Article

Eye Vergence Responses During an Attention Task in Adults With ADHD and Clinical Controls

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Abstract

Objective: ADHD patients show poor oculomotor control and recent studies show that attention-related eye vergence is weak in ADHD children. We aimed to assess vergence as a potential diagnostic biomarker for ADHD in adults. **Method:** We assessed the modulation in the angle of vergence while performing an attention task ($N = 144$), comparing the results for adults previously diagnosed with ADHD ($N = 108$) with age-matched clinical controls ($N = 36$). **Results:** Significant differences in eye vergence response modulation between clinical controls and ADHD patients were documented. Diagnostic test accuracy was 79%. **Conclusion:** In combination with an attention task, eye vergence responses could be used as an objective marker to support the clinical diagnosis of adult ADHD. *(J. of Att. Dis. 2021; 25(9) 1302-1310)*

Keywords
adults, ADHD, eye vergence, diagnosis, biomarker, binocular

Introduction

ADHD is characterized by a low degree of attention, distractibility, excessive motor activity, and the incapacity to inhibit inappropriate actions (American Psychiatric Association, 2014). It is considered a public health concern due to its high prevalence, affecting 3% to 7% of children globally (Polanczyk et al., 2007; Sayal et al., 2018). However, in the past decade, it has also become clear that ADHD is a chronic disease that continues into adulthood (Caye et al., 2016; Zalsman & Shilton, 2016). About 50% to 60% of ADHD cases persist into adult life when it is associated with clinical and psychosocial impairment. ADHD in adults causes a wide range of problems (e.g., employment difficulties, drug abuse, criminality, and increased mortality) and represents a heavy societal and economic cost (Knecht et al., 2015; London & Landes, 2016; Young & Goodman, 2016). Some of these problems and effects can be prevented or reduced if ADHD patients receive timely and appropriate treatment. For this purpose, early and accurate diagnosis of ADHD in adults is essential.

The diagnosis of ADHD is currently determined based upon a cluster of symptoms from the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*; American

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Psychiatric Association, 2013) guidelines. In children, hyperactivity, impulsivity, and inattention are the core symptoms of ADHD. In adults, these core symptoms are also present but their expression is more subtle. This makes the diagnosis of adult ADHD challenging, especially as several other psychiatric and medical entities, such as anxiety, dementia, substance abuse, depression, and bipolar disorders show similar symptomatology. Moreover, the symptoms must have started prior to 12 years of age, which is difficult to confirm retrospectively from adulthood (Brus et al., 2014; Young & Goodman, 2016).

Recent studies show evidence for eye vergence analysis as an objective marker for ADHD in children (Sole Puig et al., 2016; Varela Casal et al., 2018). Eye vergence is the movement of both eyes in opposite directions and has a role in depth perception. However, eyes also converge during orienting attention, as evidenced by visual event-related potentials at parietal locations (Sole Puig et al., 2016). Based on the recordings of attention-related eye vergence during an attention task, children with ADHD can be differentiated from controls with high (92%) accuracy (Varela Casal et al., 2018). Therefore, we hypothesized that we would find a significant difference in eye vergence between ADHD and non-ADHD participants in adults also. In this study, we aimed to assess attention-related eye vergence as a marker for ADHD in adults. We evaluated the modulation in the angle of vergence in adults previously diagnosed with ADHD while performing an attention task and compared the results with age-matched non-ADHD clinical comparison participants. Next, machine learning methods were applied to classify ADHD based on the differential features of the eye vergence responses.

Method

Participants

In total, 144 adults (90 males and 54 females) participated in this study. Patients were recruited through the Hospital Vall d' Hebron in Barcelona, Spain, Nightingale Hospital in London, UK, and ADHD Clinic in Oxford, UK. Of the participants, 108 had received an ADHD diagnosis ($M \pm SD$: 29.4 ± 12.5 years). Most of the ADHD patients were taking medication for ADHD. The non-ADHD group (made up of clinical participants with conduct disorder diagnoses) were sex/age-matched adults ($N = 36$; $M \pm SD$: 26.9 ± 8.4 years).

