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Cognition: development of a cognitive testing battery on the ipad for the evaluation of patients with Brain Mets.

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Abstract

Purpose: In order to make assessment of neurocognitive decline in patients with brain metastases more reliable and feasible, Brainlab AG developed an application ‘Cognition’ for the ipad by gamifying validated paper and pencil tests. This study aims at validating the computerized tests.

Methods: We assessed reliability and comparability of ‘Cognition’ with similar well-established paper and pencil tests in 2 consecutive sessions per participant. The electronic tests used the same assignments with different stimuli than the paper and pencil tests. Domains involved are learning and memory, attention and processing speed, verbal fluency and executive functions.

Results: In total 5 employees and 25 cancer patients without disease in the CNS participated, of whom 24 completed both sessions. Reliability was found satisfying for domains learning and memory (p=.08; p= .612; p=.4445) and verbal fluency (p=.064). A learning effect showed for attention and processing speed (p=.001) while executive functioning showed a significant decline, possibly due to radiotherapy related fatigue (p = .013). Concerning comparability between electronic and paper results, a significant correlation was found for attention and processing speed (p = .000), for verbal fluency (p=0,03), for executive functions (p= .000), but not for learning and memory (p=.41; p=.25).

Conclusion: Overall ‘Cognition’ showed moderate comparability, probably caused by the consecution of tests during sessions and the unfamiliarity with electronic test in older patients. After improving its functionality, the application needs to be validated in patients with brain metastases before it can detect cognitive decline and possible early radiation toxicity or relapses.

Key words:
Central nervous system, neurocognition, brain metastases, validation study, learning and memory, executive functioning, cognitive decline, computerized tests

Introduction

Most patients treated for brain malignancies experience cognitive decline to a lesser or greater extent. The severity depends on the number of lesions, location and tumor volume but also treatments such as intracranial radiotherapy and chemotherapy impair cognitive functions in these patients (1–3). Evaluation and follow-up of this cognitive decline or neurotoxicity after treatment are important as the impact can be significant on the functional status and hence quality of life for patients as well as their informal caregivers. Perceived cognitive decline can have a great influence on daily activities and functioning, especially in combination with fatigue caused by an intense disease trajectory or negative feelings regarding the illness and its outcomes (4). Besides, new radiation strategies such as hippocampal sparing radiotherapy and stereotactic radiotherapy for as many as 5 to 10 brain mets are being evaluated in an attempt to prevent the neurological decline after pancranial radiotherapy (5–8). Evaluation of these treatment strategies points the necessity of standardized, repeatable and east-to-use neurocognitive test batteries.

Until now, a minority of clinical trials evaluating treatments in patients with metastatic brain tumors, focused on neurocognitive decline as primary outcome measure (9). The ones that did contained limited methodological designs on the evaluation of the cognitive impairment. Most studies used a single test design to assess cognitive functioning of patients. Such single tests can lead to high misclassification rates and hence unreliable results on cognitive decline and the impact in the functioning of the patient.

The assessments of complete standardized paper and pen testing batteries, as developed by the International Cognition and Cancer taskforce, require some structural provisions which could be perceived as burdensome for caregivers as well as patients participating in trials or when included in routine care (10–12). In order to make assessment of neurocognitive functioning more reliable and feasible for patients and physicians during trials and routine care, and in order to make cognitive testing results more robust for usage in clinical trials, Brainlab AG (München, Germany) developed an online application ‘Cognition’ for patients receiving radiation therapy for brain metastases. The data gathered by the computerized cognitive test can support the neurocognitive evaluation and assessment of possible neurotoxicity of radiotherapy treatment. This electronic application is accessible via a tablet device, and is designed following the standardized testing battery of paper and pencil tests as recommended

by the International Cognition and Cancer Task Force (13). Brainlab AG redesigned the existing paper and pencil tests into similar electronic tests in English with new stimuli and lay out. This study aims at validating the computerized cognitive tests by evaluating its functionality and test-retest reliability in a cognitive healthy population and by comparing its accuracy to similar standard validated paper and pencil cognitive tests.

