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Different profiles of neurocognitive functioning in patients with brain metastases prior to brain radiotherapy

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Abstract

Objective: Patients with brain metastases (BrMs) are a heterogeneous population, with almost 50% experiencing cognitive impairment before brain radiotherapy. Defining pre-radiotherapy cognitive profiles will aid in understanding of the cognitive vulnerabilities and offer valuable insight and guidance for tailoring interventions.

Methods: The study population consisted of 58 adult patients with BrMs referred for radiotherapy. A semi-structured interview and comprehensive battery including 10 neuropsychological tests were used to assess subjective and objective cognitive performance prior to radiotherapy.

Results: A majority (69%) of patients report decline in cognitive performance compared to their premorbid level (i.e. pre-cancer). Objective testing revealed memory (52%), processing speed (33%) and emotion recognition (29%) deficits were most frequent. 21% of patients had no cognitive deficits while 55% had deficits (−1.5SD) in at least two cognitive domains. Hierarchical cluster analysis based on patient deficit profiles identified four clusters: (I) no or limited cognitive deficits selectively restricted to processing speed or executive function, (II) psychomotor speed deficits, (III) memory deficits and (IV) extensive cognitive deficits including memory. No patient or clinical-related (e.g. age, number of BrMs, previous treatment) differences were found between clusters.

Conclusions: Patterns of cognitive performance in patients with BrMs are heterogeneous, with most experiencing at least some degree of neurocognitive dysfunction. We identified four meaningful cognitive clusters. Stability of these clusters over time and in different samples should be assessed to advance understanding of the cognitive vulnerability of this patient population.

KEYWORDS
brain metastases (BrMs), brain tumor, cancer, cluster analysis, cognition, neurocognitive functioning, neuropsychology, oncology, radiotherapy

1 | INTRODUCTION

Brain metastases (BrMs) occur in 10%–30% of the adult cancer population and this incidence continues to rise.[1,2] Thereby, BrMs are the most common type of brain tumor.[3] Median overall survival despite systemic and local treatment is limited, spanning months to several years, depending on factors such as number of BrMs, Karnofsky performance status (KPS),[4] and the primary tumor.[5–7] Treatment for BrMs consists of different options, including radiotherapy, surgery, chemotherapy, immunotherapy or a combination.[8] In this vulnerable population, treatment (shared) decisions are tailored toward gaining the best disease control while maintaining acceptable quality of life (QoL) during the remaining life span.

Already before starting BrMs-specific treatment, a large percentage of patients experience cognitive problems; half of the patients demonstrate cognitive impairment on minimally one cognitive domain.[9–12] Multiple cognitive domains can be affected, with impairments reported in memory, executive function, and processing speed. However, substantial variability exists both within and between subjects in terms of cognitive domains of dysfunction. The pathogenesis of this pre-treatment cognitive performance is still incompletely understood, but both tumor-related factors (e.g. primary cancer, number of BrMs) as well as treatment-related factors (e.g. previous chemotherapy) seem involved.[11,13–15]

Previous research predominantly focused on cognitive performance on group-level using a confined set of cognitive tests. However, the heterogeneity of this patient population calls for a more individualized approach using an elaborate test battery. This will aid thorough understanding of the cognitive vulnerabilities and offer valuable insights for tailoring future interventions and optimizing patient-centered care. Therefore, the main aim was to extensively describe and classify the cognitive performance of patients with BrMs before brain radiotherapy, using both group- and individual statistics. Additionally, we used hierarchical cluster analysis to provide data-driven comprehensive understanding of the cognitive deficits and their interconnections. Additionally, we assessed the added value of an elaborate versus a core test battery in defining cognitive functioning of this heterogeneous population.

2 | METHODS

2.1 | Study set-up and population

Data was prospectively collected from the Cohort for patient-reported Outcomes, Imaging and trial inclusion in Metastatic BRAin disease (COIMBRA, NCT05267158) and Assessing and Predicting Radiation Influence on Cognitive Outcome using the cerebrovascular stress Test (APRICOT) study. The study population consisted of adult patients (≥18 years) with either radiographic and/or histologic proof of BrMS referred to the University Medical Center Utrecht (UMCU) for radiotherapy. Patients were non-eligible if they were unable to understand the Dutch language or had developmental, psychiatric, or cognitive disorders that hindered the patients' understanding of the informed consent procedure. For both studies, neurocognitive assessments (NCAs) were performed before, 3 months and ≥11 months after radiotherapy (see Supporting Information S1 for additional study procedures and exclusion criteria). The studies were performed in accordance with the Declaration of Helsinki[16] and the UMCU institutional ethical review approved both the COIMBRA and APRICOT study (#18-642 and #18-747, respectively). Written informed consent was obtained from all participants prior to participation.

