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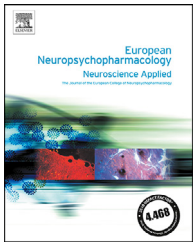

Is the computerized assessment of psychomotor speed more sensitive to cognitive effects of antiepileptic pharmacotherapy than tests with a focus on higher-order cognitive processing? Implications for the choice of sensitive test parameters

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Abstract
The study evaluated whether it is psychomotor speed or higher-order cognitive processing which is primarily affected by antiepileptic drug (AED) treatment in epilepsy and whether computerized testing versus paper-pencil testing of executive functions is more sensitive. In this retrospective observational study, 55 patients with epilepsy underwent *NeuroCog FX®*, a computerized battery assessing “psychomotor speed/alertness” and “cognitive processing” via 8 tasks, and *EpiTrack®*, a paper-pencil screening of “executive functions and working memory” based on 6 subtests. Test performance was related to the number of drugs and the Defined Daily Dose and the presence/absence of AEDs with known adverse psychotropic effects. *EpiTrack®* performance correlated with "cognitive processing" of the *NeuroCog FX®* but not with "psychomotor speed/alertness". Significant correlations with drug load were mainly yielded for *EpiTrack®* (number of AEDs: $r = -0.551$, total DDD: $r = -0.452$) and "cognitive processing" (number of AEDs: $r = -0.433$, total DDD: $r = -0.415$). "Psychomotor speed/alertness" was

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less related to drug load (number of AEDs: $r = -0.285$, total DDD: $r = -0.232$). Statistical control for "psychomotor speed/alertness" hardly changed the correlations of *EpiTrack®* or "cognitive processing" with drug load indices. AEDs with known adverse profiles negatively affected *EpiTrack®* and the "cognitive processing" but not the "psychomotor speed/alertness" domain of the computerized test. The results demonstrate that it is less basal psychomotor speed than higher-order cognitive processing which is negatively affected by antiepileptic pharmacotherapy. The results question the value of (computer-)tests with a major emphasis on psychomotor speed and alertness for cognitive drug monitoring.

1. Introduction

Cognitive side effects of antiepileptic pharmacotherapy represent a major issue in regard to the safety of drug treatment, tolerance, compliance, and drug retention (Bootsma et al., 2009; Gilliam et al., 2004). Antiepileptic medication can help to improve cognitive performance, particularly when epileptic activity and seizures are controlled (Eddy et al., 2011; Park and Kwon, 2008). However, many patients, especially those under AED polytherapy, complain about cognitive side effects with negative impact on their overall health-related quality of life (Eddy et al., 2011; Waagemans et al., 2011). In fact, if patients are asked which adverse effects they would be willing to accept in the prospect of seizure control, cognitive and psychiatric side effects belong to the least tolerated class of side effects (Witt et al., 2013a). Given the high clinical and personal relevance, cognitive side effects need to be considered in individual patient care (Witt and Helmstaedter, 2013,2017). Ideally, patients with new-onset epilepsy would undergo a cognitive screening already before the introduction of the first antiepileptic medication (Witt and Helmstaedter, 2012,2015).

From a practical point of view the question arises which type of assessment provides the best cost-benefit ratio in terms of obtaining objective and valid results while being time-economic. Subjective reports appear to be the easiest way to attain the required information but often they reflect mood and maladjustment to epilepsy rather than objective cognitive impairment (Hall et al., 2009; Helmstaedter,2001; Samarasekera et al., 2015; Tinson et al., 2018).

As regards the cognitive assessment in drug trials and studies, a huge variety of tools has been used, ranging from single test measures, test batteries, to complex multi-task measures such as intelligence (IQ) (Boshuisen et al., 2015; IJff et al., 2015). At present there is no comprehensive and particularly no comparative overview of which assessment tools are better or less well suited to monitor cognition along with AED treatment. Reviewing the 10 most recent studies addressing adverse cognitive side effects under latest generation AEDs (namely perampanel, brivaracetam, and lacosamide) clearly indicates a trend towards brief screening tools which are time-economic and suited for repeated application (Helmstaedter and Witt, 2013; IJff et al., 2015; Lancman et al., 2016; Liguori et al., 2018; Meador et al., 2011, 2016a,2016b; Meschede et al., 2018; Pina-Garza et al., 2018; Witt et al., 2018). Computerized and traditional paper-pencil tests were used with individual or compound scores on psychomotor speed, executive functions, and memory.

