NEUROCOGNITIVE FUNCTION AFTER CHEMO-RADIOTHERAPY FOR HEAD AND NECK CANCER - PROSPECTIVE STUDY

A dissertation submitted to

The Tamilnadu Dr. M.G.R. Medical University, Chennai,

In partial fulfillment of the requirements for the award of the degree of

DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY - April 2016

CERTIFICATE

This is to certify that this dissertation titled, **"NEUROCOGNITIVE FUNCTION AFTER CHEMO-RADIOTHERAPY FOR HEAD AND NECK CANCER PROSPECTIVE STUDY"** is a bonafide record of the work done by DR.HARIPRIYA.K, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of her postgraduate study for the degree of M.D. (Branch XI – Radiotherapy) from 2014-2015 under my direct guidance and supervision.

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- Dr.K.Haripriya

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ABSTRACT

AIM:

To assess and understand the impact of chemo-radiation in head and neck cancer on Neurocognitive function, and to determine the parameters to reduce treatment-related neurotoxicity. Neurocognitive function has been assessed with NIMHANS neuropsychological battery.

MATERIALS AND METHODS:

Patients who received chemo radiation for head and neck cancers have been studied in two groups, one as study arm and other as control arm. Study was done exclusively for IMRT planning technique. Both the arm included cisplatin chemotherapy. Study arm included patients in which hippocampal region received radiation and the subsets included nasopharynx, hypopharynx, oropharynx and supraglottic larynx. The control arm had patients who did not receive dose to hippocampal region and the subsets included are tongue, buccal mucosa, lip and larynx. Initial assessment and patient were selected based on mini mental stateexamination. NIMHANS neuropsychological battery was used to assess the

performance for each individual and this battery consists of 5 kinds of test in which each have different subsets.

RESULTS:

Neuropsychological assessment was done before the start of treatment and 12 weeks after completion of chemo radiation. It was found that in the control arm, the dose to the hippocampus was <12Gy (tolerance dose of hippocampus) for all the patients, whereas in the study arm, 7 patients received >12Gy to the hippocampus region. After neuropsychological assessment, it was found that cognitive impairment was present in 63-65% in study group for patients those who received >12Gy to the hippocampus and 36% for those who receive RT 10-12Gy. There was no significant variation in the control group.

CONCLUSION:

This study has shown that there is impairment in neurocognitive function of patients, receiving more than the tolerance dose to the hippocampus. It reflects that dose to hippocampus region plays an important factor in determining the memory of an individual.

INTRODUCTION:

Head and neck cancer is the fourth most common cancer worldwide. Its incidence is increasing in the recent years, due to an epidemic of infection with the increase in the human papilloma virus. The change in the epidemiology of head and neck cancer for the past decades in other countries has resulted in an increased incidence of younger generations presenting with curable disease .These epidemiological changes provide to significantly improve the patient overall outcomes .The need for the enhanced potential for curative treatment and efforts to minimize the long-term morbidities is associated with radical treatment .

Most of the patients with head and neck cancer present with locally advanced disease have no of evidence of distant metastases and are being treated with multimodality treatment to locoregional site. Multimodality approach that is combination of surgery, radiotherapy and chemotherapy is being used to control and cure the disease along with preservation of organ function.

Radiotherapy has a major role in the management of head and neck cancer and most of the patients will undergo radiotherapy, with or without or concomitant chemotherapy. The morbidity which is been associated with radiotherapy to the head and neck relates to the dose to the normal tissues and organs surrounding the

tumor target volume. Mostly they are associated with cervical lymph node metastases and mostly it lies in close proximity to the brain and other central nervous system structures, a portion of the volume of these organs lies in the path of target volume and beams used to deliver radiotherapy.

Radical radiotherapy plan delivers some radiation dose to the CNS regions mostly to basal frontal lobes, pituitary, temporal lobes, hypothalamus, olfactory bulbs, brainstem and cerebellum. The dose delivery to the CNS region depends on the location of the primary tumor.

ORIGIN OF PROPOSAL:

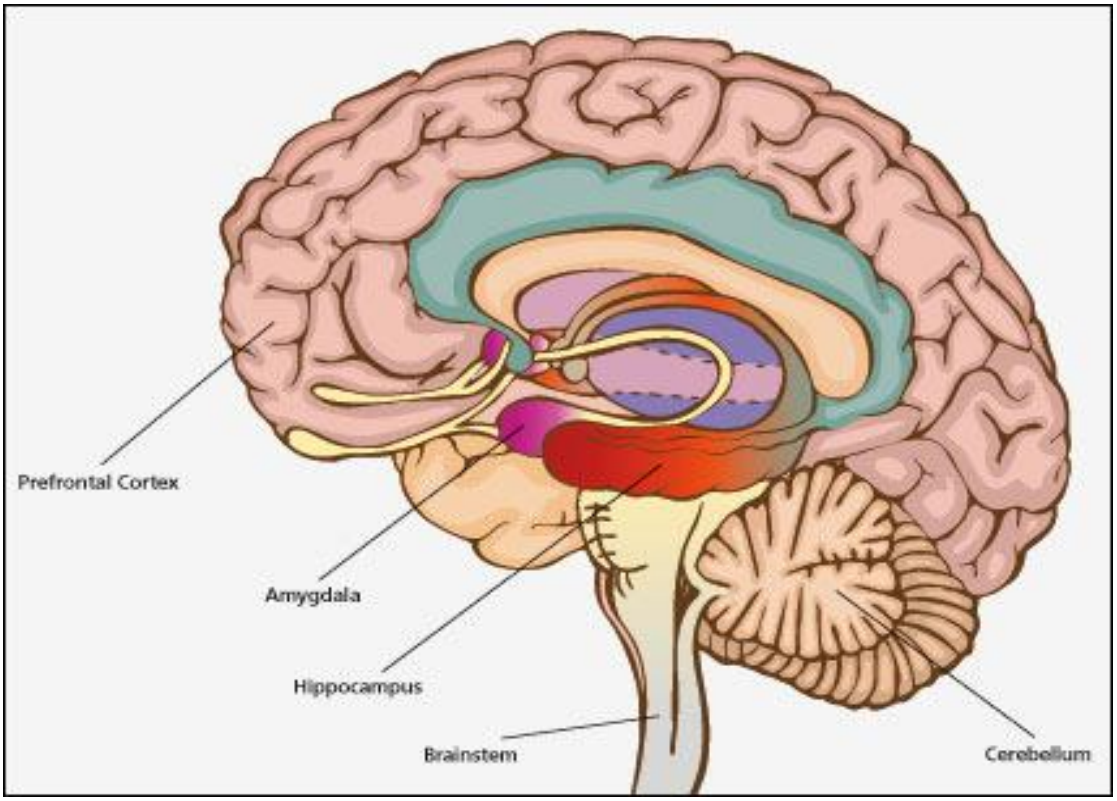
Radical radiotherapy has a major role in the management of head and neck cancer with sparing of the normal critical organs. Some patients treated with radical radiotherapy for head and malignancies receive little amount of radiation doses to large volumes of the brain tissue. The increase in the use of chemo radiotherapy for head and neck malignancies has additionally exposed this patient population to potential neurotoxicity of cytotoxic drugs.

Patients with head and neck malignancies may be at risk for the adverse late brain effects after chemo radiotherapy such as impaired neurocognitive function (NCF).It is necessary to understand the impact of chemo radiotherapy forhead and

neck malignancies on neurocognitive function, and to analyze what measures can be taken to minimize treatment related neurotoxicity.

