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# Lithium-Induced EEG Changes in Patients with Affective Disorders

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**Key Words**

Lithium · Quantitative EEG · Power spectral analysis · Affective disorder

**Abstract**

In 12 patients with affective disorders (ICD-10: F31, F32, F33), EEGs were recorded before and after 4.4 months of lithium treatment. Effects of lithium on the EEG were analyzed by power spectral analysis controlled for vigilance. We found (1) an increase in relative power in both delta and theta band which was related to the lithium plasma level, (2) a decrease in relative alpha power especially at occipital leads and (3) a reduction of the dominant alpha frequency. The changes in relative power were more pronounced in the right hemisphere, which is in contrast to the hypothesis of a site-specific localization of lithium effects only in left anterior regions.



## Introduction

The salt lithium was introduced in prophylaxis and treatment of affective disorders in 1949. However, it is well known that neurological side effects like tremor, ataxia, seizures or EEG alterations occur even when using lithium at therapeutic levels.

Starting with the first report of lithium-induced changes in EEG in 1949 [1], a number of studies using visual analysis of the EEG reported a reduction in alpha waves, an increase in delta and theta waves, an increase in paroxysmal activity and abnormalities in vigilance [2–4]. Studies using quantitative EEG analysis described almost consistently an increase of power in total, delta and theta bands and a slowing of dominant alpha frequency [5–10]. Furthermore a focussing of lithium effects in left anterior regions with intermitting slow waves is being discussed by Ulrich [11].

These findings are inconsistent and partly contradictory. The studies are barely comparable among each other because of the different recording and analysis methods, the different sample characteristics (healthy volunteers, bipolar or unipolar patients) and different medication aspects (lithium intoxication, lithium monotherapy and lithium combined with neuroleptics).

The purpose of our study was first to evaluate the effects of lithium on relative power, dominant frequencies and absolute power of the EEG spectra, controlled for vigilance, in the course of long-term lithium treatment in patients with affective disorders. Secondly, we were interested whether the hypothesis of site-specific effects of lithium in the left frontal region is replicable using quantitative EEG analysis.

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**Table 1.** Description of the studied patients with affective disorders

| | | | |
|---|---|---|---|
| Patient data | n | | 12 |
| | Age | | 59 ± 13 years |
| | Sex (F/M) | | 5/7 |
| | ICD-10 | | F31: n = 1<br>F32: n = 2<br>F33: n = 9 |
| | | T1 | T2 |
| CGI | | 4.2 ± 1.4 | 2.5 ± 0.8 |
| Analyzed 2-second EEG segments | | 52 ± 16 | 52 ± 18 |
| Medication | | | |
| | AD (number of patients) | 9 | 9 |
| | NL | 3 | – |
| | No medication | 3 | – |
| | Lithium plasma level | – | 0.67 ± 0.17 mmol/l |

AD = Antidepressives; NL = neuroleptics.

**Table 2.** Relative power of the EEG data at T1 (before lithium treatment) and T2 (under lithium treatment)

| | Electrode position | Mean T1 % | Mean T2 % | Wilcoxon test |
|---|---|---|---|---|
| Delta | $F_3$-$C_3$ | 11.4 ± 7.2 | 11.9 ± 11.5 | n.s. |
| | $F_4$-$C_4$ | 10.7 ± 8.4 | 13.1 ± 12.7 | n.s. |
| | $C_3$-$P_3$ | 8.4 ± 5.4 | 10.5 ± 7.4 | n.s. |
| | $C_4$-$P_4$ | 6.9 ± 3.1 | 9.6 ± 6.5 | 0.06 |
| | $P_3$-$O_1$ | 9.1 ± 9.5 | 10.7 ± 8.8 | n.s. |
| | $P_4$-$O_2$ | 8.6 ± 6.9 | 11.9 ± 10.9 | n.s. |
| Theta | $F_3$-$C_3$ | 18.9 ± 8.2 | 21.8 ± 9.2 | n.s. |
| | $F_4$-$C_4$ | 16.8 ± 7.2 | 21.5 ± 7.6 | **0.02** |
| | $C_3$-$P_3$ | 17.6 ± 6.1 | 23.0 ± 9.8 | **0.04** |
| | $C_4$-$P_4$ | 15.4 ± 5.3 | 24.0 ± 11.1 | **0.00** |
| | $P_3$-$O_1$ | 16.5 ± 9.2 | 23.6 ± 10.4 | **0.02** |
| | $P_4$-$O_2$ | 16.6 ± 7.6 | 23.0 ± 10.3 | **0.02** |
| Alpha | $F_3$-$C_3$ | 38.1 ± 20.2 | 39.1 ± 20.7 | n.s. |
| | $F_4$-$C_4$ | 39.5 ± 19.7 | 39.3 ± 21.4 | n.s. |
| | $C_3$-$P_3$ | 55.5 ± 13.7 | 50.6 ± 16.8 | 0.07 |
| | $C_4$-$P_4$ | 59.2 ± 12.9 | 51.3 ± 16.7 | **0.02** |
| | $P_3$-$O_1$ | 59.0 ± 22.4 | 52.8 ± 19.3 | **0.04** |
| | $P_4$-$O_2$ | 58.4 ± 20.0 | 52.4 ± 20.9 | **0.03** |
| Beta | $F_3$-$C_3$ | 31.5 ± 19.5 | 27.2 ± 21.5 | n.s. |
| | $F_4$-$C_4$ | 33.0 ± 20.2 | 26.0 ± 15.5 | 0.08 |
| | $C_3$-$P_3$ | 18.4 ± 6.8 | 16.0 ± 4.8 | n.s. |
| | $C_4$-$P_4$ | 18.5 ± 6.7 | 15.0 ± 6.1 | 0.06 |
| | $P_3$-$O_1$ | 15.4 ± 11.0 | 12.9 ± 3.6 | n.s. |
| | $P_4$-$O_2$ | 16.5 ± 11.6 | 12.7 ± 3.8 | n.s. |

