Mental slowing in relation to epilepsy and antiepileptic medication

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Objectives – Slowing of the central information-processing speed (CIPS) is frequently observed in epilepsy as a consequence of epileptic seizures and/or antiepileptic drugs (AEDs). A variety of neuropsychological tests are used to assess this ‘mental slowing,’ but it is highly questionable whether the different tasks measure the same cognitive process. Also, it remains unspecified to which degree the various tasks are sensitive to seizure- or treatment-related factors, or both. **Methods** – We used an open clinical non-comparative study design. The sample consisted of adult patients with cryptogenic localization-related epilepsy who performed different cognitive measures of CIPS and psychomotor speed (PmS). Clinical data about their seizures and antiepileptic drug treatment were collected from an electronic patient database. **Results** – Eighty patients were included. CIPS tasks mutually correlated significantly, but did not correlate with measures of PmS (finger tapping and reaction time). Also, the CIPS tasks were differently affected by treatment and seizure effects. Processing of complex information is affected by tonic-clonic seizures, while less complex tasks are more sensitive for AED effects.

Conclusions – CIPS tasks are mainly measuring central processing, and the psychomotor component of these tasks is negligible. We propose a psychometric continuum on which PmS and CIPS tasks are ordered with ascending complexity. The model shows that the tasks are affected differently by seizures, treatment, age, and education level. In neuropsychological practice, this continuum can be helpful in the detection of treatment and seizure effects on the CIPS in epilepsy.

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Key words: antiepileptic drugs; central information-processing speed; cognitive measures; epileptic seizures; psychomotor speed

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Introduction

Slowed central information-processing speed (CIPS) has been found to be a common cognitive comorbidity in several neurological diseases, including epilepsy (1). As processing speed influences higher cognitive functions both directly and indirectly, patients with epilepsy often experience additional cognitive (e.g., memory) problems which are at least partially mediated by their mental slowing (2–4). These cognitive impairments can account for a great burden in the daily life of epilepsy patients, emphasizing the need for careful monitoring of CIPS.

In neuropsychological practice, a variety of computerized and paper-and-pencil tests with different levels of complexity are used to assess

CIPS (5, 6). However, the overlap and relationship between different cognitive tasks are far from clear and it is highly questionable whether all cognitive tasks measure the same cognitive function. Part of this confusion is the variety of terminology used in the literature (‘cognitive speed,’ ‘perceptual speed,’ and ‘mental speed’) (e.g., (7, 8)). Another complicating factor for assessing central information-processing speed is that most measures also require peripheral processing, which is often referred to as psychomotor speed (PmS) (e.g., operationalized as reaction time or motor fluency (9)). It is known that PmS can be impaired by the use of antiepileptic drugs (AEDs) (10, 11). The possibility that low performance on CIPS tasks in epilepsy can thus be partly contributed to psychomotor slowing in

relation to the use of AEDs cannot always be ruled out with certainty.

Slowing of the CIPS in epilepsy can be a consequence of epileptic seizures and/or AEDs, especially in the case of GABAergic drugs (1, 12). Non-GABAergic AEDs have little effect on cognitive function or may even improve CIPS (13, 14). Possible relevant clinical factors (e.g., seizures (type, frequency) and AEDs (type, dose)) may interact with non-clinical factors such as age, intelligence quotient (IQ), or education level, which are argued to be related to CIPS in healthy populations (2, 15). It is yet unclear which clinical factors contribute to slowing of CIPS in refractory epilepsy or, rephrased, to which degree the various CIPS measures are sensitive to seizure- or treatment-related factors, or both. Being able to differentiate between seizure and treatment effects on the slowing of information-processing speed in epilepsy would be of great diagnostic value. The aim of this open clinical non-comparative study was therefore twofold. First, the psychometric relationships among neuropsychological CIPS and PmS tests that are used in clinical practice will be examined. The second purpose of this study was to clarify the sensitivity of the various cognitive tasks for seizure and drug effects.

