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Lithium and Valproate May Affect Motor and Sensory Speed in Patients with Bipolar Disorder

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ÖZET:

Lityum ve valproat bipolar bozukluğu olan hastalarda motor ve sensör hızı etkileyebilir

Amaç: Birçok çalışma lityumun (Li) motor sistemi olumsuz etkilediğini göstermiştir, fakat henüz bipolar bozuklukta valproatın (VP) motor ve sensör hıza olan etkileriyle ilgili yeterli kanıt bulunmamaktadır. Bu çalışmada Li ve VP'nin motor ve sensör hıza olan etkilerinin ilaç kullanmayan hastalar (İKH) ve sağlıklı kontrollerle (SK) karşılaştırarak incelenmesi amaçlanmıştır.

Yöntemler: DSM-IV'e göre bipolar bozukluğu olan ötimik 22 Li kullanan, 21 VP kullanan, 18 İKH ve 37 SK katılımcı çalışmaya alındı. Parmak-tıklama testi, çivi tahtası testi, görsel ve işitsel tepki süresi testi, Montreal Bilişsel Değerlendirme Testi ve Edinburgh El Tercihi Envanteri kullanılan ölçüm aygıtlarıydı.

Bulgular: Gruplar arasında çivi tahtası testinin sağ el denemesinde Li grubu SK ve İKH gruplarından, VP grubu SK grubundan daha yavaş bulundu. Parmak-tıklama testinin sağ ve sol el denemelerinde Li grubu SK ve İKH gruplarından yavaş bulundu. Görsel tepki süresi testinde tüm hasta grupları (Li, VP ve İKH) SK grubundan daha uzun ortalama tepki süresi gösterdiler. İşitsel tepki süresi testinde Li ve VP gruplarında SK'lara göre anlamlı derecede uzun tepki süresi saptandı.

Sonuç: Lityum sensör ve motor hızı valproata göre daha olumsuz etkileyebilir. İlaç kullanmayan hastaların, sağlıklı kontrollere kıyasla yalnız görsel tepki süresinde uzama tespit edildi. Lityum motor koordinasyonu sağlayan beyin yapılarının karmaşık entegrasyonunu etkileyerek hareket sistemini etkiliyor olabilir. Ayrıca bu sonuçlar bipolar bozukluğun ötimik döneminde ortaya çıkabilecek psikomotor işlevlerdeki sorunların tedavilerle ilişkili olabileceğini önermektedir.

Anahtar sözcükler: bipolar bozukluk, lityum, valproat, motor hız, tepki süresi

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ABSTRACT:

Lithium and valproate may affect motor and sensory speed in patients with bipolar disorder

Objective: Although many studies have found a negative effect of lithium (Li) on the motor system in bipolar disorder, there is a lack of evidence about the effects of valproate (VP) on motor and sensory speed. We aimed to compare the effects of Li and VP on motor and sensory speed in medication-free bipolar patients (MF) and healthy controls (HCs).

Methods: Euthymic patients with bipolar disorder according to the DSM-IV on Li monotherapy (n=22), VP monotherapy (n=21), MF (n=18) and HCs (n=37) were enrolled. The finger-tapping test, Pegboard Test, visual and auditory reaction time tests, Montreal Cognitive Assessment and Edinburgh Handedness Inventory were the measures.

Results: The Li group was significantly slower than the HC and MF groups in the right hand trial of the Pegboard Test. The Li group scored significantly lower in the right and left hand trials of the finger-tapping test in comparison to the HC and MF groups. All patient groups (MF, Li and VP) had slower visual reaction time scores than the HC group. The Li and VP groups had significantly slower auditory reaction time scores than the HC group.

Conclusion: Lithium may impair sensory and motor speed more than VP. Medication-free patients differed from healthy controls only in the visual reaction time test. Lithium may disturb movement systems by affecting the complex integration of the brain structures serving motor coordination. These results may also suggest that in the euthymic phase of bipolar disorder, disturbance of psychomotor functions may be related to medications.

