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Novel computerized neurocognitive test battery is sensitive to cancer-related cognitive deficits in survivors

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Abstract

Purpose There is increasing interest in developing new methods to improve sensitivity in detecting subtle cognitive deficits associated with cancer and its treatments. The current study aimed to evaluate the ability of a novel computerized battery of cognitive neuroscience–based tests to discriminate between cognitive performance in breast cancer survivors and controls.

Methods Breast cancer survivors ($N=174$) and age-matched non-cancer controls ($N=183$) completed the Enformia Cogsuite Battery of cognitive assessments, comprised of 7 computerized tests of multiple cognitive domains. Primary outcome measures included accuracy, reaction times (RT), and coefficients of variation (CV) for each task, as well as global scores of accuracy, RT, and CV aggregated across tests.

Results Linear regressions adjusting for age, education, and remote vs. in-office administration showed that compared to non-cancer controls, survivors had significantly lower performance on measures of attention, executive function, working memory, verbal ability, visuospatial ability, and motor function. Survivors had significantly greater CV on measures of attention, working memory, and processing speed, and significantly slower RT on measures of verbal fluency.

Conclusions The Cogsuite battery demonstrates sensitivity to cancer-related cognitive dysfunction across multiple domains, and is capable of identifying specific cognitive processes that may be affected in survivors.

Implications for Cancer Survivors The sensitivity of these tasks to subtle cognitive deficits has advantages for initial diagnosis of cancer-related cognitive dysfunction, as well as detecting changes in survivors' cognitive function over time. The remote delivery of the battery may help overcome barriers associated with in-office administration and increase access to neurocognitive evaluation.

Keywords Breast cancer · Cognitive impairment · Survivorship · Cancer-related cognitive dysfunction

Introduction

As the population of cancer survivors continues to grow, there is an increasing need to identify and address the neurocognitive deficits that may result from cancer and its treatment. Up to 50% of cancer survivors report cancer-related cognitive dysfunction (CRCD) during treatment, and for an estimated 20–30% of survivors, cognitive difficulties may persist for decades following completion of treatment [1–3]. Symptoms of CRCD include deficits in multiple cognitive domains and processes, including attention, processing speed, memory, multi-tasking, word-finding, and problem solving, and evidence of these deficits has been demonstrated using patient self-report, neuropsychological tests, and neuroimaging methods [4]. There has been increasing interest to develop new methods to improve sensitivity to subtle cognitive deficiencies associated with CRCD and

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to clarify what specific cognitive processes are affected in survivorship [5]. The NCI requested proposals to develop online, remotely deliverable cognitive measures informed by cognitive-experimental and neuroscience theory (NIH/NCI 343: An Electronic Platform for Cognitive Assessment in Cancer Patients). Through that mechanism, we have developed a battery of measures for use in assessing CRCD, followed by data collection to assess discrimination between breast cancer survivors and non-cancer controls (https://www.enformia.com/cogsuite/).

There is a growing interest in the use of computerized cognitive assessments to detect cognitive deficits in various clinical populations. However, although there is evidence that several existing batteries are able to reliably detect overt neurocognitive impairments, considerably less research has evaluated their sensitivity in detecting subtle cognitive deficits, such as are seen in cancer survivors. Among the few computerized batteries that have been used to detect CRCD, results have been mixed: for example, one study found that an online battery was able to detect differences between cancer patients and controls on working memory tests, but not on tests of processing speed, attention, or learning and memory [6], whereas another found that post-treatment changes in performance were detectable using response time but not accuracy metrics [7]. To date, only one computerized remotely deliverable battery has been designed specifically to assess CRCD [8]. However, the battery is comprised of tests based directly on traditional paper-and-pencil neuropsychological assessments, and research has suggested cognitive experimental tasks may provide greater sensitivity and specificity in detecting CRCD. Therefore, the Cogsuite battery uses cognitive neuroscience-based tasks informed by recent developments in our understanding of neurological bases of the specific cognitive processes affected in cancer survivors. All measures included in the battery were chosen based on evidence of sensitivity to CRCD in prior research. While most utilized tasks were derived from cognitive-experimental literature and methods, verbal fluency and coding are computerized analogs of standard measures. All measures follow the methodological elements of the paradigms they are based on and have been visually altered to increase engagement with each task (Fig. 1).

Attention network test

Based on our past research demonstrating that survivors may experience attention/working memory dysfunction that impairs encoding during traditional memory tasks [9–11] the battery includes a modified version of the attention network test (ANT), which measures sub-components of attentional processes, including alerting, orienting, and executive function [12]. In addition to accuracy, intra-individual variability in response time was of particular interest in this and other tasks, as past research has demonstrated that on continuous performance tests of attention, breast cancer survivors exhibit greater intra-individual variability (IIV) in response time than healthy controls, reflecting deficits in sustained attention [13]. The ANT allows for detection of these subtle differences in IIV, as well as decomposition of sub-processes of attention that are not possible in analysis of traditional neuropsychological list-learning tasks or continuous performance tests.

