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ORIGINAL ARTICLE

Investigation of second to fourth finger length ratio (2D:4D) in patients with bipolar disorder

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Objective: The etiology of bipolar disorder has yet to be fully elucidated, but differences in sex hormones have been suggested to play a role in its pathogenesis. An easily assessed marker of prenatal androgen exposure is the second-to-fourth-digit ratio (2D:4D) of the hand. In this study, we aimed to compare the 2D:4D ratio of patients with bipolar disorder to that of healthy controls.
Methods: Seventy patients with bipolar disorder and 70 healthy controls, matched for age and sex, were included in the study. Finger lengths were measured from the palmar digital crease to the tip using a digital vernier caliper.
Results: Patients with bipolar disorder had considerably higher right-hand 2D:4D ratios compared to controls. Both the right and left 2D:4D ratios of male patients were significantly greater than those of males in the control group. Female patients showed no differences in right or left 2D:4D ratio compared to healthy controls.
Conclusion: These findings suggest that a high 2D:4D digit ratio of right hand is associated with the presence of bipolar disorder in males. Further large-scale, prospective studies are needed to explain the validity of this marker and its relationship with bipolar disorder.

Keywords: Bipolar disorder; digit ratio; 2D:4D; prenatal androgens

Introduction

Bipolar disorder is a complex condition characterized by severe mood changes, from manic highs to depressive lows. The estimated incidence of bipolar disorder in adults globally is 1 to 3%.[1] Two diagnostic subtypes are recognized: bipolar disorder I, characterized by at least one episode of full-blown mania that impacts functioning; and bipolar disorder II, characterized by a more short-lived and less severe form of mania, called hypomania, which occurs alongside episodes of depression. The development of bipolar disorder has been attributed to psychological, neurophysiological, and genetic variables, yet the etiology of the disorder remains uncertain. Sex hormones have also been implicated in its etiology. Meinhard et al. reviewed several studies evaluating the effect of estrogen and tamoxifen on bipolar disorder, indicating that estrogen fluctuations might be a significant factor in the etiology of bipolar disorder, and found tamoxifen to be effective in producing antimanic effects.[2] Sher et al. suggested that testosterone concentrations correlate with the number of manic episodes, and may be related to the course of bipolar disorder.[3] Gonadal androgens, especially testosterone, play an important role in regulating nerve-cell migration, synaptogenesis, and dendritification.[4] Therefore, the evaluation of prenatal androgens may shed important light onto the etiopathogenesis of bipolar disorder.

An easy way to assess prenatal androgen exposure is the ratio of the length of the second digit (2D) to the length of the fourth digit (4D), also known as the 2D:4D ratio. This anatomical feature, determined during the 13th week of pregnancy, is a morphologic indicator of sexual dimorphism.[5] It remains relatively constant throughout adulthood, and is considered a reliable marker of intrauterine sex hormone levels.[6,7] In men, the second finger is smaller than the fourth, whereas in women, the second and fourth digits are of equal length, or the second digit is longer. Consequently, in males, 2D:4D is generally smaller than in females.[8] In the right hand, this dimorphic tendency is usually clearer than in the left, although the reason remains unclear.[9] In this context, a low 2D:4D ratio was found to be associated with higher fetal testosterone and low estrogen levels, while a high 2D:4D ratio was associated with higher fetal estrogen and low testosterone.[10]

In recent years, many studies have focused on the potential impact of 2D:4D digit ratio on mental illnesses such as anxiety, alcohol dependence, autism, and schizophrenia.[11-15] To our knowledge, only one study has investigated the relationship between 2D:4D ratio and bipolar disorder: Tegin et al. found a higher right-hand 2D:4D

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digit ratio in patients with the disorder compared to controls, and found that bipolar disorder diagnosis status was predicted by right-hand 2D:4D digit ratio and complete impulsivity scores.[16]

Within this context, the purpose of this study is to compare the 2D:4D digit ratio in patients with bipolar disorder vs. healthy controls and ascertain its potential utility as a biological marker in this disorder.

Methods

Participants and sociodemographic characteristics

Seventy consecutive adult patients with bipolar disorder treated in our department were enrolled. Seventy age- and sex-matched healthy subjects, with no history of psychiatric disorders, were recruited from hospital staff as a control group.

Patients were diagnosed with bipolar disorder type 1 or type 2 according to DSM-IV criteria. In addition, the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) were applied to measure the severity of manic and depressive symptoms, respectively. Patients with comorbid psychiatric disorders such as obsessive-compulsive disorder, intellectual disability, and psychosis were excluded, as were those with a history of substance abuse and/or other chronic diseases. Since a broken or wounded finger can result in length differences with enormous impact on 2D:4D ratio, participants with such a history were also excluded from the study.

Measurement of 2D:4D ratio

The lengths of the second and fourth digits on both hands were measured, always by the same investigator. The length of the digit was defined as the distance from the center of the palmar digital crease (basal flexion crease) on the ventral surface of the hand to the fingertip. Direct finger length measurements, obtained with a digital caliper, were used instead of indirect measurement on hand scans. The 2D:4D ratio was calculated by dividing 2D length by 4D length for each hand. Each finger was measured twice, and the arithmetic mean was computed.

