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Original Articles

Abnormal Hemispheric Lateralization as a Marker for the Neurodevelopmental Origin of Schizophrenia. Gender Impact Insights

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The gender differences in left-eyedness between schizophrenic and control subjects and the correlations with MPAs as an index of maldevelopment were studied.

The study included 98 schizophrenic patients meeting DSM-V criteria for schizophrenia and 82 control subjects without records of psychiatric disorder. Subjects with a history of drug/alcohol abuse, neurological disorder, mental disability, and ocular pathology were excluded. Three eye dominance tests and seven MPAs on the Waldrop scale were used.

Schizophrenic patients were more left-eyed than the control subjects. In males, the difference did not reach statistical significance. Female patients scored significantly higher on the eye tests. MPAs showed higher frequencies in schizophrenic vs. control subjects. Statistically significant positive correlations were found between left-eyedness and MPAs.

Left-eyedness is a useful biomarker of altered hemispheric lateralization. The cooccurrence of left-eyedness and MPAs, in one subject, appears to be a more reliable index of underlying neurodevelopment disorder.

Key words: schizophrenia, laterality, eye dominance, minor physical anomalies, sexual dimorphism

Introduction

Lateralization is the functional dominance of one of the dual organs of the body: hands, feet, eyes, and even ears, during spontaneous or purposeful actions. Lateralization is the process that organizes this asymmetry, leading to the choice of one side over the other.

The neuro-ontogenetic theory of the development of schizophrenia postulates that the disease is a consequence of aberrant brain development during the fetal or neonatal period [11, 18]. Lateralization of brain functions (including eye dominance) takes place in the early fetal stages of individual development, which suggests that cerebral asymmetry is a key dimension of neurodevelopment.

The most often used assessment for functional lateralization is hand dominance [2, 3, 10, 14]. Handedness, however, is influenced by many factors like geographic region, genetic and cultural factors, and gender. The choice of a dominant eye for vision is not a result of external influence, which makes it a strong predictor of brain lateralization. The concept of eye dominance relates to the tendency to prefer visual information coming through one of the eyes and the objects being thus more clearly and exactly reproduced, more stable, and even larger [14, 15].

However, there is a small number of studies, in which higher left eye dominance was found in schizophrenic patients than in control subjects [1, 5, 6, 7, 8, 16]. The reported percentages of left-eyedness in schizophrenic patients are extremely variable. Some authors found as high as 73% left-eyedness (male schizophrenics) [15], while others did not find a difference in eye dominance between schizophrenic and control subjects [13] A few studies considered eye dominance in relation to gender differences and the results are contradictory. Dane (2009) found left eye dominance prevalence only in male schizophrenics compared to controls but did not find such prevalence in schizophrenic females [4]. Yan et al., 1985 found just the opposite – left eye dominance in female schizophrenics was more frequent than in male schizophrenics [19]. Another author did not find any significant sex difference in eye dominance between schizophrenic patients and controls [15].

In this context, the aim of the study is to investigate sexual differences in left eye dominance as a biological marker of neuronal dysontogenesis in schizophrenic patients and control subjects. This study is part of a larger investigation project on the intriguing relations between six groups of markers of neuronal dysontogenesis - left-handedness, left-footedness, left-eyedness, minor physical anomalies, digit ratio, and cognitive (attention and memory) deficit.

Material and Methods

Subjects

The study was conducted in the Clinic of Psychiatry at the University Hospital in Sofia and the State Psychiatric Hospital in Radnevo. The sample included 98 (56 men, 42 women) consecutively admitted schizophrenic inpatients with a mean age of 34.45 years (SD=15.67, range 23-79) for men and 42.20 years (SD=11.38, range 21-63) for women.

The patients satisfied the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) criteria for a diagnosis of schizophrenia based on case records review,

DSM-V-based semi-structured interview and information obtained from relatives for stronger validation of the diagnosis. To enhance the homogeneity of the schizophrenic group, potential subjects were excluded if they had a history of drug or alcohol abuse, identifiable neurological disorder (seizure disorder, head injury, multiple sclerosis, etc.), or any signs of intellectual disability or somatic disorder with neurological components.

