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Standardization and Personalized Medicine Using Quantitative EEG in Clinical Settings

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Abstract

Two major trends have been dominant in health care in recent years. First, there is a growing consensus that standardization of health care procedures and methods can result in improved effectiveness and safety of treatments. Second, there is increased interest in "personalized medicine," which refers to the tailoring of treatments to individual patients. Here I discuss how these trends apply to the field of quantitative EEG (qEEG), where de-artifacted resting state EEGs of individuals are compared with a normative database in order to assess clinically meaningful deviations, which can be used for diagnostic procedures, to guide personalized treatment protocols, and to assess treatment effectiveness. Standardized and automated de-artifacting procedures are increasingly being used in scientific research and in clinical practice. The advantages of these procedures over manual de-artifacting will be discussed. The results of a systematic comparison between 2 commonly used qEEG databases show that these databases produce very comparable results, illustrating not only the validity and reliability of both databases but also the opportunity to move forward to a standardized use of qEEG in clinical practice. Finally, the standardization of qEEG interpretation as both a diagnostic and treatment selection tool provides an example of how qEEG can merge both personalized medicine and standardization in the treatment of psychological disorders.

Keywords

quantitative EEG, resting state, standardization, artifact

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Introduction

Standardization in Health Care

Standardization can be seen as one of the most important innovations in health care that has increased the effectiveness and patient safety of medical treatments while decreasing its costs. There has been a great effort to implement more standardization in diagnosing and treating medical conditions. For example, the World Health Organization initiated the "High 5s Project" in 2007, which aimed to facilitate the development, implementation, and evaluation of Standard Operating Protocols (SOPs; https://www.who.int/patientsafety/topics/high-5s/en/) for medical treatments in order to increase patient safety. These SOPs concern a wide range of topics, such as correct surgery, accurate medication and hygiene. Many insurance companies also require a certain degree of standardization of the medical treatments they cover. Finally, in scientific research aimed at studying medical treatments, the placebo-controlled randomized controlled trial is considered to be the gold standard. In these types of studies, large groups of individuals all receive the same treatment. Within the context of "evidence-based medicine," the medical treatments that have proved to be effective and safe in an experimental setting are then applied in the exact same way by medical professionals. Even though it is widely accepted among policy makers and researchers that standardization in healthcare is beneficial, the topic does generate a lot of debate between health care professionals.

Personalized Medicine

"Personalized medicine" or "precision medicine" seems to be representing the exact opposite to standardization in health care. This model has gained considerable traction, mainly as a result of rapid developments in genetic research[1,2] and novel methods for analyzing "big data".[3] In short, personalized medicine focuses on individual differences that can predict the outcome of a treatment or combination of treatments. Based on these "markers", a treatment is selected for an individual patient.

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Standardization and Personalized Medicine in Mental Health Care

