### NEUROTECHNOLOGY

# Predicting antidepressant response by electroencephalography

Patients who respond to an antidepressant are identified by retrospective analysis of their brain waves.

# Christoph M. Michel and Alvaro Pascual-Leone

ajor depression is one of many psychiatric conditions for which the rate of response to medications and other therapies is relatively low. As syndromic diagnostic constructs like 'depression' cover a diverse array of mechanistic dysfunctions, only an unknown subset of patients is likely to respond to a particular therapy. But if likely responders could be identified in advance of treatment, this would be of enormous clinical benefit. In this issue, Wu et al.<sup>1</sup> show that sophisticated analysis of electroencephalography (EEG) data can accurately identify individuals with major depression who responded to a specific selective serotonin reuptake inhibitor. In the future, such an approach might allow physicians to select the best treatment for individual patients in advance and thus optimize treatment response.

EEG measures synchronized neuronal activity, or 'brain waves', via electrodes placed on the scalp. Because it has a temporal resolution of milliseconds, EEG captures the oscillation frequency of neuronal activities. Oscillation frequencies convey important information about the functional state of the brain. For example, oscillations in different and specific frequency bands are tightly linked to the level of consciousness and vigilance, correlate with different sleep stages, are related to attention and memory processes, carry top-down and bottom-up information processing in large-scale neural networks, and tune the coupling of information received by different brain areas<sup>2,3</sup>.

Many quantitative pharmaco-EEG studies over the past three decades have attempted to use EEG data to distinguish different neuropsychiatric pathologies and to anticipate responses to treatment<sup>4</sup>. However, none of these studies was able to predict whether a patient would respond to a specific therapy<sup>5</sup>. In pharmaco-EEG studies, a patient's EEG at resting state is often analyzed by quantifying the spectral power at specific electrodes (or the mean of all electrodes). However, this approach ignores the fact that, because of volume conduction, any electrode may capture neuronal activity from anywhere in the brain. Consequently, such analysis is not specific to circumscribed activity within a single brain network that might be sensitive to a given treatment. 'Source localization' methods have partly overcome this challenge and have succeeded in predicting that a patient will respond to therapy in general, although not to a particular therapy<sup>6</sup>.

In the present study, Wu et al. used a novel approach to define EEG features that predict the response of depressed patients to sertraline, a selective serotonin reuptake inhibitor. They focused on the spatial distribution of the potential field of the whole-scalp multichannel EEG to define spatial filters — which they termed "latent space" — that are then used to determine the frequency modulation of a particular potential field. This approach was proposed by Koles<sup>7</sup> in the 1990s and has often been used for feature extraction in brain– computer interface procedures<sup>8</sup>.

The method of Wu et al. relies on the fact that activation of a given large-scale neuronal network produces a unique potential field on the scalp surface. There is abundant evidence from the literature on EEG, magneto-encephalography and functional magnetic resonance imaging that large-scale networks are characterized by simultaneous oscillatory brain activity in specific circuits that connect different brain regions. Therefore, this simultaneous activity will be captured by the scalp EEG as a specific potential field with a stable configuration and alternating polarity over time. Importantly, different configurations of the scalp potential field are necessarily formed by activation of different neuronal populations and thus, at least partly, different brain networks.

Wu et al. used spatial filters to selectively determine the frequency fluctuation of specific scalp potential fields. Even though the same potential map can theoretically be produced by different network configurations, the chance that the spatial filter captures the frequency modulation of one particular network is high. Once these (few) spatial filters are determined in a supervised way to optimize the outcome target, the frequency content (power spectrum) of the spatially filtered signals is determined and used as latent variables for a machine learning algorithm.

news & views

Check for updates

The authors applied their machine learning algorithm to high-density EEG data from 228 medication-free outpatients with depression who received either sertraline or placebo in a randomized trial. EEG activity of the latent signals in the alpha frequency band significantly predicted clinical treatment outcome in this population. The generalizability of the EEG signature was then successfully tested in three independent samples of patients with depression. One of these samples (n = 72) was used to validate the EEG predictive signature in an independent cohort of patients who also received antidepressant medication. A second cohort (n = 24) was used to gain insights into the neurobiological substrate of the EEG predictive signature by correlating it with a brain-MRI-based signature previously shown to predict treatment response.

Finally, in a third independent sample of 152 patients who had received either 10-Hz repetitive transcranial magnetic stimulation to the left dorsolateral prefrontal cortex or 1-Hz repetitive transcranial magnetic stimulation to the right dorsolateral prefrontal cortex (both with concurrent psychotherapy), Wu et al. were able to show the specificity of the EEG predictive signature, which differed between sertraline and repetitive transcranial magnetic stimulation treatment, presumably because of their different mechanisms of action. This finding is particularly clinically relevant as it suggests that EEG signatures may enable the selection of specific treatment modalities for specific patients.

