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Intraindividual Variability in Attentional Vigilance in Children with Epilepsy

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Abstract

Attentional vigilance, the ability to maintain focus over time, is frequently impaired in childhood epilepsy. Typically, indices of Omissions (failure to detect a target) and Commissions (responding to a non-target) are considered primary indices of attentional vigilance. Recently, the concept of intraindividual variability (IIV) has been identified as an important measure of attentional vigilance in several pediatric and adult clinical populations, but has not yet been systematically examined in childhood epilepsy. Here, we examined IIV on the Connors Continuous Performance Task-II (CCPT-II) for 144 newly diagnosed children with epilepsy (age 8–18 years) and a matched age group of healthy children (n=82). IIV showed a large effect size difference ($d = .68$) between groups. In addition, IIV significantly predicted both intellectual functioning and academic achievement. These findings support the utility of examining IIV in the assessment of attentional ability in childhood epilepsy.

Keywords

Attention; Intraindividual Variability; Intelligence; Academic Achievement; Cognitive Function; Pediatric

1. Introduction

Impairment in attention is a common cognitive co-morbidity in childhood onset epilepsy. [1, 2]. It is evident in several childhood seizure syndromes that, at the time of epilepsy diagnosis or shortly after, a negative impact is exerted on cognitive and social development, even when seizures are properly controlled [3, 4, 5, 6, 7, 8]. Given the presence and impact of

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attentional difficulties in childhood epilepsy, it is important to identify and manage attentional problems.

However, the domain of attention is a complex and heterogeneous construct and several component processes have been identified. Mirsky et al. (1991) proposed an influential model that identified four different attentional “elements”; 1) *focus-execute*, the ability to select target information from groups and use it in enhanced procession, 2) *sustain*, the capacity to maintain focus and alertness over time, 3) *shift*, the ability to flexibly change focus in an adaptive manner, and 4) *encode* a diverse process of attention that depends on the ability to receive and manipulate data, equivalent to working memory [9]. Mirsky’s model has proven to be a useful framework from which to investigate attentional dysfunction in several clinical populations including childhood epilepsy [10].

Mirsky and Duncan added *stabilize* as a fifth attentional process to their model; the ability to maintain consistency and stability of attention while individuals are responding to target stimuli over time [10]. In childhood epilepsy, increased response variability has been reported for children with complex partial seizures (CPS), absence seizures, and benign rolandic epilepsy (BRE) [11, 12, 13]. However, these studies included children with diagnosed epilepsy for several years. As a result, it is difficult to disentangle the impact of several inter-related seizure-related factors (e.g., frequency of seizures, age of onset, AED use, co-morbid psychiatric disorders). In addition, there is little currently known about the relationship between intraindividual variability (IIV) and performance on measures of intellectual functioning and performance in school.

IIV, or response variability, is a measure of the consistency of an individual’s responds to a stimulus. More specifically, in this study, it is a measure of the consistency of response time to targets in a continuous performance test. IIV is a useful tool in determining more subtle fluctuations of attention than mean response time. The objective of this study was to examine the performance of a group of children with recently diagnosed epilepsy on four commonly used indices of attentional ability: Omissions, Commissions, mean Hit RT, and IIV. We also examined the relationship between these indices and measures of intellectual functioning and academic achievement.

2. Material and methods

2.1 Participants

One hundred and forty-four children between the ages of 8 and 18 years with a recent diagnosis of epilepsy were recruited from pediatric neurology clinics at three mid-western medical centers. Inclusion criteria included a diagnosis of epilepsy within the past year (mean=8.3 months, SD =3.7), normal neurological examination, and normal clinical MRI. All children obtained a minimum Wechsler Abbreviated Scale of Intelligence (WASI-II) Full Scale IQ of 70. These children did not have another diagnosed neurological disorder. Medical records were reviewed blind to cognitive testing by an independent board-certified pediatric neurologist to establish the epilepsy diagnosis and classification. The healthy control group (HC) was comprised of 82 first-degree cousins of the epilepsy children between the ages of 8 to 18 years. Inclusion criteria included no history of seizures, no

clinical diagnosis of ADHD, no signs of neurological disease, and no loss of consciousness longer than five minutes.

2.2 Procedure and Consent

Written informed consent was obtained from legal guardians of the children and adolescents in the study. Participants aged 18 years gave their own written informed consent, and participants age 8 to 17 years provided written informed assent. University of Wisconsin School of Medicine and Public Health provided approval to conduct this study through their health sciences institutional review board. After informed consent and assent was obtained, participants underwent neuropsychological testing while parents underwent clinical interviews and completed questionnaires about their child's developmental history. Medical information regarding participant's epilepsy and treatment was obtained after parent's signed release of information.