Methods

Study Population

Patients that are diagnosed with focal epilepsies (EEG: frontotemporal focus) with an unknown cause (cryptogenic localization-related epilepsies) were included, and patients with symptomatic etiology (e.g., head trauma, brain tumor, cerebrovascular accident, cortical dysplasia, encephalitis) were excluded. To rule out other factors than AED and epileptic seizures that could be responsible for slowing of information-processing speed, we excluded patients with psychiatric comorbidity (present state), severe sleeping disorder (present state), and history of epilepsy surgery. Patients with WAIS-III Full Scale Intelligence Quotient (FSIQ) below 70 and/or age below 21 years or over 65 years were also excluded.

All patients underwent a neuropsychological examination for diagnostic purposes in a Dutch tertiary referral centre for epilepsy ('Kempenhaghe'). Patients were assessed in the period of December 2008 until December 2013. This period was chosen because in these 5 years the Dutch version of the Wechsler Adult Intelligence Scale-III (WAIS-III) was used. All patients signed a generic informed consent and gave permission to

use clinically obtained data for scientific purposes. Those patients who refused this consent are not included in this study.

Procedure

Patients were asked to perform six cognitive tasks, three of them assess their CIPS and three tasks involve their psychomotor speed exclusively (Table 1). Four subtests were part of FePsy, a computerized neuropsychological battery (16). Salthouse (2000) determined CIPS tasks often involve elementary comparison, search, and substitution operations and assess 'the speed of responding (usually on paper-and-pencil tests) with simple content in which everyone would be perfect if there were no time limits'(17). Most CIPS measures contain processing of visual information. In addition, we also took a measure of verbal information processing (Stroop word page), because reading speed is associated with visual information-processing speed (18). We also used Salthouse's definition for psychomotor measures: 'relatively simple tasks requiring repetitive finger tapping or some form of reaction time, such as choice reaction time with visual stimuli and manual keypress responses'(17).

Patients were divided into subgroups based on their clinical data which were collected from the electronic patient database.

Statistical analysis

To examine the relationship between cognitive measures, a correlation matrix of all cognitive measures was computed. The influence of demographic and clinical variables was tested with a two-way independent analysis of covariance (ANCOVA). A 2×2 design was used with two binary variables to examine the effects of epileptic seizures and antiepileptic medication. Furthermore, two covariates were added to all analyses: education and age. The statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, version 21.0, IBM Corp., Armonk, NY, USA) for Windows. For analyses, a significance level of $P \leq 0.05$ was chosen.

Results

Sample characteristics

In total, eighty patients were included in this study. The main demographic, clinical, and treatment characteristics are shown in Table 2. The patient population of the tertiary referral centre

Table 1 Cognitive measures

Cognitive domain	Test	Description
Central information-processing speed	Wechsler Adult Intelligence Scale-III Processing Speed Index (sum of raw scores) (WAIS-III PSI) (19)	The WAIS-III PSI consists of two subtests: Digit Symbol Coding. Subjects have to copy symbols paired with numbers in a 120-s time limit. Symbol Search. Subjects have to determine whether either of two target symbols matches any of the symbols in a search group and respond to as many items as possible in a 120-s time limit.
	Stroop word page (WP) (20)	Subjects have to read 100 words (red, green, blue, yellow) row by row, as quickly as possible. Words are printed in black ink.
	Computerized visual searching task (CVST) (16)	Subjects have to compare a centered grid pattern with 24 surrounding patterns, one of which is identical to the target pattern. The test consists of 24 trials. The score is the total average searching time in seconds.
Psychomotor speed	Binary choice reaction test (BCRT) (16)	Subjects have to react differentially to a red square, presented on the left side of the screen than to a green square, presented on the right side. The score is the reaction time in milliseconds.
	Visual reaction time (VRT) (16)	Subjects have to react as quickly as possible to a simple visual stimulus (white square on the screen) that is presented at random intervals, by pressing on the spacebar with the index finger.
	Finger tapping (16)	Subjects have to tap as quickly as possible on the space bar with the index finger of the right and left hand separately, five times per hand. Speed of finger tapping is measured for a period of 10 s.

is characterized by a high percentage of patients with severe or refractory epilepsy, which is reflected in a relatively small 'seizure-free' group (15%) and a relatively high percentage of patients with tonic-clonic (TC) seizure(s) in the year before neuropsychological assessment (35%). About one-fourth of the patients had TC seizures as most frequent seizure type (28%). Other seizure types that were common in this chronic patient group were simple and complex partial seizures. Exploratory analyses showed that only the occurrence of TC seizures did affect the cognitive measures. Therefore, the effect of epileptic seizures was operationalized in further analyses as the presence of TC seizures in the year before neuropsychological assessment (none or ≥ 1 TC seizure).