In mental health care, one example of standardization is the use of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*),[4] which was developed with the goal of standardizing the procedures for diagnosing psychological disorders. Even though there is no doubt that there is a need for standardizing diagnostic methods in mental health care, the fifth edition of the *DSM* generated a lot controversy.[5] There are concerns regarding the more inclusive nature of the revised *DSM*, which could lead to more false positives. Diagnosing psychological disorders relies on the use of structured interviews and questionnaires, which are inherently dependent on the subjective perception of the mental health care professional and/or the patient. While standardization does not necessarily imply objectiveness, the aim for any standardization effort should be to base its proposal on scientific studies that report findings using objectively measured outcomes. This is the reason that in other health care domains, great emphasis is given to the measurements of physiological parameters such as X-ray scans, blood pressure, body temperature, and so on. There is a clear lack of the use of physiological measurements as an objective tool for increasing the accuracy of diagnoses in mental health care. However, research that focuses on finding physiological markers or "biomarkers" for different psychological disorders has been increasing rapidly in recent years.[6] A variety of brain imaging techniques has been used to investigate possible biomarkers for psychological disorders, such as functional magnetic resonance imaging, magnetoencephalography, and electroencephalography (EEG). The analyses of so-called "resting state" measurements has gained considerable attention in EEG research. Resting state refers to the absence of any task for the subject or patient during the measurement. Many studies have demonstrated statistically significant and clinically relevant differences between patients suffering from common psychological disorders such as attention deficit/hyperactivity disorder (ADHD),[7] depression,[8] anxiety disorders,[9] insomnia,[10] autism,[11] and tinnitus,[12] to name just a few. Most of these studies focus on the specific deviations in the power of oscillatory activity in resting state EEG that can discriminate between patients and healthy controls. One of the most reliable EEG biomarkers seems to be the presence of abnormally high theta power (4-7 Hz) in combination with abnormally low beta power (12-25 Hz) at frontocentral electrode sites in ADHD.[13] The validity and reliability of this EEG biomarker as a diagnostic tool has been demonstrated by Snyder et al,[14] who showed that adding this measure to the standard diagnostic procedures can increase the diagnostic accuracy from 61% to 88%. This has led to the creation of a commercially available tool called "NEBA Health" (https://www.nebahealth.com) that received Food and Drug Administration (FDA) approval in 2013.

Another main area of research is focused on correlates of arousal in resting state EEG. Cortical hyperarousal has been associated with anxiety disorders[15] and insomnia[16] while hypo-arousal has been linked with depression[17] and ADHD.[18] Generally speaking, relatively high amplitudes of higher frequency oscillations (Beta, Gamma) combined with relatively low amplitudes of lower frequency oscillations (Delta, Theta, Alpha) can be seen as a marker for hyperarousal, while the opposite pattern is related to hypo-arousal. Paradoxically, it has been shown that the presence of spindling excessive beta (SEB) episodes, is also related with hypo-arousal.[19] The presence of this specific EEG pattern has been related with suboptimal vigilance regulation and has been described as short periods of "microsleep".[20] SEBs have been observed not only in patients suffering from insomnia but also in patients diagnosed with ADHD. It seems that for ADHD, there exists a subtype exhibiting a high Theta/Beta ratio on one hand and a subtype exhibiting SEBs on the other hand. Research on the EEG biomarkers for deviances in arousal are illustrative of many research projects that aim to find reliable EEG biomarkers for mental disorders. EEG biomarker candidates often seem to cut across DSM categories and there generally seem to be more than one EEG biomarker within a DSM category, pointing to the existence of different "endophenotypes," or EEG subtypes within a disorder.

The research on "Frontal Alpha Asymmetry" (FAA) as an EEG biomarker candidate is also worth mentioning here. FAA refers to the hemispheric difference in Alpha amplitude, where high Alpha amplitude in left frontal brain regions and low Alpha amplitude on right frontal brain areas has been associated with major depression disorder (MDD[8]). Originally studied in the context of the approach-avoidance dichotomy in behavior, it is based on the idea that the left hemisphere is related with approach tendencies, while the right hemisphere is related with avoidance tendencies.[21] Even though significant differences in FAA between patients diagnosed with MDD and healthy controls has been demonstrated in numerous studies, the validity, reliability and clinical relevance of FAA as an EEG biomarker for MDD is still highly debated.[22] Even though it is questionable whether FAA can serve as a diagnostic marker for MDD in the future, there is promising research on FAA as a prognostic tool. For example, research has shown that FAA predicts the response to common antidepressant medications.[23,24]

These examples illustrate that even though much progress has been made in the quest for finding reliable EEG biomarkers for existing *DSM* categories, a novel approach may be needed that is more independent on *DSM* categories and relies on definitions of disorders that are more grounded in neurophysiology. To this end, the "Research Domain Criteria" (RDoC) model has been put forward by the National Institute of Mental Health in 2009.[25,26] This framework offers more parsimonious explanations of the observed abnormalities in resting-state EEGs and may provide a more productive basis for exploring the potential of prognostic EEG biomarkers.