Historically, it is a commonly held position that AEDs slow patients down (Dodrill and Temkin, 1989). In this regard older studies demonstrated significant impairment of functions with a motor component respectively of psychomotor speed and alertness as a consequence of adverse effects of carbamazepine or phenytoin for example (Brodie et al., 1987; Dodrill, 1975; Dodrill and Troupin, 1977; Gillham et al., 1988; MacPhee et al., 1986a; Macphee et al., 1986b).

Facing the confusion resulting from the variety of terms used to describe adverse cognitive AED effects, i.e. reduced cognitive speed, perceptual speed, or mental speed, Grevers and colleagues in 2016 demonstrated a differential sensitivity of cognitive tasks to treatment and seizures when ranked according to their complexity (Grevers et al., 2016). Using tasks assessing central information processing speed (WAIS processing speed index, Stroop test, Computerized visual search) and tasks of psychomotor speed (finger tapping, Computerized visual and choice reaction time), seizures affected the WAIS processing speed index and Stroop performance whereas the computerized tasks of choice reaction time and visual search seemed more sensitive to treatments effects (see also van Veenendaal et al., 2016). The same group described attentional dysfunction, psychomotor slowing and alertness deficits in the context of the treatment with ethosuximide in children (IJff et al., 2016).

These studies are in part in line with the suggestions from the 1980ies, but tasks had been used which address the factors speed and cognitive processing at the same time. Indeed other studies including our own research indicate that higher-order cognitive processing rather than psychomotor speed is the major target of AEDs. In a large randomized Norwegian drug withdrawal study Hessen and colleagues employed a computerized (California computerized assessment package, CALCAP) test battery which revealed improvement particularly in the more complex functions of choice reaction, language discrimination, selective attention, response reversal and form discrimination (Hessen et al., 2006). In addition to the computerized assessment a paper-pencil test battery was employed which indicated that executive functions (Stroop Color Word Test and Controlled Oral Word Association) were sensitive to drug withdrawal (Hessen et al., 2007). Reviews of the field and our own studies concerned with cognition and antiepileptic drug treatment suggest that indeed executive functions appear to be the most sensitive measures (Witt and Helmstaedter, 2013,2017). Executive functions, different from

reaction time tests, primarily address cognitive operations, but unfortunately most often not without time measurement.

The findings so far raise the question of whether patients appear slowed down because of an affection of basal functions of psychomotor speed with secondary impact on other cognitive domains, or whether they appear slowed down because AEDs affect qualitative aspects of higher cognitive processing. Connected to this is the practical clinical question of whether to use computerized assessments which allow for an exact measurement of reaction times in milliseconds or standard paper-pencil tests assessing attention and executive functions. Besides an exact time measurement, a greater objectivity, easy application, and automatic scoring represent advantageous features of computerized tests. However, most computerized tests have high demands on psychomotor speed and primarily involve the visuo-motor loop. Several computerized tests have already been used in patients with epilepsy, and some had been used for the cognitive monitoring of AED side effects (Witt et al., 2013b).

Against this background the present study was set up to evaluate the differential diagnostic value of basal psychomotor-speed versus higher cognitive processing and to compare the sensitivity of a computerized versus a standard paper-pencil assessment tool with regard to the cognitive effects of antiepileptic pharmacotherapies.

