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Baseline neurocognitive dysfunction is ubiquitous in intrinsic brain tumors–results from a large Indian cohort of patients and analysis of factors associated with domain-specific dysfunction

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ABSTRACT

Background: Neurocognitive function (NCF) before surgery is an important marker of baseline performance in patients with brain tumors. Increasingly, neurocognitive deficits (NCD) have been demonstrated in a high proportion of patients. Selection bias (patient, tumor, and surgical procedure related) may influence the prevalence and type of domains involved in patients with gliomas.

Methods: We evaluated baseline NCF in a consecutive cohort of intra-axial tumors in Indian patients ($n = 142$). A comprehensive battery evaluating five domains – attention & executive function (EF), memory, language, visuospatial function and visuomotor abilities was used. Deficits were categorized as severe and mild-moderate. Factors associated with severe NCD were evaluated.

Results: Severe NCD was present in 90% of the patients, 70% of them having affection of at least 2 domains. Attention-EF, memory and visuomotor speed were most affected. 132 underwent surgery (69 awake, 63 under general anesthesia - GA). The awake cohort had younger patients with lower grade gliomas and more left sided tumors. Multi-domain dysfunction was seen almost equally in awake/GA groups as well as left/right sided tumors. On multivariate analysis, older age, lower educational status and larger tumor volume adversely affected NCF in many of the domains. Only language dysfunction was location specific (temporal lobe tumors) though not laterality (left/right) specific.

Conclusions: NCD were seen in a large majority of cases before surgery, including those undergoing awake surgery. Language may be affected even in tumors in the non-dominant hemisphere. Attention-EF and memory are most affected and need to be factored in while assessing patient performance intraoperatively during awake surgery as well as tailoring rehabilitative measures subsequently.

1. Introduction

Outcomes in brain tumors have seen incremental improvements over the years. Advances in surgical techniques and technological adjuncts, improved combinatorial adjuvant therapies and active rehabilitation strategies have all contributed to these improvements. Though the focus has traditionally been on improved survival outcomes, functional outcomes are equally, if not more, important. In the context of brain tumors this is accentuated by the complex functionality of the brain. Clinician reported outcome measures (ClinROM) such as motor outcomes or general performance outcomes like the Karnofsky performance score (KPS), Glasgow Outcome score (GOS) or NIH-stroke scores may not sufficiently capture the complexities of brain functional outcomes. Patient reported outcome measures (PROM) like quality of life (QOL) may provide a better understanding of the functional impact of the tumor and treatment related effects which may vary amongst patients. Performance outcome measures (PerfOM) on the other hand provide more detailed and objective evaluation of various components of organ function.[1] Neurocognitive function (NCF) is one such PerfOM. NCF can be tested by a detailed neuropsychological assessment (NPA) using a battery of

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tests.[2–4] This has been used in the context of clinical trials and has shown to correlate with progression and survival.[5,6] More importantly, NPA can unearth covert deficits and provide an accurate estimate of the burden of symptoms for patients and caregivers. It also allows clinicians to assess the impact of therapies and tailor rehabilitative efforts (physiological, orthoptic, language and cognitive).[7,8] Most studies and trials describe NPA before and after adjuvant therapies. It is well known that intervention (surgical and non-surgical) can affect NCF. However, baseline NCF before institution of any therapy (and surgery is usually the first line of treatment in most gliomas) may be impaired due to the tumor and related factors. It is crucial to understand the impact of the disease itself on the NCF prior to any intervention. Previous studies have revealed that NCF can be significantly affected in patients very early on.[2,3] Such data in the Indian population is very scarce. Here we report baseline NCF performance in a large cohort of patients undergoing surgery and analyze factors affecting it.

2. Methods

2.1. Study design

This was a retrospective study performed at a tertiary care oncology centre with an exclusive neurosurgical oncology service. IEC approval (IEC no. 3882) was obtained with waiver of consent as per institutional policies for retrospective studies. STROBE guidelines were applied for reporting this study.[9] All consecutive patients with a supratentorial intra-axial tumor planned for awake craniotomy between January 2019 and June 2022 and referred for NPA were screened. At the time, in our center, tumors involving the dominant hemisphere (frontal, parietal, temporal, insular) and selective non-dominant hemispheric tumors (viz parietal lobe) are offered awake craniotomy. Increasingly more awake surgeries are now performed even for non-dominant hemisphere tumors. Specifically, the inclusion and exclusion criteria were as follows.

2.2. Inclusion criteria

1. All adult hemispheric gliomas undergoing debulking surgery
2. Awake surgery or surgery under GA
3. At least 2 domains tested

Exclusion criteria.

1. Cases where only biopsy was planned
2. Severe neurological deficits precluding an adequate NPA
3. Emergency surgeries (severe raised intracranial pressure, altered sensorium)
4. Prior psychiatric illnesses

For the period between Jan 2021 to June 2022, we started routine perioperative neuropsychological assessment (NPA) of all suspected gliomas being planned for resections including the cases operated under anesthesia. Once clinically screened, a detailed NPA battery is administered by a neuropsychologist (KR, KJ). In cases where awake craniotomy is planned, following the NPA session, patients are counselled thoroughly about the proposed awake procedure and intraoperative assessment tests which are customized based on the location of the tumor and the findings of the NPA are also administered and rehearsed. Occasionally due to logistical reasons, some patients may not have undergone a detailed NPA. This included sick patients and those requiring surgery on a priority. Only those patients who had a formal NPA where at least 2 domains were evaluated, have been included in this analysis.

