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Effect of Lateralization on Motor and Mental Speed in Bipolar Disorder

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ÖZET:

Bipolar bozuklukta lateralizasyonun motor ve mental hıza etkisi

Amaç: Motor ve duygudurum düzenleyici sistemlerin arasındaki ilişki duygudurum bozukluklarının fizyopatolojilerinin anlaşılmasına ışık tutabilir. El tercihi, sağ elini kullanan bireylerde serebral lateralizasyonun güvenilir bir ölçüsüdür. Bu araştırmada lateralizasyonun bilişsel performansın yanı sıra motor ve mental hız üzerine olan etkilerinin incelenmesi amaçlanmıştır.

Yöntemler: Araştırmaya 68 ötimik bipolar hasta (ortalama yaş: 33.66±6.38, 33 kadın) ve 65 sağlıklı katılımcı (ortalama yaş: 33.65+7.11, 27 kadın) alındı. Tıbbi veya psikiyatrik hastalığı olanlar çalışmaya alınmadı. Montreal Bilişsel Değerlendirme (MOCA), parmak-tıklama, Peg-board, Yetişkin bellek ve bilgi işleme hızı bataryası (AMIPB), Edinburgh el tercihi envanteri ve reaksiyon zamanı testleri uygulandı.

Bulgular: Gruplar yaş, cinsiyet ve eğitim durumu bakımından benzerdi. Bipolar hastalar kontrollere göre daha lateralize idiler (p=0.027). Göz ve ayak lateralizasyonu açısından fark bulunmadı. Hastalar kontrollere göre MOCA (p=0.049), Peg-board (her iki el p<0.001), parmak tıklama testi (sağ p<0.001, sol p<0.002), AMIPB (motor ve A alt testleri p<0.001) ve görsel ve işitsel reaksiyon zamanı testlerinde (her ikisi için p<0.001) daha düşük performans gösterdiler. Lateralizasyonun derecesi yalnız bipolar hasta grubunda işlem yapma hızı ile pozitif yönlü bağıntı gösterdi.

Sonuç: Sağ elini kullanan hastaların sağ elini kullanan sağlıklılardan daha lateralize oldukları ve lateralizasyonun hastalarda işlem hızı bakımından avantaj sağladığı tespit edildi. Bu bulgu aşırı lateralizasyona neden olan fizyopatoloji ile bipolar bozuklukta interhemisferik iletişimin yavaşlaması arasında bir ilişki olabileceğini, dolayısı ile lateralizasyonun hemisferler arası iletişimin daha az kullanılması için bir kompanzasyon mekanizması olabileceğini düşündürmektedir.

Anahtar sözcükler: Bipolar bozukluk, tek el kullanabilme, serebral hemisferler, insan bilgi işleme

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ABSTRACT:

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Objective: The correspondence between the motor and mood regulation systems may shed light on the physiopathology of mood disorders. Handedness is a reliable proxy measure for cerebral lateralization for right handed subjects. In this study we have investigated the effects of lateralization on cognitive performance as well as motor and mental speed in bipolar disorder.

Methods: Sixty-eight euthymic bipolar patients (mean age: 33.66±6.38, 33 female), and 65 healthy subjects (mean age: 33.65+7.11, 27 females) were enrolled. Participants with medical or psychiatric comorbidities were excluded. The Montreal Cognitive Assessment (MOCA), finger-tapping, peg-board test, Adult Memory and Information Processing battery (AMIPB), Edinburgh Handedness Inventory and reaction time tests were the measures utilized in our study.

Results: The groups were similar in terms of age, gender and education. The bipolar patients were more lateralized than the controls (p=0.027), whereas eye and foot lateralization did not differ between the groups. The patients performed poorer than the controls on the MOCA (p=0.049), peg-board (right and left, p<0.001), finger-tapping (right p<0.001; left p=0.002), AMIPB (motor and A subtest, p<0.001 for both) and the visual and auditory (p<0.001 for both) reaction time tests. The degree of lateralization was correlated with the speed of processing in the bipolar group, but not in the control group.

Conclusion: Right handed patients with bipolar disorder are more lateralized than healthy subjects and lateralization provides an advantage for processing speed in bipolar patients. This finding may indicate a relationship between lateralizing physiopathology and slowed interhemispheric communication and thus, an increase in lateralization might be a compensatory mechanism to use less interhemispheric communication in bipolar disorder.

