Blau, 1946; Jackson, 1905; Wile, 1934)

An important theory is *Geschwind-Galaburda prenatal testosterone theory* (1987). It explains certain significant observations, as left-handedness and developmental disorders are more common in man than women, left-handers have superior right hemispheric functions and relatively more development and immune disorders and the females are superior in verbal skills while men excel in spatial tasks. The theory specifically proposes that testosterone acts during a critical period of brain development to slow the growth of certain areas of left hemisphere, particularly the
temporal speech region. High levels of testosterone may cause sufficient growth retardation to shift the left hemisphere functions, notably handedness and language, to the right hemisphere. A continuum of lateralization is proposed, with lateralization for handedness and language initially established on the left (presumably through some genetic/development process), with exposure to higher levels of testosterone shifting lateralization towards the right. This mechanism is proposed to account for the greater incidence of left-handedness and development disorders among males. Testosterone also influences the developing immune system, accounting for the relations between cerebral lateralization and immune function.

Other than hormonal effects, there are theories that emphasize physical factors like birth stress as determining handedness. Baken (1971) proposed the birth stress theory, according to which consistent right-handedness is a normative state- with all neurological connections to a controlling hemisphere being correctly established, that get disturbed due to brain damage sustained around at the time of birth leading to development of left-handedness. On the basis of indirect evidences like – left-handers were more likely to be first or fourth and later born- with
concomitant increase in prenatal problems (Baken, 1971); and left-handers report higher rate of prenatal hazards (Baken, 1971; O’Callaghan, Tudenophe, Dugdale, Money, Burns & Cook, 1987; Schwatz, 1988), he suggested that left-handedness is caused by highly localized brain damage affecting the giant betz cells of the motor cortex which are particularly sensitive to anoxia. The theory however has weakness in that it is too extreme in suggesting all left-handedness as a consequence of brain damage. It fails to account for familial handedness, and there are studies showing that, on an average, left-handers show neither cognitive deficit nor impaired motor proficiency (Kilshaw & Annett, 1983). Satz (1972, 1973) modified birth stress theory to suggest a model of pathology of left-handedness. He emphasized that higher frequency of pathology in left-handers do not require postulation of an excess of left hemispheric lesions. He suggested that, in so far as neurological damage determines left-handedness, more right-handers as compared to left-handers would be affected. Since there are more right-handers the effects of neurological damage might results in more natural right-handers become left-handers than vice versa.
Handedness has also been explained in terms of genetic mechanisms. A popular model is right shift theory proposed by Annett (1979, 1985). It holds that a single gene controls handedness and language lateralization with two alleles. The dominant allele (R) determines the ‘right-shift’ while the recessive allele (r) produces no-shift. Individuals can be homozygous dominant (RR) or heterozygous (Rr); these have the ‘right-shift’ dominant factor, thus will tend to be right-handed. For the individuals as homozygous recessive (rr) the handedness and language lateralization are determined by independent factors so that one quarter of the homozygous recessive will be left-handed and left-hemispheric for language, one quarter will be left-handed and right-hemispheric for language and so on. In determination of outcome of homozygous recessive (rr), Annett has postulated random effect due to environmental factors. The theory holds that the relative proportion of left-, and right-handers in humans and non humans were consistent with a normal distribution, which was symmetrical about ‘zero’ for non-humans but displaced slightly to the right for humans- a right shift. The current version (1998) holds that the causes of typical left-hemisphere cerebral dominance could be
independent of the causes of handedness, but could influence handedness by weighing the probabilities in favor of the right hand.

**Handedness and other lateral preferences.** The occurrence of asymmetrical handedness has also been found to be closely related with other asymmetries like, eyedness, footedness and earedness (Bourassa et al, 1996; Nachshon, Danno, & Ausand, 1983; Peters & Durding, 1979; Singh et al, 2001). It has been found that left-handers are more likely to have left-eyedness and footedness as compared to right-handers (Porac & Coren, 1981; Porac 1997). Bourassa et al. (1996) in a meta-analysis, including 43 unbiased studies, found that left-handers are 2.53 times more likely to be left-eyed than the right-handers. It has been found that lateral preferences tend to run in families (Merrell, 1957; Zoccolotti, 1978). Brackenridge (1982) has reported that the proportion of left-eyed offspring’s is 27% in both parents being right handed, 36% in one left handed and 45% in both left handed. Reiss and Reiss (1997), in a review, showed that there was a clear tendency for the proportion of left-eyed children to increase as the number of left-eyed parents increased. Language lateralization has also been found to be related with different lateral preferences. Several studies have shown that, just like handedness, footedness was closely related
with language lateralization (Porac & Coren, 1981), moreover, since cultural pressure is comparatively less effective in footedness it has been found to be a better indicator of strength and direction of language lateralization than handedness (Searlman, 1980). Bourassa et al (1996), however, have found that association between handedness and eyedness was slightly less than that of language and handedness.

Efforts have been made to explain the patterns of interrelationship between lateral preferences through a common mechanism (Peters, 1988; McManus, 1999; Annett, 1999). McManus et al. (1999) took the asymmetrical distribution of eyedness among left- (97%) and right- handers (35%) around 50%, as difficult point in explanation of eyedness in terms of existing genetic models and showed that when Peters and Servo’s (1989) subdivisions of handedness, consistent handedness and inconsistent handedness (in terms of writing hand & throwing hand) were considered, the asymmetrical distribution of eyedness among left- and right- hander’s’ become symmetrical, and therefore compatible with existing genetic models of handedness. They showed that both writing hand and throwing hand relate independently with eyedness but throwing hand is somewhat more strongly associated
with eyedness to give the proportions: 24.2% consistent right-handers being left eye dominant compared with 73.3% of consistent left-handers and 55.4% of inconsistent right-handers compared with 47% of inconsistent left-handers, and, thus eyedness is phenotypically secondary to writing and throwing hand.