2.3. Neurocognitive tests

Addenbrooke's Cognitive Examination (ACE-III - Indian English and Hindi version) was the primary screening tool used for all patients.[10] Handedness and educational status were recorded in all.[11] Based on the findings of ACE, the patients were subjected to an extensive neuropsychological test battery for a detailed evaluation of their NCF. The test battery was customized specifically for assessing 5 major cognitive domains, viz, attention and executive functions (EF), memory (verbal and visuospatial), language, visuospatial/visuoconstructive function and visuo-motor speed as described in earlier studies.[2] The entire session usually lasted between 90 and 120 min. Standardized tests were used wherever possible, but because of the wide diversity in terms of age, literacy, cultural and socio-economic status, we had to modify some of the standard tests which were tailored for our population as has been suggested by some authors.[12] One such example is the picture naming test (for language) where instead of using a standardized test like the Boston Naming Test, we modified it using a total of 60 objects (pictures which includes fruits, vegetables, body parts, tools, furniture and other objects more familiar to our population). Tests previously standardized for the Indian population were used in their respective Indian languages wherever possible.[13] Table 1[10,11,13–17] shows the battery used to assess the cognitive domains mentioned above and the interpretation criteria for the tests are listed in Supplementary Table 1. In addition to the core NCF domains, the psycho-morbid state was assessed using the General Health Questionnaire (GHQ-12).[17]

The performance for each test was recorded as normal, mild-moderate and severe. For tests where normative data was available, z scores were calculated and classified as severe ($z < -2$ SD), mild to moderate (z between 0 and -2 SD) and normal (z more than 0). Other tests were graded for severity semi-quantitatively [Supplementary Table 1]. A domain was considered affected if any one of the tests (Table 1) pertaining to that domain was abnormal, with the severity categorized based on the worst test result (if more than one test per domain was affected). Though the ACE screening tool itself encompasses many of the domains, for the purpose of interpretation of domain dysfunction, the results of the ACE were not considered. Patients with any abnormality (mild-moderate or severe deficits) were grouped as "any" deficits for additional analysis. Overall NCF was considered affected if any domain was affected (with severity graded as per the most severely affected domain). Individual level interpretation of the tests and domains were done as described above and the proportion of affected patients was expressed as a percentage of the total number of patients tested. Group level scores were not calculated. It has been shown that group level scores though useful to

Table 1
Lists of Neuropsychological assessments used in this study.

Neuropsychological Domains		Neuropsychological Tests
Handedness	1	Edinburgh Handedness Inventory (EHI)[11]
Attention and Executive Function	1	ACE-III (which includes verbal fluency)[10]
	2	Counting (1–20) forwards and backwards[14,15]
	3	Trail Making B[14,15]
Memory	1	ACE-III[10]
	2	Rey's -Osterrieth Complex Figure Test (RCFT-Immediate & Delayed recall)[13]
	3	Rey's Auditory Verbal Learning Test (RAVLT-Immediate & Delayed recall)[13]
	4	Counting BACKWARDS (random number sequence)[14]
Language	1	ACE-III[10]
	2	Picture Description**
	3	Action Words**
	4	Naming (modified 60) **
Visuospatial and visuo-constructional abilities	1	ACE-III[10]
	2	RCFT (Copy)[13]
	3	Line Bisection[16]
Visuomotor speed	1	Trail Making A[14,15]
Psychomorbid state	1	General Health Questionnaire- 12 (GHQ12)[17]

* ACE is included as it tests the various domains. However, it was used only as a screening test and for the purpose of this study, only the other specific neuropsychological tests were considered to define function of a particular domain.
** Language tests were customized and modified as per our patient population.

understand overall patterns, may misreport the burden of dysfunction in brain tumor patients.[18]

2.4. Demographic and clinico-radiological data

Relevant clinico-radiological and histopathological data was also retrieved from a prospectively maintained neurosurgical database as well as from the hospital's electronic medical records (EMR) and the PACS. Preoperative imaging was unavailable in some cases. All available images were reviewed by one of the authors (KJ) and tumor size measured in the three largest dimensions (a,b,c) on both T1 contrast and T2 FLAIR images to encompass the infiltrating/oedematous areas. We included the oedematous component as this would contribute to the overall structural mass effect of the lesion and thereby to the clinical dysfunction. It is also easier and more reproducible to measure as compared to tumor boundaries which may often be ill defined and difficult to differentiate from edema. Tumor volume was then calculated using the formula (a*b*c/2). Histology was recorded from the routine reports in all the patients who underwent surgery till the time of this analysis. Grade 2 and 3 diffuse gliomas were categorized as lower grade gliomas. IDH molecular status was routinely performed for all diffuse gliomas using immunohistochemistry. For lower grade diffuse gliomas (grades 2 and 3) negative IHC was further evaluated with sequencing to confirm presence or absence of IDH mutations as part of routine practice.

Statistical analysis: All statistical analyses were carried out using the SPSS software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Individual patient-level analyses were performed to evaluate measures of the NCF outcomes where categorical data was represented in percentage count and continuous data in mean (with standard deviation, SD) or median (with interquartile range, IQR) as appropriate. To assess the effect of various independent demographic and clinico-radiological variables on NCF, logistic univariate and multivariate regression analyses were carried out individually for only severe deficits as the dependent variable. p values of <0.2 in univariate analysis were further used to select input variables in multivariate analysis where the resulting p values (those <0.05) were considered statistically significant. A rule of 10 events per variable was employed to construct our multivariate model and backward stepwise regression analysis was used to reveal the risk factors for severe deficits present. During preliminary analysis, it was discerned that type of surgery and tumor laterality were highly correlated and hence they were not analysed in the same multivariate model.

3. Results

A total of 147 patients underwent neuropsychological assessment (NPA) during this period. Excluding 5 cases where only 1 domain was tested, a total of 142 cases were included in the final analysis (Fig. 1). Radiology was available in 124 cases and 132 underwent surgery.