Key words: Bipolar disorder, handedness, cerebral hemispheres, human information processing

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INTRODUCTION

The two hemispheres of the human brain are semi-independent, parallel processing systems, each specialized for different higher cognitive functions (1). Most of the brain functions are lateralized into one hemisphere. Although the dynamics of this complex system are vital to understanding the physiology of the brain, this topic deserves much more attention than it has received to date. Although yet to be clearly understood, this complex system has been involved in psychiatric disorders and theory suggests that language components normally lateralized into the left hemisphere come to be represented in both hemispheres and thus thoughts can be heard in psychotic spectrum disorders (2); thus, abnormal brain lateralization may represent the pathophysiology of major psychiatric disorders.

Many findings have indicated hemispheric specialization abnormalities both in bipolar disorder and schizophrenia (3-5). Generally, right (non-dominant) hemisphere insult has been implicated in mood disorders (6,7), whereas left hemispheric dysfunction has been observed more frequently in schizophrenia (see review 8). Reite and colleagues (9) have showed that functional cerebral asymmetry of a somatosensory evoked field component is reversed in psychotic bipolar patients, whereas the lateralization of non-psychotic bipolar patients did not differ from healthy controls. Recent magnetoencephalography studies have revealed abnormal auditory cortex asymmetries in bipolar disorder (10,11), and this finding was particularly important since it discriminated bipolar disorder from schizophrenia (10). These features may raise the possibility of abnormalities in certain developmental processes that might cause anomalous brain torque in major psychiatric disorders.

Various reported abnormalities, particularly reduced corpus callosum size have indicated that interhemispheric communication is weakened both in bipolar disorder and schizophrenia (12-14). The myelin production capacity of oligodendrocytes decreases in schizophrenia and bipolar disorder (15,16), which may be one of the causes of disrupted white matter integrity, both at the intercortical (17) and interhemispheric levels (12-14). Reduced gamma coherence (intercortical communication) findings from electroencephalography studies in the manic (18) and euthymic (19) phases of the disorder may also indicate disrupted connectivity from a different point of view.

The probability of left hemispheric specialization for linguistic functions is approximately 95% (20,21). Handedness is thus a reliable proxy measure for cerebral lateralization, particularly in right-handed subjects. Two different meta-analyses have showed that left or mixed handedness was significantly more prevalent in patients with schizophrenia compared with healthy controls (5,22). In bipolar disorder the prevalence of left or mixed handedness did not differ from control groups (23); however, the handedness lateralization of right-handed subjects was increased (3,23). Schizophrenia has been suggested to be a disorder with decreased lateralization (2,24); whereas, bipolar disorder has been studied in a limited fashion and is believed to be a disorder of extreme lateralization (2,3,23-25).

Lateralization dynamics are essential to understand the functional organization of the human brain and the pathological processes in bipolar disorders. The interplay between cognitive functions and lateralization is a dimension that may point to specific disturbances related with abnormal functional brain lateralization in bipolar disorder. In this study, we aimed to assess the lateralization profile of bipolar patients and furthermore the effects of lateralization on cognition and motor and mental speed. It is quite possible that bipolar patients may show a different profile from healthy control groups due to disrupted white matter connectivity (17) and inter-hemispheric information transfer (12-15). Clinical characteristics were also taken into consideration to detect correlates of disease characteristics with possible abnormalities. Abnormal lateralization characteristics may provide clues about the anomalous brain structures in bipolar disorder.

METHODS

The Participants

Sixty-eight consecutive bipolar I patients (mean age: 35.66±6.38, female/male: 33/35) and a healthy control group (mean age: 33.65±7.11, female/male: 27/38) consisting of 65 subjects were enrolled. The groups were similar in terms of age, gender and education ($p>0.05$ for all). All patients were interviewed using the Turkish version of the SCID-1 (Structured interview according to the DSM-IV) (26-27). Healthy participants were interviewed with the SCID-1 non-patient form to ascertain that there was no

current or history of psychiatric disorders. The local Ethical Committee of Bakirkoy Research and Training Hospital for Psychiatry, Neurology, and Neurosurgery approved the study. Each participant provided a written informed consent. The patients had been euthymic for at least 3 months. Patients scoring more than 7 on the Young Mania Scale (YMRS) (28,29) and the Hamilton Depression Rating Scale (HAM-D 21) (30,31) were excluded. Pregnancy, lactation, alcohol or substance use disorders, co-morbid axis-1 psychiatric diagnoses, patients on classical antipsychotics, neurological diseases or general medical conditions that may influence the locomotor system were excluded (routine laboratory tests were also assessed). All participants were at first checked to prove that there is no asymmetry of the limbs and all subjects were asked if, they had any asymmetric loss of vision or audition. Duration of sleep in the last week and the day before enrollment were controlled. Participants with sleep disturbances or acute sleep deprivation were excluded to avoid the interference of fatigue and sleep deprivation.

