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BLAST paradigm: a new test to assess brief attentional fluctuations in children with epilepsy, ADHD and normal developing children

M. Thieux ^{a,b}, J. Jung ^{a,c}, R. Bouet ^a, D. Gerard ^d, P. R. Bauer ^a, O. Bertrand ^a, M. Perrone-Bertolotti ^e, A. Arzimanoglou ^{a,b}, P. Kahane ^{f-g}, J-P. Lachaux ^{a*}, J. De Bellescize ^{b*} and V. Herbillon ^{a,b*}

a INSERM, U1028, CNRS, UMR5292, Lyon Neuroscience Research Center, (Lyon, France); **b** Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, Member of the European Reference Network on Rare and Complex Epilepsies EpiCARE, Hospices Civils de Lyon and University Lyon (Lyon, France) ; **c** Department of Functional Neurology and Epileptology, Member of the European Reference Network on Rare and Complex Epilepsies EpiCARE, Hospices Civils de Lyon and University Lyon (Lyon, France) ; **d** Department of Developmental Psychopathology of Child, Hospices Civils de Lyon (Lyon, France) ; **e** University Grenoble Alpes, CNRS, LPNC, (Grenoble, France); **f** University Grenoble Alpes, Inserm, CHU Grenoble Alpes, GIN (Grenoble, France); **g** Department of Neurology, CHU Grenoble-Alpes (Grenoble, France) ; * these authors contributed equally to this work.

Corresponding author: Marine THIEUX (marine.thieux@live.fr)

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Abstract

Background: Pure attentional deficits are still underdiagnosed in children with epilepsy. While Attention Deficit Hyperactivity Disorder (ADHD) is historically the most studied cause of attentional disorders, an important number of children with epilepsy and attentional complaints do not fully meet the DSM-V criteria for ADHD and may be excluded from specific care. Clinical tools currently available are insufficient to detect more subtle but clinically relevant attentional fluctuations.

Objective / Methods: The recently developed Bron-Lyon Attentional Stability Test (BLAST) was used to evaluate brief attentional fluctuations with a high temporal precision. Drawing on two new attentional indices we evaluated spontaneous fluctuations of response accuracy and timing, underlying attentional stability. The main objective was to assess attentional stability in children with: i) epilepsy with comorbid ADHD, ii) epilepsy without comorbid ADHD, iii) ADHD not medicated and without epilepsy and iv) normal development. Further objectives were to assess the main determinants of attentional stability in those groups, including the effect of factors related to the epileptic condition.

Results: In 122 children with epilepsy (67 with comorbid ADHD), 52 children with ADHD and 53 healthy controls we demonstrated: lower attentional stability in both the epilepsy and the ADHD groups compared with healthy children. In children with epilepsy, BLAST scores were negatively associated with earlier seizure onset and AED polytherapy, while the seizure frequency, epilepsy duration or type did not influence BLAST scores.

Conclusions: This study demonstrates that attentional stability is impaired in children with epilepsy and / or ADHD. BLAST seems to be a sensitive test to detect attentional stability deficit in children with epilepsy and with attentional complaints who did not meet all criteria of ADHD.

We propose that BLAST could be a useful clinical neuropsychological tool to assess attentional disorders in children.

Key words: Childhood epilepsy, Attention Deficit Hyperactivity Disorder (ADHD), Attentional stability, Neuropsychological, BLAST

1. Introduction

Attention is a core executive function supported by structural and functional networks which mature throughout childhood and adulthood [1-2]. Substantial deficits in all or some attentional subdomains were shown to significantly impair academic achievement, social and professional integration [3-5].

Epidemiological studies show that attentional deficits are common in the general population and the most frequent comorbidity in children with epilepsy (CWE) [6]. Attention Deficit Hyperactivity Disorder (ADHD) is the best characterized attentional disorder [7]. ADHD occurs in 5 to 7 % of children, more commonly in boys than girls and the mixed subtype (i.e. inattention plus hyperactivity) is overrepresented [7]. In children with epilepsy, ADHD is diagnosed in 30 to 40 % of both girls and boys, and the inattentive subtype is more common [4, 8-12].

There are qualitative and semi-quantitative Consensus Criteria for diagnosing ADHD, which are regularly updated [13]. These do, however, not cover all clinically relevant attentional deficits. A significant number of children with attentional complaints does not fulfil the criteria defined by DSM-V [7], leading to underdiagnoses [14-15].

To improve the detection of those deficits, behavioural performances on neuropsychological tests can be used to confirm clinical suspicion. Some children are suspected to have disturbances in sustained attention, which can be assessed by Continuous Performance Tests (CPT) [16]. There is an ongoing debate about conceptual and methodological approaches to measure “sustained attentional deficits” and their contribution to the ADHD phenotype. Traditional designs are well-adapted to study long lasting and slow drifts away from the ongoing task but brief fluctuations of attention within the task may go unnoticed, especially in tests in which only a subset of the stimuli require attentive processing (e.g. CPT).

Other approaches use the global variability of reaction times (RT) – computed across the entire task - to measure attentional instability for the assessment of ADHD [17-19], in addition to more standard measures such as average RT and error rate. None of these measures alone, however, captures the fact that when individuals are more focused, they tend to react faster, with less errors and with more stable performance. Ideally, indices revealing attentional deficits should take all these elements into account. We suggest two measures with such properties, adapted from a task designed specifically to detect brief attentional fluctuations.

Given that in children with epilepsy (CWE), attentional deficits seem characterized by slow and fluctuating responses [10, 15] and a significant number of children with attentional problems remain underdiagnosed [20], the International League Against Epilepsy (ILAE) and the American Academy of Paediatrics (AAP) advocate the urgent need for developing more objective and reliable clinical tools, taking into account the broad spectrum of attentional deficits [7, 15].