2.2 | Data collection

2.2.1 | Subjective cognitive complaints

Prior to the NCA, subjective cognitive experience was assessed using a semi-structured interview regarding complaints on six different cognitive domains (memory, orientation, attention & executive functioning, processing speed, language, emotions), comparable to the structured interview regularly used in neuropsychological settings (Supporting Information S1). Based on the answers and reported interference with everyday life, the neuropsychologist rated each domain as cognitive complaints present (yes/no). In order to be classified as present, one complaint per domain sufficed. Additionally, patients rated their subjective cognitive functioning regarding thinking, memory, attention, perception, language and processing speed using visual analog scales (VAS), similar to Schoo and colleagues.[17] The VAS consisted of a 100 mm vertical line on A3-sized paper, where the top represents perfect and the bottom worst performance. Patients marked the line at their previously experienced premorbid subjective functioning level (i.e. prior to the primary cancer diagnosis) as well as for their current level (i.e. prior to the radiotherapy). This resulted in an estimation ranging from 0 to 100. A difference score was calculated for each cognitive concept to assess change in subjective functioning compared to premorbid levels. This was categorized into stable (±5), subtle improvement/decline (±6–25), substantial improvement/decline (±26–50) and extreme improvement/decline (±>50). Patients indicated their current stress levels using the same VAS-methodology, with higher scores indicating more stress, and lower scores indicating lower stress.

2.2.2 | Neurocognitive assessment

A comprehensive NCA was used to assess objective cognitive performance. All tests are internationally widely used, standardized psychometric instruments for assessing neurocognitive deficits in the major neurocognitive domains. While neuropsychological tests often tap into more than one neurocognitive domain, tests were classified into different neurocognitive domains based on available literature and clinical experience. In our clinical practice, we assess fatigue by repeating the Digit Span Forward twice during the NCA, once

halfway and once at the end. The maximum span reached by the patient at the repeated assessments is compared to the initial maximum span. If the maximum span decreased, this is taken as indication of cognitive fatigue. This approach was also used in this study. NCAs were performed by trained personnel and were planned to be completed within approximately 90 min.

The comprehensive battery was compared to the core battery. The core battery represents tests advised by the International Cancer and Cognition Task Force (ICCTF)[18] combined with tests frequently used in previous BrMs research.[9] The comprehensive battery encompasses the core battery complemented by additional neuropsychological tests (Table S1).

For current analyses the cognitive data acquired prior to radiotherapy from October 2020 to January 2023 was used. Each neuropsychological test was scored according to standardized scoring criteria. The uncorrected scores were transformed into *z*-scores based on the mean and standard deviation of control populations derived from published norm data and corrected for age and education where appropriate (see Table S1 for references of used norm data), with lower *z*-scores representing worse performance. Overall neurocognitive domain scores were calculated using the mean of the z-scores of the available tests within a domain. Overall neurocognitive domain scores were only calculated if a patient completed at least 50% of the tasks within the domain. Additionally, neurocognitive impairment in each domain was defined as *z*-score ≤ -1.5 on any of the administered tests within the domain to ensure both specificity and sensitivity to cognitive difficulties experienced by patients.

2.2.3 | Patient characteristics

Patient characteristics were obtained from the semi-structured interview and electronic patient files (HiX, Chipsoft). This included sex, age at inclusion, level of education according to the Verhage criteria,[19] handedness, KPS,[4] primary tumor, presence of extracranial metastases, time since BrMs diagnosis, previous anti-tumor therapy, dexamethasone dose 1–5 days prior to radiotherapy, and symptoms at BrMs diagnosis. As part of standard medical care, the pre-radiotherapy MRI scans of each patient were evaluated to determine the number of BrMs, hemisphere, and lobe involvement.

2.3 | Statistical analyses

Analyses were performed using SPSS (IBM SPSS Statistics, 25.0.0). Statistical significance was set at $p < 0.05$, adjusted for multiple comparisons when necessary. Cognitive test scores were analyzed using different methods:

1. *Group-level*: comparison of mean *Z*-score of the sample with normative performance for each domain ("domain-level") and each task ("task-level") using one-sample *t*-tests (with the null hypothesis $Z = 0$, meaning no difference between patients and expected normative performance) or Wilcoxon-signed rank tests, depending on normality of data distribution.
2. *Individual-level*: the percentage of patients with test performance below the impairment threshold ($Z \leq -1.5$) was calculated for each domain ("domain-level") and each task ("task-level"). To assess the relationship between subjective and objective cognitive performance, subjective complaints were compared between patients with versus without impairment on the domain-level using chi-square tests and Mann-Whitney *U* tests for categorical and continuous data, respectively. To assess the influence of stress on cognitive performance, correlation analyses were performed between stress and domain-level cognitive performance (see Supporting Information S1). Additionally, the domain-level impairments were descriptively compared between the comprehensive and the core battery.
3. *Exploratory cluster analysis*: with a data-driven approach patients were clustered based on similarities in deficits at the domain-level using Ward's linkage with squared Euclidean distance. The number of distinguishable clusters was selected by visual inspection of the dendrogram and confirmed by discriminant function analysis. As cluster analysis uses complete cases, only patients with data for all included cognitive domains were considered. To assess how domain-level deficits differed across clusters and whether patient and/or clinical characteristics (see Table S2 for specific variables) differed across clusters, chi-square tests were performed for categorical data and Mann-Whitney *U*-test for continuous data.

