Predicting occupational outcomes from neuropsychological test performance in older people with HIV

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Objective: The ability to work is amongst the top concerns of people living with well treated HIV. Cognitive impairment has been reported in many otherwise asymptomatic persons living with HIV and even mild impairment is associated with higher rates of occupational difficulties. There are several classification algorithms for HIV-associated neurocognitive disorder (HAND) as well as overall scoring methods available to summarize neuropsychological performance. We asked which method best explained work status and productivity.

Design: Participants ($N = 263$) drawn from a longitudinal Canadian cohort underwent neuropsychological testing.

Methods : Several classification algorithms were applied to establish a HAND diagnosis and two summary measures (NPZ and Global Deficit Score) were computed. Self-reported work status and productivity was assessed at each study visit (four visits, 9 months apart). The association of work status with each diagnostic classification and summary measure was estimated using logistic regression. For those working, the value on the productivity scale was regressed within individuals over time, and the slopes were regressed on each neuropsychological outcome.

Results: The application of different classification algorithms to the neuropsychological data resulted in rates of impairment that ranged from 28.5 to 78.7%. Being classified as impaired by any method was associated with a higher rate of unemployment. None of the diagnostic classifications or summary methods predicted productivity, at time of testing or over the following 36 months.

Conclusion: Neuropsychological diagnostic classifications and summary scores identified participants who were more likely to be unemployed, but none explained productivity. New methods of assessing cognition are required to inform optimal workforce engagement.

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Introduction

People living with well treated HIV now have a near-normal life expectancy and can turn their focus to quality of life (QOL). The ability to work is amongst their top concerns [1] as employment is associated with better mental health and QOL [2–5]. HIV can have a negative impact on work by increasing absences and decreasing productivity [6,7]. Cognitive impairment has been reported in many otherwise asymptomatic persons living with HIV [8–21] and, even when mild, is associated with higher rates of unemployment and failure on standardized work assessments [22–32]. Identification of individuals with potentially work-limiting cognitive difficulties is important as identification of reversible causes of cognitive impairment and implementation of tailored compensatory strategies could help preserve function.

Neuropsychological testing is the gold standard for cognitive assessment in HIV. In the neuro-HIV literature, two broad approaches are used to interpret the results. One approach is to create a summary measure of neuropsychological performance, a continuous 'quantity of cognition', such as an NPZ-score or a Global Deficit Score (GDS) [33]. The second approach focuses on diagnostic classification, categorizing people as neuropsychological-normal or neuropsychological-impaired, most commonly using the HIV-associated neurocognitive disorders (HAND) nosology [34]. A patient is classified as neuropsychological-impaired when impairment is present in at least two cognitive domains. The definition of 'domain impairment' is central to the classification, but the operationalization of 'domain impairment' is a matter of debate in neuro-HIV [35–38] and varies across research groups, probably contributing to the variability in reported prevalence of HAND across cohorts [11,31].

Can neuropsychological performance be used to identify people at risk of occupational difficulties, and if so, what summary measure or diagnostic classifications are most informative? Some existing work has examined the degree of association between summary measures of neuropsychological performance, performance in a given cognitive domain or overall classification of neuropsychological impairment, and activities of daily living [39–41]. However, different operationalizations of the HAND criteria have not been compared in their ability to predict current or future work performance. Here, we compare two widely used continuous measures of global neuropsychological performance (NPZ and GDS) and seven classifications of neuropsychological impairment on the extent to which they can identify HIV+ adults who are not working or who experience decreased work-related productivity, at the time of neuropsychological testing or over the following 36 months.

The objective of the study is to estimate the extent to which NPZ, GDS and different classifications of neuropsychological impairment explain current work status and productivity and work productivity over the subsequent 36 months in treated HIV+ middle-aged and older adults.

Methods

Design

This is a comparative study of the concurrent and prognostic value to work status and productivity of NPZ, GDS and different classifications of neuropsychological impairment among HIV+ adults.