The computerized assessment (*NeuroCog FX®*) had been originally developed for use in patients with epilepsy and was later also employed in a neurosurgical context to monitor cognition along with treatment in patients with brain tumors (Flechl et al., 2012,2017; Hoffermann et al., 2017; Hoppe et al., 2009; Rick et al., 2018; Witt et al., 2018). The paper-pencil test (*EpiTrack®*) had explicitly been developed for AED monitoring and it has been successfully used in AED drug trials and studies (Helmstaedter et al., 2010; Helmstaedter and Witt, 2013; Liguori et al., 2018; Lutz and Helmstaedter, 2005; Reuner et al., 2016; Witt et al., 2015,2018).

The first and practical objective of the study was to determine and compare the sensitivity of the test parameters of both tests instruments in regard to quantitative (total drug load indices) and qualitative (AEDs with known adverse cognitive side effects) aspects of the antiepileptic pharmacotherapy.

NeuroCog FX®, on the basis of principal component analysis, explicitly differentiates between "psychomotor speed/alertness" and "cognitive processing" and reveals separate scores for both domains. These scores can be considered as quite independent of each other. The *EpiTrack®* in contrast provides only one total score representing "executive functions and working memory". Subtest results are not being evaluated or rated in addition. Since all but one of the subtasks of *EpiTrack®* are time-critical, i.e. the time to perform the test is being taken or the task has to be done within a given time interval, the performance itself and the speed by which the performance is being done are confounded in the test score of *EpiTrack®*.

Accordingly the other objective of this study was to segregate the impact of AEDs on psychomotor speed and higher cognitive processing which are assessed by the two tests. Therefore the relation of antiepileptic pharmacotherapy to these two domains was evaluated each by statistically controlling for the respective other domain in partial correlation analyses.

2. Experimental procedures

This retrospective study was performed at the Department of Epileptology (University of Bonn Medical Center, Bonn/Germany) and evaluated cognitive performance in relation to quantitative and qualitative aspects of antiepileptic pharmacotherapies in patients with diagnosed epilepsy.

2.1. Patients

Patients were retrospectively selected from a registry under the condition that they had been admitted for the screening of possible cognitive AED side effects and underwent paper-pencil and computerized testing.

Data sets were anonymized and prepared for analysis.

2.2. Parameters of drug treatment

Drug load was defined as the total number of concomitant AEDs and in addition by calculating the cumulative or total defined daily dose (DDD). (https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/).

As we have demonstrated before, the number of AEDs may serve as a good marker for DDD, but if all information on doses is available DDD surely is the more exact measure (Witt et al., 2015).

In addition the presence/absence of drugs with adverse psychotropic effects [phenytoin (PHT), phenobarbital (PHB), primidone (PRM), clonazepam (CZP), clobazam (CLB), topiramate (TPM), and zonisamide (ZNS)] was taken into consideration. The drugs were categorized as potentially disadvantageous according to recent reviews (Eddy et al., 2011; Witt and Helmstaedter, 2017).

2.3. Test instruments were

1 the ***NeuroCog FX®***, a computerized neuropsychological screening test battery for adolescents and adults (16–75 years) which runs on Windows PCs. This test consists of eight subtasks which according to factor analysis represent two independent domains. The first domain is "psychomotor speed/alertness". This domain comprises 3 subtests: "simple reaction time", "choice reaction time", and "inverted choice reaction time (reversed stimulus condition)". The second domain is "cognitive processing" comprising 5 subtests: a "2-back task", "digit span forward", "verbal fluency", "verbal memory", and "figural memory" (Hoppe et al., 2009). Age-corrected standardized scores of "psychomotor speed/alertness" and cognitive processing" were chosen as the dependent measures of interest. The time it takes to apply the test is between 20 and 30 min. The test has been standardized in 244 healthy subjects. Scoring is automated and provides standard values ($m = 100$, $SD = 10$). Scores lower 90 (mean minus one standard deviation) were considered as impaired.