Annett (1999), on the other hand, compared the Annett and McManus model in best fitting the family data on eyedness. She found that familial eyedness could be best explained through single-gene-right shift model, whereas the possibility of incompatibility of present genetic models of lateral preferences with eyedness in family, as proposed by Reiss and Reiss (1997), is correct for McManus theory.

However, findings that motor measure- footedness, is closely associated with handedness while sensory measures- eyedness, earedness, are distantly related with handedness (Singh et al, 2001; Dargent- Pare et al, 1992; Eyre & Schmeekle, 1933); handedness and footedness represent same factor while eyedness and earedness represent two different factors (Porac et al., 1980); and handedness and footedness show age and sex effect while no such effect is present in eyedness (Bourassa et al.,1996), raises important problems for a common explanation of lateral preferences.
Lateral preferences and other neuropsychological phenomena’s. The left-handedness has been found to be closely related with pathological conditions. Left-handedness has been found to be linked to many disorders including three leading causes of death in western society, alcoholism, smoking and breast cancer (London, 1989) as well as to several neurological and immune disorders and reading disability (Geschwind & Behan, 1992). Thus the population proportion of left-handers in these is higher than among the normal population. Left-handedness has been found to be more in proportion among mentally retarded as compared to the proportion of left-handers in normal population (Coren, 1982). Furthermore pregnancy complications, risk factors birth stress have been found to be associated with left-handedness (Bakan, Dibb & Reed, 1973; Coren, Searleman & Proac, 1982). However, some studies have failed to find such a relationship (Elliot, Gerberi & Mertin, 1979; Leiber & Axrelod, 1981; Liederman & Coryell, 1982). Left handedness has also been found to be related with mother’s age. As mother’s age increase at the time of delivery, after 25 years, the risk of being a left-handed child increases gradually (Coren, 1992).
The psychotic disorders are also found to be associated with left-handedness. Especially several studies have shown that non-right-handedness is more common in schizophrenics (Green, Satz, Smith & Nelson, 1989) and the atypical brain organization, characteristic of non-right handedness, is also linked with schizophrenia (Nelson et al., 1993; Clementz et al., 1994; Manoach, 1994). However, a substantial number of studies have failed to find a relationship between handedness and schizophrenia (O’Callaghan et al., 1995; Taylor & Amir, 1995).

**Schizophrenia and Lateralization**

Schizophrenia is a destructive mental illness that severely impacts the lives of those affected, as well as their families. Some individuals display aggravations and diminution of symptoms, whereas others remain chronically ill throughout their life spans (APA, 2000). In general, the symptoms of schizophrenia can be classified either as positive or as negative. Positive symptoms are characterized by a distortion in normal functioning, which may include the experience of delusions and hallucinations, as well as disorganized behavior and speech. On the other hand, negative symptoms is generally characterized by an reduction or loss of
normal functioning, including restrictions in emotional expression, fluency and productivity of thought and speech and initiation of goal-directed behavior (APA, 2000).

Satz and Green (1999) after reviewing several studies showed that rather then left handedness the mixed handedness is a category that is related with schizophrenia. This review of 23 studies reported that, whereas 14 studies found a relationship between handedness and schizophrenia 7 studies reported no relationship and 2 studies reported contradictory results. 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 (Flor-Henry, 1983; Gruzelier, 1981; Gruzelier, 1999). In contrast to qualitative reviews, based on meta-analysis Sommer et al. (2001) concluded that schizophrenia patients are more frequently non-right-handed than healthy individuals. Although the statistical procedure was adequate the Sommer et al grouped exclusive left-handed and exclusive mixed-handed individuals in the non-right-handed category and thus, conceptually equated two distinct handedness categories. Dragovic and
Hammond (2005) have conducted the most comprehensive review of empirical evidence. They analyzed that membership of each atypical handedness subtype identified as exclusive left-handedness, and 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.

There are several studies that reported structural and morphological deviations of the brain in schizophrenia patients. Enlarged brain ventricles are the most prominent and replicable macroscopic brain abnormality in schizophrenia patients (Wright et al., 2000). Several studies have specifically explored the relationship between ventricular dilatation and hand dominance in schizophrenia patients and it was consistently found that left- and mixed-handed schizophrenia patients tend to have larger ventricular-to-brain ratios than the right-handed patients (Andreasen, Dennert, Scott, & Damasio, 1982; Clementz et al., 1994; Katsanis & Iacono, 1989; O’Callaghan et al., 1995; Satz, Green, Bartzokis, Bledin, & Vaclav, 1990). Ventricular enlargement is usually interpreted as indication of cerebral atrophy
which, along with other brain abnormalities, is considered to be a neuropathological substrate of schizophrenia (Satz et al., 1990). 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.

Although reduction in brain mass was initially reported as an evidence of morphological abnormality in the population of schizophrenia patients McCarley et al. (1999), after a review of large number of MRI studies, concluded that there was little evidence for whole brain differences between schizophrenia and control populations. However, other meta-analytic studies do reported small but significant decrease of the overall brain size (Lawrie & Abukmeil, 1998; Wright et al., 2000). Similar to these equivocal findings, study of asymmetrical changes in brain structure also provides a mixed results which sometimes suggest a small reduction of brain size in schizophrenia patients and sometimes do not (Dragovic & Hammond, 2005). It is not clear what the real meaning of such a subtle anomaly is and how it relates to the clinical symptoms of schizophrenia. Despite enormous research efforts aimed to explore the brain differences between schizophrenia patients and controls, structural brain
changes in schizophrenia patients lack diagnostic exactness because of overlap with control subjects on brain measures. Harrison (1999) has concluded that “schizophrenia still cannot be diagnosed using either brain scan or a microscope”.

