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# Clinical Validation of Eye Vergence as an Objective Marker for Diagnosis of ADHD in Children

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## Abstract

**Objective**: ADHD youth show poor oculomotor control. Recent research shows that attention-related eye vergence is weak in ADHD children. **Method:** To validate vergence as a marker to classify ADHD, we assessed the modulation in the angle of vergence of children ($n$ = 43) previously diagnosed with ADHD while performing an attention task and compared the results with age-matched clinical controls ($n$ = 19) and healthy peers ($n$ = 30). **Results:** We observed strong vergence responses in healthy participants and weak vergence in the clinical controls. ADHD children showed no significant vergence responses. Machine-learning models classified ADHD patients ($n$ = 21) from healthy controls ($n$ = 21) with an accuracy of 96.3% (false positive [FP]: 5.12%; false negative [FN]: 0%; area under the curve [AUC]: 0.99) and ADHD children ($n$ = 11) from clinical controls ($n$ = 14) with an accuracy of 85.7% (FP: 4.5%; FN: 19.2%, AUC: 0.90). **Conclusion:** In combination with an attention task, vergence responses can be used as an objective marker to detect ADHD in children. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

## Keywords

ADHD, eye vergence, diagnosis, children, biomarker, binocular

ADHD is one of a common neurodevelopmental disorder affecting 3% to 7% of school-aged children worldwide. It is characterized by a low degree of attention, a high degree of hyperactivity and impulsivity, and the inability to inhibit inappropriate actions.

The altered behavior of ADHD patients is not limited to general conduct but it is also observed at the level of saccadic eye movement behavior. ADHD patients have more difficulty suppressing saccadic eye movements when fixation is required (Karatekin & Asarnow, 1999; Munoz, Armstrong, Hampton, & Moore, 2003) and the rate of microsaccades is reported to be higher in ADHD participants compared with controls, especially in the time intervals around stimulus onset (Fried et al., 2014) and after cue presentation, although suppression has also been reported (Engbert & Kliegl, 2003). The poor eye control of ADHD patients is furthermore expressed as an increased variability in the latencies of saccadic responses to visual stimuli compared with healthy controls (Kuntsi et al., 2006; Leth-Steensen et al., 2001). Poor control of saccadic behavior has been observed in anti-saccades (Leth-Steensen et al., 2001), visually guided saccades (Leth-Steensen et al., 2001; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Munoz et al., 2003), and memory guided saccades (Rommelse, Van der Stigchel, & Sergeant, 2008). Moreover, whereas healthy participants show an asymmetry in eye movement control where eyes move faster when controlled by the right cerebral hemisphere, ADHD children do not show this asymmetry (Rothlind, Posner, & Schaughency, 1991). In contrast to fast saccadic eye movements, slower smooth pursuit eye movements appear to be within normal range in ADHD patients (Ross, Olincy, Harris, Sullivan, & Radant, 2000).

Besides the saccadic eye movements, disconjugate eye movements or vergence, that is, where the eyes move in opposite direction (Figure 1), are affected in ADHD patients (Solé Puig et al., 2015). This finding is of relevance as recent data provide evidence showing that eyes converge during orienting attention (Solé Puig, Pérez Zapata, Aznar-Casanova, & Supèr, 2013; Solé Puig, Puigcerver, Aznar-Casanova, & Supèr, 2013). During gaze fixation, the eyes briefly converge after the presentation of

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a stimulus, which indicates the location of an upcoming peripheral target but not or weakly after a stimulus that was not informative about the location of the peripheral target (Solé Puig, Pérez Zapata, et al., 2013). The strength and timing of eye vergence correlate with the onset and strength of the visual event–related potentials (vERPs) at parietal locations (Supèr, Marco, Zapata, Crespillo, & Puig, 2014). Also, stimulus contrast is associated with strength of convergence (Sole et al., 2013a) where high stimulus contrast relates to larger modulation of the angle of eye vergence. Moreover, detected targets were accompanied by eye vergence, whereas targets, which were not detected, were not (Sole et al., 2013a).

The diagnosis of ADHD is clinical, based upon criteria established by classification systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013). Even though the clinical diagnosis shows considerable levels of concurrent and predictive validity (Faraone, 2005; Faraone et al., 2000), concerns persist, and additional tools are needed to support ADHD diagnosis. The observation that attention-related eye vergence is poorly present in children with ADHD (Solé Puig et al., 2015) led to the idea that evaluating eye vergence during an attention task can be used as an objective measure to support the clinical diagnosis of ADHD. A recent study reporting abnormalities in the brain structure, which control eye vergence, in ADHD patients supported this notion (Johnton et al., 2014). In fact, in a preliminary report, we were able to classify ADHD in children using vergence responses (Lorena Esposito et al., 2016). The aim of the present study was, therefore, to replicate our earlier findings and to validate eye vergence as a marker tool for classifying ADHD. We assessed the modulation of the angle of vergence in children previously diagnosed with ADHD while performing a child-friendly attention task and compared the results with the responses from age-matched clinical controls and healthy participants.

## Method

### Participants

Forty-three children aged between 7 and 17 years ($M \pm SD = 11.95 \pm 3.06$) diagnosed with ADHD, and 19 clinical controls ($M \pm SD = 11.57 \pm 2.86$) participated in the study. Clinical controls were children referred to the hospital for attentional and/or conduct problems but after first clinical assessment diagnosed as not having ADHD but suffering other mental problems. None of the participants was taking medication for ADHD. Patients were recruited through the Child and Adolescent Health Mental Center from the Hospital Mataró of the Consorci Sanitari del Maresme. The participants ($n = 30$) from the control group were healthy children showing no attention or conduct problems ($M \pm SD$: $8.85 \pm 0.49$ years) recruited via a public school. In addition, a separate population of 67 children ($M \pm SD$: $10.67 \pm 2.64$ years; 21 healthy controls; 14 clinical controls, and 32 ADHD children) were used for validation purposes. All the clinical diagnoses of ADHD were made by clinical psychiatrists. All cases were diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; APA, 2000) including a psychiatric and psychologist interview to assess the presence of symptoms of inattention, hyperactivity, and impulsivity during the last 6 months. Also, the beginning of the symptoms before 7 years of age and the persistence of clinical dysfunction in at least two settings (school and home) were used as criteria. Furthermore, we analyzed psychopathology and comorbidity using Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). Part of the medical examination and psychiatric evaluation of all patients for diagnosing ADHD was the inquiry about visual problems. The survey included specific questions on strabismus and accommodation insufficiency. All participants had normal or corrected-to-normal visual acuity.

### Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) between 7 and 17 years of age, (b) a diagnosis of ADHD without mental retardation, (c) Spanish mother tongue or fluency in Spanish, and (d) informed consent for the study signed by the parent or legal guardian with patient assent. The exclusion criteria were as follows: (a) a history of head injury with loss of consciousness or other neurological illness; (b) mental retardation or other significant disorders like a pervasive developmental disorder; and (c) visual or auditory problems.

### Ethics Statement

Before participating in the study, written informed consent from the parents on behalf of the children enrolled in our study was obtained in accordance with the Helsinki Declaration. The study was approved by the Ethics Committee of the University of Barcelona and of Consorci Sanitari del Maresme, and the study was registered at AEMPS (identifier: 548/15/EC).

### Apparatus

We used the BGaze system (Braingaze SL, Mataró, Spain) for presenting the visual stimuli synced with a remote eye tracker. The BGaze system includes a 30Hz binocular eye tracker (X2-30, Tobii Technology AB, Sweden). The display resolution was $1024 \times 768$ pixels.

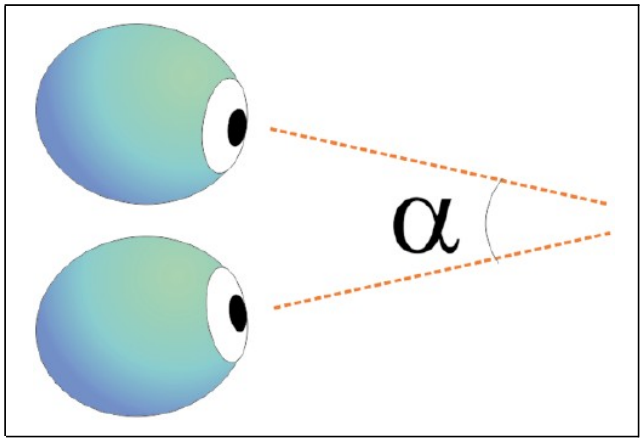


**Figure 1.** Schematic explanation of the vergence.
*Note.* The eyes focus on a single point in space where the angle of vergence ($\alpha$) is formed by the two gaze lines.