Another characteristic of the patient group is that many patients were treated with polytherapy (47.5%). The following AEDs were prescribed in mono- or polytherapy: lamotrigine ($n = 38$), carbamazepine ($n = 25$), sodium valproate ($n = 21$), levetiracetam ($n = 16$), oxcarbazepine ($n = 10$), topiramate ($n = 6$), pregabalin ($n = 4$), lacosamide ($n = 3$), vigabatrin ($n = 2$), phenytoin ($n = 2$), and gabapentin ($n = 1$). In our sample, 57 patients were treated with at least one GABAergic drug and 21 patients received only non-GABAergic drug treatment. Comparison of those two groups with independent-samples t -tests showed a significant difference on the FePsy computerized visual searching task (CVST) ($t(70)=2.61$, $P \leq 0.05$): The GABAergic group performed significantly slower than the non-GABAergic group. For the other

Table 2 Sample characteristics

Demographic	
Sex (male/female)	40 (50%)/40 (50%)
Age at testing (years)	43.1 $\pm$ 13.6 (range: 21–63)
Education (1–7) ^a	5.3 $\pm$ 1.1
Handedness (right/left/ambidexter)	72 (90%)/8 (8.8%)/1 (1.3%)
WAIS-III Full Scale IQ	96.0 $\pm$ 14.1 (range: 73–140)
Epilepsy	
Age at epilepsy onset	24.6 $\pm$ 16.8 (range: 1–59)
Duration of epilepsy (years)	18.5 $\pm$ 13.2 (range: 1–52)
Seizures	
Seizure type ^b	
Seizure free >2 years	12 (15%)
Simple partial seizures	16 (20%)
Complex partial seizures	26 (32.4%)
Tonic-clonic seizures	23 (28.8%)
Other seizures	3 (3.8%)
Seizure frequency	
Seizure free >2 years	12 (15%)
Seizure freedom >1 year, ≤ 2 years	8 (10%)
≥ 1 seizures per year	18 (22.5%)
1 seizure per 2 months	6 (7.5%)
Monthly seizures	11 (13.8%)
Weekly seizures	15 (18.7%)
Daily seizures	8 (10%)
Unknown	2 (2.5%)
Tonic-clonic seizures (none/ ≥ 1 in the year before assessment)	52 (65%)/28(35%)
AED treatment	
No. of AED (none/monotherapy/polytherapy)	2 (2.5%)/40 (50%)/38 (47.5%)
Drugload	1.6 $\pm$ 1.0

Values are mean $\pm$ SD or n (%)

^aEducation coding is based on Verhage coding system (22) which varies from 1: 'only elementary school' to 7: 'university degree.'

^b'Seizure type' resembles the most frequent seizure type per patient. Absences ($n = 1$), tonic seizures ($n = 1$), and myoclonic seizures ($n = 1$) were grouped under 'other.'

cognitive measures, there was no significant difference between the GABAergic and non-GABAergic group.

In the main analyses, AED use was operationalized as 'drugload,' which is calculated as prescribed daily dose of antiepileptic medication divided by the defined daily dose (according to criteria of the WHO Collaborating Centre for Drug Statistics Methodology) (21). The study population was divided into two drugload groups based on median split.

Cognitive measures

Descriptive statistics and correlations of the cognitive measures are shown in Table 3. Note that for the WAIS-III Processing Speed Index (PSI) and tapping, a faster performance represents a higher score, while for the other measures (CVST, BCRT, Stroop WP, VRT), a higher score (in (milli)seconds) represents a slower performance.

A significant correlation was found between the WAIS-III PSI and the CVST ($r = -0.598$, $P \leq 0.001$). Stroop word page (WP) correlated significantly with both these measures (CVST: $r = 0.330$, $P \leq 0.05$; WAIS-III PSI: $r = -0.339$, $P \leq 0.05$). The binary choice reaction time (BCRT) did only correlate significantly with the CVST ($r = 0.330$, $P \leq 0.05$). There were no significant correlations between measures of visual reaction time (VRT) and finger tapping and measures of CIPS.