Timothy J. Crow has attempted to develop a comprehensive theory to explain the relationship between schizophrenia and lateralization. According to this theory schizophrenia, cerebral asymmetries, language lateralization, and handedness are linked to each other and to a single gene (Crow, 1989; Crow, 1997; Crow, 2004). Because studies have shown that schizophrenia occurs with a strikingly similar incidence and is independent of social, economic, climatic, and cultural factors (Jablensky et al., 1992), it is likely that genes rather than environmental factors cause’s schizophrenia. Because the ventricular dilatation and reduction of brain volume predate the onset of schizophrenic illness hence, they are more likely to be an expression of a failure of development rather than a result of degeneration. Moreover, because various abnormalities of functional brain asymmetries in patients with schizophrenia such as diminished activity in the cortical motor regions (Guenther et al., 1994; Mattay et al., 1997) might be expressed phenotypically at the level of functional lateralization of
handedness the reduced functional lateralization of the motor cortex
(Bertolino et al., 2004) and atypically laterized 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.

Schizotypal Personality and Lateralization

According to DSM-IV schizotypal personality disorder is a
pervasive pattern of social and interpersonal deficits marked by
acute discomfort with, and reduced capacity for, close relationships
as well as represented by cognitive or perceptual distortions and
eccentricities of behavior, beginning by early adulthood and present
in a variety of contexts, as indicated by the following: Ideas of
reference (excluding delusion of reference), odd beliefs or magical
thinking that influences behavior and is inconsistent with sub-
cultural norms (e.g., superstitiousness, belief in clairvoyance,
telepathy, or ‘sixth sense’, in children and adolescents), unusual
perceptual experiences, including bodily illusions, odd thinking and
speech (e.g., vague, circumstantial, metaphorical, over elaborate, or
stereotyped, suspiciousness or paranoid ideation), inappropriate or
constricted affect, behavior or appearance that is odd, eccentric, or peculiar, lack of close friend or confidants other than first-degree relatives, excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self.

Schizotypal personality may be representing the predisposition and genetic factors of the schizophrenia. Kremen, Faraone, Toomey, Seidman, and Tsuang (1998) show that relatives of schizophrenics have higher scores on cognitive-perceptual factor of the Schizotypal personality questionnaire (SPQ) than controls, but there was no main effect for disorganization. For both cognitive-perceptual and interpersonal factors, male relatives in particular had high scores. Yaralian, Raina, Lencz, Hooley, Bihrlle, and Ventura (2000) also found that relatives of schizophrenics scored significantly higher on the cognitive-perceptual factor.

Vollema, Sitskoorn, Appels, Kahn, Meerkanten, and Flevo-Veluwe (2002) investigated whether the SPQ could be an indicator of the biological-genetic vulnerability to schizophrenia. They hypothesized that the mean scores on three dimensions of the SPQ of different groups of relatives of patients with schizophrenia would parallel their risk for developing schizophrenia and assessed
51 first-episode schizophrenia patients, 63 parents of schizophrenia patients, 42 siblings of schizophrenia patients and 12 children of schizophrenia patients on SPQ. Patients differed from the relatives on all three dimensions. Siblings and children scored significantly higher than parents on positive schizotypy, and the insignificant difference between the siblings and children was in the expected direction. The results could not be explained by the differences in age, sex, IQ or substance abuse. No differences were found for disorganization schizotypy between the relatives. Children scored higher than parents on negative schizotypy. The current study offers support to the hypothesis that the positive dimension of SPQ reflects the genetic vulnerability to schizophrenia.

Cadenhead, Swerdlow, Shafer, Diaz, and Braff (2000) compared 23 patients with schizophrenia, 34 relatives of the schizophrenic patients, 11 subjects with schizotypal personality disorder and 25 control subjects assessed in an acoustic startle paradigm. The eye-blink component of the startle response was assessed bilaterally by using electromyographic recordings of orbicularis oculi. Patients with schizophrenia spectrum disorders have been shown to have deficits in sensorimotor gating as assessed by prepulse inhibition of the startle response. The authors
hypothesized that non-schizophrenic relatives of patients with schizophrenia would also have prepulse inhibition deficits, thereby reflecting a genetically transmitted susceptibility to sensorimotor gating deficits. Results showed that the patients with schizophrenia, their relatives, and subjects with schizotypal personality disorder all had reduced prepulse inhibition relative to comparison subjects, and these deficits were more evident in measures of right eye-blink prepulse inhibition. Comparison subjects demonstrated greater right versus left eye-blink prepulse inhibition, whereas the probands, their relatives, and subjects with schizotypal personality disorder showed less asymmetry of prepulse inhibition. These data suggest a genetically transmitted deficit in prepulse inhibition (sensorimotor gating) in patients with schizophrenia spectrum disorders, including subjects with schizotypal personality disorder and relatives of patients with schizophrenia.

Lahti, Raikkonen, Sovio, Miettunen, Hartikainen, et al. (2009) asked participants of the Northern Finland 1966 Birth Cohort Study (n = 4976) to completed a questionnaire on positive and negative schizotypal traits at the age of 31 years. It was found that lower placental weight, lower birth weight and smaller head circumference at 12 months predicted elevated positive schizotypal
traits in women after adjusting for several confounders. Moreover, higher gestational age, lower childhood family socioeconomic status, undesirability of pregnancy, winter/autumn birth, higher birth order and maternal smoking during pregnancy predicted some augmented schizotypal traits in women, some in men and some in both genders. The results point to similarities in the aetiology of schizotypal traits and schizophrenia-spectrum disorders.