The main objective of this study was to assess attentional stability in CWE with or without comorbid ADHD, ADHD only and normally developing children. We used the recently developed BLAST (Bron Lyon Attention Stability Test [21]) to assess the ability to “stay on task” on a second-to-second basis. This ability requires continuous and undivided attention, reflecting the duration of many task-units in daily life (such as listening to an explanation integrally, reading one or two pages of a book or remaining focused on the resolution of an arithmetical school task).

We aimed to assess the specific BLAST variables reflecting the dynamic aspects of responses as accuracy, regularity and speed. They rely on reproducing series of fast and error-free responses and regular and error-free series and might be disturbed by brief attentional fluctuations.

Further objectives were to identify the most discriminating BLAST variables within the subgroups and to investigate factors related to epilepsy (i.e. seizure type and frequency, pharmacotherapy, age of onset, epilepsy duration) in order to better characterize the attentional components that are disturbed in children with attentional deficits.

We hypothesize that children with attentional deficits (i.e. children with epilepsy and ADHD and children with ADHD without epilepsy) show reduced attentional stability compared to healthy controls. We expect that the specific BLAST variables, *Intensity* and *Stability*, are more appropriate to detect these subtle attentional deficits than the measures commonly used, like RT and error, allowing for better clinical management.

2. Materials and methods

2.1. Participants

We included four groups of children: 141 children with epilepsy (80 with comorbid ADHD and 61 without comorbid ADHD), 52 children with ADHD without epilepsy and 60 children with a normal development. For all groups, inclusion criteria were: (a) age between 6 to 18 years old; (b) ordinary school curriculum; (c) no major visual or auditory impairment; (d) no motor disability of the upper limbs; (e) no epileptic seizure during the task. All children and both parents or caretakers signed an informed consent before participating.

The study protocol was approved by the ethics committee Sud-Est III (Lyon B) n°2016-013B for healthy children and by the ethics committee Sud-Est V (COGNI-AIC-38RC14.374) for CWE and/or ADHD. This study has been approved by the CNIL (HCL CNIL register n ° 18-315) and by the ethics committee of Hospices Civils de Lyon (HCL) (n ° 19-19).

Children with Epilepsy (CWE) were recruited from the department of Paediatric Clinical Epileptology of the Femme-Mere-Enfant hospital (HFME), HCL, Lyon, France between 2015 and 2017. All CWE were included in this cross-sectional study of attentional disorders regardless of the evolution of their epilepsy, their epilepsy syndrome, type of epilepsy (i.e. focal or generalized, aetiology), seizure frequency or number of anti-seizure drugs. The diagnosis and type of epilepsy were confirmed by two experienced Neurologists according to ILAE criteria [22-23].

Children with ADHD were recruited from the department of Child and adolescent psychopathology unit of the same hospital between 2015 and 2017. The diagnosis of ADHD (also in children with epilepsy) was confirmed by an experienced neuropsychiatrist and a neuropsychologist from the HFME using the ADHD-RS and the clinical questionnaire for ADHD from the DSM-V. None of the children was treated with a psychostimulant.

Healthy children without a history of seizures or clinical diagnosis of neurodevelopmental disorders were recruited between 2016 and 2017 through adverts in local newspapers and schools.

For all children, ADHD rating scale (ADHD-RS) scores and information on socio-professional status of parents [24] were collected.

2.2. Procedure

2.2.1. Task

For children with epilepsy and /or ADHD, the experiment was done during regular clinical follow-up requiring a video-electroencephalogram (EEG). An EEG was also performed in healthy children for a

separate study. For healthy controls, the task was conducted at the Lyon Neuroscience Research Center (CRNL). The paradigm was adapted for children from the original BLAST [21].

Participants were seated in front of a computer screen, in a quiet room with minimal distraction. They were informed that they were going to play a game, with the aim to find a balance between speed and accuracy. The experiment started after a 1-minute training period: there were three blocks of 3 minutes interspersed by a 30 seconds (s) break. The complete experiment took approximately 15 minutes. Visual BLAST stimuli were presented on a PC running the Presentation [®] stimulus delivery software [25] synchronized with the EEG acquisition system. For each trial, the stimulus appeared in foveal vision, in black on a grey background.

Participants were instructed to find a target letter coloured in red in an array of four letters. First, the target letter appeared on the screen during 200 milliseconds (ms), followed by a mask (#) during 300 ms, followed by a 2-by-2 array of four letters in which one of them was red in 50% of cases (Figure 1). They had to provide their responses manually using a joystick. The “Yes” responses were provided when one of the four letters was red using their non-dominant hand. The “No” responses were provided when no red letter was presented and using their dominant hand. The first letter was always the same as the red target letter. We decided to maintain this design in the simplified version as a signal to focus on the task. The next trial started 800 ms after the array if a response was given and 3800 ms after the array in case of no-response. No feedback was given after trials. This paradigm involved visual target detection, selection of response and motor transformation, all dependent on attentional resources of the participant. Visual search is automatized by the saliency of the stimulus, producing a “pop-out” effect.