Clinical variables

CIPS measures – WAIS-III PSI – For the WAIS-III PSI, a significant main effect of TC seizures was found ($F(1,74)=4.54$, $P \leq 0.05$): The WAIS-III PSI was significantly lower for the patients with TC seizures in the year before assessment

than for the patients without TC seizures. The main effect of drugload and the interaction effect were not significant. Of the covariates, the effect of age ($F(1,74)=9.86$, $P \leq 0.01$) and education ($F(1,74)=12.22$, $P \leq 0.001$) was significant.

CVST – For the CVST, a significant main effect of drugload was found ($F(1,68)=5.06$, $P \leq 0.05$): The high-drugload group performed significantly slower than the low-drugload group. The main effect of TC seizures was not significant, but the interaction effect was significant ($F(1,68)=8.94$, $P \leq 0.01$). Of the covariates, the effect of age was significant ($F(1,68)=14.38$, $P \leq 0.001$).

Stroop WP – For the Stroop WP, a significant main effect of TC seizures was found ($F(1,50)=4.78$, $P \leq 0.05$): The patient group with TC seizures in the year before assessment performed significantly slower than the patient group without TC seizures. Neither the main effect of drugload nor the interaction effect reached the level of significance. Of the covariates, the effect of education was significant ($F(1,50)=7.28$, $P \leq 0.01$).

PmS measures – BCRT – For the BCRT, a significant main effect of drugload was found ($F(1,32)=4.38$, $P \leq 0.05$): The high-drugload patient group performed significantly slower than the low-drugload group. Neither the main effect of TC seizures nor the interaction effect reached the level of significance. Of the covariates, the effect of age was significant ($F(1,32)=8.81$, $P \leq 0.01$).

VRT – There were no significant main or interaction effects of TC seizures or drugload, neither for the dominant hand measure nor for the non-dominant hand measure.

Finger tapping – There were no significant main or interaction effects of TC seizures or drugload,

Table 3 Correlation matrix

	Mean	SD	N	1	2	3	4	5	6	7
1. WAIS-III PSI	97.6	24.2	80							
2. CVST (s)	12.8	3.8	74	-0.598**						
3. Stroop WP (s)	49.7	10.0	56	-0.339*	0.330*					
4. BCRT (ms)	386.0	88.4	38	-0.249	0.330*	0.223				
5. VRT DH (ms)	294.4	41.5	74	-0.162	0.197	0.192	0.149			
6. VRT NDH (ms)	309.1	50.3	74	-0.166	0.195	0.106	0.077	0.878**		
7. Tapping DH (n/10s)	52.5	5.8	41	0.237	-0.151	-0.202	-0.139	-0.073	-0.062	
8. Tapping NDH (n/10s)	46.6	5.6	40	0.077	-0.187	.093	.033	-0.100	-0.192	0.609**

WAIS-III, Wechsler Adult Intelligence Scale-III, PSI, Processing Speed Index, CVST, computerized visual searching task, VRT, visual reaction time, BCRT, binary choice reaction time, DH, dominant hand, NDH, non-dominant hand, WP, word page.

* $P \leq 0.05$, ** $P \leq 0.001$.

neither for the dominant hand measure nor for the non-dominant hand measure.

Summary results

The main findings are shown in Figure 1. We propose a psychometric continuum with the processing of the most undemanding stimuli (PmS) on one end and the processing of complex information at the other end (CIPS). The model also shows that cognitive tasks are affected differently by seizures, treatment, age, and education.

Discussion

This open clinical non-comparative study was conducted to examine the relationship between cognitive measures of CIPS and psychomotor speed that are used in neuropsychological diagnostics of epilepsy patients. The second aim was to explore the sensitivity of these cognitive measures for seizure and treatment effects.