Fluctuating asymmetries and minor physical anomalies are markers of developmental instability, an index of the degree to which an organism was subject to genomic or environmental stress during development. Measures of developmental instability are characteristic of schizophrenia and are thought to reflect an underlying genetic liability for schizophrenia spectrum disorders. Whereas minor physical anomalies reflect developmental stress relatively early in the first trimester in utero, skeletal fluctuating asymmetries reflects developmental stress throughout the lifespan. Thoma, Gangestad, Euler, Lysne, Monnig, and Yeo (2008) collected measures of both the minor physical anomalies and the fluctuating asymmetry to provide some indications of the associated developmental time course. In addition to developmental instability measures, several psychometric measures of schizotypy were
administered in a sample of university students ($n = 81$). It was hypothesized that increased developmental instability may relate to schizotypal symptoms in a group of healthy undergraduate students. Schizotypy scores were positively correlated with fluctuating asymmetries but not minor physical anomalies. This finding suggests that developmental instability, as indexed by fluctuating asymmetries, is important for normal range variation in schizotypal characteristics, just as it is important for normal range variation in intelligence. Second, considered in the context of studies demonstrating that schizophrenia is associated with elevated minor physical anomalies, these results suggest that developmental stress likely occurs earlier in development for schizophrenia than schizotypy. Thus, it appears that schizotypal personality disorder and schizophrenia are genetically linked, but schizotypal personality disorder may offer a clearer picture of the schizophrenia spectrum, since former does not have the potentially confounding features of later, including chronic illness, medication, and hospitalization.

**Relationship of schizotypal personality with brain structures.** Interest in schizotypal personality disorder has increased in recent years concurrent with the ability to examine
morphologic brain abnormalities with MRI. Several laboratories have reported brain abnormalities in subjects with schizotypal personality disorder that were similar to findings reported in those with schizophrenia: corpus callosum shape differences (Downhill, Buchsbaum, Wei, Speigel-Cohen, Hazlett, Haznedar, et al., 2000), greater temporal horn size (Buchsbaum, Yang, Hazlett, Siegel, Germans, Haznedar, et al., 1997), enlarged cerebrospinal fluid (CSF) volume (Dickey, Shenton, Hiryasu, Fisher, Voglmaier, Niznikiewicz, et al., 2000), and thalamic abnormalities (Byne, Buchsbaum, Kemether, Hazlett, Shinvari, Mitropoulou et al., 2001).

Takahashi, Suzuki, Kawasaki, Kurokawa, Hagino, Yamashita, et al. (2002) studied the volume of the gray matter and the white matter of the anterior cingulated gyrus by three-dimensional MRI in 24 patients who met the ICD-10 criteria for schizotypal disorder (12 males, 12 females) in comparison with 48 age- and gender-matched healthy control subjects (24 males, 24 females) and 40 patients with schizophrenia (20 males, 20 females). Similar to previous reports, right anterior cingulated gyrus gray matter volume was significantly reduced in the female patients with schizophrenia compared with the female controls. On the other hand, the gray and white matter volume of the anterior cingulated gyrus in the patients
with schizotypal disorder did not differ significantly from the values in the healthy controls or the patients with schizophrenia. However, the female patients with schizotypal disorder showed a lack of right greater-than-left asymmetry of the anterior cingulated gyrus gray and white matter found in the female controls. These results suggest that both schizotypal and schizophrenic subjects share, at least in part, the same cerebral asymmetry abnormalities.

Levitt, Westin, Nestor, Estepar, Dickey, Voglmaier, et al. (2004) measured the shape of the head of the caudate nucleus with a new approach based on MRI in schizotypal personality disorder subjects in whom decreased caudate nucleus volume was reported previously by same authors. Magnetic resonance imaging scans were used to measure the shape of the caudate nucleus in 15 right-handed male subjects with schizotypal personality disorder, who had no prior neuroleptic exposure, and in 14 matched normal comparison subjects. In relation to comparison subjects, neuroleptic never-medicated schizotypal personality disorder subjects had significantly higher (more “edgy”) head of the caudate shape index scores, lateralized to the right side. Additionally, for schizotypal personality disorder subjects, higher right and left head of the caudate shape index scores correlated significantly with poorer
neuropsychological performance on tasks of visuospatial memory and auditory/verbal working memory, respectively. These data confirm the value of measuring shape, as well as volume, of brain regions of interest and support the association of intrinsic pathology in the caudate nucleus, unrelated to neuroleptic medication, with cognitive abnormalities in the schizophrenia spectrum.

Structural brain abnormalities, including larger CSF volumes, have been observed in men diagnosed as having schizotypal personality disorder (Dickey, Shenton, Hirayasu, Fischer, Voglmaier, Niznikiewicz, et al., 2000). To determine whether women with schizotypal personality disorder have abnormalities similar to those of men with schizotypal personality disorder and to elucidate specific schizotypal personality disorder regional volume deficits and symptom correlations, Koo, Dickey, Park, Kubicki, Ji, Bouix, Pohl, et al. (2006) studied thirty neuroleptic-naive women with schizotypal personality disorder and 29 female control subjects, both recruited from the community. Participants were group matched for age, parental socioeconomic status, handedness, and IQ. A new segmentation method was applied to magnetic resonance images to automatically parcel the images into CSF, gray
matter, and white matter. The neocortex was manually separated from subcortical and other non-neocortical structures. Voxel-based morphometry was applied to determine global and regional volume deficits. Smaller left (3.84%) and right (3.83%) neocortical gray matter relative volumes associated with larger left (9.66%) and right (9.61%) sulcal CSF relative volumes were found in women with schizotypal personality disorder compared with controls. Voxel-based morphometry showed that the neocortical deficits in schizotypal personality disorder were especially prominent in the left superior and middle temporal gyri, left inferior parietal region with postcentral gyrus, and right superior frontal and inferior parietal gyri. In the schizotypal personality disorder group, larger lateral ventricle volumes correlated with more severe symptoms on the structured interview for schizotypy and the SPQ. Thus, the smaller neocortical gray matter volume and larger sulcal CSF volume provide evidence of the brain basis of this personality disorder and emphasize the communality of brain abnormalities in the schizophrenia spectrum.