3 | RESULTS

3.1 | Clinical characteristics

Fifty eight patients (31 men) were included in the analyses. The median age was 66 years. Most patients had two or more BrMs (72%) and BrMs most often originated from lung cancer (50%). More than half of patients (62%) presented with symptoms at time of the BrMs diagnosis which mostly included epilepsy, motor symptoms and/or headache. The majority of patients (74%) was receiving or had received previous anti-tumor therapy (i.e. chemo- or immunotherapy; Supporting Information S1).

3.2 | Subjective cognitive complaints

During the semi-structured interview, the majority of patients reported cognitive fatigue (62%; Table S3). Additionally, both motor and sensory problems were frequently reported (38% and 22%, respectively). Cognitive complaints were reported across all domains with 59% of patients reporting cognitive problems in at least one domain. Subjective decline compared to previously experienced premorbid functioning was reported in at least one cognitive domain by 69%, with decline in two or more domains reported by 55%. Both

subjective complaints and cognitive decline were most frequently reported for memory (38% and 40%, respectively) and attention & executive functioning (38% and 43%, respectively; Figure 1). Mean self-reported stress levels were 27 (SD = 26), with 11% of patients reporting levels of ≥50. The majority of patients (64%) reported their stress was related to the cancer diagnosis and upcoming treatment.

3.3 | Neurocognitive data

3.3.1 | Neurocognitive functioning

Group-level: On the domain-level, group performance was worse compared to the normative population for memory, processing speed and psychomotor speed. On the contrary, performance on visuospatial functioning was better than the norm population. On the task-level, patients' cognitive performance was significantly lower than the norm data for multiple memory tests (Hopkins Verbal Learning Test—Revised [HVLT-R], semantic fluency), processing speed (STROOP naming), psychomotor speed (Grooved Pegboard dominant and non-dominant hand), and social cognition (FEEST total). Contrarily, mean *Z*-scores were better than the norm population for tests on attention (Trail Making Test, switching), memory (VAT—delayed), and visuospatial functioning (Hooper Visual Organization Test fragmented). Group performance for all other (sub)tests were not significantly different from the norm population (Table S4).

Individual-level: On the domain-level, severe deficits (−2.0SD) were most often observed for memory (35%), psychomotor speed (32%), and processing speed (28%). More subtle deficits (−1.5SD or −1.0SD) were found for attention (16% and 40%, respectively) and executive function (22% and 50%, respectively). Deficits in visuospatial functioning were least often found. On the task-level, cognitive impairments were detected across all tests. The percentages of patients with severe cognitive impairments (−2.0SD) were highest for HVLT-R (recognition: 32%, immediate 20%, delayed 16%), Grooved Pegboard (dominant: 26%, non-dominant 22%) and STROOP naming speed (19%). More subtle deficits (−1.5SD) were observed for the FEEST (29%) and the semantic fluency task (25%; Figure 2).

Despite signs of cognitive fatigue in approximately 20% of patients, the current patient sample successfully completed over 90% of the tests of the comprehensive NCA within the intended 90 min (Supporting Information S1). Comparison of the comprehensive with the core test battery shows that in particular patients with two or more cognitive deficits are "misclassified" into the group of patients with less cognitive deficits when using the core battery only (Figure S3). Differences were mostly due to differences in deficits within the domains of attention, executive function and processing