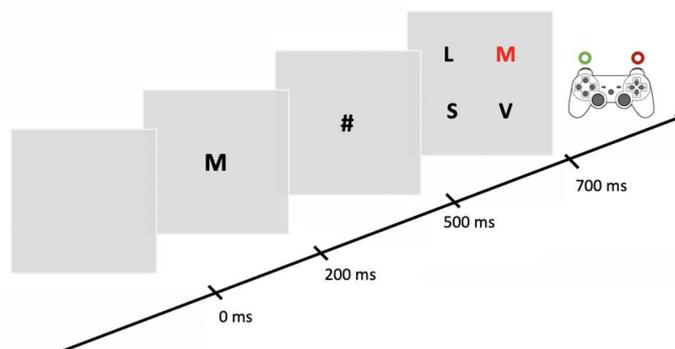


Figure 1. Typical trial of the BLAST experimental paradigm

The BLAST has good psychometric properties [21] : *i*) a good test-retest reliability ($r > 0.6$ for most measures); *ii*) a significant correlation between the subtest of processing speed index (e.g. CODE) from the Wechsler Intelligence Scale for children (WISC-IV) and the Wechsler Adult Intelligence Scale (WAIS-IV) [26,27] and most behavioural indices of the BLAST; *iii*) a high sensitivity to the Inattention component of the ADHD-RS (and more precisely with the observed inability to stay-on-task) for all the indices.

2.2.2. Behavioural measures

Three standard measures were assessed: reaction time (RT), error rate and variability of RT. The *RT* is the time (in ms) between the onset of the letter array and the motor response. The *Error* is the percentage of no-response and false alarms. The *Variability* is the variance of the RT, computed over all trials.

Two specific variables were computed: *Stability* and *Intensity*. These indices reveal momentary lapses of attention to capture the moment-to-moment dynamics of attention.

Intensity was derived from the assumption that highly focused individuals tend to respond fast and with few errors. It quantifies the ability of individuals to produce long series of fast and accurate responses, and ranges from 0 and 100 (maximal performance). The computation of *Intensity* is fully described in supplementary material.

Stability was derived from the assumption that task-irrelevant cognitive processes add "noise" to the RT [18]. It quantifies the ability of an individual to produce long series of correct responses with a stable RT, independently of its speed, and ranges from 0 and 40 (maximal performance). The *Stability* measure relies on the variation of reaction times without taking speed into account, focusing on regularity. The full details of *Stability* computation are provided in the supplementary materials.

2.3. Statistical analysis

Statistical analyses were conducted using the R software [28].

2.3.1. Demographic analysis

ANOVA and Chi2 tests were performed in order to compare socio-professional status of parents and age between the four groups and epilepsy type and duration, seizure frequency and number of anti-seizure drugs between children with epilepsy with and without comorbid ADHD. Statistical significance value was set to a *p*-value below 0.05 for each test.

2.3.2. Behavioural analysis

First, an ANOVA was conducted with a single explanatory factor (block factor) to assess the influence of the order of each block on BLAST measures (to rule out a potential influence of fatigue). Since no effect of the block factor was shown, we used trials from the three blocks for subsequent statistical analyses.

To assess the factors influencing the attentional performance during BLAST paradigm, we used an ANOVA applied on a linear mixed effect model (R-lme4 package) [29] taking into account the heterogeneity, heteroscedasticity and non-normality of data. These models were used because they take inter-subject and inter-age heterogeneity into account. The choice of the best model was made according to criteria reflecting its parsimony (AIC and BIC values). Type II variance analyses (car package version 3.0-2) [30] were performed using a Wald Chi2 test. Post-hoc tests, adjusted for the number of comparisons, were

performed using the Lsmeans package (Lsmean version 2.27-61) [32] with the Tukey method. Two analyses were performed:

- (a) the first analysis included the four groups (epilepsy with ADHD and without ADHD, ADHD and controls) considering the group and the age as explanatory variable.
- (b) the second analysis focused on the epilepsy groups by taking the age of seizure onset, the seizure frequency during the last 12 months (none, 1-5 seizures, 5-12 seizures, 13-50 seizures, 1 seizure per week or one seizure per day), the type of epilepsy (focal or generalized), the duration of epilepsy (duration in months between the age of the first seizure and the age at the test) and the number of anti-seizure drugs (none, monotherapy or polytherapy) as explanatory variables.

For each analysis, variables to be explained were RT, error rate, variability, *Stability* and *Intensity*.

A complementary analysis was performed to describe behavioural responses of children with epilepsy with attentional complaints but who did not fully meet the DSM-V criteria (i.e. 4 to 5 inattention criteria and less than 6 hyperactivity criteria) (n = 17). To this end, we established age-dependant normative values for the different BLAST scores in the control group using the R-lme4 package [29]. A polynomial fit was used to model the relationship between BLAST variables and age of the subject with a 95% confidence interval. A cut-off was established (95% confidence interval) and allowed to categorize the performance for each BLAST variable as pathological or not pathological as compared to the norm derived from the control group. The performance was considered as “pathological” when its attentional performance was out of the confidence interval of normative values established on control children.

3. Results

Six CWE with ADHD and 3 without ADHD who experienced a seizure during the EEG-BLAST session, 9 who were treated with methylphenidate (i.e. 7 children with epilepsy and ADHD and 2 children with epilepsy only) and 7 healthy subjects with practical problems during the experiment were excluded from the analysis. One CWE with a mean reaction time lower than 200ms and error percentage higher than 40% was excluded from statistical analysis because of its outlier performances. After exclusion, the epilepsy group included 122 children (67 with ADHD and 55 without ADHD), the ADHD group included 52 children and 53 healthy children formed the control group. Additional information about subjects are given in Table 1.

