Clinical EEG and Neuroscience
2015, Vol. 46(3) 192–196

DOI: 10.1177/1550059414556120
eeg.sagepub.com
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Pharmaco-EEG: A Study of Individualized Medicine in Clinical Practice

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Abstract

Pharmaco-electroencephalography (Pharmaco-EEG) studies using clinical EEG and quantitative EEG (qEEG) technologies have existed for more than 4 decades. This is a promising area that could improve psychotropic intervention using neurological data. One of the objectives in our clinical practice has been to collect EEG and quantitative EEG (qEEG) data. In the past 5 years, we have identified a subset of refractory cases (n = 386) found to contain commonalities of a small number of electrophysiological features in the following diagnostic categories: mood, anxiety, autistic spectrum, and attention deficit disorders, Four abnormalities were noted in the majority of medication failure cases and these abnormalities did not appear to significantly align with their diagnoses. Those were the following: encephalopathy, focal slowing, beta spindles, and transient discharges. To analyze the relationship noted, they were tested for association with the assigned diagnoses. Fisher's exact test and binary logistics regression found very little (6%) association between particular EEG/qEEG abnormalities and diagnoses. Findings from studies of this type suggest that EEG/qEEG provides individualized understanding of pharmacotherapy failures and has the potential to improve medication selection.

Keywords

pharmaco-EEG, qEEG, EEG, neurobiomarkers, refractory cases, focal slowing, beta spindles, encephalopathy, transient discharges, diagnoses

Received July 18, 2014; accepted September 26, 2014.

Introduction

Pharmaco-EEG studies using clinical EEG and quantitative EEG (qEEG) technologies have existed for over four decades. Galderisi and Sannita[1] noted in their prescient review that Pharmaco-EEG was a promising area that could improve psychotropic intervention using neurological data. Some studies suggest effective application of these in the diagnosis, medication response, and treatment selection.[2,3] Galderisi and Sannita[1] pointed out that Pharmaco-EEG failed to make its way into mainstream psychiatry; yet the field of psychiatry still desires evidence-based guidance for selecting and titrating medications. Currently, psychiatry uses an empirical process called "single clinical trials." Young psychiatrists with only five to 15 years of experience often lack clinical expertise to guide them when medications fail. To tackle this growing demand, we present a neurobiomarker model for use in the clinical setting based on the science of Pharmaco-EEG and our study of 386 refractory clinical cases.

Psychiatry does well in many instances; however, there are perplexing cases that do not respond to traditional psychotropic intervention. A typical psychiatric practice necessitates a thorough evaluation. At times, psychological testing will be used to refine diagnoses to assist with medication selection. However, further refinement of diagnoses fails to provide rationale needed to identify the physiological cause of the symptoms and explain medication failure. It is important to note that in such refractory cases, there are likely confounding neurobiological causes that account for repeated medication failure and/or iatrogenic side effects.

Many abnormalities seen in the EEG are considered normal variants in the general population; however, minor abnormalities are important when clinical correlation exists.[4,5] Clinical correlation is characterized by impaired functioning that corresponds with neurological abnormalities specific to the region of the brain responsible for those processes.

Equally as important as the EEG is the qEEG. QEEG studies confirmed its usefulness in the diagnostic process when coupled with behavioral testing and clinical evaluation.[3] Studies also suggest that qEEG provides sufficient evidence for prescribing appropriate medication during initial treatment.[3] This technology is not well recognized and therefore underutilized in general neurology and psychiatric

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practice and yet has promising potential for clinical application.[6,7]

It is commonly accepted that there is a synergistic relationship between brain function and behavior. Parallel to this, the capability to detect neuronal irregularities may provide insight for the selection of medication in psychiatric disorders.[6] Neurobiomarkers are electrophysiological abnormalities that can account for medication failure and subsequent treatment difficulties. The utilization of EEG and qEEG, together with clinical presentation to identify neurobiomarkers has the potential to link neuronal irregularities with presenting symptoms.