Keywords: bipolar disorder, lithium, valproate, motor speed, reaction time

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INTRODUCTION

Effects of medications on cognitive functions remain to be elucidated in bipolar disorder (1-5). Most studies have consistently showed that lithium might cause psychomotor slowing but does not significantly affect other cognitive domains (4-6). Relatively small numbers of studies have showed that valproate is mildly associated with attention and memory disturbances in bipolar patients (7,8).

Subtle motor abnormalities may exist in bipolar disorder, independent of mood state. Such neurological soft signs and impaired fine motor functions are significantly increased even in euthymia (9-11) and depression (12). Motor dysfunction could therefore be a core feature of the disorder. Swann and colleagues have showed a relationship between psychomotor impairment and catecholamine depletion in mood disorders (13). In almost all of these studies, patients were on medications and medications used in bipolar disorder may affect motor functions.

Many studies found psychomotor disturbances in patients on lithium therapy (14-17). Except for the work of Kocsis et al. (15), all studies have compared patients 'with' or 'without' lithium. Patients 'without' lithium were not taking lithium but taking various treatments for bipolar disorder. Kocsis et al. (15) showed that discontinuation of lithium reverses the impairment on psychomotor speed in a prospective design. In a recent meta-analysis, which included studies conducted with patients 'on' and 'off' lithium, Wingo and colleagues (4) demonstrated that lithium treatment was associated with impairment in immediate verbal learning and memory (effect size: 0.24) and creativity (effect size: 0.33). In addition, impairment of psychomotor performance became prominent in the long term, with a moderate effect size (effect size: 0.62).

However, valproate has been studied only to a limited extent in bipolar disorder. To our knowledge, only one study has compared motor and cognitive effects of valproate to lithium and anticonvulsants (lamotrigine, carbamazepine, oxcarbazepine and topiromate) used as mood stabilizers in bipolar patients (18). The authors reported that impairment of the valproate group was more severe than impairment of the lithium group. Finally, studies with epileptic patients have showed that valproate causes Parkinsonism (19) and psychomotor slowing (20,21).

Although many studies have found a negative effect of lithium on the motor system in patients with bipolar disorder, no studies to date have compared motor and sensory speed in patients on valproate monotherapy to medication-free patients and healthy controls. In this study, we enrolled medication-free patients, patients on lithium monotherapy, valproate monotherapy and a healthy control group. Effects of medications on the motor system were investigated in terms of manual speed and dexterity; reaction time was a measure to detect sensory speed.

METHODS AND MATERIALS

Subjects

A total number of 61 bipolar patients (mean age: 35.89±7.11, female/male: 31/30) and a healthy control group (mean age: 33.65±7.00, female/male: 14/23) consisting of 37 subjects were enrolled. Bipolar patients group included medication-free patients (n=18, mean age: 33.94±3.87, female/male: 13/5), patients on lithium monotherapy (n=22, mean age: 37.59±5.41, female/male: 10/12) and patients on valproate monotherapy (n=21, mean age: 35.76±7.99, female/male: 13/8). Gender (p=0.089, χ^2=6.51), age (p=0.075, F=2.37) and duration of education (p=0.573, F=0.67) were similar in both groups. Current medication status was required to be continued at least three months. The Turkish version of the SCID-1 (Structured interview according to the DSM-IV) (22,23) was used to check the diagnoses of the patients. Healthy participants were checked with a SCID non-patient form to prove that there was no current or past psychiatric disorder. The study was approved by the Ethical Advisory Committee.

