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Journal of the Neurological Sciences 449 (2023) 120658

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Cognitive performance in healthy clinical trial participants and patients with the NeuroCart, a neurodegenerative disease measured with an automated neuropsychological and neurophysiological test battery

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ARTICLE INFO

Keywords:
Cognition
Neurodegeneration
Age related cognitive decline
Alzheimer's disease
Parkinson's disease
Huntington's disease
Vascular dementia

ABSTRACT

Background: The prevalence of neurodegenerative diseases increases significantly with increasing age. Neurodegeneration is the progressive loss of function of neurons that eventually leads to cell death, which in turn leads to cognitive disfunction. Cognitive performance can therefore also be considered age dependent. The current study investigated if the NeuroCart can detect age related decline on drug-sensitive CNS-tests in healthy volunteers (HV), and whether there are interactions between the rates of decline and sex. This study also investigated if the NeuroCart was able to differentiate disease profiles of neurodegenerative diseases, compared to age-matched HV and if there is age related decline in patient groups.

Methods: This retrospective study encompassed 93 studies, performed at CHDR between 2005 and 2020 that included NeuroCart measurements, which resulted in data from 2729 subjects. Five NeuroCart tests were included in this analysis: smooth and saccadic eye movements, body sway, adaptive tracking, VVLT and N-back. Data from 84 healthy male and female volunteer studies, aged 16–90, were included. Nine studies were performed in patients with Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) or vascular dementia (VaD). The data were analyzed with regression analyses on age by group, sex, sex by age, group by sex and group by sex by age. Least square means (LSMs) and 95% confidence intervals (CIs) were calculated for each group at the average age of the group, and at the average age of each of the other groups, and per sex.

Results: Mean age and standard deviation (SD) for all groups was: HV 36.2 years (19.3), 68.3 CE years (8), PD 62.7 years (8.5), HD 51.4 years (9.8) and VaD 66.9 years (8.1). Performance on all NeuroCart tests decreased significantly each year in HV. Saccadic peak velocity (SPV) was increased in AD compared to age-matched HV (+26.28 degrees/s, $p = 0.007$), while SPV was decreased for PD and HD compared to age-matched HV (PD: −15.87 degrees/s, $p = 0.038$, HD: −22.52 degrees/s, $p = 0.018$). In HD patients SPV decreased faster with age compared to HV. On saccadic peak velocity the slopes between HD vs HV were significantly different, indicating a faster decline in performance on this task for HD patients compared to HV per age year. Smooth pursuit showed an overall significant difference between subject groups ($p = 0.037$. Significantly worse performance was found for AD (−12.87%, $p \leq 0.001$), PD (−4.45%, $p \leq 0.001$) and VaD (−5.69%, $p = 0.005$) compared to age-matched HV. Body sway significantly increased with age ($p = 0.021$). Postural stability was decreased for both PD and HD compared to age-matched HV (PD: +38.8%, $p \leq 0.001$, HD: 154.9%, $p \leq 0.001$). The adaptive tracking was significantly decreased with age ($p \leq 0.001$). Adaptive tracking performance by AD (−7.54%, $p \leq 0.001$), PD (−8.09%, $p \leq 0.001$), HD (−5.19%, $p \leq 0.001$) and VaD (−5.80%, $p \leq 0.001$) was decreased compared to age-matched HV. Adaptive tracking in PD patients vs HV and in PD vs HD patients was significantly different, indicating a faster decline on this task per age year for PD patients compared to HV and HD. The VVLT delayed word recall showed an overall significant effect of subject group ($p = 0.006$. Correct delayed word recall was

Abbreviations: AD, Alzheimer's disease; CHDR, Centre for Human Drug Research; HD, Huntington's disease; HV, Healthy volunteer; PD, Parkinson's disease; SPV, Saccadic peak velocity; VaD, Vascular dementia; VVLT, Visual Verbal Learning Test.

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https://doi.org/10.1016/j.jns.2023.120658
Received 5 October 2022; Received in revised form 2 April 2023; Accepted 10 April 2023
Available online 12 April 2023

decreased for AD (−5.83 words, $p \leq 0.001$), HD (−3.40 words, $p \leq 0.001$) and VaD (−5.51 words, $p \leq 0.001$) compared to age-matched HV.

Conclusion: This study showed that the NeuroCart can detect age-related decreases in performance in HV, which were not affected by sex. The NeuroCart was able to detect significant differences in performance between AD, PD, HD, VaD and age-matched HV. Disease durations were unknown, therefore this cross-sectional study was not able to show age-related decline after disease onset. This article shows the importance of investigating age-related decline on digitalized neurocognitive test batteries. Performance declines with age, which emphasizes the need to correct for age when including HV in clinical trials. Patients with different neurogenerative diseases have distinct performance patterns on the NeuroCart, which this should be considered when performing NeuroCart tasks in patients with AD, PD, HD and VaD.

1. Background

The prevalence of neurodegenerative diseases increases significantly with increasing age [1]. Neurodegeneration is the progressive loss of function of neurons, eventually leading to cell death which in turn leads to cognitive disfunction [2]. Cognitive performance can therefore also be considered age dependent. A subtle but consistent decline in cognitive performance is noticeable when a person ages, not only in case of neurodegenerative diseases but also with normal aging [3–5]. At a certain point, cognitive decline is not considered as age-related cognitive decline but decline due to neurodegeneration, which can have many causes e.g., dementia.