After the medical assessments, the patients were rated using the Montreal Cognitive Assessment (MOCA) (32,33) for a brief cognitive screening. The MOCA is a sensitive tool to detect mild cases of cognitive impairment that contains items to test visuospatial functions, executive functions, attention, working memory, speech, and abstract thinking. The sensitivity and specificity of the MOCA have been found to be better than that of mini mental state examination (32) and it currently being used in most clinical conditions in neurology and psychiatry.

The research psychiatrists (MİA, ÖDB and DY) were comprehensively trained by an experienced, licensed neuro-psychologist (CK) to administer the neurocognitive tests. Each researcher completed 5 reliable tests before being allowed to enroll participants alone.

Experimental Procedures

All experiments were done in an air conditioned, isolated room. The room was well lighted and minimally furnished to prevent distraction. Subjects were asked to refrain from consuming cigarettes, tea, coffee or energy drinks 2 hours before the experiments. All experiments were done at the same time of the day (10AM-12Noon) and before the administration of morning doses of medications.

Finger-Tapping Test

This test measures the oscillation speed of the index finger (manual motor speed). The participants were asked to tap with their index fingers of both dominant and non-dominant hand as rapidly as possible, for 10 seconds. The procedure calls for five consecutive trials within a 5-point range with each hand (34) to avoid undue influence of single deviant scores on total performance. The test procedure was required to range within a 5-point range. In case of exceeding in any trial, deviant trials were discarded. A maximum of 10 trials was allowed. Many different finger tapping apparatuses are available and changes in the test equipment may lead to different results. The device used in our study was a PARINC® product and had a specially adapted tapper and counter.

Nine-Hole Peg Board Test

According to instructions suggested by Mathiowetz et al. (35), this test should be administered by asking the participant to take the pegs from a container, one by one, and place nine wooden pegs into the holes on the board as quickly as possible. The board should be situated at the midline of the subject, with the container holding the pegs oriented towards the hand being tested. Only the hand under evaluation should perform the test and the other hand may help by holding the board for stability. A stopwatch should be used to measure the time from the moment the participant touches the first peg in the container to mount into the hole, until the moment the last peg is back in the container after being dismantled.

Adult Memory and Information Processing Battery (AMIP-B)

The AMIPB aims to measure processing speed by taking motor speed into account. Processing speed may determine the speed of response (reaction time, peg board, finger- tapping test, etc.). According to the instructions suggested by Coughlan and Hollows (36), in first trial (form A) the participant must find the second greatest number in a line of five numbers. In the second trial (form B) participants are asked to detect the number existing on only the right side of two separate groups of numbers divided by a line. The duration of each trial is suggested to

be 4 minutes. In this study, we modified the test in order to avoid exhausting the patients. Four minutes of hurried mental effort exceeded the patients' stamina in our first few training trials before the study. Thus we decided to simplify the tests and applied tit to one minute. Also in form A, we asked the participants to find the greatest number in the line.

Edinburgh Handedness Inventory

Using a Likert scale, this test aims to grade hand preference (37). It contains items like using scissors, a knife or a spoon as well as striking a match and writing activities. Some activities were simulated to inform the subject. Factor analyses confirmed the reliability and validity of the items (38).

Eye (ocular) dominancy was detected using the near-far alignment and kaleidoscope tests. For details of the near-far alignment test please see Dane et al. (39).

Reaction Time Test

A total of ten stimuli was given for the simple reaction time test. Inter-stimulus intervals were randomized between 1 to 6 seconds in order to prevent anticipation. Stimulation, recording of response intervals and reporting (average scores) were performed by using a computer aided system. The subjects were instructed to react immediately, just after perceiving (seeing or hearing) the stimulus by pressing the space bar. An extreme value may influence averages, thus we checked highest and lowest values, in order to control miscalculated averages. In the case of an extreme value, subjects were asked to take the test again. The overall mean occurrence of discarded trials was 14.1% (n=11).