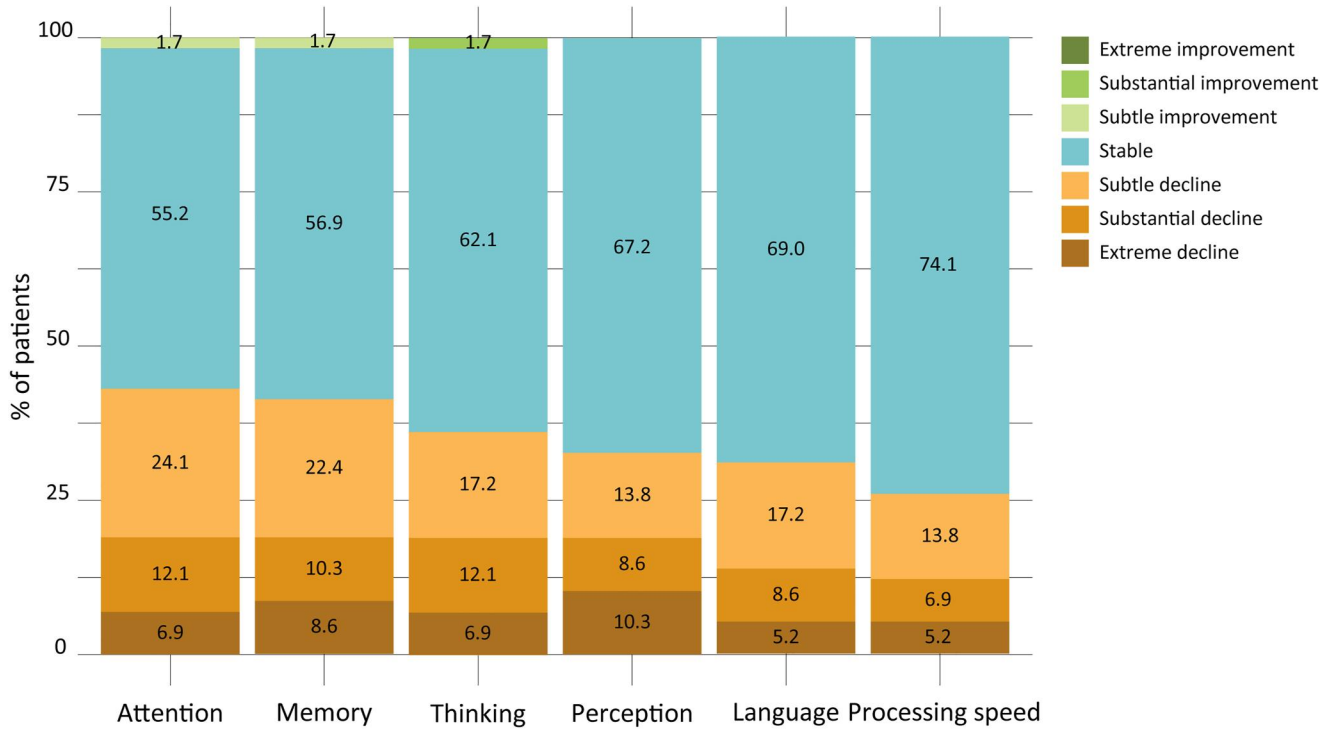


FIGURE 1 Stacked bar chart comparing pre-radiotherapy to the pre-cancer performance showing the percentage of patients reporting subjective improved, stable or declined performance for each cognitive domain ordered from most decline to least decline. Colors indicate extreme improvement (dark green), substantial improvement (green), subtle improvement (light green), stable performance (blue), subtle decline (light orange), substantial decline (orange) and extreme decline (dark orange). Values shown inside the bar are exact percentages of patients within that category. Stable performance (±5), subtle improvement or decline (±6–25), substantial improvement or decline (±26–50) and extreme improvement or decline (±>50). EF, executive functioning.