Stop signal delay

The stop signal task included in the Cogsuite battery is designed to measure executive function, sustained attention, and response inhibition [14]. Response inhibition in particular is critical to self-regulation, and deficits in this function may underlie survivors' self-reported difficulties in suppressing distractions leading to attentional lapses [15]. Indeed, neuroimaging research has found that compared to controls, breast cancer patients show differences in brain activity during response inhibition tasks both pre-treatment [16] and following chemotherapy [15]. The stop signal task is a commonly used measure of response inhibition, and has been shown to be highly sensitive to attention and inhibition deficits in a variety of populations with neurocognitive and psychiatric disorders, including cancer patients and survivors [16, 17].

N-back task

Past research has shown that cancer patients and survivors exhibit changes in working memory performance, which are correlated with alterations in both structure and function of prefrontal brain regions known to support working memory function [18–23]. To test working memory function, the Cogsuite battery includes an N-back task [24], which has been shown to be sensitive to treatment effects in other cancer populations [25].

Mental rotation

Patients and survivors also frequently exhibit changes in visuospatial abilities during or after treatment [26, 27]. Deficits in visuospatial function have been reported in men undergoing androgen deprivation therapy for prostate cancer, supporting the inclusion of this measure in the battery [27, 28]. The mental rotation task [29] included in the Cogsuite battery is a commonly used test of visuospatial abilities, and past studies have reported that prostate cancer patients have poorer performance and reduced activation in brain regions that support visuospatial function using similar mental rotation tasks [28, 30].

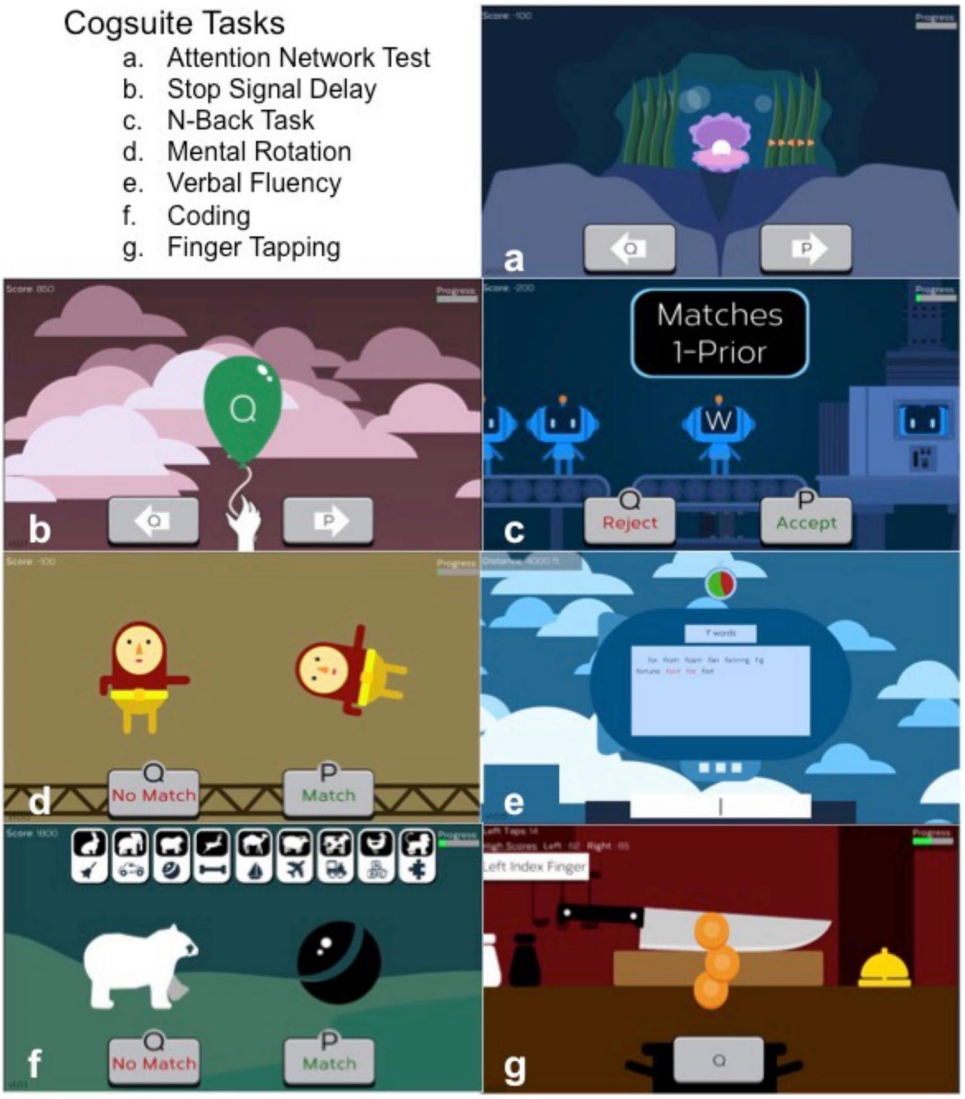

Fig. 1 Examples of trials on each of the computerized cognitive tasks in the Cogsuite battery

Verbal fluency

A change in verbal abilities, particularly word finding and word substitution, is a commonly reported symptom of CRCD. A meta-analysis of studies in survivors found that word finding and word generativity are frequently affected following cancer treatment [26], and neuroimaging studies have shown changes in structure and function of brain regions that support verbal abilities in survivors [18, 19, 21]. Work from our group has also shown that chemotherapy-treated patients have altered trajectories in verbal fluency performance from pre- to post-treatment compared to healthy controls and patients unexposed to chemotherapy [31]. Based on this evidence, the current battery includes a word generation task to measure phonemic and semantic fluency.