## Procedure

Children sat in a dimly lit room of the hospital or school, in front of the PC monitor at a distance of 55 cm. During the entire task, a chinrest was used to prevent head movements. The eye tracking equipment was calibrated (five points, binocular) for each participant at the beginning of the experiment by BGaze eye tracking software. Before starting the task, all children practiced with cue and no-cue trials (20 trials) to become familiar with the task. The entire procedure took about 12 min to complete. After testing, the saved behavioral and eye data were stored and assigned a random number. Validation was done double blinded (Figure 2).

## Visual Cue Experiment

To assess orienting visual attention, we used a paradigm in which the children were required to discriminate cartoon images of a tadpole from a fish (Figure 3). Each trial started with the presentation of a central frog (size of approx. $3 \times 4^0$) with his eyes closed, together with two small pool on either side (size of $2 \times 3^0$; eccentricity of 60). After 500 ms fixating, the frog opened the eyes looking toward the left or right side, or straight ahead. In the former case, the frog's gaze served as a cue to inform the child about the location (left or right) of the upcoming image of a tadpole or fish (informative cue condition). In the latter case, the child was unaware of the stimulus location (no-informative cue condition). In total, there were 128 trials. Fifty percent of the trials contained an informative cue and trials with different cue conditions were randomly interleaved. The fish or tadpole cartoon was presented for 1,500 ms. During the trial, the child was required to maintain fixation at the central frog image, and had to respond by pressing a button when a tadpole was presented and refrain from responding when a fish appeared. When the child correctly identified a tadpole, feedback was given by a small jump of the frog. The next trial started automatically at the end of a trial.

## Data Analysis

The data analysis was performed in two steps. In the first, we sought statistical proof of significant differences in the vergence signals between the different groups. This was done using the whole available sample. In the second step, we used the outcomes of the first part to build and test a machine-learning model that allowed prediction of ADHD for a given participant. For this, we split the original sample in two subsamples for extended validation purposes: one (S1, 90% total) for parameter adjustment and the other (S2, 10%) for final validation.

First part: In total, there were 3,354 (1,661 no-informative cue trials and 1,693 informative cue trials) trials in the healthy control group, 2,240 (1,133 no-informative cue trials and 1,107 informative cue trials) in the clinical group, and 5,036 (2,537 no-informative cue trials and 2,499 informative cue trials) in the ADHD group. The angle of eye vergence was calculated using the cross product of both gaze vectors. Gaze vectors correspond to the lines between the 3D eye positions and 2D gaze positions in a common coordinate system. Samples that gave a low validity score according to the Tobii eye tracker software were set as missing. In total, 10% to 20% of the samples were invalid. Low validity scores usually happen during saccades and blinks. From the remaining samples, we calculated the pointwise median of all trials for conditions and groups, separately. We chose to use the median instead of the mean to mitigate the effect of occasional outliers and thereby reduce bias. To reduce irregularities, the obtained signal was then smoothed using a moving median and thereafter a moving average with a 200 ms window. For statistical analysis, we used bootstrapping and permutation analysis to simulate pointwise the distributions of the medians.
Second part: The classification model (Figure 2) consists of two layers. In the first layer, a Radial Basis Function SVM model (gamma = 6.5) was trained and tested to separate healthy children from ADHD children using a set of three vergence features extracted from no-cue, left-cue, and right-cue signals. In the second layer, two nearest-neighbors models (1-NN and 3-NN) were used to distinguish between clinical controls and ADHD children. In the second layer, overall vergence level, vergence variations in velocity were used as features. The parameters of all three models were adjusted with a 30-fold stratified cross-validation routine over the S1 subsample, which, at each iteration, was further split into an 80-20 train-test random resampling. Then, the resulting model was tested on the

S2 subsample, which so far had been unseen by it. Only participants who were not classified as healthy controls and the ones that reached poor confidence levels in the first layer entered the second layer. The final classification was based on the label that gave the highest confidence level.

