Using Quantitative Electroencephalography to Predict and Monitoring Drug Treatment Response

Dr. Steven Rondeau BCN (EEG) | October 2021

Differently to most specialties in medicine, psychiatry remains a discipline in which diagnoses and treatment monitoring are only rarely based on the evaluation of well established, measurable and objective biomarkers. Further, while accumulating evidence suggests that automated and reliable tests are already available to assist clinicians in symptom detection and treatment efficacy evaluation, **mainstream medical training still fails to acknowledge research advances in translational medicine** that certainly have the potential to radically change and significantly disrupt how mental health professionals contribute on a day-to-day basis to the wellbeing of their patients.

In this context, **electroencephalography (EEG)** research has been developing for at least **four decades** both the technology and the methodology that today allows any appropriately trained physician or practitioner to gather a plethora of data on brain activity that can be automatically converted into clear and easy to interpret reports.

In particular, while **Event-Related Potentials (ERP)** have been used in hundreds of studies to investigate both electrophysiological and psychomotor anomalies in a wide range of disorders, **resting state EEG research** has produced key biomarkers of brain activity that modern computerized data analysis tools have the ability to integrate, providing an opportunity for the clinician to confidently locate and evaluate functional brain anomalies by comparing the patient's profile to a normative template. In this regard the use of **quantitative EEG (qEEG)** has been shown to be extremely useful in identifying functional anomalies in the brain, automatically generating maps where deviant activity can be visually detected and quantified implementing appropriate statistical analysis. Further, more advanced qEEG-guided analysis allows to carry out source localization studies where the EEG potentials detected from the scalp are linked to its origins of activity in the brain, with high precision and temporal resolution.

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Several lines of evidence suggest that methods employing the EEG to investigate the effects pharmacotherapy (also called **pharmaco-EEG methods**) offer the opportunity **to non-invasively predict treatment response** in a range of disorders. Below is an overview of the results obtained across a range of clinical populations.

Antidepressants

Resting state EEG studies with **depressed patients** have evaluated both **post-treatment changes** as well as differences between antidepressant treatment responders and non-responders. In general, these studies have identified post-treatment changes in **alpha and theta band** as well as in **cordance** (a measure of regional, frequency-specific activity) [1-3].

For example, there is evidence for a positive correlation between **increased alpha power** in the occipital/right frontal cortical brain regions and antidepressant response [4], although **gender has been proposed to influence treatment outcome** [5]. Also, it was suggested that higher pre-treatment activity in the rostral anterior cingulate cortex (rACC) was associated with better treatment response, although this link was demonstrated in a variety treatments and did not offer a guide to using a specific treatment. However, further research found that **increased theta activity** in the same brain region was a significant predictor of lower Hamilton Rating Scale of Depression (HAM-D) scores in patients treated with sertraline for 8 weeks [6].

The differential role of theta activity has also been explored using **cordance**. In a randomized, double-blinded, placebo controlled trial of response to fluoxetine and venlafaxine [7], **decreased frontal theta cordance** as measured **1 week after the start of medication** correlated with treatment response at 8 weeks, a pattern that was not seen in placebo responders. Importantly, response/non-response prediction when frontal theta cordance was considered was found to have an accuracy of 72%.

Finally, more insights on antidepressant treatment outcome prediction can be offered by the **antidepressant treatment response index (ATR)** a measure that combines prefrontal theta and alpha activity, measured at baseline and at week 1 [2], presented as a probability score ranging from 0 (low probability) to 100 (high probability).

In a study where persons with major depressive disorder (MDD) were administered a serotonin reuptake inhibitor (SSRI) or venlafaxine [8], 54.9% of cases exhibited a ≥50% reduction in HAM-D scores. Retrospective analysis found that **ATR predicted treatment response with 70% accuracy**. In another study [9], participants treated prospectively with escitalopram had an overall response rate of 52.1% and a remission rate of 38.4%, as measured by their HAM-D scores. Again, the ATR predicted response and remission with 74% accuracy.

Interestingly, the participants of the same study with low ATR values who were switched to bupropion treatment were then 1.9 times more likely to reach a positive treatment outcome when compared to those who remained on escitalopram. This result is important as it supports the ability of the ATR to provide objective data to compare the **efficacy of antidepressant treatments** in the same individual.

Antipsychotics

At least two qEEG profiles are associated with the administration of first generation antipsychotic (FGA) drugs: 1) **the chlorpromazinetype profile,** linked to all sedative low-potency FGA, exhibiting an increase in delta and theta, as well as a decrease in alpha power, and 2) **thehaloperidol-type profile**, described for high potency non-sedative FGA, showing little or no shift in delta or theta power and an increase in alpha and fast alpha power [10].