Cognition is defined by the ability of humans to acquire knowledge, understanding through thought, experience and senses and can be classified by different domains (e.g., memory, attention, executive functioning) in which there can be overlap of functions; for instance attention that is needed when performing a task involving memory [6]. Cognitive change is quantified by measuring performance on different domains with standardized neuropsychological tests, that can, most of the time, be corrected for education level [7]. Education can influence cognitive performance, as cognitive reserve makes a subject more resilient to deterioration of cognitive function [8]. Traditionally, neuropsychological tests are 'pen and paper' tasks, performed (as the name reveals) with pencils and paper and administered by trained neuropsychologists. However, human error and inter-rater variability are not uncommon [9,10]. The past decades multiple pen and paper tasks have been digitalized with great advantages such as standardized test administration, reduced inter-rater variability and less time-consuming procedures [11]. The NeuroCart is an example of a digital neuropsychological and neurophysiological test battery, developed and used by the Centre of Human Drug Research (CHDR) [12]. The advantage of the NeuroCart is that this test battery can easily be implemented in (early phase) drug development.

The NeuroCart has been used for over two decades in clinical studies both in healthy volunteers (HV) as well as in studies with patients suffering from neurodegenerative diseases. NeuroCart assessments are used to identify subtle cognitive changes when administering new (pro) cognitive compounds [12]. After extensive use of the NeuroCart, enough data has been gathered to make valid assumptions about age related decline measured with the NeuroCart.

Different neurodegenerative diseases have distinct profiles in cognitive decline, although overlap in decline in cognitive functions is not uncommon [13,14]. For instance, memory deficits occur in Alzheimer's Disease (AD), Parkinson's Disease (PD) and Huntington's Disease (HD) although in different forms and with different symptomatic features [15]. These neurodegenerative diseases do not have the same progression in cognitive decline and different cognitive domains are affected in different stages of the disease [16,17].

The current study investigated if the NeuroCart is able to detect age related decline on tests in healthy volunteers, and whether there is an interaction between the rate of decline and sex. This study also investigated if the NeuroCart is able to differentiate disease profiles of neurodegenerative diseases, compared to healthy volunteers in the same age group and if there is age related decline in patient groups. Implementing the results of this analysis in future research may lead to better subject selection for clinical research. If, for instance, a compound is developed to improve working memory function, normal age-related deterioration could be used as a model of cognitive impairment. Moreover, early development studies in healthy subjects that are age-matched to the target population, will provide more relevant outcomes for subsequent clinical trials in patients. Age-linked biomarkers may also be more sensitive to cognitive enhancers or other compounds for age-related diseases, than tests which are not affected by aging. Determination of NeuroCart-test related to aging or neurodegenerative diseases can also generate benchmarks for 'clinical' relevance of drug effects. This could be relevant for cognitive challenge models, aiming to induce cognitive decline in healthy volunteers (e.g., mecamylamine, biperiden, scopolamine challenge models [18–20]), which can be interpreted better by comparing results to normal aging and disease profiles. Similarly, age- or disease-related changes can provide a frame of reference for effects of cognitive enhancers and disease modifying pro-cognitive drugs. All these reasons warranted an analysis of the age-relatedness of NeuroCart tests in healthy volunteers and patients with different neurodegenerative conditions that have been collected at CHDR in the past fifteen years.

2. Methods

This retrospective study encompassed 93 studies, performed at CHDR between 2005 and 2020 that included NeuroCart measurements, which resulted in 2729 subjects with data from at least one of five NeuroCart tests. Of the 93 studies, 9 studies were performed in patients with AD, PD, HD or vascular dementia (VaD). Data from 84 healthy male and female volunteer studies, aged 16–90, were included. The following five NeuroCart tests covering different functional domains were selected that have been used in a substantial number of studies.

2.1. Eye movements - smooth and saccadic movements

Analysis of smooth pursuit and saccadic eye movements are frequently used for the assessment of (side) effects of drugs involving the central nervous system. The use of a computer for measurement of saccadic eye movements was originally described by Baloh et al. [21] and for smooth pursuit by Bittencourt et al., [22] and has been extensively validated at the CHDR, e.g., by Van Steveninck et al., [23]. The subjects were required to follow a light source with the eyes, which moved horizontally on a screen at 58 cm distance. The light source moved continuously with increasing speed for measurement of smooth pursuit and jumped from side to side with slightly varying intervals for saccadic eye movements. The duration of each of the tests was approximately 1 min. The test parameter for smooth pursuit eye movements was the percentage of time the subject's eyes were in smooth pursuit of the target. For saccadic eye movement, the parameter peak velocity (deg/s) was extracted. Eye movements were recorded in a quiet room with dimmed lightning and with only one study subject in the room.

2.2. Body movement- Body sway

The body sway meter allows measurement of body movements in a single plane, providing a simple measure of postural stability. Body sway is measured with a pot string meter based on the Wright ataxia meter [24]. At CHDR, the method has been frequently used to demonstrate effects of sleep deprivation [25], alcohol [26], benzodiazepines [26,27] among many others. With a string attached to the waist, all body movements over a period of 2 min were integrated and expressed as millimetre (mm) sway. Subjects were instructed to wear comfortable, low-heeled shoes, asked to stand still and comfortably, with their feet approximately 10 cm (cm) apart and their hands in a relaxed position alongside the body and eyes closed. Subjects were not allowed to talk during the measurement. The total period of body-sway measurement was two minutes.