Table 2 depicts the demographic and clinico-radiological characteristics of the patients as well as comparison of the features in the awake and general anesthesia cohorts. The mean age of the patient group was 42.7 years, predominantly males (68.3%) and having at least a basic schooling education (90%) Most of the patients were right-handed (96.5%) with no prior oncological treatment (78.9%). Neurological deficits at presentation were seen in less than a third of the patients. More tumors were left sided and multiple lobes were involved in 40% of the cases, with the frontal lobe being the predominant lobe involved. The average tumor volume was 89 cc. Gliomas constituted the most common histological type (90%).

The awake cohort had more left sided tumors and a larger proportion of low-grade gliomas which were IDH mutant. Tumors in the awake (GA) cohort were more often located in the insular lobe. Right-sided tumors were more likely to show preoperative motor deficits. Most patients (92%) had at least four major domains tested. The patients undergoing awake surgery were more likely to have multiple domains tested.

3.1. Neurocognitive function (NCF) outcomes

Overall, 90.8% had severe NCD and almost all patients (99.3%) had some form of NCD ("any deficit" which included mild-moderate deficits also) (Fig. 2). Memory, attention & EF, and visuomotor speed were the most affected domains, a significant proportion of them being severely affected. Language was also commonly affected, but severe deficits were fewer. The NCDs were multi-domain in nature (Fig. 3). The median GHQ-12 score was 5 (Mean 4.3, SD 2.7). 60% of the patients had a normal GHQ (less than 6). There were no differences in the mean GHQ scores between awake and GA groups as well as between right and left-sided tumors.

Since mild-moderate deficits are variably defined in literature (and may overlap with the spectrum of normal neurocognitive function), further analysis was restricted to the severe NCDs. We explored if the occurrence of severe NCDs varied depending on the number of domains tested (Fig. 4) and found it to be similar irrespective of whether three, four or five domains were tested(90–100%) and slightly lower (80%, not significant) when only two domains were. Details of individual test dysfunction are provided in Supplementary Table 3.

3.2. Factors affecting neurocognitive dysfunction

The effect of various clinical, demographic, and tumor-related factors on severe NCD was evaluated. Results of a similar analysis for "any deficits" is shown in supplementary material (Table 2 and Fig. 1). Table 3 shows the factors associated with severe domain dysfunction on univariate analysis. The strength of association of each of the significant factor are provided in the additional supplementary material.Generally, younger, well educated patients, low grade tumors, smaller tumor volumes and those without preoperative neurological deficits or raised ICP were less likely to have NCDs across domains [Table 3]. Tumor laterality

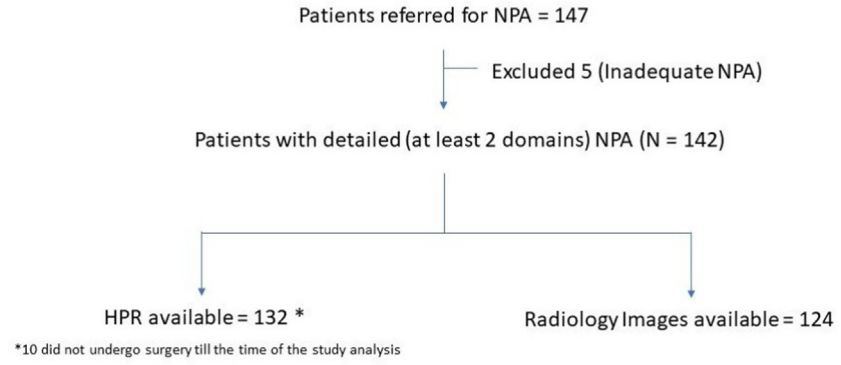

Fig. 1. Schematic outline of the study cases included for individual level analyses of neurocognitive function (NCF) outcomes in the study.

Table 2
Demographic and clinico - radiological characteristics of the group.