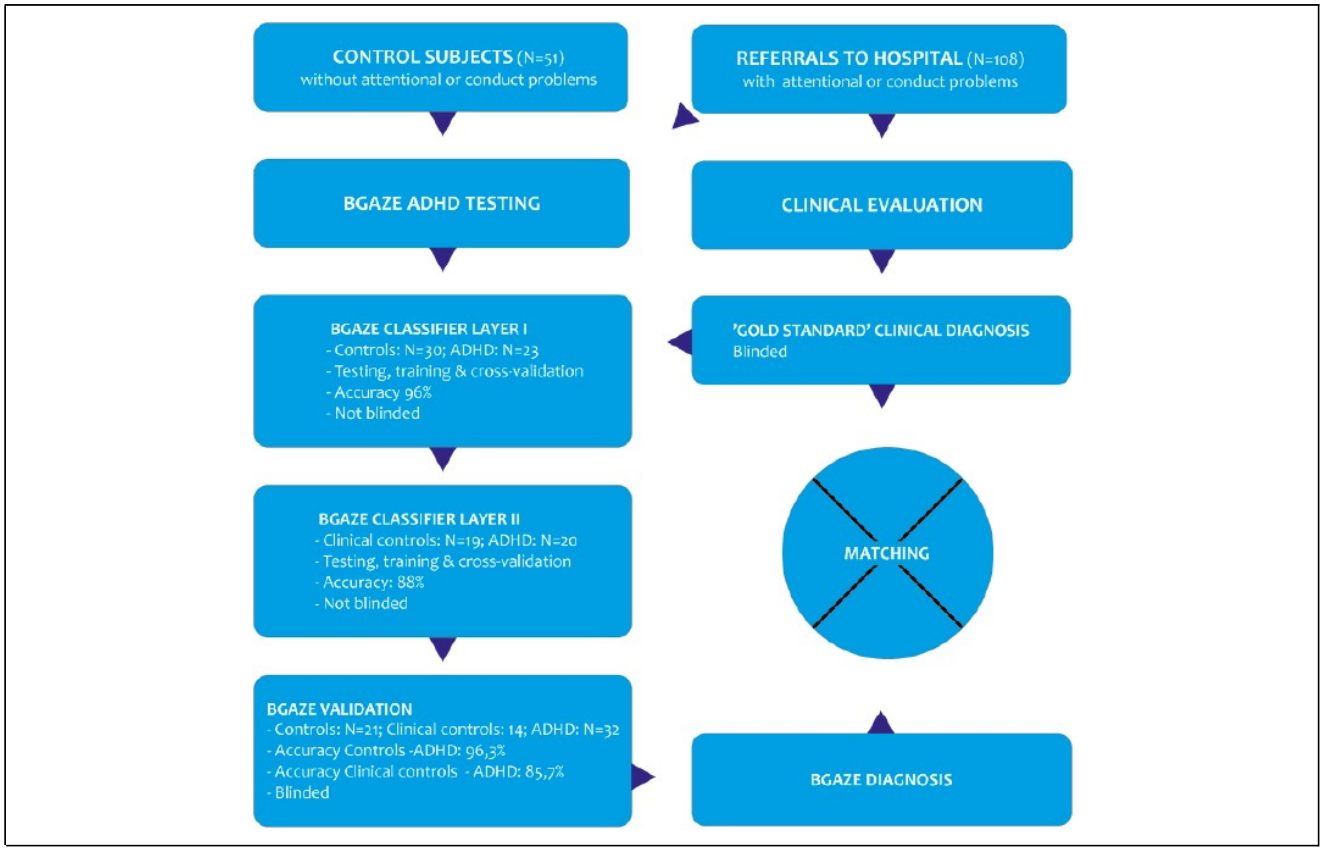


**Figure 2.** Flowchart of the clinical validation.

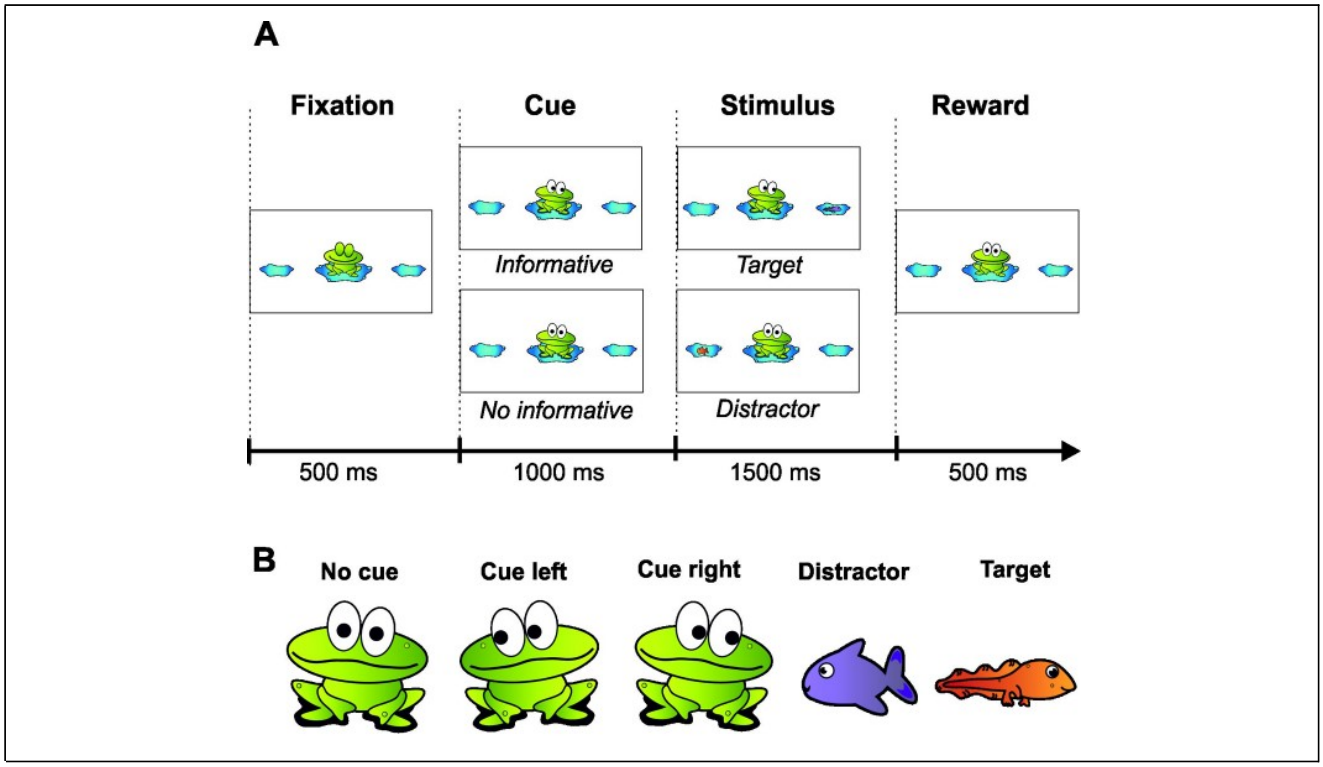


**Figure 3.** Task design and images used: (a) Illustration of the different phases of the attention task and stimulus presentation times. (b) Gaze directions of the central frog act as a cue left or right.
*Note.* The target is an image of a tadpole and the distractor is an image of a fish.

The sample size was obtained after a preliminary study of statistical power, where we supposed an effect magnitude of at least $d = 0.75$ (Cohen's) with a significance level of .05 and power = 0.75. We used R statistical software to simulate the distribution of the difference in medians and estimated a sample size of at least $n = 40$ participants. The results showed that we needed about 20 participants per group for each comparison, with at least 20 healthy controls (in this study, we have 30), 20 clinical controls (in this study, we have 19), and 20 ADHD-diagnosed participants (in this study, we have 43).

## Results

### *Behavior*

The overall behavioral reaction times to target stimuli (tadpole images) in the informative cue condition were similar for all groups ($M \pm SD$, controls: 678.8 ± 231.1 ms, clinical controls: 644.3 ± 200.8 ms, ADHD: 664.1 ± 248.8 ms; Tukey's rank test, all possible combinations $p > .05$). In the no-informative cue condition, children on average responded slower to target stimuli than in the informative cue condition. Healthy controls responded ($M \pm SD$; 712.6 ± 210.6 ms) significantly ($p < .01$) slower than the children from the other two groups ($M \pm SD$, clinical controls: 661.7 ± 194.6 ms, ADHD: 683.3 ± 240.5 ms). Between clinical controls and ADHD children, no significant differences were observed in reaction times. The variability in reaction times was different between the three groups ($p < .01$).

For healthy controls, the hit rates for targets were 81.7% and 81.7% and the correct rejection rates for the distractors were 77.3% and 75.9% in the informative and no-informative cue conditions, respectively. In the clinical control group, the hit rates were 60.0% and 64.2%, and the correct rejection rates were 64.3% and 62.2 %, in the informative and no-informative cue conditions, respectively. In the ADHD group, hit rates were 66.1% and 67.8%, and correct rejection rates were 67.6% and 67.6 % in the informative and no-informative cue conditions, respectively. The differences in the hit rates between healthy controls and the clinical populations were statistically significant in both cue conditions (Tukey's rank test, all $p < .05$). The differences in the correct rejection rates were not significant (Tukey's rank test, all possible combinations $p > .1$).

### *Eye Vergence Data*

During the trials, the angle of eye vergence was not constant even though participants maintained gaze fixation

at the central image. Notably, at the end of the trial during the stimulus period (when the target/distractor is presented), the angle of eye vergence decreased, which means that the eyes diverged (Figure 4). Around 600 ms after the onset of the target/distractor, the angle of eye vergence reached a minimum and returned to the initial baseline level. The changes in the angle of eye vergence are observed in trials belonging to the informative cue and no-informative cue conditions but they are more pronounced in the former condition. In contrast to the results obtained from healthy participants, the results from the clinical groups show remarkably less modulation in the angle of eye vergence. Especially, children of the ADHD group showed little to no changes in the angle of eye vergence during the task.

### *Cue Versus No-Cue Vergence*

In the healthy and the clinical control groups, eye vergence responses are stronger (i.e., the angle of eye vergence is larger, meaning that the eyes converge) during the informative cue period compared with the vergence responses during the no-informative cue period (Figure 5). In the ADHD group, no difference in vergence responses during the cue period is observed (Figure 5).

### *Distractor Versus Target*

To appreciate the relation of eye vergence to stimulus relevance, we compared the vergence responses to targets (tadpole images) with the responses to distractors (fish images). In the healthy control group, the angle of eye vergence decreased equally strongly during the stimulus period in both cases (Figure 6). In the clinical control group, eye vergence to distractors was as strong as in the healthy control group but was less noticeable in the target condition (Figure 6). In the ADHD group, for both targets and distractors, no changes in the angle of eye vergence were observed.

