

Handedness in Schizophrenia: Any Familial Difference?

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Abstract

Background: The search for possible endophenotype in schizophrenia research is a focus for many researchers in the field of biological psychiatry. The present study sought to assess the handedness differences in the familial risk of schizophrenia.

Methods: The present study elicited information on hand preferences of schizophrenia probands using Annett Hand Preference Questionnaire. The family history approach using Family Interview for Genetic Studies (FIGS) was used to elicit family history information about the relatives of the patients. Data were analyzed to compare handedness and family history of schizophrenia using Chi-square test.

Results: The mean age of schizophrenia probands was 31.76 ± 10.40 , the prevalence of right-and non-right-handedness in the schizophrenia probands were 95.7% and 4.3%, respectively. Handedness was not significantly associated with family history of schizophrenia ($\chi^2 = 2.744$, $df = 1$, $p = 0.098$).

Conclusion: The finding of this study does not support handedness as a possible endophenotype in schizophrenia research. This underscores the need to further search of heritable intermediates that will enhance the search for the genetic basis of the disease.

Keywords: Schizophrenia; Handedness; Family History

Introduction

Most people are right-handed and show left-hemispheric language lateralization, but a minority exhibit left-handedness and right-hemispheric language lateralization [1]. This atypical laterality pattern is observed significantly more in schizophrenia patients than in the general population [2,3]. It has been suggested that a failure in the brain lateralization process orchestrated by genes, could be the primary cause of schizophrenia [4].

The notion that schizophrenia is characterized by increased non-right-handedness (i.e. left-handedness and mixed-handedness) is the cornerstone of the theory that schizophrenia arises from, and is genetically linked to abnormal brain lateralization [5]. Franck, *et al.* reported that the first potential gene influencing human handedness, the Leucine-Rich Repeated Transmembrane Neuronal 1 (LRRTM1) gene on chromosome 2 is over transmitted paternally to patients with schizophrenia [6]. This finding indicates a potential association between this gene, schizophrenia and handedness. However, other researchers [6,7], have postulated that the atypical lateralization in schizophrenia may represent neurodevelopmental markers of insult during intrauterine life and are nongenetic in origin. Dane *et al.*, on the other hand, suggested that cerebral lateralization may be associated with sex-related hormonal factors [8].

Reviews and meta-analyses have reported higher rates of non-right handers in patients with schizophrenia [9,10]. Orr, *et al.* found an excess of non-right handedness in the schizophrenia group compared with controls [9]. However, some studies have found no differences in handedness between schizophrenia patients when compared to healthy controls [11,12]. Others have suggested that the reported excess non-right-handedness in patients with schizophrenia is as a result of gender artifact or a hidden bias in self-report handedness questionnaire [11,13]. They concluded that theories of schizophrenia based on atypical lateralization related to handedness were not supported by their data. However, other studies that controlled for gender found increased rate of non-right-handedness in schizophrenia patients [5].

In Africa, a search of the literature revealed only a few studies evaluating handedness and schizophrenia. Gureje [14] examined sensorimotor laterality in schizophrenia patients compared with a healthy control group in Nigeria and found no difference with regards to right, mixed or left handedness, or foot or eye dominance. He, however, reported that cross-dominance (i.e. full left eye dominance and full right handedness) significantly differentiated the two groups.

In summary, schizophrenia is robustly associated with non-right-handedness, this finding makes a strong case for genetic links between schizophrenia, brain lateralization and handedness [10]. It has been suggested that the excess of non-right-handedness in schizophrenia is the result of subtle brain damage [4], but there is little support for this notion [12]. The genes and exact mechanism that underlie handedness have not been identified, but empirical evidence clearly demonstrates that hand preference is under strong genetic influence [2]. The most plausible explanation is thus that the genetic origin of non-right-handedness is linked to schizophrenia as suggested by Crow in his theory of the "speciation event" [15].

The concept of atypical behavioural lateralization (e.g. handedness) is an important factor in schizophrenia research because of its subtle and intricate association with brain structures and functional brain lateralization [16], as well as its possible association with the genetics of schizophrenia. Hence, behavioural lateralization has been considered as a possible endophenotype, which means a possible intermediate along the line between the gene and the clinical expression [17,18]. This position is reinforced by the finding of excess of non-right handedness in the first-degree relatives of patients with schizophrenia, but not in the relatives of affective or other psychotic disorder patients [9]. This result indicates that the excess of non-right handedness in schizophrenia may have a genetic basis.