Sr. No	Variables	Overall (n = 142; %)	Type of surgery (n = 132) [10 patients did not undergo surgery]			Tumor laterality (n = 141) [In 1 patient radiology review was not available]		
			Awake (n = 69)	GA (n = 63)	p value	Left (n = 89)	Right (n = 52)	p value
1.	**Type of surgery**				–			**<0.001**
	Awake		-	-		54 (64.3)	15 (31.9)	
	GA		-	-		30 (35.7)	32 (68.1)	
2.	**Age (in years) [Mean (SD)]**	42.7 (13.6)	38.9 (11.1)	46 (15.1)	**<0.001**			0.32
3.	**Gender**				0.86			0.93
	Male	97 (68.3)	47 (68.1)	42 (66.7)		61 (68.5)	36 (69.2)	
	Female	45 (31.7)	22 (31.9)	21 (33.3)		28 (31.5)	16 (30.8)	
4.	**Education (in category)**				0.49			0.33
	Illiterate	15 (10.6)	7 (10.1)	8 (12.7)		12 (13.5)	3 (5.8)	
	School educated	52 (36.6)	30 (43.5)	21 (33.3)		30 (33.7)	21 (40.4)	
	College educated	75 (52.8)	32 (46.4)	34 (54.0)		47 (52.8)	28 (53.8)	
5.	**Handedness**				1.00			0.55
	Right	137 (96.5)	67 (97.1)	61 (96.8)		85 (95.5)	51 (98.1)	
	Left	3 (2.1)	1 (1.4)	1 (1.6)		2 (2.2)	1 (1.9)	
	Ambidextrous	2 (1.4)	1 (1.4)	1 (1.6)		2 (2.2)	0 (0)	
6.	**Prior treatment**				**0.02**			0.69
	Yes	30 (21.1)	9 (13.0)	19 (30.2)		18 (20.2)	12 (23.1)	
	No	112 (78.9)	60 (87.0)	44 (69.8)		71 (79.8)	40 (76.9)	
7.	**Pre-operative deficits**				**<0.001**			**<0.001**
	Motor	23 (16.2)	4 (5.8)	17 (27.0)		8 (9)	15 (28.8)	
	Speech	13 (9.2)	4 (5.8)	8 (12.7)		12 (13.5)	1 (1.9)	
	Both	9 (6.3)	4 (5.8)	5 (7.9)		6 (6.7)	3 (5.8)	
	None	97 (68.3)	57 (82.6)	33 (52.4)		63 (70.8)	33 (63.5)	
8.	**No. of lobes involved**				0.36			0.89
	Single	83 (58.9)	38 (55.1)	39 (62.9)		52 (58.4)	31 (59.6)	
	Multiple	58 (41.1)	31 (44.9)	23 (37.1)		37 (41.6)	21 (40.4)	
9.	**Individual lobe involved***							
	Frontal	82 (58.2)	44 (63.8)	34 (54.8)	0.30	50 (56.2)	32 (61.5)	0.53
	Parietal	39 (27.7)	19 (27.5)	17 (27.4)	0.99	26 (29.2)	13 (35)	0.59
	Temporal	63 (44.7)	33 (47.8)	26 (41.9)	0.50	43 (48.3)	20 (38.5)	0.26
	Occipital	6 (4.3)	0 (0.0)	3 (4.8)	0.10	4 (4.5)	2 (3.8)	1
	Insular	39 (27.7)	26 (37.7)	12 (19.4)	**0.02**	25 (28.1)	14 (26.9)	0.88
10.	**Tumor laterality**				**<0.001**			–
	Left	89 (63.1)	54 (78.3)	30 (48.4)		–	–	
	Right	52 (36.9)	15 (21.7)	32 (51.6)		–	–	
11.	**Histology (n = 132)**				**<0.001**			0.30
	Low grade glioma	66 (50.0)	50 (72.5)	16 (25.4)		47 (56)	19 (40.4)	
	High grade glioma	53 (40.2)	15 (21.7)	38 (60.3)		30 (35.7)	23 (48.9)	
	Metastases	4 (3.0)	3 (4.3)	1 (1.6)		3 (3.6)	1 (2.1)	
	Others	9 (6.8)	1 (1.4)	8 (12.7)		4 (4.8)	4 (8.5)	
12.	**IDH Mutant (n = 115)**				**<0.001**			0.20
	Positive	64 (55.7)	45 (72.6)	19 (35.8)		45 (60)	19 (47.5)	
	Negative	51 (44.3)	17 (27.4)	34 (64.2)		30 (40)	21 (52.5)	
13.	**No. of domains tested**				**0.04**			0.88
	2	15 (10.6)	3 (4.3)	12 (19)		10 (11.2)	5 (9.6)	
	3	3 (2.1)	1 (1.4)	2 (3.2)		2 (2.2)	1 (1.9)	
	4	21 (72.5)	10 (14.5)	11 (17.5)		14 (15.7)	6 (11.5)	
	5	103 (72.5)	55 (79.7)	38 (60.3)		63 (70.8)	40 (76.9)	
14	Lesion Volume (cc) ***n* = 124** [Median, IQR], (SD)	88.89 [47.23–133.15], (58.23)	90.47 [50.71, 130.35], (54.85)	90.00 [50.27, 147.32], (63.63)	0.63	89.29 [50.59, 134.58], (59.72)	85.99 [44.24, 129.54], (55.68)	0.59

GA – General anesthesia, SD – Standard deviation, IQR – Inter-quartile range, IDH – Isocitrate dehydrogenase.
* Numbers do not add up to 100 as more than 1 lobe was affected in many patients.

did not influence the domains affected. Patients undergoing awake surgery [Fig. 5a] had better performance in memory and language domains but had a similar quantum of deficits as the GA cohort in the other domains. The type of surgery did not affect the NCF, rather the presence or absence of significant deficits could have influenced the selection of the type of surgery. Laterality of the tumor did not seem to impact the NCF [Fig. 5b].

On multivariate analysis (Table 4) younger age, better education and smaller tumors were independent predictors of better NCF across domains. Tumor location was significant only for language with temporal lobe tumors showing more deficits in this domain. Lower grade histology was associated with lower language deficits; males had better visuomotor performance and prior treatment seemed to cause more memory deficits. Tumor laterality did not influence domain dysfunction. There was no difference in the domain deficits and the type of surgery performed (awake versus GA) except language which was significantly better in the awake cohort. No factor was significantly associated with overall NCF.

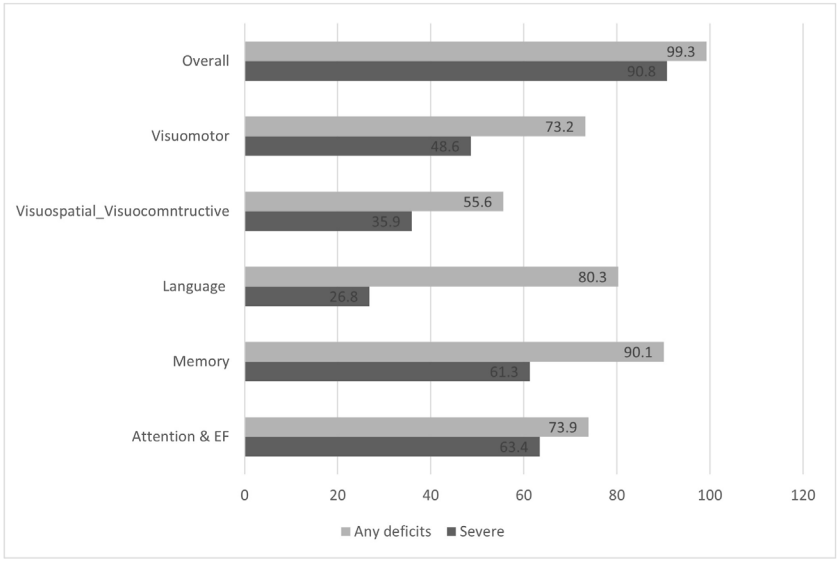

Fig. 2. Distribution of neurocognitive dysfunction (both severe and any) depicted for each domain and overall Neuropsychological assessment (NPA).