ANATOMY OF HIPPOCAMPUS:

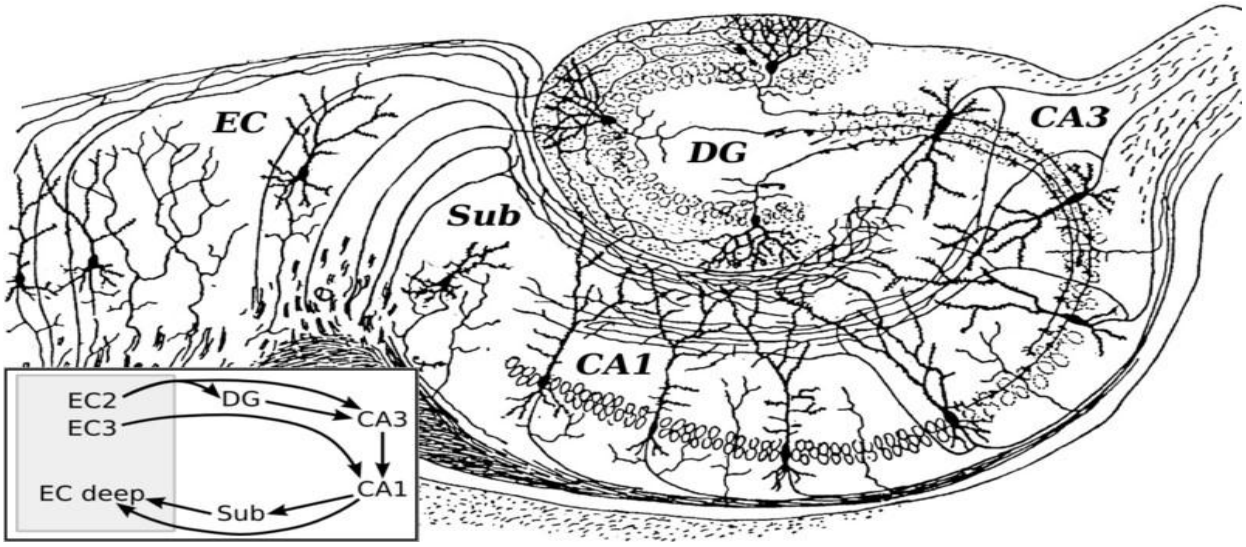
HIPPOCAMPUS is one of the brain structure situated in the medial temporal lobe, underneath the cortical surface of the brain .It can be classified intodifferent zones where the cortex mediates into a single layer of densely packed neurons, which gives a tight S shaped structure. It belongs to the group of limbic system (limbus meaning border) and it has an important role in long term memory and spatial navigation.



Hippocampus is a paired structure which is located both on left and right sides of the brain. Subsets include hippocampus region, cortex region into cingulate and olfactory and amygdala. It is divided into ventral and dorsal compartment, but are different inneural circuits.In human brain or on a monkey's brain, it indicates part of the hippocampus at the bottom, nearer to the temporal lobe base.

The greatest source of hippocampal input is the entorhinal cortex and is interrelated with other parts ofthe brain. The most prominent input is the outer layer of EC and the prominent ouput is the deep layers of EC.

There is an extra output pathway connecting other cortical areas with the prefrontal cortex, which extends to the lateral septal area. The flow of information is uni-directional inside the layer of hippocampal region. The signal is communicated within a series of tightly packed cell layers, first communicating to dentate gyrus then travelling through CA 3layer and to CA1layer,and then to subiculum layer which is outside the hippocampus to the EC.



Basic circuit of the hippocampus, I :

dentate gyrus. Sub: subiculum. EC: entorhinal cortex

Modulatory input from the serotonin, norepinephrine,dopamine and from nucleus reunions of the thalamus is received by the hippocampus. The median part of

septal area regulates cholinergic and GABAergic fibers to all the parts. The septal area is used in controlling the physiological activity of hippocampus that is destruction of the septal area which terminates the theta rhythm which leads to impairment in certain types of memories.

An adjacent cortical regionof the hippocampus called as the parahippocampus. The EC and also the perirhinal cortex lies next to the rhinal sulcus. Perirhinal cortex has a role in visual recognition and in memory.

When hippocampus gets affected there is a memory loss and disorientation appears as theinitial symptom. They have difficulty to form or remember new memories. The hippocampus in rodents have been studied in detail regarding the spatial memory and navigation.

Different neuronal cells are organized into many layers in the hippocampus. Neural plasticity is called as long term potentiation (LTP) and it was first identified to occur in hippocampus. Long term potentiation is one of the main neural mechanism by which memory is retained in brain.

Initially in the olden days, the hippocampus is ‘the ridge’ running along the floor of the temporal horn of the lateral ventricle, mentioned by the anatomist in 1587 initially as having silkworm appearance then into a seahorse ,Latin – meaning horse and in Greek – meaning sea monster. The German scientist in 1729,

explained the structure difference between seahorse and silkworm appearence. Garengot used the word ‘cornu Ammonis’ which survives in three main histological divisions of the hippocampus as CA 1,CA 2, CA3.

HISTORY:

Historically, in the earliest hypothesis hippocampus was found to be involved in olfaction as its primary function. Over the years hippocampus function have shown the literature related to inhibition, memory and assessment of special memory. The behavioural inhibition theory was proposed by O’Keefe and Nadel and it was famous in 1960’s. It is derived from the justification of two observationsmade, in first that concludes, animals with hippocampus damage tend to be very hyperactive, secondly they find difficulty in learning and inhibits the response which has been learned previously.

The results of surgical destruction of the hippocampus is been related to memory of the hippocampus and was related with a patient named Henry Gustav Molaison. The outcome of the surgery in order to relieve epileptic seizures had severe anterograde amensia and partial retrograde amnesia. Patient was unable to perform further new episodes of memories after surgery and he could not remember any event which occurred before surgery, rather he retained memories which occurred

earlier in childhood days. This case has produced such an enormous interest in the history of medicine.

In the upcoming years other patients with similar complaints have been studied extensively and many sorts of experiments studied regarding the physiological activity have showed changes in synaptic connections in the region of hippocampus. There is an universal declaration that the hippocampus plays an important role in the memory,although some parts remain as controversial.

The third important theory of hippocampus function relates the hippocampus to space. The spatial theory which has been proposed by O'Keefe and Nadel , and were influenced by other theories about "cognitive maps" in human being and animals. The memory theory suggest that spatial coding has an an important role in functioning of the hippocampus.

ROLE IN MEMORY:

Important function in the formation of new memories is guided by hippocampus. Some researchers have suggested that hippocampus is a major part of larger medial temporal lobe, and the memory system is responsible for declarative memory that can be verbalized, these include memory facts in addition to the episodic memory.

Difficulties in forming new memories is related to damage to the hippocampus which is called anterograde amnesia and that is often related to memories which has been formed before the brain damage which is known as retrograde amnesia. Even though the retrograde effect extends some years before the brain damage, in some cases past memories remains the same and the sparing of past memories leads to the consolidation over times which involves the transferring of memories out of the hippocampal regionto other parts of the brain .

The hippocampal damage does not affect only certain type of memories such as ability to learn new things related to motor or cognitive function, for example like playing keyboard instrument, or solving problems. Abilities mostly depend upon on different kinds of memory, such as procedural memory. Patients frequently exhibit ‘implicit’ memory even in the absence of conscious knowledge. Some scientists have differentiated between the conscious recollection,which depends on portions of the medial temporal cortex.

ROLE IN SPATIAL MEMORY AND NAVIGATION:

Studies have been experimented on the moving rats and mice with many hippocampal neurons having ‘place fields’ that is they tend to explodeaction potentials when a rat crosses through a particular part of the environment.The evidence for place cells in primates is not much explored, and it is difficult to

record and sequence the brain activity from freely moving monkeys. Place related hippocampus neural activity have suggested that in monkeys move around inside a room while seated in a movable chair, meanwhileanother study described hippocampal cells that fire in relation to the place a monkey is looking at, rather than the place its body is located.