Each participant signed a written informed consent. Patients had been euthymic for at least 3 months. Participants scoring more than 5 points on the Young Mania Scale (YMRS) (24,25) or 7 points on the Hamilton Depression Rating Scale (HAM-D) (26,27) were excluded. Global assessment of functioning was used to assess functionality (28). Alcohol or substance use disorders, co-morbid axis-1 psychiatric diagnosis, neurological diseases, general medical conditions that may influence the locomotor system, pregnancy or lactation were exclusion criteria. Routine laboratory tests were assessed. All participants were initially checked to see if they had any problems with their locomotor, visual or auditory systems. Participants were asked to use their glasses or earpiece if they were prescribed to use the device for precise vision or audition. Participants with sleep disturbances or acute sleep deprivation were excluded. Participants were asked to cease smoking or drinking stimulant drinks like coffee or energy drinks 2 hours before the study. All experiments were carried out before administration of the morning doses of the medications and at the same time of day as the preceding trial (10-12 am).

Initially a Montreal Cognitive Assessment (MoCA) test was done (29,30) for a brief cognitive screening. The MoCA is a sensitive tool to detect mild cognitive impairments. It includes items testing attention, executive functions, working memory, visuospatial functions, speech and abstract thinking. Sensitivity and specificity of the MoCA have been found to be better than the mini mental state examination (29) and it is frequently used in clinical studies in neurology and psychiatry.

Cognitive and Motor Tests and Apparatus

Tests were done in an isolated, minimally furnished, well lighted and air conditioned room. Eye (ocular) dominancy was detected with near-far alignment and kaleidoscope tests. For details of near-far alignment test please see Dane et al. (31).

Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory aims to grade hand preference in a Likert fashion (32). Its items ask about hand preference during use of scissors, a knife, and a spoon, and for match striking and writing activities. Some activities were simulated before informing the subject.

Nine-Hole Pegboard Test

For this test, the board should be placed at the midline of the subject, with the container holding the pegs oriented closer to the hand being tested. According to instructions by Mathiowetz et al. (33), it should be administered by asking the subject to take the pegs one by one from a container and stick nine wooden pegs into the holes on the board as quickly as possible. Only the hand being evaluated should perform the test and the passive hand may hold the board for stability. Time should be measured with a stopwatch from the moment the participant touches the first peg in the container to put into the socket until the moment the last peg is back in the container after dismantling.

Finger Tapping Test

Oscillation speed of the index finger (manual motor speed) is measured in this test. Participants were asked to tap as rapidly as possible with their dominant and non-dominant hand index fingers for 10 seconds. Five consecutive trial series (to avoid undue influence of single deviant scores on total performance) were performed with each hand, each trial taking 10 seconds with 15 second to 2 minute breaks in between (34). To avoid exceeding time 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 was a PARINC® product and had a specially placed counter and tapper on a board.

Reaction Time Test

Ten stimuli were given and reaction intervals were measured for the simple reaction time test. Inter-stimulus intervals were randomized between 1 to 6 seconds in order to prevent anticipation and automatic responses. Software recorded the response intervals and the average scores. The number of stimuli was 10. An extreme value may influence averages, so we checked the highest and lowest values in order to control miscalculated averages. Trials with extreme values were discarded and subjects were asked to take the test again. Subjects were instructed to pay extreme attention and react immediately, just after perceiving (seeing or hearing) the stimulus, by pressing the space bar. Stimuli were given by means of software.

Visual

A Samsung® (model BX2231) 22" LED monitor was used. Its refresh rate was 75 Hz, its brightness 250 cd/m^2 and response time 2 milliseconds. The background of the screen was orange in color and the stimulus object was a green square (6X10 cm) appearing in the middle of the screen. Participants were instructed to react just after seeing the green square.

Auditory

The same software as in the visual paradigm was adapted for auditory stimulation. A white screen appeared and two speakers located on two sides of the screen were utilized. Speakers for auditory stimuli were adjusted to 80 dB and 1500 Hz. Participants were asked to react just after perceiving the stimulus.