2.3 IQ and Academic Achievement

All participants were administered the Wide-Range Achievement Test-3 (WRAT-3) and the WASI-II. Both tests are commonly used in clinical and research with pediatric populations and have excellent psychometric properties [14]. The WRAT-3 subtests include reading, spelling, and arithmetic [14]. The WASI includes an abbreviated measure of Verbal and Performance IQ based on subtest scores on Block Design, Matrix Reasoning, Similarities, and Vocabulary [14].

2.4 Conner's Continuous Performance Test-II (CCPT-II)

The CCPT-2 is considered a hallmark test of attentional vigilance with excellent discriminative and convergent validity, and has been used extensively in both research and clinical assessment of child and adult populations including children with epilepsy [14, 15, 16]. The CCPT-2 is a computerized task lasting 14-minutes in duration which is divided into six sub-blocks of twenty trials with letters presented at varying speeds. Subjects are asked to press a computer key when any stimulus appears on the computer screen other than a specific symbol ('x'). Four variables of interest were selected: (1) *Omission errors*, which represent the failure to respond to non-targets (i.e., failure to respond to letters other than "x"), (2) *Commission errors*, which indicate targets that were responded to in error (i.e., respond to "x"), (3) *Standard hit rate reaction time* (Hit RT), a gauge of inattention when reaction time is slow and impulsivity when it is fast, and (4) *Variability* (IIV), which is calculated as the standard deviation of the standard error values for reaction times for each of the 18 sub-blocks.

2.5 Statistical Analyses

Raw scores were converted to T-scores based on the CCPT-2 standardization sample [14]. All distributions were examined for normality allowing for kurtosis. In cases where the assumption of normality was violated, a Mann-Whitney U-test was used. First, independent between group t-tests were conducted to examine group differences for the four CCPT-2 indices: errors of Omission, errors of Commission, IIV, and Hit RT. We also examined group differences on the Verbal (VIQ) and Performance (PIQ) sections of the WASI-II, and the

three subtests of the WRAT (word recognition, spelling, and arithmetic). Subsequently, hierarchical multiple regression models were conducted with the IQ and academic measures serving as the dependent variable and the CCPT-2 indices as predictor variables. In all the regression models, age at diagnosis (months), seizure syndrome (generalized, localized), and gender were entered on step one, and on step two each of the four CCPT-2 variables were included in separate models. Of importance is the amount of increased variance produced by each of the CCPT-2 indices after accounting for the seizure variables. In addition, we examined the relationship between the clinical seizure variables, age of diagnosis and epilepsy syndrome and IIV. We did not include AED in these analyses because over 93 % were being treated with a single AED and only nine children were being treated with two or more AEDs.

3. Results

Table 1 provides descriptive demographic and clinical seizure characteristics for the epilepsy and healthy control groups (HC). No significant group differences for age, education, or gender ($p's > .05$) were found. The epilepsy group performed significantly lower than HC on all measures of academic and intellectual functioning ($p's < .001$), however, performance was within the generally “average” range for both groups on all measures.

3.1 Group Differences

Scores in Table 2 show that the epilepsy group performed more poorly than HC on all CCPT-2 measures examined: Omissions ($z=2.36$, $p < .01$, $d = .41$), Hit RT ($t=3.62$, $p < .001$, $d = .51$), and IIV ($t=4.93$, $p < .001$, $d = .68$), and Commissions approached significance ($t=1.90$, $p = .06$, $d = .26$).

3.2 Multiple Regression Analysis

Findings examining the relationship between the CCPT-2 indices and WASI IQ and academic achievement are presented in Table 3. In all analyses, the demographic and seizure variables were entered in a single block followed by entry of one of the four CCPT-2 indices resulting in a total of four distinct models. Similar analyses were conducted including ADHD diagnosis as a predictor variable on block and results were similar to findings presented below. When more than one CCPT-2 score added a significant increase in predicted variance, a model combining both scores together on the second block was conducted.

3.3 WASI IQ Scores

Table 3 provides the specific findings from the regression analyses. Demographic and seizure variables produced a significant model ($F = 3.27$, $p = .02$) for Performance IQ, but not Verbal IQ. Models examining the addition of IIV ($t = 3.84$, $p < .001$) and Omissions ($t = 3.22$, $p < .01$) provided a significant increase in variance after the demographic and seizure variables were entered. In contrast, the addition of Commissions and Hit RT did not yield a significant increase in explained variance ($p's > .05$). When both IIV and Omissions were included together in the same model, only IIV emerged as a significant predictor ($p=.02$), and Omissions ($p=.19$) was no longer significant. For Verbal IQ, the addition of IIV ($t =$

2.44, $p = .04$) added significantly to the overall model based after demographic and seizure variables were put in the model. None of the other three CCPT-2 indices produced a significant increase in explained variance for VIQ.