Table 1. Demographic and clinical characteristics of the study sample

| Epilepsy with ADHD | Epilepsy without ADHD | ADHD | Control |
|--------------------------|-----------------------------|------|---------|
|--------------------------|-----------------------------|------|---------|

| | N | 67 | 55 | 52 | 53 |
|--|----------|----------|-----------|-----------|----------|
| Demographic characteristics | | | | | |
| Age (months, mean, SD) | | 124 (39) | 131 (40) | 133 (25) | 139 (42) |
| Gender (male / female) | | 33 / 34 | 23 / 32 | 43 / 9 | 33 / 20 |
| Epilepsy | | | | | |
| Age of seizure onset (months, mean, SD) | | 64 (41) | 78 (39) | - | - |
| Type of epilepsy (n, percentage) | | | | | |
| <i>Focal</i> | 26 (39%) | 27 (49%) | - | - | |
| <i>Generalized</i> | 41 (61%) | 28 (51%) | - | - | |
| Seizure frequency (last 12 months) (n, percentage) | | | | | |
| <i>None</i> | 26 (39%) | 16 (29%) | - | - | |
| <i>1-5 seizures</i> | 16 (24%) | 17 (31%) | - | - | |
| <i>5-12 seizures</i> | 3 (5%) | 2 (4%) | - | - | |
| <i>13-50 seizures</i> | 6 (9%) | 4 (7%) | - | - | |
| <i>1 seizure per week</i> | 3 (5%) | 6 (11%) | - | - | |
| <i>1 seizure per day</i> | 12 (18%) | 10 (18%) | - | - | |
| Number of anti-seizure drugs (n, percentage) | | | | | |
| <i>None</i> | 21 (31%) | 15 (27%) | 52 (100%) | 53 (100%) | |
| <i>Monotherapy</i> | 29 (43%) | 26 (47%) | 0 | 0 | |
| <i>Polytherapy</i> | 17 (26%) | 14 (26%) | 0 | 0 | |

ADHD - mean (SD)

ADHD-RS

| | | | | |
|----------------------|--------|--------|--------|-------|
| <i>Global</i> | 29 (9) | 12 (6) | 31 (9) | 8 (6) |
| <i>Inattention</i> | 16 (6) | 8 (4) | 21 (4) | 5 (4) |
| <i>Hyperactivity</i> | 12 (7) | 5 (4) | 10 (7) | 4 (3) |

3.1. Participant demographics

The four groups were not different in terms of age ($F(3, 223) = 1.691, p > .05$) and socio-professional status of parents ($\chi^2(15) = 13.398, p > .05$).

The two groups of CWE were not different in terms of duration of epilepsy ($F(1, 120) = 1.049, p > .05$), type of epilepsy ($\chi^2(1) = 0.915, p > .05$), seizure frequency ($\chi^2(5) = 3.219, p > .05$), number of anti-seizure drugs ($\chi^2(2) = 0.276, p > .05$) and the age of first seizure ($F(1, 120) = 3.719, p > .05$).

3.2. Attentional performances

First, we performed an ANOVA on the “block” factor for each score of the BLAST, to check for a possible learning and/or fatigue effects during the experiment. This analysis showed no significant effect ($F(2, 672) < 2, p > .05$).

Regardless of the group, attentional performances assessed by BLAST improved with age. RT and error rate decreased significantly (RT: $Wald \chi^2(3, 45906) = 130.67, p < .0001$; error percentage: $Wald \chi^2(3, 45906) = 50.88, p < .0001$) while *Intensity* and *Stability* increased significantly with age (*Stability*: $Wald \chi^2(3, 45906) = 104.68, p < .0001$; *Intensity*: $Wald \chi^2(3, 45906) = 161.31, p < .0001$).

Type II variance analyses performed with Wald's Chi 2 showed that there was no significant difference between the groups for the RT (Figure 2-a), the error percentage (Figure 2-b) and the variability (Figure 2-e). There were significant differences between groups for the *Stability* ($Wald \chi^2(3, 45906) = 28.369, p < .0001$) (Figure 2-c) and *Intensity* ($Wald \chi^2(3, 45906) = 9.084, p < .05$) (Figure 2-d). Post-hoc analyses showed that CWE with and without ADHD and children with ADHD performed worse than the control group. Controls had a higher *Stability* than CWE with ADHD ($t(220) = 4.383, p < .0001$) and than children with ADHD ($t(219) = 4.806, p < .0001$) (Figure 2-c). The control group also had a higher *Intensity* than CWE with ADHD ($t(218) = 2.738, p < .05$) (Figure 2-d). Mean scores for each group are shown in Table 2.

There was no significant interaction between age and groups: thus, difference between groups appear independently of the age effect.

Table 2. Mean scores on BLAST test for each group

| | Epilepsy with ADHD | Epilepsy without ADHD | ADHD | Control |
|----------------------------------|-----------------------|--------------------------|-------------|-------------|
| N | 67 | 55 | 52 | 53 |
| BLAST - mean (SD) | | | | |
| Reaction time (<i>seconds</i>) | 0.75 (0.26) | 0.71 (0.28) | 0.65 (0.19) | 0.63 (0.18) |
| Error rate (<i>percentage</i>) | 7 (7) | 6 (7) | 6 (6) | 4 (4) |
| Variability | 0.31 (0.4) | 0.21 (0.35) | 0.15 (0.22) | 0.13 (0.23) |
| Stability | 23 (14) | 28 (16) | 24 (13) | 36 (15) |
| Intensity | 54 (20) | 58 (21) | 58 (18) | 66 (17) |