One area in which this approach has been used for many years is the field of "qEEG-informed neurofeedback".[27] Quantitative EEG or qEEG refers to the analyses of frequency band power of resting state EEGs. In clinical practise, these amplitudes are then compared with the appropriate age range within a normative EEG database in order to assess deviations

from the norm. These age-specific comparisons are necessary because it has been shown that resting state EEG characteristics change as a result of maturation and ageing of the brain.[28-31] The aim of qEEG-informed neurofeedback treatment is to reduce clinically relevant deviations in the resting state EEG of a patient using a form of operant conditioning.[32]

The recent developments in the scientific literature show great promise for the use of qEEG in clinical practice as both a diagnostic and prognostic tool. However, the use of qEEG has been hampered by methodological issues. One of the main concerns is the lack of standardized procedures for measuring, analyzing, and interpreting resting state EEG in both research and clinical practice. Here I will focus on 3 important aspects of the clinical implementation of qEEG. First, the issue of de-artifacting resting state EEG is addressed. Second, the validity of commercially available, age-regressed, normative qEEG databases is studied by systematically comparing 2 internationally used, FDA-registered normative databases. Finally, a case will be made for the implementation of standardized procedures regarding the interpretation of qEEG results.

Standardized De-artifacting Procedures

Resting state EEG recordings are frequently contaminated with artifacts. This means that the EEG contains signatures that are not of neural origin, which can influence the results of a qEEG analysis. The most well-known sources of EEG artifacts are eye blinks, eye movements, movement of the head or body, line noise artifacts, and tonic or phasic muscle contractions. Traditionally, EEGs are de-artifacted manually: EEG editing software is used to mark segments containing artifacts, which are then removed from the EEG and the de-artifacted EEG is used for further analyses. Recognizing artifacts in resting state EEG requires proper training and experience. However, it is well known that manually de-artifacting EEG recordings suffers from suboptimal inter- and intrarater reliability. Despite these disadvantages, manual de-artifacting is still being used almost exclusively by researchers and clinicians. Considerable effort has been devoted to creating effective and reliable automated de-artifacting methods.[33] These methods rely on different techniques, but broadly speaking they can be categorized as either artifact "correction" or artifact "rejection" methods and as either semiautomatic and fully automatic. Artifact rejection methods remove segments of EEG that are identified as being contaminated by artifacts, while artifact correction methods apply techniques that remove artifacts without removing the underlying EEG signal. One example of an artifact correction method is the use of "blind source separation" (BSS) that identifies different independent sources of variance in the EEG. These components can subsequently be manually or automatically categorized as artifacts or nonartifacts. There have been numerous proposals regarding semiautomatic de-artifacting methods,[34] but relatively few methods have been put forward that implement fully automatic de-artifacting. Even though semiautomatic de-artifacting has its advantages, it still relies on subjective evaluation by human interpreters. In contrast, fully automatic de-artifacting methods eliminate this factor and guarantee that each EEG will be de-artifacted using the exact same set of criteria. One example of a fully automatic, artifact *correction* method is called ADJUST,[34] which is available for the MATLAB programming environment. ADJUST has been validated by comparing a set of well-studied event-related potential components that were computed after artifact correction based on ADJUST on one hand and based on expert human interpreters on the other hand. The results show that the event-related potentials were highly similar for both ADJUST and human interpreters, illustrating the equivalence of both methods. An example of a fully automatic artifact *rejection* method is S.A.R.A (https://www.qeeg.pro). S.A.R.A has been validated by comparing *z*-score results from resting state EEGs that have been de-artifacted using either S.A.R.A or expert human interpreters. The results show that there were no clinically relevant differences in *z*-scores between S.A.R.A and the human interpreters. It is currently not clear whether the existing standardized and automated de-artifacting procedures produce comparable results for resting-state EEGs. Future research should directly compare different methods in order to determine which methods can be used interchangeably without jeopardizing the validity of the qEEG results.