and previously reported to be related with abnormalities in schizophrenia, using diffusion tensor imaging in un-medicated subjects with schizotypal personality disorder. Fifteen male schizotypal personality disorder subjects and 15 male control subjects were scanned with line-scan. Bilaterally reduced fractional anisotropy in the uncinate fasciculus of schizotypal personality disorder subjects was found. For cingulum bundle, there was no significant group difference for fractional anisotropy or mean diffusivity measures. Additionally, in schizotypal personality disorder, reduced fractional anisotropy in the right uncinate fasciculus was correlated with clinical symptoms, including ideas of reference, suspiciousness, restricted affect, and social anxiety. In contrast, left uncinate fasciculus area was correlated with measures of cognitive function, including general intelligence, verbal and visual memory, and executive performance. These findings in schizotypal personality disorder suggest altered fronto–temporal connectivity through the uncinate fasciculus, similar to findings in schizophrenia, and intact neocortical–limbic connectivity through the cingulum bundle, in marked contrast with what has been reported in schizophrenia.
Studies of schizotypal personality disorder are important because the condition is genetically related to schizophrenia and because data accumulating to confirm its biological underpinnings are challenge some traditional views about the nature of personality disorders. Dickey, McCarley, and Shenton (2002) reviewed 17 structural imaging studies in schizotypal personality disorder indicates that individuals with this disorder show brain abnormalities in the superior temporal gyrus, para-hippocampus, temporal horn region of the lateral ventricles, corpus callosum, thalamus and septum pellucidum as in total CSF volume, similar to those seen in persons with schizophrenia. Difference between schizotypal personality disorder and schizophrenia include lack of abnormalities in medial temporal lobes and lateral ventricles in schizotypal personality disorder. Whether the normal volume, and possibly normal functioning, of the medial temporal lobes in individuals with schizotypal personality disorder may help to suppress psychosis in this disorder remains an intriguing but still unresolved question. Such speculations must be tempered due to a paucity of studies and additional work is needed to confirm these preliminary findings. The imagined findings do suggest, however, that schizotypal personality disorder probably represents milder
form of disease along the schizophrenia continuum. With further clarification of the neuro-anatomy of schizotypal personality disorder, researchers may be able to identify which neuro-anatomical abnormalities are associated with the frank psychosis seen in schizophrenia.

Siever and Davis (2004) focused on neurobiological abnormalities found in subjects with schizotypal personality disorder, the prototype of the schizophrenia spectrum disorders, and chronic schizophrenia in the context of common vulnerabilities shared by schizotypal personality disorder and schizophrenia, as well as the factors that protect against the severe cognitive/social deficits and frank psychosis of chronic schizophrenia. A pathophysiological model of the relationship between schizotypal personality disorder and schizophrenia was developed based on this data. They found that people with schizotypal personality disorder share phenomenological, genetic, and cognitive abnormalities with people with chronic schizophrenia. While temporal volume reductions appear to be common to both groups, there may be preservation of frontal lobe volume in schizotypal personality disorder compared to schizophrenia. Findings to date regarding striatal volume, metabolic rate, and dopamine release in subjects
with schizotypal personality disorder compared to subjects with chronic schizophrenia are consistent with hypotheses of reduced striatal dopaminergic activity in schizotypal personality disorder compared to schizophrenia. Genetic or environmental factors that promote greater frontal capacity and reduced striatal dopaminergic reactivity might contribute to sparing people with schizotypal personality disorder from the psychosis and severe social and cognitive deterioration of chronic schizophrenia.

**Gender differences in schizotypal personality.** Raine (1992) found about the gender differences that female score higher on positive symptom sub-scales (ideas of reference and odd beliefs/magical thinking) and the factor of cognitive/perceptual dysfunction. Miller and Burnes (1995) also found that males scored higher on negative symptoms using the SPQ. However, they did not find females scoring higher than males on positive schizotypal features. Langdon and Colheart (1999) found higher cognitive-perceptual scores in females, and high interpersonal deficits in males. Roth and Baribeau (1997) found that males score higher on the ideas of reference, odd beliefs/magical thinking, and social anxiety subscales of the SPQ whereas females also scored higher on the interpersonal deficits factors. Paño-Pineiro, Fonseca-Pedrero,
Lemos-Giraldez, and Muniz (2008) studied the dimensionality of schizotypy and differences, according to sex and age, with a new instrument called the Thinking and perceptual style questionnaire. Participants were 789 young people with a mean age of 19.7 years (SD = 1.65). The results indicated that men scored higher on anhedonia and illusion subscales, whilst women scored higher on negative evaluation, social paranoia and hallucination subscales. By age, the youngest participants tend to score higher on the physical anhedonia and hallucination subscales.

Previous single studies have found inconsistent results on sex differences in positive schizotypy, women scoring mainly higher than men, whereas in negative schizotypy studies have often found that men score higher than women. However, information on the overall effect is unknown. Miettunen and Jaaskelainen (2010) in a meta-analytic study estimated sex differences in Wisconsin schizotypy scales developed to measure schizotypal traits and psychosis proneness. Studies on healthy populations were extensively collected. According to the results, men scored higher on the scales of negative schizotypy, that is, in the physical anhedonia scale ($n = 23$ studies, effect size, Cohen $d = 0.59$, $z$ test $p < .001$) and social anhedonia scale ($n = 14$, $d = 0.44$, $p < .001$).
Differences were virtually nonexistent in the measurements of the positive schizotypy, that is, the magical ideation scale \((n = 29, d = 20.01, p = .74)\) and perceptual aberration scale \((n = 22, d = 20.08, p = .05)\). The sex difference was larger in studies with nonstudent and older samples on the perceptual aberration scale \((d = 20.19 vs d = 20.03, p < .05)\). The gender differences in social anhedonia both in nonclinical samples and in schizophrenia may relate to a broader aspect of social and interpersonal deficits.