2 the ***EpiTrack®***, a brief paper-pencil screening test for adolescents and adults (16–87 years) assessing executive functions via six tasks addressing response inhibition, anticipation, psychomotor speed, mental flexibility, verbal fluency and working memory (Lutz and Helmstaedter, 2005). The second revised edition of this test has been standardized in 689 healthy subjects. One total score is calculated by adding transformed subtest scores. This total score is age-corrected resulting in the

EpiTrack® score. The *EpiTrack®* score which can range from 9 to 49 points represents the measure of interest for this study. Scores lower than mean minus one standard deviation of the healthy subject normative sample were considered as impaired. The application time for this test ranges between 10 and 15 min. Scoring is easily done using a single scoring sheet. The sheet requests transformation of raw scores, age correction of the sum of transformed scores and the categorization of the *EpiTrack®* score into performance categories.

The tests were applied on consecutive days, at the same daytime, under unchanged medical treatment and not subsequent to seizures (Helmstaedter et al., 1994). The order of testing was not fixed and not expected to play a role in regard to the test results.

2.4. Statistics

Correspondence of the test results in regard to frequencies of impaired vs. unimpaired performances was calculated by means of tabulation statistics.

The relation between test and drug load parameters was analyzed by Pearson correlation statistics. According to Cohen (Cohen, 1988) coefficients $0.1 \leq r < 0.3$ were rated as small, coefficients $0.3 \leq r < 0.5$ as moderate, and coefficients $r \geq 0.5$ as large correlations/effect sizes.

Differences in the magnitude of correlation coefficients were statistically compared via the Fisher-z-test for dependent samples (Eid et al., 2010).

In order to separate the drug load effects on speed and cognitive processing partial correlations were calculated by which the relation between cognitive processing tasks and drug load indices were statistically controlled for psychomotor speed and vice versa.

Performance differences dependent on the presence/absence of drugs with known adverse cognitive effects were evaluated via an analysis of variance (ANOVA). Cohens *d* was chosen to determine effect sizes. According to Cohen (Cohen, 1988) $d = 0.2$ represents a small effect, $d = 0.5$ a medium, and $d = 0.8$ a large effect.

For the figures, and in order to be able to compare the scores from paper-pencil and computerized testing, the age-corrected EpiTrack scores were transformed into standard scores with mean of 100 and a standard deviation of 10.

All statistics were conducted using IBM SPSS Statistics 24.

3. Results

A total of 55 patients with mostly pharmacoresistant symptomatic epilepsies were included, thereof 33 women (60%). The average age of the patients was 35.7 years (SD 12.0 years) and the average age at epilepsy onset was 23.2 years (SD 13.2 years), the average duration of epilepsy was 12.6 years (SD 12.3 years). (see Table 1)

For the purpose of group statistics, off-drug patients (3 patients) and patients under monotherapy as well as patients with four or five drugs (1 patient) were merged into one group each. 21 out of 55 patients (38.2%) were off-drug or on monotherapy; 18 patients (32.7%) on two drugs; 11 patients (20%) on three drugs; and 5 patients (9.1%) on four or five drugs. Mean number of AEDs was 2.0 (SD 1.0), the average total DDD was 2.3 (SD 1.7). Number of AEDs and total DDD were highly correlated ($r = 0.74$, $p < 0.001$; effect size: large).

EpiTrack® performance turned out to be impaired in 30 out of the 55 (55%) patients, "psychomotor speed/alertness" of the *NeuroCog FX®* in 22 patients (40%), and "cognitive processing" in 32 patients (58%).

Table 1 Patient characteristics.

Variables	N	
Gender (male/female)	55	22/33 (40%/60%)
Age, M (SD)	55	35.7 (12.0)
Education > 10 years	55	24 (43.6%)
Age at seizure onset, M (SD)	55	23.2 (13.2)
Duration of epilepsy, M (SD)	55	12.6 (12.3)
Seizure types:	55	
Simple-partial		18 (32.7%)
Complex-partial		33 (60.0%)
Generalized tonic-clonic		25 (45.5%)
Seizure frequency /month	51	13.8 (35.1)
Number of AEDs, M (SD)	55	2.0 (1.0)
Off drug		3 (5.5%)
1 drug		18 (32.7%)
2 drugs		18 (32.7%)
3 drugs		11 (20.0%)
4 drugs		4 (7.3%)
5 drugs		1 (1.8%)
Total Defined Daily Dose (DDD), M (SD)	52	2.3 (1.7)
Drugs with adverse effects	55	21 (38%)

M, mean; SD, standard deviation; AEDs, antiepileptic drugs.