Statistical Analyses

The Kolmogorof-Smirnov test was used to detect distribution characteristics and all of the independent variables were normally distributed. A one way ANOVA was used to compare demographic and clinical variables between groups. Tukey's HSD test was the posthoc test. Categorical variables were compared with the Chi-square test. One-way analysis of variance (ANOVA) was used to detect mean group differences in the finger-tapping test, pegboard test, auditory and visual reaction time tests; age and education were the covariates. Dominant and non-dominant hand trials of the pegboard test and auditory reaction times test scores were not homogeneous variances in the Levene's Homogeneity of Variance Test, so a logarithmic transformation was performed on these variables. The Tukey HSD was the post-hoc test, used to detect group differences following one-way ANOVA. Effects of age, education and clinical parameters including age at disease onset, duration of the disease [log transformed], duration of euthymia [log transformed], number of episodes, psychosis, serum concentrations of the mood stabilizers, T4 and TSH and duration of current medication status were analyzed with analyses of covariance (ANCOVA) only including related groups.

RESULTS

Demographic and clinical characteristics of the groups are presented in Table 1. The groups were

Table 1: Demographic and clinical characteristics of the groups

	MF (n=18)	Li (n=22)	VP (n=21)	HC (n=37)	F	p
Age	33.94±3.87	37.59±5.41	35.76±7.99	33.22±7.00	2.37	0.075
Education (years)	9.72±3.01	10.95±4.12	11.52±3.74	11.05±4.73	0.67	0.573
Gender (Female)*	13 (72.20%)	10 (45.45%)	13 (61.90%)	14 (37.84%)	6.51**	0.089
Edinburgh HI	82.50±9.43	83.86±12.90	85.24±9.01	80.41±12.88	0.89	0.447
MoCA total	27.00±2.11	26.32±2.17	26.57±1.86	27.30±1.47	1.52	0.214

One-way ANOVA. (Means ± Standard Deviations) Edinburgh HI: Edinburgh Handedness Inventory; MoCA: Montreal Cognitive Assessment; MF: Medication-Free Patient Group; Li: Lithium Group; VP: Valproate Group; HC: Healthy Control Group; *Categorical Variable (percentages), **Chi-Square value

Table 2: Clinical Characteristics of bipolar patient groups

	MF (n=18)	Li (n=22)	VP (n=21)	F	p
YMRS	0.61±0.85	0.36±0.95	0.38±0.97	0.42	0.659
HAM-D	0.94±1.26	0.82±1.43	1.81±1.91	2.46	0.094
Age at Onset	21.94±6.68	20.27±5.26	24.38±5.93	2.60	0.083
Duration of the Disease[1]	154.39±78.11	224.95±116.98	142.19±82.51	4.68	0.013[a]
Duration of Euthymia[1]	39.22±26.04	83.55±103.84	26.76±20.71	4.49	0.015[b]
Total Number of					
Episodes	4.22±3.28	6.52±2.91	5.05±3.23	2.73	0.074
Mania	1.89±1.61	2.71±2.10	2.64±2.15	1.00	0.374
Depression	1.58±1.62	2.05±2.46	1.82±2.02	0.27	0.763
GAF	78.33±9.70	74.32±10.94	71.67±12.97	1.68	0.195
Duration of Current Medication Status[1]	18.67±9.80	82.59±44.89	78.33±51.02	14.74	<0.001[c]
Serum Concentrations	-	0.79±0.12	81.82±11.61	-	-

One-way ANOVA. [1]Months; YMRS: Young Mania Rating Scale; HAM-D: Hamilton Depression Rating Scale; GAF: Global Assessment of Functioning; MF: Medication-Free Group; Li: Lithium Group, VP: Valproate Group; [1]Months; [a][VP<Li, p=0.017]; [b][VP<Li, p=0.016]; [c][MF<Li, p<0.001; MF<VP, p<0.001]