Participants

Participants were drawn from the Positive Brain Health Now Canadian cohort (+BHN; $N = 856$), described previously [42]: individuals over the age of 35 who were HIV+ for at least 1 year were enrolled; those with dementia, non-HIV-related neurological disorder or substance use disorder within the past year were excluded. Selected cohort participants were invited to undergo a neuropsychological evaluation. To ensure that there were enough people with and without cognitive impairment according to each classification method, we oversampled people with cognitive difficulties as measured by a brief computerized measure of cognition performed at each cohort study visit, the Brief Cognitive Ability Measure (B-CAM) [43]. Participants with comorbid conditions that preclude diagnosing HAND [34] were excluded from testing, such that those who were classified as neuropsychological-impaired could be classified as having HAND. The study was approved by the Research Ethics Board of each participating institution and all participants provided written informed consent.

Procedures/measures

Participants underwent neuropsychological testing at one of three sites across Canada (Montreal, Toronto, Vancouver), between October 2014 and March 2017 [44]. Testing was performed by trained research assistants, either in English or French. Relevant demographic, educational and medical information as well as presence of symptoms of anxiety, depression (Hospital Anxiety and Depression Scale, HADS [45]) and self-reported cognitive difficulties

(Patient Deficit Questionnaire [46]) were drawn from the parent study database.

Information on work status and productivity was obtained at each of four cohort study visits that took place 9 months apart. The information obtained closest to the date of the neuropsychological testing was chosen for the cross-sectional analysis and measures over time were used for the longitudinal, prognostic component.

Neuropsychological tests

The neuropsychological test battery assessed seven cognitive domains, with two to four test measures per domain [47]: Hopkins Verbal Learning Test–Revised (HVLT-R) learning and recall [48]; Brief Visuospatial Memory Test-Revised (BVMT-R) learning and recall [49]; Tower of London [50]; Trail Making Test A and B (TMT-A and B) [51]; Stroop [52]; Letter/Number Sequencing, Symbol Search, Digit Symbol Coding [53]; Letter and Category Fluency [52]; Grooved Pegboard dominant and non-dominant hand [54] (see Table 1 in Supplemental Digital Content, http://links.lww.com/QAD/C130).

Continuous measure of global neuropsychological performance: Two continuous summary measures reflecting global neuropsychological performance were computed: NPZ and the GDS. The NPZ was produced by averaging all the z-scores in a given domain, then averaging the mean z-scores for all domains; a higher score reflects better cognition. The GDS was calculated by transforming the z-score for each test measure into deficit scores (normal performance $= 0$ and impaired performance graded $1-5$) [33], and then averaging all the deficit scores; a higher value on the GDS reflects more deficits, or worse cognition.

Definition of domain impairment and classification of neuropsychological-impaired cases: Raw scores were converted to demographically corrected z-scores using appropriately matched normative data (see Table 1 in Supplemental Content, http://links.lww.com/QAD/C130). We applied several published definitions of 'domain impairment': the Clinical Rating method [55,56] recommended in the current HAND nomenclature; the z-score algorithm derived from Gates and Cysique adapted for missing data (Method A) [57]; the criteria proposed by Gisslén *et al.* [36] (Method B) and by Meyer *et al.* [38] (Method C); and impairment based on the lowest scoring test measure per domain using two cut-offs: 'Mild' (lowest measure <-1 SD and ≥ -2 SD) and 'Severe' (lowest measure <-2 SD) [12,19,38,58]. Following the HAND nosology, a participant was diagnosed as neuropsychological -impaired when impairment was present in at least two cognitive domains [47]. Although the GDS approach is distinct from HAND nosology, because it is not based on the number of domains impaired, a GDS at least 0.5 has been shown to accurately classify HIV+ individuals with neuropsychological impairment [33] and so was also tested as a classification method here.

Work status and productivity

Participants were classified as 'working' if they reported working for pay at least 15 h/week; people working less than this or not at all were contrasted with those classified as 'working'. In those who were working, work productivity was documented with the Stanford Presenteeism Scale (SPS), a widely used self-report measure of the impact of cognitive, psychological and physical manifestations of health conditions on work in the previous 4 weeks [59]. We used the 10 items of the Work Impairment Score (WIS) of the SPS, scored from 0 to 100, with higher scores reflecting better productivity [7].

