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European Journal of Cancer 186 (2023) 38–51

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

# Association between objective neurocognitive functioning and neurocognitive complaints in recurrent high-grade glioma: Longitudinal evidence of cognitive awareness from EORTC brain tumour trials

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Received 17 January 2023; Received in revised form 25 February 2023; Accepted 27 February 2023
Available online 8 March 2023

DOI of original article: https://doi.org/10.1016/j.ejca.2023.113385
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https://doi.org/10.1016/j.ejca.2023.02.029

**KEYWORDS**
Glioma;
Neurocognitive functioning;
Neurocognitive complaints;
Cognitive awareness

**Abstract** ***Background:*** Patients' reduced awareness of neurocognitive functioning (NCF) may negatively affect the reliability of patient-reported outcomes (PROs) and clinical decision-making. This study evaluated cognitive awareness, defined as the association between NCF and neurocognitive complaints, over the disease course of patients with recurrent high-grade glioma (HGG).

***Methods:*** We assessed NCF using the EORTC core clinical trial battery and neurocognitive complaints using the Medical Outcome Study questionnaire. Patients were categorised as impaired or intact, based on their neurocognitive performance. Spearman's rank correlations were calculated between NCF and neurocognitive complaints at baseline and each 12 weeks, until 36. The association between changes in NCF and neurocognitive complaints scores between these follow-up assessments was determined using Pearson's correlation.

***Results:*** A total of 546 patients were included. Neurocognitively impaired patients ($n$ = 437) had more neurocognitive complaints (range: 10.51 [$p < 0.001$] to 13.34 [$p = 0.001$]) than intact patients ($n$ = 109) at baseline, at 12 and 24 weeks. In intact patients, NCF and neurocognitive complaints were correlated for only one domain at baseline (0.202, $p = 0.036$), while in impaired patients correlations were more frequently found in various domains and time points (range: 0.164 [$p = 0.001$] to 0.334 [$p = 0.011$]). Over the disease course, NCF and neurocognitive complaints were correlated for only one domain at baseline (0.357, $p = 0.014$) in intact patients while in impaired patients they were correlated for more domains and time points (range: 0.222 [$p < 0.001$] to 0.366 [$p < 0.001$]).

***Conclusion:*** Neurocognitively impaired patients with recurrent HGG are aware of their neurocognitive limitations at study entry and during follow-up, which should be considered in clinical decision-making and when interpreting PRO results.


## 1. Introduction

World Health Organization (WHO) grade 2–4 gliomas are characterised by dire prognosis, with survival of 5–7 years for grade 2, 2–3 years for grade 3 and 12–14 months for grade 4. Furthermore, patients with high-grade gliomas (HGGs) not only have a limited life expectancy, but are also confronted with a myriad of treatment and tumour-related symptoms. Therefore, their potential survival benefits should be carefully balanced against their impact on patient functioning and well-being.

The notion that a significant number of patients with neurological disease are unaware of their physical, neurocognitive, social, and/or psychological deficits, even, or particularly when they are profound and have debilitating effects on patients' functioning, has already been recognised decades ago [1,2]. However, it was only recently that brain tumour patients' ability to evaluate their own functioning was investigated, specifically in view of the neurocognitive deficits that most of these patients develop over time [3]. This so-called cognitive awareness refers to a broad and rather abstract concept that has been operationally defined as the concordance between the patients' objective neurocognitive functioning (NCF) and their neurocognitive complaints [4].

Limited cognitive awareness is associated with poor decision-making skills, difficulty in taking the right decisions concerning health and in anticipating and preventing potential future work and administrative issues [5]. Finally, patients may have unrealistic therapeutic goals regarding tumour treatment [6]. These issues not only complicate clinical decision-making, but also pose significant stress on the patient and informal caregiver.

While the aetiology and pathology of neurocognitive deficits in brain tumour patients have been reasonably well investigated [7–9], there is no consensus on the conceptualisation of cognitive awareness and how to measure it in these patients [10–12].

In line with earlier work [4], we studied cognitive awareness of brain tumour patients by comparing patient's objective NCF to self-reports of NCF. We initially hypothesised that brain tumour patients with severe cognitive deficits would have limited cognitive awareness, but surprisingly our recent cross-sectional study [13] in the same patient population reported here, showed that HGG neurocognitively impaired patients seem to have a certain degree of cognitive awareness.

Although, the aforementioned results seemed promising, the time dependency of neurocognitive awareness in this patient population is unknown. Therefore, the aim of this longitudinal study was to evaluate whether and how cognitive awareness changes over the disease course in patients with HGG. Insight in cognitive awareness of these patients over the course of the

disease is crucial in the collection of patient-reported outcomes (PROs) in clinical trials and in clinical decision-making.

## 2. Methods

This study was performed as a side-study to EORTC trials 26101 (EudraCT number: 2010-023218-30) and 26091 (EudraCT number: 2009-017422-39) [14,15]. The original trial sample consisted of 731 patients with grade II–IV glioma [14,15]. For this subanalysis, only HGG patients were eligible. Since data have been collected prior to 2016, the 2007 WHO tumour classification applies in selection of WHO grade 3 and 4 tumours [16]. In addition, patients with more than half of the NCF or neurocognitive complaints outcomes missing at baseline were excluded, as well as patients without a first follow-up measurement.

Data were collected prior to randomisation and every 12 weeks thereafter including neurocognitive and full clinical assessment, as well as patient-reported cognitive complaints.

### 2.1. Outcome measures

*Objective NCF* was assessed using the internationally adopted clinical trial battery for testing NCF in patients with intracranial or extracranial tumours: Hopkins Verbal Learning Test – Revised (HVLT-R) [17]; the Trail Making Test (TMT part A and part B) [18] and the Controlled Oral Word Association (COWA) test [19]. These tests were selected because of their wide use in clinical trials and their sensitivity to the impact of tumour and tumour treatment–related variables [20,21]. The three NCF tests yielding six outcome measures were administered by centrally trained and certified healthcare personnel (e.g. research nurse, neuropsychologist).

*Neurocognitive complaints* were measured using the cognitive functioning questionnaire of the Medical Outcome Study (MOS) [22]. This six-item questionnaire assesses day-to-day problems in NCF over the past month, asking patients whether they had become confused, reacted slowly to things, had difficulty reasoning, been forgetful, had trouble keeping attention, or had difficulty concentrating. The MOS questionnaire was administered as part of the NCF test package to ensure concurrent collection of data on NCF and complaints. Following formal guidelines, responses to the items of the MOS were transformed into scores ranging from 0 to 100, and subsequently their average was calculated [22]. A higher score indicates higher self-perceived NCF.