2.3. Attention and eye-hand coordination- adaptive tracking

The adaptive tracking test was performed as originally described by Borland and Nicholson [28,29], using customised equipment and software (based on TrackerUSB hard−/software (Hobbs, 2004, Hertfordshire, UK)). Adaptive tracking is a pursuit-tracking task that measures (sustained) attention and executive functioning. A circle moved randomly on a screen, and the subject had to try and keep a dot inside the moving circle by operating a joystick. As long as this effort was successful, the speed of the moving circle increased. Conversely, the velocity was reduced if the test subject was unable to maintain the dot inside the circle. The percentage of correct performance (dot in circle) was used for analysis. The tests took 3.5 min, including a run-in time of 0.5 min, in which data are not recorded.

2.4. Memory consolidation - visual verbal learning task, delayed recognition

Visual verbal learning [30,31] contains three different subtests that cover basic aspects of learning behaviour: acquisition, consolidation, storage, and retrieval. Subjects that performed the Visual Verbal Learning Test (VVLT) were presented 30 words (or 15 words for subjects with dementia) in three consecutive word trials, i.e., word learning test (VVLT30 or VVLT15). Approximately thirty minutes after start of the first trial, the subjects were asked to recall as many words as possible (delayed recall- this test measures active retrieval from long term memory). Subjects were not allowed to write down words at any time during the test. Correct words were recorded (correct response), as well as words that were mentioned more than once (double response) and words that were mentioned but not presented (incorrect response). For this study, the number of correct recalls during the delayed recall condition were used in the analyses. CHDR created a computerized VVLT script based on a script from the University of Maastricht. Since the VVLT aims to avoid ceiling effects while also preventing overtaxing of subjects, patients with Alzheimer's disease performed the VVLT15 version with 15 words, as memory performance is strongly affected in this group. All other studies included the VVLT30 words version.

2.5. Working memory – N-Back, one-back

The N-Back test measures working memory. Different versions of the N-Back test were employed in studies investigating the neural basis of working memory [32]. The test has also been widely used for measuring working memory deficits [32–34]. Performing the N-Back test requires buffering and updating consonants, matching, encoding and responding [35]. The version of the N-Back used at CHDR is a shorter version compared to the original version of Rombouts et al. [34]. The maximal duration for this test was 10 min. Following Rombouts et al. (2002) [34], the N-Back test consisted of three conditions, with increased working memory load. In condition 0 ("X" condition), subjects were required to indicate whether the presented letter is a "X" (=target) or another letter. In Condition 1 and 2, letters were presented sequentially (1.5 s for a letter [consonant, except for the letter "z"], followed by a black screen for 0.5 s). Key "z" was pressed for a target and "/" was pressed for a non-target. Condition 1, "1-back" condition, in which subjects were required to indicate whether the letter presented earlier, was a repetition without any other letter intervening (e.g., B … B); In condition 2, "2-back" condition, subjects were required to indicate whether a letter was repeated with one other letter in between (e.g., B … C … B). The 3 conditions were presented in 3 blocks with increasing working memory load. Each condition started with a training (7 consonants; target:non-target 3:4), followed by the test (24 consonants; target:non-target 1:3). For the current analysis, the 1-back condition was used in the analyses.

Only the baseline values (before possible drug intervention) of these tests were used in this analysis, except for the VVLT. The VVLT was measured once during the intervention (no baseline), and so only the values measured under placebo were used. When more baseline values per subject were available, the average of the baseline values was analyzed. All tests except body movement and the n-back test, were performed in all five groups: HV, AD, HD, PD and VaD. To prevent falls in the most fragile subjects with dementia, body sway was measured in only three groups: HV, HD and PD. The N-back was not performed in patients with HD and VaD as other tests to measure cognition (e.g. VVLT) were used in these studies and memory was not the main outcome measurement.

Main inclusion criteria for the HV studies were normal ECG, blood pressure and heart rate measurements. Also, no clinically significant abnormalities in blood hematology and chemistry results. Physical and neurological examination did not show abnormalities and no neurological or psychiatric disorders were apparent from medical anamnesis. The patients studies included patients with a relevant confirmed diagnosis (e.g. Alzheimer's disease, Parkinson's disease) by a specialist and patients were otherwise healthy confirmed by general health tests comparable to tests performed in HV.

2.6. Statistical analysis

The data of selected NeuroCart tests were analyzed with regression analyses on age by group, sex, sex by age, group by sex and group by sex by age. The regression results are presented as the age, group, sex and interaction effects; the intercept and slope per group; the contrasts of the slopes of the groups; and the 'age-matched' contrasts of each disease group and HV at the mean age of the disease group. Least square means (LSMs) and 95% confidence intervals (CIs) are given for each group at the average age of the group, and at the average age of each of the other groups, and per sex and average ages.