Statistical methods

Distributional parameters were used to characterize the sample that underwent neuropsychological testing and the remaining, untested, cohort. Comparisons between the two samples were made using Chi-square tests and t tests depending on the distribution of the variable tested.

Factors associated with work status were examined using logistic regression, yielding odds ratios (ORs) and associated 95% confidence interval (CI). Explanatory variables that were not log linear with work status were dichotomized.

To inform the interpretation of the results, we tested the extent to which the mean NPZ and GDS values differed across the classifications of neuropsychological impairment, using ordinary least squares regression (NPZ) or quantile regression (GDS), according to the outcome distribution. The regression parameters indicate how much being classified as neuropsychological-impaired changes the NPZ and the GDS scores (β) and their associated standard error.

Associations between work *status* and each classification of neuropsychological impairment, the NPZ, and the GDS, were also estimated using logistic regression. Associations between work *productivity* and each classification of neuropsychological impairment, the NPZ and the GDS were tested using ordinary least squares regression. The regression parameter (β) is interpreted as how much work productivity is affected by being classified as neuropsychological-impaired.

To estimate the extent to which the classification methods predicted work productivity over time, we followed a two-step process. First, the value of the WIS for each person was regressed over visits immediately prior to and subsequent to the neuropsychological testing (representing time, to a maximum of 36 months), and the slope of the line was retained as the outcome for the subsequent model. This outcome was then regressed on each

classification of neuropsychological impairment and on the two continuous measures of global neuropsychological performance (NPZ, GDS). All models were adjusted for the number of visits with a score for work productivity and the mean work productivity per person, along with site, age, sex and education. Persons with at least two WISs were included in the analysis.

Results

Neuropsychological testing was conducted with 265 participants. After removing two participants who completed fewer than half of the tests, data were available on 263 participants, of whom 88 worked for at least 15 h/week; 84 of 88 had available information on productivity. Work status was stable over time but changes in productivity were observed over the study period.

Table 1 gives the characteristics of the neuropsychological-tested sample ($N = 263$) and the rest of the cohort that was not tested ($N = 602$). There were few meaningful differences between the neuropsychological-tested sample and those not sampled for neuropsychological testing. Even though we oversampled +BHN cohort participants with low cognition as measured by the B-CAM, the mean performance on that measure was not different among those who completed the neuropsychological testing and those who did not. Participants in the neuropsychological-tested sample reported somewhat more cognitive difficulties than those not sampled (a difference of ~0.4 SD) and were less likely to be working (33.5 vs. 49.1%); they also reported more symptoms of anxiety and depression on the HADS [45] but the difference was small (~0.3 SD). Both groups reported a range of job-related responsibilities with occupations ranging from clerical or service to professional or executive positions.

Table 2 compares the characteristics of those working for pay at least 15 h/week and those not working or working for pay less than 15 h/week. For many variables, those working less or not at all had less optimal characteristics such as older age, lower education, lower current $CD4^+$ cell count, more symptoms of depression, more reported cognitive difficulties, and poorer cognitive ability (B-CAM).

Table 1. Characteristics of the neuropsychological sample and the rest of the Positive Brain Health Now cohort that was not tested.