### *Classification*

By applying machine-learning algorithms, we assessed whether, using features of the modulation in the angle of eye vergence, we were able to discriminate ADHD participants from the healthy and clinical controls. We used a three-step classification procedure (Figure 2). In the cross-validation stages, we obtained accuracy of 96% in Layer 1 and 88% in Layer 2. In the validation stage with unseen participants, the results show (Figure 7) that with a 96.3% precision (area under the curve [AUC]: 0.99), ADHD participants can be separated from healthy participants. The false positive rate, that is, healthy patient diagnosed as ADHD, was 5.12% and the false negative rate, that is, ADHD patients classified as healthy was 0%. The separation between clinical groups reached an accuracy of 85.7% with an AUC of 0.90. False positive and false negative rates were 4.5% and 19.23%,

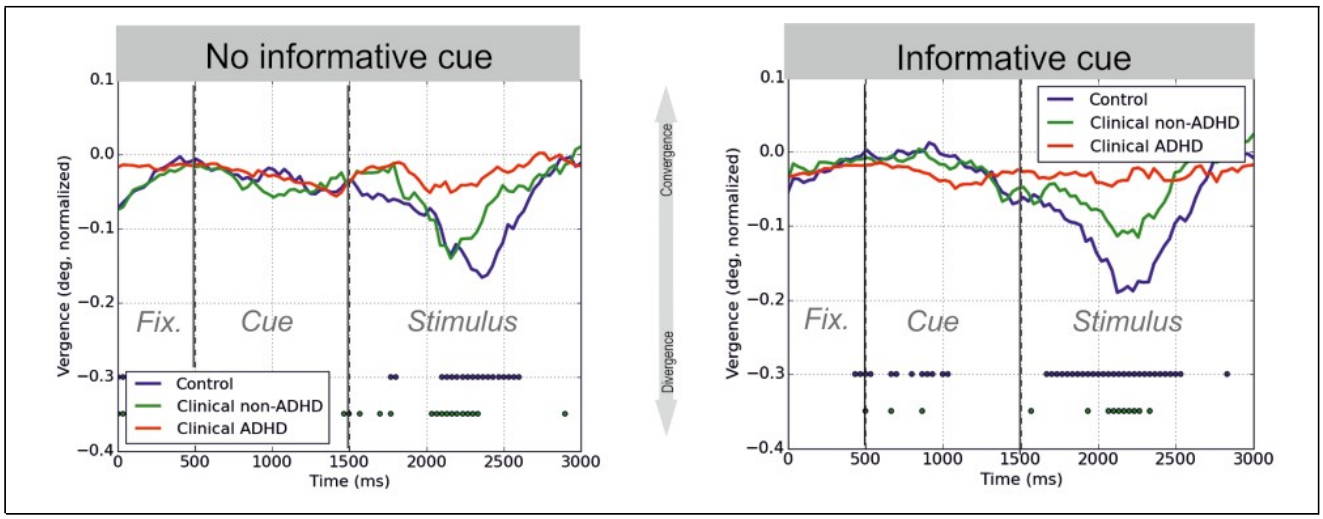


**Figure 4.** Average modulation of the angle of vergence.
*Note.* Blue traces denote average angle of eye vergence from healthy control participants. Green and red traces represent the vergence responses from Clinical control and ADHD participants, respectively. Phases in the task are demarcated by vertical lines (Fix.: denotes fixation period, Cue: the cue period, and Stimulus: the period of target presentation). The lower dots indicate the time points when vergence responses significant ($p > .05$) differ between healthy and ADHD participants (blue dots) and Clinical controls and ADHD participants (green dots).

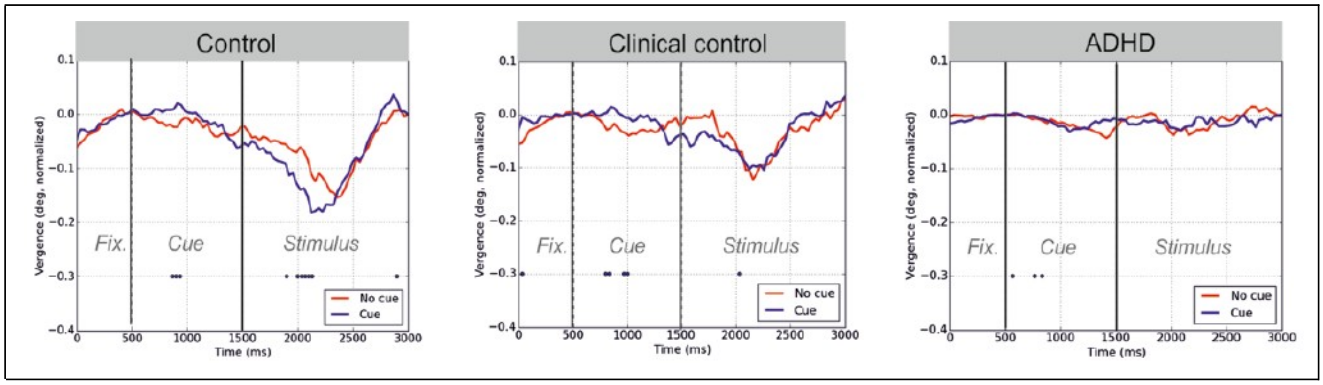


**Figure 5.** Average modulation of the angle of vergence.
*Note.* Blue and red traces denote average angle of eye vergence from cue and no-cue conditions. Labeling as in Figure 4.

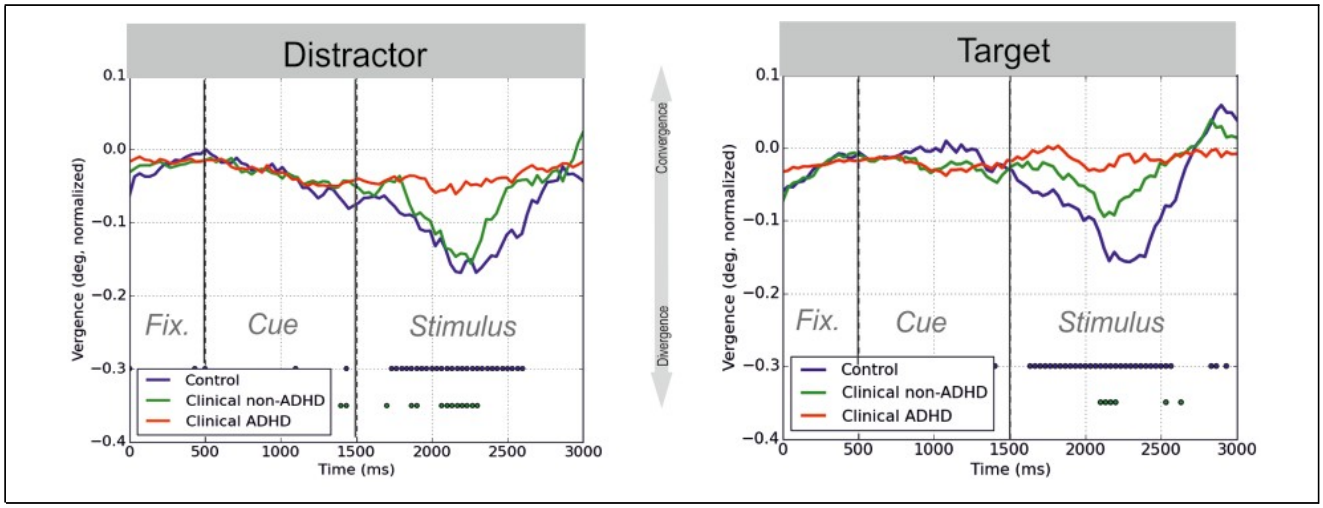


**Figure 6.** Average modulation of the angle of vergence for distractor and target stimuli.
*Note.* Labeling as in Figure 4.

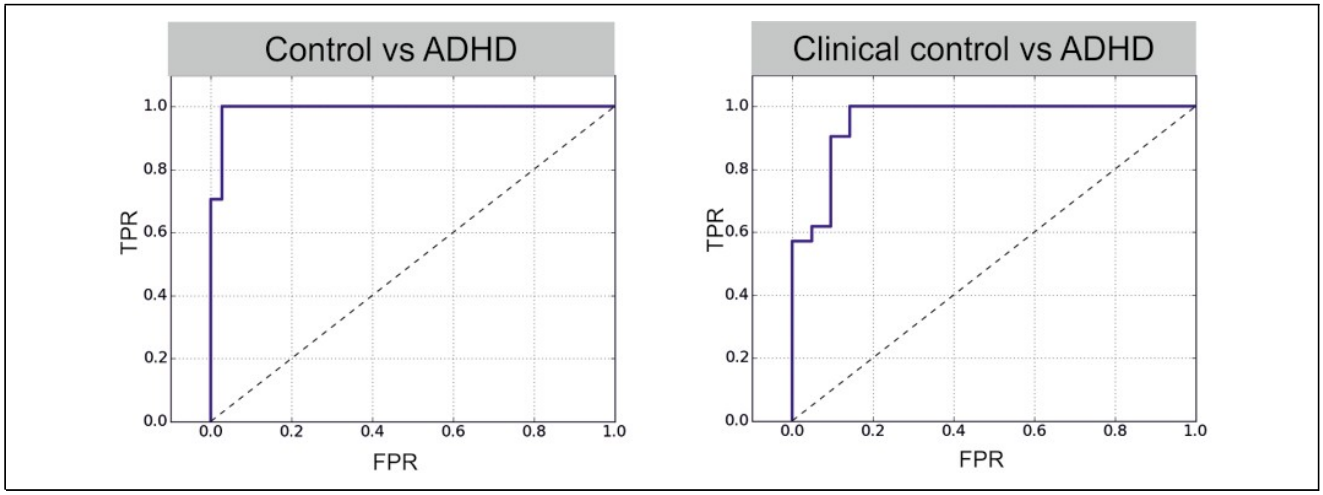


**Figure 7.** ROC curves based on eye vergence.
*Note.* ROC = receiver operating characteristic; TPR = true positive rate; FPR = false positive rate.