When a subject participated in multiple studies of this batch analyses, the average age of this subject was used to calculate the mean age of the total group. For calculating age effect per NeuroCart test, the exact age at the time of test performance was calculated, but floor age (e.g., age 30.5 = age 30) was used for graphs and in the regression for all subjects.

All calculations were performed using SAS (version 9.4, SAS, Cary, NC).

3. Results

In Table 1 the basic characteristics of the subjects included in this study are presented. Subjects were categorized into HV or patient (AD, PD, HD, VaD) as a total group. This table also demonstrates the average scores on the NeuroCart tests for the groups.

Table 2 presents the decrease in performance per age year compared to no (0) decrease, for each of the tests on the NeuroCart for HV and patients in the different neurogenerative disease groups. Performance on all NeuroCart tests decreased significantly each year in HV, compared to no decrease. Performance on the adaptive tracking task decreased

Table 1
Basic characteristics and average test scores on NeuroCart tests for healthy volunteers, Alzheimer's Disease patients, Parkinson's Disease patients, Huntington's Disease patients and Vascular dementia patients.

	Healthy volunteers	Alzheimer's Disease patients	Parkinson's Disease patients	Huntington's Disease patients	Vascular dementia
Mean age (median, total range)	$N = 2511$ 36.2 (26, 15–89)	$N = 63$ 68.3 (69, 49–90)	$N = 74$ 62.7 (64, 40–80)	$N = 51$ 51.4 (53, 21–69)	$N = 30$ 66.9 (68, 46–82)
Sex, female, mean age (median, total range)	$N = 711$ 40.7 (31, 16–83)	N = 30 67.9 (70, 49–90)	$N = 27$ 60.6 (61, 40–75)	$N = 22$ 47.8 (51, 21–69)	$N = 9$ 65.3 (66, 55–73)
Sex, male, mean age (median, total range)	$N = 1800$ 34.5 (25, 15–89)	$N = 33$ 68.6 (69, 57–82)	$N = 47$ 63.9 (65, 46–80)	$N = 29$ 54 (54, 39–67)	$N = 21$ 67.6 (71, 46–82)
Saccadic peak velocity (degrees/s), mean (SD)	$N = 2232$ 490.1 (59.31)	$N = 39$ 498.1 (58.05)	N = 71 453.8 (59.30)	$N = 44$ 459.1 (66.13)	N = 30 479.0 (79.08)
Smooth pursuit (%), mean (SD)	$N = 1835$ 43.65 (10.700)	$N = 50$ 23.77 (12.500)	N = 74 33.19 (8.891)	$N = 48$ 37.30 (7.090)	N = 30 30.85 (7.930)
Body sway (mm), geometric mean (SD)	$N = 1994$ 250.2 (52.0)	Not available	$N = 72$ 363.0 (64.7)	$N = 49$ 649.3 (96.9)	Not available
Adaptive Tracking (%), mean (SD)	$N = 2185$ 26.86 (6.245)	$N = 62$ 15.01 (7.531)	N = 74 15.05 (5.942)	N = 48 19.43 (7.588)	N = 30 17.15 (5.590)
VVLT-delayed recall (number correct), Mean (SD)	$N = 912$ 10.630/30 (6.403)	N = 62 1.048/15 (1.750)	$N = 14$ 5.571/30 (2.827)	$N = 40$ 6.400/30 (4.112)	N = 27 2.111/30 (1.928)
N-back (one back ratio), mean (SD)	$N = 853$ 0.9134 (0.1709)	$N = 10$ 0.3710 (0.6088)	N = 25 0.8804 (0.1508)	Not available	Not available

Table 2
Change in performance per age year (=slope) per group, Healthy volunteers, Alzheimer's disease, Parkinson's disease, Huntington's disease and Vascular dementia patients.

	Healthy volunteers	Alzheimer's Disease patients	Parkinson's Disease patients	Huntington's Disease patients	Vascular dementia
Saccadic peak velocity (degrees/s)	−0.557*	−1.230	−0.619	1.486	0.131
Smooth pursuit (% point)	−0.202*	0.127	−0.181	−0.003	−0.372
Body sway (%)	0.328*	Not available	1.18	0.961	Not available
Adaptive tracking (% point)	−0.130*	−0.281*	−0.295*	−0.026	−0.232
VVLT delayed word recall (number correct)	−0.166*	−0.001	−0.135	−0.013	−0.087

* Significant: $p \leq 0.05$.

significantly for both HV as AD and PD patients.

Fig. 1 visually plots the data per NeuroCart test per age year and per subject group. Regression lines were added to the figures to visually represent the decrease in performance. The body sway data was log transformed as the data was not normally distributed. Since the performance on the 1-back task is expressed as a ratio score no regression analyses could be performed, hence no graphical representation is provided for the N-back test. Fig. 2 represents all individual scores on the N-back of HV, AD and PD. A pattern of decrease after the age of 50 can be assumed based on this data, which also suggested worse performance in AD compared to HV.

To investigate the overall effect of age on the NeuroCart tests, linear regression analyses were performed. In addition to this, least square means (LSMs) and 95% confidence intervals (CIs) were calculated for each patient group, comparing performance between patient and HV at the average age of the respective patient group.