Table 2 Correlation EpiTrack® and NeuroCog FX®.

NeuroCog FX®-scores		
	Cognitive processing	Psychomotor speed/Alertness
EpiTrack®	$r = 0.568^{**}$	$r = 0.178$ n.s.

$^{*}p < 0.05$
$^{**}p < 0.01$.
n.s. not significant.

The concordance of impairments in the *EpiTrack®* with impairments in "cognitive processing" of the *NeuroCog FX®* was obtained in 47 patients (85%) ($chi^2 = 12.9$, $p < 0.001$), the concordance with impairments in "psychomotor speed/alertness" of the *NeuroCog FX®* in 29 (53%) only ($chi^2 = 0.30$, n.s.).

Concordant unimpaired performances for the *EpiTrack®* and *NeuroCog FX®* were seen in 16 patients for the "cognitive processing" parameter and in 17 patients for the "psychomotor speed/alertness" parameter.

In line with these findings, *EpiTrack®* performance correlated significantly with the "cognitive processing" ($r = 0.568$, $p < 0.01$) but not with the "psychomotor speed/alertness" component of the *NeuroCog FX®* ($r = 0.178$, n.s.) (Table 2). The two components of *NeuroCog FX®* did not significantly correlate with each other ($r = 0.162$, n.s.).

Significant moderate and large correlations with the total drug load indices were yielded for *EpiTrack®* ($r = -0.551$, $p < 0.01$ for the number of AEDs, $r = -0.452$, $p < 0.01$ for the total DDD). The "cognitive processing" component of the *NeuroCog FX®* showed significant moderate correlations with drug load parameters ($r = -0.433$, $p < 0.01$ for the number of AEDs, $r = -0.415$, $p < 0.01$

Table 3 Correlations and partial correlations of drug load indices with EpiTrack® and NeuroCog FX®.

	N.o. AEDs	Total DDD
EpiTrack®	$r = -0.551^{**}$	$r = -0.452^{**}$
- controlled for "psychomotor speed"	$r_{par} = -0.525^{**}$	$r_{par} = -0.425^{**}$
NCFX "cognitive processing"	$r = -0.433^{**}$	$r = -0.415^{**}$
- controlled for "psychomotor speed"	$r_{par} = -0.409^{**}$	$r_{par} = -0.394^{**}$
NCFX "psychomotor speed/alertness"	$r = -0.285^{*}$	$r = -0.232$ n.s.
- controlled for EpiTrack®	$r_{par} = -0.160$ n.s.	$r_{par} = -0.176$ n.s.
- controlled for "cognitive processing"	$r_{par} = -0.242$ n.s.	$r_{par} = -0.184$ n.s.

* $p < 0.05$.
** $p < 0.01$.