All the clinical diagnoses of ADHD were made by clinical psychiatrists using the American Psychiatric Association's *DSM*, Fourth Edition, Text Revision criteria, including a psychiatric and psychological interview to assess the presence of symptoms of inattention, hyperactivity, and impulsivity during the previous 6 months. Psychiatrists assessed adult ADHD with the semistructured interview DIVA 2.0 (Ramos-Quiroga et al., 2019). Furthermore, psychologists evaluated ADHD severity using the Wender Utah Rating Scale, Conners' Adult ADHD Rating Scale, the ADHD Rating Scale, and a neuropsychological assessment. In addition, symptom onset before 7 years of age and the persistence of clinical dysfunction in at least two settings were used as diagnostic criteria. Differential diagnoses were considered as part of a complete clinical psychiatric evaluation.

No discrimination was made according to subtypes of ADHD as previous studies have not shown differences between the vergence responses of ADHD subtypes (Varela Casal et al., 2018).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) aged between 18 and 65 years at recruitment, (b) a diagnosis of ADHD without mental retardation, (c) fluency in Spanish or English, and (d) signed informed consent for participation in the study. The exclusion criteria were (a) a history of head injury with loss of consciousness or other neurological illness, (b) mental retardation or other significant disorders such as a pervasive developmental disorder, and (c) visual or auditory problems.

Ethics Statement

Before participating in the study, written informed consent from the patients enrolled in our study was obtained in accordance with the Helsinki Declaration. The study was approved by the ethics committees of the University of Barcelona and the Hospital Vall d' Hebron.

Apparatus

We used the BGaze system (Braingaze SL, Mataró, Spain) for presenting the visual stimuli synced with a remote eye tracker (X2-30, Tobii Technology AB, Sweden). The screen size (AOC) was 21.5 in. Participants viewed the screen from a distance of 50 to 60 cm.

Procedure

Participants sat in a dimly lit room of the hospital or clinic in front of the PC monitor (width = 503 mm and height = 375 mm) at a distance of 55 cm. During the totality of the task, a chin rest was used to prevent large head movements. The eye tracking equipment was calibrated (5 points, binocular) for each participant at the beginning of the experiment by BGaze eye tracking software. Before starting, the task was explained by the experimenter and all participants practiced with 20 trials to become familiar with the task. The entire procedure took approximately 15 min to complete.