QEEG Normative Database Comparisons

There are several commercially available qEEG normative databases that can be used for assessing clinically relevant deviances in resting state EEGs of an individual patient. These qEEG databases are all very different in terms of the EEG acquisition hardware used, number of subjects, de-artifacting methods of the included EEGs, and so on. This raises the question whether there are also differences in the resting state EEG deviancies of individual patients when using different qEEG databases. Two commonly used qEEG normative databases in clinical practice are the "qEEG-Pro" database (qEEG-Pro B.V.) and the "Lifespan" database (Applied Neuroscience, Inc). Both databases are FDA registered and are used by mental health care clinics across the world. Table 1 depicts the characteristics of both the Lifespan database and the qEEG-Pro database.

It is clear that the 2 databases show many differences in the way they were constructed. However, the important question is whether comparing a patient's resting state EEG with either the qEEG-Pro or the Lifespan database yields different results. In order to compare both databases, 3 artificial EEG signals were systematically compared with each database. Only the *z*-scored amplitudes of standard frequency bands and 1 Hz frequency bins were analyzed, because the vast majority of research on EEG biomarkers is based on frequency amplitudes.

Methods

Three artificial signals were constructed that consisted of the sum of sine waves that ranged between 1 and 30 Hz (total of 30 sine waves) using the MATLAB programming environment. A

Table 1. Characteristics of the "qEEG-Pro" Database and the "Lifespan" Database.

	qEEG-Pro		Lifespan	
	Eyes Open (n = 1482)	Eyes Closed (n = 1232)	Eyes Open (n = 625)	Eyes Closed (n = 625)
Age range, years	6-83		0.16-83	
De-artifacting method	Automatic		Manual	
Frequency range, Hz	1-45		1-30	
Data collection method	2004-2013		1979-1987; 2000	
Age regression method	Sliding window		Age bins	

1/*f* transformation was applied to the power of this sum of sine waves. This resembles the power spectral energy commonly observed in typical human EEG. The 3 signals had different average powers (see Figure 1). Three different artificial EEG sets were constructed using the same 3 signals for 19 electrode sites, according to the international 10-20 system: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. The 3 signals had a duration of 60 seconds and a sampling frequency of 256 Hz was used. Each of these artificial EEGs was compared with both the qEEG-Pro and Lifespan database and *z*-scores were generated for the power on each electrode for each discrete frequency and for ages ranging between 6 and 60 years, with a 1-year interval. This resulted in a total number of *z*-scores of 3 signals * 19 electrodes * 30 discrete frequencies * 55 discrete ages = 94050 *z*-scores for each database, for both the eyes closed and eyes open condition. Correlations were calculated for each discrete frequency bin and for 5 frequency bands: Delta (1-3 Hz), Theta (4-7 Hz), Alpha (8-12 Hz), Beta (13-20 Hz), and High Beta (21-30 Hz), by pooling the *z*-scores from the discrete frequencies within each frequency band.

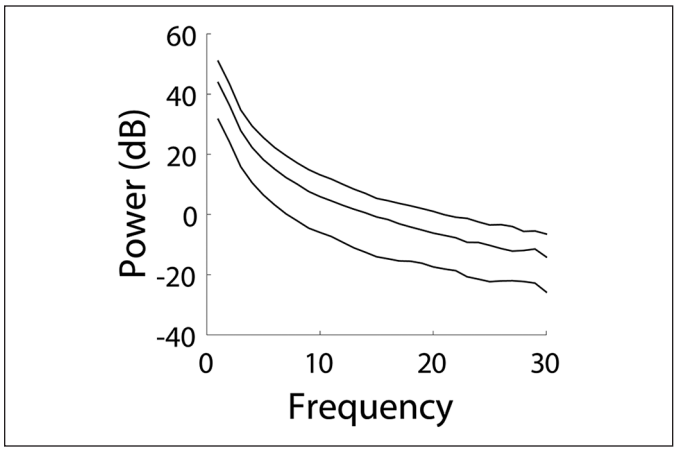

Figure 1. The power envelope of 4 artificial signals consisting of the sum of sine waves ranging between 1 and 30 Hz.