Studies that have examined schizotypal personality traits using self-reported measures have found gender differences in the expression and degree of schizotypy, however, putative gender differences have been almost entirely derived from studies of Western populations. Guo, Collinson, Subramaniam, and Chong (2010) examined the gender effect of schizotypy in a broad sample of the Chinese population in Singapore using the SPQ. The questionnaire was administered to 538 (308 males and 230 females) subjects (age range of 21–55). As with previous studies, gender differences were related to the presence of negative schizotypal personality traits, namely no-close-friends and constricted affect. The spectrum of differences in schizotypy was also extended to the psychosocial sphere as marital status and years of education were
significantly associated with several SPQ domains. The findings suggest that there are common elements in Asian and Caucasian populations and that psychosocial risk is an important correlate of schizotypy.

**Relationship of schizotypal personality with cerebral functions.** Poor memory is found to characterize high scores on the SPQ, particularly those scoring high on social functioning (Park & McTigue, 1997). Males with high SPQ scores on the interpersonal deficits factor made more olfactory identification errors than did low-scoring males, finding not attributable to differences in olfactory acuity per se. Daneluzzo (1998) found significant relationships between total and subscale score on the SPQ and performance on the Wisconsin card-sorting-tasks. In continuous performance task, high SPQ scores have been shown to perform more poorly on the continuous performance task. Chen, Hsiao, and Lin (1997) found that high score on the interpersonal and a disorganized factor (but not the cognitive-perceptual factor) was associated with poor performance on the continuous performance task. Gruzelier, Burgess, Stygall, and Raine (1995), showed that high scores on the more positive SPQ traits are associated with left temporo-parietal dysfunction, where as more negative SPQ traits
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are associated with right temporo-parietal dysfunction. Similar findings were again reported by Gruzelier and Doig (1996) in which drawn scales (Loneliness and constricted affect) were associated with a right hemisphere, face advantage asymmetry, while active scales (odd behavior and odd speech) were associated with self report activation. Skosnik (2001) also found that high SPQ score show reduced negative priming. In contrast with the exception of social anxiety, no “negative” subscale was associated with negative priming. Wuthrich and Bales (2001) in contrast in an Australian sample observed significant non-linear relationship between auditory latent inhibition and the SPQ, with both low and high scores showing reduced latent inhibition. The same effects were observed for priming. Braunstein-Bercovitz (2000) observed disrupted latent inhibition in those scoring high on the SPQ and argued that the anxiety component of the SPQ, more than the cognitive-perceptual and disorganization features, that accounts of latent inhibition deficits.

Sarkin Dionisio, Hillix, and Granholm (1998), using the SPQ showed that negative schizotypal symptoms were associated with early reaction-time crossover pattern, while positive schizotypal symptoms related to longer overall reaction time. High scores on
the SPQ show greater left hemisphere EEG activation (Kidd & Powell, 1993). This same finding was shown for persistent schizotypal (defined as those high on the measure of schizophrenia at age 17 years and the SPQ at age 23 years). Such individuals showed reduced slow-wave EEG power (delta, theta, and alpha) over the left (but not right) hemisphere during the beginning of the continuous performance task.

Subject screened on the SPQ (top 10% scores) who also get a confirmed clinical diagnosis of schizotypal personality disorder were found to have significantly poorer eye tracking abnormalities (Lencz, Raine, Scerbo, Holt, Redmon & Bird, 1993). Raine et al. (1997) have found that those scoring in the top 10% of the SPQ and who have a diagnosis of schizotypal personality disorder show retarded habituation relative to low scoring subjects. It was hypothesized that this retarded habituation reflects a deficit in pre-attentive template matching which may partly relate to the working memory and prefrontal deficits observed in both schizophrenics and schizotypal (Park & Holzman, 1992).

Schizotypal personality is characterized by a variety of traits, such as magical thinking, unusual perceptual experiences, and anhedonia. Factor analytic studies have shown that these
Lateral preferences and schizotypal characteristics tend to cluster into at least two separate dimensions (positive and negative schizotypy). Schizotypy is associated with vulnerability to schizophrenia. However, it is also related to higher scores on measures of creativity and increased right-hemisphere brain activity (Wuthrich & Bates, 2001). Fisher, Mohanty, Herrington, Koven, Miller, and Heller (2004) showed that positive schizotypy was associated with better performance on measures of creativity, enhanced responsivity to threatening emotional stimuli, and more right-prefrontal cortical activity. These results support earlier psychological studies suggesting that positive schizotypy is related to patterns of cognitive and emotional function (e.g., divergent thinking, heightened emotion) that are common to both creativity and psychopathology.

Drug users, current cannabis users, have been found to have higher scores on the SPQ than past users and controls (Skosnik, 2001). Irwin (2001) found significant positive correlation between all three SPQ-B sub-factors and the physical, sexual and emotional trauma in a sample of Australian adults drawn from university and community settings. Roth and Baribeau (2000) in an investigation of schizotypal and obsessive-compulsive personality found that the
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strongest links with the SPQ were for compulsive checking as opposed to compulsive washing, slowness or doubting.

