Clinical Neurophysiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

Quantitative EEG (QEEG) in psychiatry: Diagnostic or prognostic use?

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In July 2013 the FDA approved marketing of the '*first brain wave test to help assess children and teens for ADHD*'[1] which is commercialized by NEBA.[2] This brain wave test employs the often-published Theta/Beta ratio obtained from the EEG and this milestone has generated significant debate about its veracity, clinical utility and scalability. Most of the media referred to it as a first brain test to *diagnose* children with ADHD. So should we be positive or cautious about this unprecedented endorsement of EEG into the psychiatric diagnostic process? Or perhaps a bit of both? On one hand it finally heralds an FDA sanctioned objective biological brain marker into Psychiatry and Pediatrics, which will hopefully be exemplar of more to come. On the other hand it may inadvertently be over-used simplistically as a diagnostic tool.

Explicit cautions include the reality that even its use diagnostically has limitations. Theta/Beta ratio has often been reported in the literature to deviate in children with ADHD, especially from the beginning of this century. However, a recent meta-analysis that only incorporated standardized data (same recording condition of Eyes Open and same EEG Cz recording site) concluded that this Theta/Beta ratio is *not* a reliable diagnostic marker for ADHD (Arns et al., 2012). The data and further details from this meta-analysis are summarized in Fig. 1.

In this issue of Clinical Neurophysiology, Poil and colleagues (Poli et al., 2014) report another EEG analysis in ADHD that complements this overall trend. Poil and colleagues included 46 patients with ADHD and 68 controls and recorded high-density EEG from 60 electrodes under resting eyes closed conditions. They were unable to find any differences in theta for children with and without ADHD. When calculating the Cohens' D effect size for the Theta/Beta ratio between these 2 groups in children, an effect size of 0.17 is obtained (Poil et al., personal communication), which fits in with the trend described in Fig. 1, but contrasts to the large effect sizes (ES: 1.6–1.8) described in the early studies by Monastra et al. (1999, 2001) and Snyder et al. (2008). These data all together suggest that the Theta/Beta ratio is not an unambiguous diagnostic marker in all cases, and it seems unlikely that a single biomarker can differentiate all ADHD patients from controls.

A nuance which did appear in the FDA press release but was incorrectly interpreted by most of the media releases is that the brain wave test referred to is not approved as a standalone diagnostic test, but rather: '*When used as part of a complete medical and psychological examination, the device can help confirm an ADHD diagnosis or a clinician's decision that further diagnostic testing should focus on ADHD or other medical or behavioral conditions...*'.[1] Combined with the above data on this metric in ADHD, this metric as a diagnostic tool should be judiciously used as a complement to clinical context.

There is also a circular reasoning in investigating the EEG to 'diagnose' a psychiatric disorder. By definition the criterion from the DSM-IV and DSM-V making a set of behavioral criteria a mental disorder is the criterion of clinical significance (distress or impairment in social, occupational or other areas of functioning), which is not something the EEG is expected to quantify. Therefore, in healthy control groups there is always a subgroup of people having the same behavioral issues (and supposedly the same underlying neural signature), but for whom there is no 'clinical significance' and thus do not have the diagnosis 'ADHD.' Also, these same behavioral issues can be a limitation for one person, but a benefit for another person or in another time-period. For example the well-known DRD4 7-repeat gene is a known candidate gene associated with ADHD, but also associated with novelty seeking (Swanson et al., 2007). This also explains the typical geographical distribution of this gene, where the prevalence of this gene is higher in areas such as South-America and the US (related to the 'distance Out-of-Africa' Matthews and Butler, 2011; Chen et al., 1999). So the 'trait' of novelty seeking, in the early days, is what resulted in the discovery of new continents, but is a trait now more often seen in ADHD.

The primary reason that this criterion of clinical significance is used in the DSM 5 and earlier versions is related to: '*...the absence of clear biological markers or clinically useful measurements of severity for many mental disorders...*' (DSM 5, p. 21). A notable attempt to break this circular reasoning is the U.S. NIMH Research Domain Criteria (RDoC) and personalized or precision medicine,[3] in which EEG's could be used to inform core psychopathological instabilities, rather than investigate the EEG correlate of signs and symptoms that have an '*inescapable heterogeneity*'.[3]

Poil and colleagues partly tried to address the above circular reasoning, and more specifically assumed heterogeneity within their group of ADHD patients. Rather then looking at a single biomarker (e.g. Theta/Beta ratio), they employed a multi-dimensional classification method (a support vector machine – SVM) in order to test if that method could better separate between ADHD and

[1] FDA News release: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm360811.htm?source=govdelivery.

[2] http://www.nebahealth.com.