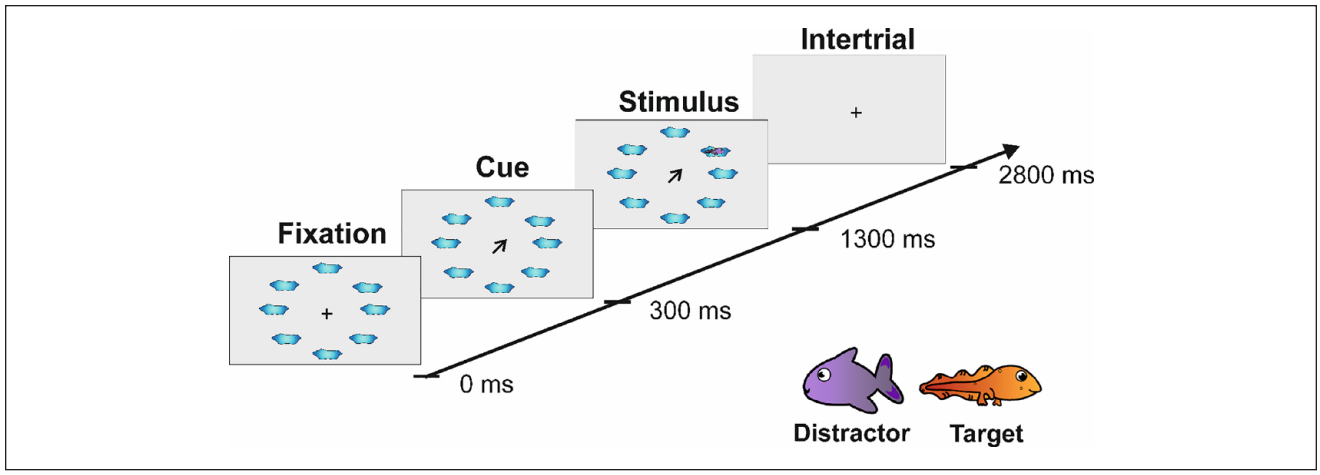

Figure 1. Task design and stimuli used.
Note. The panels illustrate the sequence of the different visual presentations on the monitor during a trial. In this example, a central arrow cues the location of the upcoming distracter (fish). The target is an image of a tadpole.

Visual Cue Experiment

To assess orienting visual attention, we used a more demanding paradigm adapted from our child paradigm in which the participants were required to discriminate cartoon images of a tadpole from a fish (Figure 1). Each trial started with the presentation of a fixation point in the middle of the monitor surrounded by eight possible target locations (images of pools; size of 2 × 3°; eccentricity of 6°). After 300 ms fixation, the fixation cross was replaced by an arrow or an x mark. The arrow pointed to one of the eight pools and served as a cue to inform the observer about the location of an upcoming image of a tadpole or fish (informative cue condition). In the case of an x mark, the observer was unaware of the target location (noninformative cue condition). A total of 128 trials were performed. Fifty percent of these contained an informative cue and the distribution of trials with different cue conditions was random. The fish or tadpole cartoon was presented for 1,500 ms. For the length of the trial, the observer was required to maintain fixation at the central cue image and was instructed to respond by pressing a button when a tadpole was presented while refraining from responding when a fish appeared. The following trial started automatically when the previous trial ended.

Data Analysis

In total, there were 12,960 (6,480 noninformative cue trials and 6,480 informative cue trials) trials in the ADHD group and 4,320 (2,160 noninformative cue trials and 2,160 informative cue trials) trials in the clinical control group. The angle of eye vergence was obtained using the cross product of both gaze vectors. Gaze vectors correspond to the lines between the 3-D eye positions and 2-D gaze positions in a common coordinate system. Samples with a low validity score according to the Tobii eye tracker software were set as missing (˜10%–20% of the samples). Low validity scores usually occur during saccades or blinks. Validity scores are given by the Tobii X2-30 tracker as an integer ranging from 0 to 3, where 0 means the tracker has adequately recorded the pupils of both eyes and a number 3 that means that it was unable to detect any eye metrics. This score is computed as a function of which and how Purkinje images were detected by the device (see the tracker documentation). In our signal-cleaning process, we discarded all those signals that did not have a score of 0 points. This happened in about 20% of the total recorded samples.

For the rest of the samples, the pointwise median of all trials was calculated for the conditions and groups separately. The median was selected, instead of the mean, to mitigate the effect of outliers and thereby reduce bias. To decrease irregularities, the obtained signal was then smoothed, using a moving median and thereafter a moving average with a 200 ms window.

Regarding the statistical analysis, the *t* test was used for the comparison of the behavioral responses. For the comparison of vergence responses, bootstrapping and permutation analyses were performed to simulate pointwise distributions of the medians. Vergence was evaluated on a sample-by-sample basis. Taking into account that large sets of time series are used as input data, machine learning was applied for inference of the vergence data for classification of patients because it is able to capture these complex relationships.

A feature selection strategy on vergence signal was followed to obtain relevant parts of the signal that were later used to train a random forest classifier for ADHD prediction. Both methods were tested using a participant-wise, leave-one-out (LOO) cross-validation procedure on 80% of

the original data set (24 controls and 73 ADHD adults). The final validation was done with the remaining 20%, which up till that point had been unseen by any stages in the model (eight controls and 35 ADHD adults).