Saccadic peak velocity (SPV) was increased in AD compared to age-matched HV (+26.28 degrees/s, $p = 0.007$). In PD, SPV was decreased compared to age-matched HV (−15.87 degrees/s, $p = 0.038$. This was also the case in HD-patients (−22.52 degrees/s) who showed an age-related decrease in SPV compared with HV, as demonstrated by the significant difference in slope (Fig. 1).

Smooth pursuit eye movements showed an overall significant difference between subject groups ($p = 0.037$). Significantly worse performance was found for AD (−12.87%, $p \leq 0.001$), PD (−4.45%, p ≤ 0.001) and VaD (−5.69%, $p = 0.005$) compared to age-matched HV.

Body sway significantly increased with age ($p = 0.021$). Furthermore, both PD and HD show decreased postural stability compared to age-matched HV (PD: +38.8%, p ≤ 0.001, HD: 154.9%, p ≤ 0.001).

Adaptive tracking decreased significantly with age ($p \leq 0.001$). Adaptive tracking performance by subjects with AD (−7.54%, $p \leq 0.001$), PD (−8.09%, p ≤ 0.001), HD (−5.19%, p ≤ 0.001) and VaD (−5.80%, p ≤ 0.001) was decreased compared to age-matched HV. The differences in slopes between PD vs HV and PD vs HD were significant, indicating a faster decline on this task per age year for PD patients compared to HV and HD.

The VVLT delayed word recall showed an overall significant effect of subject group ($p = 0.006$), indicating worse memory performance in patients. Correct delayed recall was decreased for AD (−5.83 words, p ≤ 0.001), HD (−3.40 words, p ≤ 0.001) and VaD (−5.51 words, p ≤ 0.001) compared to age-matched HV.

A spider plot was created to visualize the NeuroCart disease profiles for AD, PD, HD and VaD compared to HV. The spider plot summarizes the performance on the NeuroCart per group and per test, see Fig. 3. As age is not distributed equally between groups, the HV plot should be viewed with caution. Median age of HV is 36.2 years and therefore much lower than mean age in the patient groups (median ages: AD 68.3, PD 62.7 HD 51.4, VaD 66.9).

4. Discussion

This study investigated whether the NeuroCart can detect age-related decline in NeuroCart performance in close to 3000 healthy volunteers and specific patients, and whether there is an interaction between group, age and sex. Based on these results the NeuroCart showed age-related decreases in performance in HV, which were not affected by