Visual

A Samsung® (model BX2231) 22" LED monitor was used. Its refresh rate was 75 Hz, brightness was 250 cd/m^2 and response time was 2 milliseconds. The stimulus object was a green square (6x10 cm) appearing in the middle of the screen with an orange background

Auditory

As in the visual paradigm, the same software was adapted for auditory stimulation. A white screen and two speakers located on either side of the screen were utilized. The speakers for the auditory stimulus were adjusted to 80 dB and 1500 Hz.

Statistical Analyses

Continuous variables were compared with the t test or the Mann Whitney U test selected according to the distribution characteristics of the examined variable. p and t/z values are reported. Categorical variables were compared with the Chi-square test and p and chi-square values are reported. Correlation analyses were done with Pearson's correlation test.

RESULTS

The socio-demographic characteristics of the groups are presented in Table 1. No significant difference was detected between the groups in terms of age, gender, or education. Handedness lateralization significantly differed between groups on the Edinburgh (p=0.039) lateralization test score. Footedness also differed between groups (p=0.016,

Table 1: Demographic and clinical characteristics

	Bipolar Group (n=68)	Healthy Controls (n=65)	t/χ^2	p
Age	35.66 + 6.38	33.65 + 7.10	-1.72	0.087
Gender (females)	33 (48.5%)	27 (41.5%)	0.66	0.418
Education (years)	11.13 + 3.80	11.40 + 4.39	0.38	0.707
GAF score	75.00 + 11.39			
Age at Onset	22.07 + 5.91			
Disease Duration*	173.44 + 97.71			
Duration of Euthymia§	51.79 + 67.59			
Total Number of Episodes	5.28 + 3.11			
Depression	1.84 + 1.99			
Mania	2.43 + 1.93			
Psychosis**	45 (66.2%)			

GAF: Global Assessment of Functioning, *Months, §Weeks, **History of any psychotic episode.

Table 2: Comparison of the groups in terms of motor and mental speed tests

	Bipolar Patients (n=68)	Healthy Controls (n=65)	t	p
Edinburgh	84.41 + 12.02	79.46 + 13.55	-2.23	0.027
Foot Lateralization (left)	11 (16.2%)	14 (21.55)	0.63	0.508
Eye lateralization (left)	15 (22.1%)	19 (29.2%)	0.90	0.427
MOCA total Score	26.76 + 2.02	27.35 + 1.30	1.99	0.049
Peg Board				
Right	18.98 + 2.86	16.71 + 1.59	-5.63	<0.001
Left	20.51 + 3.07	18.50 + 2.34	-4.23	<0.001
AMIPB				
Motor	43.25 + 9.41	36.17 + 7.47	-4.80	<0.001
A test	30.06 + 6.65	34.28 + 6.86	3.60	<0.001
B test	15.54 + 3.99	15.98 + 3.41	0.68	0.496
Finger Tapping				
Right	51.83 + 6.97	56.38 + 5.63	4.13	<0.001
Left	47.96 + 5.81	50.93 + 5.16	3.12	0.002
Reaction Time				
Visual	0.306 + 0.026	0.270 + 0.033	-6.79	<0.001
Auditory	0.259 + 0.030	0.234 + 0.016	-5.81	<0.001

Table 3: Correlations of cognition, mental speed and lateralization in groups

	Education	MOCA total	Edinburgh Handedness Inventory	AMIPB A Score
Bipolar Patients				
MOCA total	0.31¥			
Edinburgh Handedness Inventory	0.03	0.09		
AMIPB A Score	0.34¥	0.17	0.25*	
AMIPB B Score	0.40¥	0.29*	0.26*	0.58¥
Healthy Controls				
MOCA total	0.26*			
Edinburgh Handedness Inventory	-0.13	0.22		
AMIPB A Score	0.43¥	0.27*	-0.08	
AMIPB B Score	0.44¥	0.30*	0.08	0.56¥

χ^2=5.78), however the difference in eye dominancy between the groups was not significant (Table 1).