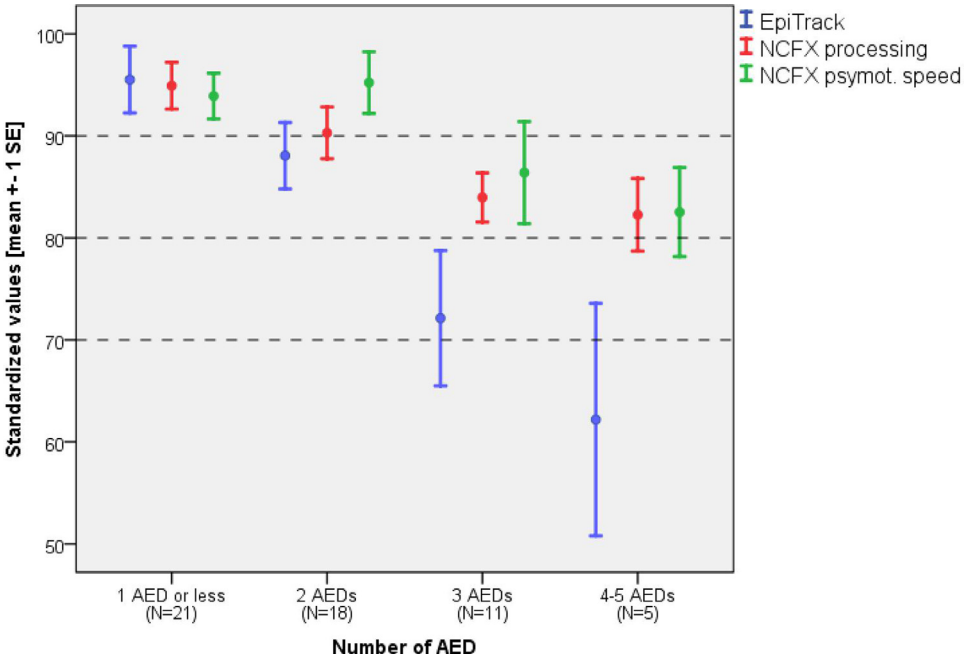

Fig. 1 Performance in computerized vs. paper-pencil testing as a function of drug load. Displayed are standardized scores of the three test scores ($m = 100$ SD $= 10$). The dotted lines mark the mean minus one, two, three standard deviations.

for the total DDD) (Table 3 & Fig. 1). For "psychomotor speed/alertness" a significant small correlation with the number of AEDs ($r = -0.285$, $p < 0.05$) was obtained. The correlation with the total DDD did not reach statistical significance ($r = -0.232$, n.s.).

When statistically comparing the magnitude of the correlation coefficients, we found a significant higher correlation between the total drug load and *EpiTrack®* performance than between the total drug load and "psychomotor speed/alertness" of the *NeuroCog FX®* ($z = 1.92$, $p < 0.05$, one-sided testing). The correlations of the total drug load with components of the *NeuroCog FX®* did not differ significantly ($z = 0.94$, $p > 0.1$, one-sided testing, with consideration of the nonsignificant correlation between the two test parameters).

Table 3 shows the findings from partial correlation analyses. When controlling for "psychomotor speed/alertness" the associations between *EpiTrack®* and "cognitive processing" with indices of drug load did not change significantly. (The partial correlations of *EpiTrack®* and "cognitive processing" with number of AEDs were $r_{partial} = -0.525$ and $r_{partial} = -0.409$, respectively, the partial correlations with the total DDD were $r_{partial} = -0.425$ and $r_{partial} = -0.394$, respectively)

In contrast, the correlation of "psychomotor speed/alertness" with the number of AEDs lost significance when statistically controlling for *EpiTrack®* performance or "cognitive processing".

In addition the differentiation of the presence/absence of drugs with known adverse profiles negatively affected *EpiTrack®* performance ($F = 8.2$, $p < 0.01$; Cohens $d = 1.1$) and the "cognitive processing" domain of *NeuroCog FX®* ($F = 15.7$, $p < 0.001$; Cohens $d = 0.8$) (Fig. 2). Performance on "psychomotor speed/alertness" did not differ for treatments with or without AEDs with known adverse cognitive side effects ($F = 0.51$, $p = 0.45$).

4. Discussion

The present study in 55 patients with diagnosed epilepsy evaluated whether antiepileptic pharmacotherapy does