Beginning in 2009, investigators started identifying EEG/qEEG neurobiomarkers consistent with refractory cases. These findings provided valuable data to assist physicians in their medication decision-making process. These cases were considered neuroatypical for their unexpected response to medications and their abnormal EEG/qEEG findings. There are 4 emerging neurobiomarkers in these cases: encephalopathy, focal slowing, beta spindles, and transient discharges.

Encephalopathy (EN) can be defined as a diffuse disturbance in brain function producing neurological and psychological manifestations. Diffuse EN has abnormally low voltage and alpha speed. According to Yamada and Meng,[4] there are at least 81 different causes of EN, including metabolic disorders, vitamin deficiencies, endocrine and degenerative disorders, inflammatory/infectious diseases, dementia and many others. If diffuse EN is identified, the medical problem should first be addressed before attempting neurologic/psychological/psychiatric treatment.[4,7] Medications may have limited success if the medical problem is not identified and resolved first.

Focal slowing (FS) is characterized by a predominance of slower electrical activity (compared to the rest of the brain) in a particular area of the brain. The majority of the cases we studied had a left temporal dominance of focal slowing. Common causes are brain injury, underlying cortical lesions, or tumors.[4,6,8] Medications are excellent at adjusting diffuse tuning in the brain; however, there are no medications approved by the Food and Drug Administration that adjust focal deficits caused by brain injury. In attempts to use medication designed to target the frequency of the whole brain for treatment of focal issues, adverse side effects are commonly experienced.

Beta spindles (BS) are identified as synchronous activity in the beta range around a specific frequency and are indicative of hyperarousal and most often seen frontocentrally. Gibbs and Gibbs identified beta spindling as a component of epilepsy in the 1930s.[9] Beta spindles have also been recognized in bipolar disorder, autism, obsessive-compulsive disorder, some forms of anxiety and attention deficit hyperactive disorder.[10,11] Medications that increase beta where endogenous beta spindles exist are contraindicated and will result in greater risk for cortical irritability.

Transient discharges (TDs) are defined as "EEG cerebral dysrhythmias identified by isolated episodic paroxysmal bursts of slow activity, controversial/anomalous spikey waveforms and/or true non-controversial epileptiform discharges."[10] The majority of the cases we studied had a left temporal dominance of TD. TDs have been identified in persons with schizophrenia, criminal behavior, violence, and disorders of mood, anxiety, panic, obsessive-compulsion, eating, personality, as well as psychogenic nonepileptic seizures.[12] Detecting TD can also aid in the identification of cerebrovascular disorders.[5] If there is clinical correlation at the location of the TD, the EEG will prove to be an effective technique for detection of a psychiatric problem. Medications that lower seizure threshold would likely contribute to the abnormal activity.

Methods

Data Set

The data were obtained from the Tarnow Center for Self-Management (Houston, TX) EEG/qEEG archival database. The database contains demographic information, diagnosis, neurobiomarkers, and the number of medications prescribed for 386 clinical cases. The individuals were divided into three non–gender-specific age groups: 5 to 11, 12 to 17, and 18 to 69 years. The institutional review board of The University of Texas at Arlington deemed that this study is exempt from institutional review board approval since no identifiable patient information was required for data analysis by the investigators thereby protecting the confidential rights of all patients. The Tarnow Center practices all HIPAA (Health Insurance Portability and Accountability Act) regulations.

Electroencephalography Data Collection Equipment

A Deymed TruScan 32 was used to record the EEGs of the participants. Linked ears and averaging montages were referenced according to the international 10/20 system.

Design

There were 4 presenting diagnoses in this sample of sufficient numbers for statistical analysis: attention deficit disorder (ADD), autism spectrum disorders (ASD), major depressive disorder (MDD), and anxiety disorders (ANX).