For the eye tests exclusion criteria were any previous or present eye and upper limb disorders hampering the performance of the eye tasks. Impaired visual acuity, higher than +/-2 dioptres, and more than +/-1 dioptre difference between the two eyes were exclusion criteria, as these have been proven to confound the performance of eye tasks.

The control group consisted of 82 subjects (30 men, 52 women) with a mean age 34.70 years (SD=16,82, range 18-79) for men and 44.50 years (SD=10.73, range 23-67) for women. Normality was defined as the absence of a previous or present psychiatric disorder, according to DSM-V. Controls satisfied exclusion criteria like those applied to schizophrenic patients. In addition, for better separation between the control and the schizophrenic group, we implemented another exclusion criterion for controls - having a first-degree relative with a history of a psychotic disorder, major affective disorder, or suicide.

To avoid eventual confound due to ethnic and racial differences related to lateralization, both schizophrenic patients and controls were of Bulgarian origin. Individuals were excluded if their parental or grandparental ethnic group was other than Bulgarian.

The refusal rate of potential participants was insignificant [below 5%], excluding selectivity bias.

The study was approved by the Local Ethics Committee and all subjects gave written informed consent prior to participation.

Instruments

Eye Dominance Scale

Eye dominance (ocular sighting dominance) was measured by a set of three eye dominance tests, administered as performance assessments, not as preference questionnaires.

Each test was performed twice and the subject was asked to perform the test again if there was any inconsistency in the preference.

1. Looking through a monocle test – the participant is asked to take with both hands a monocle and look through it.

2. Hole-in-card test - the participant is asked to hold the card with both hands at arm's length and look with both eyes through the hole at an object. While continuing to focus on the object and keeping the object centered in the hole with both eyes open, the participant must slowly bring the card towards the face until it touches his nose. The card is positioned over one of the subject eyes.

3. Porta test (modified Miles test) - the participant is asked to extend one arm and to align a forefinger with a distant object with both eyes open, then to close his left eye and then the right eye consequently. The object is still aligned with the index finger when seen with the dominant eye. A potential limitation of the test is the impact of the arm that the patient uses according to his hand dominance.

Each eye test is rated: 0 – Preference for right eye; 1 – No preference (both eyes equally); 2 – Preference for left eye. Each test score ranges from 0 to 2; the eye set total score ranges from 0 to 6.

All assessments were performed by the same examiner.

Statistical analysis

As our data is not continuous and lacks normal distribution, the non-parametric Mann-Whitney test for means difference between two independent groups was used. For comparing categorical data χ^2-test (in 2x2 table with Yates' correction for continuity) was used for comparing categorical data, χ^2-test (in 2x2 table with Yates' correction for continuity) was used for comparing categorical data.

The categories of the eye tests can be treated as ordinal data – graded, in ascending order of leftedness: 0 - Preference of right eye; 1– No preference -both eyes equally; 2 – Preference of left eye. Ordinal data allows for calculating the mean left-eyedness for every single eye test. A variable mean is usually more sensitive than its categories in detecting a difference between groups. Besides, it enables comparing the important differences between the mean sum of left-eyedness of the Eye Dominance Subscale and the mean sum of the Eye Dominance Scale (3 eye tests) between schizophrenic and control subjects.

Statistical significance was defined as $p < 0.05$; two-tailed. Data was analyzed with SPSS 25.0.

Results

Comparison of eye dominance between schizophrenic and control subjects

The frequency of left eye dominance is significantly higher in schizophrenic than in control subjects in the three eye tests – Looking through a monocle (40.0% vs. 19.5%, $p<0.004$), Hole test (42.1% vs. 19.5 %, $p< 0.03$) and Porta test (42.4% vs. 20.7%, $p<0.06$). But this general comparison of left eye dominance between schizophrenic and control subjects, when examined by gender demonstrate marked difference in men and women. *Comparison of eye dominance between schizophrenic and control subjects by gender.*

Intra-gender comparisons

Schizophrenic men versus control men

Male schizophrenic patients show higher left eye dominance than the same-sex controls for the 3 eye tests and Sum 3 eye tests. The frequency of left eye preference is higher in male schizophrenics than the same-sex control subjects in the three tests - Looking through monocle (35.8% vs.16.7%), Hole test (35.8% vs. 23.3%) and Porta test (41.7% vs. 23.3%).