Coding

There is substantial evidence that cancer patients and survivors experience difficulties with psychomotor speed, which may interfere with their ability to successfully perform higher-order cognitive tasks. Processing speed deficits have been detected in breast cancer patients and survivors [32, 33], and neuroimaging research has demonstrated significant associations between processing speed performance and changes in cerebral white matter integrity following chemotherapy [22]. The Cogsuite measure of processing speed is a substitution task similar to traditional digit symbol coding tests, but which allows for more precise measure of trial by trial response times and accuracy.

Finger tapping

Simple motor dexterity and speed have been found to be a sensitive and non-specific indicator of lateralized hemispheric involvement [34], white matter integrity [35], and cognitive dysfunction [36]. As well, survivors frequently report peripheral neuropathy, and previous studies have found evidence of decreased motor functioning in chemotherapy-treated survivors [37, 38]. The finger-tapping test is included to assess potential motor dysfunction stemming from central or peripheral nervous system damage.

By incorporating reliable cognitive-experimental tasks and current research in the cognitive neuroscience of CRCD, the Cogsuite battery addresses a significant need for measures that can improve detection of subtle and specific cognitive changes in survivors following cancer treatment. Furthermore, because the Cogsuite battery can be administered remotely, it has the potential to limit the burden on clinicians' and participants' time and resources, and circumvent barriers to accessibility associated with in-office assessments. The current study aimed to test whether Cogsuite can reliably detect CRCD by comparing performance on the above tasks between a cohort of breast cancer survivors and age-matched non-cancer controls. Here, we report the performance of the Cogsuite battery to discriminate groups based on global values of mean accuracy, reaction time, and intra-individual variability, and then by individual measures. We also assess differences in dispersion between survivors and controls. Group differences on all variables within each measure are reported in the supplemental material.

Methods

Participants

Breast cancer survivors ($N = 174$) were recruited through the Army of Women as well as the survivorship clinic at Memorial Sloan Kettering Cancer Center (MSKCC). Non-cancer controls ($N = 183$) were recruited through the Army of Women, now called the Love Research Army, and community advertisement. Survivors were eligible if they were 40–65 years old, had a history of AJCC stages 0–3 breast cancer, and were between 6 months and 10 years post-treatment. Survivors were excluded if they had a history of another type of cancer, except non-melanoma/basal cell skin cancer/squamous cell skin carcinoma, or early-stage secondary cancer treated only with surgery. Controls were eligible if they were females aged 40–65 years, with no history of cancer except non-melanoma/basal cell skin cancer/squamous cell skin carcinoma, or early-stage secondary cancer treated only with surgery. For both groups, inclusion criteria also included (1) a score of < 11 on the Blessed Orientation-Memory-Concentration Test (BOMC), (2) if currently taking psychoactive medications (excluding gabapentin) on a daily basis, dose must have been stable for at least two months prior to enrollment, and (3) per-self report, English fluency of "well" or "very well", and having a reasonable comprehension of the study conversation and informed consent in the opinion of the research staff. For both groups, exclusion criteria included (1) diagnosis of neurodegenerative disorder that affects cognitive function; (2) history of stroke or head injury resulting in a structural lesion on neuroimaging; (3) persistent cognitive difficulties impacting work or daily life or required cognitive rehabilitation; (4) fine motor/motor impairments that interfere with participant's ability to use a keyboard; (4) self-reported diagnosis of a schizophrenia spectrum disorder, substance use disorder, bipolar disorder, or schizotypal personality disorder; (5) self-reported visual or auditory impairment that would preclude ability to complete the assessments; and (6) use of methotrexate or rituximab for rheumatoid arthritis, psoriasis or Crohn's disease, or cyclophosphamide for lupus. Age range was limited to 40–65 years because most breast cancer survivors are diagnosed and treated over the age of 40, and cognitive performance over 65 years may be confounded by effects of normal cognitive aging. Treatment timeframe was limited to 6 months–10 years post-treatment based on the majority of past research demonstrating this is the time during which cancer-related cognitive difficulties can be detected [39]. Individuals currently using methotrexate, rituximab, and cyclophosphamide for auto-immune disorders were excluded to limit the potential acute effects of those agents on cognition. All methods and procedures were approved by the institutional review board at MSKCC.

For survivors, mean age was 55.14 years (SD = 6.94). Seventy-eight percent had an education of bachelor's degree or higher. Eighty-one percent identified as White/Caucasian, 9% Black/African American, 6% Asian, Native Hawaiian, or other Pacific Islander. Ninety-five percent identified as non-Hispanic or Latino. Sixty-four percent received chemotherapy, and 71% received hormonal therapy, and 64% received radiation treatment. Ninety-one percent were right hand dominant. For controls, mean age was 55.91 years (SD = 7.02). Eighty-five percent had education of bachelors' degree or higher. Ninety-five percent identified as White/Caucasian, 2% Black/African American, 0.5% American Indian/Native Alaskan, 1% Asian, Native Hawaiian, or other Pacific Islander. Ninety-six percent identified as non-Hispanic or Latino. Ninety percent were right hand dominant. There were no significant differences in mean age or education, or in percentages of ethnic groups or dominant hand between survivors and controls. Groups differed in racial diversity ($p < 0.01$) (Table 1). Twelve percent of controls and 31% of survivors completed assessments in-office ($p < 0.001$); all others completed assessments remotely online.

