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 primary diagnosis.

In summary, test-result subgroups are formed based on the clinician’s ADHD evaluation and the EEG result. Recommendations are associated 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 RDC),
- 4. IQ and achievement testing (WASI and WRAT-4),
- 5. scales of severity and dysfunction (CDI-S and CIQAS),
- 6. physical exam,
- 7. hearing and vision screens,
- 8. medical, neurological, and medication histories,
- 9. questionnaire on socioeconomic status, education, family history.

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 reviewing the clinical evaluation data with blinding to EEG and prior diagnosis (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.
- Data were collected with blinding between three sources: 1) site clinical data collection and clinician’s diagnoses, 2) EEG site collection and off-line 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 subgroups are designated:
1. recommendation for further testing for other conditions before proceeding with ADHD as primary diagnosis.
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.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test-result subgroup</th>
<th>Confirmed recommendation for ADHD as primary diagnosis</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD diagnosis</td>
<td>Positive</td>
<td>75 (78.5%)</td>
<td>4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>15 (16.7%)</td>
<td>2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
<td>5 (5.3%)</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 (15 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.

<table>
<thead>
<tr>
<th>Specficity</th>
<th>Sensitivity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician alone</td>
<td>94 (94%)</td>
<td>55 (55%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Clinician plus EEG</td>
<td>97 (97%)</td>
<td>58 (58%)</td>
<td>17 (17%)</td>
</tr>
</tbody>
</table>

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 using EEG could be more likely to converge upon a 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.

References and Regulatory