### 2.2. Statistical analyses

Raw scores of the six NCF test outcomes and the MOS questionnaire were first transformed into Z-scores using available normative data [17–19]. Cognitive awareness was operationally defined as the correlation between the averaged MOS questionnaire Z-score and Z-scores of each of the six NCF test outcomes: 1) HVLT-R Total Recall, 2) HVLT-R Delayed Recall, 3) HVLT-R Delayed Recognition, 4) TMT Part A, 5) TMT Part B, and 6) COWA. Correlations were calculated for two subgroups separately, based on the presence of impaired NCF test outcomes.

To do so, a deviation of ≤−1.5 standard deviation (SD) from the Z-score mean was used as cutoff to define NCF impairment in any test, at baseline and every 12 weeks. Patients scoring above the threshold on *all* six test outcomes were classified as neurocognitively intact, while patients scoring below the threshold on at least one of the test outcomes were classified as neurocognitively impaired [23]. The strength of the association between neurocognitive complaints and NCF in these subgroups was subsequently determined using Spearman's $\rho$ correlation coefficients (with 95% confidence interval [95% CI]). Spearman correlation was calculated for this analysis since both scores in exam originate from ordinal scales. Spearman's $\rho < 0.3$ was considered weak; $0.3 \leq \rho \leq 0.6$ as moderate, and $\rho > 0.6$ as strong [24].

While the cutoff of 1.5 SD below the performance of healthy controls to define neurocognitive impairment is widely used in clinical practice, it is rather arbitrary since it cannot be directly translated to everyday life functioning. Therefore, a sensitivity analysis raising the threshold for neurocognitive dysfunction per test outcome (> 2 SD) was performed. By doing so, we aimed at including only patients with more severely impaired NCF.

Tables showing the results of the sensitivity analysis can be found in the Supplementary Material of this manuscript.

To begin with, independent sample t-test were used to calculate cross-sectional differences in neurocognitive complaints between impaired and intact patients adjusting the α for multiple testing with Bonferroni correction. Then, to investigate whether the changes in NCF between each follow-up moment were associated with correspondent changes in cognitive complaints, Pearson's correlation coefficients (with 95% CI) were calculated between follow-up moments. Average change scores were calculated subtracting the score of the previous follow-up to the following one for each patient and then calculating the average for the whole group. Pearson's correlation coefficients were calculated due to the fact that the difference between scores is considered an interval scale. The interpretation of Pearson's coefficient was the same as for Spearman's.

In addition to these group level analyses, where changes in the opposite directions might average each other out, we also explored change in associations over time at the individual patient-level. To achieve this, the difference between consecutive follow-ups of NCF and

Table 1
Clinical characteristics of study patients.

| | | | | | |
|---|---|---|---|---|---|
| Histology | | | | | |
| | Glioblastoma | 472 (86.4%) | | | |
| | Astrocytoma WHO grade 3 | 37 (6.8%) | | | |
| | Glioblastoma with oligodendroglial component | 24 (4.4%) | | | |
| | Gliosarcoma | 8 (1.5%) | | | |
| | Giant cell glioblastoma | 4 (0.8%) | | | |
| | Missing | 1 (0.2%) | | | |
| Tumour location | | | | | |
| | | Hemisphere | | | |
| | | Left | Bilateral | Right | |
| | Total | 230 | 24 | 251 | |
| | Frontal | 63 | 6 | 70 | 25.5% |
| | Temporal | 81 | 0 | 86 | 30.6% |
| | Parietal | 20 | 0 | 21 | 7.7% |
| | Occipital | 21 | 1 | 21 | 10.8% |
| | Other | 21 | 16 | 11 | 6.0% |
| | Multi-site | 24 | 1 | 42 | 12.1% |
| | Missing | 40 | | | 7.3% |
| ASMs | | | | | |
| | Yes | 332 | | | 60.8% |
| | No | 169 | | | 31% |
| | Missing | 45 | | | 8.2% |
| Corticosteroids | | | | | |
| | Yes | 250 | | | 45.8% |
| | No | 251 | | | 55% |
| | Missing | 45 | | | 8.2% |
| WHO performance status at baseline | | | | | |
| | 0 | 196 (35.9%) | | | |
| | 1 | 295 (54.0%) | | | |
| | 2 | 55 (10.1%) | | | |
| Cognitive status | **Follow-up** | | | | |
| | **Baseline (n)** | **1st (12 weeks)** | **2nd (24 weeks)** | **3rd (36 weeks)** | |
| Impaired (%) | 437 (80.0%) | 249 (78.1%) | 129 (77.2%) | 59 (67.8%) | |
| Intact (%) | 109 (20.0%) | 70 (21.9%) | 38 (22.8%) | 28 (32.2%) | |

| Cognitive shift | | | | |
|---|---|---|---|---|
| | **Follow-up** | | | |
| | **0–12** | **12–24** | **24–36** | |
| Stable | 265 (48.5%) | 129 (79.1%) | 71 (89.9%) | |
| Worse | 260 (47.6%) | 22 (13.5%) | 1 (1.3%) | |
| Better | 21 (3.8%) | 12 (7.4%) | 7 (8.9%) | |
| Total | 546 | 163 | 79 | |

WHO, World Health Organization; ASM, anti-seizure medication.

neurocognitive complaints scores was calculated for each patient separately. In a similar fashion to the approach used by Ediebah et al., the difference in scores on NCF outcomes and neurocognitive complaints between follow-up moments were summarised in five categories: 1) no difference between consecutive follow-ups; 2) between −1 and 0 SD difference between follow-ups; 3) between 1 and 0 standard score difference between follow-ups; 4) more than −1 standard score difference between consecutive follow-ups; and 5) more than 1 standard score difference between consecutive follow-up moments [25].

## 3. Results

Data of 546 HGG (grade III and IV) patients were used for the current analyses: 509 from EORTC study 26101 and 37 patients from EORTC study 26091. From the original patient cohort of 731 patients, 82 were excluded due to insufficient NCF and neurocognitive complaints data and 103 patients did not meet the side-study-specific additional histological criterion of being HGG.