Methods

Design

We conducted a single center evaluation study in a cognitive healthy population as a first phase of a larger research project to validate the electronic device in the targeted population, ie patients with brain metastases. In the first validation phase described in this paper, we assessed functionality and test-retest reliability of the Dutch and French version of the computerized testing battery and compared its accuracy to similar standard validated paper and pencil cognitive tests..

Population and setting

Since this first exploratory study involved a test-retest validation and comparison with the paper and pencil testing battery in 2 sessions, which is quite burdensome for patients involved in a disease trajectory, we chose to conduct this feasibility study in what we defined as a cognitive healthy population. We selected employees and cancer patients (18+) receiving radiotherapy treatment for breast cancer or prostate cancer at the UZ Brussel, without involvement of the central nervous system (CNS). The employees were recruited via the study coordinator (KL). The patients were evaluated and recruited by the treating physician on the ward (MDR) based on following inclusion criteria: no brain lesions, no brain radiation therapy in the past, being able to read in Dutch or French, being able to speak, and being able to operate an electronic device. In this study we excluded patients with brain tumors or brain metastases and patients who received stereotactic intracranial radiotherapy.

Course of each testing session

We performed 2 sessions of 40-45 minutes each per testing person to assess the test-retest reliability. This testing session took place at a moment convenient to the patient. This could be before radiation, after radiation, or during other follow up consultations. Per session the participant completed the paper and pencil tests and the electronic app. The assessment of paper and pencil and electronic device was counterbalanced between groups: half of testing persons started their session with the paper tests and half started with the electronic application. This order stayed the same in session 2.

In each session the researcher and psychologist (KL) was present to observe the patient. The researcher started the app and test and then handed the tablet to the patient without any further instructions.

Testing battery

Paper and pencil tests (Dutch and French)

Following paper and pencil tests were used, according to the domains of neurocognitive functioning as defined by the International Cognition and Cancer taskforce:

1) Hopkins verbal learning Test-R (HVLT-R)
    a. Immediate recall (IM): score = total number of words correctly recalled over 3 trials.
    b. Delayed recall (DR): score = total number of words correctly recalled
    c. Recognition (Rec): score = total number of list words correctly identified minus total number of non-list words incorrectly identified.
2) Digit symbols modalities test (SDMT). Matching symbols and corresponding numbers during 90 seconds. A score is calculated by totaling the number of correct answers.
3) Controlled word association test (COWAT): score = total number of words correctly generated (no numbers, no proper names) during the trial. For session 1 letter N was used, for session 2, letter A.
4) Trial making test (TMT) part A: score = total time in whole seconds to complete the array.
5) Trail making test (TMT) part B: score = total time in whole seconds to complete the array.

Electronic 'Cognition' test (Dutch and French)

This application was developed by Brainlab AG (Munchen, Germany) and designed to simplify and gamify the traditionally used paper and pencil testing battery of neurocognitive assessment in patients with possible cognitive decline after cancer treatment. Administration of 'cognition' requires an Apple inc. tablet device with internet connection. Following electronic tests were designed by Brainlab based on corresponding and validated paper and pencil tests (figure 1 and table 1):