Table 1 Participant demographic and treatment variables

	Controls ($N=183$)	Survivors ($N=174$)	Sig. (p)
Age	55.91 (7.02)	55.14 (6.94)	0.303
Education			0.317
High school/GED	8 (4.4%)	11 (6.3%)	
Associate degree/some college	19 (10.4%)	23 (13.2%)	
Vocational/technical school	1 (0.5%)	5 (2.9%)	
Bachelor's degree	72 (39.3%)	61 (35.1%)	
Advanced degree	83 (45.4%)	74 (42.5%)	
Ethnicity			0.917
Non-Hispanic or Latino	174 (95.6%)	165 (95.4%)	
Hispanic or Latino	8 (4.4%)	8 (4.6%)	
Racial identity			0.002**
American Indian, Native Alaskan	1 (0.5%)	0 (0%)	
Asian, Native Hawaiian, other PI	2 (1.1%)	11 (6.3%)	
Black, African American	4 (2.2%)	16 (9.2%)	
Other	2 (1.1%)	4 (2.2%)	
White, Caucasian	173 (94.5%)	141 (81.3%)	
Dominant hand			
Right	164 (89.6%)	159 (91.4%)	0.825
Left	17 (9.3%)	13 (7.5%)	
Ambidextrous	2 (1.1%)	2 (1.1%)	
Mode of administration			
In-office	22 (12.0%)	54 (31.0%)	<0.001***
Remote	161 (88.0%)	120 (69.0%)	
Years since treatment	–	5.15 (3.21)	
Chemotherapy			
No	–	62 (35.6%)	
Yes	–	112 (64.4%)	
Hormone treatment			
Never	–	50 (28.7%)	
Past	–	34 (19.5%)	
Current	–	90 (51.7%)	
Radiation treatment			
No	–	62 (35.6%)	
Yes	–	112 (64.4%)	

Mean (SD) reported for continuous outcomes, count (percentage) reported for categorical outcomes. p values reflect differences between groups based on one-way ANOVAs for continuous variables, and Pearson's chi-square tests of all categories by group for categorical variables. *PI:* Pacific Islander. $^{**}p<0.01$, $^{***}p<0.001$

Procedures

Enformia Cogsuite neurocognitive assessment

Participants completed the Enformia Cogsuite Battery suite of assessments [40], which was prototyped and tested for usability, tolerability, and feasibility in previous research and phase-I development funding (NCI SBIR grant # HHSN261201600024C). Participants completed the battery on a Macbook laptop (in-office), or on their personal home computers (remote). Participants were instructed during consent, in an instruction email prior to downloading the battery, and in the Cogsuite platform itself, that the battery should be completed in quiet space that is free of distractions. Prior to testing, all participants completed several practice sessions to ensure familiarity with each task and with using the keyboard to submit responses. Research assistants were present in office and available during remote administration to address any challenges related to task completion. The battery is comprised of 7 computerized tests of attention, executive function, working memory, verbal ability, visuospatial ability, motor function, and processing speed in a fixed order of presentation (Table 2).

Attention network test Participants are asked to determine the direction of the center arrow in a flanker array that may appear either to the left or right of fixation. The target is preceded by one of four cue conditions: no cue — no cue is presented; double cue — both cue boxes flash briefly to indicate when but not where the target will appear; valid cue — the left or right cue box flashes when and where the target will appear; invalid cue — the opposite cue box from where the target will appear flashes. Two conditions of flanker targets are included: congruent — all arrows point in the same direction; and incongruent — the center arrow points in the opposite direction from that of the flankers. A total of 144 trials are divided into 12 blocks of 12 trials each, counterbalanced across cue types. Fixation time: 50ms; cue presentation time: 100ms; target presentation time: 1500ms; inter-trial interval: pseudo-random, 1000–8000ms.

Stop-signal task The task consists of go and no-go trials: in go trials (75% of trials), participants are presented with a fixation cross, followed by a target to which a speeded response is required. In no-go trials (25%), the same fixation and target are presented, but are then followed by an auditory stop-signal at varying intervals post-target offset, depending on the participant's success in inhibition on the most immediate, prior inhibition trial. The task consists of 3 blocks of 64 trials for a total of 192 trials. Target display time: 1000ms; input wait time: 1250ms; inter-trial interval: 2000ms. Stop-signal delay: initially set for 250ms, increases or decreases by 50ms increments based on inhibition performance.

N-back test The task consists of the successive presentation of single letters to which the participant makes a finger press in response. Participants are required to determine if the currently presented letter is a match depending on the condition criteria. Four conditions are presented in randomized block order that vary with regard to matching criteria: 0-back (currently presented letter matches a pre-specified individual letter), 1-back (currently presented letter is the same as the one immediately preceding), 2-back (currently presented letter is the same as the one two back from it), 3-back (currently presented letter is the same as the one three back from it). A total of 144 total trials are administered over 4 blocks of 36 trials each. Targets display time: 1000ms; inter-trial interval: 1500ms.

