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Cordance derived from REM sleep EEG as a biomarker for treatment response in depression – a naturalistic study after antidepressant medication

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ABSTRACT

Objective: To evaluate whether prefrontal cordance in theta frequency band derived from REM sleep EEG after the first week of antidepressant medication could characterize the treatment response after 4 weeks of therapy in depressed patients.

Method: 20 in-patients (15 females, 5 males) with a depressive episode and 20 healthy matched controls were recruited into 4-week, open label, case–control study. Patients were treated with various antidepressants. No significant differences in age (responders (mean ± SD): 45 ± 22) years; non-responders: 49 ± 12 years), medication or Hamilton Depression Rating Scale (HAM-D) score (responders: 23.8 ± 4.5; non-responders 24.5 ± 7.6) at inclusion into the study were found between responders and non-responders. Response to treatment was defined as a ≥50% reduction of HAM-D score at the end of four weeks of active medication. Sleep EEG of patients was recorded after the first and the fourth week of medication. Cordance was computed for prefrontal EEG channels in theta frequency band during tonic REM sleep.

Results: The group of 8 responders had significantly higher prefrontal theta cordance in relation to the group of 12 non-responders after the first week of antidepressant medication. This finding was significant also when controlling for age, gender and number of previous depressive episodes ($F_{1,15} = 6.025$, $P = .027$). Furthermore, prefrontal cordance of all patients showed significant positive correlation ($r = 0.52$; $P = .019$) with the improvement of HAM-D score between the inclusion week and fourth week of medication.

Conclusions: The results suggest that prefrontal cordance derived from REM sleep EEG could provide a biomarker for the response to antidepressant treatment in depressed patients.

1. Introduction

The lifetime prevalence of major depressive disorder (MDD) in United States is 16.6% (Kessler et al., 2005). Unfortunately, approximately 50% of patients with MDD do not respond to initial treatment (Trivedi et al., 2006; Zajecka, 2003) and it takes usually 4 weeks to evaluate whether a patient responded to therapy (Gelenberg and Chesen, 2000; Souery et al., 2007). It is therefore of great interest to find biomarkers which could characterize treatment outcome in much shorter time. Several biomarkers that have the potential to maximize treatment effects and minimize adverse reactions emerged from academic research. Previous studies have discovered genetic (Kirchheiner et al., 2004; Uhr et al., 2008) and systemic markers such as quantification of proteins, lipids and carbohydrates as well as measures from neuroimaging, endocrinology and sleep-electroencephalography (EEG) (Dresler et al., 2014; Holsboer, 2008). However, biomarkers are still not used in daily psychiatric practice and the initial medication is tested for several weeks on a trial-and-error basis.

A further possibility to improve this situation is offered by quantitative electroencephalography (QEEG) obtained from awake patients (Leuchter et al., 2010). Among others, cordance (Leuchter

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et al., 1994) is a promising candidate to characterize the treatment response. Cordance correlates with regional brain activity by combining information from the absolute and relative EEG spectral power. It was shown that cordance computed for theta (4–8 Hz) frequency band has a positive correlation with cerebral perfusion (Leuchter et al., 1999). Depressed patients compared to controls were found to have significantly higher theta cordance in the prefrontal midline region (Cook et al., 2014). Furthermore, prefrontal theta cordance was reported to be a promising correlator of antidepressant treatment outcome. In several studies, responders showed a significant decrease in prefrontal theta cordance as measured during wakefulness after the first week of therapy when compared to baseline, irrespective of investigated medication (Bares et al., 2010, 2008, 2007; Cook et al., 2005 and Cook et al., 2002). However, the waking state is characterized by a wide variance of sub-states ranging from alert over relaxed wakefulness to drowsy-awake. These sub-states are composed of heterogenous EEG characteristics and they differ in function as indicated by fMRI (Olbrich et al., 2009). Therefore, measuring a more homogenous state of consciousness has the potential to increase the discrimination power of cordance. Tonic rapid eye movement (REM) sleep is such a homogenous state and can be characterized by objective and clear-cut criteria (American Academy of Sleep Medicine (2009)); lack of rapid eye movements, muscle atonia and a low-amplitude EEG with mixed frequencies.

Prefrontal theta cordance may reflect activity of prefrontal cortex and anterior cingulate cortex (ACC) (Asada et al., 1999), which both seem to be crucial in MDD (Drevets, 2000 and Drevets, 1999). Particularly increased rostral ACC (rACC) activity at baseline was shown to be a marker of antidepressant treatment response backed by the emerging evidence indicating that the rACC represents one of the main 'hubs' within the default network, an intrinsically organized functional network that has been associated with a variety of self-referential processes like brooding (Pizzagalli, 2011). During REM sleep, the ACC activity level is maximal, whereas the surrounding frontal cortex activity is minimal (Braun et al., 1997; Hobson and Pace-Schott, 2002). Furthermore, during REM sleep, ACC has prominent oscillatory activity in the theta frequency band (Nishida et al., 2004) marking an ideal frequency band to be detected by the prefrontal theta cordance.