Statistical analysis

Data were analyzed in PASW Statistics, Version 18 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. Data were described as mean and standard deviation and evaluated using descriptive analysis. When required, analysis of covariance (ANCOVA) was used to control for covariates. An age- and sex-adjusted ANCOVA (general linear model) was run for the 2D:4D digit ratio. P-values less than 0.05 for two-sided tests were considered statistically significant.

Ethics statement

The study was approved by the local ethics committee (protocol 252/2018), and written informed consent was obtained from all participants.

Results

A total of 140 participants, 70 with bipolar disorder and 70 healthy controls, were enrolled in the survey. Table 1 summarizes the groups' demographic and clinical variables. There were no significant between-group differences in mean age, male:female ratio, or other demographic characteristics, nor in smoking rates (Table 1).

Comparisons of 2D:4D ratios between the two groups are presented in Table 2. Patients with bipolar disorder had significantly higher right-hand 2D:4D ratios compared to controls ($p = 0.020$). ANCOVA showed that this difference remained significant even after controlling for age and sex ($F = 5.516$, $\eta_p^2 = 0.039$, $p = 0.020$). The left-hand 2D:4D ratio was not significantly different between patients and controls ($F = 3.052$, $\eta_p^2 = 0.022$, $p = 0.083$) (Table 2).

Since the 2D:4D ratio is indicative of sexual dimorphism, we also assessed the difference for each sex individually between the two groups. Both the right-hand and left-hand 2D:4D ratios of male patients were significantly

Table 1 Demographic and clinical characteristics of patients with bipolar disorder and controls

	Bipolar disorder (n=70)	Controls (n=70)	t/χ^2	p-value
Age	39.7±12.8	38.7±7.7	-0.540*	0.590
Sex, n				
Male	42	42		
Female	28	28		
Marital status, n				
Single	27	21		
Married	43	49	1.141†	0.285
Education				
Primary	15	17		
Secondary	29	22		
Higher	26	31	1.524†	0.467
Smoking				
Smoker	33	29		
Nonsmoker	37	41	0.463†	0.496
Duration of illness (years)	9.8±7.8			
Duration of hospitalization (months)	2.1±3.4			
Duration of pharmacotherapy (years)	6.7±5.3			
History of suicide attempt				
Yes	18			
No	52			
YMRS	14.4±10.6			
HDRS	5.1±2.7			

Data presented as mean ± standard deviation, unless otherwise specified.
HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.
* Student *t*-test; † chi-square test.

Table 2 Mean 2D:4D ratio of patients with bipolar disorder and controls

					ANCOVA		
	Bipolar disorder	Controls	*t*	p-value	F	p-value	η_p^2
Total (n=70)							
Right 2D:4D	0.988±0.022	0.980±0.021	2.354	**0.020***	5.516	**0.020*†**	0.039
Left 2D:4D	0.994±0.031	0.986±0.024	1.674	0.096	3.052	0.083	0.022
Male (n=42)							
Right 2D:4D	0.986±0.016	0.977±0.023	2.071	**0.042***	4.546	**0.036*‡**	0.053
Left 2D:4D	0.993±0.024	0.979±0.023	2.620	**0.010***	6.881	**0.010*‡**	0.078
Female (n=28)							
Right 2D:4D	0.992±0.028	0.985±0.018	1.263	0.213	1.737	0.193	0.032
Left 2D:4D	0.996±0.023	0.997±0.023	-0.036	0.971	0.117	0.733	0.002

Data presented as mean ± standard deviation.
2D = length of second finger; 4D = length of fourth finger; ANCOVA = analysis of covariance; *t* = Student *t*-test.
* $p < 0.05$.
† After adjustment for age and sex for comparisons between two groups.
‡ After adjustment for age alone for comparisons between two groups.
Bold type denotes statistical significance.

higher than those of male controls (p = 0.042 and p = 0.010, respectively). Conversely, women showed no differences in right-hand or left-hand 2D:4D ratio between patients and healthy controls (p = 0.213, p = 0.971 respectively) (Table 2).

Fifty-three patients had bipolar type 1 and 17 patients had bipolar type 2 disorder. There was no difference in right-hand or left-hand 2D:4D ratio between bipolar 1 and 2 patients (*t* = -0.453, p = 0.652; *t* = -0.351, p = 0.726, respectively).

There was no correlation between 2D:4D ratio in either hand and YMRS scores, HAM-D scores, duration of illness, or duration of pharmacotherapy in the patient group ($p > 0.05$).