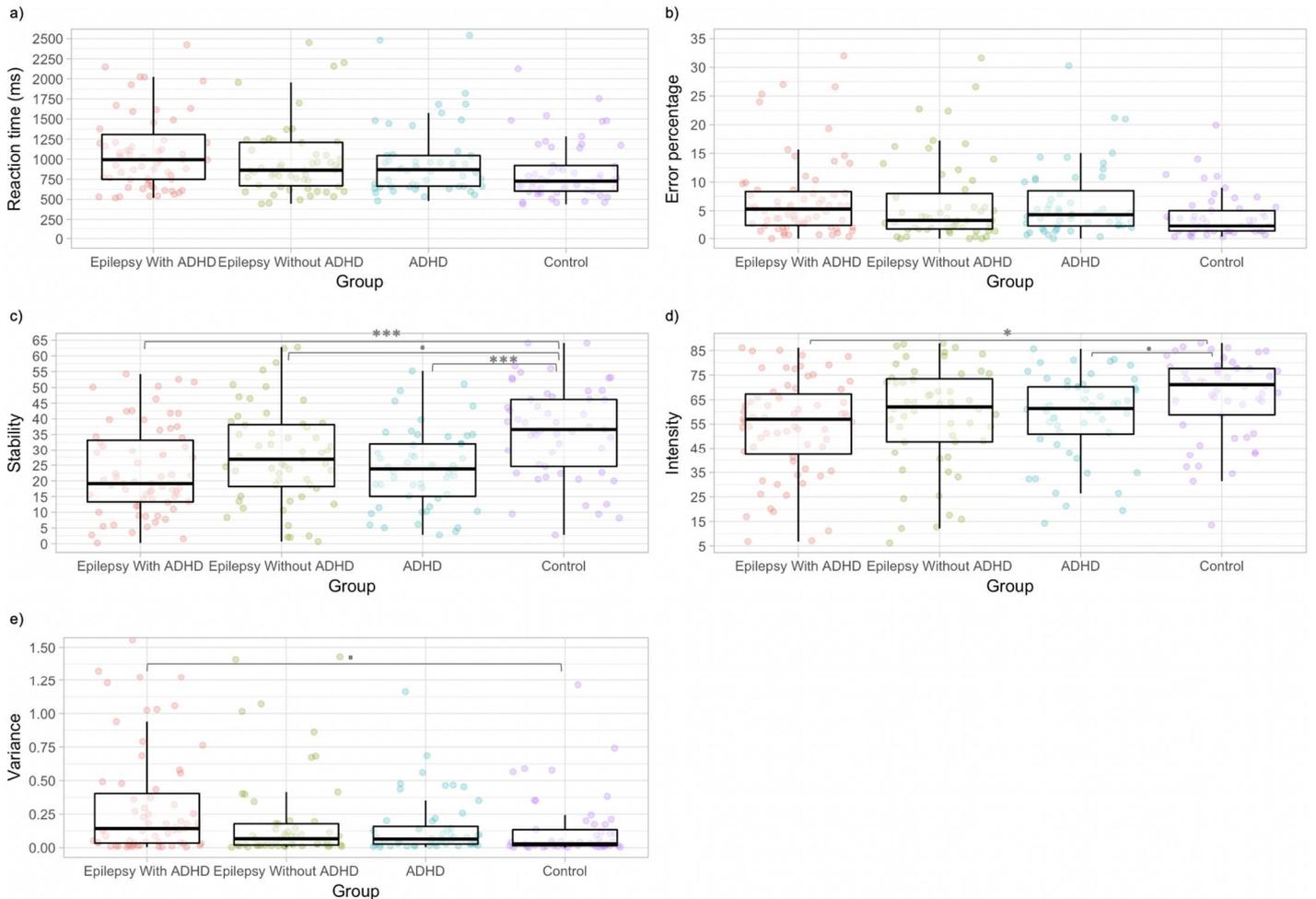


Figure 2. Each point represents the median reaction time (a), the error rate (b), the Stability (c), the Intensity (d) and the variability (e) for each subject according to the groups (red: epilepsy with ADHD, green: epilepsy without ADHD, blue : ADHD, purple : control). The central line of the boxplot corresponds to the median of each score, the upper and lower parts corresponds to the first and third quartiles. Difference between groups are represented by star: ***: $p < .001$; *: $p < .05$; . : $p < .1$

3.3. Relationship between characteristics of epilepsy and attentional performances

In CWE (with and without ADHD), earlier age of the seizure onset was associated with a higher RT ($Wald \chi^2(1, 23453) = 22.399, p < .0001$) (Figure 3-a), a higher error percentage ($Wald \chi^2(1, 23453) = 5.269, p < .05$) (Figure 3-d) and lower Stability ($Wald \chi^2(1, 23453) = 9.469, p < .01$) (Figure 3-c) and Intensity ($Wald \chi^2(1, 23453) = 9.904, p < .01$) (Figure 3-b).

In these children, a higher number of anti-seizure drugs, was correlated with lower performances. It was significant for the RT ($Wald \chi^2(2, 23453) = 11.727, p < .001$) and the error rate ($Wald \chi^2(2, 23453) = 7.394, p < .01$) and not significant for Stability and Intensity ($p > .05$). Post-hoc analyses demonstrated that children with polytherapy had a higher RT ($t(81) = 2.979, p < .05$) and error percentage ($t(94) = 2.712, p < .05$) than children with monotherapy. There was no significant difference in performances between children without anti-seizure drugs and children with monotherapy ($p > .05$).

Neither epilepsy type, groups (with and without ADHD), seizure frequency nor epilepsy duration were related to the BLAST outcome measures (RT, error percentage, *Intensity* and *Stability*) ($p > .05$).