The clinical characteristics of the patient group and psychomotor and mental speed test results are presented in Table 2. The control group was superior to the patient group on the MOCA (p=0.011)as well as the first and second trials of the Peg Board test (p<0.001 for all trials), motor (p<0.001), A (p=0.003) and B (0.032) tests of the AMIPB, right (p<0.001) and left (p=0.002) hand trials of the finger-tapping test, finger-tapping asymmetry (p=0.021) and visual and auditory (p<0.001 for both) reaction time tests.

Correlation Analyses

Two different correlation analyses were run to detect relationships between variables. Age, education, MOCA total score, Edinburgh Handedness Inventory test, Peg-board, AMIPB, finger tapping and reaction time scores were included in the analyses for both groups. Disease parameters such as duration of euthymia, age at disease onset and number of episodes were also added in the analysis of the bipolar group. Correlations between lateralization and measures of cognition and mental speed are given in table 3; correlations of motor speed tests are given in the text.

Healthy Controls

The Edinburgh lateralization test score correlated with the non-dominant (left) hand trial of the Peg-board test score (r=0.42, p=0.001), the left hand trial of the finger-tapping test (r=-0.33, p=0.007) and the visual reaction time test score (r=0.38, p=0.002). Education was correlated

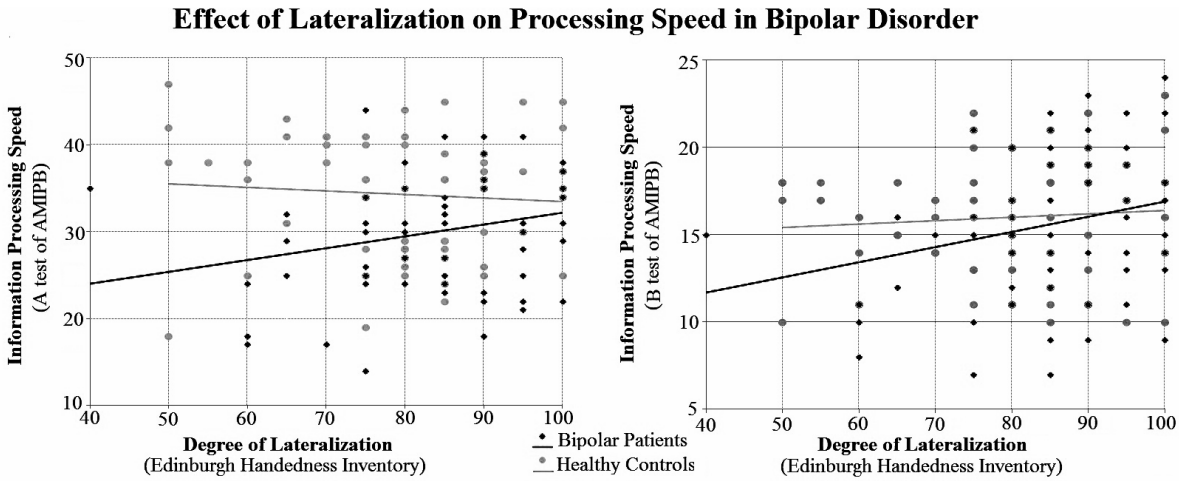

Figure 1: Scatter plots of lateralization effect on processing speed in bipolar disorder. Slope angles of regression lines of bipolar patients (black) differ from those of healthy controls (gray). The two tests of the AMIPB (A and B) consistently displayed a similar pattern.

with the MOCA total score (r=0.26, p=0.035), motor (r=-0.45, p<0.001), A (r=0.43, p<0.001) and B (r=0.44, p<0.001) scores of the AMIPB, right (r=0.36, p=0.004) and left (r=0.31, p=0.011) hand trials of finger-tapping, visual (r=-0.26, p=0.036) and auditory scores (r=-0.27, p=0.030). The MOCA total score was correlated with A (r=0.43, p<0.001) and B test (r=0.44, p<0.001) scores of the AMIPB. A test of the AMIPB strongly correlated with B test (r=0.56, p<0.001). Visual reaction time correlated with B test of the AMIPB (r=-0.32, p=0.011). Auditory reaction time correlated with A (r=-0.27, p=0.027) and B (r=-0.39, p=0.001) tests of the AMIPB.