1) a. Verbal recall: different stimuli than HVLT-R immediate recall are used. Score = total number of words correctly recalled over 3 trials. Stimuli are presented oral and in wording which is different from the paper and pencil test. Patients record recall by pressing a recording button.
   b. Verbal revision: score = total number of words correctly recalled. Patients record recall by pressing a recording button. This test is presented 15 minutes after the verbal recall test.
   c. Verbal recognition: score = total number of list words correctly identified minus total number of non-list words incorrectly identified. Patients click yes or no after presentation of the stimuli. This test is presented after the verbal revision test.
2) Symbols matching: matching symbols and corresponding numbers during 90 seconds; different stimuli are used than the SDMT. Score = total number of correct answers.
3) Words that start with …: different letters were used from the COWA test. Score = total number of words correctly generated (no numbers, no proper names). Patients record generated words by pressing a recording button. For session 1 the letter 'E' was used, for session 2 the letter 'N'.
4) Ordering letters and numbers test 1: ordering numbers from 1 to 13 by tapping them as fast as possible in consecutive order; score = total time in whole seconds to complete the array.
5) Ordering letters and numbers test 2: ordering numbers and letters from 1 to 13 and from A to M by tapping them as fast as possible in consecutive and alternating order; score = total time in whole seconds to complete the array.

The application has a testing area with an individual login code per patient as well as a caregiver area for entering patient and illness characteristics. In latter area individual test results and its progress throughout the different testing sessions can be consulted per patient at any time with the caregiver login.

Calculation of test scores

For the paper and pencil tests, results were manually calculated as described above by one researcher (KL) and reviewed by a second researcher (MDR). For the digital application, results were generated in an online database linked to the Cognition app and calculated in excel as described above.

Feasibility questionnaire and naturalistic observation

In order to evaluate the functionality and usefulness of the application in terms of user experiences, all participants in session 1 completed a questionnaire on usability and feasibility of the electronic tests. Different themes were questioned: overall experience, attraction, visualization of the stimuli and written words, understandability of the spoken words, intelligibility of the instructions, concentration and future use. Furthermore, naturalistic observations of the researcher during the sessions were gathered in field notes and evaluated together with the user experiences. At the end of the questionnaire, participants were able to provide feedback in an open-ended question. During the testing phase the researcher observed the patient and made some field notes. These were added to the evaluation of the feasibility in order to better understand the results of the testing data and feasibility questionnaire.

Statistical analyses

In order to explore the overall validity of the electronic application, we evaluated the testing results for comparability and test-retest reliability. All statistical analyses were based on the calculated test scores using IBM SPSS version 26.0. When comparing changes between sessions (test-retest reliability) and correlations between tests within a session (comparability), patients served as their own control. Changes in raw scores from session 1 to session 2 (test-retest reliability) were evaluated via paired samples t-tests. Scores on tests of session 1 and 2 were seen as similar when $p>.05$. Associations among the tests for session 1 and session 2 (Comparability) were analyzed using Pearson correlations using only complete pairs. Scores on paper and pencil and corresponding electronic tests were seen as similar when $p<.05$. The significance level for both analyses was set to alpha = 0.05, because of the small data sample.

Ethics

All parameters were collected under supervision of the treating physician (MDR). We obtained approval of the ethics committee of UZ Brussel (2018-041), and was registered at EUDRACT (No: 2017-004733-89)
At enrollment, all participants received and signed an informed consent on the research objectives and data retrieved. We analyzed anonymized data only)

Results

Characteristics of subjects:

In this study, 83,7% of patients were female and 56,7 % were Dutch speaking (table 2). The mean age was 58 year (range 36-83). Eighty percent of participants completed and performed all tests twice (two separate sessions) with a mean interval of 11 days (range 3 to 32 days). The other 20% of patients only participated in the first testing session. Reasons for drop out were fatigue, disinterest in the study and disease burden.

Feasibility questionnaire and naturalistic observation

Overall, the participants scored high on the questions regarding usability and feasibility of the computerized tests during the evaluation. According to the patients, the instructions of all computerized tests were clear and understandable, except for 'verbal recall'. From the field notes we learned that 10 patients had problems to understand some of the instructions of the computerized tests without explanation when using the app for the first time. Two participants didn't understand that the button had to be held to record words for 'verbal recall' and two other patients found that the sound should be louder. All patients indicated that they could easily read the instructions in the computerized tests, and that they were able to clearly see images and animations. Most of participants agreed that they would use the computerized tests on a regular basis at request of their healthcare provider.