Discussion

In the present study, we compared the 2D:4D digit ratio – an indirect indicator of prenatal androgen exposure – in patients with bipolar disorder and healthy controls. In our sample, the right-hand 2D:4D ratio was higher in the bipolar disorder group than in the control group. In the literature, to the best of our knowledge, only one previous study has investigated this relation; in line with our findings, those authors found a higher right-hand 2D:4D ratio in the bipolar disorder group.[16] In addition, in our study, we also demonstrated that men with bipolar disorder have higher right- and left-hand 2D:4D ratios than healthy control men. Conversely, in women there was no such difference in either the right or the left hand. Our results also reproduce consistent findings of greater digit ratios in women compared to men. These findings may suggest that having a reduced exposure to prenatal testosterone and a greater level of exposure to prenatal estrogen is a risk factor for development of bipolar disorder in males. There are several methods to interpret the observed connection between bipolar disorder and high 2D:4D ratio. First, bipolar disorder would directly induce a higher 2D:4D ratio. This is unlikely, however, as prior studies have shown that the 2D:4D ratio remains continuous throughout life after birth.[17] Second, both elevated 2D:4D values and bipolar disorder might be caused by a common mechanism.

While the mechanisms for such opposite hormonal effects on men can not be speculated, we find that they are consistent with other studies on the relationships between sex hormones and bipolar disorder. For example, Wooderson et al. found that testosterone concentrations in men with bipolar disorder were significantly lower than in male controls.[18] Johnson et al. found that certain subgroups of men with depression had low levels of testosterone.[19] A recent study found a positive correlation between testosterone levels and number of both manic episodes and suicide attempts in bipolar disorder; the authors implied that testosterone concentrations may be associated with the course of bipolar disorder and suicidal behavior.[3] The results reported herein provide further evidence for a biological basis of bipolar disorder.

In men and women, the lifetime incidence of bipolar disorder is approximately the same, although the prevalence of manic episodes in men with the disorder is higher.[20] Research suggests an increased incidence of bipolar disorder type 2 and hypomania in women.[20] In our sample, there were more males in the bipolar type 1 subgroup and more women in the bipolar type 2 subgroup, which is contistent with the literature. It is not evident whether there are sex variations in the number of depressive or manic episodes experienced; the evidence is inconsistent.[20]

It is not yet apparent why 2D:4D ratio variations in male sex and the right hand are prominent.[9] Indeed, the difference in 2D:4D ratio between men and women has been shown to be more prominent on the right hand in a meta-analysis.[9] The authors proposed that the right-hand 2D:4D could be a stronger marker of prenatal androgen exposure than the left-hand ratio. This may explain why the right-hand 2D:4D ratio was associated with bipolar disorder in our study.

It has been reported that, in the developing brain, prenatal exposure to sex hormones can affect corticolimbic networks that play a role in stress management,

including structures such as the amygdala and the hippocampus.[21] It is also assumed that prenatal testosterone and prenatal estrogen modulate the expression of Hox genes, which play vital roles both in brain formation and in finger development.[22-24] A defect in hormone levels may cause abnormal expression of a Hox gene, which might in turn lead to anomalies in brain development and finger ratios. From this perspective, it may be suggested that exposure to elevated prenatal estrogen or reduced prenatal testosterone levels during fetal development may cause an increase in the 2D:4D ratio as well as in the risk of developing bipolar disorder in adulthood.

As in all research, some methodological limitations in this study are worth noting. The small sample size limits generalization of our findings to a larger population. There are also constraints to using the 2D:4D ratio. First, the sex difference in 2D:4D digit ratio is small compared to the actual differences in prenatal hormone concentrations between the sexes.[10] Our results may thus underestimate the real connection between prenatal exposure to sex hormones and the risk of bipolar disorder development. In addition, the 2D:4D digit ratio is not an optimal measure of prenatal hormone concentrations; unexplained variability is probable in our results. While our findings provide initial insight into the association between prenatal androgen exposure and bipolar disorder development, they also raise some important theoretical and clinical issues. Our results provide further evidence that the prenatal environment affects the odds of developing bipolar disorder in future life. While this research should be replicated in a larger and broader sample, our findings contribute to understanding how prenatal sex hormone exposure influences mood and the importance of hormones in the development of bipolar disorder. The 2D:4D ratio usually differs by age and sex; the strength of our study is that this ratio in patients remained different from that of controle even after controlling for age and sex.

Further evidence clarifying the association between androgen exposure and bipolar disorder may pave the way to novel pharmacological approaches that optimize androgen concentrations in patients with bipolar disorder. A high 2D:4D ratio alone is not diagnostic of bipolar disorder, but when used in combination with other indicators, may support such a diagnosis. A high 2D:4D ratio may also help detect people at high risk of developing bipolar disorder in future, thus facilitating protective interventions. Such predictive models may allow effective preventive strategies to be developed.

In conclusion, low levels of exposure to testosterone in utero may be suspected of playing a significant role in bipolar disorder etiology; however, there is little information on this issue. Our findings suggest that a high 2D:4D digit ratio of the right hand, an index of fetal androgen exposure, is associated with the presence of bipolar disorder. Further large-scale, prospective studies are required to explain the validity of this index and its relationship with the onset and incidence of bipolar disorder.

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Disclosure

The authors report no conflicts of interest.

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