respectively. As behavioral performance data showed statistical significance, we added behavioral features (average response time, variability in response time, hit rate, and correct rejection rate) to the models to improve accuracy. Instead of improvement, reduced accuracies were obtained. Neither adding pupil size data to the model improved classification outcomes.

### *Pupil Diameter*

Neural circuits for controlling eye vergence partly overlap with those that control pupil size. To see if the size of the pupil changes during the attention task, we calculated pupil diameter. The results show that the diameter of the pupil increases during the task. This increase was stronger in the healthy control group than in the clinical groups. There was no significant difference in pupil diameter between the clinical groups, except in the no-informative cue condition where the clinical control group showed a stronger increase in pupil diameter compared with the pupil changes of the ADHD group (Figure 8). Because healthy participants showed different pupil modulations, we tried to classify ADHD children based on pupil size. However, classification in the validation stage gave poor results with maximal AUCs of 0.6 (Figure 9).

### *Behavioral and Vergence Responses*

Previous research has shown an absence of vergence responses when participants fail to detect a stimulus (Solé Puig, Pérez Zapata, et al., 2013). To know whether healthy and clinical groups differ, we compared the vergence responses with the behavioral responses (Figure 10). For correct responses to targets (hits), a strong vergence response in the healthy and clinical control groups was noticed. In contrast, when participants fail to respond to targets (misses), a clear modulation in the vergence angle was absent. For correct rejections and false alarms, healthy participants showed vergence responses, but no or weak modulation in the angle of eye vergence was seen in the clinical groups.

We next aligned the vergence responses at onset of the behavioral response, that is, when participant pressed the response button (Figure 11). In the healthy control group, there was a clear dip in the vergence responses centered on the behavioral response. This was also true for the clinical control group in the no-informative cue condition and for responses to distractors (false alarms). No clear response dip was observed in the informative cue condition and for hit trials. ADHD participants showed no response modulation around behavioral response onsets.

### *Task Duration*

During the 12-min task, participants may become fatigued or bored by stimulus repetition, especially those in the ADHD group, as they have difficulties remaining focused. To assess the possible influence on vergence responses, we compared the modulation in the average vergence angle during the first half of the task and compared that with the responses of the second half of the task. There is a slightly lower modulation in the first half during the stimulus period in the healthy group and during the cue period in the ADHD group (Figure 12). In the clinical control group, no difference was seen.

### *Stimulus Laterality*

Many studies report compromised brain lateralization in patients with ADHD. We therefore tested whether vergence responses show such laterality effect. We analyzed vergence to stimuli presented on the left and right sides separately. In none of the groups was there a clear difference in the modulation in the angle of eye vergence between left and right conditions (Figure 13).

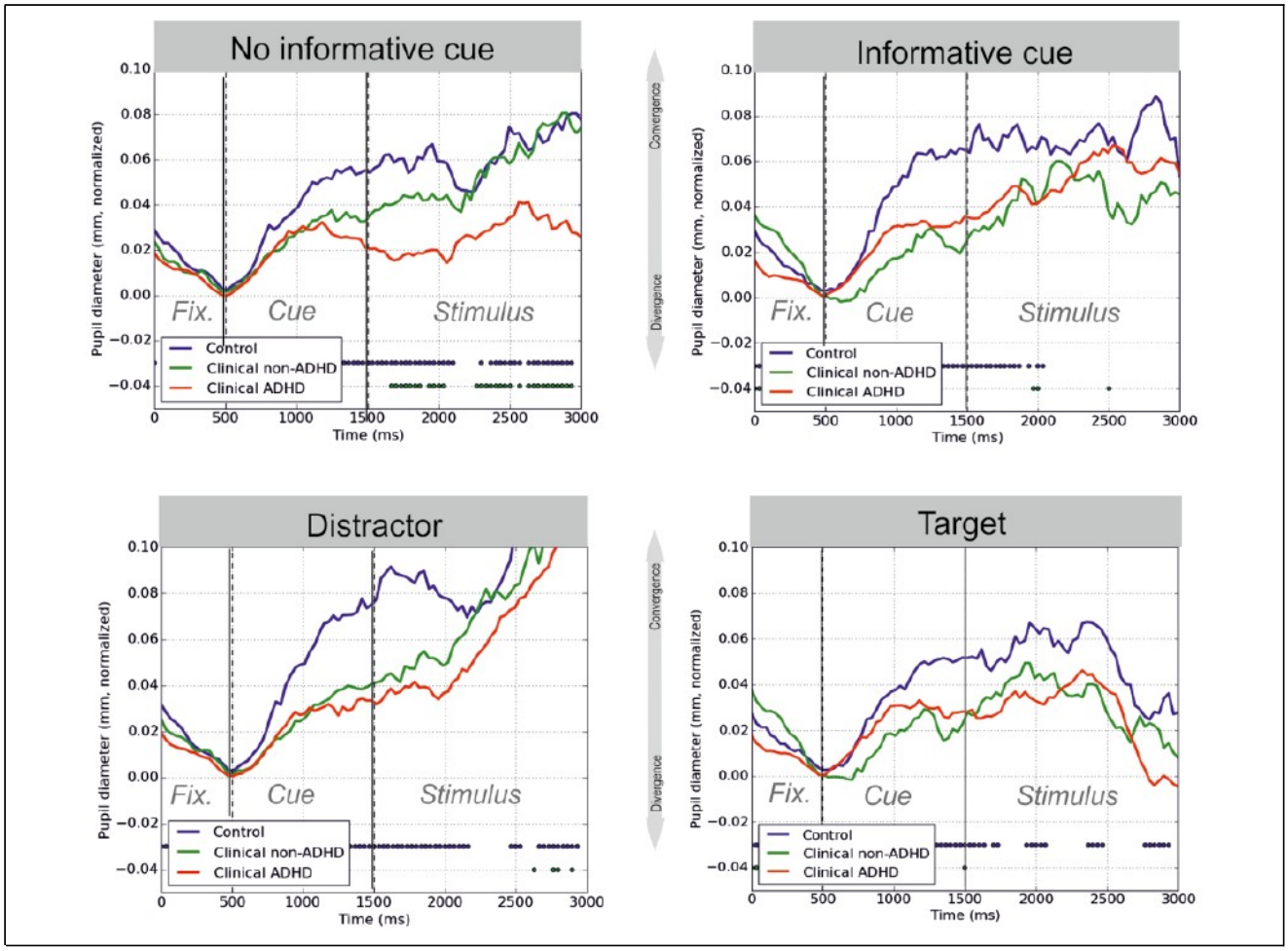


**Figure 8.** Average modulation of pupil diameter.
*Note.* Blue traces denote pupil responses from healthy control participants. Green and red traces represent the pupil responses from Clinical control and ADHD participants, respectively. Labeling as in Figure 4.