Test-retest reliability between session 1 and session 2:

Evaluation of test-retest reliability between session 1 and session 2 showed a significant improvement (i.e. learning effect) across session 1 and session 2 for two paper and pencil tests: 'SDMT' ($t = 4.54$; $p= .000$) and 'COWA' ($t= 3.75$; $p=.001$) (table 3). On the other hand, the paper and pencil test 'HVLT-R-Rec' showed a significant decline ($t=-3.52$; $p= .0018$).

For the computerized tests, good test-retest reliability between session 1 and session 2 was found for 'Verbal revision' and 'Verbal recognition' ($p= .612$; $p=.4445$). A learning effect showed for 'Symbol matching' ($t=3.64$; $p=.001$) while 'Numbers and letters ordering' showed a significant decline ($t=-2.7$; $p = .013$).

Comparability between computerized and paper and pencil tests:

Table 4 shows comparability between results of paper and pencil tests and the computerized tests within the same cognitive domains. High comparability was found for the domain 'Learning and Memory' between 'HVLT-R-DR' and 'Verbal Revision' (r=0.394; p=.03) and between 'Verbal Recognition' and 'HVLT-R-Rec' (r=0.453; p=.01). On the other hand, comparability was low for 'HVLT-R-IMM' and 'Verbal recall' (r=0,29; p=0,11). High comparability was also found for the domain of 'Attention and speed of processing' between 'SDMT' and 'Symbol matching' (r=0.82; p = .000), for 'Verbal fluency' between 'COWA' and 'Words that start with …' (r=0,395; p=0,03) and for the domain 'Executive functions' between 'TMT part B' and 'Numbers and letters ordering' (0.82; p= .000). 'TMT part A' and 'numbers ordening' showed low comparability (r=0,33; p=0,075).

Discussion

In this study, an electronic neurocognitive testing battery was presented to a healthy population in order to test its test-retest reliability and comparability to the traditional paper and pencil testing battery. This first exploration of the newly developed electronic testing application overall shows moderate functionality, test-retest reliability and comparability. Regarding the test-retest reliability, a learning effect was detected in the results of the executive and speed tasks in both the paper and pencil tests and the electronic application. This was presumably caused by the short interval between the 2 sessions, and the consecutive order of both testing batteries. Although we counterbalanced between sessions, learning effect cannot be excluded. On the other hand, a small decline occurred in the delayed memory and executive functioning tasks. A possible explanation can be found in the fatigue experienced by some of the participants as they progressed in their radiation therapy. Regarding comparability of the paper and pencil testing results and the results of the electronic tests, good results were detected for the domains attention and speed, verbal fluency and executive functions, hence these electronic tests show a promising future use in the evaluation of cognitive functioning. However, for the domains learning and memory and fine motor and speed, the results were not satisfying, especially since these domains are mostly affected for patients with brain metastases (2,3). Some functional problems occurred during the learning and memory tasks in the electronic application in terms of clarity of the assignments and overall familiarity with electronic applications. These problems probably influenced reliability and comparison of the results with the paper and pencil tests. In some cases, the

participants were not able to correctly record their answer or were influenced by the written words in the assignment of the memory task in the application. The latter might have caused other cognitive processes in memorizing the words of the electronic test and the paper and pencil test. For the trial making test, participants experienced difficulties in performing the task on the ipad after performing the task on paper first. In the paper version, participants were asked to keep their pen on the paper while connecting the numbers, which is not the case in the electronic application. Most participants needed to adapt to the functionality of the ipad, possibly causing less reliable results. This explanation is supported by the fact that reliability was good in the second part of the trial making test and for both parts in the second session. Hence, in order for radiation oncologists to use the electronic application in practice to detect neurocognitive decline for patients irradiated for brain metastases, first, the functionality of the application needs to be further improved. Especially for the first testing moment in the electronic environment, assignments in the application need to be clarified, the functionality of the record button needs to be explained and the written words need to be removed from the memory test. Afterwards, test-retest reliability and comparability can be briefly retested in cognitive healthy patients by making use of a standardized protocol to minimize learning effect or interference between different tests. Before use in clinical practice, the application still needs to be validated in patients with brain metastases. This can be done by measuring neurocognition before the start of the therapy and 1 month, 3 months and 6 months after in order to investigate compliance, usability and accuracy (1). The results of this neurocognitive follow-up can be discussed together with the patients during consultation. This newly developed neurocognitive application can hence help radiation oncologists to efficiently detect possible early radiation toxicity, cognitive decline and possible relapses. In addition, it is a standardized easy to use tool for the evaluation of new radiation techniques.