It is yet to be understood how atypical lateralization (e.g., non-right handedness) and schizophrenia is related at the genetic level. The question is whether the risk of non-right handedness varies with genetic loading among schizophrenia probands? Or is it simply an epiphenomenon in this population? The objective of this study was to assess handedness differences in familial risk of schizophrenia.

Materials and Methods

Study design and population

This was a cross-sectional study of 138 in-patients admitted into the wards of the Federal Neuropsychiatric Hospital, Enugu, South-Eastern Nigeria. This is a 300-bed hospital located within Enugu metropolis. The state was created from the old Anambra state in 1991. Enugu was the capital of the old Eastern region of Nigeria. The hospital serves the entire South-Eastern states and neighbouring geopolitical zones. It also provides mental health services to all age groups and in the various branches of psychiatric services including occupational rehabilitation. Participants were 138 patients admitted to the various wards of the hospital from 1st October 2015 to 31st March 2016.

Probands with diagnosis of schizophrenia made at least one year prior to sampling, aged between 18 - 64 years, stable enough to understand and follow the interview process were included. Those with schizophrenia of suspected organic aetiology and other major co-morbid physical and psychiatric illness were excluded. All were sampled after obtaining a written informed consent.

Procedure and Measurement

Each patient was re-assessed by the researcher and diagnosis made using the ICD-10 criteria for schizophrenia and confirmed using the Mini International Neuropsychiatric Interview. The MINI differs from other diagnostic instruments in that is semi-structured and

administered by experienced clinical interviewers in a much shorter time, as opposed to highly structured Composite International Diagnostic Interview (CIDI) or Diagnostic Interview Schedule (DIS) used by lay interviewers [19].

Those who met the diagnostic criteria for schizophrenia and fulfilled other study criteria were further interviewed with the socio-demographic questionnaire. Hand preference was assessed using The Annett Hand Preference Questionnaire (Annett, 1970) [20] which is a 12-item scale for the assessment of hand preference. Participants are required to indicate whether they use their right, left or either hands for six primary and six non-primary common actions.

Family history of schizophrenia was assessed using Family Interview for Genetic studies (FIGS). The Family Interview for Genetic Studies (FIGS) was developed by principal investigators in the National Institute of Mental Health (NIMH) Schizophrenia and Bipolar Disorder Genetics initiatives and NIMH extramural program staff in 1992, as a guide for systematically collecting information about relatives in family genetic studies of these disorders. It comprises of the general screening questions, the face sheet, and the symptom checklists [21].

Ethics

Approval for this study was obtained from the Ethics and Research Committee of the Federal Neuropsychiatric Hospital, Enugu. Written informed consent was obtained from all the participants. Participation was voluntary.

Data Analysis

The results were analyzed using the Statistical Packages for Social Sciences, version 20. Hand preference between the two groups was compared using Chi-square test.

Results

One hundred and thirty-eight in-patients admitted during the period of the study in the various wards of the hospital participated. The mean age of the participants was 31.76 ± 10.40 years. Seventy-three (52.9%) were males, never married (76.8%), secondary education (58.0%), unemployed (72.4%) (Table 1).

Characteristics	(N = 138)	Statistics
Mean Age		31.76 ± 10.40
Sex		
Male	73	52.9%
Female	65	47.1%
Marital Status		
Never Married	106	76.8%
Married	21	15.2%
Separated/Divorced/Widowed	11	8.0%
Educational Status		
No formal education	3	2.2%
Primary education	18	13%
Secondary education	80	58.0%
Tertiary education	37	26.8%
Employment Status		
Unemployed	100	72.4%
Working part-time	10	7.2%
Working full time	28	20.4%

Table 1: Socio-demographic profile of the patients.

Table 2 shows the frequency distribution of handedness among the participants. One hundred and thirty-two (95.7%) of the schizophrenia probands were right-handed. When left-handedness was combined with mixed-handedness as non-right-handedness, 6(4.3%) of the patients were non-right-handed.

Handedness	Probands (N = 138)
Right-handedness	132 (95.7%)
Left-handedness	4 (2.9%)
Mixed-handedness	2 (1.4%)
Right-handedness	132 (95.7%)
Non-right-handedness	6 (4.3%)

Table 2: Handedness among the Participants.