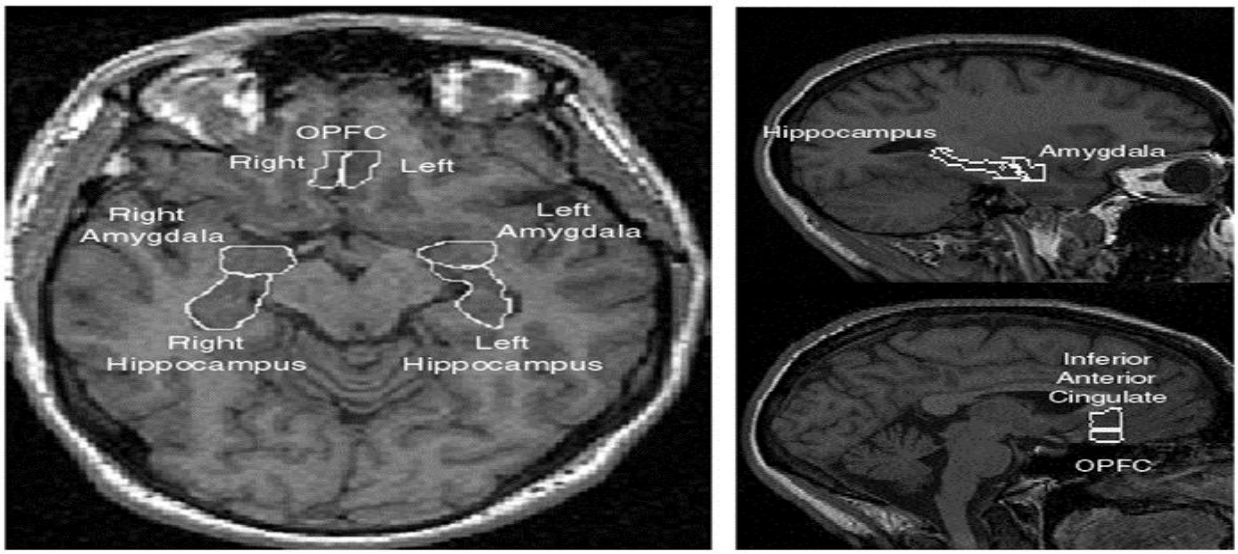
In humans, place cells have been reported in a study of patients had diagnostic electrodes implanted in their hippocampus and then used a computer to move around in a virtual reality town [26].Place cell responses are shown by pyramidalcells in the hippocampus proper and granule cells in the dentate gyrus. These constitute the majority of neurons in densely packed hippocampal layers.

Inhibitory interneurons, which make up most of the remaining population, frequently show significant place related variations in firing rate, but much weaker than slow by pyramidal or granule cells.For representing spatial topography – cells lying next to each other in the hippocampus generally have spatial firing patterns.

Place cells are typically silent when the rat is moving around outside the place fields,but reach sustained rates as high as 40Hz when the rat is near the center. The size of place fields varies in a gradient along the length of the hippocampus, with the cells at the dorsal end showing the smallest fields and cells near the center showing larger fields, and cells at the ventral tip fields that cover the entire

environment and it depends not only on place but also in the direction in which rat is moving, the destination toward which it is travellingor other task related variables.

The origin of place cells in 1970's led to atheory that the hippocampus might act as a cognitive map- neural representation of the layout of the environment.The 'cognitive map hypothesis' has been further studied further for recent advances in discoveries of head direction cells, grid cells, border cells in several parts of the rodent brain that are strongly connected to the hippocampus.



PATHOPHYSIOLOGY OF CONCURRENT CHEMORADIATION:

The mechanisms of radiation induced brain injury is still in research. But a impact is suggestive of multifactorial response involving all the cellular constituents of the brain now emerging from recent preclinical work .The response to brain irradiation depends on the total dose of radiation delivered and the fractionation schedule used.

The increase in the use of concomitant chemotherapeutic agents during radiotherapy caused more side efects, as cytotoxic drugs typically used to treat head and neck malignancies mostly 5-fluorouracil and cisplatin are associated with direct neurotoxicity and blood brain barrier disruption during radiation increases brain exposure to concomitantly administrated platinum drugs .

Four mechanisms of radiation induced brain injury have been proposed by Greene-Schloesser *et al.* (i) depletion of the vascular and glial clonogenic cells, leading to hypoxia, demyelination and white matter necrosis; (ii) impaired neurogenesis is produced due to depletion of neuronal stem cells in the hippocampal dentate gyrus and the sub-ventricular zone; (iii) altered neuronal function leading to altered synaptic plasticity; (iv) neuronal-inflammation secondary to the generation of pro-inflammatory cytokines by glial cells, including microglia and astrocytes.

While these mechanisms dominates radiation induced brain injury presumably depending on individual genetic and treatment factors, at present unknown, and may vary according to which brain structures are irradiated,such that it is conceivable that radiation induced brain injury pathophysiology will vary from patient to patient.

The mechanisms of radiation induced brain injury remain to be controversial, the four mechanisms proposed by Greene-Schloesser *et al.* helped for thinking about the potential strategies to prevent or mitigate RIBI. There is an clear evidence that injury to the hippocampus region have clearly implicated by the pattern of NCF impairment reported in studies of patients treated with radiotherapy for nasopharyngeal carcinoma .The hippocampus is situated within the medial temporal lobe and its function involved with declarative memory and the hippocampal dentate gyrus is also one of two sites of adult neurogenesis. Impaired hippocampal neurogenesis has been directly addressed in preclinical studies by injecting NSC's into rodent brains after radiotherapy, and this man oeuvre has been found to partially restore neurogenesis and hippocampal-dependent neurocognitive function.

Radiation induced neural inflammation has been studied in preclinical experiments testing the neuron protective ability of anti-inflammatory drugs able to cross the Blood brain Barrier, including peroxisome proliferator-activated receptor (PPAR)-α and PPAR-γ agonists, and blockers of the renin-angiotensin system (RAS).

The PPAR-γ agonist, pioglitazone,have been given to rodents before, during and after the whole brain radiation therapy and found to have reduced microglial activation at 30 weeks after radiotherapy and was able to prevent the occurrence of neurocognitive function impairment at 52 weeks after radiotherapy. Interestingly, in these experiments, neither PPAR agonists nor RAS blockade, prevented radiotherapy-induced decreased neurogenesis.

Why to avoid hippocampus area?

The central role of the hippocampus in supporting memory function was first understood more than fifty years ago, in the case study of H.M., a gentleman who underwent a bilateral medial temporal lobectomy for the relief of medically intractable epilepsy. Immediately following the procedure, H.M. showed a severe

anterograde amnesia characterized by impairment in declarative memory (the conscious recollection of facts and events).

H.M.'s amnesia, however, did not include the remaining components of his neuro-cognition, including perception, intelligence, working memory, and motor skill learning, all of which remained largely intact.Building on these observations, subsequent neuropsychology studies of median temporal lobe lesions have demonstrated that declarative memory impairment due to hippocampal injury occurs regardless of the sensory modality in which information is presented and without affecting immediate memory, perception, and intellectual functions.