	NP tested sample, $n = 263$	Remaining cohort (not tested), $n = 602$		
	Mean (SD) or, *n* (%)	*n*	Mean (SD) or, *n* (%)	*P* value
Sociodemographic				
Age (years)	54.35 (8.0)	602	53.07 (8.4)	0.04
Sex		601		0.90
Male	221 (84.0)		507 (84.4)	
Female	42 (16.0)		94 (15.6)	
Education (years)	13.87 (2.5)	566	13.84 (2.4)	0.86
Ethnicity		532		0.53
White	177 (74.4)		384 (72.2)	
Other	61 (25.6)		148 (27.8)	
HIV immune markers				
$CD4^+$ cell count (cells/μl)	611 (272)	553	644 (274)	0.11
Nadir $CD4^+$ cell count (cells/μl)	193 (165)	564	224 (165)	0.01
Brain health outcomes				
HADS depression (0–21)[a]	5.58 (4.0)	550	4.42 (3.7)	<0.0001
HADS anxiety (0–21)[a]	7.88 (4.2)	548	6.77 (4.3)	<0.001
B-CAM (0–100)[b]	57.95 (14.5)	546	58.82 (14.4)	0.42
PDQ (0–100)[a]	38.77 (16.9)	557	31.80 (17.1)	<0.0001
Work-related variables				
Paid employment ≥15 h/week	88 (33.5)	578	284 (49.1)	<0.0001
Productivity (0–100)[c]	74.38 (15.2)	254	77.74 (15.9)	0.09
Self-rated degree of responsibility, high and moderate	$n = 248$	566		0.15
High	131 (52.8%)		336 (59.4%)	
Moderate	94 (37.9%)		193 (34.1%)	
Low or none	23 (9.3%)		37 (6.5%)	
Level of writing requirement	$n = 243$	554		0.38
Responsible for or participates in reports and documents	138 (56.8%)		296 (53.4%)	
Edits, types or formats reports and documents. writes brief messages or e-mail	105 (43.2%)		258 (46.6%)	

HADS, Hospital Anxiety and Depression Scale; NP, neuropsychological; PDQ, Patient Deficit Questionnaire.
[a]Higher is worse.
[b]Brief Cognitive Ability Measure, higher is better.
[c]When paid employment at least 15 h/week, higher is better ($N = 84$).

Table 2. Odds ratios associated with working less than 15 h/week or not working at all according to sociodemographic, clinical and brain health characteristics of the 263 participants who completed more than half of the neuropsychological tests.

	Working ≥15 h/week, $n = 88$		Working <15 h/week, $n = 175$		
	n	Mean (SD) or %	*n*	Mean (SD) or %	OR[a] (95% CI)
Sociodemographic					
Age (years)	88	52.2 (7.4)	175	55.4 (8.1)	1.07 (1.03–1.11)
Sex					
Men	81	92.1%	140	80.0%	Referent
Women	7	8.0%	35	20.0%	3.18 (1.29–7.79)
Education (years)	88	14.4 (2.6)	173	13.6 (2.5)	0.87 (0.78–0.97)
Ethnicity					
White	59	68.6%	118	77.6%	1.79 (0.91–3.52)
Other	27	31.4%	34	22.4%	Referent
HIV immune markers					
$CD4^+$ cell count (cells/μl)[b]	86	654 (253)	171	589 (279)	0.88 (0.79–0.97)
Nadir $CD4^+$ cell count (cells/μl)[b]	88	215 (169)	175	183 (162)	0.87 (0.74–1.03)
Brain health outcomes and work-related variables					
HADS (0–21)[c]					
Depression	85	4.4 (3.5)	169	6.2 (4.1)	Nonlinear
0–6	68	80.0%	89	52.7%	Referent
≥7	17	20.0%	80	47.3%	4.14 (2.16–7.92)
Anxiety	85	7.7 (4.3)	169	8.0 (4.1)	1.03 (0.96–1.10)
B-CAM (0–100)[d]	87	63.3 (13.4)	173	55.2 (14.2)	0.97 (0.95–0.99)
PDQ (0–100)[e]	88	35.3 (15.4)	173	40.5 (17.4)	Nonlinear
<50	73	84.9%	118	68.6%	Referent
≥50	13	15.1%	54	31.4%	2.76 (1.36–5.59)
Work productivity[f]	84	74.4 (15.2)			

CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio; PDQ, Patient Deficit Questionnaire.
[a]OR is interpreted as the effect of working less than 15 h/week or not at all per 1-unit difference on measure. Adjusted for age, sex and education; 2 participants missing education were assigned the mean.
[b]OR for $CD4^+$ cell count (current and nadir) are presented per 100 cells/μl.
[c]HADS, higher is worse, 0–6: non case.
[d]Higher is better.
[e]PDQ, higher is worse.
[f]Higher is better.