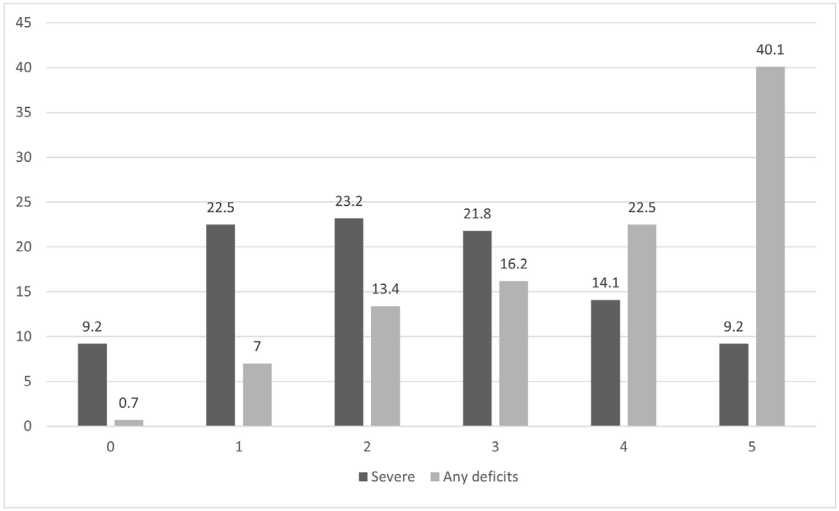

Fig. 3. Distribution of neurocognitive deficits based on the number of domains affected.

4. Discussion

Our study shows that global multi-domain neurocognitive dysfunction is widely prevalent in patients with brain tumors in the Indian population. NCF is an important outcome indicator in the treatment of brain tumors and is increasingly being adopted as an endpoint in many trials in neuro-oncology, particularly those evaluating the role of radiotherapy. The prevalence of dysfunction prior to any treatment has been less studied. NCF before surgery (or any oncological therapy) predominantly reflects the effect of the tumor itself. Over the last decade, data on NCF at baseline is slowly accumulating.[2,18–21] These reports highlight the prevalence of significant neurocognitive deficits (NCD) at the time of presentation. There remains variability in the tools used to assess NCF.[3] Moreover, geographical, ethnic and socio-economic factors may influence the prevalence of NCD in brain tumor patients leading to significant heterogeneity in reported literature.

Data on NCF at baseline in the Indian population is scarce. Most studies reporting NCF have done so in the postoperative setting prior to adjuvant therapy.[22–25] NCDs in such patients may be mistakenly attributed to the surgical intervention. In the preoperative setting, Borde et al assessed prevalence of frontal lobe disfunction in 50 patients using the frontal assessment battery (FAB) and reported 76% dysfunction.[26] Global NCF was however not evaluated. With our current understanding of brain networks, domain dysfunction is less likely to be location specific though preponderance of network connections within specific lobes may lead to apparent location-specific dysfunction in certain domains. Our data now shows that multi-domain (three or more) severe NCD can be found in almost 70% of all patients preoperatively, even when majority of them have no overt neurological deficits. Including those with even one or two domains affected, 90% had severe NCD. This underlines the burden of true functional deficits which are often underestimated and unreported. A comprehensive review of NCF at baseline, showed a prevalence of severe NCD in 62.5% patients.[2] One of the largest studies reporting baseline NCF revealed 48.6% severe NCD.[21] Not only was the proportion of overall NCD high in our study, but almost 70% of the severely affected patients had multi-domain dysfunction (Fig. 3). The higher rate of NCD in our study could be due to the larger volumes of tumors in our population (89 cc) and late presentation compared to the populations reported in other studies. The tumor volumes could also have been higher because we included all T2/FLAIR abnormality in calculating lesion volume as has been described in a couple of papers,[2] though some studies exclude the edema component.[27] It is often very difficult to differentiate edema