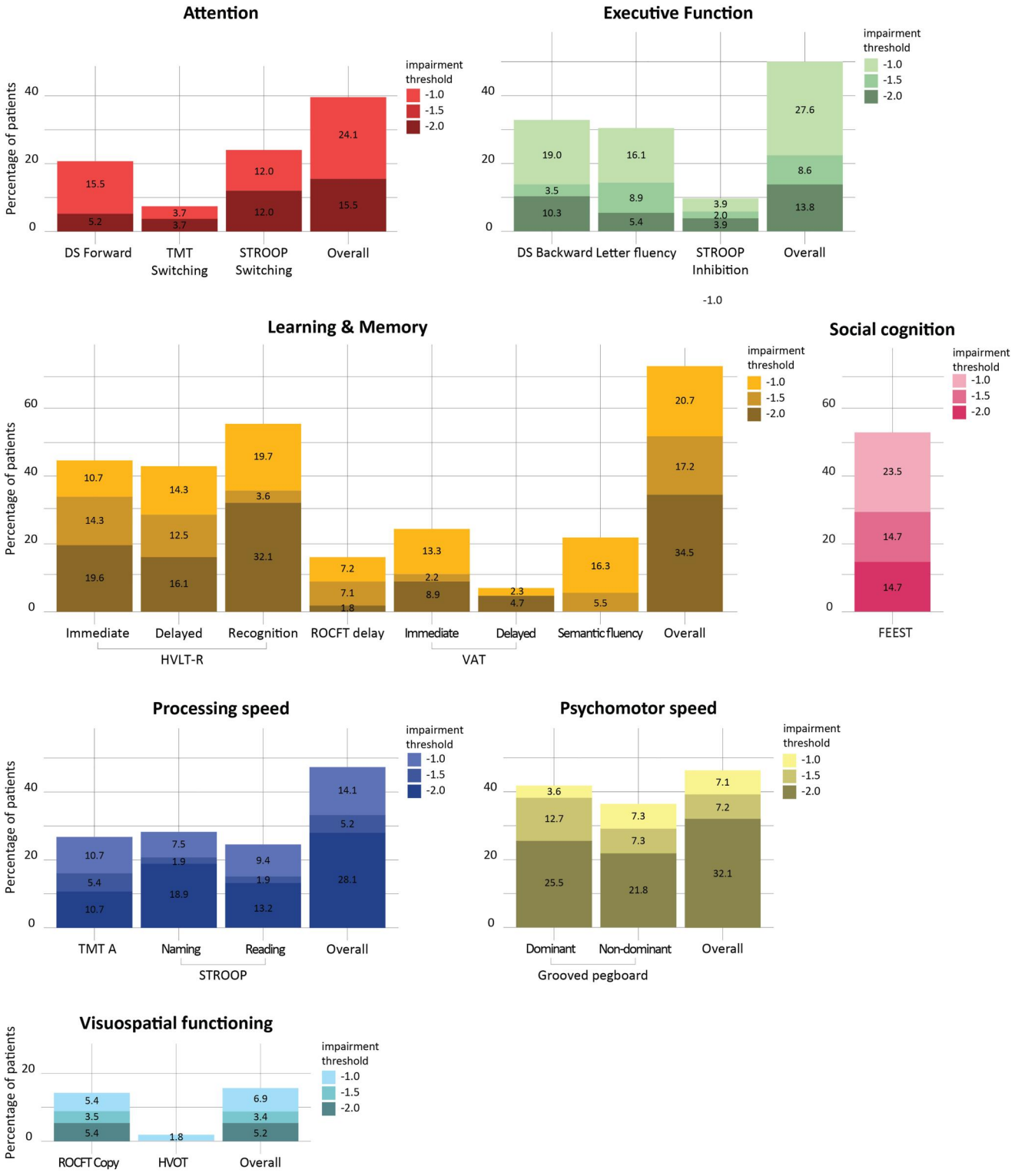


FIGURE 2 Stacked bar graphs of percentage of patients with a cognitive impairment pre-radiotherapy at certain thresholds grouped per cognitive domain. Each task and overall domain scores are shown. Colors indicate the cognitive impairment at different threshold of ≤−2.0 (dark colored), ≤−1.5 (medium colored), and ≤−1.0 (light colored). Values within the bars represent the exact percentage of patients within an impairment category. DS, digit span; FEEST, Facial Expressions of Emotion—Stimuli and Tests; HVLT-R, Hopkins Verbal Learning Test—Revised; HVOT, Hooper Visual Organization Test; ROCT, Rey Osterieth Complex Figure Test; TMT, trail making test; VAT, Visual Association Test.

speed (based on STROOP performance), while almost no differences were found for memory (Table 1).

3.3.2 | Exploratory cluster analysis

Cluster analysis was performed for 56/58 patients using the individual domain-level impairment for the cognitive domains, as two patients were excluded due to missing data regarding psychomotor speed and/or processing speed. Scores for social cognition were not included in this cluster analysis due to a substantial number of patients ($n = 24$) with missing data (Figure S2). The dendrogram provided evidence for two-, three-, four-, and five-cluster solution, with reasonable separation between clusters. A multivariate test of group differences was performed using canonical linear discriminant function analysis, which confirmed a maximum of four clusters could be adequately differentiated with 97% classification accuracy ($\wedge = 0.03$, $\chi^2(18) = 196.75$, $p < 0.001$). This indicates that each cluster showed distinct intra-individual profiles regarding the cognitive impairment across domains.

Subsequently, all clusters were compared regarding the proportion of patients with cognitive impairments (Figure 3). Attention impairments did not differ between any of the clusters. Cluster IV had significantly more patients with an executive function impairment (55%) compared to both cluster I (14%) and cluster II (0%), but did not differ from cluster III (22%, $p = 0.032$, $\varphi = 0.397$). When considering memory impairment, cluster III and IV both had more patients with an impairment (100% and 91%, respectively), than the clusters I and II (0% and 17%, respectively, $p < 0.001$, $\varphi = 0.936$). Cluster IV had most patients with impairments in processing speed (100%) compared to all other clusters. Additionally, Cluster I had more patients with processing speed impairments (33%) than Cluster III (0%, $p < 0.001$, $\varphi = 0.786$). Psychomotor impairments were more frequent among cluster II (100%) than cluster I (0%) and cluster III (33%). Cluster IV also had more patients with psychomotor impairment (73%) than cluster I ($p < 0.001$, $\varphi = 0.634$). Lastly, cluster II had significantly more patients with a visuospatial functioning impairment (33%) than cluster I (0.0%; $p = 0.049$, $\varphi = 0.375$). There were significant differences between clusters regarding the number of impaired cognitive domains ($p < 0.001$). Post-hoc tests indicated cluster IV had significantly more impaired cognitive domains compared to all clusters (all $p \leq 0.001$), and cluster III had more cognitive impairments than cluster I ($p = 0.008$). Thus, cluster I and II represent the patients with the least number of cognitive impairments.