Table 2 Cogsuite tasks and cognitive domains assessed by each task

Cogsuite task	Cognitive domains
Attention Network Test	Orienting; Alerting; Executive Control
Stop Signal Reaction Time	Response Inhibition
N-Back	Working Memory
Mental Rotation	Visuospatial Reasoning
Verbal Fluency	Phonemic and Semantic Word Generation
Coding	Psychomotor Speed
Finger Tapping	Manual Dexterity/Speed

Mental rotation task Participants are presented with paired stimuli and asked to decide whether the pair is identical after mentally rotating one or the other stimulus to the orientation of the target stimulus. Eighty total target stimuli are rotated 0, 40, 80, 120, or 160°, divided over 8 blocks of 10 trials each. Target display time: 3000ms; inter-trial interval: 1500ms.

Verbal fluency task Participants are asked to generate, via keyboard, words that belong in a given semantic category or begin with a given letter. Four total trials consist of 3 phonemic cue trials (words beginning with F, A, and S) and 1 semantic cue trial (animal words). Trial time: 60,000ms per cue.

Coding Paired stimuli are presented that are either matched correctly according to a code key, or mismatched. The code key remains on the screen for participant reference while each stimuli pairing is presented and a choice is made for either a match or a mismatch. Trial time: 120,000ms; target display time: 2500ms.

Finger tapping The bimanual finger-tapping test is used to efficiently sample left and right-handed motor responses. Participants are asked to tap left or right index fingers, using the P or Q keys, as fast as possible for a 10-s span over 5 sessions for each side, with a 5-s resting period in between each of 10 sessions. Performance is measured by total number of taps on all trials, separately for each hand. Trial time: 10,000ms; inter-trial interval: 5000ms.

Data

Cogsuite data were transformed prior to analyses using the Box-Cox transformation [41] so that the scores resembled a normal distribution to correspond to the normality assumption in statistical analyses. Descriptive statistics and plots were done on the original scales for ease of interpretation. For all tests (ANT; mental rotation, N-back; stop signal, and coding), variables of interest included (1) reaction time; (2) global accuracy; and (3) coefficient of variation (CV). The CV was defined as standard deviation of intra-individual reaction time/mean reaction time in each task/condition [13]. First, global accuracy, reaction time, and coefficient of variation variables were calculated by averaging accuracy, reaction time, and coefficient of variation variables for all choice reaction time measures (ANT; mental rotation; N-back; stop signal; coding), and performance was compared between groups; performance differences between groups were then assessed for each individual measure.

Statistical analyses

Linear regression was used to estimate between-group differences between survivors and controls in the outcomes of accuracy, median RT, and CV. Additional covariates included age, education, and mode of administration (remote vs. in-office). Group differences in dispersion were assessed by calculating the standard deviation of accuracy, reaction time, and coefficient of variation between all choice reaction time measures [42]. Data were prepared using the MASS package [43] in R version 4.0.4 [44] for Box-Cox power transformations, and analyses were conducted using SPSS Version 27.0 [45]. Results were considered significant at $p < 0.05$ and marginally significant at $p < 0.1$, and unstandardized regression coefficients (B) reflect survivors relative to controls. Regression coefficients and confidence intervals were back-transformed to original scales for interpretation.

Results

Primary outcome measures of interest included accuracy rates, median reaction times (RT), and coefficients of variation (CV; standard deviation of RT/mean RT). Each metric was analyzed as a global score across tasks, for each task individually, and within task conditions where applicable (Tables 2 and S1).

Global variables

For survivors, aggregate performance across ANT, N-back, mental rotation, stop signal delay, and coding measures was significantly lower for accuracy ($B = -0.013$, $p < 0.01$) and higher for coefficient of variation ($B = 0.009$, $p < 0.01$) relative to controls, with no differences in mean reaction time.

Attention network test

Survivors had lower accuracy than controls across all conditions ($B = -1.010$, $p < 0.01$) (Table 3), and this pattern was consistent across incongruent, congruent, valid cue, invalid cue, double cue, and no cue trial types (Table S1). Across all conditions, CV was also significantly higher for survivors compared to controls ($B = 6.969$, $p < 0.01$) (Table 3), and this pattern was seen consistently within congruent, valid cue, invalid cue, double cue, and no cue trial types (Table S1).

Stop-signal delay

Survivors had significantly lower mean accuracy than controls on no-go trials ($B = -1.004$, $p < 0.05$), and marginally lower mean stop signal delay (SSD) on no-go trials ($B = -3.293$, $p = 0.084$). There were no significant group differences in stop signal reaction time (mean go trial RT – mean SSD) for no-go trials, or in mean accuracy or CV for go trials. Unexpectedly, survivors had marginally significantly lower median RT than controls on go trials ($B = -31.041$, $p = 0.093$) (Table 3).