Patients in the final analyses ($n$ = 546) had a mean age of 55.3 years ($SD$ = 11.3), and 202 patients (37%) were

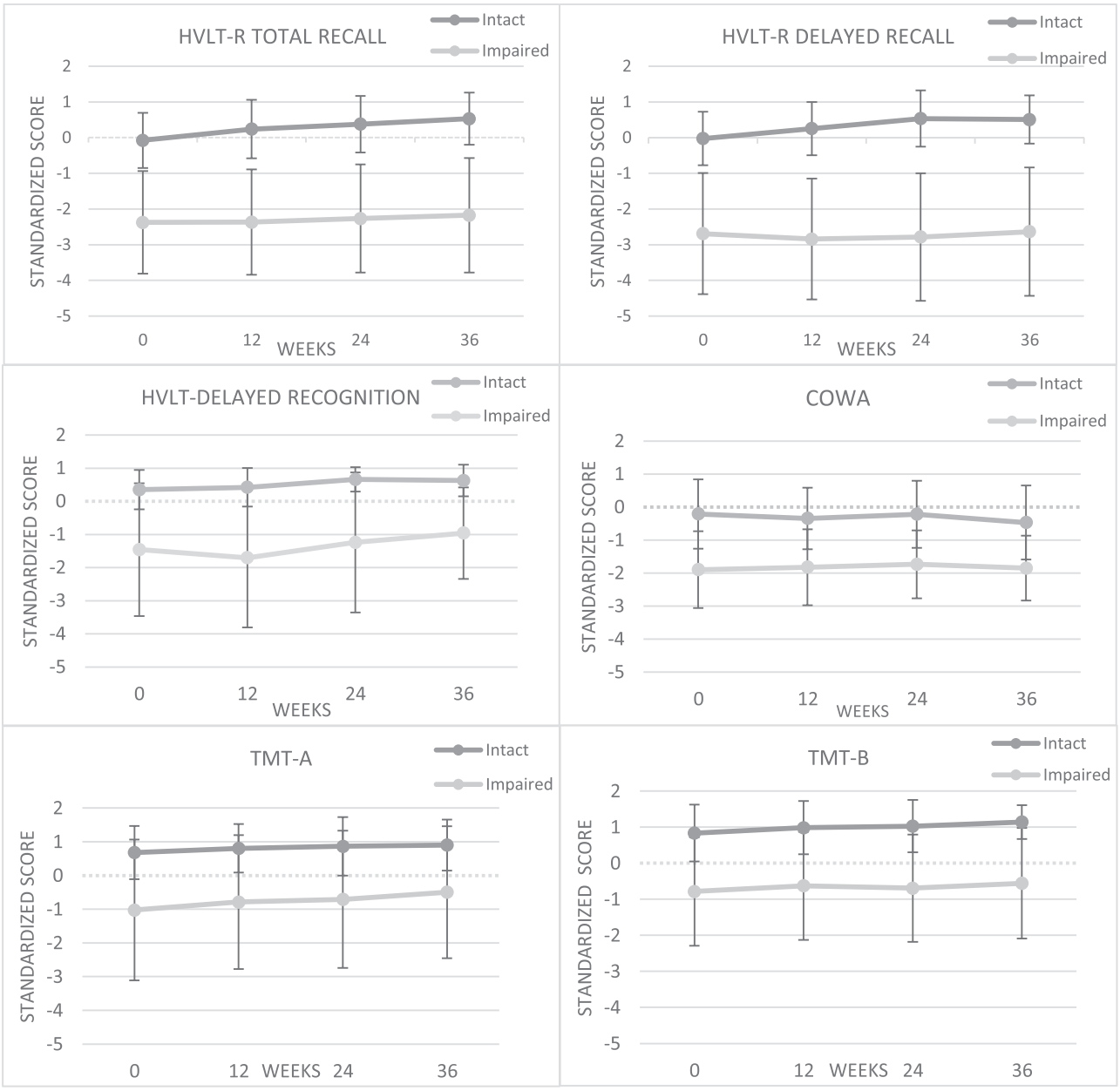



Fig. 1. Hopkins Verbal Learning Test – Revised (HVLT-R) Total Recall, Delayed Recall, Delayed Recognition, Controlled Oral Word Association (COWA), Trail Making Test (TMT) part A and B scores and standard deviation at each follow-up for neurocognitively impaired and intact patients. The dotted line (Z-score = 0) indicates performance of healthy controls.

female. Due to rapid progression of the disease, patient compliance dropped dramatically. While at baseline data of 546 patients (100%) were available, between 12-, 24-, and 36-week follow-up this dropped to 319 (58%), 167 (31%), and 87 (16%) evaluable patients, respectively. Detailed clinical information is reported in Table 1.

### *3.1. NCF and complaints in neurocognitively impaired and intact patients*

At baseline, 437 patients were classified as neurocognitively impaired and 109 as intact. After 12 weeks (i.e. the first follow-up moment), 249 (78%) were neurocognitively impaired and 70 (22%) intact. At the second follow-up at 24 weeks, 129 (77%) patients were impaired and 38 (23%) intact. At the third and last follow-up, after 36 weeks, only 87 patients were still in the study, comprising 59 (68%) impaired and 28 (32%) neurocognitively intact patients. It is important to note that the percentage of patients with impaired NCF decreased over time, suggesting that our data are likely biased towards patients with a favourable neurological status and longer (progression-free) survival.

Standardised scores based on normative data of healthy populations for each test of the neurocognitive test battery are shown in Fig. 1A–F. Due to our

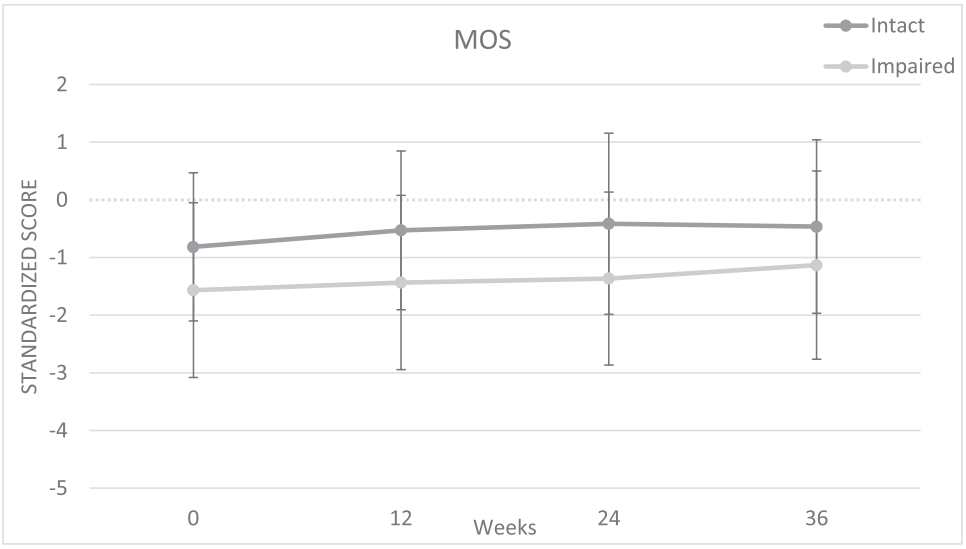



Fig. 2. Self-perceived cognitive functioning measured by the Medical Outcome Study (MOS) questionnaire and standard deviations at each follow-up for impaired and intact patients.

classification, performance of neurocognitively intact patients is higher on all six test outcomes.