Based on the different neurocognitive profiles, the clusters were identified as "no or limited cognitive deficits restricted to processing speed or executive function" (cluster I), "psychomotor speed impairment" (cluster II) and two clusters with memory impairments (cluster III and IV). Cluster IV exhibited multiple additional cognitive impairments and was therefore named "Memory + multiple impairments" (Figure 3). None of the clusters differed regarding any of the patient or clinical characteristics listed in Table S2.

4 | DISCUSSION

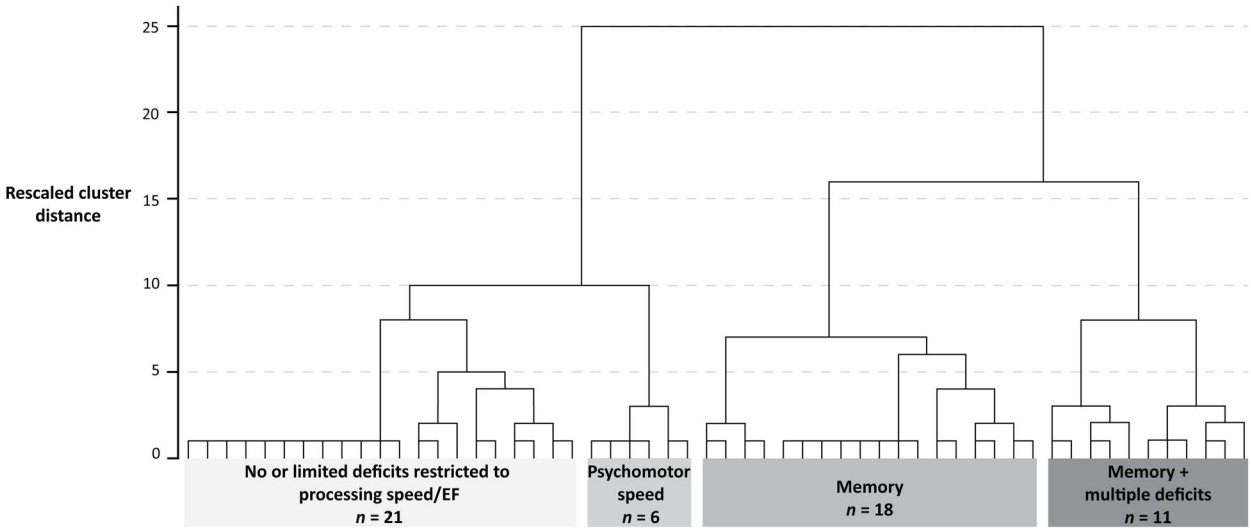
This prospective study aimed to describe and classify the individual cognitive performance of patients with BrMs prior to radiotherapy. Results indicated that impairments in neurocognitive functioning occur frequently; almost 80% of patients had cognitive deficits ($Z \leq -1.5$) in at least one cognitive domain before starting radiotherapy. The most commonly affected cognitive domains included memory, processing speed, psychomotor speed, and social cognition. When applying more stringent thresholds ($Z \leq -2.0$), less than one third of patients were not affected. Thus, nearly all BrMs patients

TABLE 1 Number and percentage of patients with an impairment within a domain when either determined using the core versus the comprehensive battery.

Cognitive domains	Core, *n* (%)	Comprehensive, *n* (%)	Task contributing to difference
Attention	4 (6.9)	9 (15.5)	STROOP IV/III ($n = 5$)
Executive function	12 (20.7)	13 (22.4)	STROOP III/I ($n = 1$)
Memory	28 (49.1)	30 (51.7)	VAT immediate ($n = 2$)
			ROCFT delay ($n = 1$)
Processing speed	9 (15.5)	19 (33.3)	STROOP I ($n = 8$)
			STROOP II ($n = 7$)
Psychomotor speed	22 (39.3)	22 (39.3)	NA
Visuospatial functioning	NA	5 (9.1)	Rey copy ($n = 5$)
Social cognition	NA	10 (29.4)	FEEST ($n = 10$)

Note: Number of patients mentioned behind task names indicate the number of patients this specific task made a difference for when comparing the core with the comprehensive battery. As task deficits are not mutually exclusive, patients can exhibit deficits on more than one task within one domain both contributing to the difference between core and comprehensive. For example, one patient with a memory impairment had deficits on both the VAT immediate recall and the Rey delayed recall.