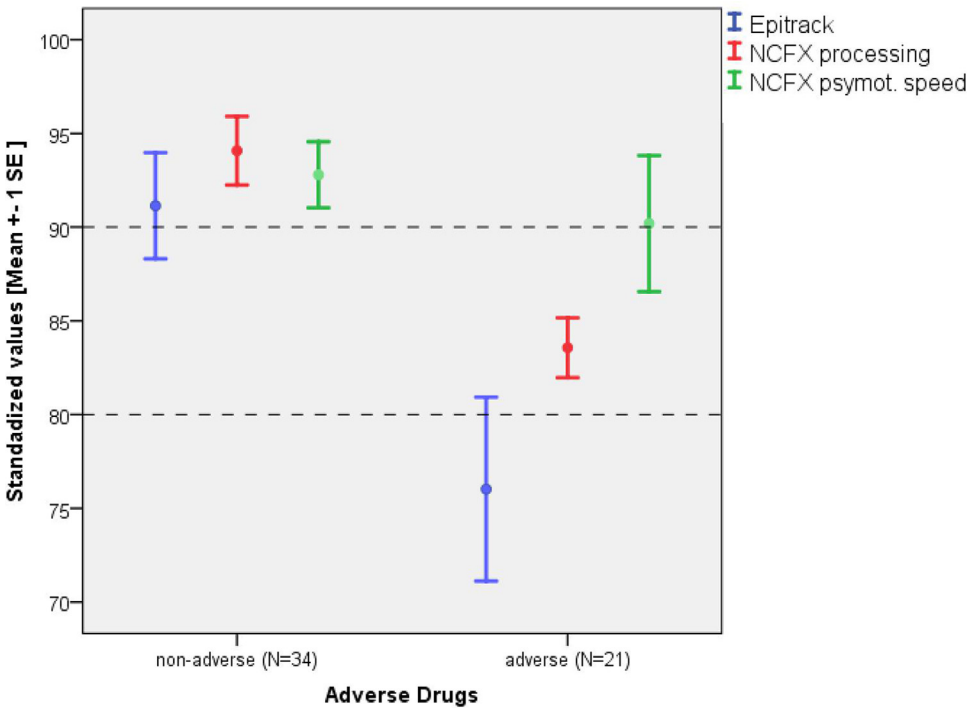

Fig. 2 Performance in computerized vs. paper-pencil testing as a function of the presence/absence of drugs with negative cognitive profiles in mono-or polytherapy. Displayed are standardized scores of the three test scores ($m = 100$ SD $= 10$). The dotted lines mark the mean minus one and two standard deviations.

primarily affect psychomotor speed or higher-order cognitive processing. We sought to derive implications for the choice of sensitive test parameters and whether the mode of assessment (computerized vs. paper-pencil) is of relevance.

The commonly held position in regard to antiepileptic drugs is that they "slow patients down!" and that psychomotor speed is the contaminating factor which affects cognitive performance in treated patients (Dodrill and Temkin, 1989). More recent research suggests that independent of whether individual functions like language or memory may be impaired under a given drug, attention and executive functions are the most vulnerable/sensitive cognitive domain (Witt and Helmstaedter, 2017). Meta-analyses comparing different test instruments and test parameters used for the assessment of adverse AED effects are not available yet. Many functions assessed by paper-pencil tests and most functions assessed via computerized batteries are time-critical, i.e. the time to perform the tasks is registered or a task has to be done within a predefined time interval. Accordingly, tests used for AED monitoring often comprise confounded measures of cognitive processing and operations on the one hand and cognitive or psychomotor speed on the other hand.

Taking this into consideration the question of this study was twofold. First we evaluated whether it is the basal psychomotor speed or higher-order cognitive processing which is preferentially sensitive to AED induced cognitive side effects. Second, and this is implicated by the first question, we compared the sensitivity of the test scores resulting from computerized versus paper-pencil testing in regard to drug treatment.

In contrast to the expectation that measures assessing psychomotor speed in milliseconds might be more sensitive than complex tasks with an additional time component, the results demonstrate that it is less likely the basal psychomotor speed than the higher-order cognitive processing which is negatively affected by quantitative (number of AEDs, total DDD) and qualitative (cognitive side effect profiles) aspects of the antiepileptic pharmacotherapy. The *EpiTrack®* as well as the "cognitive processing" component of the computerized test battery *NeuroCog FX®* differentiated drug load better than the factor "psychomotor speed/alertness". However, 5 of 6 *EpiTrack®* tasks are time/speed sensitive. In contrast, only 1 out of 5 subtests which constitute the "cognitive processing" component of the computer test is time-critical. Because AED effects on psychomotor speed may also affect other time-critical performances, the speed component was partialed out when correlating the *EpiTrack®* performance and the cognitive processing component of *NeuroCog FX®* to drug load indices. Of note, this did not significantly change the moderate to large correlations. Vice versa, the initially already small correlation of "psychomotor speed/alertness" and drug load became non-significant when "cognitive processing" was partialed out.

