# An Auditory Electrophysiological Intervention in Migraine: A Randomized Placebo Controlled Add On Trial

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ABSTRACT. Background. The aim of the study was to assess the efficacy and tolerability of a new electrophysiological intervention technique as an add on treatment in patients with migraine.

Methods. A randomized double-blind placebo-controlled study with a parallel group add on design and a 12-week treatment phase was conducted in a large outpatient headache clinic in a neurological center. Thirty-two patients (mean age 42.6 years, SD 11.8; range 23 to 79) with

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migraine without any pharmacological migraine prophylaxis in the past three months were studied. The electrophysiological stimulation with sound therapy applied via headphones three times a day for 10 minutes was compared against a placebo audiotape. The main outcome measure was a change in the headache subtest of a self-report test instrument, Giessener Beschwerdebogen (GBB), after 12 weeks of treatment.

Results. Significant decreases in the scores of the GBB were found in the treatment group after 12 weeks of treatment in the subtests "headaches" ($p < 0.05$), "stomach complaints" ($p < 0.05$), as well as "general physical complaints" ($p < 0.05$). In the placebo group only, the decreases in "fatigue proneness" and "general physical complaints" reached statistical significance ($p < 0.05$) between the pre- and post-treatment scores. No adverse events occurred during the treatment period.

Conclusions. In the small sample studied here a proprietary method, Psychofonie®, is effective as an add on treatment in reducing subjective pain in migraine patients, although some of the effect could be attributed to placebo. 

KEYWORDS. Audio stimulation, electrophysiological stimulation, sound therapy, migraine

## INTRODUCTION

Though there is reasonable progress in the pharmacological treatment of patients with migraine, adverse drug effects and in some cases the development of drug addiction (Schoenen, 1997; Saper, 1987; Edmeads, 1994) are still unsolved problems in migraine therapy. Therefore, a non-pharmacological therapy without unwanted side effects, withdrawal symptoms, and without the development of addictive behavior would be a promising alternative.

Many relaxation techniques are used as adjunctive treatment, including biofeedback and hypnosis. Sound therapy represents a new electrophysiological stimulation method, comparable to music therapy and neurofeedback methods. With this method, a specific audiotape is prepared for subjects based on their EEG data. A music synthesizer makes use of beta and theta frequency spectra from the subject's EEG to produce a special 10-minute music-like stimulus stream that the patient lis-

tens to three times a day. The beta/theta ratio is a well-known measure of the EEG vigilance as it has been used in many studies such as Herrmann and Scharer (1987) and Wieser (1990). The time series of such theta/beta ratios are called vigilance profiles. Vigilance profiles show irregular and rapid fluctuations in short observation windows over seconds and express individual fluctuations in attentiveness or awareness (Müller, Federspiel, Fallgatter, & Strik, 1999). The frequency bands used (theta and beta) are the same as those used in common neurofeedback protocols for treating attention deficit disorder and attention deficit hyperactivity disorder (Lubar, 1997; Nash, 2000). The theta/beta vigilance profile patterns differ among individuals (Conte, Ferlazzo, & Renzi, 1995). In sound therapy, these profiles are used for controlling the pitch frequencies and the durations of chromatic musical notes and are converted into a "natural music" that has a relaxing quality. In this way the individual vigilance profiles can be expressed as auditory tones that are musical in quality. The proprietary sound therapy system used in this study is Psychofonie® and is described in detail under the Method section of this paper.

Although the effects of sound therapy on patients with migraine have previously been described in open trials (Trinka, Unterrainer, & Trzopek, 1998; Meister, Einsle, Brunner, & Rhyner, 1999), it is not clear whether the effect on migraine is due to a non-specific relaxation response while listening in a relaxed condition to the music like stream of sounds, or if there is a more specific effect compared to well established relaxation techniques. The aim of this study was to investigate the efficacy and acceptance of sound therapy with Psychofonie® as an add on treatment in patients with migraine in a placebo controlled trial. The main outcome measure was a change in the headache subtest of the Giessener Beschwerdebogen (GBB), which is a widely used self-report test instrument in German speaking countries for measuring subjective experienced somatic and emotional complaints (Brähler & Scheer, 1983). In order to evaluate a specific effect of sound therapy on migraine additional test instruments, a personality inventory (Freiburger Persönlichkeitsinventar, FPI-R; Fahrenberg, Hampel, & Selg, 1994), anxiety and depression scales (State-Trait Anxiety Inventory, STAI and Self Rating Depression Scale [SDS]; Spielberger, 1983), were obtained to control for unwanted side effects or non-specific effects on mood and anxiety states through a relaxation mechanism.