As shown in Fig. 2, neurocognitively intact patients had significantly less (−10.51 ± 2.21) neurocognitive complaints at baseline (73.73 ± 17.91), $t$ (534) = 4.756, $p < 0.001$ than neurocognitively impaired patients (63.21 ± 21.14). Similar differences (−12.67) were found at the 12-week follow-up with intact patients reporting less complaints (77.72 ± 19.20), $t$ (310) = 4.483, $p < 0.001$ than neurocognitively impaired patients (65.05 ± 21.14). Again, at the 24-week follow-up, results were similar (−13.34), with less complaints from the intact patients group (79.38 ± 21.93), $t$ (163) =3.412 , $p < 0.001$, than from the impaired patients one (66.03 ± 20.92). No significant differences were found at 36-week follow-up ($p > 0.05$).

### 3.2. Correlations between NCF and neurocognitive complaints over time

Neurocognitive awareness was assessed with Spearman's rank correlation coefficients between the six NCF test outcomes at each follow-up moment and neurocognitive complaints, and results for intact patients are reported in Table 2. In the *neurocognitively intact* group, only HLVT-R Total Recall measured at baseline was significantly associated with neurocognitive complaints (r = 0.202, $p = 0.036$). Analyses of the other five test outcomes did not yield any statistically significant associations with neurocognitive complaints.

As showed in Table 3 in *neurocognitively impaired* patients, several NCF test outcomes were associated with neurocognitive complaints, as the stronger being the correlation with the HLVT-R Delayed Recognition at 12 weeks ($\rho = 0.328$) and with HLVT-R Delayed Recall ($\rho = 0.320$) and the COWA ($\rho = 0.334$) at 36 weeks.

### 3.3. Associations between changes in neurocognitive complaints and NCF scores

Tables 4 and 5 show Pearson's correlation coefficients between changes on each of the six NCF test outcomes and corresponding changes in neurocognitive complaints, separately for intact and impaired patients, respectively. Within the *neurocognitively intact group*, between baseline and 12 weeks, only the HLVT-R Delayed Recognition score was ($\rho = 0.357$, p = 0.014) associated with self-perceived NCF. The lack of any other significant correlations indicates that changes in neurocognitive performance across follow-up moments are not associated with changes in neurocognitive complaints.

In the *neurocognitively impaired group*, changes between baseline and 12 weeks on HVLT-R Total Recall, Delayed Recognition and the COWA and changes between 12 and 24 weeks on HVLT-R Delayed Recall were correlated with self-perceived NCF (range = 0.219–0.278, $\rho < 0.001$). Correlations were also found for the HVLT-R Total Recall and Delayed Recognition between 12 and 24 weeks (range = 0.328–0.366, $p < 0.001$).

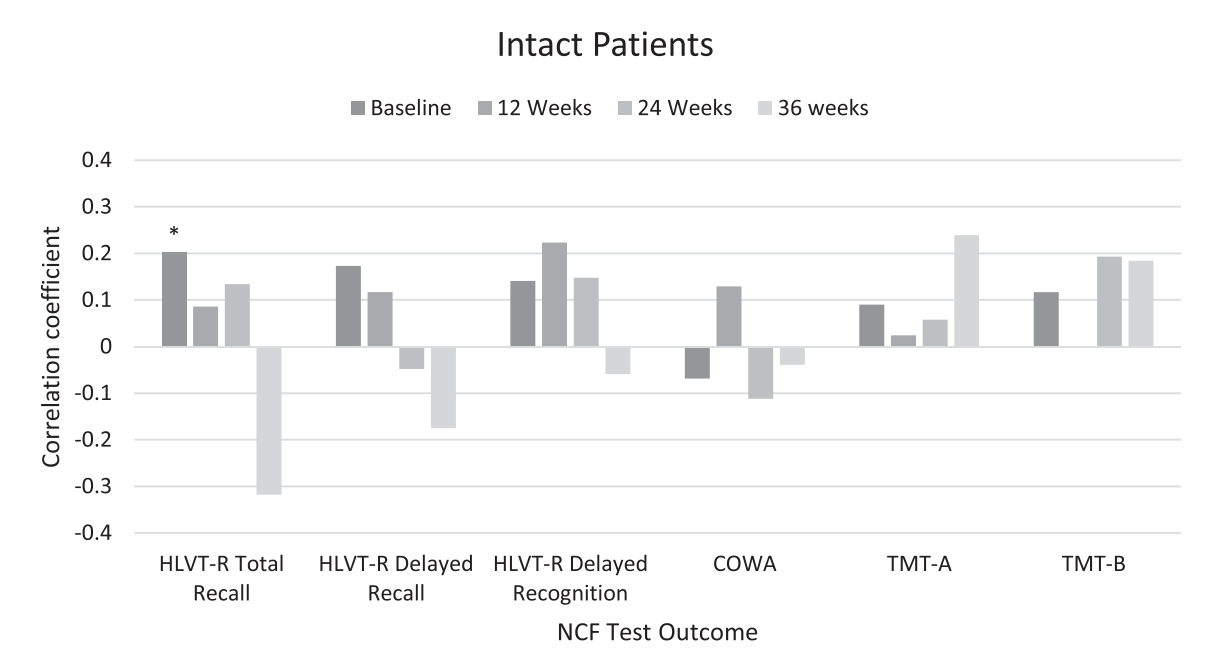
### 3.4. Individual patient-level analyses of changes in NCF and neurocognitive complaints between consecutive follow-up moments