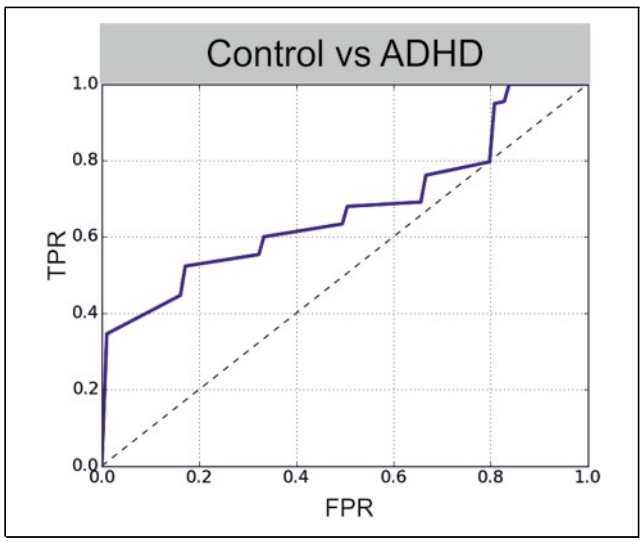


**Figure 9.** ROC curves based on pupil size.

*Note.* ROC = receiver operating characteristic. TPR = true positive rate; FPR = false positive rate.

## Discussion

In this study, we tested eye vergence modulation while performing an attention task as a tool to discriminate ADHD from non-ADHD children. We applied a child-friendly attention task for 10 to 12 min and recorded with a remote eye tracker eye position data from which vergence was calculated. The principal finding is that children belonging to the healthy control group showed clear modulation in the angle of eye vergence whereas children in the clinical groups showed weak to no significant modulation in the angle of eye vergence while performing the attention task. Healthy children were younger than the clinical participants. This, however, may not be relevant for the classification outcomes. At the age of 8 to 9 years, children can follow task instructions in a gaze contingency task (Paus, Babenko, & Radi, 1990). In our task, healthy children performed better than ADHD children. Also, at

these ages, development of binocular coordination is completed, which can be appreciated in the observed vergence responses in healthy children.

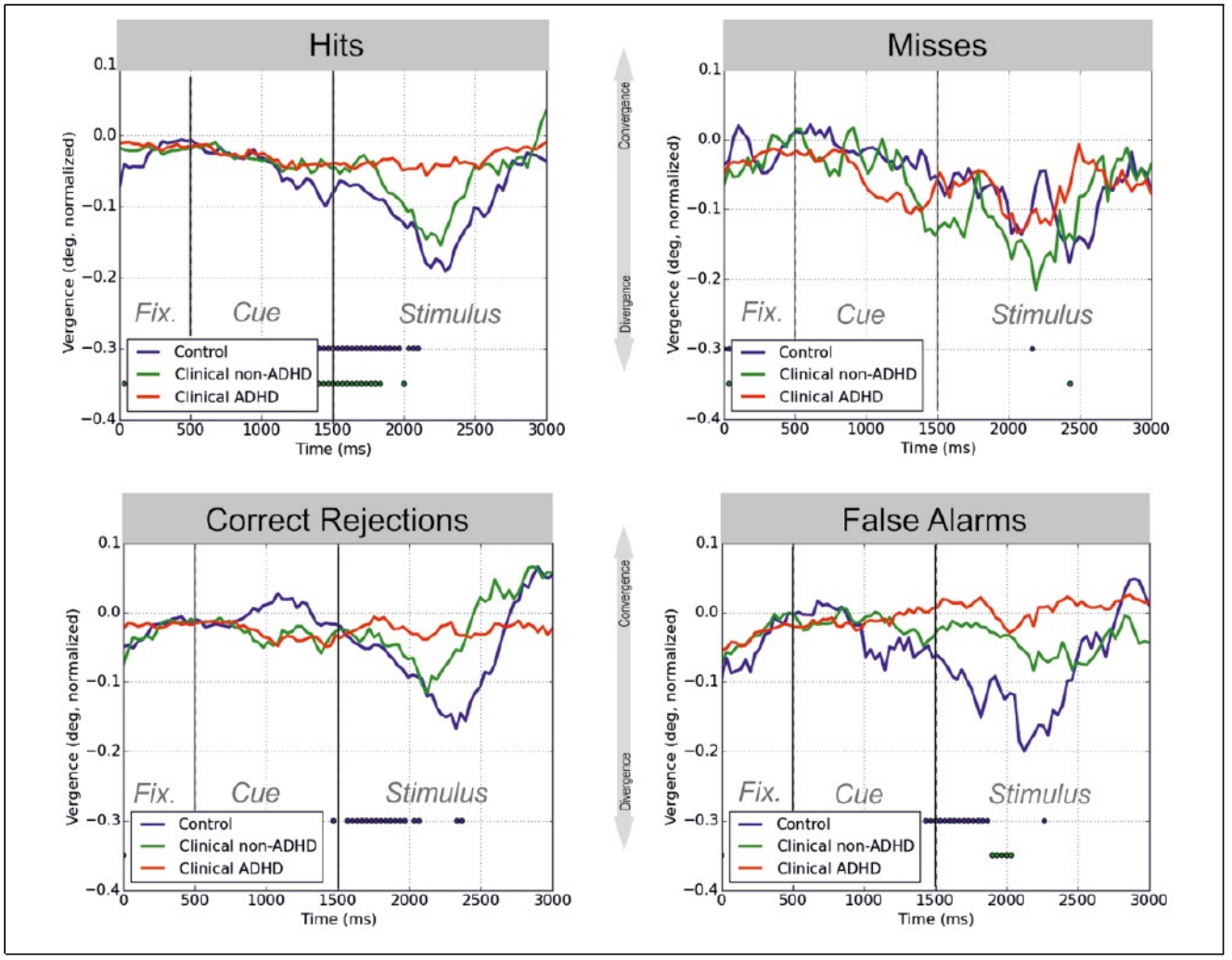


**Figure 10.** Average modulation of the angle of vergence separated by behavioral response outcomes.
*Note.* Labeling as in Figure 4.

The angle of eye vergence decreased during the stimulus period when the target/distractor stimulus was presented. This signifies that the eyes diverged. In addition, the vergence angle from the healthy control group was larger in the informative cue condition than in the no-informative cue condition during the period of cue presentation. These findings agree with our earlier observations of attention-related eye vergence in children (Solé Puig, Pérez Zapata, et al., 2013). Furthermore, we show modest vergence responses in a clinical control group. Even though children of the clinical control group showed, in general, weaker modulation in the angle of eye vergence, there was a small significant difference in vergence between the cue conditions. Children from the ADHD group, however, showed weak vergence responses and no difference in vergence between cue conditions was observed. Thus, ADHD children appear less sensitive to visual stimulation, but they are also vulnerable when orienting attention is required.

The current results confirms our previous findings showing poor attention-related eye vergence in ADHD children (Solé Puig et al., 2015) and that vergence can be a used to discriminate ADHD in children (Lorena Esposito et al., 2016). In the latter study, we evaluated four classes of supervised machine-learning classifiers (in total 138 different models) with a validation set of 232 children of a school cohort. The average accuracy of these models was 90% (minimum: 86.21%; maximum: 95.26%). In the current study, we applied a two-step classifier. This was

necessary because we included a clinical cohort, which compared with healthy controls gave more subtle differences in the angle of eye vergence.