## Method

EEG was obtained from 12 patients with affective disorders (ICD-10: F31, F32, F33) of the Outpatient Clinic for Relapse Prophylaxis in Affective Disorders who were included in a prospective study. EEG was recorded before lithium treatment (T1) and 4.4 ± 3.5 months after baseline under lithium (T2). The patients had analyzable recordings for quantitative EEG analysis at both time points. The age of the patients (5 females, 7 males) ranged from 38 to 76 years (mean 59 ± 13 years). Before lithium treatment (T1), 3 patients were treated with neuroleptics and antidepressants, 6 patients had antidepressive treatments without other psychotropic drugs, and 3 patients were not treated with any psychotropic medication. At T2, 3 patients were only treated with lithium, and 9 patients received additional antidepressive medication (table 1).

For EEG recording, patients were seated with eyes closed in a comfortable chair located in a quiet room. Digital EEG was recorded by electrocaps with the international 10/20 configuration and by use of Cz as reference. The recordings were amplified and filtered by the BEST system with a low-pass filter of 70 Hz and a high-pass filter of 0.5 Hz; the sampling rate was 256 Hz. For quantitative EEG analysis, two experienced neurophysiologists visually selected artifact-free 2-second segments (52 ± 16 segments at T1, 52 ± 18 segments at T2), controlled for vigilance. At least 50% occipital alpha rhythm had to be present in each segment.

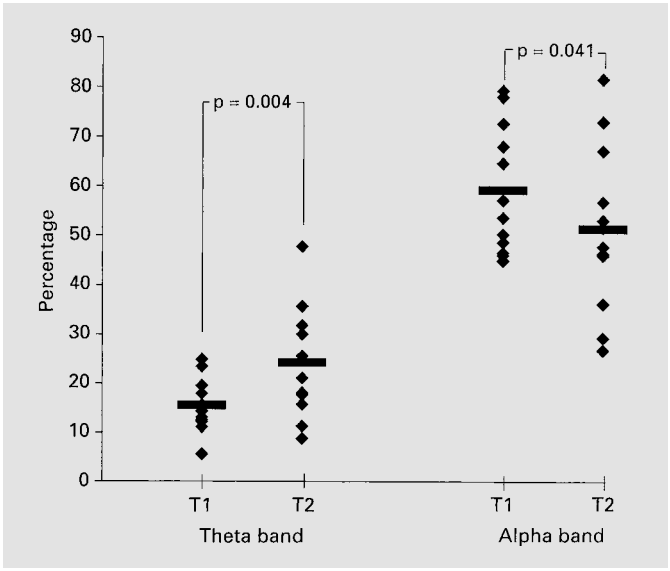
Fast Fourier transformation was performed in the BEST system for bipolar electrode pairs $F_3$-$C_3$, $F_4$-$C_4$, $C_3$-$P_3$, $C_4$-$P_4$, $P_3$-$O_1$ and $P_4$-$O_2$. Absolute and relative power, and the dominant frequency for delta (2–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz) and beta bands (12–32 Hz) were calculated and statistically compared for T1 and T2, using nonparametric Wilcoxon tests.

The lithium plasma level was correlated (Pearson correlation coefficients) with relative theta and relative alpha power at T2, with the difference in relative theta and relative alpha power between T1 and T2 and with the dominant frequency in the alpha band at T2.