Figure 1 illustrates why the spatially oriented frequency analysis might have been more successful in treatment prediction



**Fig. 1** | **Effect of spatial filters on EEG alpha activity.** EEG alpha activity fluctuates over time in the sub-second range. Different electrodes on the scalp surface (the figure shows a left and a right central electrode) record different temporal dynamics because different brain networks are activated over time. The neuronal activity of these networks spreads in different ways to the scalp, leading to unique potential configurations at any time point (illustrated as potential maps below the traces). Traditional quantitative EEG analysis ignores the spatial variability of this activity. In contrast, Wu et al. apply spatial filters to the data and calculate the frequency power for each of these "latent space" components. This decodes the different networks contributing to the scalp activity. In the example here, the spatial filters are the canonical EEG microstate maps. The alpha power as well as the temporal dynamics are distinctly different for the five spatially filtered signals.

than previous approaches. The top of the figure reproduces the alpha fluctuation of two selected scalp electrodes over time and the potential field (constructed from all electrodes) at different time points. Maps at different time points of alpha activity show different spatial configurations, and, as a consequence, the same frequency at a given electrode was produced by different networks in the brain. (But note that some brain areas might contribute to different networks.) The bottom of the figure shows the alpha power fluctuations after applying different spatial filters to the data. The spatial filters (that is, potential maps) used in this figure for illustration are so-called EEG microstate maps, which are spatial EEG features often used in clinical EEG studies<sup>1,9</sup>.

Only a few prototypical microstate maps exist in the human brain at rest, and they

reflect short-lasting, sub-second synchronous activity of large-scale brain networks whose temporal characteristics are highly sensitive to distinct levels of consciousness, different neuropsychiatric diseases and cognitive contents<sup>10</sup>. Wu et al. selected the spatial filters (maps) in a data-driven, supervised way. In so doing, they kept the number of spatial filters as low as the number of microstates maps. This contrasts with other spatial filter approaches, such as independent component analysis and principal component analysis, which Wu et al. found did not predict treatment response, partly because of overfitting. It remains to be seen how much the topographies of the spatial filters determined by Wu et al. resemble canonical microstate maps.

While the figure makes clear that the power (in this case, of the alpha frequency) varies across different spatially filtered signals, it shows another important aspect: the alpha power dynamically varies over time in the sub-second range, and this temporal modulation is different for the different spatially filtered signals. These temporal dynamics might carry additional relevant information about the fluctuation and interactions of brain networks that the static approach of Wu et al. did not consider.

Despite this limitation, by combining spatial and frequency information of the resting-state EEG with machine learning approaches, Wu et al. make an important advance in establishing EEG as an easyto-use, inexpensive and non-invasive approach to predict treatment response in neuropsychiatric disorders. The work sets the stage for precision treatment in psychiatry, whereby individual patients are evaluated with EEG to identify signatures

news & views

that predict their response to potential treatments, allowing selection of treatments that are highly likely to be effective. A prospective study is now needed to test this potentially transformative approach to psychiatric therapeutics.

# Christoph M. Michel<sup>1,2 ⊠</sup> and Alvaro Pascual-Leone<sup>3,4</sup>

<sup>1</sup>Functional Brain Mapping Laboratory, Department of Fundamental Neurosciences, University of Geneva, Geneva, Switzerland. <sup>2</sup>Centre for Biomedical Imaging (CIBM) Lausanne-Geneva, Geneva, Switzerland. <sup>3</sup>Marcus Institute for Aging Research, Hebrew Senior Life, and Department of Neurology, Harvard Medical School, Boston, MA, USA. <sup>4</sup>Guttmann Brain Health Institute, Institut Guttmann, Universitat Autonoma, Barcelona, Spain. <sup>™</sup>e-mail: christoph.michel@unige.ch

e-mail. enristoph.mienet@unige.en

## Published online: 17 March 2020

https://doi.org/10.1038/s41587-020-0476-5

#### References

- Wu, W. et al. Nat. Biotechnol. https://doi.org/10.1038/s41587-019-0397-3 (2020).
- Fries, P. Neuron 88, 220–235 (2015).
  Hanslmayr, S., Axmacher, N. & Inman, C. S. Trends Neurosci. 42, 485–499 (2019).
- Mucci, A., Volpe, U., Merlotti, E., Bucci, P. & Galderisi, S. Clin. EEG Neurosci. 37, 81–98 (2006).

- 5. Olbrich, S. & Arns, M. Int. Rev. Psychiatry 25, 604-618 (2013).
- Pizzagalli, D. A. et al. JAMA Psychiatry 75, 547–554 (2018).
  Koles, Z. J. Electroencephalogr. Clin. Neurophysiol. 79, 440–447 (1991).
- Liang, C., Li, Y. & Luo, J. IEEE/ACM Trans. Comput. Biol. Bioinformatics 13, 549–556 (2016).
- Khanna, A., Pascual-Leone, A., Michel, C. M. & Farzan, F. Neurosci. Biobehav. Rev. 49, 105–113 (2015).
- Michel, C. M. & Koenig, T. *Neuroimage* 180 (Part B), 577–593 (2018).

#### Acknowledgements

We thank M. Seeber for the code used to analyze the data presented in Fig. 1 and L. Brechet for comments on the text.

#### **Competing interests**

The authors declare no competing interests.