Table 3: Comparisons of motor and sensory speed tests between groups

	MF (n=18)	Li (n=22)	VP (n=21)	HC (n=37)	F	p
Pegboard Test*						
D_1	17.77±1.61	20.99±4.39	19.95±2.97	17.52±1.97	8.71[a]	<0.001
ND_1	19.59±2.09	21.68±3.42	21.19±2.57	19.50±1.94	4.52[b]	0.005
Finger-Tapping Test[¥]						
D	55.17±4.97	48.45±5.74	52.36±8.66	56.41±6.32	7.36[c]	<0.001
ND	51.17±5.08	45.05±4.38	48.36±6.92	50.64±5.60	5.75[d]	0.001
Reaction Time						
Visual	0.297±0.012	0.318±0.027	0.302±0.031	0.272±0.030	14.29[e]	<0.001
Auditory[1]	0.254±0.018	0.266±0.027	0.258±0.040	0.236±0.018	7.27[f]	<0.001

One-way ANOVA. *Total time to complete mantling and dismantling all pegs, [¥]Mean taps of 5 trials (scores of each trial included total number of taps in 10 seconds) [1]Log Transformed D: Dominant (right), ND: Non-Dominant (left), [a][Li<HC, p=0.001; Li<MF, p=0.009; VP<HC, p=0.035], [b][Li<HC p=0.014], [c][Li<HC, p<0.001; Li<MF, p=0.002] [c][Li<HC, p<0.001; Li<MF, p=0.009], [d][Li<HC, p<0.002; Li<MF, p<0.005], [e][MF<HC, p=0.013; Li<HC, p<0.001; VP<HC, p=0.001], [f][Li<HC, p<0.001; VP<HC, p=0.020]

similar in terms of age, gender and education. There were no differences between groups in terms of handedness or brief cognitive assessment scores. All participants were right handed.

Clinical characteristics of the groups are presented in Table 2. There was no difference between groups in terms of YMRS and HAM-D scores. Age at disease onset and number of total episodes of mania and depression did not differ between groups. Number of mixed episodes (p<0.001, F=9.87), duration of the disease (p=0.013, F=4.68) and duration of euthymia (p=0.015, F=4.49) differed between groups. Duration of the disease in the lithium group was significantly longer than in the valproate group (p=0.017). Posthoc tests showed that duration of euthymia in the Li group was significantly longer than in the VP group (p=0.016).

Motor and sensor speed test results are presented in Table 3. There were statistically significant differences between groups in right (p<0.001, F=8.71) and left (p=0.005, F=4.52) hand trials of the Pegboard Test. The posthoc test showed that the lithium and the valproate group differed significantly from healthy controls and MF patients in right hand trials (Li<HC p=0.010; Li<MF p=0.022; VP<HC p=0.014; VP<MF p=0.042), whereas in left hand trials only the lithium group differed from healthy controls (Li<HC p=0.014). Results of the right (p<0.001, F=7.36) and left (p=0.001, F=5.75) hand trials of the finger-tapping test differed between groups. The posthoc test revealed that the lithium group differed from healthy controls and MF patients in right (Li<HC p<0.001; Li<MF p=0.009) and left (Li<HC p=0.002; Li<MF p=0.005) hand trials. Visual (p<0.001,

F=14.29) and auditory (p<0.001, F=7.27) reaction time tests differed significantly between groups. The posthoc test showed that all bipolar patients reacted slower than healthy controls in visual reaction time tests (MF<HC p<0.013; Li<HC p<0.001; VP<HC p=0.001), whereas only the lithium group and the valproate groups differed from healthy controls in auditory reaction time tests (Li<HC p<0.001; VP<HC, p=0.014).

Correlation analyses in MF patients revealed that Thyroid Stimulating Hormone (TSH) levels significantly correlated with the dominant (r=-0.73, p=0.003) and non-dominant (r=-0.70, p=0.005) hand trials of the finger-tapping test; number of total episodes correlated with the dominant (r=0.60, p=0.009) hand trial of the Pegboard Test; total number of depressive episodes correlated with the dominant (r=0.60, p=0.009) hand trials of the Pegboard Test; Hamilton Depression Rating Scale scores correlated with the dominant (r=-0.49, p=0.040) and non-dominant (r=-0.68, p=0.002) finger-tapping and auditory reaction times (r=-0.59, p=0.009); Young Mania Rating Scale scores correlated with the visual reaction time test (r=-0.61, p=0.008) (not shown).