Rates of neuropsychological impairment

The number of people classified as neuropsychological-impaired according to each definition of domain impairment as well as the concordance between these classifications are presented in Table 3. Method C (Meyer) classified the fewest people as neuropsychological-impaired (28.5%), whereas Method D (Mild) classified the most (78.7%). The concordance between classification methods ranged from 36 to 100%: for example, only 47% of those impaired by classification Method A were also impaired by Method C. The mean NPZ value among the impaired in each neuropsychological classification ranged from −0.6 to −1.1 (i.e. performance that is, on average, 0.6–1.1 SD below normative means), and the adjusted difference in NPZ values between those impaired vs. not (β) was on average 0.9 SD worse than for the unimpaired. The median GDS value in the impaired ranged from 0.7 to 1.2, and the average adjusted difference in median GDS values between those impaired vs. not (β) was 0.69 points higher (more impaired) among those who were classified as neuropsychological-impaired compared with those who were not.

Work status

Table 4 presents the association between each classification method and work status at the time of neuropsychological testing, contrasting working for pay at least 15 h/week vs. not working or working for pay less than 15 h/week. For ease of interpretation, we present the OR (95% CI) for *not working* and, to allow for comparison of the ORs, we rescored the NPZ such that a higher score indicates *worse* performance (NPZ rev), as is the case with all the other variables. Age, sex and education were themselves significant predictors of work status, so only adjusted associations are presented. Being classified as neuropsychological-impaired by any classification method carried a two-fold increase in the odds of not working for pay at least 15 h/week. For the continuous measures of global neuropsychological performance, a 1-unit difference in the NPZ or GDS was associated with an OR for *not working* of 2.32 (95% CI: 1.88–2.87) and 2.26 (95% CI: 1.24–4.09), respectively.

Work productivity

Table 5 shows the association between each classification of neuropsychological impairment and work productivity (0–100, higher is better) among the 84 participants who were working for pay at least 15 h/week and had available information on productivity at the time of testing; 76 had at least two measures between the visit just prior to neuropsychological testing and the subsequent 36 months. A difference of 7.6 points in productivity (0.5 SD) would be considered clinically important [60]. For

Table 3. Number of people in the neuropsychological tested sample ($n = 263$) classified as neuropsychological impaired according to different definitions of domain impairment and values for two continuous summary measures of neuropsychological performance (NPZ and Global Deficit Score) for each classification.

Classification methods and agreement[a]								
	n (%)	CR[b]	A[c]	B[d]	C[e]	D[f]	E[g]	GDS[h] ≥ 0.5
CR	179 (68.1%)	179	151 (84%)	151 (84%)	75 (42%)	168 (94%)	118 (66%)	138 (77%)
A	159 (60.5%)	151 (95%)	159	151 (95%)	75 (47%)	159 (100%)	118 (74%)	132 (83%)
B (Gisslén)	155 (58.9%)	151 (97%)	151 (97%)	155	75 (48%)	155 (100%)	118 (76%)	131 (85%)
C (Meyer)	75 (28.5%)	75 (100%)	75 (100%)	75 (100%)	75	75 (100%)	71 (95%)	75 (100%)
D (mild)	207 (78.7%)	168	159 (77%)	155 (75%)	75 (36%)	207	117	138 (67%)
E (severe)	118 (44.9%)	118 (100%)	118 (100%)	118 (100%)	71 (60%)	118 (100%)	118	110 (93%)
GDS ≥ 0.5	138 (52.5%)	138 (100%)	132 (96%)	131 (95%)	75 (54%)	138 (100%)	100 (80%)	138
Measures of NP performance								
NPZ[i]	Mean (SD)	−0.7 (0.6)	−0.8 (0.5)	−0.8 (0.5)	−1.1 (0.5)	−0.6 (0.6)	−0.9 (0.5)	−0.9 (0.5)
	β (SE)[j]	−0.8 (0.1)	−0.9 (0.1)	−0.9 (0.1)	−0.9 (0.1)	−1.0 (0.1)	−0.9 (0.1)	−0.9 (0.1)
GDS[k]	Median (SD)	0.8	0.8	0.8	1.2	0.7	1.0	0.9
	β (SE)[l]	0.68 (0.04)	0.69 (0.05)	0.68 (0.05)	0.80 (0.07)	0.57 (0.05)	0.72 (0.05)	0.71 (0.04)