Recent clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in the neurocognitive decline of patients who received radiation to hippocampal areas. In particular, deficits in learning, memory, and spatial processing observed in patients who have received radiation to whole brain, nasopharyngeal, hypo-pharyngeal area.Moreover, irradiation of the hippocampus has been associated with pronounced cognitive impairment in the learning and memory domain in patients receiving radiation therapy for maxillary tumors, pituitary tumors, and base of skull tumors.However,in recent preclinical work done by Michelle Monje and colleagues and others has begun to challenge this

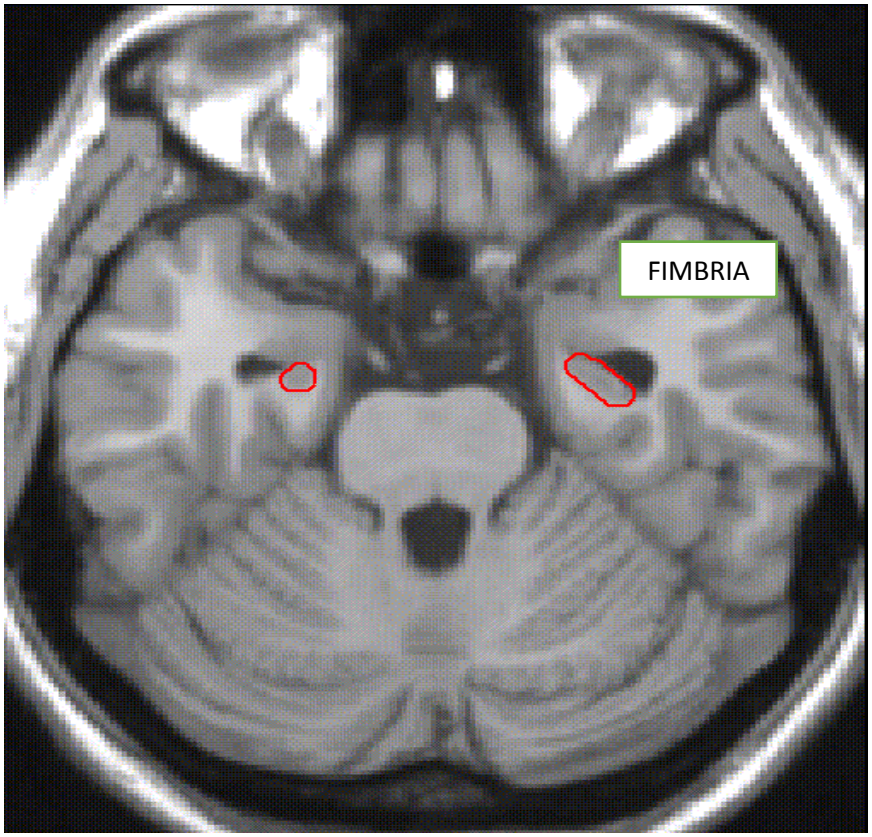
“anatomic” explanation, in the favor of a “stem-cell compartmental” hypothesis. Memory function has been associated with the pyramidal and granule cells which is been located in the dentate gyrus of the hippocampus.

In all adult mammals, including humans, new granule cells are generated from mitotically active neural stem cells (NSCs), whichare located in the subgranular zone of the dentate gyrus and which migrate into the granular cell layer.Monje et al. have demonstrated that the pathogenesis of radiation-induced neurocognitive deficit may involve radiation-induced injury to this NSC compartment.

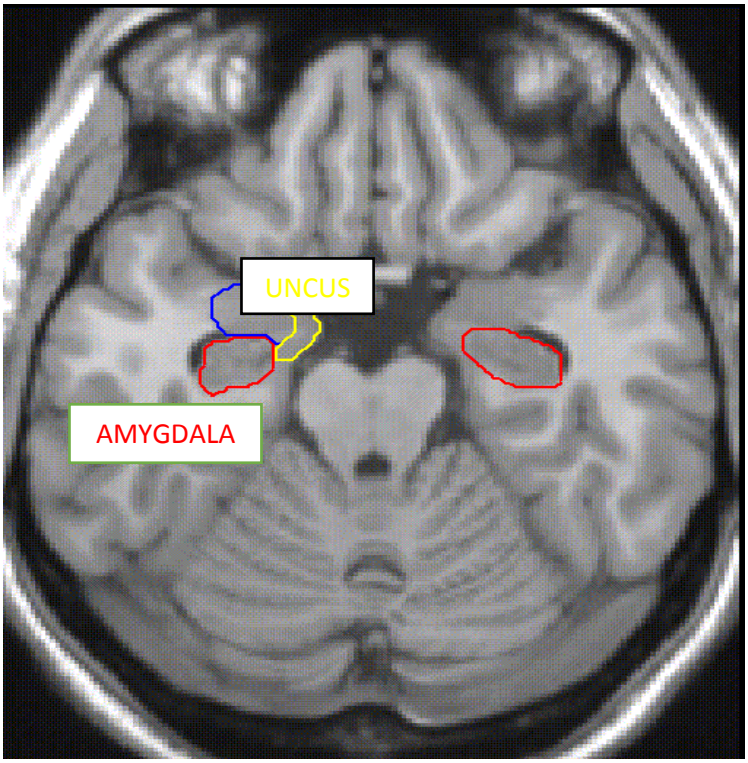
It has been found that relatively modest doses of radiation can cause apoptosis and a sharp and prolonged decline in neurogenesis in the subgranular zone of young rats and mice, and that this compartmental cell loss is associated with extinction of short-term memory, with increasing failure rates on hippocampal-dependent tasks. On the other hand, little to no apoptosis is observed in other areas of the cerebrum and no loss of function is observed in hippocampal-independent tasks.

Contouring of hippocampus:

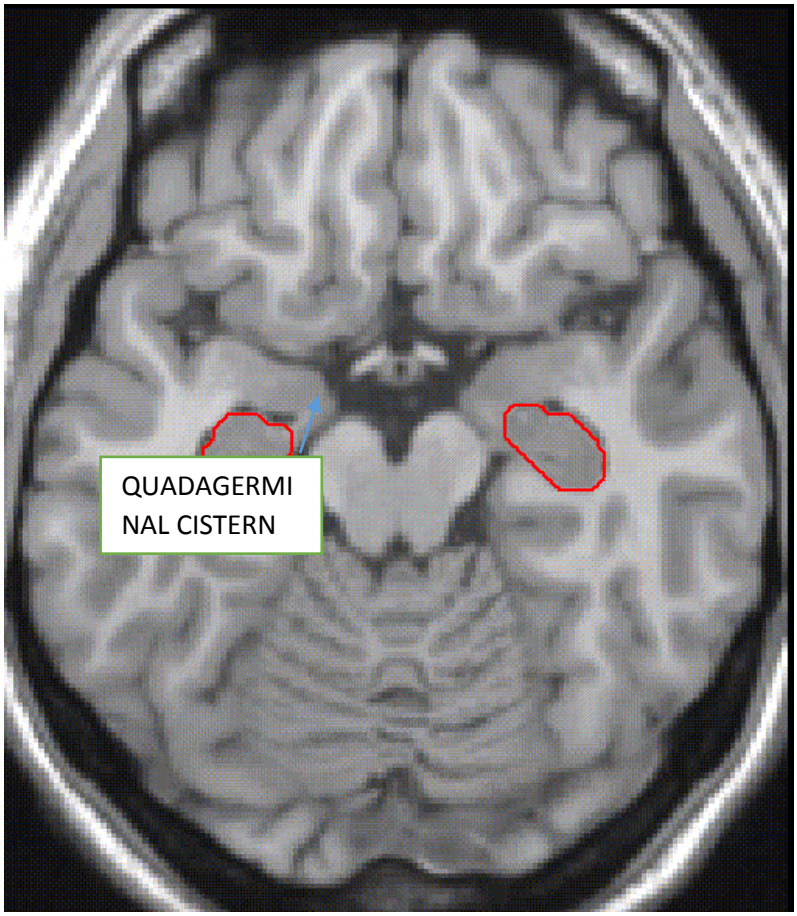
Contouring is done in coronal plane beginning at the most caudal (inferior) extent of the crescentic-shaped floor of the temporal horn of the lateral ventricle and contour the hypointense grey matter located medial to the CSF hypointensity, not the white, bright white matter.Continue contouring in a cephalad (superior) direction, medial to the temporal horn of the lateral ventricle and contour the hypointense grey matter, not the white, bright white matter.