#### 3.4.1. Intact patients

##### 3.4.1.1. Impaired patients

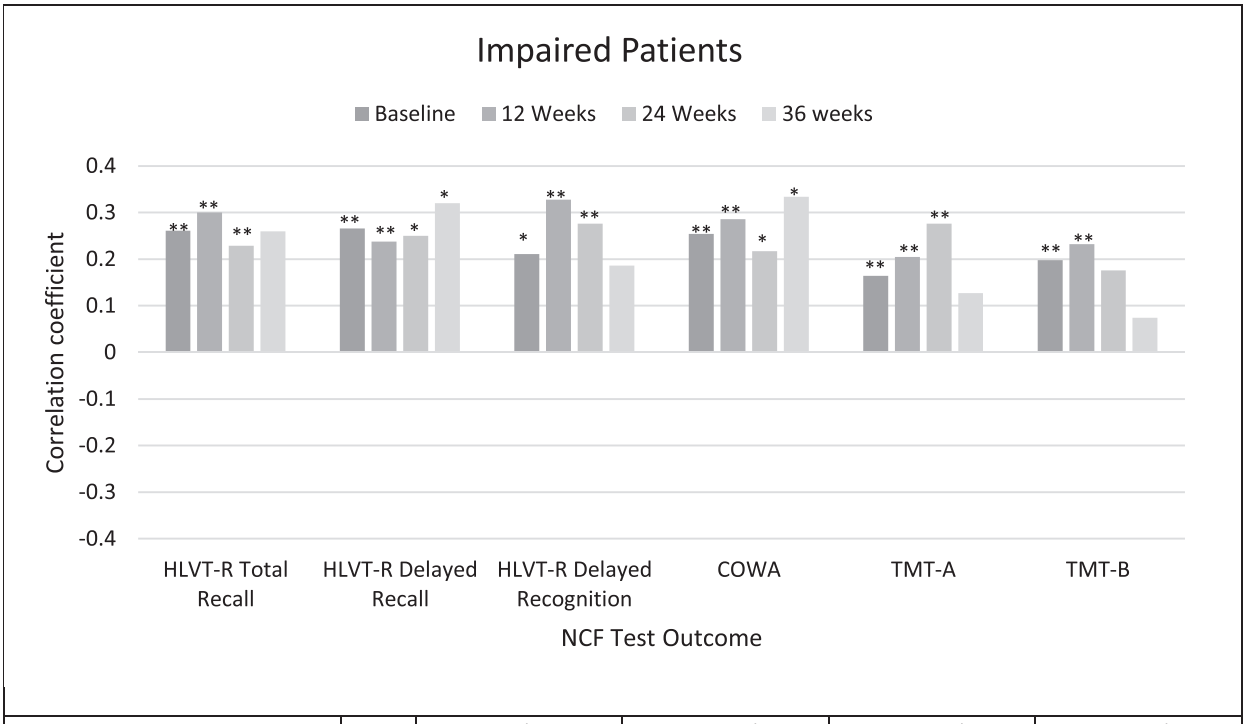
As can be observed in Tables 6 and 7, individual patient-level analysis gives more insight over the changes in neurocognitive performance and the reported cognitive complaints between follow-up moments. Indeed, from a quick glance at the group-level analysis, it might appear

Table 2
Correlations between NCF outcomes and neurocognitive complaints for neurocognitively intact patients at each follow-up (with 95% CI) on Total Recall, Delayed Recall, Delayed Recognition of the HVLT-R (Hopkins Verbal Learning Test – Revised), TMT (Trail Making Test), and COWA (Controlled Oral Word Association Test); *p < 0.05, **p < 0.01.



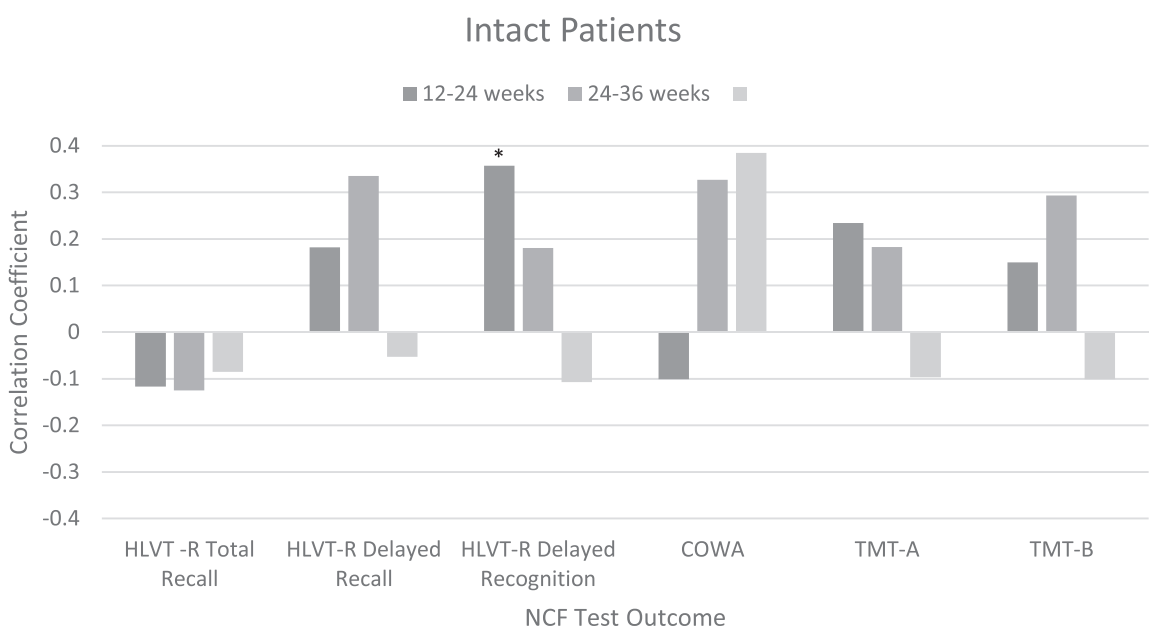

| NCF Test Outcome | | Baseline | 12 Weeks | 24 Weeks | 36 weeks |
|---|---|---|---|---|---|
| HLVT-R Total Recall | Corr | 0.202* | 0.086 | 0.134 | -0.318 |
| | C.I | (-0.016 – 0.387) | (-0.166 – 0.337) | (-0.168 – 0.425) | (-0.655 – 0.077) |
| | N | 108 | 69 | 38 | 28 |
| HLVT-R Delayed Recall | Corr | 0.173 | 0.117 | -0.048 | -0.175 |
| | C.I | (-0.022 – 0.375) | (-0.139 – 0.356) | (-0.394 – 0.276) | (-0.552 – 0.193) |
| | N | 107 | 69 | 38 | 28 |
| HLVT-R Delayed Recognition | Corr | 0.141 | 0.223 | 0.148 | -0.059 |
| | C.I | (-0.048 – 0.325 | (-0.011 – 0.438) | (-0.135 – 0.456) | (-0.449 – 0.356) |
| | N | 108 | 68 | 36 | 28 |
| COWA | Corr | -0.069 | 0.129 | -0.112 | -0.039 |
| | C.I | (-0.263 – 0.126) | (-0.138 – 0.370) | (-0.419 – 0.223) | (-0.414 – 0.350) |
| | N | 108 | 58 | 38 | 28 |
| TMT-A | Corr | 0.09 | 0.024 | 0.058 | 0.239 |
| | C.I | (-0.132 – 0.300) | (-0.213 – 0.261) | (-0.307 – 0.361) | (-0.181 – 0.592) |
| | N | 103 | 68 | 38 | 28 |
| TMT-B | Corr | 0.117 | 0. 031 | 0.193 | 0.184 |
| | C.I | (-0.092 – 0.301) | (-0.129 – 0.328) | (-0.139 – 0.495) | (-0.191 – 0.501) |
| | N | 102 | 68 | 38 | 28 |

Table 3
Correlations between NCF outcomes and neurocognitive complaints for neurocognitively intact patients at each follow-up (with 95% CI) on Total Recall, Delayed Recall, Delayed Recognition of the HVLT-R (Hopkins Verbal Learning Test – Revised), TMT (Trail Making Test), and COWA (Controlled Oral Word Association Test); *p < 0.05, **p < 0.01.