As mentioned previously, the neurobiomarkers identified in this study were FS, BS, EN, TDs. Some subjects exhibited more than 1 neurobiomarker. The relationship between the diagnoses and neurobiomarkers was examined separately for each age group. Interrater reliability is ensured by having the same team do all of the artifact and conversion of the data to topographical brain maps. Similarly, the same electroencephalographer and qEEG researcher wrote reports on all 386 cases. Last, the onsite clinical researcher excluded all cases where clinical correlation was not found. For example TDs are considered normal variants; however, if the TD was found in the left posterior temporal area and there were no neither expressive nor receptive language issues, the case would be excluded.[5]

Electroencephalography Data Acquisition and Processing

Researchers obtained written informed consent from the participants or their parents for children and adolescents. The EEG electro-caps were used to collect the EEG data and Electrogel was applied to the 19 sites (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) until impedances were <5 ohm. The researchers transferred demographic information, patient diagnoses and medication history to a master Excel spreadsheet for the study. The participants were recorded resting for a minimum of ten minutes with their eyes open and ten minutes with their eyes closed, and were given the choice of which came first. Participants were also permitted to take mental breaks throughout to prevent restlessness that might obscure the recording. The recordings were paused and then resumed when the participant was ready. Following the session, the EEG went through the process of artifact and qEEG topographical brain mapping at the Human Brain Institute in Saint Petersburg, Russia. An electroencephalographer identified any abnormalities in the raw EEG. A qEEG researcher analyzed all the topographical brain maps. All 386 were individual clinical cases. No repeat EEGs or qEEGs were included.

Clinical Correlation Acquisition Process

Each patient in the study had failed on at least two medications and was referred by a psychiatrist who provided the diagnosis using the *DSM-IV* (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria. To provide consistency of clinical presentation, each patient (or parent if the patient was <14 years old) answered a Likert-type scaled set of questions designed to identify their clinical symptoms. It is important to note that neurobiomarkers became a variable in the patient's data set only when (*a*) abnormalities (even minor deviations) were identified in the raw EEG, (*b*) these abnormalities reached a level of significance expected in the qEEG, and (*c*) the patient identified issues related to the same area.

Results

Preliminary data analysis examined each neurobiomarker's relationship to the diagnoses by conducting Fisher's exact tests and the three age groups were analyzed separately (Table 1). The relationship between EN and ANX in children showed only 5.3% of subjects with EN had an ANX diagnosis (P = .003), as opposed to 40% of children without EN and with an ANX diagnosis. In adolescents, a significant relationship was identified between BS and MDD, where 35% of subjects with BS also were diagnosed with MDD (P = .019). This was contrary to the 11.8% of subjects without BS who had MDD. A similar pattern was found in adults, with 47.8% of subjects with BS also having a diagnosis of MDD (P = .008), as opposed to the 25% of subjects without BS who had a diagnosis of MDD. No other significant relationships were found between neurobiomarkers and diagnoses.

Table 1. Fisher's Exact Test Significant *P* Values.

	ADD	ASD	MDD	ANX
Children, 5-11 years old (n = 119)				
EN	.209	.325	.788	.003**
FS	.811	.538	.724	.620
BS	.093	.203	.588	.619
TD	1.00	1.00	.819	.836
Adolescents, 12-17 years old (n = 105)				
EN	.612	.070	.732	.262
FS	.757	.470	.384	.619
BS	.619	.560	.019**	.420
TD	1.00	.789	.067	.204
Adults, 18-69 years old (n = 162)				
EN	.371	.788	.341	.063
FS	.621	.436	.384	.865
BS	.480	.209	.008**	.865
TD	.108	.536	.610	.618

Abbreviations: ADD, attention deficit disorder; ASD, autism spectrum disorders; MDD, major depressive disorder; ANX, anxiety disorders; EN, encephalopathy; FS, focal slowing; BS, beta spindles; TD, transient discharges. **Significant *P* values.

A binary regression analysis was conducted for each diagnosis at every age group (Table 2). The diagnosis was the dependent variable, while each of the neurobiomarkers acted as an independent variable. For age group 5 to 11 years, a test of the full model against a constant-only model was statistically significant indicating that the neurobiomarkers as a set reliably distinguished a between-subjects both with and without ANX (χ^2 = 11.23, P = .024, df = 4). Prediction success overall was 65.5% (100% correct for people without ANX, 0% for people with ANX). When investigating the neurobiomarkers separately, only EN was significant (P = .019). The exp(B) value found was .086, meaning that the subject would be more than 11 times less likely to have an ANX diagnosis if he or she had EN.