The contours progressively should move in a supero-posterior direction, keeping in line with the curved banana shaped structure of the hippocampus.



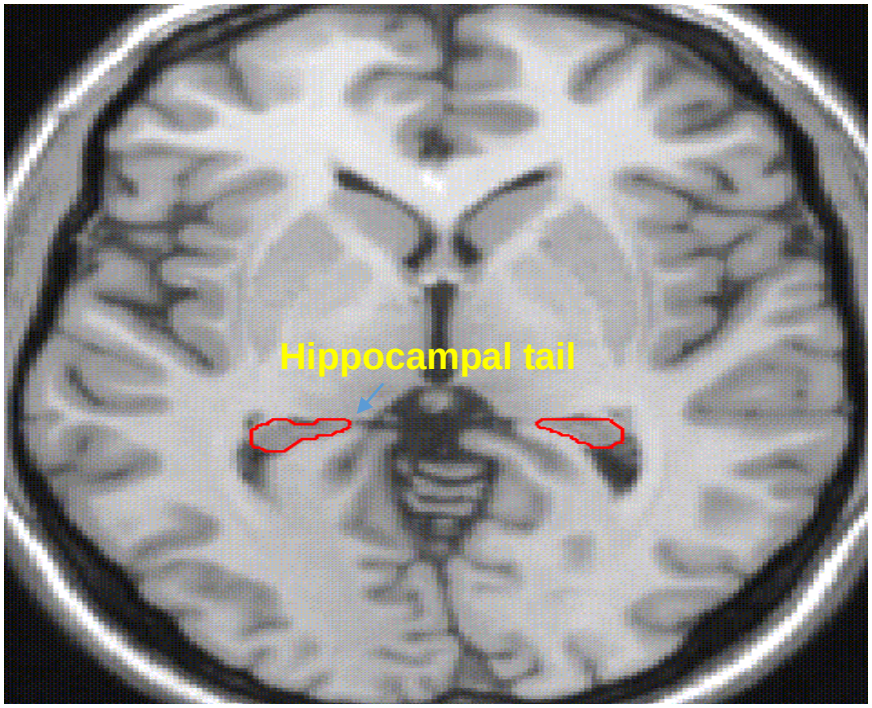
Avoid the fimbriae and also avoid the grey matter (amygdala and uncus) located anterior to the tip of the temporal horn of the ventricles, andcontinued in a cephalad (superior) direction, medial to the temporal horn of the lateral ventricle and contour only the hypointense grey matter, not the white, bright white matter. Continue to avoid the fimbriae and also avoid the grey matter (amygdala and uncus) located anterior to the tip of the temporal horn of the ventricles.



The hippocampus remains medial to the temporal horn of the lateral ventricle throughout its extent, and so on slices where you can visualize it, use it as a consistent reference.

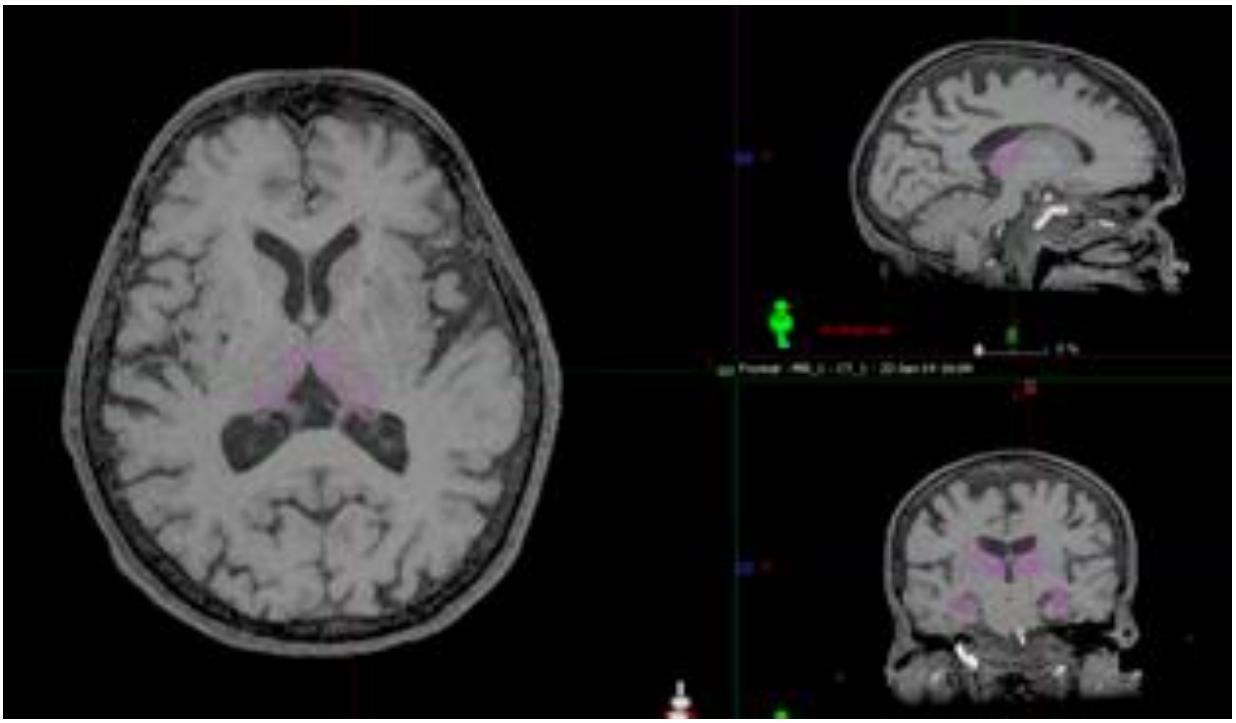
The quadrigeminal cistern remains a good medial landmark.The hippocampal tail remains posterior to the thalamus as it curves medially towards the splenium of the corpus callosum.

Noted that it is still medially located relative to the lateral ventricle. Also note that the thalamus, basal ganglia and the internal capsule now become visible.