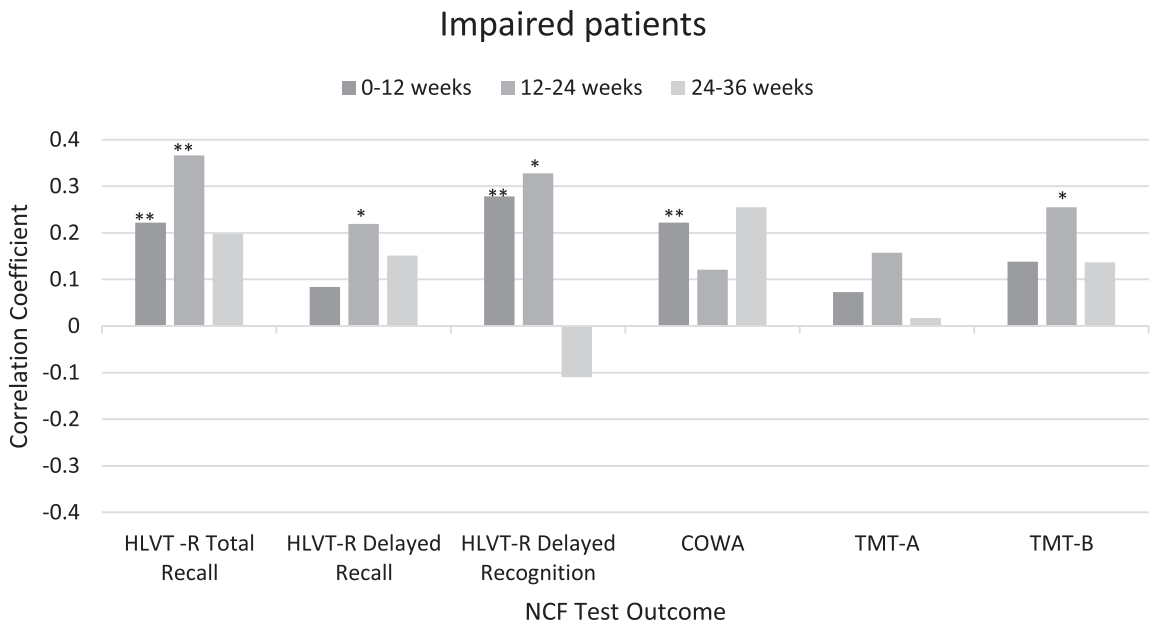

| NCF Test Outcome | | Baseline | 12 Weeks | 24 Weeks | 36 weeks |
|---|---|---|---|---|---|
| HLVT-R Total Recall | Corr | 0.261** | 0.300** | 0.229** | 0.26 |
| | C.I | (0.174 - 0.345) | (0.193 - 0.418) | (0.050 - 0.406) | (-0.023 - 0.510) |
| | N | 425 | 243 | 127 | 57 |
| HLVT-R Delayed Recall | Corr | 0.266** | 0.238** | 0.25* | 0.32* |
| | C.I | (0.169 - 0.346) | (0. 071 - 0.358) | (0.058 - 0.423) | (0.062 - 0.543) |
| | N | 423 | 239 | 125 | 57 |
| HLVT-R Delayed Recognition | Corr | 0.211* | 0.328** | 0.276** | 0.186 |
| | C.I | (0.107 - 0.310) | (0.211 - 0. 431) | (0.118 - 0.432) | (-0.097 - 0.426) |
| | N | 413 | 237 | 126 | 55 |
| COWA | Corr | 0.254** | 0.286** | 0.217* | 0.334* |
| | C.I | (0.164 - 0.342) | (0.154 - 0.408) | (0.056 - 0.380) | (0.056 - 0.567) |
| | N | 422 | 221 | 126 | 57 |
| TMT-A | Corr | 0.164** | 0.205** | 0.276** | 0.127 |
| | C.I | (0.069 - 0.256) | (0.084 - 0.326) | (0.088 - 0.441) | (-0.156 - 0.388) |
| | N | 412 | 235 | 121 | 55 |
| TMT-B | Corr | 0.198** | 0.232** | 0.176 | 0.074 |
| | C.I | (0.097 - 0.294) | (0.093 - 0.364) | (0.004 - 0.361) | (-0.207 - 0.325) |
| | N | 396 | 229 | 119 | 55 |

Table 4
Correlations between concurrent weekly changes in neurocognitive complaints and NCF test outcomes (over intervals of approximately 12 weeks) for intact patients on Total Recall, Delayed Recall, Delayed Recognition of the HVLT-R (Hopkins Verbal Learning Test – Revised), TMT (Trail Making Test), and COWA (Controlled Oral Word Association Test); *p < 0.05, **p < 0.01.