## Results

A significant increase of relative power under lithium treatment was found in the theta band at all electrode positions ($F_4$-$C_4$, $C_3$-$P_3$, $C_4$-$P_4$, $P_3$-$O_1$ and $P_4$-$O_2$) except for left frontocentral $F_3$-$C_3$ (table 2). A strong increase in relative theta power from T1 to T2 was related to a high lithium plasma level ($F_3$-$C_3$: $r = 0.81$, $p < 0.01$; $F_4$-$C_4$: $r = 0.61$, $p < 0.05$). In the alpha band, the relative power was unchanged at $F_3$-$C_3$ and $F_4$-$C_4$ and reduced at the central-parieto-occipital electrodes ($C_4$-$P_4$, $P_3$-$O_1$ and $P_4$-$O_2$). Figure 1 shows that relative theta power at $C_4$-$P_4$ increased by 8.6% and relative alpha power decreased by 7.9% under lithium treatment. The relative power in the delta band was slightly increased at all electrodes without statistical significance. The relative power of the beta band was generally reduced, but also without statistical significance.

The analysis of the dominant frequency revealed a general slowing of the EEG in the total band at the electrodes

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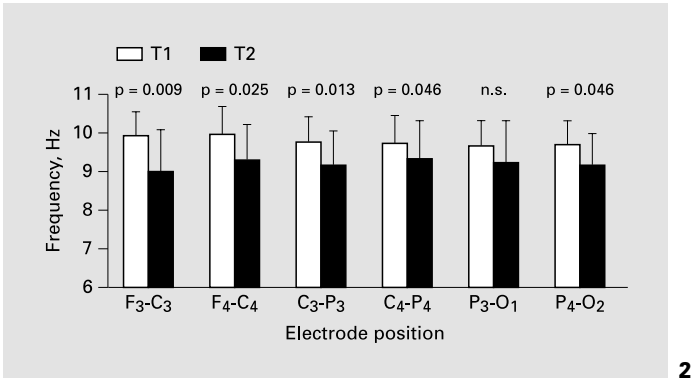


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**Fig. 1.** Changes in relative theta and alpha power at electrode pair $C_4$-$P_4$ before and under lithium treatment.
**Fig. 2.** Changes in the dominant frequency of the alpha band before and under lithium treatment. For each electrode position, the averaged dominant frequency is displayed.

$C_4$-$P_4$ and $P_4$-$O_2$ under lithium therapy. The dominant alpha frequencies were significantly slower at leads $F_3$-$C_3$, $F_4$-$C_4$, $C_3$-$P_3$, $C_4$-$P_4$ and $P_4$-$O_2$, except for $P_3$-$O_1$ (fig. 2). Figure 3 presents the power spectra of 1 patient, demonstrating the slowing of the dominant alpha frequency under long-term lithium treatment. In the delta, theta and beta bands, no significant changes of the dominant frequency were found.

A statistically significant increase in absolute power was only found in the theta band at $F_3$-$C_3$, $F_4$-$C_4$, $C_3$-$P_3$, $C_4$-$P_4$ and $P_3$-$O_1$.

## Discussion

The aim of our study was to examine the effects of long-term treatment with lithium on the EEG in patients with affective disorders. Increased relative theta power and decreased relative alpha power under lithium treatment were found for both hemispheres with slightly higher significance for the right hemisphere. In addition, a significant correlation between lithium plasma level and increase of the theta power from T1 to T2 was found. Slowing of the dominant frequency in the alpha band was observed at all leads except the left occipital electrode. Taking these findings together, the hypothesis of typical EEG alterations in anterior regions of the left hemisphere [11] cannot be supported. It seems more likely that lithium affects the CNS without any preference of region. This corresponds well to findings on the way of action of lithium, indicating that lithium acts unspecifically on neuronal cells in the whole brain by influencing second-messenger mechanisms.

It is unlikely that our above-mentioned findings are the result of improved psychopathology. The CGI score of the patients improved by 1.7 points from T1 to T2. Studies concerning the EEG of depressive patients described enhanced delta, theta and alpha activity compared to normals [12–14]. Thus, with improvement in psychopathology, an acceleration of the dominant alpha frequency combined with an increase in relative alpha power and a decrease in relative theta activity has to be expected. With respect to the improvement in our group of patients in the CGI score, we had to expect a decrease of theta activity and an increase of alpha power at T2 due to the psychopathology. However, the outcome of our examination was the opposite. At T2, we found increased relative theta power, decreased relative alpha power and slowing of the dominant alpha frequency at T2 under lithium therapy. Therefore, these EEG effects seem to be induced by lithium.