Results

Figure 2 shows the scatterplots and correlations between the *z*-scores for the qEEG-Pro database and the Lifespan database for discrete frequency bins between 1 and 30 Hz. The overall correlations are .94 for both the eyes closed and the eyes open condition (*P*s < .0001, Figure 2). Figure 3 shows the scatterplots and correlations for the 5 frequency bands. The correlations range between .97 ($P < .0001$) for Theta and .89 for High Beta ($P < .0001$). Figure 4 shows the envelope of the correlations for each discrete frequency bin. These correlations range between .98 for 4 Hz ($P < .0001$) and .85 Hz for 29 Hz ($P < .0001$).

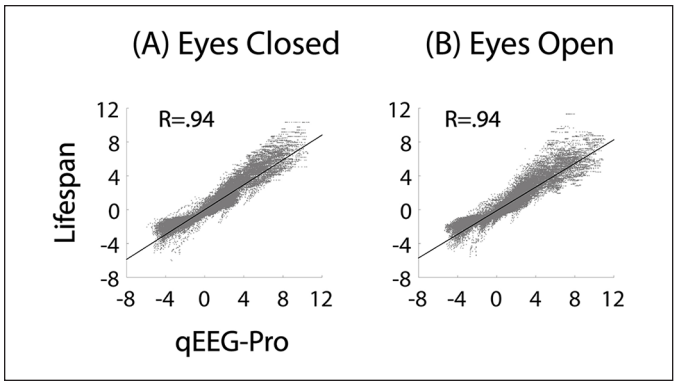

Figure 2. Scatterplots, least-squares lines, and correlations between the z-scores resulting from comparisons with the qEEG-Pro and the Lifespan qEEG normative databases for the eyes closed (A) and eyes open (B) condition and for discrete frequency bins between 1 and 30 Hz.

The results show that there is a high level of similarity between the results of both databases, despite their inherent differences. Figure 4 shows that the correlations start to drop in the Beta and High Beta band. In order to investigate the cause of the lower correlations in higher frequencies, the correlations for the entire Beta band (13-30 Hz) were calculated for each electrode and eyes condition and plotted on a topographic map (see Figure 5). For both the eyes closed and eyes open conditions, the correlations in the Beta band are relatively low for the frontal and temporal electrode sites. Research has shown that the Beta band is vulnerable for muscle artifacts, especially at the electrode sites that show a low correlation in Figure 5.[35,36] It seems very likely that the relatively low correlations in the Beta band are the result of differences between the 2 databases in the amount of contamination by muscle artifacts and in the de-artifacting methods that were used to remove those artifacts.

