Evaluation of a method that integrates an electroencephalographic biomarker with a clinician's assessment of attention-deficit/hyperactivity disorder

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Conflict of Interest Statement
Dr. Snyder is employed by and owns stock shares with NEBA Health, which holds patent rights to EEG systems and methods applied to ADHD and Mood Disorders. Dr. Rugino has been a consultant to and/or speaker for Shire, Bristol-Myers Squibb, and NEBA Health. Dr. Rugino's employer, Children's Specialized Hospital, has received research funding from NEBA Health, Forest Labs, Shire, Eli Lilly and Company, Supernus Pharmaceuticals, and Bristol-Myers Squibb. Dr. Hornig has received funding from NEBA Health, Chronic Fatigue Initiative, Stanford University (private donor), and Korein Family Foundation. Dr. Hornig is a consultant and scientific advisory board member for Coronado Biosciences, and she has filed a patent application for autism biomarkers. Dr. Stein has received research support from NEBA Health and Shire, and he is a consultant for Novartis, Alcobra, and Genco Life Sciences.

Objective

We proposed a method to integrate an EEG biomarker together with a clinician's ADHD evaluation. We evaluated whether this method would provide further information beyond the clinician's initial evaluation and thereby improve accuracy.

Integration Method

In the proposed integration method, the clinician's ADHD evaluation and an EEG test are conducted in series. Rules for integration were established as follows:

1. The clinician first performs a diagnostic evaluation and designates primary diagnosis.
2. The biomarker (EEG theta/beta ratio) separates *patients with ADHD as primary diagnosis* into 2 groups:
   i. Group with confirmatory support for presence of ADHD as primary diagnosis.
   ii. Group with recommendation for further testing with focus on other conditions before proceeding with ADHD as primary diagnosis.
3. The biomarker separates *patients with uncertainty regarding ADHD as primary diagnosis* into 2 groups:
   i. Group with recommendation for further testing with focus on ADHD.
   ii. Group with recommendation for further testing with focus on other conditions.
4. The clinician always solely determines *negative for ADHD as the primary diagnosis.*

In summary, test-result subgroups are formed based on the clinician's primary diagnosis and the EEG result. Recommendations are associated with each subgroup (Table 1). These recommendations were validated as part of the clinical investigation.

		EEG Result		
		Low TBR	**Moderate TBR**	**High TBR**
Clinician's ADHD Evaluation	**Positive for ADHD***	*Strongly recommend further clinical testing (other conditions)*	*Suggest further clinical testing (other conditions)*	*Confirmatory support for ADHD as primary diagnosis*
	Uncertain for ADHD*	*Strongly recommend further clinical testing (other conditions)*	*Suggest further clinical testing (other conditions)*	*Suggest further clinical testing (ADHD)*
	Negative for ADHD*	*Negative for ADHD as primary diagnosis*	*Negative for ADHD as primary diagnosis*	*Negative for ADHD as primary diagnosis*

*Note: *as primary diagnosis. TBR=theta/beta ratio.*

Table 1. The integration method forms test-result subgroups with predefined recommendations.

Clinical Investigation

Subjects:

- Children (ages 6.00-11.99 years) and adolescents (ages 12.00-17.99 years)
- consecutively presenting with attentional and behavioral concerns
- at 13 clinics (5 pediatric, 3 psychological, and 5 psychiatric).

Of 364 subjects recruited, 275 met protocol criteria, completed the study, and had complete EEG recordings. All 275 were included in analysis of diagnostic accuracy.

Investigators collected comprehensive clinical evaluation data:

1. *clinician's interview based on DSM-IV-TR criteria,*
2. *semi-structured clinical interview (K-SADS-PL and supplements),*
3. *behavior rating scales (ADHD-IV RS),*
4. *IQ and achievement testing (WASI and WRAT-4),*
5. *scales of severity and dysfunction (CGI-S and CGAS),*
6. *physical exam,*
7. *hearing and visions screens,*
8. *medical, neurological, and medication histories,*
9. *questionnaire on socioeconomic status, education, & family history,*
10. *any further testing if deemed necessary by the clinician.*

Using these data, a qualified clinician at each site performed differential diagnosis and designated the primary diagnosis (blinded to EEG).

A separate team collected EEG (blinded to clinical evaluation data and clinician's diagnosis).

To produce recommendations (after blind-break):

- The integration method parsed subjects into test-result subgroups based on the clinician's ADHD diagnostic result and the EEG result (standardized theta/beta ratio).
- The integration method assigned to each subgroup predefined recommendations regarding ADHD as primary diagnosis.

To evaluate the accuracy of the recommendations:

- A reference standard was produced by an independent multidisciplinary team.
- The team was comprised of a child and adolescent psychiatrist, a clinical psychologist, and a neurodevelopmental pediatrician.
- The team determined consensus best estimate diagnosis by review of the clinical evaluation data with blinding to EEG and prior diagnoses (as well as parent rating scales, to avoid the bias of repeating information already covered in K-SADS-PL by the same informant).

To minimize bias:

- Independent third-party agencies maintained regulatory standard protocols for blinding, monitoring, data management, site queries, and database compilation and locking.
- All data were collected with blinding between three sources: 1) site: clinical data collection and clinician's diagnoses, 2) EEG: site collection and off-site processing, 3) multidisciplinary team: diagnoses.
- Prior to blind-break, clinical data, EEG, and diagnostic results were locked in databases by third-party agencies independent of study sponsor.
- After blind-break, all analyses were performed on data from the locked and controlled databases per predefined statistical analysis plans or regulatory agency guidance.