Abbreviations: FEEST, Facial Expressions of Emotion—Stimuli and Tests; ROCFT, Rey Osterieth Complex Figure Test; VAT, Visual Association Test.



	I	II	III	IV
Attention, n (%)	2 (9.5)	0 (0.0)	4 (22.2)	3 (27.3)
Executive function, n (%)	3 (14.3)[a]	0 (0.0)[a]	4 (22.2)[a,b]	6 (54.5)[b]
Memory, n (%)	0 (0.0)[a]	1 (16.7)[a,b]	18 (100)[b]	10 (90.9)[b]
Processing speed, n (%)	7 (33.3)[a]	0 (0.0)[b]	0 (0.0)[b]	11 (100)[c]
Psychomotor speed, n (%)	2 (9.5)[a]	6 (100)[b]	6 (33.3)[a,c]	8 (72.7)[b,c]
Visuospatial functioning, n (%)	0 (0.0)[a]	2 (33.3)[b]	1 (5.6)[a,b]	2 (18.2)[a,b]
N impaired domains, M(SD)	0.81 (1.0)[a]	1.7 (0.8)[a,b]	2.0 (1.0)[b]	3.9 (1.6)[c]

FIGURE 3 Dendrogram of the cluster analysis performed on the presence/absence of cognitive impairments across all cognitive domains except social cognition. Numbers I–IV indicate the different clusters. The table below shows number and percentage of patients per cluster with a cognitive impairment (−1.5SD) on the different cognitive domains. Clusters with different subscripts showed a statistically significant difference ($p < 0.05$). EF, executive functioning.

referred for radiotherapy experience some degree of neurocognitive dysfunction.

Correspondingly, almost 70% of patients experienced a decline in subjective cognitive functioning compared to their indicated premorbid level, with decline in two or more domains reported by 55%. Decline was reported across all domains, but were most often labeled as attention, memory and thinking. Interestingly, the majority reported stable functioning, with some (2%) even reporting improved performance. There could have been a positive bias due to dexamethasone-induced euphoria, which could have led to overall more positive self-reported cognitive functioning.[20] While subjective experience was not directly related to the objective cognitive performance, as in the majority of previous studies,[21] both measures did show differentiated profiles across the distinctive neurocognitive domains. Firstly, this indicates that patients are able to differentiate between their premorbid and their current cognitive functioning using VAS. Secondly, our results suggest patients have domain-specific self-awareness of their cognitive functioning, similar to participants in a previous study.[17] These findings demonstrate that utilizing domain-specific questions, specifically through the application of VAS, can offer valuable understanding of subjective experiences and serve as a practical tool for psychoeducation.

Neurocognitive functioning prior to radiotherapy was characterized by large intra-individual differences. Previous studies have reported 53%–67% of BrMs patients exhibit cognitive impairments on at least one cognitive test prior to radiotherapy.[11,12,22,23] While we found 79% of patients had at least one cognitive impairment, this difference is likely due to the more comprehensive NCA performed in the current study, suggesting the reported numbers in the literature may be too low. On some tests patients with BrMs, however, outperformed the norm scores, which should be interpreted in term of their motivation and effort to perform well.[24] Stress appeared unrelated to their cognitive performance, pointing out that experienced stress cannot explain the differences with the norm population. While cognitive fatigue half-way through the NCA was related to overall slower information processing speed, it was unrelated to deficits within this domain.

Using a data-driven, exploratory hierarchical cluster analysis we examined patterns of cognitive profiles in our BrMs sample and found a four-cluster solution providing meaningful cognitive profiles. Separation between clusters was mainly based on the presence or absence of memory deficits. The group of patients with memory deficits ($n = 29$) included a subgroup ($n = 11$) with impairments across domains and worst overall cognitive performance. In the non-memory group, a substantial number of patients ($n = 21$) had either

no impairments or impairments restricted to processing speed or executive function. The discerned clusters can contribute to patient-centered care through development of psycho-education for patients and caregivers, thereby enhancing coping mechanisms and managing expectations in line with their profile. Moreover, knowledge of these clusters offers insights into cognitive strategies for each specific cluster. For example, Cluster III patients with intact cognitive functions except for memory impairment may require different strategies (e.g. metacognitive training[25]) compared to Cluster IV patients with a wide range of cognitive impairments which limits rehabilitation possibilities (e.g. attention needed for cognitive training). While our sample size ($n = 56$) may be considered small for cluster analyses, the significant cognitive differences observed and the meaningfulness of these differences, support the value of this exploratory cluster analysis and its potential relevance to reduce the cognitive heterogeneity in this population. No patient- nor clinical factors (e.g. number of BrMs, primary tumor, previous treatment) were related to the clusters. In future studies we will assess whether cluster membership has predictive value for the trajectory of cognitive performance after treatment and whether they can be linked to biological substrates. If so, this could improve understanding of the pathophysiology of cognitive performance in these patients.