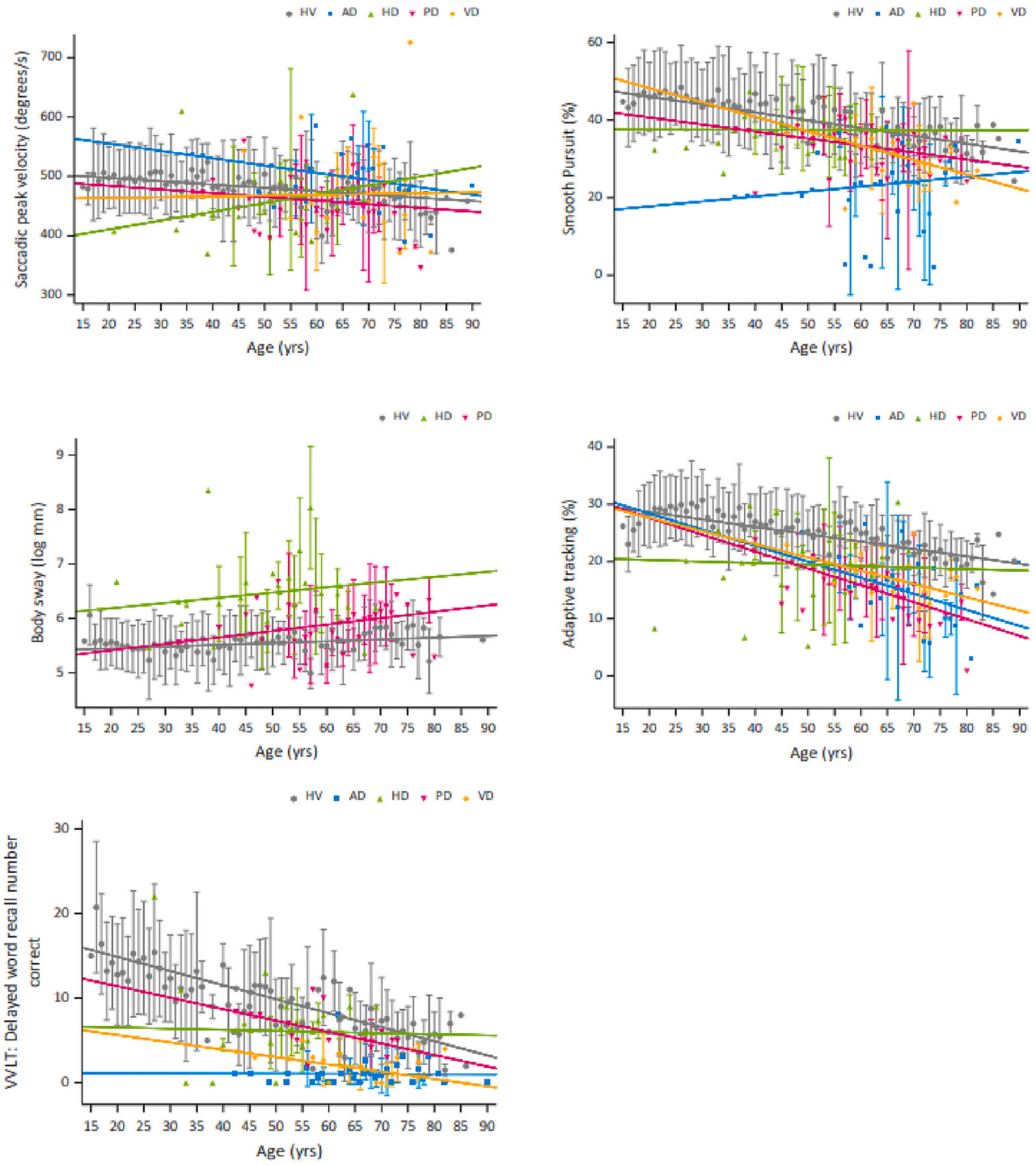

Fig. 1. Overall plots of estimated regression lines per subject population (Healthy volunteers [HV], Alzheimer's disease [AD], Parkinson's disease [PD], Huntington's disease [HD] and Vascular dementia patients [VaD] for Saccadic peak velocity (degrees/s), Smooth pursuit (%) eye movements, Body sway (log mm), Adaptive tracker (%) and VVLT delayed word recall (number correct).

sex. The NeuroCart was able to detect significant differences in performance between AD, PD, HD, VaD and age-matched HV. Because disease durations were unknown, this cross-sectional study was not able to show age-related decline after disease onset. Therefore, the rate of deterioration as a consequence of neurodegenerative disease independent of age could not be quantified reliably.

The NeuroCart is a digitalized neuropsychological- and neurophysiological test battery, used in early phase drug development to detect (subtle) changes in performance of healthy volunteers and patients after the administration of a CNS-active (including pro-cognitive) compounds, and (thereby) to detect penetration of the blood brain barrier and target engagement [12]. Age-related decreases in performance in healthy volunteers were demonstrated on five different NeuroCart tests: smooth and saccadic eye movements, adaptive tracking, body sway, VVLT and N-Back. Age-related decline on cognitive tests corresponds to previous literature on cognitive decline at older age [36], but this was not yet reported for most digitalized tests within the NeuroCart.

Patients with PD and VaD performed comparable to HV on the smooth and saccadic eye movement task. AD patients performed worse