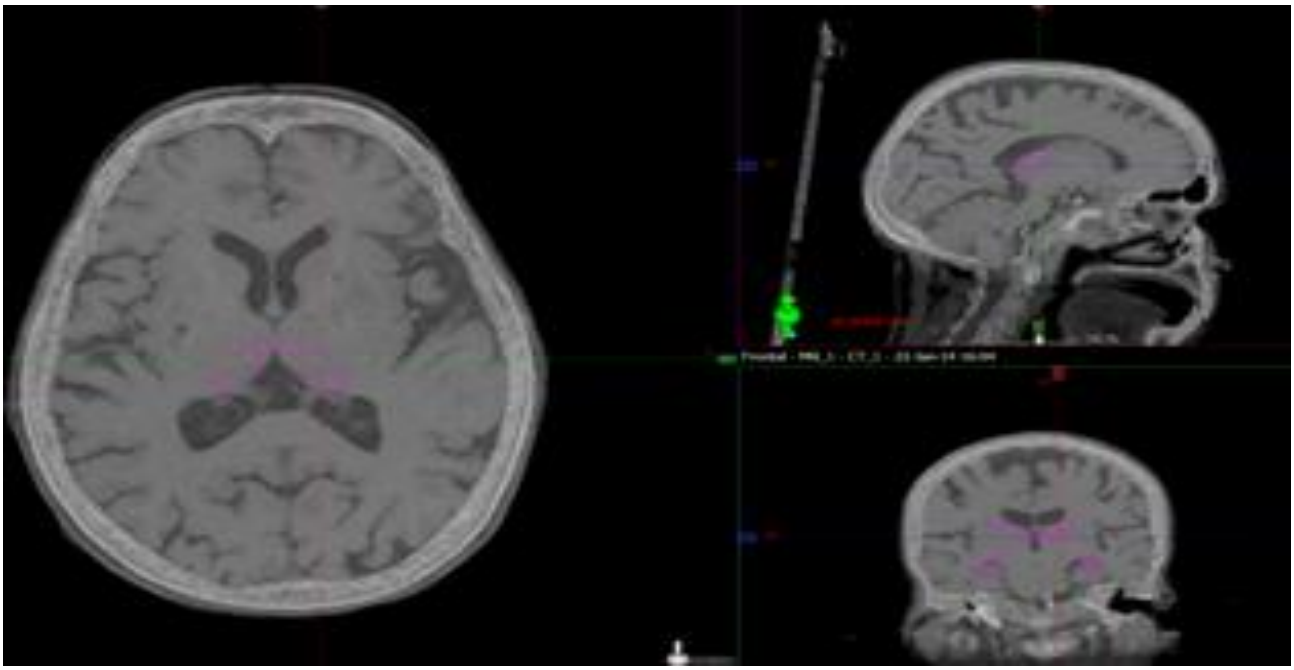


Should terminate hippocampal contours at the point where the T1-hypointense structure no longer borders the atrium of the lateral ventricle. At this point, the crux of the fornix emerges anteriorly and the splenium of the corpus callosum can be visualized posteriorly.

MRI CONTOURING

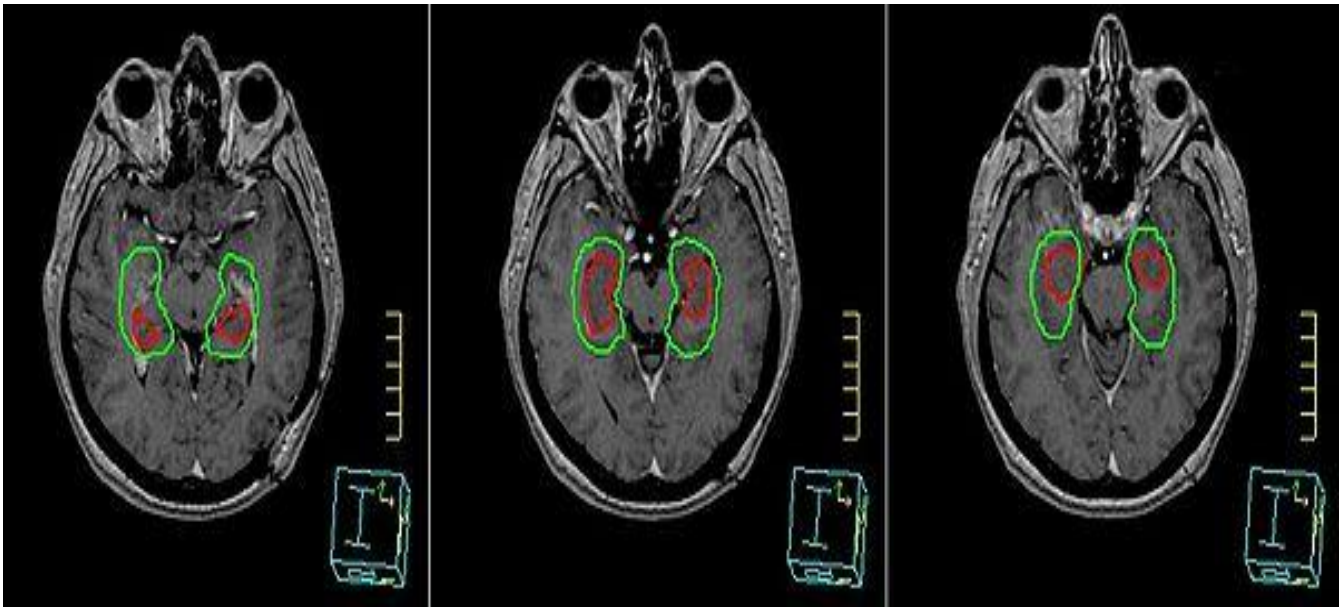


FUSION OF MRI AND CT CONTOURING

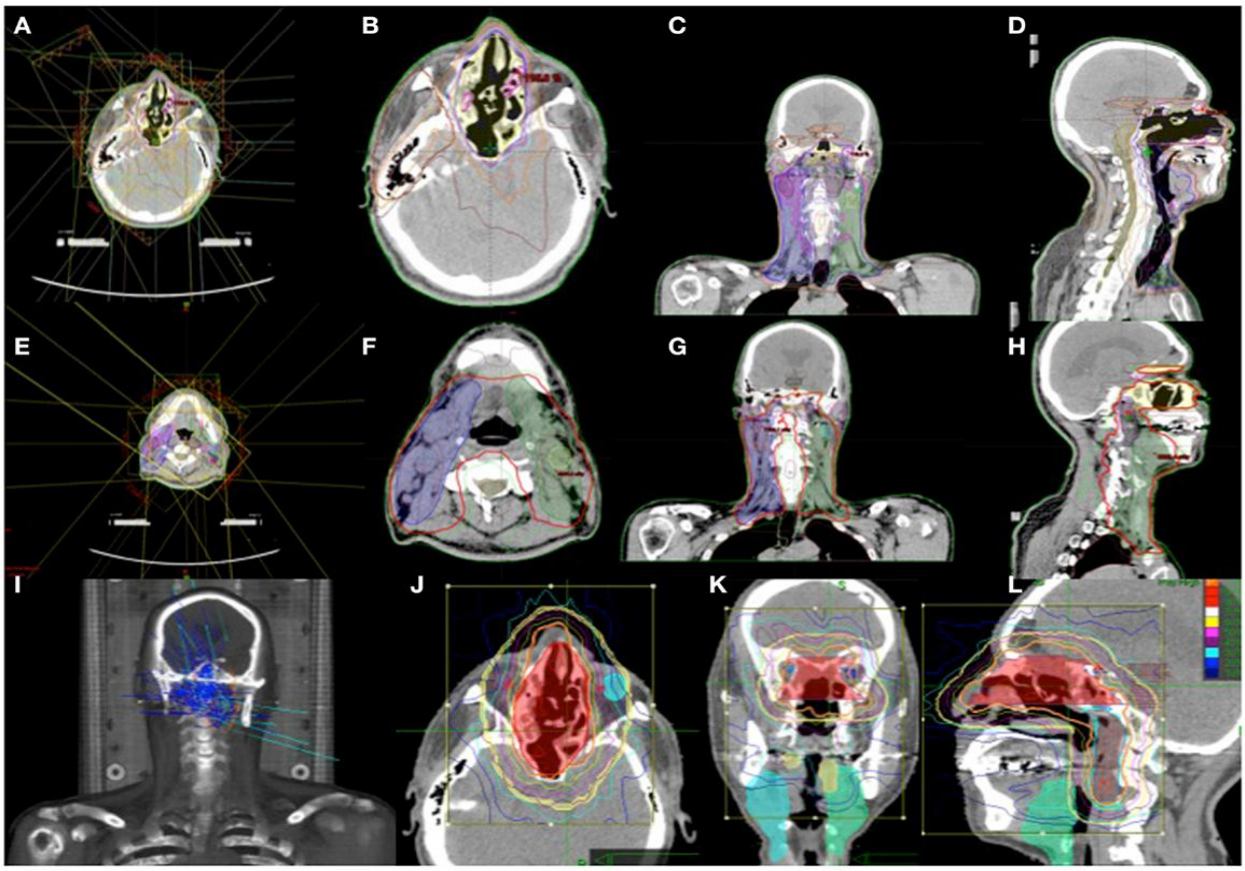


HIPPOCAMUS WITH HIPPOCAMPAL AVOIDANCE

ZONE



NASOPHARYNGEAL CARCIMONA - IMRT



Work Plan:

Aim of the study:

To assess and understand the impact of (chemo)radiotherapy in head and neck cancer on Neurocognitive function, and to analyze what measures can be taken to minimize treatment related neurotoxicity. Neurocognitive function has been assessed with NIMHANS neuropsychological battery.