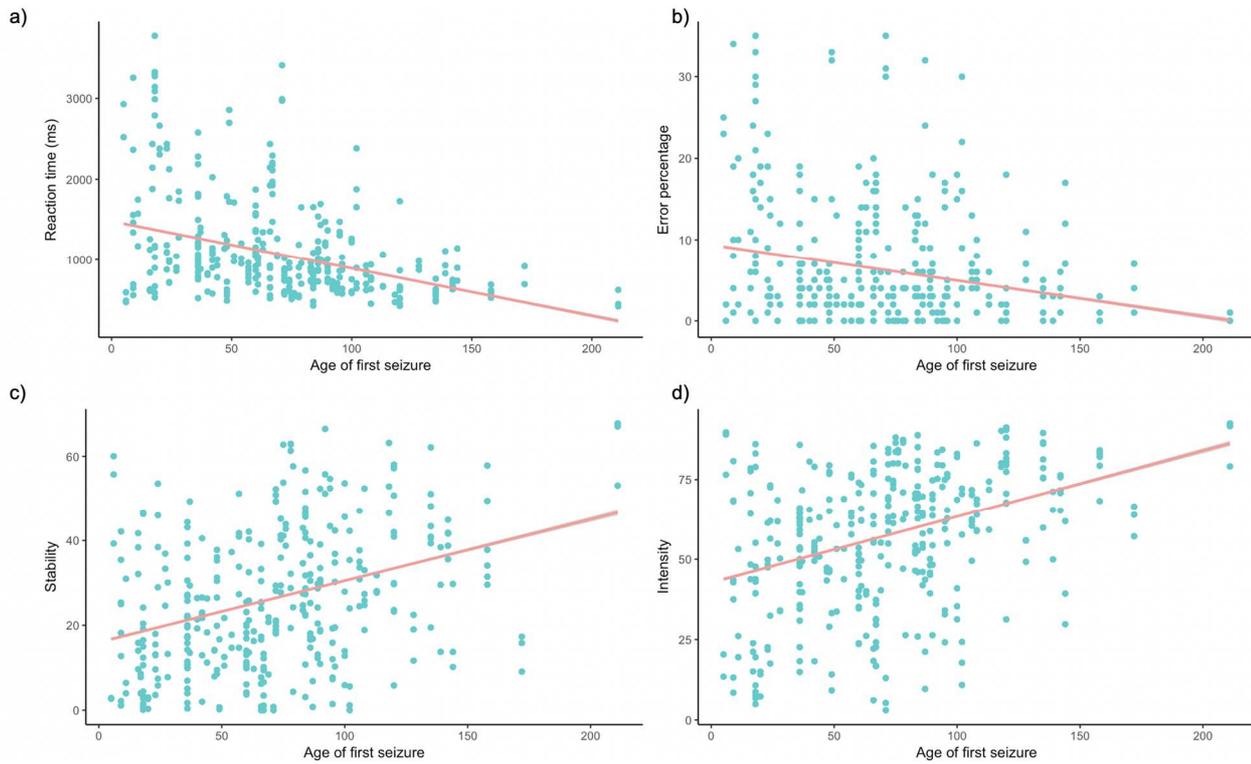


Figure 3. Each point represents the median reaction time (a), Intensity (b), Stability (c) and rate of error (d) for each subject according to the age of the first seizure (in months).

3.4. Relationships between attentional performances on BLAST and ADHD criteria

There were 17 CWE without ADHD who did not fully meet DSM-V criteria for ADHD and who did not have pathological scores on the ADHD-RS. The BLAST highlighted difficulties in attentional stability in six of those children using the RT, in eight using error rates, in 16 using *Stability* and in 13 using *Intensity* (see table 3).

Table 3. BLAST performance scores in children with epilepsy

| BLAST | | | | | | | |
|----------------|---------------|----------------|---------------|----------------|---------------|----------------|---------------|
| Reaction time | | Rate of errors | | Stability | | Intensity | |
| <i>Deficit</i> | <i>Normal</i> | <i>Deficit</i> | <i>Normal</i> | <i>Deficit</i> | <i>Normal</i> | <i>Deficit</i> | <i>Normal</i> |
| 6 | 11 | 8 | 9 | 16 | 1 | 13 | 4 |

4. Discussion

The recently described BLAST paradigm evaluates the ability to stay on-task by assessing the dynamics of brief attentional fluctuations. Our study aimed at evaluating the clinical utility of a simplified BLAST version in children with high prevalence of attentional deficits: children with ADHD and children with a broad range of epileptic disorders. Few studies have been performed to better characterize the nature of attentional complaints in those populations and focused mostly on sustained attention [32]. To the best of our knowledge, none specifically measured the influence of very brief attentional fluctuations on attentional stability.

We compared the impact of intra-task attentional fluctuations on attentional stability between CWE with and without comorbid ADHD, children with ADHD without epilepsy and in typical developing children. We found that CWE and/or ADHD performed worse on the BLAST than healthy controls. Two new specific measures, *Stability* and *Intensity*, showed deficits in attentional functioning that are not captured by classical variables such as reaction time, error rate or the global variability of reaction time across trials. In line with our hypothesis, *Stability* differentiated controls from the three disease groups (ADHD, CWE with and without ADHD). *Intensity* distinguished the children with an ADHD component (i.e. CWE with ADHD or children with ADHD only) from controls.

These results indicate that standard measures such as reaction times, error rates or variability alone are insufficient to detect fluctuations in attentional stability, which is an essential component of cognitive functioning in everyday life. Traditional attention tests (e.g. CPT) that assess performance over the entire test do not capture intra-task dynamics, which can lead to an incomplete assessment of attentional deficits. These very brief attentional fluctuations can be explained by momentary lapses of attention (MLA) lasting a few moments (seconds or less) during which cognitive resources are side-tracked towards processes unrelated to the task [33]. Previous studies suggested that MLA manifest by isolated errors or a transient increase in RT [34-35]. With its high temporal resolution and its new specific variables, the BLAST captures the dynamics of attentional performances throughout the task and allows to compare the fluctuations of speed and quality of response underlying attentional stability.