CR, clinical rating; GDS, Global Deficit Score; NP, neuropsychological.
[a]Interpretation of top portion of the table: proportions are based on the row classification, that is among the 179 classified by CR, 151 (84%) were also classified by A.
[b]CR: *z*-score at least 0.55 = 1; *z*-score 0.54 to −0.50 = 2; *z*-score −0.49 to −1.00 = 3; *z*-score −1.01 to −1.50 = 5; *z*-score −1.51 to −2.00 = 6; *z*-score −2.01 to −2.50 = 7; *z*-score −2.51 to −3.00 = 8; *z*-score −3.01 or less = 9. Domain score: worst test score minus one if one test is more impaired than the others. Definition of NP impaired: worst domain score minus one if one domain is more impaired than the others CR at least 5.
[c]A (derived from Gates and Cysique adapted for missing data): domain impaired = *z*-score on one measure less than −1.5 or; if 2 measures only in the domain, both *z*-scores less than −1 or; if 2 measures only in the domain and one value is missing, 1 *z*-score less than −1 or; if more than 2 measures in the domain, 1 *z*-score less than −1.5 or at least 2 scores less than −1.
[d]B (Gisslén *et al.*): domain impaired = *z*-score on one measure −1.5 or less.
[e]C (Meyer *et al.*): domain impaired = mean of all *z*-scores is −1.5 or less.
[f]D (mild): domain impaired = lowest scoring test measure less than −1 SD and at least −2 SD.
[g]E (severe): domain impaired = lowest measure less than −2 SD.
[h]GDS: Deficit Score: *z*-score at least −1.00 = 0; *z*-score −1.01 to −1.50 = 1; *z*-score −1.51 to −2.00 = 2; *z*-score −2.01 to −2.50 = 3; *z*-score −2.51 to −3.00 = 4; *z*-score −3.01 or less = 5. NP impaired = average of all Deficit Scores at least 0.5.
[i]Higher is better.
[j]Beta and standard error of beta from linear regression and adjusted for site, age, sex and education.
[k]Higher is worse.
[l]Beta and standard error of beta from quantile regression of GDS at median adjusted for site, age, sex and education.

the cross-sectional analysis, the regression parameter (β) is interpreted as the effect of being classified as neuropsychological-impaired on the mean productivity score. The regression parameters range from −2.21 points (Clinical Rating method) to +3.51 points (C: Meyer) with very wide CIs, indicating no appreciable effect of any classifications of neuropsychological impairment on work productivity. The same was true for the NPZ and the GDS. The lack of association persisted after including demographic (age, sex, education) and mood variables (HADS depression and HADS anxiety). The model excluding the neuropsychological classification explained

Table 4. Association between each classification method and work status at the time of neuropsychological testing, contrasting working for pay ≥ 15 h/week versus not working or working for pay < 15 h/week.

	Working ≥15 h/week, $n = 88$		Working <15 h/week, $n = 175$		
	n[b]	Mean (SD) or %	*n*[b]	Mean (SD) or %	OR[a] (95% CI)
Clinical rating	48	54.5%	131	74.9%	2.11 (1.19–3.72)
A	41	46.6%	118	67.4%	2.01 (1.15–3.49)
B (Gisslén)	39	44.3%	116	66.3%	2.07 (1.19–3.61)
C (Meyer)	15	17.0%	60	34.3%	2.07 (1.06–4.08)
D (mild)	62	70.5%	145	82.9%	1.82 (0.96–3.44)
E (severe)	26	29.5%	92	52.6%	2.39 (1.34–4.26)
GDS ≥ 0.5	33	37.5%	105	60.0%	2.09 (1.20–3.65)
NPZ (rev)[c]	88	0.16 (0.61)	175	0.53 (0.65)	2.32 (1.88–2.87)
GDS[d]	88	0.46 (0.47)	175	0.72 (0.6)	2.26 (1.24–4.09)

CI, confidence interval; GDS, Global Deficit Score; OR, odds ratio.
[a]Adjusted for age, sex and education; two participants missing education were assigned the mean.
[b]*n* is the number classified as impaired.
[c]NPZ score is reversed, higher is worse.
[d]GDS, higher is worse.