Results

Behavioral Performance

For non-ADHD participants, the average hit rates for targets were 96.0% and 94.4% and the correct rejection rates for the distracters was 87.4% and 94.2% in the informative and noninformative cue conditions, respectively. In the ADHD group, the hit rates were 96.8% and 96.4%, and the correct rejection rates were 88.8% and 90.9% in the informative and noninformative cue conditions, respectively. The average reaction times in the non-ADHD group were 284 ms and 283 ms in the informative cue and noninformative cue conditions, respectively. In the ADHD group, this was 303 ms (informative cue condition) and 270 ms (noninformative cue condition). The reaction times were significantly ($p < .01$) different between the non-ADHD and ADHD groups both in the informative cue and noninformative cue conditions. The variability in reaction times between both groups was weakly different between non-ADHD and ADHD participants in the noninformative cue condition (302 ms vs. 316 ms; $p = .04$) but not in the informative cue condition (334 ms vs. 344 ms; $p = .1$).

Eye Vergence Responses

We measured the angle of eye vergence as a function of time. An increase in the angle by the inward movement of the eyes signifies convergence and a decrease in the angle where both eyes move outward means a divergence response (Figure 2). The results show that the angle of eye vergence does not remain constant and appears to decrease throughout the trial, that is, the eyes diverge. In both cue conditions, this divergent response is noticeable in non-ADHD participants and to a lesser extent in ADHD patients (Figure 3). The divergent vergence response in controls appears to start during the cue period and continue all the way through the stimulus period where the difference in vergence responses between the two clinical populations becomes significant (black dots in upper row in Figure 3). Besides the tendency to diverge, during the cue period there is a brief convergence of the eyes in the informative cue condition. This is particularly evident in the non-ADHD participants but not in the ADHD patients (Figure 3). This differential pattern is displayed in Figure 3, which shows the average population mean according to group and conditions. The time points where vergence responses significantly ($p < .05$) differ are indicated by the gray bar in the graphs.

A difference in modulation of vergence response is what is needed to be able to classify individual patients, which was the aim of the current study. Therefore, we had to apply machine learning techniques that searched for differences in the vergence responses, as we had done in a previous study of ADHD children (Varela Casal et al., 2018). The model estimated the average ADHD probability for control participants (0.3462) and ADHD participants (0.6630) in the validation sample. A t test shows that this difference is significant, with $p < 2.2 \times 10^{-16}$. This convergence response has been reported before and is suggested to relate to the orientation of visuospatial attention (Sole Puig et al., 2016).

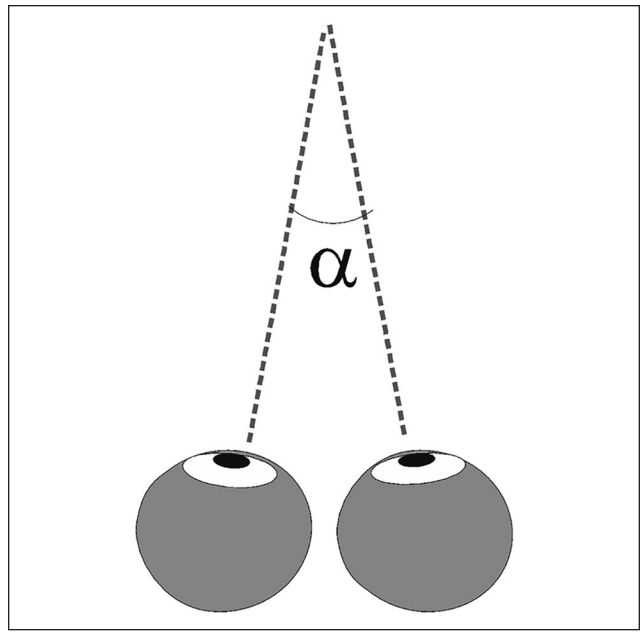

Figure 2. To obtain a binocular image, the eyes focus on a single point in space where the angle of vergence (α) is formed by the two gaze lines.