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Conflict of interest

The developers of the electronic tool, Brainlab AG, funded the study as part of a research agreement with the radiotherapy department of UZ Brussel. Brainlab AG developed a new app for the treatment of multiple brain mets. Cognition is available for clinicians free of

charge. The authors state to have evaluated the tool neutral and correct, as it will help clinicians to improve quality of care for their patients.

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Availability of data and material

All data are available after reasonable request

Authors contribution

Both authors KL and MDR were responsible for design of the study, data collection, statistical analyses, preparation and revision of the manuscript.

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Table 1: overview of correspondence between paper and pencil tests and 'Cognition' tests divided per domain in neurocognition

DOMAIN NEUROCOGNITION	PAPER AND PENCIL BATTERY	TESTS IN THE 'COGNITION' APPLICATION
LEARNING AND MEMORY	HVLT-R-IMM	Verbal recall
	HVLT-R-DR	Verbal revision
	HVLT-R-Rec	verbal recognition
ATTENTION AND SPEED OF PROCESSING	SDMT	Symbols matching
VERBAL FLUENCY	COWAT	Words that start with..
FINE MOTOR AND SPEAD	TMT A	Numbers ordering
EXECUTIVE FUNCTIONS	TMT B	Numbers and letters ordering

Table 2: overview of participant characteristics

Demographics n=30		
Age		
	Mean (SD)	58,3 (12)
	Median	59
	Range	36-83
Sex		
	Female	25 (83,7%)
	Male	5 (16,7%)
Language		
	Dutch	17 (56,7%)
	French	13 (43,3%)
Participants' conditions		
	Breast tumor	23 (76,7%)
	Other tumor	2 (6,7%)
	Employee	5 (16,7%)
Participants per session		
	First session	30
	Second session	24

Table 3: scores on the evaluation survey

	Median	Std. Deviation
Overall experience of the application	5,00	0,736
Simplicity of the assignments	5,00	0,783
Attractivity of the visual presentation of the tests	5,00	0,733
Being able to concentrate until the end	4,00	0,889
Comprehension of the oral wordings	5,00	0,649
Readability of the visual wordings	5,00	0,351
Clear vision of the screen and animations	5,00	0,491
Future use when asked by healthcare provider	5,00	0,809
Comprehension of the instructions		
Verbal recall	4,00	1,052
Symbol match instructions	5,00	0,897
Words start with… instructions	5,00	1,015
Numbers ordering instructions	5,00	0,511
Letters/numbers ordering instructions	5,00	0,491
Verbal revision instructions	5,00	0,827
Verbal recognition instructions	5,00	0,602

Table 4: Test-retest reliability measures: Mean and p-value expressed as raw scores for each test for session 1 and session 2:

	RESULTS OF ALL PARTICIPANTS IN SESSION 1 * (N=30)	**RESULTS OF SESSION 1 OF COMPLETED PARTICIPANTS (N=24)**	**RESULTS OF SESSION 2 (N=24)**	**T PAIRED TEST**
PAPER AND PENCILTEST	Mean (SD)	Mean SD	Mean SD	T (*P*)
Hvlt-r-imm	29,33 (±4,85)	30,42 (±3,63)	29,17 (±3,42)	-1,39 (*0,1769)*
HVLT-R-DR	9,9 (±3,11)	10,46 (±2,6)	9,75 (±2,49)	-1,49 (0,1501)
Hvlt-r-rec	22,9 (±3,49)	23,21 (±1,53)	22,25 (±1,84)	-3,52 ***(0,0018)***
SDMT	46,9 (±9)	48,38 (±8,54)	52,08 (±7,12)	4,54 **(0,000)**
Cowat	9,23 (±3,95)	9,92 (±3,93)	13,25 (±4,43)	3,75 ***(0,001)***
TRAILS A	52 (±7,12)	35 (±11,86)	33,08 (±9,99)	-1,04 (0,31)
TRAILS B	90,13 (±46,43)	81,71 (±39,32)	78,42 (±40,33)	-0,48 (0,6382)
COGNITION TESTS				
Verbal recall	15,7 (±6,21)	16,29 (±6,3)	18,08(±6,88)	1,78 (*0,0891)*
Verbal revision	5,6 (±2,55)	5,88 (±2,47)	6,13 (±2,82)	0,51 (*0,612)*
Verbal recognition	22,73 (±2,19)	22,83 (±2,2)	22,5 (±2,06)	-0,78 (*0,4445)*
Symbols matching	23,73 (±7,13)	24,83 (±6,91)	28,42 (±7,78)	3,64 ***(0,0014)***
Words that start with…	7,3 (±5,22	7,83 (±5,3)	10,13 (±5,636)	1,94 (*0,0649)*
Numbers ordering	21,46 (±8)	23,56 (±17,19)	31,72 (±10,59)	2,07 (*0,05)*
Letters/numbers ordering	64,97 (±63,9)	63,76 (±31,95)	46,16 (±21,78)	-2,7 ***(0,013)***

Hvlt-r imm = hopkins verbal learning test-revised immediate; hvlt-r dr = hopkins verbal learning test-revised delayed recall; hvlt-r rec = hopkins verbal learning test-revised; trails a = trail making test part a; trails b = trail making test part b; recognition; SDMT = symbol digit modalities test; Cowat = controlled oral word association test.

*** Six participants dropped out after session 1 and did not participate in session 2**

Table 5: correlation between paper & pencil and cognition application tests within selected domains.

Domain	Test comparaison		Session 1 (n=30)	Session1 (n=24)	Session 2 (n=24)
Learning and memory	HVLT-R-IMM	r	*0,29*	0,154	-0,176
	Verbal Recall	*p-value*	*0,11*	*0,473*	*0,412*
	HVLT-R-DR	r	*0,394*	0,212	0,24
	Verbal revision	*p-value*	***0,03***	*0,32*	*0,258*
	HVLT-R-Rec	r	*0,453*	0,282	0,399
	Verbal recognition	*p-value*	***0,011***	*0,182*	*0,053*
Attention and speed of processing	SDMT	r	*0,82*	0,772	0,69
	Symbols matching	*p-value*	***0,0***	***0,0***	***0,0***
Verbal fluency	COWAT	r	*0,395*	0,456	0,797
	Words that start with…	*p-value*	***0,03***	***0,025***	***0,0***
Fine motor and speed	TMT A	r	*0,33*	-0,164	0,671
	Numbers ordering	*p-value*	*0,075*	*0,445*	***0,0***
Executive functions	TMT B	r	*0,822*	0,625	0,7
	Numbers and letters ordering	*p-value*	***0,0***	***0,001***	***0,0***

Hvlt-r imm = hopkins verbal learning test-revised immediate; hvlt-r dr = hopkins verbal learning test-revised delayed recall; hvlt-r rec = hopkins verbal learning test-revised; trails a = trail making test part a; trails b = trail making test part b; recognition; SDMT = symbol digit modalities test; Cowat = controlled oral word association test.