However, none of these differences is statistically significant at $p<.05$ - Hole test ($p=.348$), while Looking through monocle ($p=.080$), Porta test ($p=.164$) and Sum 3 eye tests ($p=.089$) merely approach statistically significant difference.

Schizophrenic women versus control women

Female schizophrenic patients show markedly higher left eye dominance than the same-sex controls for the 3 eye tests and Sum 3 eye tests. The frequency of left eye

Table 1. Comparison of eye dominance between schizophrenic and control subjects by gender

	Men (N=83)						Women (N=94)					
	Schizophrenia (N=53)*		Controls (N=30)*		Statistical Significance**		Schizophrenia (N=42)*		Controls (N=52)*		Statistical Significance**	
EYE TESTS	n	%	n	%	χ^2	p	n	%	n	%	χ^2	p
Looking through monocle					5.040	.080					6.202	**.013**
Right	32	60.4%	25	83.3%			23	54.8%	41	78.8%		
Both	2	3.8%	0	0.0%			0	0.0%	0	0.0%		
Left	19	35.8%	5	16.7%			19	45.2%	11	21.2%		
Hole test					2.113	.348					11.428	**.001**
Right	33	62.3%	23	76.7%			21	50.0%	43	82.7%		
Both	1	1.9%	0	.0%			0	0.0%	0	.0%		
Left	19	35.8%	7	23.3%			21	50.0%	9	17.3%		
Porta test					3.618	.164					6.028	**.014**
Right	27	56.3%	23	76.7%			21	56.8%	42	80.8%		
Both	1	2.1%	0	0.0%			0	0.0%	0	0.0%		
Left	20	41.7%	7	23.3%			16	43.2%	10	19.2%		
Sum 3 eye tests					9.546	.089					8.504	**.037**
0	18	37.5%	19	63.3%			15	40.5%	36	69.2%		
2	13	27.1%	4	13.3%			6	16.2%	7	13.5%		
3	1	2.1%	0	0.0%			0	0.0%	0	0.0%		
4	6	12.5%	6	20.0%			6	16.2%	4	7.7%		
5	1	2.1%	0	0.0%			0	0.0%	0	0.0%		
6	9	18.8%	1	3.3%			10	27.0%	5	9.6%		

* Valid cases - the sum of the Right, Both and Left categories does not always add up to the total number, due to missing data for some cases
**Pearson Chi-Square

preference is higher in female schizophrenics than the same-sex controls in the three tests – Looking through monocle (45.2% vs. 21.2%), Hole test (50.0% vs. 17.3%) and Porta test (43.2% vs. 19.2%). In contrast to the male intra-gender comparison, all the differences in women are statistically significant - Looking through monocle ($p=.013$), Porta test ($p=.014$) and Sum 3 eyes tests ($p=.037$) have statistical significance at $p<.05$, while Hole test reach a very strong statistically significant difference at $p<.001$.

Difference between the two intra-gender comparisons of left eye dominance

The two intra-gender comparisons show that schizophrenic patients are more left eye dominant than controls in both sexes, but this difference is much more pronounced in women than in men for all three eye tests. Thus, women contribute the bigger part to this strong overall difference in left eye preference between schizophrenic and control subjects.

It is noteworthy that the small number of subjects with no eye preference (category Both) is entirely in the male schizophrenic group**.** Intermediate degrees of left eye dominance are those between grade 0, which indicates the exclusive right eye dominance, and grade 6, which shows the maximum leftward shift for left eye dominance i.e., subjects with grades 2,3,4, and 5 of Sum 3 eye tests. Importantly, the number of such "intermediate" men are almost twofold the corresponding number of "intermediate" woman (21 vs. 12).

Correlations between minor physical anomalies and left eye dominance

All seven MPAs show higher frequencies in schizophrenic vs. control subjects. The greatest differences are found for single transverse palmar crease of the left hand ($p<.002$), transversally furrowed tongue ($p<.006$), single transverse palmar crease of the right hand ($p<.054$). Importantly, the sum of the seven MPAs is significantly higher ($p<.003$) in schizophrenic vs. control subjects.