Therefore, the aim of this study was to measure the prefrontal theta cordance during tonic REM sleep. We hypothesized that at the end of the first week of antidepressant treatment, absolute prefrontal theta cordance values could differ between responders compared to non-responders.

2. Methods

2.1. Study sample

The length of the open-label, case–control study was four weeks (see Fig. 1). We screened 28 and enrolled 20 patients treated according to the doctor's choice with antidepressant drugs within a few days after admission. Patients who were admitted while on antidepressant medication (85%) were switched to another antidepressant within a few days after admission, the others (15%) were initially unmedicated.

Subjects were adults who met DSM-IV criteria for a major depression or a bipolar I or II disorder (depressive episode), as diagnosed by 2 senior psychiatrists, and had HAM-D scores $\geq$14 on the 21-item scale at inclusion. Subjects were excluded in case of pregnancy, a serious risk of suicide, a history of drug/alcohol dependence, history of head trauma, personality disorder and severe somatic diseases. None of the participants experienced therapeutic sleep deprivation, electroconvulsive therapy, shift work or transmeridian travel within 3 months prior to investigation. To avoid withdrawal effect and possible EEG changes, the continuation of benzodiazepine or non-benzodiazepine anxiolytics was allowed in low unchanged dosages. Patients on long-acting medication including fluoxetine and depot neuroleptics were not admitted.

For the present analysis, eight patients were excluded according to these criteria. Twenty subjects (5 males, 15 females, age mean (SD): 47.6 (16.6) years) were included. They had the following diagnoses: four subjects with a First Depressive Episode (ICD-10 F 32.1 (n = 2), F 32.2 (n = 2)), two subjects with a Severe Depressive Episode within a Bipolar Affective Disorder (ICD-10 F 31.4) and 14 subjects with a Recurrent Depressive Disorder (ICD-10 F33.1 (n = 2), F33.2 (n = 10), F33.3 (n = 2)). Twenty paid healthy volunteers matched for age and gender had no current or past psychiatric disorders.

During our study, 40% of the patients (n = 8) were treated with a combined serotonin-noradrenaline reuptake inhibitor, 15% (n = 3) with a selective serotonin reuptake inhibitor, 20% (n = 4) with a tricyclic antidepressant, 15% (n = 3) with a noradrenaline-dopamine reuptake inhibitor, and 10% (n = 2) with a noradrenergic and specific serotonergic antidepressant. 10% (n = 1) of all patients received an atypical antipsychotic drug in addition to the antidepressant medication. Plasma concentration of antidepressant medication was monitored weekly to ensure clinically efficient drug levels.

2.2. Experimental procedures

Subjects were inpatients recruited from the clinic of the Max Planck Institute of Psychiatry. The Ethics Committee of the Ludwig Maximilian University of Munich approved all experimental procedures, and written informed consent was obtained after experimental procedures were explained to the subjects. Patients slept two consecutive nights (from 11 p.m. till 7 a.m.) in our sleep laboratory after the first week of antidepressant treatment and two consecutive nights after the fourth week of antidepressant treatment (Fig. 1), whereas healthy control subjects slept two consecutive nights (from 11 p.m. till 7 a.m.) in the sleep laboratory once. The first night served for adaptation and exclusion of sleep disorders.

2.3. EEG recording and analysis

Polysomnographic recordings were acquired with a Comlab 32 Digital Sleep Lab amplifier (Schwarzer GmbH, Munich, Germany) using Ag/AgCl electrodes. Nineteen electrodes were placed according to the international 10–20 system as described in the first publication about cordance by Leuchter and colleagues (Leuchter et al., 1994), and referenced to the electrode situated between electrodes Cz and Pz in the midline (CPz).

The sampling rate for EEG channels was 250 Hz with a band-pass filter from 0.53 to 70 Hz. Electrode impedances were below 5 kOhm. Additionally, we monitored electrocardiogram, electromyogram, horizontal and vertical electrooculogram (EOG, two electrodes for each direction) referenced to the left mastoid electrode. EOG was band-pass-filtered from 0.095 to 30 Hz. Experienced raters unaware of the study protocol visually scored sleep stages according to standard guidelines (Rechtschaffen and Kales, 1968).

In previous studies (Bares et al., 2010, 2008, 2007; Cook et al., 2005 and Cook et al., 2002), cordance was computed from the wake QEEG, using signal fragments within a 30 s range. These studies have shown that short signal fragments could be sufficient to use cordance as a biomarker of antidepressant treatment outcome. Referring to these findings, we computed cordance from the first 30 s epoch of artifact-free tonic REM sleep of the night, which was preceded and followed by at least one epoch of REM