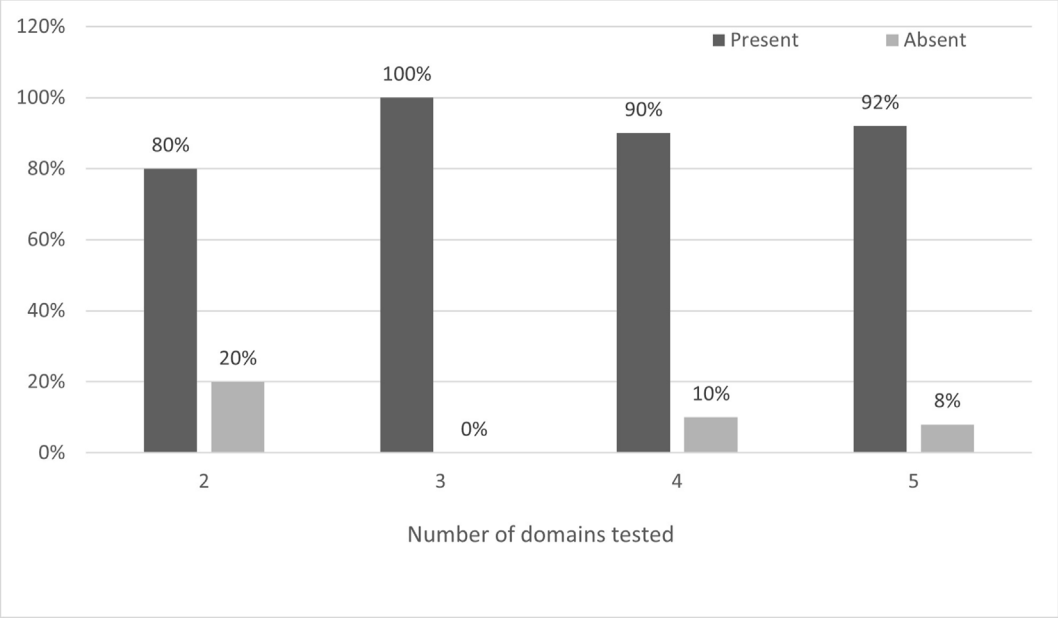

Fig. 4. Correlation of severe neurocognitive dysfunction with the number of domains tested.

Table 3
Factors affecting neurocognitive outcomes (only severe deficits) and the corresponding *p* values on univariate analysis. The factors with *p* values < 0.2 which were included in the multivariate models are highlighted in bold.

	Attention & Executive	Memory	Language	Visuoconstructive & Visuospatial	Visuomotor speed	Overall NCF
Type of surgery	0.78	**0.02**	**<0.001**	0.64	0.69	0.87
Age	**<0.001**	**0.05**	**<0.001**	**0.02**	**<0.001**	0.24
Gender	0.21	**0.18**	**0.09**	0.28	**0.01**	1
Education category	**0.08**	0.30	**0.01**	0.65	**<0.001**	0.80
Handedness	0.68	0.92	0.53	0.44	0.28	0.31
Prior treatment	0.58	**0.01**	0.23	0.69	0.75	0.30
Preoperative seizures	**0.04**	0.20	**0.005**	0.98	0.18	0.39
Preoperative raised ICP	0.11	**0.03**	**0.004**	**0.06**	**0.02**	0.13
Pre-operative deficits	0.29	**0.05**	**0.01**	**0.01**	**0.03**	0.25
No. of lobes involved	0.83	**0.1**	0.89	0.33	0.36	0.33
Frontal	0.31	0.77	0.33	1	**0.11**	0.36
Parietal	0.71	0.32	0.49	0.72	0.66	1
Temporal	**0.11**	0.82	**0.06**	**0.15**	0.54	**0.20**
Occipital	0.62	1	0.67	1	1	0.45
Insular	0.62	0.22	0.97	0.86	0.34	1
Tumor laterality	**0.18**	0.46	0.81	0.39	0.29	0.90
Histology	0.29	0.49	**<0.001**	**0.16**	**0.01**	0.93
IDH type	0.52	0.77	**0.01**	**0.13**	**0.05**	0.71
Lesion volume	0.52	0.97	**0.002**	**0.03**	**0.02**	0.39

from infiltrating tumor and regardless of the pathological nature of the radiological abnormality, all of it is likely to affect the function and hence can be regarded as the offending "lesion". Including even subtle NCDs, our population showed 100% dysfunction. Similarly, higher levels of subtle dysfunction have also been reported by other studies.[2,3,5,19,20] Many studies using NPA batteries with normative scores use a cutoff of z scores less than two standard deviations (SD) as severe dysfunction. The definition of mild or moderate deficits is more ambiguous.[3] The clinical implication of such subtle deficits is also not very clear. Further, though it is recommended to use NPA tests with normative data wherever possible, there are often tests where normative data is not available and hence dysfunction is assessed semi-quantitatively as was done for evaluating language in our study where a modified picture naming test was used.[12] In such a situation, a severe deficit is less likely to be incorrectly defined. Nonetheless, it must be highlighted that developing and using tests with validated psychometric properties and normative data for the population specific to the study is important. Normative data is essential when calculating group level scores.[2,3] However, group level scores are of questionable value in a heterogeneous population of patients with brain tumors. They tend to exaggerate the NCD.[28] In some studies, group level scores of certain subsets of patients (like low grade gliomas) have even been reported as being above normal at baseline.[29] Therefore, rather than group level scores, the percentage of affected individuals (or individual level scores) is more meaningful. Moreover, when evaluating serial NCF over time, group level scores have been seen to be less sensitive and may not reflect changes in individual patients.[28] For tailoring neurocognitive rehabilitation too, it is imperative to know individual scores rather than group level scores.

NPA batteries which incorporate multiple domains are most suitable to assess NCF. In a large review, van Kessel et al included only studies where at least two domains were tested.[2] The more the number of domains that are tested, the higher the chance of picking up a NCD. In our study, we found that when 2 or more domains are tested, the incidence of severe NCD is consistent and high. This is probably explained by the fact that the brain does not function in a strictly compartmentalized fashion, and neural substrates of different domains overlap leading to multiple