3.4 WRAT Academic Achievement

Demographic and seizure variables did not produce a significant model for Reading, Spelling, and Arithmetic (p 's $> .05$). For Reading, both IIV ($p = .02$) and Commissions ($p = .05$) added significant increase in variance prediction, but the Omissions and Hit Rate did not (p 's $> .05$). When both IIV and Commissions were entered together, IIV remained significant ($\beta = -.20$, $p = .03$), but Commissions did not ($\beta = -.14$, $p = .10$). For Spelling, errors of Commission emerged as the only significant predictor ($t = 2.10$, $p = .04$), and IIV showed a marginally significant added contribution after the demographic and clinical seizure variables ($t = 1.90$, $p = .06$). For the Arithmetic subscale, the addition of IIV on step 2 added a significant amount of variance ($t = 2.66$, $p < .01$). Hit RT was also significant, $t = 2.02$, $p = .05$. When both IIV and Hit Rate were both entered on the second step, IIV remained significant ($\beta = -.25$, $p < .01$) while Hit RT was not ($\beta = -.13$, $p = .13$).

3.5 IIV and Clinical Seizure Variables

IIV was significantly correlated with age of diagnosis ($r = -.39$, $p < .01$) as was Omissions ($r = -.26$, $p < .01$) indicating worse performance in children with a younger age of onset. Hit rate and Commissions did not show a significant relationship with age at diagnosis. None of the CCPT-2 indices were significantly associated with syndrome type (Localization, Generalized).

4. Discussion

The assessment of attentional vigilance in childhood epilepsy has typically focused on errors of Omission and errors of Commission. Here we found that a measure of IIV produced the strongest effect size difference on the CCPT-2 performance between the recent onset epilepsy children and HC groups. IIV was also the most reliable and strongest predictor of IQ and academic achievement. These findings extend previous findings with epilepsy children with several years duration of epilepsy to children recently diagnosed.

The impact of IIV was particularly evident on Performance IQ and WRAT Arithmetic subtests; two areas of greatest group difference between the epilepsy group and controls. Both of these measures include a processing speed component, which may explain the stronger IIV relationship. In addition, both measures put particular demands on working memory. Mella, Fagot, Lecerf, and Ribaupierre (2014) found that IIV in reaction time explained a moderate amount of variance in working memory measures of a reading span test [17]. Increased IIV has also been shown to negatively impact performance on nonverbal reaction times tasks, such as simple and choice computerized reaction time tasks [18]. In a study with ADHD children, the integrity of the central executive component of working memory accounted for 88% to 100% of the relationship between diagnostic status and RT variability [19].

Here we found that inconsistency in attentional vigilance was evident for children regardless of seizure syndrome. Increased IIV was also associated with an earlier age of diagnosis, similar to findings in other areas of cognition and behavioral adjustment [20, 21]. It is important to note that increased IIV in the child epilepsy group was found despite IQ scores and academic achievement scores broadly in the normal range. Therefore, deficits in attentional vigilance may remain undetected in these children unless specific assessment is conducted.

Transient cognitive impairment (TCI) are temporary periods of cognitive dysfunction that occur during interictal discharges of activity [22]. TCI has been found to occur in up to 47% of children with epilepsy. TCIs have also been linked to slower reaction times, and lower IQ and educational achievement scores [22]. A review by Aldenkamp and Arends (2004) suggested that tasks that have a high information processing demand, visual input mode, and long test duration may better highlight the negative effects of TCIs [23]. It is possible that IIV is related to episodes of TCI, but a direct study of their relationship is needed to confirm that possibility. However, baseline EEG measurements were not conducted in this sample.

The neural substrate of IIV has been linked to white matter integrity. Killory et al. (2011) reported that measures of inattention during CCPT-2 performance in childhood absence epilepsy were correlated with decreased medial frontal lobe connectivity [12]. This is consistent with previous findings that developmental reductions in IIV were reflective of white matter integrity [24]. White matter integrity is also disrupted in new onset childhood epilepsy [25]. However, additional investigation is necessary before the neurophysiological mechanisms underlying attentional variability in childhood epilepsy are better understood.

