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Letter to the Editor

## Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia

Dear Editors,

Deficits in declarative memory are among the most severe neuropsychological impairments in schizophrenia and contribute to poor clinical outcomes (Green et al., 2000). Sleep disturbances like deficits in slow wave sleep or slow wave activity might essentially contribute to these memory impairments (Göder et al., 2008; Manoach and Stickgold, 2009; Lu and Göder, 2012). Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique using weak electric currents to induce shifts in excitability in the human cortex (Nitsche and Paulus, 2000). When applied during non-rapid eye movement sleep tDCS oscillating at the frequency of the sleep slow oscillation (~0.75 Hz; so-tDCS) enhanced sleep-associated memory consolidation in young healthy subjects (Marshall et al., 2006). The aim of the present study was to test the hypothesis, whether so-tDCS is able to enhance sleep related declarative memory consolidation in patients with schizophrenia.

The sample consisted of 14 patients (mean age 33 ± 8 years) with paranoid schizophrenia diagnosed according to ICD 10. The mean total PANSS score was 45 (range from 30 to 82). All patients were on stable antipsychotic medication. Drug abuse was excluded by urinary drug screenings. The study was approved by the local ethics committee.

An adaptation night preceded each of the two experimental sessions, the stimulation (so-tDCS) and sham-stimulation conditions, which were given in pseudo-randomised order. For each participant the two sessions were separated by an interval of one week and medication was unchanged between both conditions. Stimulation was conducted with a commercial direct current stimulator (NeuroConn, Ilmenau, Germany). Sinusoidal currents at a frequency of 0.75 Hz were applied via stimulation electrodes (8 mm diameter) positioned bilaterally at frontolateral locations F3 and F4 (according to the 10–20 system) and at the mastoids. Current oscillated between 0 and 300 μA. Stimulation started 10 min after subjects entered stage 2 sleep. Five blocks of 5-min so-tDCS were applied separated by 1-min intervals free of stimulation. In the sham-session electrodes were applied as in the stimulation session but the stimulator remained off. Sleep was recorded and visually scored according to standard criteria (Rechtschaffen and Kales, 1968).

Neuropsychological testing was conducted at 9 pm prior to polysomnographically recorded sleep and at 7:30 am on the morning thereafter. To test declarative verbal memory we used a German version of the Rey Auditory–Verbal Learning Test (Helmstaedter et al., 2001). In the evening a list of 15 words was read to the participants 5 times. We assessed final acquisition (recalled words in trial 5 in the evening) and free recall (number of recalled words in the morning), and calculated retention (number of words in trial 5 in the evening subtracted from the number of recalled words in the morning). Two different standardized word lists given in a randomised order were used for the stimulation and sham conditions. Procedural learning was assessed by testing the subjects' mirror-tracing skills (Göder et al., 2008). Digit span was used as a control for short-term memory. Mood and tiredness of the patients were assessed by a 6-point analogue scale. Statistical analyses relied basically on analyses of variance (ANOVA). The order of manipulation (stimulation-sham versus sham-stimulation) was included as a group factor.

So-tDCS was well tolerated by the patients. Concerning sleep parameters there were no significant differences between stimulation and sham conditions. For verbal memory retention, repeated measures ANOVA revealed no effect of order, but a significant main effect of condition (Table 1). Post-hoc paired t-test showed a lower forgetfulness for words after stimulation than in the sham condition. The number of

**Table 1**
Neuropsychological performance and mental state before and after slow oscillation stimulation and sham stimulation.