ADHD Classification

The machine learning model we built was divided into two stages: feature selection and classification. In the feature selection stage, the aim was to test which parts of the signal were relevant for ADHD classification. We took vergence signal data as well as their corresponding perturbations both by participant age and sex as potential features. Then, an LOO loop was used to apply univariate goodness-of-fit tests for such collections of points. At each iteration, all the signals corresponding to one participant were removed from the total data set. Then, an additional random subsampling was performed to make sure that we produced a sample that was class-balanced (i.e., we had approximately the same amount of control and ADHD signals per LOO iteration). On this sample, pointwise goodness-of-fit tests were performed on the signal and each time a point produced a p value of $p < .2$, when tested against diagnosis, such point was selected as a useful feature. At the end of the LOO loop,

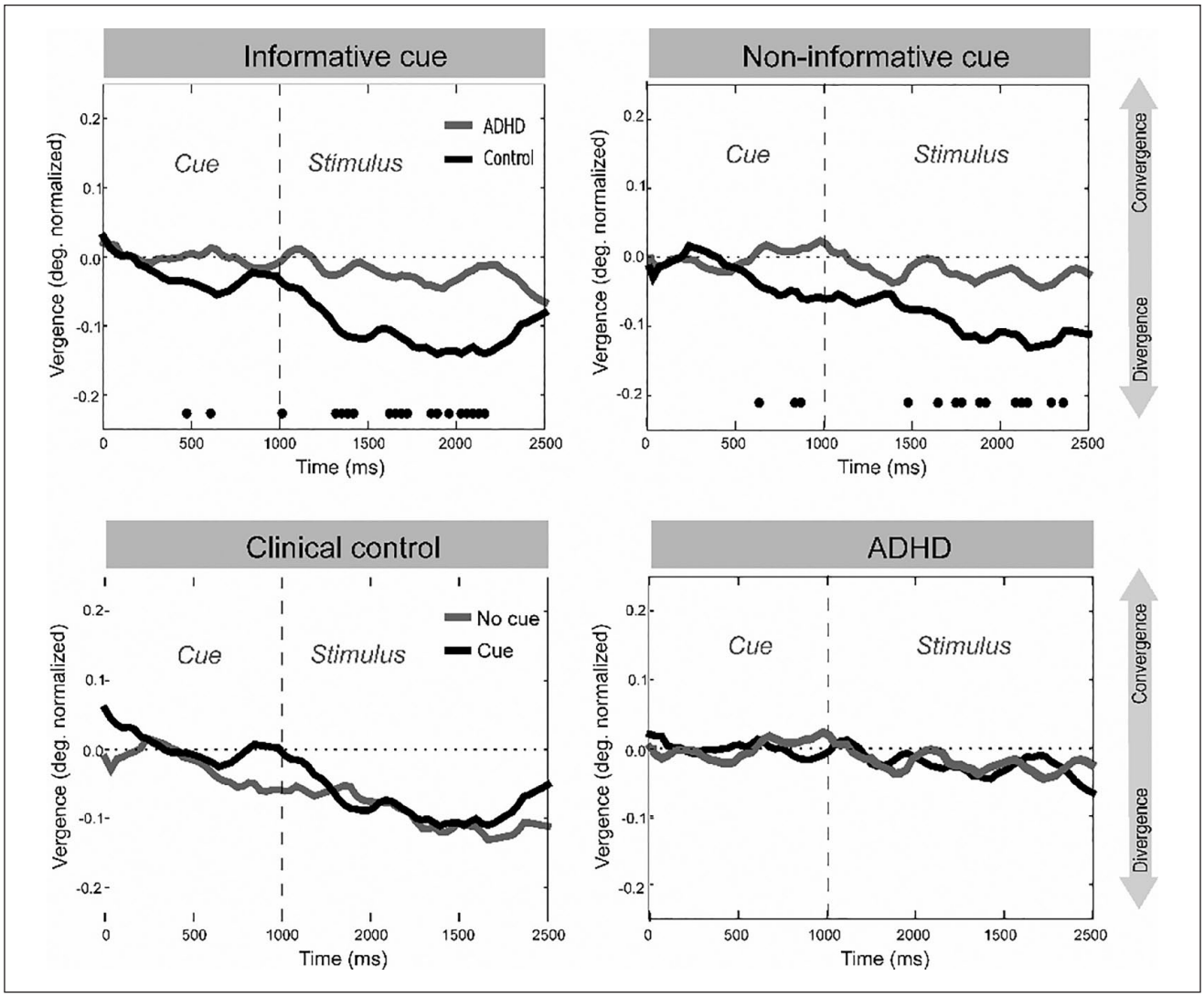

Figure 3. Average modulation of the angle of vergence.
Note. In the upper panels, the black and gray traces denote average angle of eye vergence from clinical control participants and ADHD patients, respectively. In the lower panels, they represent the vergence responses from cue and no cue condition, respectively. Vertical dotted lines indicate onset of the stimulus (target or distracter). The lower dots indicate the time points when vergence responses significantly ($p < .05$) differ between the shown conditions.

a collection of points and the times they were deemed significant was produced. This means that each point would appear, at most, as many times as participants are in the study. Those points that were selected at least in 75% of total iterations were considered the final selected features. Let this feature set be called F.