Bipolar Group

In the bipolar group the Edinburgh lateralization test score correlated with A (r=0.25, p=0.042), and B (r=0.26, p=0.031) tests of the AMIPB, unlike the healthy control group. The Edinburgh score was also negatively correlated with duration of the disease (r=-0.34, p=0.005). The MOCA total score correlated with education (r=0.31, p=0.011), the right hand trial of the Peg-board (r=-0.25, p=0.044), motor (r=-0.40, p=0.001),, and B tests (r=0.29, p=0.015) of the AMIPB and right (r=0.38, p=0.001) and left (r=0.28, p=0.019) hand trials of the finger-tapping test. Education correlated with A (r=0.34, p=0.005) and B (r=0.40, p=0.001) tests of the AMIPB. Duration of euthymia correlated with the MOCA total score (r=-0.24, p=0.049), all trials of the Peg-board test (D: r=0.48, p<0.01; ND: r=0.35, p<0.01), the AMIPB motor (r=0.62, p<0.001) and right (r=-0.33, p=0.007) and left (r=-0.34, p=0.005) hand trials of the finger-tapping test. Age at disease onset and number of previous episodes did not show any correlation with any test variables. A test of the AMIPB correlated with B test (r=0.58, p<0.001).

Effects of Psychosis

Patients who had ever had psychotic episodes were compared to patients who had never had any psychotic symptoms (non-psychotic bipolar patients). The MOCA total score differed between the groups; non-psychotic patients were superior to psychotic patients (p=0.023, z=-2.28). The Peg-board left hand trial differed (p=0.045, z=-2.00) between the non-psychotic and psychotic groups.

Effect of Lateralization on Mental Speed

Unlike the healthy controls, in bipolar patients the degree of lateralization was positively correlated with both A (r=0.25, p=0.042) and B (r=0.26, p=0.031) tests of the AMIPB, which is a measure of processing speed. Both tests were consistently correlated and tests were reliable.

DISCUSSION

Bipolar patients were more lateralized and slower than healthy controls on motor and mental speed measures.

There was a significant positive correlation between lateralization and processing speed in bipolar patients, unlike healthy controls. These findings replicate the increased lateralization finding of Savitz et al. (23). In addition, we also found that lateralization was related to increased processing speed in patients with bipolar disorder. However, eye and foot lateralization frequencies did not differ between groups. Among the clinical factors, only duration of euthymia correlated with motor speed.

Although it is a very important aspect of the organization of the human brain, effect of lateralization cognitive performance has been studied only in a limited manner in either healthy populations or in psychiatric disorders. Some studies have found normal or superior intelligence and decreased spatial and linguistic skills in more lateralized subjects from healthy populations (40,41). Leask and Crow (42) have showed that among right handed subjects, less lateralized ones performed poorer on verbal learning and this was more common in children, who later developed schizophrenia or (rarely) bipolar disorder. Although the organization of the human brain is much more complex than birds or reptiles, some animal experiments have showed that lateralization is advantageous for visuospatial skills (43,44). Annett has suggested that right handed subjects were not better with their right hands but left or mixed handed subjects were better with their left hands (45); in addition, Annett proposed that arithmetic abilities were better in right handed subjects (46). However, some other studies (47-49) were incongruent with Annett and Manning (45,46) and stated that lateralization provide an advantage for cognition. We did not find an association between general cognitive performance and lateralization in our healthy control group, but our sample may be a relatively small one to test such a relationship. Psychomotor speed is a matter of speed and a temporal processing advantage does not necessarily point to an advantage in global cognitive performance. A major finding of the study was increased processing speed with stronger lateralization in bipolar disorder, which has not previously been reported to our knowledge.