| | Stimulation | Sham | Condition | Order | Interaction |
|---|---|---|---|---|---|
| *Short term memory* | | | | | |
| Digit span forward evening | 8.3 ± 2.3 | 7.9 ± 2.2 | 0.2 | 0.4 | 0.2 |
| Digit span forward morning | 8.6 ± 2.1 | 8.4 ± 2.3 | 0.8 | 0.7 | 0.3 |
| Digit span backward evening | 6.4 ± 2.1 | 6.1 ± 1.4 | 0.6 | 0.9 | 0.9 |
| Digit span backward morning | 6.9 ± 2.2 | 6.9 ± 1.5 | 0.9 | 0.9 | 0.6 |
| *Declarative memory* | | | | | |
| Final acquisition evening (words) | 11.7 ± 3.1 | 12.8 ± 2.4 | 0.11 | 0.7 | 0.8 |
| Recall morning (words) | 8.4 ± 4.0 | 8.3 ± 3.1 | 0.6 | 0.4 | 0.2 |
| Retention /forgetfulness (words) | −3.3 ± 2.7* | −4.5 ± 2.7 | 0.02 | 0.12 | 0.14 |
| *Procedural Learning* | | | | | |
| Mirror tracing time evening (s) | 76 ± 81 | 82 ± 63 | 0.9 | 0.98 | 0.02 |
| Mirror tracing time morning (s) | 58 ± 27 | 53 ± 25 | 0.5 | 0.2 | 0.1 |
| Mirror tracing errors evening | 6.3 ± 6.7 | 5.2 ± 4.2 | 0.2 | 0.9 | 0.005 |
| Mirror tracing errors morning | 3.1 ± 3.7 | 2.3 ± 2.6 | 0.5 | 0.2 | 0.1 |
| *Mental state* | | | | | |
| Mood evening | 4.0 ± 0.8 | 4.1 ± 1.1 | 0.3 | 0.4 | 0.7 |
| Mood morning | 4.6 ± 1.1* | 4.0 ± 1.2 | 0.02 | 0.7 | 0.7 |
| Tiredness evening | 3.1 ± 1.0 | 3.3 ± 0.9 | 0.2 | 0.06 | 0.1 |
| Tiredness morning | 3.8 ± 2.0 | 3.4 ± 0.6 | 0.6 | 0.5 | 0.3 |

Mood 1 = depressed, 6 = lighthearted.
Tiredness 1 = weary, 6 = fresh.
Means and standard deviations.
Three rightmost columns indicate P-values for ANOVAS. In the case of significant condition or interaction effects, post-hoc pairwise comparisons between stimulation and sham conditions were conducted using t-tests.
* $P<0.05$.

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words remembered during final acquisition before sleep did not differ between sessions. Mood in the morning after stimulation was significantly more positive than after the control night.

This is the first study analysing the effects of tDCS during sleep in patients with schizophrenia. The main results in comparison to nights with sham stimulation were greater retention of verbal material together with a more positive mood the following morning. According to a recently reviewed model for memory consolidation slow oscillations originating from neocortical networks provide a temporal frame for the dialogue between the neocortex and the hippocampus that is necessary for redistributing memories for long-tem storage (Diekelmann and Born, 2010). Interestingly also mood in the morning following nocturnal stimulation was improved in our patients. In accordance with this, earlier studies found that tDCS applied during wake may have antidepressant effects in depressed patients and in healthy subjects (Nitsche et al., 2009).

As a limitation, effect sizes seem small and our present results should in future be confirmed by a larger patient group size. Taken as a whole our results are promising and should stimulate further research investigating the link between sleep and memory in psychiatric disorders and on attempts to improve memory performance and thereby functional outcome in schizophrenia.

**Disclosure statement**

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Robert Göder*
Paul Christian Baier
Bente Beith
Cora Baecker
Mareen Seeck-Hirschner
*Department of Psychiatry and Psychotherapy, University Hospital Schleswig-Holstein, Kiel, Germany*
*Corresponding author at: Department of Psychiatry and Psychotherapy, University hospital Schleswig-Holstein, Niemannsweg 147, 24105 Kiel, Germany. Tel.: +49 431 9900 2681; fax: +49 431 9900 2568.
*E-mail address:* r.goeder@zip-kiel.de (R. Göder).

Klaus Junghanns
*Department of Psychiatry and Psychotherapy, University Hospital Schleswig-Holstein, Lübeck, Germany*

Lisa Marshall
*Department of Neuroendocrinology, University of Lübeck, Lübeck, Germany*

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