Studies on the neurocognitive correlates of schizotypy dimensions have found inconsistent results. This might stem from the fact that correlational methods, in contrast to cluster analysis, do not account for the possibility that a subject presents high scores on more than one dimension simultaneously. Barrantes-Vidal, Fananas, Rosa, Caparro, Riba, and Obiols (2002) aimed to establish clusters of normal adolescents based on schizotypy dimensions and compare them on neuro-cognitive, behavioral, and neuro-developmental markers. Two hundred seventy normal adolescents from the general population (mean age 13.4, SD = 0.72) attending obligatory education were evaluated. A K-means iterative cluster analysis was performed with the perceptual aberration, revised social anhedonia and physical anhedonia scales. A forced four-cluster model yielded the ‘negative schizotypy’, ‘high or mixed schizotypy’, ‘positive schizotypy’, and ‘normal scorers’ clusters. Comparisons with ANOVAs showed that ‘high schizotypes’ performed poorly on neurocognition (Wechsler Intelligence Scales for Children-Revised and verbal fluency) and obtained the highest teacher ratings of behavioral problems. ‘Negative schizotypes’ had
the worst Wechsler intelligence scores results and more dermatoglyphic abnormalities. Both clusters had more neurological soft signs than ‘normal scorers’ and ‘positive schizotypes’.

Positive schizotypy has been associated with a leftward spatial bias (pseudo-neglect) in different tasks and populations. Liouta, Smith, and Mohr (2008) tested whether this relationship (i) can be observed for two different hemispatial tasks in the same participants, and (ii) is specific to positive schizotypy. Forty right-handed men performed a conventional line bisection task and a whole-body movement task. In the latter task, participants were presented with illuminated target locations on the floor, and had to visit the remembered locations (equal number in right and left hemispace) after a short time interval. Side preferences were assessed in both tasks. Positive schizotypy, negative schizotypy, and cognitive disorganization were assessed with a validated self-report questionnaire. Irrespective of schizotypy, pseudoneglect was observed in both tasks. Also, a rightward bisection and walking bias as a function of positive schizotypy, and also as a function of cognitive disorganization for walking initiation was found. It was suggested that different schizotypy questionnaires and their
Lateral preferences and schizotypal presentation mode might be a potential contributor to the opposite findings in the literature.

**Schizotypal personality and lateral preferences.** Mixed-handed subjects have higher scores on the cognitive-perceptual factors and its sub-scales of unusual perceptual experiences, paranoid ideation, odd/eccentric behavior, and odd speech (Kim, Raine, Tryphon, & Green, 1991). The single best correlation of mixed handedness was the odd speech sub-scale. Poreh, Levin, and Teves (1997) found that high scores on the SPQ were more likely to be non-right handed, especially for skilled tasks. Gruzelier and Doig (1996) found that left handedness, and to a lesser extent mixed handedness, were associated with odd speech, odd behavior, and negative SPQ traits.

While there is broad agreement that schizophrenia/schizotypy is associated with a shift away from typical (strong right) handedness, it is not entirely clear what aspect of atypical handedness is implicated: 'ambiguous' handedness (the absence of hand preference for given actions) or 'mixed handedness'(different hand preferences for different actions). Shaw, Claridge, and Clark (2001) used several indices of handedness (derived from the Annett scale) to address these questions in 3000 plus (mostly) university
student subjects recruited by electronic mail. It was found that positive schizotypy (indexed by a scale of 'unusual experiences') was associated with both aspects of atypical handedness.

Annett & Moran (2006) examined the associations between schizotypy and handedness in 733 undergraduates for the Sta and Unex scales of the O-Life inventory and several measures derived from the Annett hand preference questionnaire. Higher schizotypy scores were found for mixed-handers defined in various ways, including inconsistent preference for any item of the questionnaire and also the presence of either hand responses. There was a marked elevation of schizotypy scores \( (p < .001) \) for right-handed writers who prefer the left hand for other 'primary' actions (throwing, racket, match, hammer, toothbrush and scissors). This observation was replicated in 182 students assessed on the Rust scale of schizotypal cognitions. Several findings agree that inconsistent hand preference is associated with a raised probability of schizotypal thinking.

Recently it has been suggested that the relationship between positive schizotypy and mixed handedness is limited to questionnaire measures, and thus reflects some aspect of questionnaire-taking behavior as opposed to some aspect of atypical
brain organization. Bryson, Grimshaw, and Wilson (2008) explored this possibility by asking undergraduate psychology students to complete the magical ideation scale, the Waterloo handedness questionnaire, a manual dot-filling task, and an inventory measuring the personality trait of intellectual openness. On the questionnaire measure, magical ideation was related to mixed handedness on unskilled but not skilled hand preference; however, this relationship was partially mediated by intellectual openness. Magical ideation was not related to the behavioral measure of handedness. These findings suggest that responses on handedness questionnaires partially reflect personality variables, and such effects should be considered in future research on the nature of the relationship between handedness and schizotypy.

Schizophrenia and schizotypal personality have been linked to sinistrality as well as ambidextrality. Nicholls, Orr, and Lindell (2005) clarifies the relation between laterality and schizotypal personality by administering a battery of laterality questionnaires to measure hand, eye, ear, and foot preference in a group of 933 university students. To determine whether the relationship between schizotypy and laterality is limited to self-report measures, performance asymmetries between the hands were measured with
tapping rate. There was no difference between dextrals and sinistrals in schizotypal personality, as indexed by the magical ideation scale. Magical ideation was higher, however, for individuals with a weak preference for either hand or eye compared to those with a strong dominance. In addition, individuals inconsistent in their lateral preference across modalities showed higher magical ideation scores. Performance asymmetries had no effect on magical ideation scores. This lack of effect was attributed to the inability of performance measures, such as tapping rate, to identify ambidextrals. The results support research linking schizotypal personality to ambidextrality and weak cerebral dominance and demonstrate that the association extends to modalities other than hand preference.