The overall weak modulation in the angle of eye vergence in ADHD children may indicate that the vergence system is less sensitive to visual stimulation. This may explain the absence of clear vergence responses in healthy controls when failing to detect the target (Solé Puig, Pérez Zapata, et al., 2013; current study). The

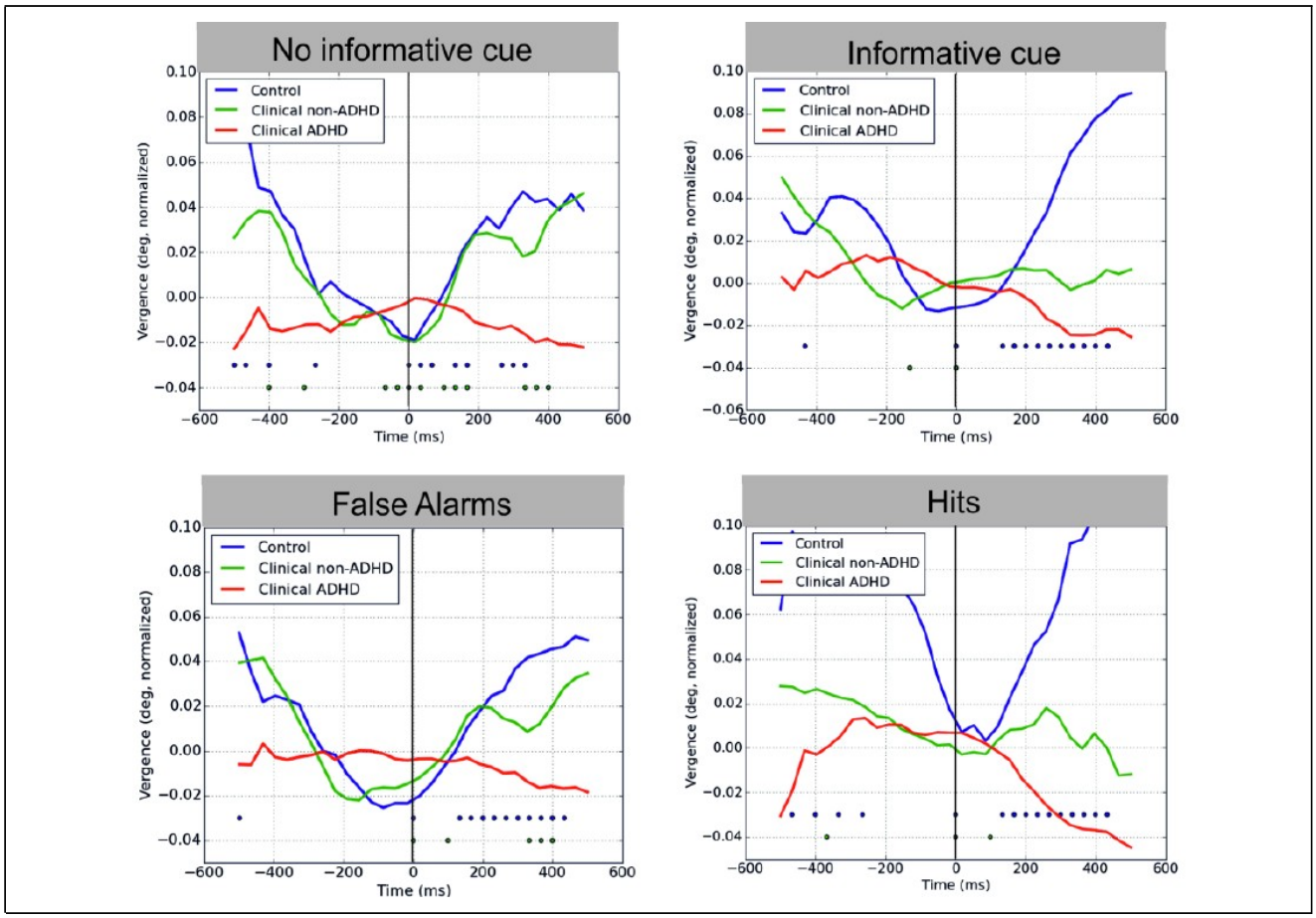


**Figure 11.** Average modulation of the angle of vergence aligned on behavioral responses onset, that is, the moment of button press.
*Note.* Labeling as in Figure 4.

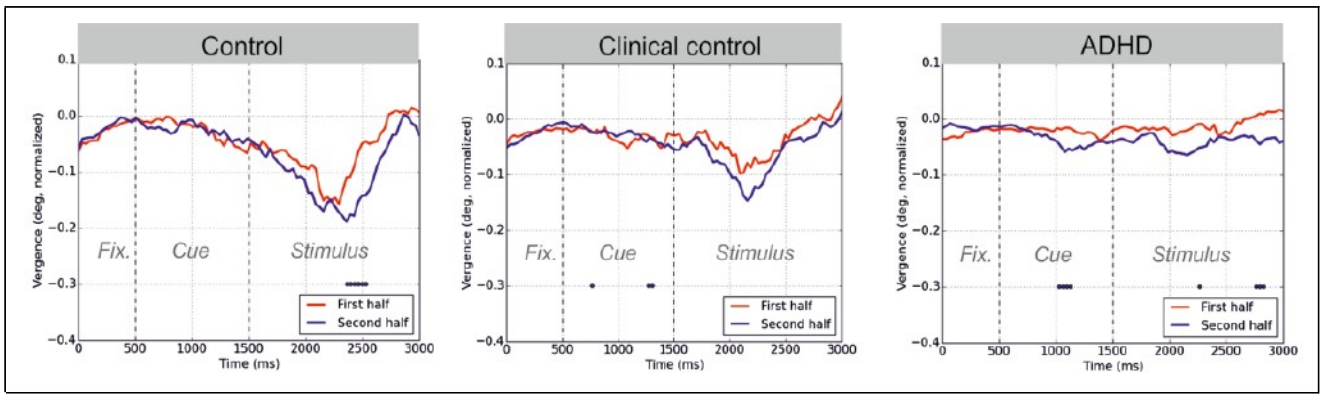


**Figure 12.** Average modulation of the angle of vergence according to task period.
*Note.* Blue and red traces denote average angle of eye vergence from cue and no-cue conditions. Labeling as in Figure 4.

absence of a difference between vergence responses from the informative and no-informative cue condition suggests that attentional control of eye vergence by presumably higher cortical areas is impaired or the vergence system is still immature (Bucci, Nassibi, Gerard, Bui-Quoc, & Seassau, 2012; Kirkby, Blythe, Drieghe, & Liversedge, 2011; Prado, Dubois, & Valdois, 2007).

### *Markers of ADHD*

The clinical diagnosis of ADHD shows considerable levels of concurrent and predictive validity (Faraone, 2005; Faraone et al., 2000). Nevertheless, concerns about diagnostic accuracy persist. The diagnosis has been called "subjective" because it relies on clinician evaluation of

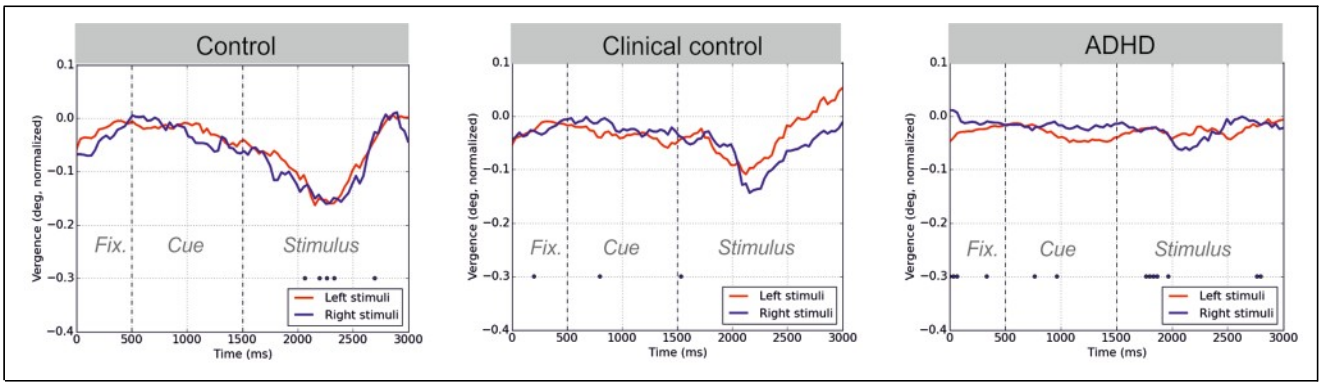


**Figure 13.** Average modulation of the angle of vergence according to stimulus side.
*Note.* Blue and red traces denote average angle of eye vergence from cue and no-cue conditions. Labeling as in Figure 4.

responses from patients, parents, and/or informants. Some suggest that the use of subjective diagnostic procedures leads to the overdiagnosis of ADHD (Bruchmuller, Margraf, & Schneider, 2012; Visser et al., 2014), while other studies have raised concerns about the underdiagnosis of ADHD. In response to such concerns, researchers have sought to develop objective measures to diagnose ADHD.