The *Stability* measure relies on the variation of reaction times without taking speed into account, focusing on regularity. It differentiated controls from the three disease groups and interestingly revealed lower performances in CWE without ADHD, despite normal speed. This result shows that slowness, which is frequently reported in previous studies, does not fully describe attentional disorders in those children [36]. In children who do not fully meet criteria of ADHD, but have problems at school or reported by parents, difficulties in attentional stability can be more easily identified by the BLAST than by conventional measures. We found that especially *Stability* was sensitive to attentional deficits that were not detected by the ADHD-RS. This new test may thus increase the diagnostic sensitivity for attentional disorders, as recommended by the ILAE and the AAP.

The *Intensity* measure of the BLAST distinguished children with an ADHD component (i.e. CWE with ADHD or children with ADHD only) from controls. This specific measure, which integrates processing speed and accuracy of the responses, seems to best reflect the core behavioural attentional disorders, shared by ADHD and CWE with ADHD.

As a whole, our results suggest that the BLAST highlights attentional difficulties that are not measured by conventional scales. Thus, BLAST can complement the assessment of attentional deficits to provide a better diagnosis of attentional disorders. The new specific measures, *Stability* and *Intensity*, may also be computed for other neuropsychological tests that measure reaction time and errors, such as the kiTAP battery [37].

In CWE (with and without ADHD), we found that an earlier seizure onset was associated with lower performances on RT, error percentage, *Stability* and *Intensity*. As expected, the number of anti-seizure drugs also impacted performances [38-39]. CWE with polytherapy had higher RT and error percentages and tended to have lower *Stability* and *Intensity* than CWE with monotherapy or without treatment. *Stability* and *Intensity* were thus less impacted by the number of anti-seizure drugs than classical measures.

In line with earlier results showing that fluctuations in attention were associated with an earlier age at diagnosis [9-10,35], our results show that the age of the first seizure had an impact on attentional stability, independent from the duration of epilepsy. In addition, attentional deficits were not linked to epilepsy-related clinical characteristics such as seizure frequency or epilepsy type. These results suggest that early seizure onset impacts attentional skill development at crucial developmental milestones in childhood. On the contrary, it appears that the diagnosis of focal versus generalized epilepsy was not a major determinant of attentional deficits, within the limits of our relatively small cohort of patients regarding epilepsy types.

The capacity to maintain attention focused matures in childhood [40-41]. The neuroanatomical network involved in the BLAST was recently described [21]. It involves the Dorsal Attentional Network (DAN) [42], a network at the interface of the pre-motor areas and the anterior cingulate gyrus involved in maintaining attention throughout time. This activation pattern was also associated with a deactivation of the Default Mode Network (DMN), in line with previous studies showing deactivation of the DMN in active tasks [43]. Studies using intracranial EEG, however, show a brief reactivation of this network between each trial [21]. Good BLAST performance seems to depend on the interplay between the DAN and the DMN. We suggest that children with reduced attentional stability may have an imbalance between these two networks, resulting in the intermittent reactivation of the DMN or limited activation of the DAN.

Limitations of our study include the recruitment of CWE from a tertiary epilepsy centre, potentially leading to a high prevalence of comorbid disorders such as cognitive difficulties and a high heterogeneity of the population. Moreover, CWE and/or ADHD were investigated at different stages of the disease in a cross-sectional design. More large-scale studies are thus needed to evaluate attentional performance in different

epilepsy syndromes and longitudinal studies may be performed to evaluate the influence of epilepsy duration. In CWE, we excluded the impact of potential seizures on task results, but interictal epileptiform discharges were not considered. This will be the aim of future studies.

5. Conclusion

Attentional deficits are a major concern in CWE and / or ADHD. Using a novel test, we demonstrate that attentional stability is altered by brief attentional fluctuations in CWE with or without ADHD and in children with ADHD only, compared to controls.

The BLAST improved the detection of deficits in attentional stability in children with epilepsy and attentional complaints, who did not meet all criteria for ADHD. The BLAST identified differences in attentional functioning in children with ADHD, with or without epilepsy compared to controls. This test could also show the cognitive impact of a polytherapy with anti-seizure drugs.

The BLAST with its innovative specific attentional indices should be included in neuropsychological assessments of attentional disorders, particularly in syndromes with a high prevalence of pure attentional deficits. This ergonomic test lasts 15 minutes and can be easily performed in the setting of standard follow-up. It is well adapted to children and may thus be evaluated in a broad range of neurodevelopmental disorders impacting cognitive skills.

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Supplementary Material

Description of outcomes measures [21] :

“ *Intensity* (see figure below), derives from the natural assumption that highly focused individuals tend to respond fast and with few errors. In other words, a performance graph showing reaction times (y-axis) for all the trials (x-axis) should display long series of hits below a given time limit T (horizontal line), even when T is low. If we cumulate the length of all successful series below T (i.e. with a reaction time consistently faster than T), we reach a measure $P(T)$ which should be high for "highly-focused" individuals even when T is small (i.e., 500 ms). To penalize errors and to be consistent with the adaptive designs which required participants to generate successful series of five trials, we computed a measure $P(T)$, which included only series longer than five consecutive wins, cumulating $N-5$ « points » for every such series (where N is the length of that series). $P(T)$ is the number of points for time limit T ; it is computed for every value of T between 300 ms and 1500 ms (no one could generate series of hits faster than 300 ms). That scoring system penalized errors, as any error interrupted the ongoing series and the participant had to succeed at least five new times before her score increased again. Graph $P(T)$, which increases with longer T , immediately distinguishes visually between several types of participants/strategies : fast reaction times with many errors ('globally impulsive participants'), slow reaction times with few errors ('globally meticulous'), slow reaction times with many errors ('slow inattentive' type) and fast reaction times with few errors ('fast and focused'). Fast and focused participants are characterized by a large area under the curve $P(T)$: for that reason, we defined a behavioral indice of attention, $Intensity = 100 \times AUC(P) / \max(AUC)$, where AUC is the area under the curve $P(T)$ and $\max(AUC)$ its maximal theoretical value. *Intensity* refers to, and is high for, the "fast and focused» type. One might object that lower values of *Intensity* might not disambiguate the 'impulsive' and the 'meticulous' types, but those two profiles can be differentiated by considering also the median of their reaction times (and graph $P(T)$).”