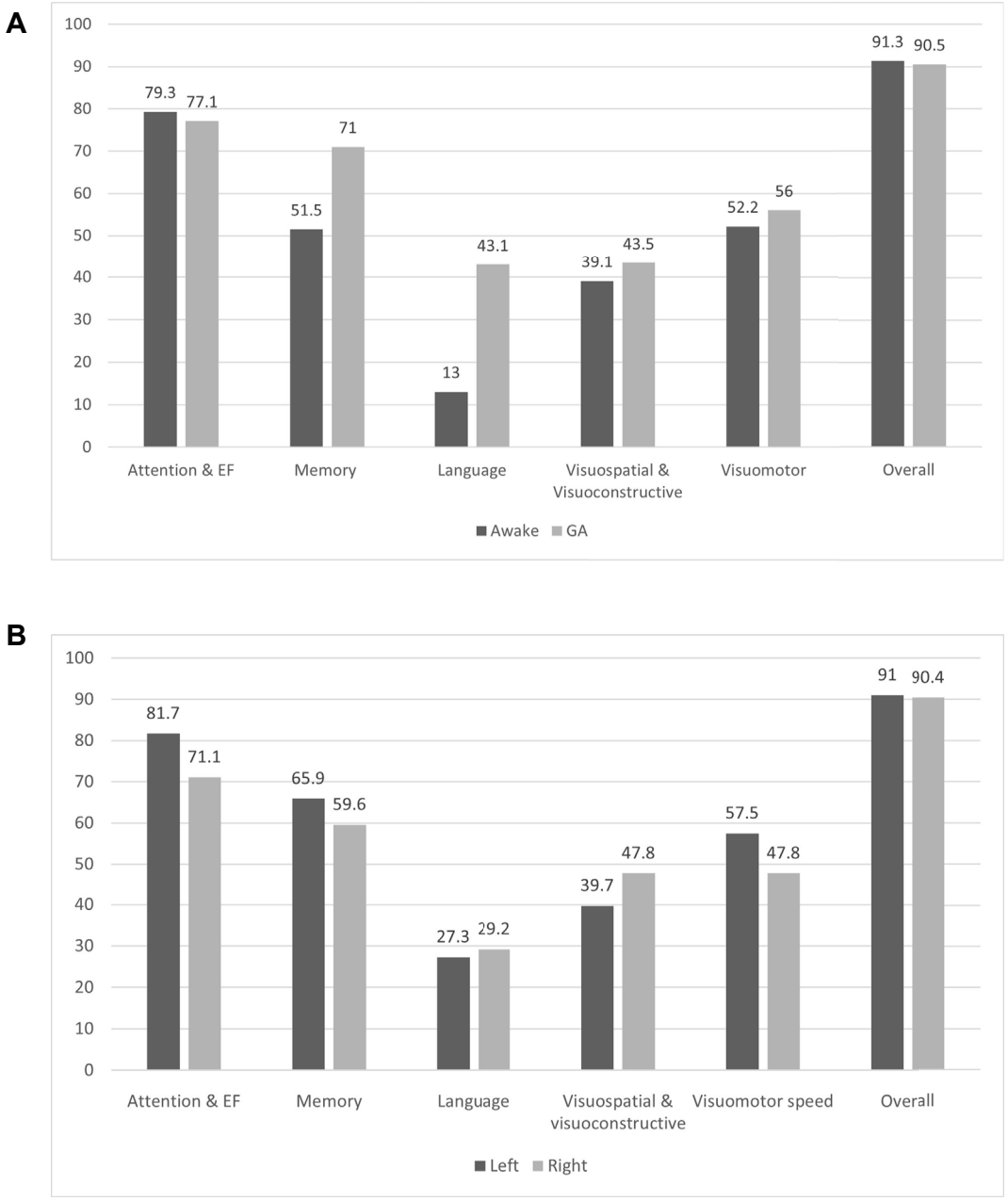

Fig. 5. Distribution of severe neurocognitive deficits between awake and GA groups (a) as well as left and right sided tumors (b).

domain affection by a tumor in a particular location, which could be potentially missed if limited NCF is assessed. This is also important if a tailored rehabilitation program is to be provided to individual patients strategies for rehabilitation differ depending on the type (and severity) of domain dysfunction. Though testing multiple domains is essential, the number of tests per domain may vary and are unlikely to influence the detection of NCD.[29]

Attention & EF as well as memory were the most affected domains in all cases. This is similar to the finding by other larger studies.[2,27] We were keen to understand if NCDs between patients selected for awake surgery and surgery under GA are different. Selection criteria for offering awake craniotomy may vary across centres and therefore patient cohorts may not always be comparable. One of the largest studies of 168 patient by Kessel et al reported significant differences in the profile of patients selected for awake craniotomy compared to those undergoing surgery under anesthesia.[29] Like their experience, we also found that patients undergoing awake surgery were more likely to have lower grade, IDH-mutant gliomas and more often involved the temporal lobes. However, unlike their population where awake surgeries were offered for both right and left sided tumors, in our setup we prefer awake surgery for left sided tumors (though increasingly we now perform awake surgeries even for right sided tumors). In a homogeneous group of low-grade gliomas, it was found that those undergoing awake surgery, more often had IDH mutated tumors and were predominantly left sided.[18] Whether this left sided preponderance introduces a selection bias in such studies, is debatable. Despite these selection biases, there was no significant difference in the overall NCDs as well as deficits in attention, executive function and memory between awake and GA groups. Significant dysfunction in attention & EF as well as memory domains in left sided tumors (many of whom undergo awake craniotomy) can influence the performance on the more commonly mapped functions like language which could be impaired because of these domains being affected. This highlights the interdependence of the various NCF domains and strengthens the case for multi-domain assessment during NPA. However, language deficits were significantly less seen in our awake

Table 4
Multivariate analysis for the various factors affecting individual domain dysfunction.

	AOR	95% C. I	P value
	Attention & Executive		
Age	1.09	1.04 - 1.15	<0.001
Education category (school vs college educated)	5.34	1.56 - 18.23	0.007
	Memory		
Age	1.04	1.00 - 1.06	0.04
Prior Treatment	5.28	1.74 - 15.98	0.003
	Language		
Location (Temporal)	4.58	1.60 - 13.06	0.005
HPR (LGG)	0.24	0.07- 0.75	0.01
Type Surgery (Awake)	0.27	0.09 – 0.85	0.03
Lesion volume	1.01	1.00-1.02	0.01
	Visuo-constructive & Visuospatial		
Lesion volume	1.01	1.00-1.02	0.02
	Visuo-motor speed		
Age	1.08	1.03 - 1.14	0.001
Gender (Male)	0.28	0.08 - 0.91	0.03
Education category (school vs college educated)	7.08	2.39 - 20.99	< 0.001
Lesion volume	1.01	1.00 – 1.02	0.01

AOR – Adjusted Odds ratio, C. I – Confidence Interval

cohort, reflecting a possible preference for patients with intact language function.