Left or mixed-handedness, footedness, and eye dominance are thought to indicate abnormalities in lateralization related to schizophrenia. Increased left or mixed-dominance in schizophrenia suggests possible hemispheric abnormalities associated with the disorder. A related body of research suggests that some indications of lateralization abnormalities may be evident prior to the onset of schizophrenia, suggesting that disruptions in lateralization are inherent to the developmental course of the disorder. Schiffman,
Pestle, Mednick, Ekstrom, Sorensen, and Mednick (2005) attempted to replicate and extend upon findings indicating differences in lateralization between children who later developed a schizophrenia spectrum disorder (n = 26) and those who did not develop a schizophrenia spectrum disorder (n = 216), among a high-risk and control, longitudinal sample. The rate of left or mixed-footedness, eye dominance, and any anomalous lateralization, but not handedness, discriminated between those who developed schizophrenia spectrum disorders and those who did not. Left or mixed-laterality appears to signal neurological disruption relevant to the development of schizophrenia spectrum disorders.

Kelley and Coursey (1992) administered a battery of 11 schizotypy questionnaires to 316 male undergraduates. The scores of the 266 white subjects were subjected to a principal components analysis, and 73 subjects scoring at the upper and lower ends of the factor score distribution based on the first unrotated component were recalled for neuropsychological testing. The battery of neuropsychological tests consisted of four tests of motoric performance, four subtests from the Wechsler adult intelligence scale-revised, the conjugate lateral eye movement test, and a lateral preference questionnaire. Subjects high on schizotypy did not differ
Lateral preferences and schizotypal personality traits from low scorers on overall neuropsychological performance or performance asymmetries. High scorers did show a sinistral shift in hand and foot preference and more crossed dominance compared with controls. Asians scored significantly higher than whites on several schizotypy scales, raising the question of a possible ethnic bias in these measures.

Study of atypical cerebral lateralization in motor and language functions in regard to schizotypal personality traits in healthy populations, as well as among schizophrenic patients, are important because these traits may represent a risk factor for schizophrenia. Although the relationship between handedness and schizotypal personality has been widely examined, few studies have adopted an experimental approach. Asai, Sugimori, and Tanno (2009) conducted three experiments focusing on motor and language functional lateralization in regard to schizotypal personality in the absence of mental illness: line-drawing, finger tapping, and a semantic go/no-go task. The results suggested that positive schizotypal personality might be related to functional non-lateralization in regard to at least some functions (e.g., spatial motor control and semantic processing in the present study). Subjects with high schizotypal personality traits performed equally
with their right and left-hands in the line-drawing task and they reacted equally with their right and left-hands in a semantic go/no-go task involving semantic auditory stimuli presented in both ears. However, those low in schizotypal personality traits showed typical lateralization in response to these tasks.

Language functions in schizophrenia patients are represented more bilateral, i.e. less lateralized than in healthy subjects. This decreased lateralization is also observed in individuals at increased risk for schizophrenia. Language lateralization is related to handedness; in that left- and mixed-handed individuals more frequently have decreased lateralization in comparison to right-handed subjects. Population schizotypy can be considered part of the schizophrenia spectrum disorders. In line with this, population schizotypy has repeatedly, though inconsistently, been associated with left-handedness. In order to define the exact association between handedness and schizotypy, Somers, Sommer, Boks, and Kahn (2009) performed meta-analyses on the available literature. They found that non-right-handed subjects, but not strong left-handers, had higher scores on schizotypy questionnaires than right-handed subjects. Mixed-handers showed a trend towards higher schizotypy in comparison to strong left-handers. It is argued that
the higher schizotypy in non-right-handed individuals reflects the higher incidence of bilateral language lateralization in this group. Bilateral language organization may underlie loosening of association, possibly leading to higher schizotypy scores.

Association between schizotypy and mixed/ambiguous-handedness has mostly been studied in western societies, however, little is known about this relationship outside Western cultures. For the first time, Gregory, Claridge, Clark & Taylor (2003) examined the relationship between handedness and schizotypal personality in an Asian sample of 413 Japanese students by administering (in Japan) the Annett handedness questionnaire and a schizotypy scale (STA). Conventional analyses of current hand preference, using several indices derived from the Annett scale, mostly failed to replicate previous findings. However, there was a significant tendency for greater use of either hand in highly schizotypal males. Furthermore, a significant association between schizotypy and non-right-handedness was found—again only in males—after correcting for the effects of early switching of hand usage, presumed to be due to cultural pressure against left-handedness in Japanese society. These results were found to be highly convergent with findings previously reported for clinical schizophrenia.
Chen and Su (2006) aimed to evaluate the relation of handedness to schizotypal personality, with the influence of different handedness measures and age on the relationship investigated as well among representative samples of school students and community adults in Taiwan. In a total of 175 primary school students, 1020 junior high-school students, and 342 adult participants aged 20 to 65 years, all the participants completed the 12-item Annett handedness questionnaire, and the latter two groups further completed the schizotypal SPQ and the perceptual aberration scale. There was a trend of increasing non-right handedness with younger age groups. Two classification methods in handedness, Annett's or Briggs-Nebes' three-category classification, led to very different frequency distribution and relation to schizotypy. For the adolescents, either Annett's classification or quantitative measures (Hand Preference Index and either-hand use scores) in handedness exhibited an association with schizotypy, whereas for the adults the either-hand use score was the only measure that did so. In contrast, no such difference was found using the Briggs-Nebes' classification method. The association of the non-right or mixed handedness was more consistent and of greater magnitude with the positive aspect of schizotypy, especially the
perceptual aberration scale and the cognitive-perceptual
dysfunction of the SPQ.

Postulating the involvement of cultural pressures against left-
handedness as a factor in failure of earlier studies in Asian cultures
to show a significant association between mixed-handedness and
schizotypy Asai and Tanno (2009) examined the relationship
between handedness and schizotypy among Japanese participants
(N=231, study 1; N=274, study 2) using a modified handedness
scale in addition to the traditional scale developed in Western
cultures. As a result, they reported for the first time that mixed-
handed Japanese participants have the strongest schizotypal traits,
particularly positive schizotypy traits (p < .05). These results
suggest that positive schizotypal traits may be universally
associated with mixed-handedness or atypical cerebral
lateralization, even in non-Western cultures.