In the second stage, a second LOO procedure was used to train a random forest classification model with the feature set F. At each iteration, all signals from Participant S would be removed from the sample and the remaining ones would be resampled to produce a class-balanced subsample, just as with the previous stage. Then, the model would be trained with this subsample and tested over the signals corresponding to Participant S. We considered that a participant was correctly identified as ADHD or otherwise if the model correctly predicted the class of more than 50% of their signals (i.e., if Participant S is ADHD and the model identified more than 50% of their signals as ADHD signals, then we would consider that the model had correctly identified S as an ADHD participant). This value threshold was selected based on our previous model to classify children, where we tested different random forest classification models (Varela Casal et al., 2018).

The machine learning model that had learned to classify participants was blind to the ADHD status. When we tested the results on the final validation subsample (20% of original data set, as yet unseen by the model), we obtained the following results: ADHD participants were correctly

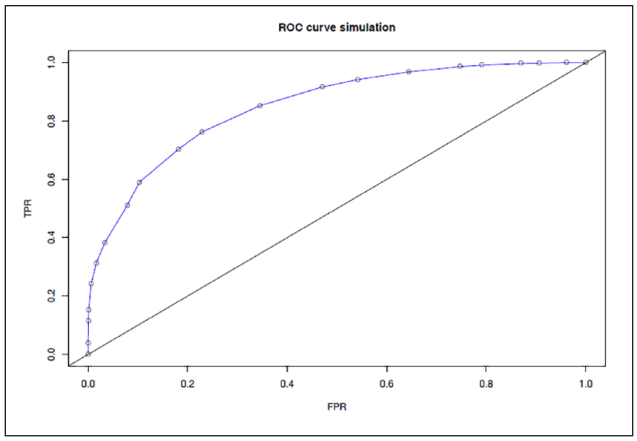

Figure 4. ROC curve for classification on validation sample.
Note. ROC = receiver operating characteristic; TPR = true positive rate; FPR = false positive rate.

differentiated from non-ADHD participants with 79% (95% CI = ±6.6%) accuracy (area under the curve [AUC] = 0.77). We documented a false positive rate (i.e., non-ADHD participants classified as ADHD) of 25.00% and a false negative rate (ADHD classified as non-ADHD) of 20.55% (Figure 4).