N-back

Survivors had significantly lower overall accuracy ($B = -1.007$, $p < 0.01$), and marginally higher overall CV ($B = 2.168$, $p = 0.062$) compared to controls (Table 3). Within working memory load conditions, survivors demonstrated significantly lower accuracy on 1-back and 2-back conditions, significantly higher CV in the 0-back condition, and marginally higher CV in the 3-back condition (Table S1). Unexpectedly, survivors had lower median RT compared to controls in the 3-back condition ($B = -40.473$, $p < 0.05$). There were no significant group differences in median RT within other conditions, overall, or in d-prime measure of discriminability (Table S1).

Mental rotation

Survivors had marginally lower accuracy than controls in the 0° rotation condition ($B = -1.008$, $p = 0.065$) (Table S1), but there were no significant group differences seen overall, or within other rotation conditions, for accuracy, CV, or RT (Table S1).

Verbal fluency

Survivors had marginally lower mean words generated than controls on the FAS task ($B = $ v2.579, $p = 0.05$), but there was no group difference in overall performance on animal word generation task ($B = -1.166$, $p = 0.492$). Median type time per word was significantly slower for survivors than for controls on both FAS ($B = 1.010$, $p < 0.01$) and animal tasks ($B = 1.007$, $p < 0.05$). Median type time per character was also significantly slower for survivors compared to controls for FAS ($B = 1.006$, $p < 0.05$) and marginally slower for the animal task ($B = 1.003$, $p = 0.085$) (Table 3).

Coding

Survivors had higher mean CV than controls ($B = 1.764$, $p < 0.05$), with no significant group differences in mean accuracy ($B = -1.000$, $p = 0.888$) (Table 3).

Finger tapping

Survivors had significantly lower mean taps than controls using the left hand ($B = -19.298$, $p < 0.05$), but not the right hand ($B = -8.677$, $p = 0.356$) (Table 3).

Table 3 Group differences between BCS and NCC on overall accuracy, coefficient of variability (CV), and reaction time (RT) across all trials of each Cogsuite task

Cogsuite measure	B	95% CI		Sig. (*p*)
		LL	UL	
Global performance				
Accuracy	−0.013	−0.022	−0.003	0.009**
Median RT	−7.887	−37.561	21.788	0.602
CV	0.009	0.003	0.015	0.004**
Global Dispersion				
Accuracy	0.009	0.000	0.019	0.056†
Median RT	3.706	−29.740	−37.152	0.828
CV	0.004	−0.004	0.011	0.334
Attention Network Test				
All Trial Accuracy	−1.010	−1.016	−1.003	0.002**
All Trial RT Median	1.000	1.000	−1.000	0.896
All Trial CV	6.969	1.895	23.658	0.003**
Stop Signal Reaction Time				
All GO Trial Accuracy	−1.000	−1.006	1.005	0.870
All GO Trial RT Median	−31.041	−58.922	7.364	0.093†
All GO Trial CV	1.066	−1.131	1.274	0.503
All NOGO Trial Accuracy	−1.004	−1.007	1.001	0.015*
All GO Trial Incorrect RT Median	1.090	−2.353	2.700	0.872
All GO Trial Incorrect CV	1.154	1.048	1.379	0.135
All NOGO Trial SS Delay Mean	−3.293	−8.156	1.219	0.084†
All NOGO Trial SS RT	1.000	−1.000	1.000	0.913
N-Back				
All Trial Accuracy	−1.007	−1.012	−1.002	0.004**
All Trial CV	−1.000	−1.000	1.000	0.121
All Trial RT Median	2.168	−1.034	4.747	0.062†
Mental Rotation				
All Trial Accuracy	−1.006	−1.015	1.002	0.147
All Trial CV	1.097	−1.044	1.236	0.177
All Trial RT Median	−15.800	−165.724	159.545	0.955
Verbal Fluency				
FAS Correct	−2.579	−4.469	1.001	0.050†
FAS Type Time Median	1.010	1.003	1.021	0.008**
FAS Type Time/Char Median	1.006	−1.001	1.012	0.028*
FAS Gen Time Median	−1.014	−1.224	1.183	0.859
Animal Words Correct	−1.166	−1.697	1.317	0.492
Animal Words Type Time Median	1.007	1.000	1.014	0.047*
Animal Words Type Time/Char Median	1.003	1.000	1.007	0.085†
Animal Words Gen Time Median	1.552	−1.709	3.901	0.384
Coding				
All Trial Accuracy	−1.000	−1.004	1.004	0.888
All Trial CV	1.764	−1.040	−2.912	0.037*
Finger Tapping				
Left Hand Total Taps	−19.298	−30.533	−6.059	0.012**
Right Hand Total Taps	−8.677	−21.030	9.490	0.356

B: unstandardized regression coefficients, with 95% Wald confidence intervals (*LL:* lower limit; *UL:* upper limit). *SS:* stop signal; *Char:* character; *Gen:* generation; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, †$p < 0.10$

Dispersion

With regard to between task variability, when performance was assessed for dispersion, survivors were marginally more variable in accuracy of response ($B = 0.009$, $p = 0.056$) but not in reaction time or in coefficient of variation (Table 3).