Stronger lateralization in bipolar disorder is a complex feature because functional brain lateralization is a complex trait determined by many different dynamic processes. Considerations of intra- and interhemispheric certain neural networks stressed dynamic, complementary sharing of work and cooperation through neural networks (50). Another intriguing model is Delayed Interhemisheric Information Transfer (DIHIT) (for review see 1). The DIHIT hypothesis suggests that one of the hemispheres is stimulated earlier than the other, which is assigned to that function more specifically. The earlier hemisphere inhibits the later one by interhemispheric connections. According to Miller (51) the right hemisphere has a greater number of fast conducting, myelinated neurons. However, neurons in the left hemisphere may have a greater repertoire of conduction velocities. Human type cerebral lateralization may be due to these differences between the right and left hemispheres which may support serial and parallel processing (51). Although right to left transfer is faster than left to right transfer in healthy subjects (52) in line with the proposal of Miller (51), schizophrenic patients showed symmetric transfer properties (53,54). Barnett and colleagues' (54) comment depended on the loss of rapidly conducting myelinated axons in the right hemisphere in line with Miller (51). Galaburda suggested that (55) in symmetric brains, callosal connections and hence the speed of interhemispheric communication would increase and this proposal is coherent with the DIHIT hypothesis. However, DIHIT is not supported by right hemispheric superiority in transfer speed estimations (52,54). If that were the case, the operations of the right hemisphere should inhibit the left (dominant) hemisphere. It is clear that specific networks will have their own lateralization characteristics (49) and one model cannot fully explain the dynamics of all of the networks. Stronger lateralization in bipolar disorder may be due to right hemispheric neuropathology. Nevertheless, if extreme lateralization is not necessarily associated with any neuropsychiatric or intellectual disability, many other factors contribute to the physiopathology of bipolar disorder beside the lateralizing physiopathology.

Interhemispheric interactions may occur with inhibitory and excitatory influences mediated by different sub-regions of the corpus callosum that are activated at different stages of information processing (reviewed in 1) and callosal disturbances in psychiatric disorders (12-14) may indicate that interhemispheric cooperation should be disadvantaged for both hemispheres in cases of disturbed interhemispheric communication (56). This approach, to some extent explains the lateralization advantage for processing speed in bipolar patients. Further neuroimaging studies focusing on interhemispheric transfer of

information may show the lateralizing physiopathology that may be related with increased delay of interhemispheric transfer in major psychiatric disorders.

Another important finding of this study is that patients were slower than healthy controls, in almost all of the paced rhythmic activities. The patients with bipolar disorder were found to have various neuropsychological deficits including psychomotor slowing (57), rhythm (timing) dysfunction (58), reduced processing speed, and worsened reaction time scores (59). It appears neural loops including the basal ganglia (60,61), cerebellum (62,63), and the inferior olive (64) are critical for early temporal processing and rhythm production and therefore paced rhythmic activity (65). Timing dysfunction in bipolar disorder might be addressed as a future direction for neurophysiological and neuroimaging studies. On the other hand, transfer of sequence formation is also depends on the delays in the cortical information flow (66). Performance disadvantages of the non-dominant arm result from inter-hemispheric transmission delays associated with dominant hemisphere commands for non-dominant arm movements (67). Dopaminergic gating of motor sequences in the basal ganglia (68) can also be influenced by chronic serotonergic blockade as this interaction has been shown in animal experiments (69) and may impair psychomotor functions in bipolar disorder. Motor slowness findings may also be related to psychotropic medications, another future direction for prospective follow up studies. Functions of the prefrontal cortex (70) particularly regulation of dopamine in the striatum (71) are highly related to Catechol-O-methyl-transferase (COMT) function. The COMT gene has been found to be associated with hand skills in bipolar patients (23). COMT therefore may account for both motor and mental slowness of bipolar patients.

Elias and Bryden (72) suggested that footedness is stronger than handedness to predict language lateralization because it is not impacted by cultural and environmental factors as much as handedness. In other words eye or foot lateralization is relatively more stable than handedness and would be less affected by environmental factors. Only one study, to our knowledge, reported that footedness lateralization was increased in bipolar disorder (23). Although left footedness and eyedness was more prevalent in the control group, the difference did not reach statistical significance in this study. This dimension should be further investigated in future studies.

A major limitation of this study is that we only assessed behavioral lateralization (handedness). Lateralization of language functions might have given more precise lateralization traits. The digit symbol substitution test is frequently used to test processing speed; however, we used a different test. This study may encourage researchers to consider using an alternative test for measuring processing speed. We could not eliminate medication effects. The sample of this study consists of right-handed participants and therefore before generalizing these findings, left and mixed handed patients should also be studied in future studies.

CONCLUSION

Correspondence between motor and mood regulation systems (7) may shed light on the pathophysiology of mood disorders. Generally it can be concluded that bipolar patients are more lateralized, but this relationship is not bidirectional and should not be generalized as a rule for mood disorders, before testing and confirming the same findings in left handed subjects. Motor slowing may indicate rhythm dysfunction that may indicate disturbed dopaminergic gating in above mentioned structures. Hence, using anti-dopaminergic treatments may worsen motor disturbances and should be avoided.

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