The administration of high potency FGA drugs to patients with schizophrenia has been shown to induce an increase in qEEG alpha power, more often in the slow alpha range (7.5-9.5 Hz) [11, 12]. Importantly, several studies have found **a relationship between these qEEG changes and a favorable clinical response**. Interestingly, in a study with treatment-resistant patients, none of the two qEEG profiles was observed for any of the FGA drugs administered [13], suggesting a prediction of negative treatment outcome.

Other research suggests that the **increase of slow alpha** following the administration of **haloperidol decanoate** correlates with clinical improvement [14]. Moreover, Moore et al. [15] found that an increase in alpha power after 6 weeks of treatment with **haloperidol or remoxipride** was indicative of a favorable clinical response. Other studies that compared responders and non-responders to treatment with **neuroleptics** found greater alpha activity only in responders [16, 17] and opposite changes in the same frequency band in non-responders [16].

Contrasting results have been reported by studies that explored the **qEEG profile of clozapine.** Clozapine is rated the main drug of second generation antipsychotics (SGA), recommended in the absence of cataleptogenic activity. It exerts weak antagonism at striatal D2 receptors as well as stronger blockade of D1, D4, 5HT2, H1, alpha1, alpha2 and cholinergic receptors [18, 19]. While early pharmaco-EEG studies on clozapine could not identify a specific predictor of antipsychotic activity following the oral administration of a single dose 10 or 15 mg to healthy persons, other authors [20, 21] identified instead a low potency **sedative antipsychotic profile for a 50 mg single dose,** although some studies could not replicate the results at the same dose [22].

Of note other qEEG research in patients with schizophrenia treated with clozapine did not find a link between clinical response and amplitude changes in any frequency band, but found that **reduced coherence in alpha and theta bands** was associated with a favorable response to the drug [23].

Psychostimulants

Psychostimulants are most often employed to treat **Attention-Deficit Hyperactive Disorder (ADHD)**. In this context, the acute administration of **dextroamphetamine and rnethylphenidate,** has been found to induce an increase in alpha and slow beta, accompanied by a reduction in delta and fast beta activity, in healthy participants [12, 21]. The qEEG profile of these drugs is similar to that of patients treated with antidepressants or nootropic drugs. However, a greater increase in slow beta activity is found after psychostimulant administration when compared to antidepressants and the reduction of delta is smaller than the one found in patients treated with nootropics. Importantly, for both psychostimulants and nootropics the post-treatment qEEG profile is markedly influenced by baseline-pre-treatment EEG characteristics, and more marked effects of these drugs can be observed in subjects with prevalence of slow activity accompanied by reduced alpha.

The most frequently reported qEEG abnormalities in young patients include **excessive theta, lower alpha and increased theta/beta ratio.** While, ADHD is an heterogeneous disorder and baseline qEEG imbalances can vary in distinct subtypes [24], responders to psychostimulant drugs usually exhibit higher delta and theta [25, 26].

For example, Clarke and co-workers [26, 27] showed that **methylphenidate** induces a decrease in theta and an increase in beta, accompanied by a reduction of the theta/beta ratio. However, Chabot et al. [24] found that after the administration of a stimulant drug to ADHD children, qEEG parameters normalized in only 57% of participants, while in 34% of them no change was detected and in 9% the profile worsened.

Finally, other studies reported that in ADHD patients, a single dose of methylphenidate had beneficial effects on cognitive performance and that their qEEG profile exhibited a decrease in theta and alpha as well as an increase in frontal beta power, whereas those who did not show any improvement exhibited the opposite pattern of EEG changes [28].

Acetylcholinesterase inhibitors

A study with Alzheimer-type Dementia (AD) patients whose cognitive performance improved after a single dose of tacrine, found a higher **alpha/theta ratio** over the right frontal region of the scalp when compared with those patients who did not improve, suggesting a relationship between this qEEG metric and the response to acetylcholinesterase inhibitor treatment, although long-term effects could not be confirmed [29].

Other research, however, reported that qEEG changes observed following the administration of a single dose of tacrine predicted the clinical response to short- (4 weeks) and medium-term (7 to 12 weeks) treatment with the drug [30-32]. In particular, only responders exhibited a drug-induced **increase in alpha and alpha/theta ratio.**

Knott et al. [32] reported a **reduction of theta power only in responders** treated for 12-weeks with tacrine and Adler et al. [33] found that qEEG changes induced by a 6-month chronic treatment with **rivastigmine** were predictors of a clinical improvement. In particular, among the all the patients who were treated, only responders showed a reduction of theta power after 1-week of treatment, with respect to baseline values. These results suggest that some qEEG metrics should also be considered as predictors of long-term cognitive amelioration.

Conclusions

Psychiatrists regularly prescribe drugs that can induce profound functional and sometimes structural changes in the central nervous system. Nonetheless, objective assessments are rarely available or carried out to increase the likelihood for a positive clinical response, while minimizing adverse effects. Over at least four decades, clinical research has provided extensive proof of evidence suggesting that qEEG should be employed to non-invasively predict and monitor drug treatment response.

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