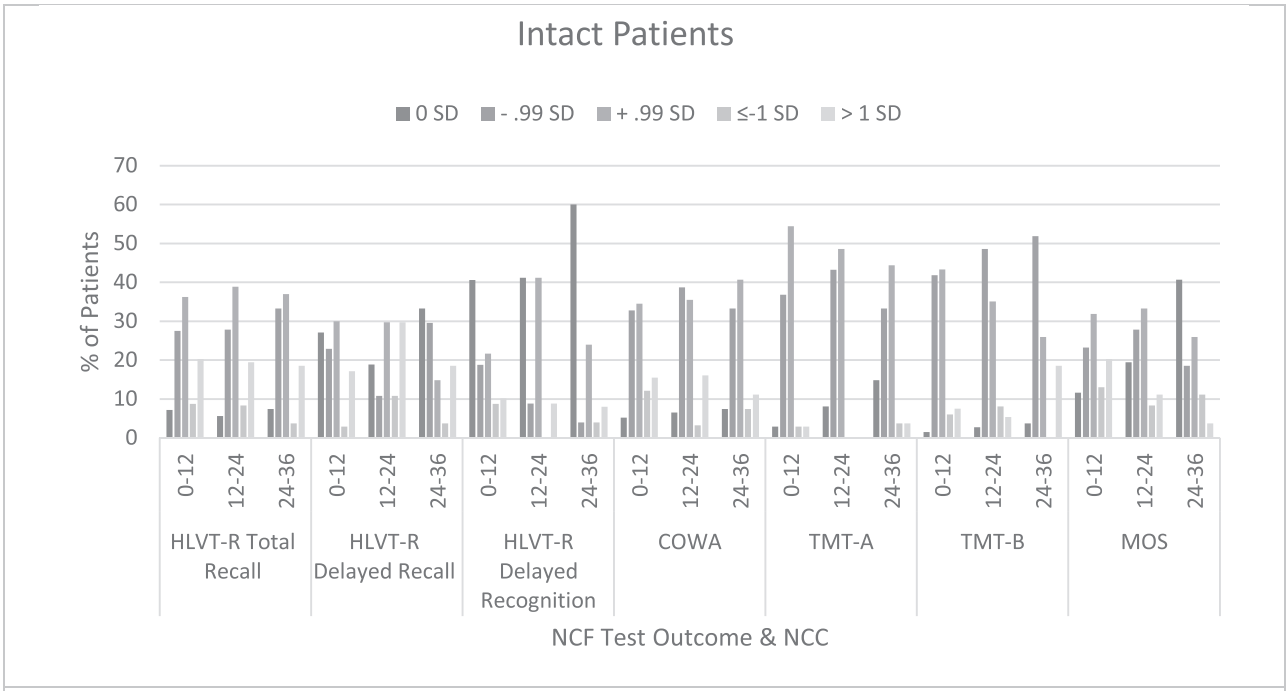

| NCF Test Outcome | | 0-12 weeks | 12-24 weeks | 24-36 weeks |
|---|---|---|---|---|
| HLVT-R Total Recall | Corr | -0.117 | -0.125 | -0.085 |
| | C.I | (-0.390 – 0.201) | (-0.478 – 0.292) | (-0.442 – 0.341) |
| | N | 48 | 24 | 20 |
| HLVT-R Delayed Recall | Corr | 0.182 | 0.335 | -0.053 |
| | C.I | (-0.136 – 0.504) | (-0.049 – 0.633) | (-0.414 – 0.370) |
| | N | 48 | 24 | 20 |
| HLVT-R Delayed Recognition | Corr | 0.357* | 0.181 | -0.107 |
| | C.I | (0.055 – 0.595) | (-0.285 – 0.554) | (-0.560 – 0.283) |
| | N | 47 | 23 | 20 |
| COWA | Corr | -0.101 | 0.327 | 0.385 |
| | C.I | (-0.316 – 0.151) | (-0.192 – 0.797) | (0.094 – 0.607) |
| | N | 42 | 20 | 20 |
| TMT-A | Corr | 0.234 | 0.183 | -0.097 |
| | C.I | (0.029 – 0.436) | (-0.162 – 0.582) | (-0.553 – 0.254) |
| | N | 46 | 24 | 20 |
| TMT-B | Corr | 0.15 | 0.293 | -0.101 |
| | C.I | (-0.147 – 0.379) | (-0.077 – 0.596) | (-0.633 – 0.347) |
| | N | 45 | 24 | 20 |

Table 5
Correlations between concurrent weekly changes in neurocognitive complaints and NCF test outcomes (over intervals of approximately 12 weeks) for impaired patients on Total Recall, Delayed Recall, Delayed Recognition of the HVLT-R (Hopkins Verbal Learning Test – Revised), TMT (Trail Making Test), and COWA (Controlled Oral Word Association Test). *p < 0.05; **p < 0.01.




| NCF Test Outcome | | 0-12 weeks | 12-24 weeks | 24-36 weeks |
|---|---|---|---|---|
| HLVT -R Total Recall | Corr | *0.222** | *0.366** | *0.198* |
| | C.I | *(0.082 – 0.349)* | *(0.193 – 0.531)* | *(-0.248 – 0.512)* |
| | N | *207* | *91* | *49* |
| HLVT-R Delayed Recall | Corr | *0.084* | 0.219* | 0.151 |
| | C.I | *(-0.056 – 0.223)* | (-0.028 – 0.416) | (-0.249 – 0.482) |
| | N | *204* | 89 | 49 |
| HLVT-R Delayed Recognition | Corr | *0.278** | 0.328* | -0.11 |
| | C.I | *(0.128 – 0.404)* | (0.120 – 0.514) | (-0.449 – 0.171) |
| | N | *199* | 89 | 48 |
| COWA | Corr | *0.222** | 0.121 | 0.255 |
| | C.I | *(0.070 – 0.372)* | (-0.091 – 0.330) | (-0.047 – 0.460) |
| | N | *189* | 81 | 49 |
| TMT-A | Corr | *0.073* | 0.157 | 0.017 |
| | C.I | *(-0.120 – 0.261)* | (-0.092 – 0.415) | (-0.196 – 0.243) |
| | N | *195* | 88 | 47 |
| TMT-B | Corr | *0.138* | 0.255* | 0.137 |
| | C.I | *(-0.003 – 0.287)* | (-0.021 – 0.508) | (-0.144 – 0.395) |
| | N | *189* | 86 | 47 |

Table 6
Percentage of patient-level NCF and neurocognitive complaints score differences between follow-ups in neurocognitively intact patients (%) on Total Recall, Delayed Recall, Delayed Recognition of the HVLT-R (Hopkins Verbal Learning Test – Revised), TMT (Trail Making Test), COWA (Controlled Oral Word Association Test), and MOS (Medical Outcome Scale).




Number of patients at each assessment

| Weeks | HLVT-R Total Recall | HLVT-R Delayed Recall | HLVT-R Delayed Recognition | COWA | TMT-A | TMT-B | MOS |
|---|---|---|---|---|---|---|---|
| 0-12 | 69 | 70 | 69 | 58 | 68 | 67 | 69 |
| 12-24 | 36 | 37 | 34 | 31 | 37 | 37 | 36 |
| 24-36 | 27 | 27 | 25 | 27 | 27 | 27 | 27 |

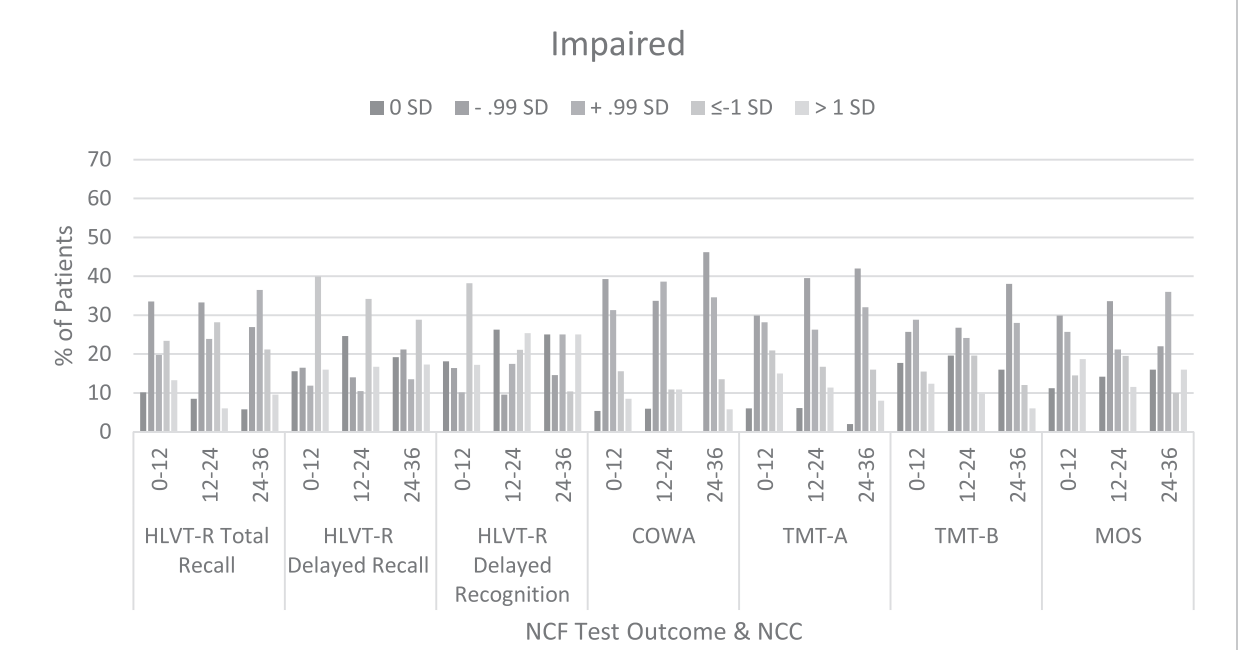
that patient's scores on test outcome remain relatively stable during the time interval in exam (Figs. 1 and 2). However, looking at patient-level analysis, the fact that a number of patients both neurocognitively impaired and intact show a clinically relevant difference between NCF and neurocognitive complaint scores is clear.