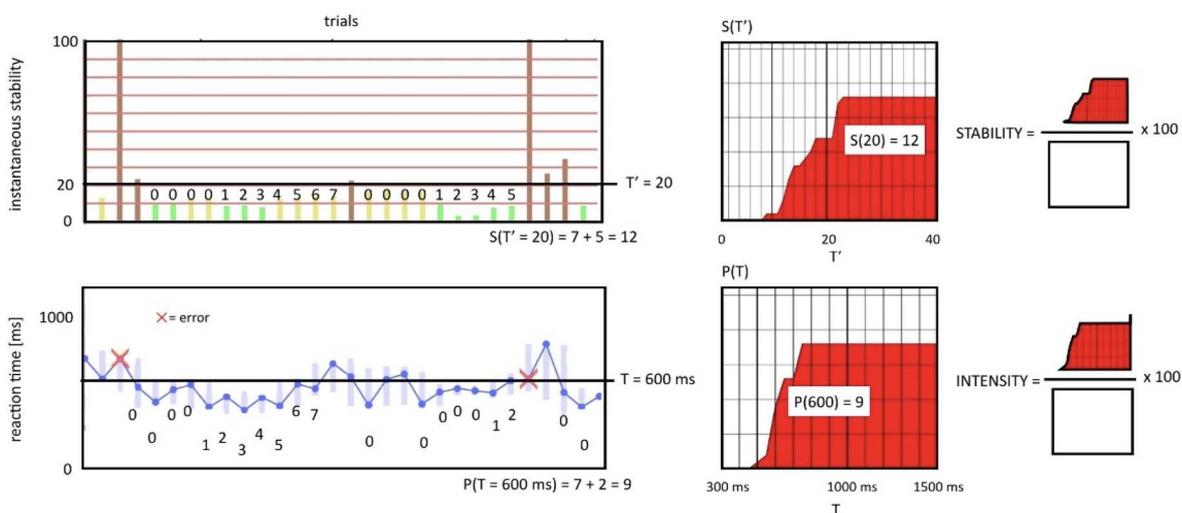


Figure : Scoring systems for *Intensity* and *Stability*. *Intensity* and *Stability* are computed from graphs P(T) and S(T') respectively (bottom and top right panels, respectively), from the ratio of the area under the curve (red) divided by the total area of the square englobing that curve (white). The bottom left graph illustrates the calculation of P(T) from the reaction times for an example value of T (600 ms : 9 points) (« instantaneous » standard deviations of reaction times - computed over three consecutive trials, are shown as gray vertical bars). The procedure is repeated for all T between 300 ms and 1500 ms to generate red plot P(T). The top left graph illustrates the calculation of S(T') from the « instantaneous » standard deviation s(trial) of the normalized reaction times (r'(trial)) for an example value of T' (20 : 12 points). The normalized reaction times r'(trial) are simply reaction times expressed as % of the median reaction time. S is depicted in the top left graph as vertical bars (green = s less than 10; yellow = s less than 20; red otherwise, note that s is set to 40 for every error) and red vertical bars in the upper left graph). The procedure is repeated for all T' between 0 and 40 to generate red plot S(T') on the right.

“One limitation of *Intensity* is that it is mathematically lower for participants with slower reaction times (typically, elderly people). Yet, it is clear that someone with slow but close to constant reaction times, and no errors, is fully « on-task ». Therefore, *Intensity* should be complemented with another measure which emphasizes stability more than speed: this is *Stability* (see figure above). *Stability* was derived from the assumption that task-irrelevant cognitive processes add "noise" to reaction times [18]: it was thus computed from the "instantaneous" stability of reaction times $r(\text{trial } i)$. And since our intention was to minimize the effect of the overall speed, we considered the stability of "normalized reaction times"; i.e. reaction times expressed in % of the median reaction time for the entire task: $r'(\text{trial } i) = 100 * r(\text{trial } i) / \text{median}(r(\text{all trials}))$. We defined the instantaneous stability of attention for trial i as $\text{instab}(\text{trial } i) = \text{std}(r'(\text{trial } i-1):r'(\text{trial } i+1))$, it is computed over sliding windows of three consecutive trials for maximal temporal precision. *Stability* was computed from $\text{instab}(\text{trial } i)$ following a procedure similar to the computation of *Intensity* from $r(\text{trial } i)$. To penalize errors as in *Intensity*, instab was set to a maximal value (40) for unsuccessful trials. As with *Intensity*, we devised a scoring system S(T') which accumulates N-5 points for each series of N>4 winning trials for which instab stays below T' (a procedure repeated for T' values between 0 and a maximum of 40). Graphically, instab measures the width of the « tube » in which the reaction time plot seems to be confined locally (i.e. for three consecutive trials) (see figure above), and S(T') integrates the length of such series, excluding series shorter than 5 for the same reason as in *Intensity*. In short, *Stability* evaluates the ability to generate long and narrow “tubes” of reaction times: $\text{Stability} = 100 * \text{AUC}(S) / \text{max}(\text{AUC})$, where AUC is the area under the curve S(T') and max (AUC) its maximal theoretical value.”