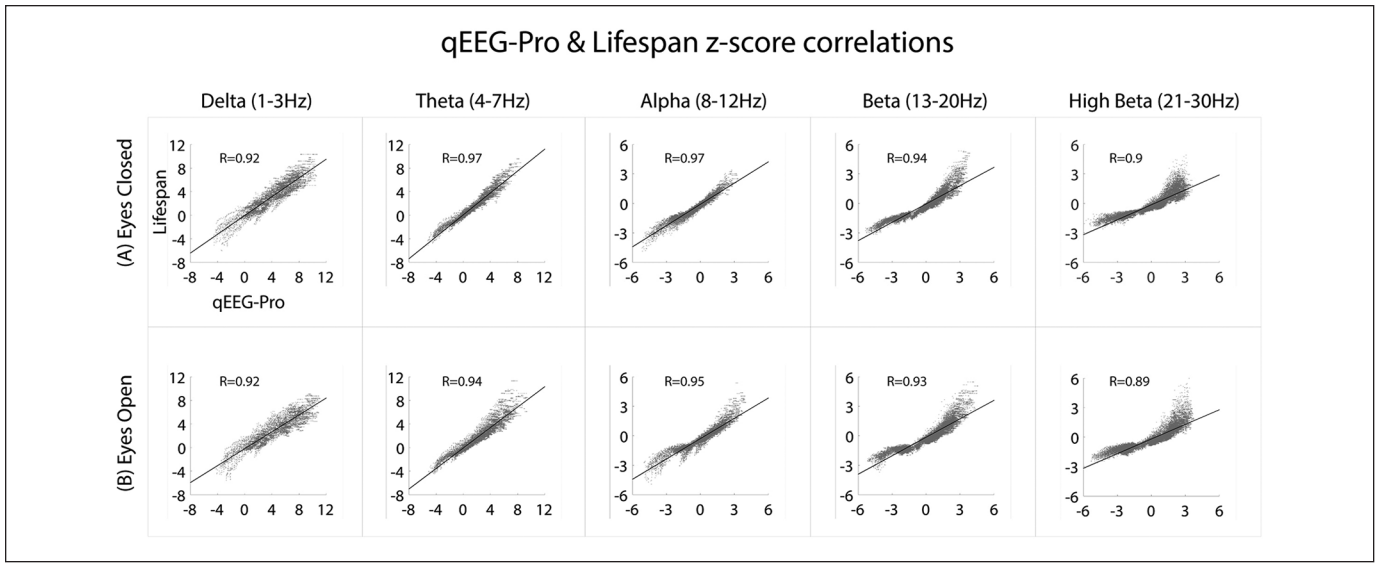

Figure 3. Scatterplots, least-squares lines, and correlations between the z-scores resulting from comparisons with the qEEG-Pro and the Lifespan qEEG normative databases for the eyes closed (A) and eyes open (B) condition and for Delta (1-3 Hz), Theta (4-7 Hz), Alpha (8-12 Hz), Beta (13-20 Hz), and High Beta (21-30 Hz).

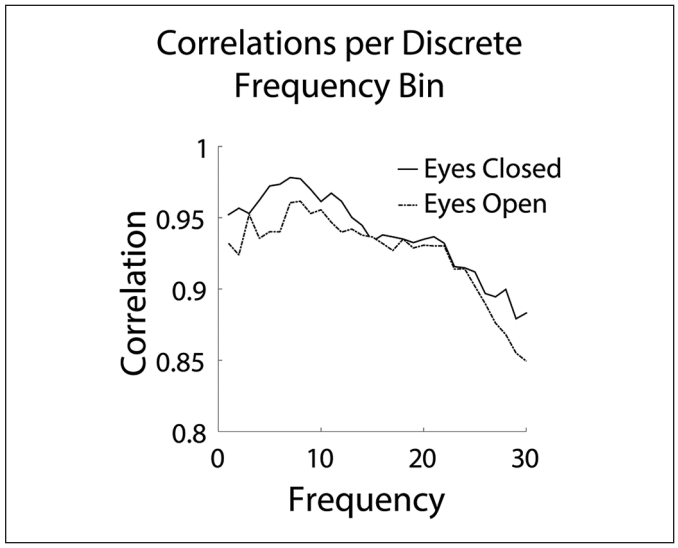

Figure 4. Correlation between the qEEG-Pro and Lifespan z-score results as a function of frequency (1-30 Hz) and eyes condition (eyes closed and eyes open).

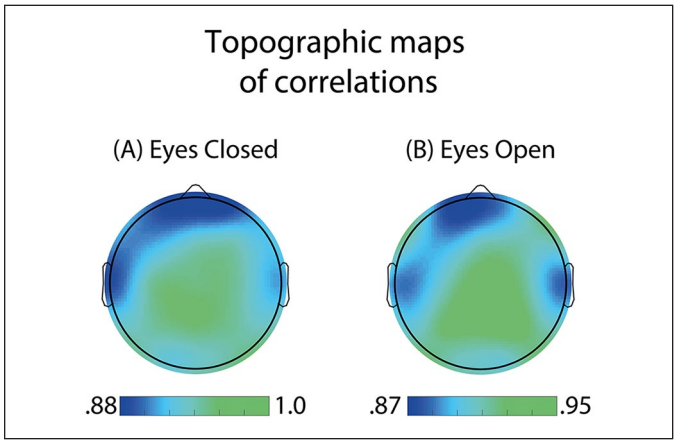

Figure 5. Topographic maps of correlations between the qEEG-Pro and Lifespan databases within the Beta band (13-30Hz), for the eyes closed condition (A) and the eyes open condition (B).