## METHOD

Patients. Two hundred and thirty-seven patients were screened at the headache outpatient clinic at the Department of Neurology (Christian Doppler Klinik, Salzburg) between March 1996 and January 1997.

Trained neurologists diagnosed one hundred and twenty-seven patients with migraine according to the International Headache Society Classification (1988). Ninety-nine patients met the necessary criteria. Thirty-eight patients agreed to participate in the study and gave written informed consent. Six patients (four in the placebo group) were absent at subsequent examinations, so 32 patients (25 female and 7 male) were analyzed.

Inclusion criteria were as follows: (a) a minimum duration of migraine with or without aura of two years, (b) a diagnosis based on the criteria of the IHS-classification, (c) at least five but less than 20 migraine attacks during the past year, and (d) age range of 16 to 60 years. Exclusion criteria were: (a) progressive neurological diseases and psychotic disorders, (b) a pharmacological migraine prophylaxis (e.g., beta-blocker or calcium antagonist) in the past three months, and (c) female patients taking oral contraceptives.

The patients were divided randomly into a placebo group (n = 13) and a treatment group (n = 19). Examiners and evaluators were blinded for the assignment to the groups.

During an initial phase of four weeks, the patients were instructed to use one of the two treatment regimes listed below, and to control for any other well-known individual precipitating factors, like avoidance of tyramine containing food. Treatment regime: (a) aspirin 1000 mg or paracetamol 1000 mg P.O. with or without 10 mg metoclopromide P.O. or (b) 50 to 100 mg sumatriptan P.O. or 6 mg S.C.

During the initial four weeks after the screening visit, the individual tapes were prepared for convenient use with ambulatory tape recorder and headphones. A battery of self-report tests, including the following instruments Freiburger Persönlichkeitsinventar (FPI-R; Fahrenberg et al., 1994), Giessener Beschwerdebogen (GBB; Brähler, & Scheer, 1983), State Trait Anxiety Inventory form A and B (STAI; Spielberger, 1983) and Self Rating Depression Scale (SDS; Zung, 1965) was performed at the beginning and the end of the treatment phase (duration 12 weeks). The main outcome measure was a mean change in the headache subtests of the GBB after 12 weeks of treatment.

The patients applied the treatment themselves via headphones. They carried out an auditory stimulation three times a day. Each stimulation

lasted 10 minutes, using a standard tape recorder (e.g., Walkman®). The patients were instructed to rest quietly and listen without effort to the auditory stimulation.

A digital EEG (Neurofile® Nihon Kohden) was recorded from each subject during relaxed wake state with eyes closed, according to the standard criteria (sampling rate 256 Hz). The epoch length was one second. Only EEG epochs, which were rated as normal with predominating alpha rhythm by experienced, board certified electroencephalographers were further processed with the Psychofonie® software (1.1, INTEGRA). If the initial EEG of a patient showed continuous, focal or localized slow activity, or abnormally high beta activity, the recording was repeated until we were able to obtain a normal EEG in all patients. Frequency analysis was performed for four electrode positions (C3, C4, T3, T4) after an initial visual analysis and artifact rejection, according to the guidelines of the German EEG Society (Hermann et al., 1989). For frequency analysis we used short-time Fast Fourier Transformation (floating point FFT) with bell tapering which outputs spectral amplitude estimates in microvolts as a function of frequency in the following bands: 0.5 to 3.5 Hz (delta), 4 to 7 Hz (theta), 8 to 13 Hz (alpha) 14 to 30 Hz (beta). Each Psychofonie® unit consists of an artifact-free record of 4,096 epochs which were off line transformed into the frequency domain resulting in successive estimates of the mean spectral amplitude density. The successive ratios of two amplitude values averaged in adequate frequency bands are converted into pitch values of musical notes in chromatic scale. The duration of each note is determined by such EEG values too. The results of the offline transform were four lines of musical notes. They were replayed simultaneously by piano sounds of a synthesizer in about the same speed as the EEG was originally recorded. The Psychofonie® sound patterns were recorded on audiotapes of 10 minutes duration. The placebo sound patterns were generated by random selection of ratio values and cannot be distinguished from sequences generated by the subjects real EEG. No individual contents of subjects' EEGs were in the audio placebos.