In summary, the different sensitivity of the test parameters of the two tests to drug load questions the value of tests with a major emphasis on psychomotor speed for the cognitive drug monitoring. The practical advice from this study would be not to go the easy way and just rely on reaction time measures. Adverse cognitive side effects may well be missed. It should be noted that the results do not vote for or against computerized testing. They rather suggest that tasks with demands on higher cognitive processing

and basal psychomotor speed should be kept separate and that tasks with higher demands on cognitive processing and operations should probably be preferred.

With this study some shortcomings need to be mentioned. First of all the study has a cross-sectional and not longitudinal study design. One would surely like to have follow-up testing along with drug changes. This would require running computerized and paper pencil-tests in parallel in future drug trials. Second, psychomotor speed and cognitive processing are per se very difficult to separate, i.e. is a performance slow because of the speed or because the cognitive process is impaired? Different from the *NeuroCog FX®* scores which represent quite independent scores because they are based on a factor analysis, the speed and processing components are confounded in the *EpiTrack®* score. We did not go into subtest analyses of the EpiTrack® because all but one of its subtests are time-critical, and because subtest interpretation is not being considered in the test application and clinical practice. If one would like to go into more detail and depth an experimental setting would be required which explicitly aims to separate and control speed and cognitive operations. Nevertheless, the partial correlation analysis which allows the subtraction of speed from the correlation of drug treatment with other test scores reveals a quite convincing result.

For clinical practice and for the design of drug trials which include neuropsychological outcome measures it is important to know that the choice of the test instrument and test parameters can determine the probability by which adverse cognitive events are detected or not. This information is useful for test selection and for the rating of past and upcoming cognitive AED trials which reveal or do not reveal cognitive side effects. Hypothetically, this result is also of interest for the assessment of AED effects on the capability of car driving in seizure free patients.

5. Conclusion

The valid assessment of cognitive side effects of antiepileptic drugs primarily depends on the cognitive demands of the applied instruments and less on the mode of assessment. Antiepileptic pharmacotherapy appears to primarily affect higher-order cognitive processing, especially executive functions, rather than psychomotor speed. This needs to be considered when choosing cognitive instruments for the cognitive monitoring of antiepileptic pharmacotherapies in clinical trials and in clinical practice. An evidence-based test selection is strongly recommended.

Role of funding source

There was no funding source for this study.

Conflict of interest

C. Helmstaedter reports grants from the EU, honoraries by UCB, Eisai, GW pharma, travel support by Desitin, a honorary for editorial work for the Journal Seizure (Elsevier), honoraries from incurance companies and court for testemonies, license fees from UCB and licence fees from Eisai.

P. Durch has no disclosures.

Ch. Hoppe receives licence fees for the NeuroCog FX computer test from Eisai

J.-A. Witt reports personal fees from Eisai and UCB, outside the submitted work.

CRediT authorship contribution statement

Christoph Helmstaedter: Formal analysis, Writing - original draft, Writing - review & editing. **Philipp Durch:** Data curation, Investigation, Writing - original draft, Writing - review & editing. **Christian Hoppe:** Writing - review & editing. **Juri-Alexander Witt:** Conceptualization, Formal analysis, Writing - review & editing.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional (UKB) and/or national research committee and with the Helsinki Declaration of 1975 (as revised in 1983). The data for the present study were retrospectively extracted from a database and anonymized for further analyses. The database has been approved by the Ethics Committee of the University Clinic Bonn #002.17

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