Standardization of qEEG Interpretation

Both increased standardization of EEG de-artifacting procedures and qEEG normative databases has the potential to increase the reliability and validity of individual *z*-scored qEEG measures. However, a typical qEEG report contains a myriad of results that need to be interpreted correctly by a clinician in order to be of added value in diagnostic procedures, selecting optimal treatment protocols and evaluating the effects of those treatments. This is far from trivial, since there are many factors that determine whether specific deviations in resting-state EEG can be considered clinically relevant. The first thing that needs to be ruled out is that a qEEG deviance is caused by an artifact of some sort. Even though this can be partly be prevented with the use of an effective de-artifacting procedure, a "perfect" de-artifacting method does not yet exist. This means that it is always necessary to evaluate whether a qEEG deviance is caused by artifacts, whatever de-artifacting method is used. It is therefore essential that the EEG recording is of high quality with as few artifacts as possible, which can be challenging with patient populations. Second, there are several qEEG normative databases that are commercially available for qEEG comparisons, but as the comparative analyses between 2 FDA-approved, commonly used qEEG databases have shown, differences between databases do exist and may influence the

qEEG results of an individual patient. Third, in order to reach valid conclusions about clinically relevant qEEG deviations, the clinician needs to have up-to-date knowledge of the scientific literature regarding the association between EEG deviations and psychological disorders or symptoms. These 3 basic factors form the foundation for accurately interpreting qEEG results, but there are many more factors that determine whether a qEEG deviation is clinically relevant. Generally speaking, the presence of certain biomarkers should always be interpreted in the context of other qEEG characteristics. For example, it has been shown that increased Theta/Beta ratio, an EEG biomarker for ADHD, can be caused by a low "alpha peak frequency" (APF).[37] This means that the peak power of the Alpha rhythm is relatively low, causing power in the adjacent Theta band to be increased. Therefore, even though the Theta/Beta ratio is increased, the cause of this increase should be taken into account in order to accurately interpret this deviation. Similarly, the deviance within a certain frequency band should always be evaluated in the context of deviances in adjacent bands. For example, when the EEG contains high power exactly at 3 Hz (at the edge of the Delta band), the frequency decomposition results will also show increased power of frequencies adjacent to the 3-Hz bin and the excess power at 3 Hz will therefore "spill over" to the Theta band. Again, in order to interpret the qEEG results accurately, the context of the excess in the Theta band should be taken into account. Finally, when the qEEG results of an individual contains multiple qEEG deviances, the clinician needs to decide which qEEG deviance(s) are clinically relevant and how the pattern of qEEG deviances can best be linked with the patient's symptoms.

The interpretation of individual qEEG results by human interpreters is prone to suffer from high inter- and intrarater variability, which calls for the development of automatic, standardized methods for qEEG interpretation. This is especially relevant for qEEG-informed Neurofeedback therapy, which aims to treat psychological disorders by selectively reducing qEEG deviations that are thought to be associated with that particular disorder. qEEG-Pro has developed automated qEEG-informed Neurofeedback treatment protocol recommendations in the form of weighted decision trees for a number of psychological disorders, which takes into account many factors that co-determine the clinical relevance of a qEEG deviation, such as the examples stated above. There have also been efforts to create automated discriminant analyses for application in diagnostic procedures, for example, for traumatic brain injury[38] and for ADHD.[14] Finally, the "Psychiatric Encephalography Evaluation Registry" (PEER) utilized a machine-learning approach to predict response to antidepressant medication, which can be used as a tool for guiding pharmacotherapy for depression.[39]