Much research has examined peripheral biochemical markers. Meta-analyses of these studies indicate that five measures differentiated ADHD and control patients (Norepinephrine [NE], 3-Methoxy-4-hydroxyphenylethylene glycol [MHPG], monoamine oxidase [MAO], zinc, and cortisol; Faraone, Bonvicini, & Scassellati, 2014; Scassellati, Bonvicini, Faraone, & Gennarelli, 2012). Moreover, NE, MHPG, MAO, b-phenylethylamine, and cortisol were responsive to ADHD medications. Meta-analysis also shows that peripheral measures of oxidative stress differ between ADHD and control participants (Joseph, Zhang-James, Perl, & Faraone, 2015). Other approaches to biomarker development for ADHD have used neuropsychological (Ritsner, 2009), electroencephalographic (Snyder, Rugino, Hornig, & Stein, 2015), actigraphy (Dane, Schachar, & Tannock, 2000), structural imaging (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009), and functional imaging (Bush, Valera, & Seidman, 2005) methods. Continuous performance tests (CPTs; for example, Corkum & Siegel, 1993; Homack & Riccio, 2006; Riccio & Reynolds, 2001) have been evaluated in many studies.

Most methods that are currently being used to support the clinical diagnosis quantify symptoms of ADHD. The AULA Nesplora (AULA) is a CPT that shows clear correlations with the Conners' CPT (Díaz-Orueta et al., 2014). AULA reports >90% accuracy at their company website, and may be useful in establishing a differential ADHD diagnosis (Areces, Rodríguez, García, Cueli, & González-Castro, 2016). Quotient reports a cross-validated AUC of 0.716 (unpublished data at company website) based on comparing ADHD patients with healthy controls. They report higher receiver operating characteristic curves (ROCs) that have not been cross-validated. The ability of the QbTest to identify ADHD in children is moderate with sensitivity ranging from 47% to 67% and specificity from 72% to 84% (Hult, Kadesjö, Kadesjö, Gillberg, & Billstedt, 2015; Reh et al., 2015). The adult version of the QbTest gives similar results with an overall correct classification of 72.1% (Edebol, Helldin, Holmberg, & Gustafsson, 2011; Edebol, Helldin, & Norlander, 2013; Söderström, Pettersson, & Nilsson, 2014). Measuring body movements with wireless inertial sensors gives a classification of >95% (O'Mahonya, Florentino-Liano, Carballo, Baca-García, & Artés Rodríguez, 2014) and classification based on microsaccades yields an accuracy of 70% (sensitivity: 59%; specificity: 82%; Fried et al., 2014). The Neuropsychiatric EEG-Based Assessment Aid (NEBA) is an EEG brainwave test for ADHD based on theta/beta ratio (TBR). Integration of NEBA outcomes with a clinician's ADHD evaluations improves diagnostic accuracy from 61% to 88% (Snyder et al., 2015). A study examining the TBR in ADHD and normal children reported a sensitivity of 0.86 and a specificity of 0.57 (Sangal & Sangal, 2015).

So far, no method has shown sufficient sensitivity and specificity when predicting "gold standard" clinical diagnoses of the disorder. According to the task force of the World Federation of ADHD (WF-ADHD), a useful biomarker needs to meet the following criteria (Thome et al., 2012): sensitivity exceeding 80%, specificity exceeding 80%, the putative biomarker is reliable, reproducible, inexpensive, noninvasive, easy to use, and has been confirmed by at least two independent studies. The use of eye vergence recordings to classify ADHD meets all of the WF-ADHD criteria but needs to be confirmed by additional studies. So far, the marker could be a diagnostic support tool to complement clinical ADHD diagnosis. The marker tool could demonstrate attention deficits in children without showing clear symptomology or vice versa. It could be useful for the assessment of borderline cases when ADHD diagnosis is difficult to make. Also, the objectivity may help to convince patients of the outcome of the clinical diagnosis and to adhere to their treatment protocols. Furthermore, as the method assesses attention, it may be helpful for diagnosing children who show little hyperactivity symptoms—for instance, girls. The test uses a child-friendly frog game, and the outcomes alone could be used to support ADHD diagnosis but classification accuracy remains to be tested.

### *Binocular Vision Difficulties in ADHD*

The finding of altered vergence in ADHD is not surprising given that binocular vision in ADHD children is impaired. Convergence insufficiency (CI), which is a common binocular disorder characterized by the inability to obtain a single visual field while working at a near distance (Borsting et al., 2011; Borsting, Rouse, & Chu, 2005; Borsting et al., 2003; Rouse et al., 1999), is prevalent in children with ADHD (Granet, Gomi, Ventura, & Miller-Scholte, 2005), and has been shown to relate to attention problems (Borsting et al., 2003; Poltavski, Biberdorf, & Petros, 2012; Rouse et al., 2009). The primary source of CI symptoms may be accommodative insufficiency (Marran, De Land, & Nguyen, 2006) and thus occurs at close distances. In our study, the target distances fell well outside the range of distances of CI for children. This means that our observed disruption in vergence modulation does not reflect CI but represents a novel role of eye vergence in visual attention (Solé Puig, Pérez Zapata, et al., 2013; Solé Puig, Puigcerver, et al., 2013).

### *Role for Vergence in Attention*

Top down attention originates in the frontal cortex (Arnsten & Rubia, 2012; Bisley, 2011; de Zeeuw, Mandl, Hulshoff Pol, van Engeland, & Durston, 2013; Thompson, Biscoe, & Sato, 2005) and reduced or distorted activation in prefrontal regions of ADHD patients has been observed (Bush, 2011; Di Michele, Prichep, John, & Chabot, 2005; Kraina & Castellanos, 2006; Soliva, 2011; Valera, Faraone, Murray, & Seidman, 2007). The frontal cortex controls eye vergence (Gamlin & Yoon, 2000) and may be the source of our observed attention-related vergence. Thus, reduced functionality of the frontal cortex in ADHD patients may produce a distorted modulation in attention-related vergence. The frontal cortex is connected to the reticular formation in the brainstem, where premotor neurons reside that control eye vergence (Chaturvedi & Van Gisbergen, 2000; Coubard, 2013; Gamlin, 2002; Judge & Cumming, 1986; Mays, 1984; Suzuki, Suzuki, & Ohtsuka, 2004). The reticular formation of the brainstem forms part of a broader pathway, including the frontal and parietal regions of the cerebral cortex (Alvarez, Jaswal, Gohel, & Biswal, 2014; Gamlin & Yoon, 2000; Gnadt & Mays, 1995) and cerebellum (Alvarez et al., 2014; Nitta, Akao, Kurkin, & Fukushima, 2008; Versino, Hurko, & Zee, 1996). These structures, which form part of the attention system of the brain, also are involved in the control of vergence. This suggests that the neural circuits controlling vergence and attention are closely linked.

### *Study Limitations and Future Research*

Together with our earlier study (Solé Puig et al., 2015), this is the second study validating attention-related vergence in children as an objective marker for ADHD diagnosis. In this study, we have 19.2% false negative cases which are ADHD children classified as not-ADHD. The relatively high number of false negatives may be because of shared symptomology. The methods assess attentional processing, which is impaired in ADHD patients but also in the clinical controls, which were patients referred to the hospital for learning and/or conduct problems. ADHD is a multifaceted neurodevelopment disorder and therefore more testing is desirable using different cognitive tasks. The ability of eye vergence to classify ADHD presentation "specifiers" (subtypes) and the effect of medication on vergence responses needs to be investigated in future studies. The findings of disrupted eye vergence in ADHD children agree with the general impression of poor binocular control in children with attention problems. However, further studies are needed to assess role of eye vergence in attention.

## Conclusion

Our observations show that attention-related vergence differs between healthy controls, clinical controls, and children with ADHD. Solely based on features of the modulation in the angle of eye vergence, we were able to classify ADHD from healthy and clinical control participants with high precision. The results therefore

clearly demonstrate that assessment of vergence during a child-friendly attention task is a useful, observer-independent tool supporting clinical diagnosis of child ADHD.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: F.L.E. and I.M. are employees of Braingaze, and H.S. is co-founder of Braingaze.

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