Table 3 shows that, although the number of subjects with non-right handedness was too small to make meaningful statistical analysis, it is noteworthy that all such subjects (i.e., non-right handed) had family history of schizophrenia. That is, all the patients without family history of schizophrenia were right-handed.

	Handedness (N = 138)		x ² stat.	df	p-value
	Right handedness (n = 132)	Non-right handedness (n = 6)			
Positive family history	90(68.2%)	6(100.0%)	2.744	1	0.098
No family history	42(31.8%)	0(0.0%)			

Table 3: Handedness and family history of schizophrenia in the probands.

Discussions

In the present study, handedness was classified using Annett-Maudsley criteria [20] but, because the number of left and mixed handed category participants was too small, the two were pooled together as non-right handedness.

The majority of the index schizophrenia population was right-handed (95.7%), a small proportion (4.3%) was mixed or left-handed (non-right handed).

The present study tested the hypothesis that schizophrenia probands with family history of mental disorders are significantly more likely to be left-handed than those without family history. Though, not statistically significant, all the schizophrenia patients who were non-right handed 6 (100.0%) had family history of mental disorders compared to the 0 (0.0%) of non-right handedness in those without a history. In other words, all such subjects (non-right handed) had family history of mental disorders compared with those without family history, of which all were right-handed. The difference was not statistically significant. This is similar to previous reports [3], for example; Cannon., *et al.* evaluated the association between handedness and family history of schizophrenia in schizophrenia patients. They found that non-right handedness was associated with negative family history [3].

The present study only used a questionnaire based assessment of handedness. Performance based measures and other indices of lateralization were not assessed. Hence, the present finding may have been influenced by culture. Cultural influences on hand preference have been reported, Laland., *et al.* noted that negative stigma associated with left-handedness and encouragement of left-handed individuals towards right-handedness, may influence reported rates of non-right handedness in some cultures [23]. Therefore, handedness has been found to be a biased indicator, which might be explained by ubiquitous external and societal pressure promoting right-handed preference among actual non-right handed people.

Handedness has been extensively studied in terms of heritability, primarily via twin studies [24].

A large-scale twin study of the heritability of handedness estimated that 24% of sample variance was due to “additive genetic effects”, while the remaining 76% was due to non-shared environmental influences [25]. Of interest is the putative link of non-right handedness and increased risk of schizophrenia, namely whether the phenotype of non-right handedness tends to run in families of patients with schizophrenia. Studies examining this have generated mixed results, with some finding no evidence of a heritable component [26,27]. By assessing rates of non-right handedness among schizophrenia probands with and without family history, the present study did not find evidence that non-right handedness was familial in this sample or that it was linked to increased genetic risk for schizophrenia. From the above findings (i.e., that non-right handedness was not significantly over-represented in probands with family history of mental disorders), handedness is unlikely to be a good phenotype for assessing genetic vulnerability to schizophrenia [25]. The most consistent associations are found between non-right handedness and clinical presentations of schizophrenia. It seems that there is enough evidence to claim that ‘atypical’ lateralization is more prevalent in the so-called, ‘neurodevelopmental type’ of schizophrenia. That is, schizophrenia characterized by impaired cerebral development, poor premorbid adjustment, abnormalities of early motor and cognitive development, higher obstetric adversities, and negative family history [28]. Therefore, some have viewed the deviation in lateral preference as an epigenetic event that, when aggregated with genetic factors, may result in a more severe form of schizophrenia [25].

Limitations

One of the limitations of this study is the assessment tool used to classify handedness which can be based on multiple-item preference questionnaire (self-report) or a multiple-item demonstration test. This study only used the self-report method which does not allow for a more direct measure of hand preference, and could easily be affected by cultural influences. Second, is the use of family history method to elicit family history information; although it saved cost and time, but lack of sensitivity for many psychiatric disorders is a major drawback. Direct interview, while having its problems such as selection bias could have made more rigorous diagnosis possible.

Conclusions

The concept of atypical behavioural lateralization (e.g. handedness) is an important factor in schizophrenia research because of its subtle and intricate association with brain structures and functional brain lateralization [16], as well as its possible association with the genetics of schizophrenia. This study shows that handedness is unlikely to be a good endophenotype for assessing genetic vulnerability to schizophrenia [25]. Hence, the need to for further search of heritable markers that will fulfill the criteria of endophenotype in schizophrenia research.

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