Methodology/organization of work elements:

Primary Objective:

To assess and understand the impact of (chemo) radiotherapy in head and neck cancer on Neurocognitive function.

Secondary Objective:

1. To assess relationships between neurocognitive function and socio demographic and clinical symptoms.

2. To explore what measures can be taken to minimize treatment related neurotoxicity.

Eligibility criteria:

Inclusion criteria:

Disease characteristics:

1. Histological proven head and neck cancers of any histology (squamous cell carcinoma, adenocarcinoma and neuroendocrine carcinoma).
2. Locally advanced head and neck cancers of TNM stage I- III are included.

Patient characteristics:

1. Ages >20-<60 years
2. Both sexes
3. Stage I - III, IVA

4. Site- Oral cavity, orophraynx, nasopharynx, hypopharynx, larynx.
5. Educational status – 6th and above.
6. ECOG 0,1 and 2
7. No metastatic disease

Exclusion criteria:

Disease characteristics:

1. Disease with metastatic spread to distant organs.
2. Recurrent disease either after radiation or surgery is also excluded.
3. Brain tumors.

Patient characteristics:

1. No psychiatric or addictive disorders or other conditions that would preclude the patient from meeting the study requirements.
2. Educational status – below 6th standard.
3. Patients presenting with previous history of other malignancies, who received high dose chemotherapy or radiation are also excluded.

Methodology:

Tools

The following tools were employed in the present investigation:

1. Socio-demographic data sheet.
2. General Health Questionnaire- used for screening the healthy normal subjects for the matched group.
3. NIMHANS neuropsychological battery- administered in both the patient and the matched group.

STUDY PERIOD:

The study will last from Jan 2015 to September 2015.

Socio-demographic Data Sheet.

Two separate semi-structured socio demographic data sheets were prepared, Study arm included patients in which hippocampal region received radiation, and another control arm- non spared hippocampal region. These were used to document the socio demographic characteristics of the subjects. The basic details like age, education and marital status were collected from all the subjects in the two groups (the study arm and the control arm). For the patient group, additional information related to disease, such as history of the illness, details of risk factors was included.

General Health Questionnaire.

The General Health Questionnaire is a mini mental assessment self-administered screening tool, which is used to assess the presence of diagnosable psychiatric disorders in community settings and non-psychiatric clinical settings. This questionnaire has a total score of 30 and is easy to administer. The tool was used in the present study to screen the healthy normal matched subjects for the absence of psychiatric symptoms. The total score ranged from 0 to 30. Performance is based on this selection criteria.

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

8.

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.

NIMHANS Neuropsychological battery.

The neuropsychological tests used in the present study have been taken from the NIMHANS neuropsychological battery. The battery consists of21 different neuropsychological subtests which were originally developed by different authors and standardized in the Indian population by Rao, Subbakrishna, and Gopukumar (2004). This battery has been extensively used in researches on neuropsychological performances of a wide variety of groups including normal individuals and clinical populations, and hence has proven validity and applicability.

The different areas of functions covered in the test battery are: attention and concentration; motor speed; executive functions such as planning ability, category fluency, phonemic fluency, working memory, set shifting and response inhibition, verbal learning and memory; visual learning and memory; expressive and receptive speech; visuo-constructive ability; and focal signs.

From this neuropsychological test battery, the following eight tests were used in the present investigation. In this study 16 subsets of test are used .Each test have been explained in detail to the patient before they perform the tasks and it mostly associated only with memory function. The different test include verbal, for speed, attention, visual, concept formation .These tests are performed at start of treatment and 6 weeks after end of treatment.

Different subsets of tests used for assessing:

1. Test of speed- Digital Symbol Substitution Test.

2. Test of attention –a. Color Trails Test

b. Digit Vigilance Test

c. Triads Test

3. Test of executive function- a. COWA Test

b. Animal names Test

c. Design Fluency Test

d. N Black test

e. Tower of London

f. Wisconsin Card Sorting Test

g. Stroop Test

4. Test of Comprehension – a. Token Test

5. Tests of Learning and Memory – a. Auditory Verbal Learning Test

b. Logical Memory Test

c. Complex Figure Test

d. Design Learning Test

Test of speed:

Digit symbol substitution test:

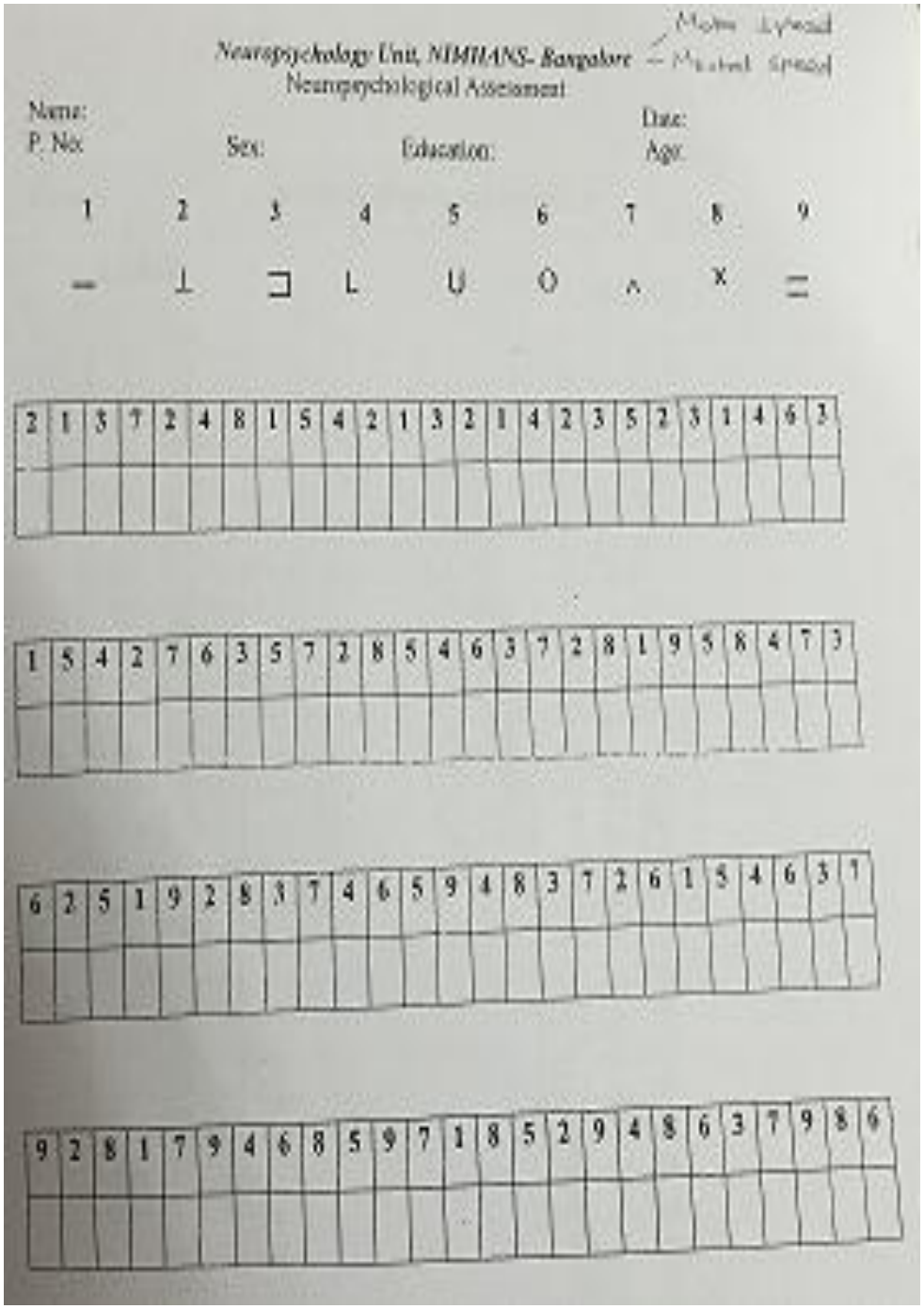
Digit symbol substitution test (Wechsler, 1981) is a test of visual–motor co-ordination, motor persistence, information processing and speed. The test sheet have numbers from one to nine that are randomly arranged infour rows of 25 squares each.The subject has to substitute each number with a specific symbol using a number–symbol key given on top of the page. The first ten squares are for practice. The test takes about seven minutes.