4.1 Limitations

This study was a cross-sectional baseline analysis of attentional vigilance within the first year of epilepsy diagnosis in a pediatric population. Additional longitudinal study is necessary to determine the longer time stability and predictability of IIV. Longitudinal analysis will also be beneficial in determining if the remittance of epilepsy has a significant effect on IIV. In addition, this study focused on general IQ and academic achievement scores. A more detailed examination of the relationship of IIV and other cognitive abilities may be useful in the assessment and intervention of children with epilepsy. Finally, most of the epilepsy children were being maintained on a single AED, but AED type was quite variable and precluded more detailed analysis. These were children with “uncomplicated epilepsies”—how the results would generalize to the large population of children with medication resistant/difficult to control epilepsies remains to be determined.

4.2 Conclusion

The results of this study suggest that IIV plays a significant role in both IQ and academic achievement in children with epilepsy. Despite scores within the average range, these fluctuations in attention may prevent children with epilepsy from performing up to their abilities. Furthermore, due to their average overall academic performance these difficulties may not be readily identified in the classroom or at home. Examining IIV in this population

may be beneficial in identifying children at risk for inconsistent performance leading to a subtle decline in academic performance.

These findings confirm the ubiquitous impact of impairment in attentional vigilance at time of epilepsy diagnosis and emphasize the need for careful assessment of these difficulties. IIV may be an early marker of potential of disruption in the ability to show consistent vigilance over time, which is critical for academic success and cognitive development.

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Abbreviations

IIV	Intraindividual Variability
CCPT-2	Conner's Continuous Performance Test-II
WASI-II	Weschler Abbreviated Scales of Intelligence-Second Edition
WRAT-3	Wide-Range Achievement Test-3

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Highlights

- IIV displayed better discrimination than traditional measures of attention.
- IIV significantly contributes to cognitive functioning in children with epilepsy.
- Age of epilepsy diagnosis contributes to degree of IIV in children with epilepsy.
- More research is needed to determine the long-term impact of IIV on functioning.

Table 1

Demographic and Clinical Seizure variables for Children with Recent Onset Epilepsy and Healthy Controls

Demographic Variable	Epilepsy N=144 M (SD)	Healthy Controls N=82 M (SD)	t-score	p-value
Age (years)	11.91 (3.12)	12.20 (2.93)	.68	.50
Education (grade)	6.28 (3.12)	6.51 (2.84)	.55	.59
Gender (M/F)	68/76	38/44		1.00
Full Scale IQ	102.06 (13.76)	108.27 (11.56)	3.45	<.01
Performance IQ	100.13 (14.07)	107.15 (11.85)	3.81	<.001
Verbal IQ	103.23 (14.31)	107.62 (12.98)	2.29	.02
Word Recognition	101.25 (12.46)	104.55 (10.70)	2.01	.05
Spelling	100.63 (13.15)	104.79 (12.31)	2.33	.02
Arithmetic	97.10 (12.96)	107.20 (12.17)	5.76	<.001
Localized/Generalized Syndrome	70/69			
Duration of Illness (Months)	8.33 (3.74)			
Age of Diagnosis (Months)	140.14 (37.52)			
Number of Medications (Multiple/one or less)	9/135			

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Table 3

Hierarchical Regression Models with entry of CCPT-II variables

Test Indices	Variable	β	t-value	R ²	p-value	Model P-value
Performance IQ	IIV	-.33	-3.84	.09	<.001	<.001
	Omissions	-.27	-3.22	.07	<.01	<.01
	Commissions	-.08	-.92	.01	.36	.04
	HIT RT	-.03	-.029	.00	.77	.05
Verbal IQ	IIV	-.19	-2.10	.03	.04	.03
	Omissions	-.17	-1.91	.03	.06	.04
	Commissions	-.08	-.87	.01	.39	.14
	HIT RT	.09	1.06	.01	.29	.12
Reading	IIV	-.22	-2.44	.04	.02	.06
	Omissions	-.09	-1.03	.01	.31	.40
	Commissions	-.17	-1.96	.03	.05	.15
	HIT RT	-.07	-.87	.01	.39	.44
Spelling	IIV	-.18	-1.90	.03	.06	.14
	Omissions	-.04	-.48	.00	.63	.47
	Commissions	-.18	-2.10	.03	.04	.10
	HIT RT	-.11	-1.24	.01	.22	.30
Arithmetic	IIV	-.25	-2.66	.05	<.01	.08
	Omissions	-.13	-1.45	.02	.15	.49
	Commissions	-.01	-.011	.00	.92	.86
	HIT RT	-.17	-2.02	.03	.05	.25