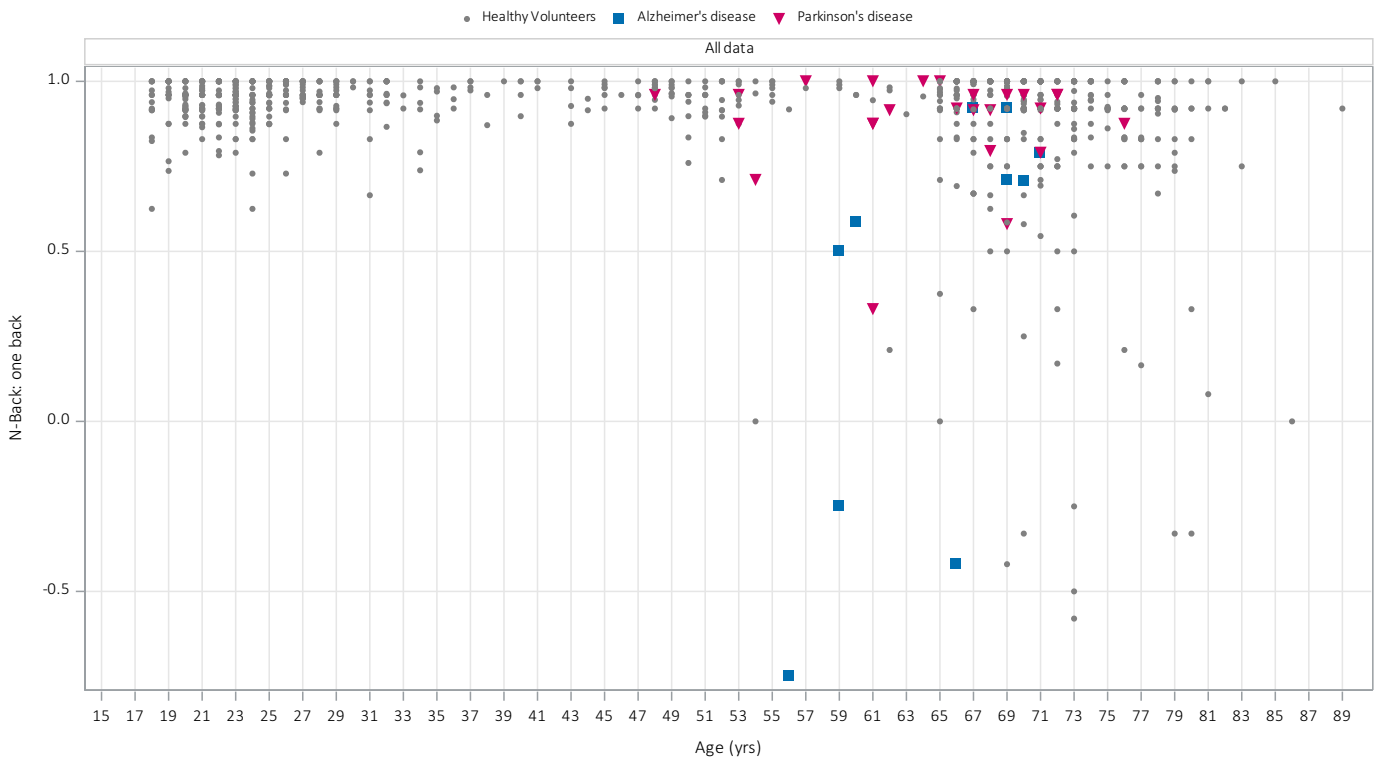

Fig. 2. Individual plot of N-Back: one-back condition in Healthy volunteers, Alzheimer's disease and Parkinson's disease.

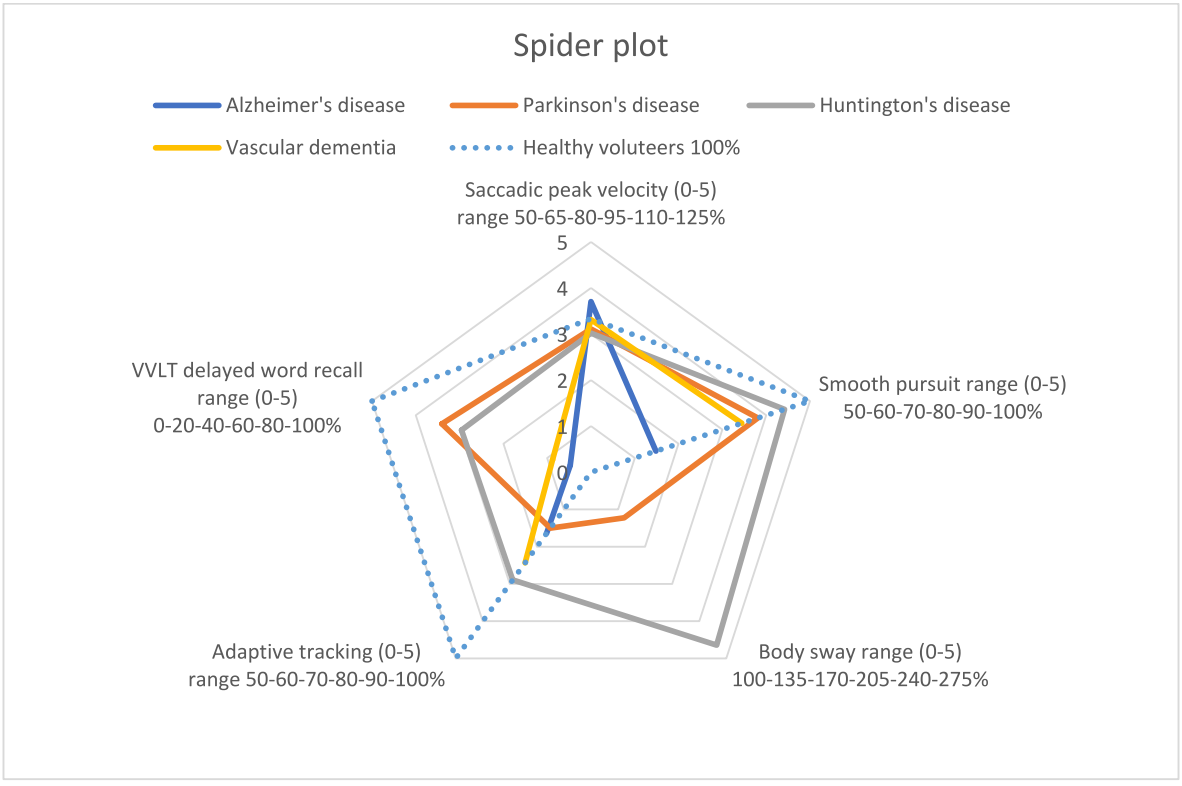

Fig. 3. Spider plot summarizing the NeuroCart performance of patients with Alzheimer's Disease, Parkinson's Disease, Huntington's Disease and Vascular Dementia, compared to healthy volunteers at 100% at median age of the represented group.

on the smooth pursuit eye movement task but better on the saccadic eye movement task compared to the other patient groups and HV. In AD, abnormalities of both smooth pursuit eye movements and saccadic eye movements have been previously reported [37]. A study found decreased saccadic peak velocity in a small number of AD patients compared to age-matched HV, which contrasts with our findings.

However, this was only the case when visual stimuli were 'unpredictable', which may have been different from our test setup [38]. These authors also detected more abnormal or delayed saccades in AD, which was not analyzed in the current study. In another study, smooth pursuit eye movements differed significantly between AD and HV, similar to what was found in this current study with a significant difference between AD and age-matched HV [39]. As Moser et al., (1995) suggest, these somewhat discrepant results could be due to the different phases of the disease in the AD patients. In the current dataset the mean age was 68.3 years old with an age range of 49 till 90 years old meaning early onset AD patients were also included. Despite the large age range, patient call still be considered to be in the early phase of the disease which was confounded by the requirement for legal competence in the studies in which they participated. Partly for safety reasons, body sway was not performed in AD and VaD patients, but this test resulted in worse postural stability for HD and PD compared to HV. Both PD and HD are movement disorders and previous literature confirm these findings using similar tests as the body sway [40,41].