Statistics. The Wilcoxon Test was used as a non-parametric method for paired samples. For comparison of independent groups, we used the Mann-Whitney U test. The data were analyzed using the SPSS version for Windows (release 6.0).

## RESULTS

Thirty-two patients (25 females) were analyzed. Mean age was 42.6 years (SD 11.8; range 23 to79). Nineteen patients (17 females) were in

the treatment group (mean age 44 years, SD 11.3, median 44 years, range 23 to79) while there were 13 (8 females) age-matched patients in the placebo control group (mean age 41.3 years, SD 12.9, median 43 years range 23 to 60; $p$ = n.s.).

The FPI-R showed no significant differences between the placebo and the treatment group. Subtests of the GBB revealed significantly lower results in the post treatment tests for the placebo group: "general physical complaints" ($p < 0.05$) and "fatigue proneness" ($p < 0.05$). The treatment group showed significantly lower results after the treatment phase compared to pre-treatment values in the subtests "headache" ($p < 0.05$) and "stomach complaints" ($p < 0.05$); additional reductions were achieved in the subtest "general physical complaints" ($p < 0.05$). As both groups improved in the raw values of the "headache" subtest of the GGB, we calculated an improvement-score (pre-minus post-treatment values) and compared treatment and placebo group using the Mann-Whitney U test. Though the improvement scores were highest in the "headache" subtest, the results did not reach statistical significance ("headache" $p = 0.2$; "fatigue proneness" $p = 0.9$; "stomach complaints" $p = 0.5$; "heart complaints" $p = 0.9$; "general physical complaints" $p = 0.8$).

The State Trait Anxiety Inventory (STAI) Form A, which assesses the current state, revealed a slight but not significant improvement in both groups after the treatment phase. The STAI Form B, which describes the general anxiety state, showed no changes in either group.

No group could be rated as depressed on the Self Rating Depression Scale (SDS) at the beginning of the treatment. After the treatment both groups showed lower values, but they were not significant. Table 1 shows the summarized results.

## DISCUSSION

A specific efficacy of sound therapy can be deduced, as the raw values in the subtest for "headaches" improved significantly ($p < 0.05$) after the 12-week treatment phase in the verum group compared to placebo group. Additionally, the treatment group listed fewer complaints concerning stomach pains, which are frequently found as an accompanying symptom in migraine patients. These findings are confirmed by a positive correlation between the strength of the headaches (GBB subtest "headaches") and of the stomach pain (GBB subtest "stomach complaints") during the first measurement ($r = 0.6$; $p < 0.001$). The GBB re-

TABLE 1. Pre- and Post-Test Raw Scores for Placebo and Treatment Group

| | Placebo group | | | | | Treatment group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N = 13 | | | | | N = 19 | | | | |
| | Pre-test | | Post-test | | | Pre-test | | Post-test | | |
| | Mean | SD | Mean | SD | P | Mean | SD | Mean | SD | P |
| GBB | | | | | | | | | | |
| Fatigue proneness | 9.85 | 4.99 | 7.31 | 5.14 | .036* | 11.16 | 3.7 | 8.53 | 5.67 | .061 |
| Stomach complaints | 8.0 | 4.28 | 6.32 | 3.19 | .119 | 8.89 | 4.7 | 6.05 | 4.77 | .039* |
| Headaches | 13.08 | 4.33 | 12.08 | 4.48 | .327 | 13.21 | 4.54 | 11.05 | 5.04 | .023* |
| Heart complaints | 4.92 | 2.53 | 3.62 | 2.1 | .059 | 6.95 | 9.96 | 4.0 | 4.67 | .177 |
| General physical complaints (total score) | 35.85 | 13.61 | 28.77 | 12.32 | .028* | 38.0 | 13.92 | 29.63 | 18.10 | .013* |
| | | | | | | | | | | |
| STAI-A | 40.54 | 8.84 | 37.85 | 13.19 | .235 | 37.84 | 9.28 | 36.26 | 12.83 | .268 |
| STAI-B | 40.69 | 9.76 | 39.54 | 11.28 | .286 | 41.47 | 11.34 | 41.32 | 11.42 | .965 |
| | | | | | | | | | | |
| SDS | 37.15 | 8.95 | 33.54 | 8.28 | .059 | 36.89 | 9.99 | 35.58 | 11.42 | .352 |