To address the low internal consistency of the MPAs of the Waldrop Physical Anomaly Scale (40) and to capture more subtly and diversely the multiple correlations between left-eyedness and MPAs, the 7 MPAs were divided into 3 groups in descending order of their differentiating strength between schizophrenic and control subjects.

1. Sum 3 MPAs = Single transverse palmar crease of the left hand, transversely furrowed tongue, and Single transverse palmar crease of the right hand
2. Sum 5 MPAs = Sum 3 MPAs + left/right adherent earlobes
3. Sum 7 MPAs = Sum 5 MPAs + left/right curved fifth finger

Correlation matrix between the 3 eye tests and MPAs

The Spearman's rank correlation matrix shows that positive correlations are highly predominant between left-eyedness and MPAs, with multiple statistically significant correlations:

Females

– Looking through a monocle with transversally furrowed tongue ($p<.005$) and Sum 3 MPAs ($p<.05$).
– Hole test with Sum 3 MPAs ($p<.05$), adhered ear lobule left ($p<.05$), transversely furrowed tongue ($p<.05$).

– Sum of 3 eye tests with transversely furrowed tongue (p<.05).
– Some correlations are close to statistical significance:
– Sum of 3 eye tests with Sum 3 MPAs (p=.053).

Males

– Porta test with Sum 3 MPAs (p<.05), transversely furrowed tongue (p<.05).
– Sum of 3 eye tests with transversely furrowed tongue (p<.05).
– Close to statistical significance
– Porta test with Sum of 5 MPAs (p=.066)

Discussion

By selecting three different eye dominance tests, we confirmed the strongly higher prevalence of left-eyedness in schizophrenics versus controls. Another thing that contributed to these strong results was the application of performance assessments, not preference questionnaires.

As in all other aspects, lateralization has gender differences. The male brain is thought to be more lateralized than the female, however, these facts remain the result of the next studies [9,12, 17].

In our data, male schizophrenic patients show a higher frequency of left-eyedness than the same-sex controls for the 3 eye tests separately and as a sum, however, none of these are statistically significant. In contrast, female schizophrenic patients show statistically significantly higher left-eyedness than the same-sex controls in the 3 eye tests separately and as a sum.

This shows that schizophrenic patients are more left-eyed than normal controls in both sexes, but this difference tends to be much more pronounced in women than in men for all three tests. Thus, women contribute the greater part to this overall difference between schizophrenic and control subjects.

Our findings are consistent with those reported by Yan [19], who also found much more pronounced left-eyedness in schizophrenic women than in men, but are opposite to Dane (2009), who found left-eye dominance only in male schizophrenic patients.

It is evident that schizophrenic men in terms of eye dominance become less polarized in eye preference, matching normal women in that regard and schizophrenic women become more polarized in eye preference, matching normal men in that regard.

Considering eye dominance as a continuum shows that, except for homogeneous left dominance, schizophrenic men show twofold more ambilateral eye dominance than schizophrenic women.

Our analysis shows that with respect to the right eye dominance, the frequency arrangement in hierarchical order is as follows: schizophrenic women - 45.2%, 50.0%, 43.2%, schizophrenic men - 35.8%, 35.8%, 41.7%, control women - 21.2%, 17.3%, 19.2%, control men - 16.7%, 23.3%, 23.3%.

Data from the literature concludes that healthy women are less lateralized than healthy men. There is an opposite trend in schizophrenics. Schizophrenic men become less polarized matching normal women in left-eye dominance and schizophrenic women become more polarized matching normal men in left-eye dominance.

The dysfunction in the left hemisphere will determine both schizophrenia and sinistrality- and we may tentatively speculate that this will make schizophrenic men less lateralized than normally and schizophrenic women more lateralized than normally.

Thus, if left hemisphere dysfunction is related to schizophrenia, then eye dominance is directly related to cerebral hemispheric dominance and females with schizophrenia might have a greater chance of showing left eye dominance.

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