Results

The integration method forms test-result subgroups and designates predefined recommendations regarding primary diagnosis. For patients 'positive' or 'uncertain' for ADHD as primary diagnosis per clinician's initial evaluation, possible subgroup designations are:

1. recommendation for further testing for other conditions before proceeding with ADHD as primary diagnosis, or
2. confirmatory support for ADHD as primary diagnosis or recommendation for further testing for ADHD.

In Table 2, these subgroups are shown to have clinical differences that are consistent with the recommendations of the integration method.

	Test-Result Subgroups: designations by integration method		
Condition	***'Further testing for other conditions'*, (n = 130), $n_{subgroup}$ with condition (%)**	***'Confirmatory support or further testing for ADHD'*, (n = 115), $n_{subgroup}$ with condition (%)**	***Difference p****
1) Psychiatric disorders that could lead to ADHD exclusion[i]	29 (22%)	18 (16%)	0.187
2) Medical or neurological conditions known to mimic ADHD[ii]	29 (22%)	5 (4%)	**<0.001**
3) Uncorrected vision or hearing problems	42 (32%)	23 (20%)	**0.029**
4) History of no improvement on ADHD medications	10 (8%)	1 (1%)	**0.010**
5) History of adverse events on ADHD medications	20 (15%)	6 (5%)	**0.010**
6) Presentation with primary concern of anger issues	22 (15%)	5 (4%)	**0.007**
7) Presentation with primary concern of aggression issues	49 (38%)	30 (26%)	0.052
8) Satisfactory academic and intellectual performance[iii]	17 (13%)	5 (4%)	**0.017**
9) Evidence of dissatisfaction with ADHD diagnosis[iv]	15 (12%)	3 (3%)	**0.008**
10) Multidisciplinary team: Further testing may be needed for conditions 1-9	66 (51%)	27 (24%)	**<0.001**
11) Multidisciplinary team: Information may be needed for differential diagnosis	29 (22%)	10 (9%)	**0.004**
12) Interviewing clinician: initial impression did not favor ADHD	50 (39%)	21 (19%)	**0.001**
13) Teacher rating scales: inconsistent with ADHD	34 (27%)	25 (22%)	0.424

*Note: *In bold when significant difference (p≤0.05); i) Pervasive developmental disorders, psychotic disorders, bipolar disorders, and disorders caused by stressing event (post-traumatic stress disorder and adjustment disorder); ii) Head injury with ongoing impairment, sensory integration dysfunction, auditory processing disorder, substance abuse, tobacco exposure, anemia, headaches affecting attention, congenital encephalopathy, cerebral palsy, mild mental retardation, neuro-maturational delays/soft signs, and influence of asthma medications; iii) Reported in interview and/or questionnaire as doing well academically/intellectually; no special education; no repeated grade. iv) Patient may have presented because further evaluation was sought after a previous ADHD diagnosis, or because evaluation was sought for disorders other than ADHD. Patient may have had general dissatisfaction with ADHD treatment. All parent and teacher behavioral rating scale scores may have not been consistent with ADHD (all scale scores <80th percentile).*

Table 2. The test-result subgroups are shown to have clinical differences that are consistent with the predefined recommendations of the integration method.

In Table 2, subjects receiving recommendations regarding other conditions were more likely to have complicating conditions that could have an impact on the clinician's decision regarding ADHD as primary diagnosis (10 significant differences). Conversely, subjects receiving recommendations regarding ADHD were less likely to have these complicating conditions. The results support that the biomarker offers additional information beyond the clinician's initial ADHD evaluation.

To examine whether the integration method could improve diagnostic accuracy, Table 3 presents accuracy results for the integration method (clinician plus EEG) and for the clinician alone, with each compared against multidisciplinary team as reference standard.

	Integration Method (Clinician + EEG)	n	Clinician[i]	n	Clinician[ii]	n
Specificity, % (95% CI)	94 (89-97)	145	36 (29-44)	145	19 (13-26)	145
Sensitivity, % (95% CI)	82 (74-87)	130	89 (83-93)	130	98 (93-99)	130
Positive Predictive Value*, % (95% CI)	92 (86-96)	115	56 (49-62)	209	52 (46-58)	245
Negative Predictive Value*, % (95% CI)	85 (79-80)	160	79 (67-87)	66	90 (74-97)	30
Overall Accuracy, % (95% CI)	88 (84-91)	275	61 (55-67)	275	56 (50-62)	275

*Note: *Reference prevalence for positive condition: 47% (130/275). i) In analysis, 'uncertain' for clinician alone handled as 'other condition'. ii) In analysis, 'uncertain' for clinician alone handled as 'ADHD'.*

Table 3. Diagnostic accuracy results for integration method (clinician + EEG) and for clinician alone, with each compared against multidisciplinary team as reference standard.

Results support that a diagnosis rendered by a clinician using the integration method would be more likely to converge upon the diagnostic results of a multidisciplinary team.

Discussion / Conclusions

To evaluate the proposed integration method, we examined concordance with a reference standard based upon an independent multidisciplinary team. Previous clinical findings have shown that when a multidisciplinary model is applied, a significant number of patients presenting with ADHD-like concerns may be determined as having other primary diagnoses (Pearl, Weiss and Stein, 2001). Similarly, the current investigation showed that a clinician could use EEG to improve identification of ADHD-like patients who are more likely to have other conditions that could impact the primary diagnosis (10 significant results). By virtue of this improvement, a clinician using EEG would be more likely to converge upon diagnostic evaluation results of a multidisciplinary model (overall accuracy: clinician plus EEG, 88%; clinician alone, 61%). Therefore evidence supports that the EEG biomarker provides additional information beyond the clinician's initial ADHD evaluation, and the proposed integration method may improve diagnostic accuracy.

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References and Regulatory

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