Correlation analyses in the lithium group showed that GAF scores correlated with the dominant (r=-0.57, p=0.006) and non-dominant (r=-0.48, p= 0.024) hand trials of the finger-tapping test; duration of euthymia correlated with the dominant (r=0.65, p=0.001) and non-dominant (r=0.62, p=0.002) hand trials of the Pegboard Tests and the dominant (r=-0.61, p=0.002) and non-dominant (r=-0.55, p=0.008) hand trials of the finger-tapping test. The number of total episodes correlated with the non-dominant (r=0.46, p=0.031) hand trial of the finger-tapping test (not shown).

Correlation analysis in the valproate group revealed that age at disease onset correlated with auditory reaction time (r=0.57, p=0.009); number of depressive episodes in the past correlated with the dominant (r=-0.61, p=0.003) and non-dominant (r=-0.73, p<0.001) hand trials of the Pegboard Tests; HAM-D scores correlated significantly with the dominant (r=0.58, p=0.005) and non-dominant (r=0.47, p=0.033) hand trials of the Pegboard Tests; YMRS scores correlated with the non-dominant hand trial (r=-0.46, p=0.035) and visual reaction time scores (r=-0.57, p=0.008) (not shown).

In the lithium and valproate groups, duration of the current medication status and serum concentrations of the agents did not correlate with any score or clinical variable.

In the ANCOVA, the dependent variables were right and left hand scores of the finger-tapping test and the pegboard test, and auditory and visual reaction time test scores. Covariates were age, education, duration of current medication status, duration of the disease, duration of euthymia, age at disease onset, number of episodes (total, manic and depressive), TSH and T4 scores, HAM-D scores, YMRS scores, Edinburgh Handedness Inventory scores, MoCA scores and the GAF scores. Duration of euthymia was significantly related to the right (p=0.001, F=12.01) and left (p=0.007, F=7.99) hand scores of the pegboard test. MoCA total score had an effect on the right hand score of the finger-tapping test (p=0.014, F=6.52). There was a trend that duration of euthymia (p=0.053, F=3.95) and HAM-D (p=0.051, F=4.01) affected the left hand score of the finger-tapping test. Age, education, duration of the current medication status, GAF score, duration of the disease, age at disease onset, number of episodes (total, depressive and manic), and T3, T4, TSH and YMRS scores were not related to motor and sensory speed tests (not shown).

DISCUSSION

The main findings of the present study are that lithium might impair motor speed in paced rhythmic tasks, whereas valproate may only slightly impair motor speed in bipolar disorder. Both lithium and valproate prolong auditory and visual reaction times. Medication-free patients differed from healthy subjects only in the visual reaction time test. Lithium may disturb the movement system in bipolar patients and may also disturb the formation of rhythms and motor coordination by affecting the complex integration

of the structures serving motor functions and motor coordination. Finally, the MF patient group did not differ from the HC group in any of the motor tests.

Development of motor codes may progress faster for tasks requiring minimum numbers of muscles and joints such as the finger-tapping test. The test involves a serial pattern of muscle activation, with a precise regulation of forces in a well-organized order of flexion and extension movements. This specific nature of the finger-tapping test may show the effects of lithium and valproate on forming and maintaining rhythm for paced rhythmic activities. Fine motor dexterity and reaction times can also reflect the effects of these medications on motor and sensory functions.

Rao et al. (35) have showed that the supplementary motor area, the cerebellum, the thalamus, the putamen, the superior temporal gyrus and the inferior frontal gyrus are active brain regions during self-paced finger-tapping. The cerebellum, the basal ganglia and the premotor cortex are the most important structures among all brain regions involved in paced rhythmic motor activities (36-38). The cerebellum and basal ganglia are critical structures involved in motor coordination as well as perceptual, cognitive and affective functions via their connections to the limbic networks (39-43). The inferior olive participates in the encoding of temporal information for motor or cognitive processes (44).