Summary and General Discussion

Standardization and personalized medicine are 2 important trends in healthcare that seem to represent opposing views on improving the effectiveness and safety of medical treatments. Standardization in mental healthcare can be seen in diagnostic procedures such as the use of *DSM*-based criteria and questionnaires. In contrast to other medical fields, diagnostic procedures in mental healthcare are seldomly based on physiological measurements. However, there has been accelerated progress in the establishment of "EEG biomarkers" for psychological disorders. QEEG embodies the application of this research in clinical practice by comparing the oscillatory power from de-artifacted resting state EEGs of a patient with an age-regressed normative database. QEEG can provide objective information about the underlying physiological causes of a psychological disorder, which can complement the information gained from structured interviews and questionnaires. Moreover, this information can be used to guide treatment selection and to evaluate treatment success. The use of QEEG in clinical practice may increase both the accuracy of diagnostic procedures and the effectiveness and safety of treatments and therefore represents a personalized medicine approach to mental health care. However, one of the main concerns for the implementation of qEEG in clinical practice is the lack of standardization in de-artifacting procedures, normative databases, and qEEG interpretation. A typical resting state EEG contains artifacts from many different sources. These artifacts can significantly influence the qEEG results and the application of an effective de-artifacting method is therefore vitally important in order to get valid qEEG results. Many automated de-artifacting procedures have been proposed in the scientific literature, but there is currently no consensus about the most effective and reliable approach. In order to reach such a "gold standard" for automated de-artifacting, future research needs to evaluate different de-artifacting procedures by directly comparing results from different methods.

Standardization is also required for qEEG normative databases. Currently, there exist a number of commercially available qEEG databases that can be used in clinical practice, but until now there have not been any studies comparing the results of different qEEG databases directly. Here, 2 commonly used, FDA-registered qEEG databases were directly compared. The results show that the overall correlation between these 2 databases is very high, illustrating the validity of both databases. The correlations were relatively smaller in higher frequency bands ($>$13 Hz), which are known to be susceptible to muscle artifacts. A post hoc analysis revealed that the relatively lower correlations were mainly caused by lower correlations at electrode sites that are known to be especially vulnerable for muscle artifacts. Therefore, it seems likely that the relatively lower correlations in the Beta band are caused by either differences in recording quality, de-artifacting procedures or number of subjects in particular age bins. The likelihood that the difference between the 2 databases is caused by a difference in muscle artifacts illustrates the importance of standardization of de-artifacting procedures for both the individual EEGs of a patient and the EEGs that are used for the creation of a qEEG database. Future research should aim to compare multiple databases and establish norms that are cross-validated across a wide age range.

The final and perhaps most challenging part of standardizing qEEG procedures in clinical practise is the standardization of qEEG interpretation. There are many factors that determine

whether a qEEG deviation of a patient is clinically relevant. This calls for the development of standardization and automation of qEEG interpretation. Thus far, specific discriminant analyses have been developed for use in diagnostic procedures[14,38] alongside automated neurofeedback protocol recommendations (https://www.qeeg.pro) and automated antidepressant medication selection (PEER).[39] In order for qEEG to become more broadly applicable in mental health care, efforts should be made to create automated and standardized qEEG interpretation methods that enable clinicians to apply qEEG as a tool that can aid both diagnostic procedures, effective treatment selection and treatment evaluation.

Conclusion

The use of qEEG in clinical practice shows great potential as a tool that provides information about the underlying neurophysiological correlates of psychological disorders. QEEG can combine a high level of standardization with a personalized medicine approach to mental health care. However, the validity, reliability, and usability of qEEG in clinical practice depends on the development of automated and standardized processing pipelines. The integration of standardized de-artifacting techniques, qEEG databases, and qEEG interpretation methods is necessary for qEEG to reach its full potential in clinical practice.

Declaration of Conflicting Interests

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