The results of this study indicate that tasks that demand central processing of complex visual information are related (WAIS-III PSI and CVST), also to processing of verbal information (reading speed, Stroop WP), in accordance with previous findings (18). In contrast to other research, BCRT is related to one of the CIPS tasks (CVST) and not to simple visual reaction time (23). This could be because the complexity of choice reaction time lays in a ‘gray area’ between the pure CIPS measures and the pure PmS measures. In other words, the BCRT task may be simpler than CIPS tasks and more complex than PmS tasks, because BCRT contains a decision component in addition to a psychomotor component (24). The information-processing tasks are unrelated to the PmS measures without decision component (visual reaction time and finger tapping), which indicates that impaired CIPS is not related to slowing of psychomotor speed, implying that CIPS tasks are mainly measuring

central processing and that the peripheral processing component of these tasks is negligible. Following this line of reasoning, we ordered cognitive tasks in an ascending manner with regard to complexity of processed information in the ‘information-processing continuum’. In neuropsychological practice, this continuum can be helpful for the detection of treatment and seizure effects of mental slowing in cryptogenic localization-related epilepsy. Our results indicate that CIPS tasks are differently affected by clinical and treatment effects. We found that the presence of tonic-clonic seizures (TC seizures) in the year before assessment is associated with lower scores on the WAIS-III PSI and Stroop WP. This is not found for the presence of simple and complex partial seizures, which is in line with the consensus that TC seizures are more likely to impair cognition than partial seizures (25). However, TC seizures are only associated with impaired performance on the CVST when in interaction with treatment effects. In general, the computerized tasks (CVST and BCRT) seem to be more sensitive for treatment effects. These tasks are part of the computerized test battery ‘FePsy’ which is accepted as sensitive to cognitive side effects of AEDs (6, 26). It should be mentioned that some non-GABAergic AEDs are known to have little effect on CIPS or may even improve cognitive functioning (13, 14). In this study, the CVST proved to be a sensitive measure to differentiate between the cognitive effects of non-GABAergic and GABAergic drugs.

In our sample, no effect of clinical and treatment variables is found on PmS tasks without decision component (visual reaction time and finger tapping). This indicates that processing of mentally undemanding stimuli is not influenced by AED and seizure effects, as opposed to CIPS. This is in line with previous findings in samples of newly diagnosed and seizure-free epilepsy patients (1, 12). However, this does not exclude the possibility that some AEDs (e.g., topiramate) can affect PmS (10, 11). A limitation of the

Figure 1. A summary of the results of the present study. A psychometric ‘information-processing’ continuum is proposed, on which cognitive tasks are ordered in ascending complexity. The model shows that the tasks are affected differently by seizures, treatment, age, and education. Abbreviations: WAIS-III, Wechsler Adult Intelligence Scale-III; PSI, Processing Speed Index; CVST, computerized visual searching task; VRT, visual reaction time; BCRT, binary choice reaction time; WP, word page.

current research is that it was not possible to distinguish the effects of different AEDs, because the majority of the patients in a tertiary epilepsy centre are treated with polytherapy.

Although the risk of possible confounders was reduced by excluding patients with symptomatic epilepsy or psychiatric and neurologic comorbidity, we could not control our findings for neuronal correlates that are known to be associated with CIPS in epilepsy. For example, white matter volume is associated with CIPS impairment in chronic temporal lobe epilepsy (27, 28). Other neuronal correlates of interest are regional cerebral blood flow in the anterior cingulate cortex, brain network efficiency, or cortical brain morphology (29–31). Future research is needed to clarify the relationship between neuronal correlates and seizure and treatment effects on CIPS in epilepsy.

Conclusion

To our knowledge, the present research is the first attempt to differentiate for treatment and seizure effects on the CIPS of patients with non-symptomatic epilepsy. We found that CIPS tasks are affected differently by treatment and seizure effects. These findings have some important implications for neuropsychological diagnostics in epilepsy, because different information-processing tasks are not interchangeable but complementary in differentiating between seizure and medication effects. In clinical practice, it is highly recommended to use tasks with different administration modes (computerized and paper-and-pencil tests) (32, 33). We propose a model in which speed of processing of more complex information is affected by TC seizures, while less complex tasks are more sensitive for AED effects. This model contributes to specialized neuropsychological diagnostics of epilepsy and can improve fine tuning of pharmacological treatment for individual patients. Furthermore, a more specified monitoring of CIPS will indirectly improve daily (cognitive) functioning of patients and therewith their quality of life.

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Conflicts of interest

We declare that there are no conflict of interests associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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