* $p < .05$

vealed lower values in both groups for the total score "general physical complaints" after the treatment phase. It can be concluded that the latter is not due to any specific effect of the method but rather to the intervention itself. A supposed relaxation effect may be the decisive factor. This assumption is confirmed by the slight, though not significant improvement in the STAI (form A) and SDS tests in the placebo control group as well as in the treatment group.

These findings suggest that the Psychofonie® sound therapy offers a more powerful effect in migraine patients than mere relaxation, which is offered also by the audio placebo. It seems reasonable to assume, that the auditory stimulation with sound therapy activates the primary auditory processing pathways in the brain stem and therefore may influence the intensity dependence of the auditory evoked response, consequently increasing serotoninergic transmission and exhibiting thereby an antimigraine effect (Goadsby, Zagami, & Lambert 1991; Goadsby & Gundlach, 1991; Goadsby & Hoskin, 1996; Wang, Timsit-Berthier, & Schoenen,

1996; Wang & Schoenen, 1998; Schoenen, 1997; Proietti-Cecchini, Afra, & Schoenen, 1997). Additional effects on the ongoing EEG are likely, as there is a clearly demonstrated influence of music on the EEG (Brüggenwerth, Gutjahr, Kilka, & Machleidt, 1994; Petsche, 1994; Petsche, Pockberger, & Rappelsberger, 1985; Petsche, Lindner, Rappelsberger, & Gruber, 1988; Gutjahr et al., 1994). Why specifically the theta and beta power, which are used in the algorithm of the Psychofonie® software, is relevant in this context is hard to explain. Theta waves are commonly associated with the hippocampal formation, but they can also be found in other cortical limbic areas, namely in the entorhinal and the cingular cortices (Steriade, Gloor, Llinas, Lopes da Silva, & Mesulam, 1990), where they are under the modulating influence of ascending fibers from the brain stem (Vertes, 1982). Beta activity is regarded as an index of the focused arousal in motor programming representing an optimal periodicity for maximal synaptic transmission in cortical circuits (Steriade et al., 1990). The frequency bands used are the same as those used in common neurofeedback training protocols for Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder for the improvement of vigilance (Lubar, 1997; Nash, 2000). One might speculate that the sound sequences, derived by the theta activity and their association with the brain stem structures may lead to an augmentation of serotoninergic transmission and thereby developing an anti-migraine effect. Analogously, the beta derived sound sequences may influence the focused arousal and the cortical synaptic activity, leading to the hypothesized relaxation effect. It seems possible that sound therapy achieves these changes through the mechanisms of neuromodulation and long term potentiation (LTP), similar to rhythm changes in the electrical activity of the brain due to neurofeedback methods (Abarbanel, 1995). These assumptions are speculative and we cannot explain the mechanism of action from our data, but future research on this topic should clarify the pathophysiological basis of this intervention technique.

The main outcome measure was a change in a self-report test instrument (headache subtest of the GBB), which is a weakness of the study and deserves further comment. Because of the fluctuations in the attack rate of patients suffering from migraine during the "natural course" of the disease, a larger sample size and a longer treatment period would have been advisable. Since this is a new treatment method, with an unknown mechanism, the risk of unwanted side effects was not predictable at the beginning of the study, therefore we decided for the shortest possible period and a surrogate measurement (GBB) as the main out-

come measure instead of the usual attack rate. Larger placebo controlled studies with a longer treatment period, a cross-over design, and further research on the mechanism of action are necessary to clarify the value of this method in the therapy of patients with migraine.

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