

European College of Neuropsychopharmacology (ECNP) – press release

Measuring brainwaves while sleeping can tell if you should switch antidepressants

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Type of study: not peer-reviewed/experimental study/people

Scientists have discovered that measuring brainwaves produced during REM sleep can predict whether a patient will respond to treatment from depression. This enables patients to switch to a new treatment rather than continue the ineffective treatment (and the depression) for weeks without knowing the outcome.

As study leader, Dr Thorsten Mikoteit said, *“In real terms it means that patients, often in the depths of despair, might not need to wait weeks to see if their therapy is working before modifying their treatment”*. This work is presented at the ECNP Congress.

Around 7% of adults suffer depression (also known as MDD, Major Depression Disorder) in any one year. It's a huge health burden, costing economies hundreds of billions of Euros/dollars each year. Around 27m European and 17m Americans suffer from MDD every year.

The standard treatment is antidepressants, normally Selective Serotonin Reuptake Inhibitors (SSRI's), such as Prozac and Fluoxetine. However, these can take weeks or months to show an effect, meaning that patients often have to face the depth of their depression for several weeks before even knowing if the treatment they are taking will work. Around 50% of sufferers don't respond to initial antidepressant treatment, which means that after four weeks of ineffective treatment, doctors have to change treatment strategy, and again have to wait for response for another four weeks. Being able to predict the response as early as after one week of treatment would be of huge benefit to depressed patients, and would shorten the treatment response time.

A team led by Dr Thorsten Mikoteit, of the University of Basel, has conducted a randomised controlled trial on 37 patients with Major Depression. All were treated with antidepressants, but 15 were assigned to the control group, while the remaining 22 had their details given to the psychiatrist in charge of treatment. All then had their brainwaves monitored during REM* sleep (technically, this was a measurement of *prefrontal theta cordance in REM sleep*). The psychiatrists in charge of the treatment group patients were under instructions to interpret the brainwaves to see if the treatment was working, and if not to change the treatment. The overall aim was to see a 50% reduction in symptoms of depression, measured by the standard Hamilton Depression Rating Scale.

Doctors tested patients as early as one week after starting treatment, to see if the brainwaves indicated that the antidepressant treatment was likely to work. Those patients who were unlikely to have successful treatment were immediately switched to a different treatment. After 5 weeks it was found that 87.5% of these patients had an improved response, as opposed to just 20% in the control group.

Thorsten Mikoteit said:

“This is a pilot study, but nevertheless it shows fairly significant improvements. We have been able to show that by predicting the non-response to antidepressants we were able to adapt the treatment strategy more or less immediately: this enables us to significantly shorten the average duration between start of antidepressant treatment and response, which is vital especially for seriously depressed patients.

It needs to be repeated with a larger group of patients to make sure that the results are consistent. Patients need to be in a situation where their REM sleep can be monitored, so this requires more care than just giving the pill and waiting to see what happens. This means that the treatment monitoring will be more expensive, although we anticipate that will be offset by being able to give the right treatment much earlier. We are working on ways of streamlining this.

What it does mean is that we may be able to treat the most at-risk patients, for example those at risk of suicide, much quicker than we can currently do. If this is confirmed to be effective, it will save lives”.

Commenting, Professor Catherine Harmer, University of Oxford and ECNP Executive Committee member, said:

“Most of the time, patients need to wait for around 4 weeks before they can tell if they are responding to a particular antidepressant or not. This is a hugely disabling and lengthy process and often a different treatment then needs to be started. The study results presented by Mikoteit are interesting and suggest that it may be possible to tell if a treatment is working much more quickly - even after a week of treatment - by using a physiological measure of response (REM sleeping pattern). If this is replicated in larger, blinded study then it would have enormous implications for the future treatment of individuals with depression”.

Professor Harmer was not involved in this work, it is an independent comment.

**REM sleep is “Rapid Eye Movement” sleep. This is a normal period of sleep when one’s eyes move rapidly from side to side. People tend to dream more during REM sleep.*

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Notes for Editors

European College of Neuropsychopharmacology (ECNP)

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 33rd annual ECNP Congress – ECNP Virtual - takes place from 12th to 15th September. It is Europe’s premier scientific meeting for disease-oriented brain research. In 2020 it is a virtual congress. The regular congress annually attracting up to 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: <https://www.ecnp.eu/Congress2020> The 2021 congress is scheduled to take place in Lisbon next September.

Abstract, P.733 Guidance of treatment with the biomarker prefrontal theta cordance in rapid eye movement sleep improved response rates in major depression

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Introduction: To date, the medication treatment of major depression is associated with unsatisfactory response rates, delayed treatment improvements, unpleasant side effects, and a high burden of disease. In line with this, reliable algorithms to choose the appropriate medication are scarce. However, the current research on possible biomarkers suggests that rapid eye movement (REM) sleep appears to be a promising source to predict treatment outcome. More specifically, higher quantitative electro-encephalography (QEEG) derived prefrontal theta cordance in REM sleep correlated with more favorable frontocingulate regulation of the amygdala activity [1]. Further, prefrontal theta cordance in REM-sleep seemed to be capable to predict antidepressant treatment response with high accuracy as early as after one week of treatment.

Aims: The aim of this study was to examine, if providing the prediction of prefrontal theta cordance in REM sleep prospectively and changing the antidepressant medication in case of predicted non-response would increase the final response rate.

Methods: At treatment onset with antidepressants, 37 adult male and female in-patients with major depressive disorders were randomly assigned either to the intervention condition (IG, N = 22, mean age: 39.5 years; 45.5 % females) or the control condition (CG, N = 15, mean age: 45.4 years; 46.7 % females). The biomarker prefrontal theta cordance in REM sleep was assessed from a polysomnogram as early as after one week of treatment. Only in the IG, the cordance was provided prospectively for guidance of treatment: Physicians were told to adapt antidepressant treatment strategy in case of predicted non-response, or to maintain treatment strategy in case of predicted response. Experts rated the depression severity with the Hamilton Depression Rating Scale (HAMD) at baseline, at week one after treatment onset, and at the end of the study at week five. Response to treatment at week five was defined as a $\geq 50\%$ reduction of baseline HAMD score.

Results: Response rates were 16/22 (72.7 %) in the IG vs. 9/15 (60 %) in the CG (OR = 1.77, 95% CI: 0.44-7.17). If Cordance predicted non-response at week one, and if physicians were asked to modify antidepressant treatment immediately, the cordance predicted non-responder had an 85.7% chance of response at week five instead of 20% in the CG where the prediction of non-response by cordance was prospectively unknown ($F_{\text{Response} \times \text{Group}} = 4.18, p = .03, \eta^2 = .29$). In contrast, there was no significant difference between IG and CG response rates in the cordance predicted responders, when medication was maintained in both, IG and CG ($F_{\text{Response} \times \text{Group}} = .26, p = .77$).

Conclusion: Prefrontal theta cordance in REM sleep seems to be a promising biomarker for response prediction in a naturalistic in-patient setting. Given the preliminary small sample size of the ongoing study, we were unable to claim for prediction power, although the results were consistent with previous studies. Furthermore, the preliminary results suggested that cordance has the capability to increase treatment response in inpatients with major depressive disorders.

References

[1] Pawlowski, M.A., Gazea, M., Wollweber, B., Dresler, M., Holsboer, F., Keck, M.E., Steiger, A., Adamczyk, M., Mikoteit, T., 2017. Heart Rate Variability and Cordance in Rapid Eye Movement Sleep as Biomarkers of Depression and Treatment Response. *J. Psychiatr. Res.* 92, 64-73.

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