For the age group 12 to 18 years, a test of the full model against a constant-only model was statistically significant as well, indicating that the neurobiomarkers as a set reliably distinguished between-subjects both with and without MDD (χ^2 = 12.55, P = .014, df = 4). Prediction success overall was 81.9% (96.6% correct for people without MDD, 5.9% for people with MDD). Looking at the predictors separately, only BS was significant (P = .010). The exp(B) value of 5.37 means that a subject would be more than 5 times more likely to have an MDD diagnosis if he or she had BS.

Examining age group 18 to 69 years, a test of the full model against a constant-only model was statistically significant, indicating that the predictors as a set, reliably distinguished between-subjects both with and without MDD (χ^2 = 10.59, P = .032, df = 4). Prediction success overall was 71.0% (92.8% correct for people without MDD, 23.5% for people with MDD). Analyzing the predictors separately, only BS was significant (P = .006). The exp(B) value of 2.86 means that a subject would be almost three times more likely to have an MDD diagnosis if he or she had BS.

Table 2. Binary Logistics Regression Significant *P* Values.

	ADD	ASD	MDD	ANX
Children 5-11 years old (n = 119)				
EN	.138	.370	.778	.019**
FS	.457	.741	.131	.654
BS	.050	.224	.483	.826
TD	.984	.860	.550	.909
Adolescents, 12-17 years old (n = 105)				
EN	.445	.036	.282	.210
FS	.752	.279	.709	.420
BS	.521	.486	.010**	.374
TD	.988	.460	.062	.123
Adults, 18-69 years old (n = 162)				
EN	.394	.740	.159	.067
FS	.298	.201	.765	.916
BS	.273	.110	.006**	.892
TD	.080	.339	.394	.708

Abbreviations: ADD, attention deficit disorder; ASD, autism spectrum disorders; MDD, major depressive disorder; ANX, anxiety disorders; EN, encephalopathy; FS, focal slowing; BS, beta spindles; TD, transient discharges. **Significant *P* values.

Discussion

Fisher's exact test showed only three significant findings out of 48 possible combinations; one finding in each age group. The significant finding was that children with EN are rarely diagnosed with ANX (5.3%, $P = .003$). This is likely because of their lack of maturity and being unaware of their shortcomings.

A significant finding was that adolescents with BS were diagnosed also with MDD (35%, $P = .019$). In contrast, adolescents without BS were diagnosed also with MDD (11.8%). A similar pattern was found in adults, with 47.8% of subjects with BS having an MDD diagnosis ($P = .008$), as opposed to the 25% of subjects without BS who had a diagnosis of MDD. No other significant relationships were found between neurobiomarkers and diagnoses. These findings in adolescents and adults may have resulted from including bipolar disorder in the variable MDD, which reflects the bifurcation of diagnoses. No other significant relationships were found between neurobiomarkers and diagnoses using Fisher's exact test.

The same three combinations identified by Fisher's exact test were found to be significant using binary regression analysis. Children with EN were 11 times less likely to have ANX. As in Fisher's exact test findings, children who do not have EN are those with normal alpha frequency. Children with normal alpha frequency are less likely to be maturationally delayed and thus would be more aware of anxiety provoking external stressors.

The validity of the finding that children who have EN are far less likely to have an ANX diagnosis is arguably suspected statistically. In examining the relationship between ANX and EN, we found only one case among children with ANX diagnosis and EN. The fact that the ANX and EN co-occurrence is rare (among children) is useful information for psychiatric diagnosis. Although the data analysis techniques such as odds ratios, Fisher's exact test, and binary regression are widely used to analyze relationship among disproportionate categories, it is necessary to investigate further to determine if the vast difference in proportions of the categories is sample specific. In general, a minimum expected cell size of five is recommended for the use of most chi-square-based data analysis methods such as logistic regression.[13] In this preliminary study exploring the relationships between neurobiomarkers and psychiatric diagnoses, we cautiously reject the significant relationship between EN and ANX.