Tumor laterality and location has been traditionally thought to influence the specific NCF domains affected.[2,29,30] Tumor localization maps provide a probabilistic map of spatial distribution of tumor locations affecting specific domains.[27] Whereas some domains like attention, EF and memory are considered location neutral (though left lateralization has been shown), others like language (temporal) and visuospatial (parietal) functions show a tendency to affect certain locations in different hemispheres. In our study, only language deficits were noted to be significantly more in the temporal lobe tumors though there was no difference between left and right sided tumors. Language deficits occurring in patients with non-dominant (right) hemisphere lesions could be explained by the fact that speech articulatory networks tend to be bilateral, as do the semantic association pathways subserved by the ventral stream.[31] Further, as pointed out earlier, attention & EF dysfunction may impair language assessments and lead to indirect language dysfunction. In addition, while comparing studies, there could be differences in the NPA tests performed for each domain and the criteria (normative cutoff thresholds) used to define dysfunction which could confound the interpretation of results.

Besides tumor location, various other patient and tumor related factors can affect baseline NCF.[19,27,29,30,32] IDH mutant status appears to correlate with NCF, with a lower likelihood of NCDs, probably attributed to the slow rate of growth of these tumors. In our group, IDH mutant tumors were significantly less likely to have language and visuospatial deficits on univariate analysis, though there was no such correlation with these (or any of the other domain) deficits in the multivariate model. Lower grade tumors (diffuse gliomas grades 2 and 3) did show significant lower likelihood of language deficits than grade 4 tumors. This apparent discrepancy between tumor grade and IDH mutant status could be due to the fact that IDH mutation analysis was done in 115 of the 132 cases. Besides tumor type, size has been shown to correlate with NCDs, and in our cohort too language, visuospatial and visuomotor domains were more affected in larger tumors.

Preoperative NCF should be regarded as a baseline marker of function for all clinical studies especially trials evaluating brain tumor therapies. Understanding the various domains that can be affected is important to be able to provide a customized surgical plan for the patient. For example, in patients being planned for awake surgery, existence of severe memory and attention & EF dysfunction would raise a red flag, precluding optimal patient cooperation and the surgical plan could be revisited to consider surgery asleep. Similarly, absence of any major deficits increases the surgical team's confidence in selecting and interpreting responses to domain specific intraoperative tests used for evaluation during awake surgery, Finally, understanding the preop level of dysfunction is crucial to monitor the effect of surgery and subsequent therapies and tailor suitable and customized rehabilitative strategies for the patient.

Limitation of our study: The test battery we used was customized to our patient group. Referral of patients for NPA as well as our preference of awake craniotomy for left sided tumors could have introduced a selection bias. Nevertheless, the inclusion of both left and right sided tumors, including those operated under anesthesia provided us with the opportunity to assess and compare the prevalence of NCD in the cohort of gliomas in the Indian population and by using multivariate analysis to adjust for confounding factors and multicollinearity, we could reach valid inferences.

Conclusion: Our findings suggest that NCF is affected in a large majority of gliomas preoperatively (and is severe in many) even though most of them have no overt neurological deficits. The NCD affects multiple domains especially attention & EF and memory which are location-neutral domains. Cases selected for awake craniotomy can have dysfunction in these domains and this needs to be carefully borne in mind while preparing these patients and testing them intra-operatively. Language deficits were less prevalent overall, especially in lower grade tumors and non-temporal locations; though right sided tumors also exhibited language deficits making a case for awake mapping in right sided tumors. Older age, lower educational status and larger tumor volume contribute to multi-domain dysfunction. Routine comprehensive neuropsychological assessment is crucial to unearth the true burden of deficits and to tailor treatment as well as to institute domain-specific rehabilitative measures.

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CRediT authorship contribution statement

Aliasgar Moiyadi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. **Kanchi Jain:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Prakash Shetty:** Data curation, Methodology, Writing – review & editing. **Keerthi Radhakrishnan:** Data curation, Methodology, Writing – review & editing. **Pallavi Rane:** Formal analysis, Methodology. **Parthiban Velayutham:** Data curation, Methodology, Writing – review & editing, Data curation, Methodology, Writing – review & editing.

Declaration of competing interest

I, Aliasgar Moiyadi, certify that this manuscript titled "Baseline neurocognitive dysfunction is ubiquitous in intrinsic brain tumors– results from a large Indian cohort of patients and analysis of factors associated with domain-specific dysfunction." is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium On behalf of the authors, I state that there are no Conflicts of Interests to declare.

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Appendix A. Supplementary data

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Abbreviations

NCF – Neurocognitive function
EF – Executive function
NCD – Neurocognitive deficit
GA – General Anesthesia
ClinROM – Clinician reported outcome measures
GOS – Glasgow outcome score
PROM – Patient reported outcome measures
QOL – quality of life
PerfOM – Performance outcome measures
NPA – Neuro psychological Assessment
ACE – Addenbrooke's Cognitive Examination
GHQ – 12 - General Health Questionnaire – 12
SD – standard deviation
EMR – Electronic medical record
PACS – Picture archiving and communications system
FLAIR – fluid attenuated Inversion recovery
IQR – interquartile range
IDH – Isocitrate dehydrogenase

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