4.1 | Clinical implications

Similar to previous studies, memory deficits were prominent in our sample[11,12,22,23] with severe memory impairment in one out of every three patients. Moreover, in the cluster analysis the presence of memory deficits was a major determining factor. As declines in memory performance have been reported in up to 50% of patients one to 4 months after radiotherapy,[11,22,26] this highlights the cognitive vulnerability of this patient population. Additionally, in both the group- and individual analyses processing speed and psychomotor speed deficits were frequent. Processing speed relies on a widespread neural network, which can be altered by the presence of a tumor within that network.[27,28] Psychomotor slowing is often experienced as a consequence of chemotherapy-induced neuropathy.[29,30] Accordingly, a significant majority of patients with psychomotor impairment had received chemotherapy (68%), compared to half of those with processing speed impairments. Patients who reported sensory problems were more likely to have psychomotor speed impairments, regardless of whether sensory problems were attributed to neuropathy by patients themselves or not. Overall, this implies it is important to distinguish psychomotor from processing speed deficits within this population.

Almost one third of the BrMs patients showed impaired social cognition, specifically emotion recognition. This significantly impacts both patient and caregiver QoL as it enables us to process social information and respond appropriately in social contexts.[31,32] Stress has been linked to worse emotion recognition,[33,34] and can also be a side-effect of dexamethasone.[20] Nevertheless, neither self-reported stress levels nor dexamethasone use were related to emotion recognition in our sample. Social cognition has not received widespread attention yet, and thus only few studies in brain tumor patients exist.[35–38] A recent study found that before surgery patients with low-grade glioma performed worse on emotion recognition than healthy controls and these deficits remained after surgery.[35] Further research is needed on social cognition in the long-term to gain better understanding of the underlying mechanisms and the potential effects of brain radiotherapy.

In the current study we employed an elaborate cognitive test battery comprising 10 neuropsychological tests. While signs of cognitive fatigue were present in about 20% of patients throughout the NCA, the current patient sample was able to complete more than 90% of the tests and most finished within the intended 90 min. This illustrates that performing a comprehensive NCA within this vulnerable patient sample is feasible. The comparison between the comprehensive and the core battery indicated that the core battery cannot adequately detect the severity of cognitive deficits. That is, the extent of cognitive deficits (i.e. number of impaired domains) is often underestimated when solely using the core battery. The differences mainly stemmed from performance variations on the STROOP task, which measures attention, executive function, and information processing speed, while minimal differences were observed in the memory domain. Hence, the STROOP task holds significant potential for assessing cognitive performance in this population. Next, we will investigate the value of the comprehensive battery in assessing treatment-related cognitive decline in order to develop a concise yet comprehensive battery for future use in this heterogeneous population.

4.2 | Study limitations

Selection bias may have played a role in our study as only those patients willing and fit enough to perform a comprehensive NCA were included in the studies. We compared patient and clinical characteristics between the patients included in the less intense COIMBRA versus the APRICOT study. Only KPS was slightly higher in the patients of the APRICOT study, indicating no major differences in patient selection between studies (Supporting Information S1). Additionally, we grouped tests based on their shared conceptual background ("domain") in order to enhance power and aid interpretation, even though performance on one task relies on more than one cognitive concept. For comparability, we reanalyzed the data using the domain categorization defined by the ICCTF, which indicated that differences between the comprehensive and core battery remained unchanged.

5 | CONCLUSION

In the current study we demonstrated the pre-existing cognitive vulnerability of BrMs patients as nearly all experienced some degree of neurocognitive dysfunction prior to brain radiotherapy. This

neurocognitive dysfunction could be clustered into meaningful cognitive profiles, but future studies with larger samples should validate these profiles. Advancing our understanding of the vulnerability that results in treatment-related cognitive decline and the origins of the cognitive dysfunction, is likely to facilitate the development of new strategies for patient-centered treatment and rehabilitation.

AUTHOR CONTRIBUTIONS

Eva E. van Grinsven: Conceptualization; data curation; methodology; formal analysis; investigation; visualization; writing – original draft; writing - review & editing. **Fia Cialdella**: Data curation; investigation; writing – review & editing. **Joost J. C. Verhoeff**: Supervision; writing – review & editing. **Marielle E. P. Philippens**: Conceptualization; supervision; resources; funding acquisition; writing – review & editing. **Martine J. E. van Zandvoort**: Conceptualization; methodology; supervision; writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

After completion of the full trial and answering the primary and secondary research questions as stated in the study protocol, data will be made available upon request. The requesting research should submit a formal project outline, and assessed whether this is in line with the original research protocol for the study. If not, additional approval from the local ethics committee may be necessary.

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