Eye blinking abnormalities (45) and timing dysfunction (46) findings point to cerebellar dysfunction in bipolar disorder. Setta and colleagues (47) have detected kinematic abnormalities and commented that chronic lithium treatment is related to impairment of the cerebellar control of fast single-joint movements. Functional neuroimaging (43,48) studies have showed alterations and dysfunction in the basal ganglia in bipolar disorder. The basal ganglia are involved in movement/muscle selection (efferent motor) and the neocerebellum might be related to sensory information processing and monitoring the outcome (afferent sensory) and optimizing sensory information (49). The mechanism of the neurotoxicity of lithium in the cerebellum is not clear. Lithium may act both directly and indirectly on Purkinje cell calcium homeostasis, resulting in excitotoxic effects (50). Lithium overdose has been associated with cerebellar sequela and degeneration (51,52), but no correlation has been detected between vermian atrophy and blood levels of lithium by DelBello et al. (53) and Mills et al. (54). Serum levels of the drugs did not correlate to any measure in this study. However, brain and plasma concentrations of lithium were weakly correlated (55) and rather than serum concentrations, brain lithium concentrations were related to motor system effects (56) and clinical responses (57,58) to lithium.

The lithium and valproate groups differed from healthy control group in auditory and visual reaction time measures in this study. Medication-free patients differed from healthy subjects only in visual reaction time measures. Mental chronometry studies suggested that lithium might cause prolongation in reaction times. Three prospective studies have showed prolongation in reaction times in lithium-using bipolar patients (59-61). Kropf et al. (62) have found that dose reduction leads to improvement of visual signal detection in patients on lithium therapy. However, Lund et al. (63) did not find significant differences between patients on and off lithium in their long-term double blind prospective study in reaction time and processing speed tests. Reaction speed might be related to attention and activating related response systems as quickly as possible. Bipolar patients have been shown to have neuronal activation (64) and connectivity deficits (65). Psychosensory speed has also been suggested to be a function of the cerebellum (49) and may also further suggest that lithium and valproate may influence cerebellar functions. Further functional neuroimaging studies focusing on cerebellar functions during motor and sensory tasks should focus on this future direction.

A major limitation of the current study would be that patients in the valproate group had more mixed episodes than other groups, which may mean that more severe cases may be more

prevalent in the valproate group. Another limitation would be the relatively small sample size. The medication-free patient group provided a comparison group and was the major advantage of this study. It would be better if treatment responses were detected with scales and correlation between treatment response, motor/mental speed and clinical data were determined routinely.

CONCLUSION

In contrast to the findings of Gualtieri et al. (18) lithium was found to impair motor and sensory speed more than valproate in this study. These results indicate that lithium may disturb motor functions, which may be the reason for motor slowing during paced rhythmic activities, probably due to impaired coordination. Further studies should focus on the related brain regions to determine the effects of lithium on motor functions. The close relationship between the motor system (voluntary control, speed, scale and coordination) and mood disorders (and also mood stabilization) may provide clues for future studies. The effects of mood stabilizers have been of particular interest in order to understand the pathophysiology of mood disorders. Therefore the effects of mood stabilizers on motor and sensory speed may be a future direction for studies aiming to investigate the pathophysiology of mood disorders.

Clinicians should inform patients and alert them to avoid risky conditions (e.g. driving) in the case of subjects with slowed motor and mental functions. Psychomotor impairment may cause discontinuation of the drug and disturb young patients more than elderly patients. Using lithium at the lower limit of the therapeutic dose range would help to avoid motor side effects and thus may increase compliance. The mechanism of the impact of mood stabilizers on psychomotor and sensory functions is still an intriguing question requiring further research.

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