Discussion

We assessed attention-related vergence responses in adults during a visuospatial attention task. Our results show differences in eye vergence response modulation between ADHD participants and non-ADHD participants, which allow for discrimination between them. This is in agreement with previous observations in children (Sole Puig et al., 2016; Varela Casal et al., 2018). During the attention task, eyes slowly diverge; notwithstanding, brief convergence responses are observed when orienting attention. An undifferentiated vergence response between the informative and noninformative cue conditions was observed in ADHD patients only. This is in agreement with previous reports and may point to a possible impairment in the attentional control of eye vergence by higher cortical areas (Varela Casal et al., 2018).

In this study, the response modulation (for both divergence and convergence) was stronger in the non-ADHD participants than in adult ADHD patients. More specifically, the vergence response from non-ADHD participants deviates from zero starting from the onset of the trial, whereas vergence responses from ADHD patients tend to fluctuate around zero. This may be explained by the existence of a close relationship between the neural circuits that participate in the control of attention and eye vergence. The frontal cortex is involved in attention processes (Arnsten & Rubia, 2012; Bisley, 2011) and it also has a role in eye vergence (Gamlin & Yoon, 2000). The premotor neurons that control eye vergence are located in the reticular formation in the brainstem that is connected to both frontal and parietal cortices as well as the cerebellum, all of which also participate in the regulation of attention function (Alvarez et al., 2014; Chaturvedi & Van Gisbergen, 2000; Coubard, 2013; Gamlin, 2002; Gamlin & Yoon, 2000; Gnadt & Mays, 1995; Judge & Cumming, 1986; Mays, 1984; Suzuki et al., 2004). Therefore, alterations in the modulation of attention-related eye vergence may be a product of dysfunction at these circuits in ADHD patients. Furthermore, a strong relationship between binocular rivalry transitions and the severity of ADHD symptoms in adult ADHD patients has been reported, strengthening the case for an association between the processes that control binocular eye movements and attention (Jusyte et al., 2018).

Eye vergence relates to and possibly has a role in attentional selection (Sole Puig et al., 2016). Part of the population of the retinal ganglion cells project to the locus coeruleus and dorsal raphe nucleus located in the midbrain. These last two structures are the main norepinephrine and serotonergic nuclei, respectively, and modulate neural activity through their substantial innervation to the forebrain. The neuromodulators are critical regulators of arousal and attention, and alterations in norepinephrine and serotonergic modulated neuro-circuitry are associated with neuropsychiatric disorders such as ADHD. It is possible that via the activation of neurons in the locus ceruleus and dorsal raphe nucleus, vergence eye movements control attention and that disrupted vergence responses result in poor attention, which is a hallmark of ADHD.

However, the differences in vergence responses observed in our study are small compared with previous observations (Sole Puig et al., 2016; Varela Casal et al., 2018). Partly, this could relate to the fact that we tested clinical controls that have weaker vergence responses than healthy controls (Varela Casal et al., 2018). In addition, the use of a remote eye tracker, instead of a head-mounted one, and different visual stimulation may cause variances in vergence responses. Nevertheless, changes in distance of the eyes to the screen, which induce vergence eye movements, are assumed to be negligible because of the head stabilization by the chinrest. Moreover, the calculation of vergence angles is corrected for viewing distance. Earlier studies have ruled out a possible effect of changes in pupil size (Sole Puig et al., 2016; Varela Casal et al., 2018).

Currently, the diagnosis of ADHD is clinical, based upon criteria established by classification systems such as the *DSM-5*. Authors have raised their concerns regarding this practice and the possibility of under- or overdiagnosis of this disorder (Sciutto & Eisenberg, 2007; Taylor, 2017; Young & Goodman, 2016), motivating research into more "objective" measures that could contribute to improving diagnostic accuracy. Furthermore, in adult patients, objective measures that support the clinical assessment of ADHD

symptoms are desired as the expression of core symptoms may be weaker in this age group than in children.