In adolescents, those with BS were more than five times more likely to be diagnosed with MDD. Likewise, adults with BS were three times more likely to be diagnosed with MDD. Clinically, these findings suggest that BS is associated with MDD, the degree of maturity, and anxiety. No other significant relationships were identified.

Limitations

It would be preferable that all participants would be medication free prior to the EEG. However, in many cases it was not advisable to remove medications from refractory patients in an outpatient setting. In this study, most of the participants were actively taking medications prior to the EEG, which may have altered the results of the study. Since medications have a clear identifiable effect on the EEG/qEEG, this effect was accounted for in the analysis for each participant. For example, we ruled out sedative medication effects in cases where BS was identified.

Since this study was a clinical sample, a few things could not be standardized, including time of day, eyes open or closed first during the EEG, mental breaks, and the last time the participant had a meal. However, the researchers determined that if the client chose the time of day for their appointment, which EEG recording was completed first, and when or if they needed a mental break, would result in an EEG with fewer artifacts. We consider 386 patients as a suitable number for the study; however, a larger sample size is always desirable.

There were cases where abnormalities were seen either in the eyes open or eyes closed phase only but these differences were beyond the scope of this study. Longer assessments times may also have revealed additional information.

Future Directions

To allow for outcome comparison, patients would be randomly assigned to either a traditional treatment group or the neurobiomarker identification group.

This model could be easily validated in studies that would assess the long-term impact of medications on children and adolescents, two populations that are especially vulnerable during neurological development.

A better way to test the predictive power of the neurobiomarker identification process is to use a pretest/posttest design with random selection assigning patients to either a control group using typical psychiatric approaches or an experimental

group using neurobiomarker identification. This design would allow researchers to have a baseline group to compare the success rate of medications based on the original diagnoses.

Another future direction would be to apply this technique to individual disorders to study the reliability and validity of neurobiomarker identification for each disorder. The present DSM system uses a phenomenological system. The neurobiomarker model uses a system based on biology. Neurobiomarkers, genetic, and genotypic investigations are the direction in which psychiatry needs to go as proposed by Thomas Insel, MD, Director of the National Institute of Mental Health (NIMH).[14] Studies are underway by investigators funded by the NIMH and as proposed by President Obama's Executive Order—National Research Action Plan.[14,15]

Conclusions

There is a paucity of published information on refractory cases mainly because of the difficulty in publishing negative results. However, studying refractory cases has proven to be invaluable. We developed and used this model in our clinic for five years and found it to be valuable for improving management of these cases. The existence of these neuronal irregularities appeared to reflect indisputable evidence of brain dysfunction that affect psychiatric pathologies.[12]

The results of this study suggest that when used separately, an EEG, a qEEG, and clinical presentation lack synergy. However, when all 3 were combined, the shortcoming of each was minimized.

Using this neurobiomarker model, we found that identification of the neurobiomarkers that were most prominent in refractory cases was important. If left unidentified, any substantial improvement in psychiatric medication management and treatment planning would be thwarted. In particular for refractory cases, the neurobiomarker model adds very important information to guide medication treatment.

Authors' Note

This study was first presented at the International Society for Neuronal Research 21st Annual Conference, September 2013, Dallas, Texas. The study was also presented at the Biofeedback Federation of Europe 17th Annual Meeting, February 2014, Venice, Italy, and at the 2014 Joint Meeting of EEG & Clinical Neuroscience (ECNS) Society for Neuroimaging in Psychiatry (ISNIP) and International Society for Brain Electromagnetic Topography (ISBET) in Halifax, Nova Scotia, Canada in September 2014.

Authors' Contributions

RS, GK, JT substantially contributed to conception or design of the paper and contributed to acquisition, analysis, or interpretation of data; RS, GK drafted the manuscript; RS, GK, JT critically revised the manuscript for important intellectual content; RS, GK, JT gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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