Most of the NeuroCart tests (smooth and saccadic eye movements, body sway, VVLT and N-Back) did not show age-related decline within any of the patient groups. Only adaptive tracking test demonstrated age-related decline not only in HV but also in patients with AD and PD, whereas a non-significant decline was seen in HD and VaD patients. Adaptive tracking is affected by different CNS-functions, particularly sustained attention, eye-hand coordination and vigilance, which may render this test more sensitive to worsening not only during normal aging, but also to different forms and sites of neurodegeneration.

Attention is controlled by the prefrontal cortex, which is one of the first brain areas that deteriorates in both normal aging and most age-related neurodegenerative diseases [42,43]. The memory test VVLT was specifically worse in AD and VaD patients compared to HV, HD and PD. AD patients did not show a significant additional decline in word recall with age, but an overall poorer performance compared to the other groups [44]. It must be noted that in the current dataset, AD patients took an adjusted version of the test with 15 words instead of 30, to avoid overstraining, but this test was still performed worse than the more difficult 30-word version in all other subject groups. Looi et al., (1999) compared neuropsychological test performance between AD and VaD and found VaD to perform better on memory tasks than AD patients [44], which is in line with the current data set. Although no quantitative regression analyses could be performed on the percentage scores of the N-back test results, the results do suggest decreased performance with age. A pattern of decrease after the age of 50 can be surmised based on the data from the individual scores of HV, AD and PD on the one-back task;. Furthermore, the AD population seems to score lower on accuracy on the one-back paradigm of the N-Back task than HV. Fraga et al., (2018) measured event-related desynchronization with EEG in AD patients while performing the N-Back task and found a clear difference between the performance of HV and AD, which was already present in the mild cognitive impairment stage [45].

No apparent age-related decline could be detected in the patient groups, other than on the adaptive tracking test for AD and PD. This might be explained by the decrease in cognitive performance in patients after disease onset, which could have obscured detection of additional effects of aging. Linear analyses were appropriate to investigate the decline in performance in HV with a large age range of 16 to 90 years old. In the patients' groups however, linear regression analysis may not be appropriate in patients as age ranges were smaller. Moreover, in neurodegenerative diseases performance does not decrease in a linear fashion [46]. No conclusion can be made about the rate of decline in performance on the NeuroCart of patients compared to HV, as our data did not comprise longitudinal data. Patients were generally younger (~62 years) than in comparable studies, in which the disease may have progressed for a longer period. In AD patients, memory decline was worse than expected for their age, as indicated by their particularly poor performance on a simpler VVLT version. As using a linear model did not suit the patient data, the average age per patient group was compared to the performance of healthy volunteers at that same age. All patients with neurodegenerative disease show worse performance compared to age-matched HV. Overall, the NeuroCart seems to differentiate patient groups from HVs, which is of relevance when administering NeuroCart tests in clinical research, as this can be expected to affect study outcome.

Several studies tried to mimic cognitive neurodegenerative disorders by inducing cognitive deficits in otherwise healthy subjects, and furthermore to reverse these deficits by administering a pro-cognitive compound; the so-called pharmacological challenge models of cognitive impairment [18–20]. Bakker et al., (2021) investigated the effect of 4 mg biperiden p.o. in healthy elderly subjects and found a decrease in performance on several NeuroCart tests (adaptive tracking −3.04% to −1.15%; VVLT delayed recall −5.9 to −0.2 words; body sway 79.7 mm increase; and smooth pursuit eye movements −5.58% to −1.53%) [19]. The effect of this challenge test on cognitive test performance is less than the decreased performance of AD patients found in this study (adaptive tracking −7.5%; VVLT delayed recall −5.9 words; smooth pursuit eye movements −12.9%). Baakman et al., (2017) [20] used another challenge model, where they administered 0.5 mg scopolamine in healthy male subjects. Their findings seem to agree better with our results in patients (adaptive tracking −10.4% accuracy; VVLT delayed recall −7.1 words), but the sedative effect of scopolamine is known to negatively influence results of cognitive performance [47].

This study shows the importance of investigating age-related decline on digitalized cognitive test batteries. The fact that performance declines with age emphasizes the need to correct or match for age when including HV in clinical trials. Patients with neurogenerative diseases have different performance patterns on the NeuroCart and this should be considered when performing digitalized neurocognitive tasks in patients with AD, PD, HD and VaD. In addition, the current dataset provides a frame of reference for impairment models and (adverse or pro-cognitive) effects of CNS-active drugs.

Author's contributions

The study design, conceptualization, collection of data, formal analysis, interpretation of the data and writing orginal draft and review and editing has been a mutual effort of the authors. The authors read and approved the final manuscript.

Funding

This study was investigator initiated and funded by CHDR.

Declarations

All studies included in this manuscript have been approved by an ethical committee. The studies were conducted according to the Dutch act on Medical Research Involving Human Subjects (WMO) and in compliance with Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. Written and informed consent was obtained from all the included participants.

Declaration of Competing Interest

All authors declare to have no potential conflicts of interest.

Acknowledgments

The authors thank all staff involved in collecting the data at CHDR throughout the years.

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