Exploratory analyses

Based on past evidence that cognitive symptoms may differ by type of treatment [46, 47], and by time since treatment [48, 49], we conducted exploratory analyses to test whether there were any differences in performance for participants who had undergone chemotherapy ($n = 112$) vs. those who had not been treated with chemotherapy ($n = 62$), as well as whether cognitive performance was associated with years since treatment. Linear regressions controlling for the effects of age, education, and mode of administration showed that treatment with chemotherapy was not a significant predictor of performance on any tasks (Table S2). Linear regressions controlling for the effects of age and education showed that years since treatment was a significant predictor of performance on multiple tasks. All trial accuracy on N-back, mental rotation, and verbal fluency tasks was positively associated with time since treatment. Greater time since treatment also significantly predicted lower reaction times on ANT and mental rotation, and lower type time and generation time on verbal fluency tests (Table S2).

Discussion

The present study aimed to evaluate the ability of a novel, cognitive neuroscience–based test battery to discriminate between breast cancer survivors and women without a history of breast cancer. Results indicate high sensitivity to cognitive difficulties in breast cancer survivors, with survivors exhibiting lower global accuracy and higher global intraindividual variability (IIV) with no differences in global reaction time. Across measures, survivors exhibited marginally significantly greater dispersion in performance accuracy than controls indicating greater variability in performance between tasks.

The pattern of findings for intra-individual variability (IIV) indicates consistently greater variability in reaction time in the attention network test in all but one target condition, greater variability overall in the coding task and marginally significantly greater variability in the N-back task. Previous research has found that breast cancer survivors exhibit greater IIV, interpreted as reflecting deficits in sustained attention, and work from our lab has suggested these attention deficits may underlie common complaints of memory dysfunction in cancer survivors [4, 9–11]. Interestingly, in addition to greater reaction time variability within each measure, survivors also exhibited marginally increased variability in performance accuracy between each measure. Significantly, intraindividual variability, as reflected by inconsistency, i.e., within-task, trial to trial variability, or by dispersion, i.e., between task variability, has previously been found to be associated with aging [50, 51], with subsequent cognitive decline [52], and with white matter integrity [53].

With regard to performance accuracy, the pattern of findings indicates consistently lower performance in survivors in the attention network test in every cue and target condition, and lower accuracy overall in the N-back task. For verbal fluency, survivors generated significantly fewer words to a phonemic prompt. For finger tapping, survivors generated significantly fewer taps with what, for the majority of participants (8.4%), was the non-dominant, left hand.

The pattern of findings for accuracy and IIV differences suggests both a specific and general effect between and across cognitive tasks. Most significantly, survivors exhibited most difficulty with the attention network test as indicated by both consistently lower accuracy and higher variability across conditions, and in the N-back task in which results followed a similar but less consistent pattern across working memory load conditions. This pattern suggests what may be a specific weakness in maintenance of attention/vigilance, and in working memory, two processes with significant contributions of prefrontal regions [54]. We did not detect specific differences in performance between survivors and controls within any of the four ANT network effect scores. This may suggest that attentional capacity as a whole is diminished, or may reflect lower reliability, and as a result sensitivity, of network scores due to the fact that each network is calculated as a contrast between conditions [55]. Past research has also suggested the reliability of network scores varies by network and statistical approach [56], and scores may be contaminated by significant interactions between networks [57, 58]. While the strongest effects were exhibited in these measures, that there may be also a more general deficit is suggested by findings of significantly higher variability in coding, and nominally higher variability in mental rotation and stop signal tasks.

Exploratory analyses on the effects of treatment-related factors in survivors showed that there were no significant differences in performance between survivors who had received chemotherapy compared to those who had not, but greater time since treatment was a significant predictor of better performance across multiple tasks. These findings are consistent with past research, but further research is warranted to examine possible effects of other treatment variables (e.g., different hormone therapies) on cognitive function, as well as the utility of Cogsuite in detecting cognitive changes at varying intervals post-treatment.

Strengths and limitations

Strengths of the present study include a large sample of survivors and controls. The suite of assessments included in the

Cogsuite battery is based on valid, reliable tests commonly used in experimental cognitive psychology, neuroscience, and neuropsychology, which have been successfully utilized in a breadth of neurological and psychiatric patient populations, as well as to examine cognition in healthy adults across the lifespan.

Despite its strengths, limitations to the current study should be noted. Our participant cohort lacked sufficient diversity in racial, ethnic, cultural, socioeconomic, and educational factors, each of which have been shown to predict differences in general cognitive performance and vulnerability to neurocognitive decline in non-cancer populations [59–63]. In the current sample, there was a significant difference in racial distribution between controls and survivors, with a greater proportion of racial minorities in the survivor group, with no sub-group making up a majority of the minority sample. Future research would benefit from using samples with greater racial/ethnic diversity to examine whether such factors impact the sensitivity of Cogsuite to differences in cognition between controls and survivors. To this end, the use of a remotely delivered cognitive test battery has the potential to increase the breadth of CRCD research to examine cognitive function in groups that may be more vulnerable to treatment-related effects or who have more significant barriers to assessment.