Table 5. Association between each classification of neuropsychological impairment and work productivity, at time of testing and over a maximum of 36 months.

	Work productivity, $N = 84$ (0–100)		Change in work productivity over 36 months, $N = 76$	
	Adjusted for site, age, sex and education		Adjusted for site, age, sex, education, mean productivity and number of visits	
Classification method	β[a]	95% CI	β[b]	95% CI
Clinical rating	−2.21	−8.90–4.48	−0.0002	−0.08–0.08
A	1.51	−5.11–8.13	−0.004	−0.08–0.07
B (Gisslén)	−0.46	−7.09–6.16	−0.0004	−0.07–0.07
C (Meyer)	3.51	−6.02–13.04	−0.018	−0.11–0.08
D (mild)	−1.35	−8.29–5.60	−0.004	−0.08–0.07
E (severe)	−0.61	−8.02–6.80	−0.001	−0.08–0.08
GDS ≥ 0.5 (vs. <0.5)	−1.15	−8.02–5.71	0.012	−0.07–0.09
NPZ[c] mean (SD): −0.14 (0.61)	3.01	−2.83–8.84	0.005	−0.06–0.07
GDS[d] mean (SD): 0.44 (0.47)	−0.03	−7.67–7.60	−0.004	−0.09–0.09

CI, confidence interval; GDS, Global Deficit Score.
[a]Beta from linear regression done on 84 participants who reported paid work at least 15 h/week and responded to the Stanford Presenteeism Scale based on work, adjusted for site, age, sex and education; two participants missing education were assigned the mean.
[b]Estimates are from quantile regression at median among participants with at least 2 outcomes of work productivity, adjusted for mean and number of visits with work productivity, age, sex, education and site.
[c]Higher is better, estimate is per week in view.
[d]GDS, higher is worse.

43.4% of the variance on work productivity; classifications of neuropsychological impairment explained less than 1% of the variance, providing confirmation that the lack of association between neuropsychological variables and work productivity was not explained by confounding effects of demographic or mood variables. Table 5 also shows the relationship between *change* in work productivity over time (maximum of 36 months) and classifications of neuropsychological impairment, adjusted for the number of visits with a score for work productivity and the mean work productivity per person. The regression parameter (β) is interpreted as the *change* in work productivity over time among those classified as impaired by each method. All CIs included the null, showing a lack of associations between change in work productivity over time and any method of classifying neuropsychological impairment. The regression parameters were very small: for example, among those classified as impaired by the Clinical Rating method, productivity declined by 0.0002 points/week over the study period, translating to a change per year of -0.0002×52 (-0.01 points), far from the clinically important difference of 7.6 points.

Discussion

In the context in which people living with well treated HIV have a near-normal life expectancy, the ability to work is a priority concern. Identification of individuals whose cognitive impairment increases the risk of occupational difficulties is thus clinically relevant. Here, we asked whether neuropsychological test performance was associated with work status and productivity at baseline and change in work productivity over the subsequent 36 months, comparing different methods of combining results from a comprehensive neuropsychological evaluation.

The rates of neuropsychological impairment in this sample showed marked differences depending on the operationalization of domain impairment, ranging from 28.5 to 78.7%, and agreement between classifications could be as low as 36%. This discrepancy has been reported previously, comparing just two methods [12,61]. Despite the wide variation in the rates of neuropsychological impairment, those classified as neuropsychological-impaired by any method exhibited poorer overall cognitive performance (NPZ) and performance in the deficit range across domains (GDS). Thus, the classifications are not driven by a few aberrant low scores, but rather identify individuals with lower ability on several test measures. A clear illustration of this fact is the performance of Method 'D', which classified as many as 78.7% of the participants as neuropsychological-impaired; such a high rate of impairment may seem implausible but finds some validation in the large difference of 1 SD on mean NPZ between impaired and unimpaired participants.