## 4. Discussion

In this study, we aimed at assessing whether, and if so how, patients' cognitive awareness changes over the disease course**.** We found neurocognitively impaired patients with recurrent HGG to report significantly more neurocognitive complaints than patients with intact NCF. Importantly, within those patients defined as neurocognitively impaired, we found these patients to be cognitively aware. Furthermore, awareness of neurocognitive impairments was higher in the earlier stages of the disease course than later on.

Regarding the strength of the associations, we found slightly stronger correlations between NCF and neurocognitive complaints in neurocognitively impaired patients than in neurocognitively intact subjects. When we measured the correlation between change scores in NCF outcomes and neurocognitive complaints at each subsequent follow-up, the pattern was similar to more and stronger correlations in neurocognitively impaired patients and only one significant correlation in neurocognitively intact patients early in the follow-up. The latter makes complete sense, since we do not expect neurocognitively intact patients to have neurocognitive complaints unless they may, for instance, have depressed mood or severe fatigue. An explanation for the finding that neurocognitive outcomes and complaints are more often correlated at baseline and early follow-up than later in the disease course might be derived from a recent meta-analysis on awareness of neurocognitive decline in patients with Alzheimer's Disease [26]. They propose that patients may be aware of their initial subtle neurocognitive changes, but awareness of cognitive decline would soon start to decrease. Though this may apply to patients with neurodegenerative conditions and

Table 7
Percentage of patient-level NCF and neurocognitive complaints score differences between follow-ups in neurocognitively impaired patients on Total Recall, Delayed Recall, Delayed Recognition of the HVLT-R (Hopkins Verbal Learning Test – Revised), TMT (Trail Making Test), COWA (Controlled Oral Word Association Test) MOS (Medical Outcome Scale).




Number of patients at each assessment

| Weeks | HLVT-R Total Recall | HLVT-R Delayed Recall | HLVT-R Delayed Recognition | COWA | TMT-A | TMT-B | MOS |
|---|---|---|---|---|---|---|---|
| 0-12 | *248* | *243* | *238* | *224* | *234* | *236* | *241* |
| 12-24 | *117* | *114* | *114* | *101* | *114* | *112* | *113* |
| 24-36 | *52* | *52* | *48* | *52* | *50* | *50* | *50* |

a relatively long survival, this might not be the case in brain tumour patients with progressive disease and poor prognosis.

In the light of our definition of cognitive awareness, it is important to draw attention to the fact that the correlations between NCF and neurocognitive complaints were rather weak. However, this is a very common finding and our results are in line with those of a recent study by Gehring et al. [27]. It is quite rare to have strong correlations between subjective and objective measurements in most of the neurological conditions that often compromise NCF (i.e. cancer, stroke, mood disorders, and dementia) [28–32]. The literature on the issue is full of contradictory results and what is striking is the lack of a golden standard that defines neurocognitive awareness or at least a commonly accepted approach to compare the diverse study results.

There certainly are limitations to this study. The treatment course and disease duration prior to inclusion of patients in the clinical trials may have been different between patients in EORTC trials 26091 and 26101. This might have affected treatment outcome and follow-up length. Furthermore, as it happens for all clinical trial studies, generalisability might be limited due to the selection bias which characterises clinical trial populations in general [33]. Finally, and importantly, our definition of neurocognitive impairment is somewhat arbitrary because it is unknown how this definition translates to limitations in daily life functioning of individual patients. It is conceivable that by grading the extent of neurocognitive impairment in levels rather than in a dichotomised way as we did, results might be different. Unfortunately, the amount of missing cognitive outcomes for some tests did not allow us to perform meaningful imputations.

Nonetheless, the results of the sensitivity analysis available in the appendix show that raising the neurocognitive impairment threshold produces little difference compared to the −1.5 SD cutoff we used in the present study. This suggests that the threshold adopted in the present study does not limit the meaning of its outcomes.

We believe that more research is needed to address awareness in HGG patients. Future studies need to focus

on a dedicated tool to measure awareness which could help to solve the debate of whether and to what extent to rely on PROs. Such a tool might test the accuracy of pre-test predictions (i.e. ask the patient how he/she thinks he/she will perform relative to healthy controls) or post-test estimates of neurocognitive performance (i.e. ask the patient how he/she thinks he/she did) [34].

Altogether, the findings of the present study suggest that neurocognitively impaired patients with recurrent HGG are aware of their neurocognitive limitations at study entry and during follow-up. This should be considered in clinical decision-making and when interpreting PRO results.

### Funding

The study was made possible by unconditional Grant 007/2016 of the EORTC Quality of Life Group.

### Research involving human and animals rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Authors' contribution

**I.C:** Conceptualisation, Methodology, Formal analysis, Writing – Original Draft, Writing – Review & Editing; **J.R:** Conceptualisation, Supervision, Writing – Review & Editing, Funding acquisition; **P.V.V:** Methodology, Writing – Review & Editing; **M.V.B:** Trial design, Investigation, Writing – Review & Editing; **A.I:** Trial design, Investigation, Writing – Review & Editing; **W.W:** Trial design, Investigation, Writing – Review & Editing; **M.T:** Writing – Review & Editing; **L.D:** Writing – Review & Editing; **A.B:** Writing – Review & Editing; **M.K:** Conceptualisation, Supervision, Writing – Review & Editing, Funding acquisition.

### Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgements

The authors are grateful to the medical and nursing staff of all the facilities which took part in the clinical trials.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.02.029.

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