We also recognize that cancer patients and survivors may experience physiological and psychological comorbidities, such as fatigue, anxiety, and depression, which have been associated with cognitive deficits in patients with CRCD in intervals closer to treatment [4, 64–66]. Because it remains unclear whether these factors contribute to CRCD directly or whether they present in parallel with primary cognitive deficits, we did not control for the potential impact of these factors in our analyses of cognitive performance; nevertheless, future research would benefit from evaluating the precise relationship between psychological and cognitive symptoms to better understand possible interactions between these factors. Furthermore, because the aim of the current study was to explore differential sensitivity of the Cogsuite battery and specific measures to CRCD, we analyze all available data and report all results of a large number of variables, from global to task-specific to condition-specific performance. Future research using Cogsuite will clarify where performance differences between breast cancer survivors and non-cancer controls are specifically and consistently different between groups.

It is also worth noting that the current study involved a relatively large number of outcome variables, and our statistical analyses did not adjust for multiple comparisons. However, our primary aim was to demonstrate the discriminant validity of the Cogsuite battery to distinguish between known groups, rather than testing a hypothesis related to the pattern of cognitive deficits seen in survivors. Therefore, the issue of multiple comparisons is less relevant given that we did not hypothesize specific group differences in performance that could potentially be inflated due to multiple comparisons. Furthermore, despite the number of comparisons within each task, we found consistency in group differences across task types (e.g., higher CV for survivors relative to controls in multiple tests), suggesting a core deficit that is exhibited across cognitive domains and is unlikely to result from the impact of multiple comparisons within one task. However, future research aimed at testing the hypothesis that survivors perform worse than controls on specific cognitive functions should consider the impact of multiple comparisons when evaluating multiple trial conditions within each task.

Lastly, differences in cancer treatment regimens may underlie some variability in performance in survivors, and previous research has suggested that cognitive domains affected may differ by treatment modality, as well as by type of cancer [4]; therefore, future research should examine potential differences in the effects of cancer type and treatment type on cognition in patients and survivors.

Implications for cancer survivors

The battery of assessments used in the current study uses computerized cognitive experimental tasks, largely informed by cognitive-experimental neuroscience, to detect subtle cognitive deficits in CRCD, which has benefits for clinical care of cancer survivors. Although standard neuropsychological measures have been shown to be sensitive to some deficits in CRCD, the use of precise metrics of cognitive performance in the current battery may allow clinicians and researchers to distinguish between discrete cognitive processes, as well as detect deficits in early processes that may have downstream effects on performance in multiple domains, leading to more precisely tailored treatment regimens.

The use of a remotely administered computerized test battery also has the potential to increase patient access to neurocognitive testing, by overcoming potential barriers to in-clinic evaluation such as geographical and scheduling restrictions. Moreover, compared to administration of in-clinic neuropsychological test batteries, the remotely delivered battery allows for a less time- and resource-intensive method for clinicians to administer comprehensive cognitive assessments. The anticipation is that this battery would be used as a supplement to in-person standard, comprehensive neuropsychological assessment where in-person assessment is possible; it could also potentially be used as a standalone assessment or in conjunction with standard measures delivered remotely when in-person assessment is not possible or feasible. Some previous research has suggested participants have poorer performance on remotely administered cognitive assessments compared to in-office assessments [67, 68]. However, our results showed that participants completing Cogsuite remotely actually had better performance than those completing the battery in-office, suggesting the Cogsuite battery is able to accurately detect cancer-related cognitive dysfunction in unsupervised remote settings.

Furthermore, although the primary focus of the current project was to assess CRCD, the cognitive assessments included in the battery are applicable to the evaluation of

cognitive function in a wider subset of syndromes in which subtle but significant cognitive dysfunction is present, such as post-concussive injury, attention deficit disorder, multiple sclerosis, mild cognitive impairment, early stages of Parkinson's disease and dementia, and normal cognitive aging [69–74].

Conclusions

The current study is the first to date to utilize a comprehensive computerized battery of neurocognitive tests designed to remotely detect CRCD in survivors. We address a significant gap in current CRCD research by presenting evidence that remotely delivered cognitive measures demonstrate sensitivity to CRCD and are capable of identifying specific processes that may be affected. The sensitivity of these tasks to subtle cognitive deficits has advantages not only for initial diagnosis of CRCD, but also potentially for detecting changes in cognitive performance in survivors over time, leading to tailored treatment interventions that more precisely target affected cognitive functions in cancer survivors.

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Author contribution AMG: data curation, formal analysis, writing—original draft, writing—review and editing, and visualization. AA: data curation, writing—review and editing, and visualization. DJ: conceptualization, funding acquisition, resources, investigation, data curation, and writing—review and editing. LS: formal analysis and writing—review and editing. YL: formal analysis and writing—review and editing. TAA: conceptualization, investigation, and writing—review and editing. JCR: conceptualization, funding acquisition, resources, investigation, data curation, and writing—review and editing.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Code availability Not applicable.

Declarations

Ethics approval This study involving human participants was performed in accordance with the ethical standards of the institution and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the ethics committee and the Institutional Review Boards at Memorial Sloan Kettering Cancer Center and City of Hope National Medical Center.

Consent to participate Informed consent was obtained from all participants in this study.

Consent for publication Not applicable.

Conflict of interest Duane Jung is the CEO of the Enformia, Inc., the publisher of the Cogsuite battery. All other authors certify that they have no conflicts of interest to disclose.

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