In terms of the impact of cognitive difficulties on work, those who were classified as neuropsychological-impaired by any method had odds for a lack of paid employment at least 15 h/week that were 1.82–2.39 times higher, with no method emerging as clearly superior in its predictive ability. Although most classifications of neuropsychological impairment predicted unemployment/poor employment status, amongst those working more than 15 h/week, there

was no association between any classification or summary neuropsychological measure and work productivity, in cross-sectional or longitudinal analyses, even after adjusting for effects of anxiety and depression. Taken together, these findings indicate that all the classifications tested here identify the most neuropsychologically impaired cases. However, those with milder impairment who are experiencing decreased productivity are not well identified by any of the classification methods or the measures of global neuropsychological performance tested here.

The current study adds to the available evidence regarding the negative impact of neuropsychological impairment on work among HIV+ individuals. In cross-sectional studies, neuropsychological impairment has been associated with higher rates of unemployment [8,19,22,25,28,62–64], complaints of difficulties with job performance [25] and worse performance on standardized work samples [22]. Only two studies to date have reported on the impact of neuropsychological impairment on work status over time. In the pre-HAART era, among 123 HIV+ men who were initially asymptomatic, incident neuropsychological impairment over 4.5 years of follow-up was associated with an increased risk of work disability, independent of symptom status and $CD4^+$ cell count [26]. More recently, among 267 HIV+ individuals in the United States, performance on laboratory-based work assessments was compared with the previous occupational level estimated from work histories; this comparison suggested that, among those who were neuropsychological impaired, a decrease in vocational functioning had occurred in the years prior to neuropsychological testing [22].

Our study has several strengths. As the sample was selected from participants who were well characterized on outcomes related to brain health, we were able to ascertain that the tested sample was representative of the entire Brain Health Now cohort, thus addressing the concern that individuals who agreed to undergo neuropsychological testing could be systematically different in important ways from those who did not complete neuropsychological testing. We combined rigorous selection and application of normative data and development of *z*-scores informed by two expert neuropsychologists (L.A.C. and L.K.), complemented by several post-hoc validation analyses. We concurrently tested several definitions of cognitive impairment. The information collected as part of the cohort study visits (over 36 months) also allowed us to study work status and productivity over time.

Importantly, our study is the first to focus on cognition and productivity in HIV+ adults of working age using a validated measure of work productivity that was well suited to the range of occupations found in our sample, as it captures the impairment found in both production-based and knowledge-based jobs. One study in the pre-HAART era documented a decrease in job-related abilities among HIV+ adults with neuropsychological impairment but did not use a validated measure of these abilities [25]. The AGEhIV cohort assessments included a validated measure of work ability [65] but its association with neuropsychological impairment has not yet been reported.

One potential criticism of our measure of productivity is its self-report nature. There is a concern that individuals with severe cognitive impairment may lack insight into their limitations and fail to notice and report important difficulties; however, this was not the population under study here. Another concern is the possibility that the presence of depression accounts for most of the variance on the self-report measure of productivity: this hypothesis was tested and rejected. The use of self-report instruments to assess function is customary in the neuro-HIV literature, including among those who experience mild cognitive impairment. The measurement of occupational impairment for knowledge-based jobs presents a methodological challenge [66]; for this reason, we applied the recommendation from the American College of Occupational and Environmental Medicine to use self-report questionnaires in the assessment of health-related productivity loss [67].

In the current study, we aimed to contribute evidence on the vocational impact of neuropsychological impairment, given the economic, social and psychological importance of work. We found, as others have, that the presence of neuropsychological impairment is associated with a lesser degree of paid employment. However, we did not find an association between any of the classifications of neuropsychological impairment and decreased productivity at work, a predictor of future unemployment [59]. The systematic assessment of multiple methods of diagnostic classification and global neuropsychological scoring argues that this lack of association is not an artefact of how neuropsychological is summarized. The results suggest that new approaches to identify the presence of mild cognitive difficulties that interfere with the most demanding cognitive tasks associated with work are required. To address this clinical-applied question, it may be helpful to validate such novel assessments of cognition directly against work status or productivity, rather than validating them against existing neuropsychological scores or HAND classifications that fail to identify the mild impairment associated with decreased productivity.

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Conflicts of interest

There are no conflicts of interest.

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