On the other hand, the EEG alterations found in our study could be the result of changes in the medication other than lithium. At baseline, 9 patients were treated with antidepressants, 3 of them additionally with neuroleptics. At T2, 9 patients under lithium treatment were still on antidepressants, but none of the patients received neuroleptics anymore. Neuroleptic-induced EEG changes are associated with an increase of slow activity in the delta and theta band and a decrease of alpha activity [14, 15]. Stopping medication with neuroleptics should lead to a

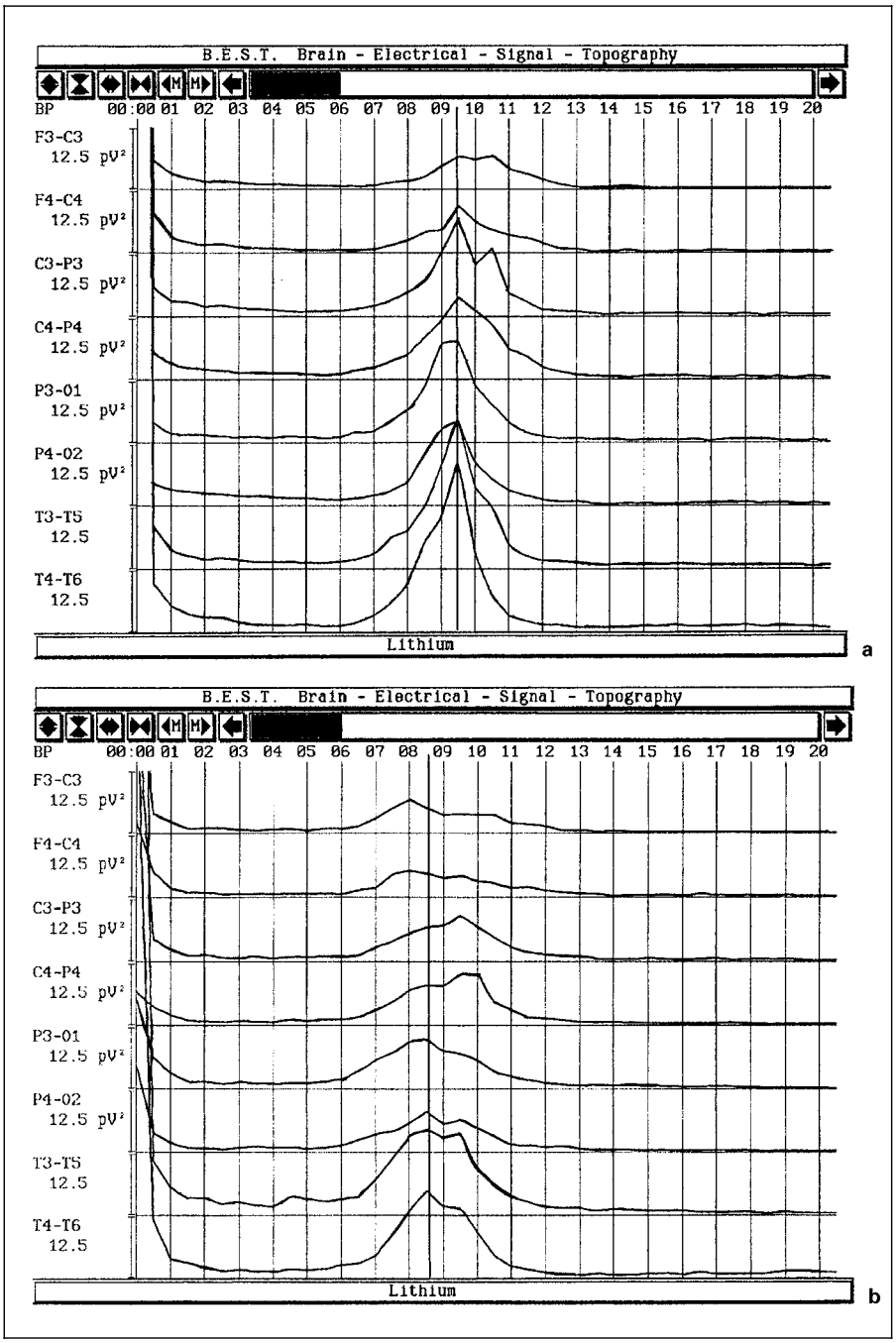


**Fig. 3.** Example of the EEG power spectrum in 1 patient with affective disorder. The line at 9.5 Hz and 8.5 Hz respectively indicates the dominant alpha frequency before (**a**) and under (**b**) lithium treatment.

decreased theta activity and an increased activity in the alpha band. However, we did not find such changes in our study. Under lithium treatment without any neuroleptic additional medication, theta activity was found to be increased and alpha activity was reduced. Because the number of patients treated with antidepressants did not vary from T1 to T2, the effects of this medication on the EEG may be negligible. Thus, it is unlikely that the changes in the EEGs of our patient group can be explained by changes in neuroleptic or antidepressive medication.

Furthermore, the correlation between the lithium plasma level and the increase in theta power is an additional argument that the change in theta power observed in this study was induced by lithium.

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