[3] http://www.nimh.nih.gov/about/director/2012/research-domain-criteria-rdoc.shtml.

http://dx.doi.org/10.1016/j.clinph.2014.01.014
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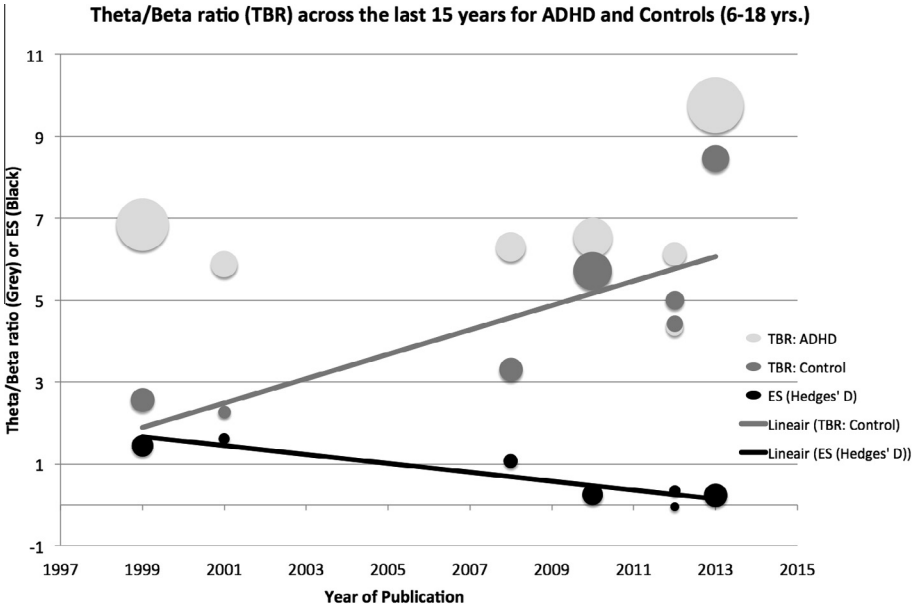

Fig. 1. The Theta/Beta ratio (TBR) for different studies across the last 15 years for ADHD groups (light grey) and control groups (dark grey). The size of the circles provides an indication of the sample sizes of the studies. Only for control groups a significant correlation with year of publication was found ($p = .036$; $r^2 = 62\%$), suggesting the theta/beta ratio of healthy children has increased across the last 15 years, but remained unchanged for children with ADHD. The black line demonstrates the effect size of the difference between ADHD and control groups, which significantly decreased across time. This figure is modified from the meta-analysis of Arns et al. (2012) and updated with the Liechti et al. (2012) data.

controls. In their attempt they were partly successful in adults (sensitivity of 67% and specificity of 83%), whereas this approach failed in children. However, Poil and colleagues still relied on the behavioral diagnosis of ADHD from the DSM-IV. In order to finally break the above circular reasoning we should start shifting to better-defined sub-groupings that also make sense from a neurobiological perspective. For example a more specific characterization e.g. impaired vs. normal default mode function (Helps et al., 2010), impaired vs. normal circadian function (van der Heijden et al., 2005), low vs. high vigilance regulation (Hegerl and Hensch, 2012) etc. An even more relevant metric could be to use treatment response as a sub-group. For example, even though the above mentioned Theta/Beta ratio is a poor diagnostic measure, in 25–30% of ADHD patients this measure is consistently found to deviate and it has been repeatedly shown that excess theta is associated with a favorable treatment outcome to stimulant medication and neurofeedback (see Arns et al., 2012), suggesting that Theta/Beta ratio might serve a prognostic rather then a diagnostic purpose. However, this needs to be tested prospectively. A disadvantage of studies assuming heterogeneity and thus focusing on subgroups, is that they require much larger sample sizes, since the total patient group needs to be divided by the number of sub-groups resulting in reduced statistical power.

Recently several of such multicenter large-scale studies are underway that are also measuring EEG amongst other biomarkers e.g. the EMBARC study (Establishing Moderator and Biosignatures of Antidepressant Response in Clinical Care) in Depression and the iSPOT studies (International Study to Predict Optimized Treatment Response) in Depression and ADHD. The iSPOT-ADHD study serves to test treatment outcome (including baseline pre-treatment EEGs) and aims to include ADHD patients who are prescribed with stimulant medication and 672 matched controls. The first half of these data have currently been collected and the first data analyses are underway and expected to be published in the first half of this year and replicated in the second half. These data will be available to selected academics to test their specific hypotheses related to the potential prognostic value of EEG (or other biomarkers such as genomics, fMRI, heart rate, DTI, MRI, etc.). The study by Poil and colleagues has laid a solid foundation for transforming the single-metric biomarker approach to a multidimensional classification approach. These new initiatives will hopefully add the prognostic use to diagnostic approaches in the multidimensional deployment of EEGs in research and clinical practice.

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Accepted 23 January 2014

Available online xxxx