Most of the existent objective methods are designed to measure the level of symptoms presenting in a patient. For instance, the adult version of the QbTest quantifies hyperactivity by measuring head and body movements (Edebol et al., 2013; Söderström et al., 2014). However, ADHD adults have reduced activity compared with children and hyperactivity is not present in all participants with ADHD. The adult version of the QbTest has an overall correct classification of 72.1% (Edebol et al., 2013; Söderström et al., 2014). Other types of diagnostic methods have shown similar limitations in discriminating ADHD adults from controls. A previous study using age and sex-matched controls showed a correct diagnostic classification rate of 74% for the Conners' Continuous Performance Test and a correct classification rate of 72% for the Flicker Task (Cohen & Shapiro, 2007). With regard to genetic, pharmacogenetic, and biochemical markers for the diagnosis of ADHD, a recent meta-analysis suggested that certain polymorphisms of the BAI1-associated protein 2 may be distinctly associated with adult ADHD, as is also the case for lower serum levels of docosahexaenoic acid (DHA) in ADHD adults compared with controls. However, the same authors clarified that at this time there are not enough studies on these biomarkers to determine their utility in adult ADHD diagnosis (Bonvicini et al., 2016).

By measuring eye vergence during an attention task, we report a test accuracy of 79% for the differentiation of ADHD patients from clinical controls. Our current results confirm previous findings in children (Varela Casal et al., 2018), showing good classification properties, in line with the diagnostic accuracy that has been previously recommended for biomarkers for ADHD (Thome et al., 2012).

To the best of our knowledge, this is the first study evaluating attention-related eye vergence as a diagnostic marker for ADHD in adult participants. This finding is relevant for clinical practice. We describe a test involving a novel, noninvasive, reproducible, and easy to use method, answering in this way to the requirements formulated by an expert task force consensus report on potential biomarkers for ADHD (Thome et al., 2012). Finally, another strength is that this test relies on the objective measurement of underlying neural processes, which is an ideal characteristic for a diagnostic biomarker.

Nevertheless, despite the encouraging results, this study has some limitations. The use of clinical controls, as opposed to the recruitment of healthy controls, may have provided more subtle differences in the angle of eye vergence between ADHD and non-ADHD groups. Other potential limitations include overfitting, implying artificial increase in performance although we have employed a large-sample method (thousands of trials) to reduce this risk, or that findings could reflect a subtle increase in head motion in ADHD participants. However, this is unlikely, considering that our study employed the use of a chinrest and artificial intelligence to control for possible confounders. In this study, a device with a 30-Hz sampling rate was used. Although it is true that a higher sampling rate could allow for a more detailed data analysis, vergence responses are relatively slow eye movements that a 30-Hz eye tracker can capture. In fact, this same device has been used previously in similar studies (Esposito & Supèr, 2018, 2019; Varela Casal et al., 2018). Furthermore, it is not known how pharmacological treatment for ADHD could affect vergence responses; however, this factor is unlikely to explain our findings as they are similar to what has been reported in a similar study with children who were not taking medication (Varela Casal et al., 2018). In addition, our findings still require confirmation by another independent study. Moreover, further research is needed to answer whether attention-related vergence is also disrupted in patients with other psychiatric or medical disorders presenting with ADHD-like symptomatology and whether vergence studies could be used for differential diagnosis.

Conclusion

Our observations show that attention-related vergence differs between ADHD patients and clinical controls. Based on these vergence responses, adult ADHD patients could be discriminated from clinical controls. The findings show that assessment of vergence responses during an attention task is a promising observer-independent tool that could support the clinical diagnosis of ADHD in adults.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Flavia Lorena Esposito and Imanol Morata are employees of Braingaze. Hans Supèr is cofounder of Braingaze.

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