Administration.

The subject was seated comfortably and the test sheet was placed in front of him or her. The principle of substituting symbols for digits was explained. Practice was given for the first ten squares after which the test started. The subject was instructed to complete the task as fast as possible. Scoring. The time taken to complete the test constituted the score of the test; the longer the time taken, poorer the performance.

Scoring: The time taken for completion of test indicates the score. Errors are noted while performing the tests.

Digit symbol substitution test:



Neuropsychology Unit, NIMHANS- Bangalore
Neuropsychological Assessment

Name:
P. No:
Sex:
Education:
Date:
Age:

1	2	3	4	5	6	7	8	9
—	⊥	⊐	L	U	O	∧	X	=

2	1	3	7	2	4	8	1	5	4	2	1	3	2	1	4	2	3	5	2	3	1	4	6	3

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

Test of attention:

Attention is one of the factors of cognition effect. Attention have been characterized in different types namely focused attention, sustained attention and divided attention (Ponser, 1978). Focused attention means performing task with distracting stimuli.

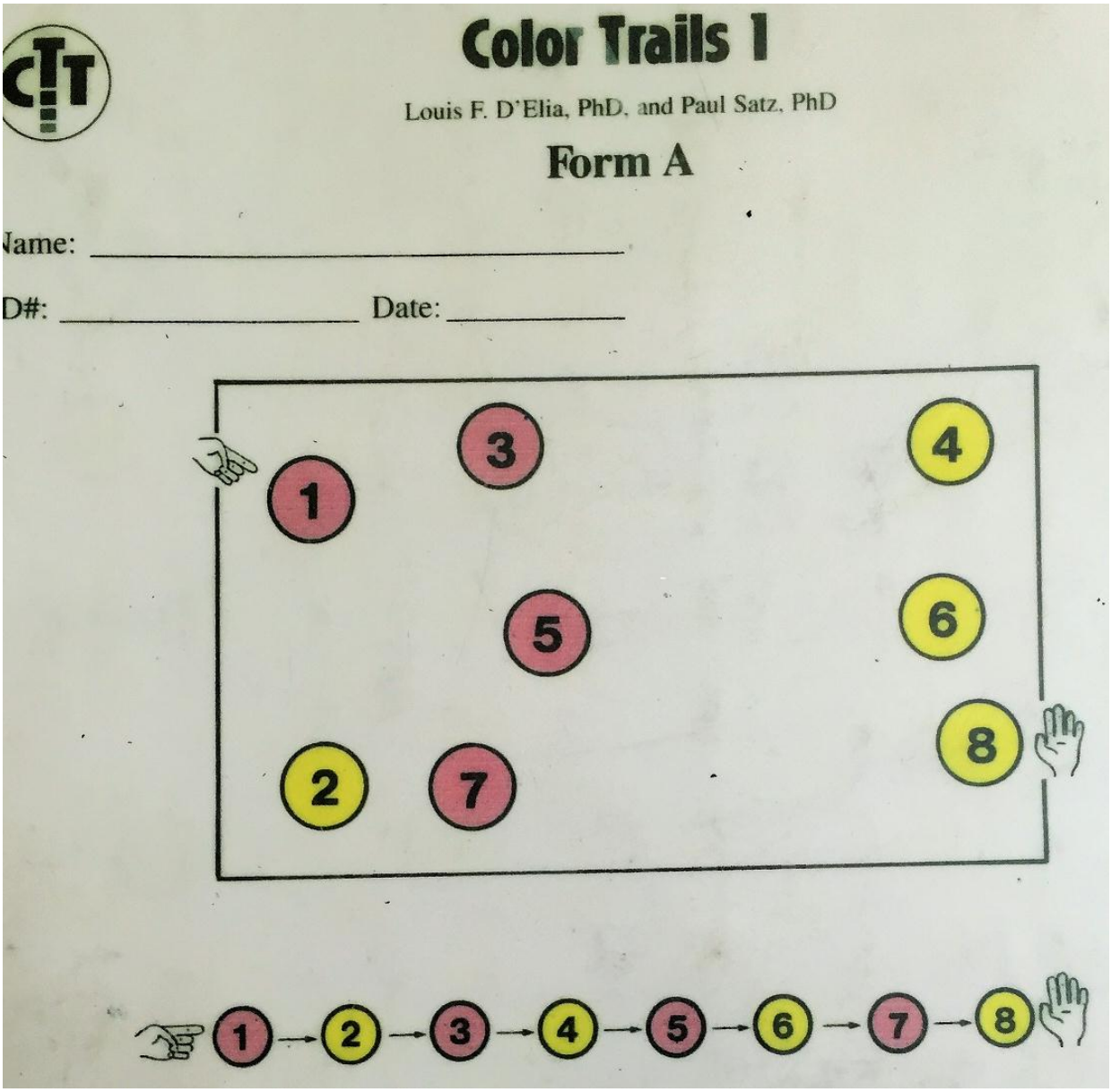
Sustained attentionmeans able to perform a task with in short limit of time. It is closely related to performing a difficult task. Divided attention means performing two or three tasks at a single time. It is associated with effort and attention (Kinsbourne 1978).When dual tasking performance is worked out, the tasks should not overlap these parameters that is stimulus, way of processing and type of response.

Prefrontal cortex involves in focused attention which focusses on orbitofrontal area. Right fronto parietal region focusses on sustained attention. Divided attention is associated with central executive functioning of working memory. It depends of determining shapes, color and speed. Bilateral dorsolateral prefrontal cortices mediate the central executive function and it was analysed by performing dual task (Detre, David, Shin, Atlas Grossman 1995).

Color Trails Test.

The color trail test denoted the focused attention. It was developed DÉlia, Satz, Uchiyama and White in 1996. It mainly focuses on the influence of language. It is divided into two task. First task is to concentrate on sustained attention, tracking and sequencing of the task and the second task requires mental flexibility. This test the subject has to ignore irrelevant numbers while scanning for numbers in next series by pointing fingers.In each part first practice is given followed by the test.

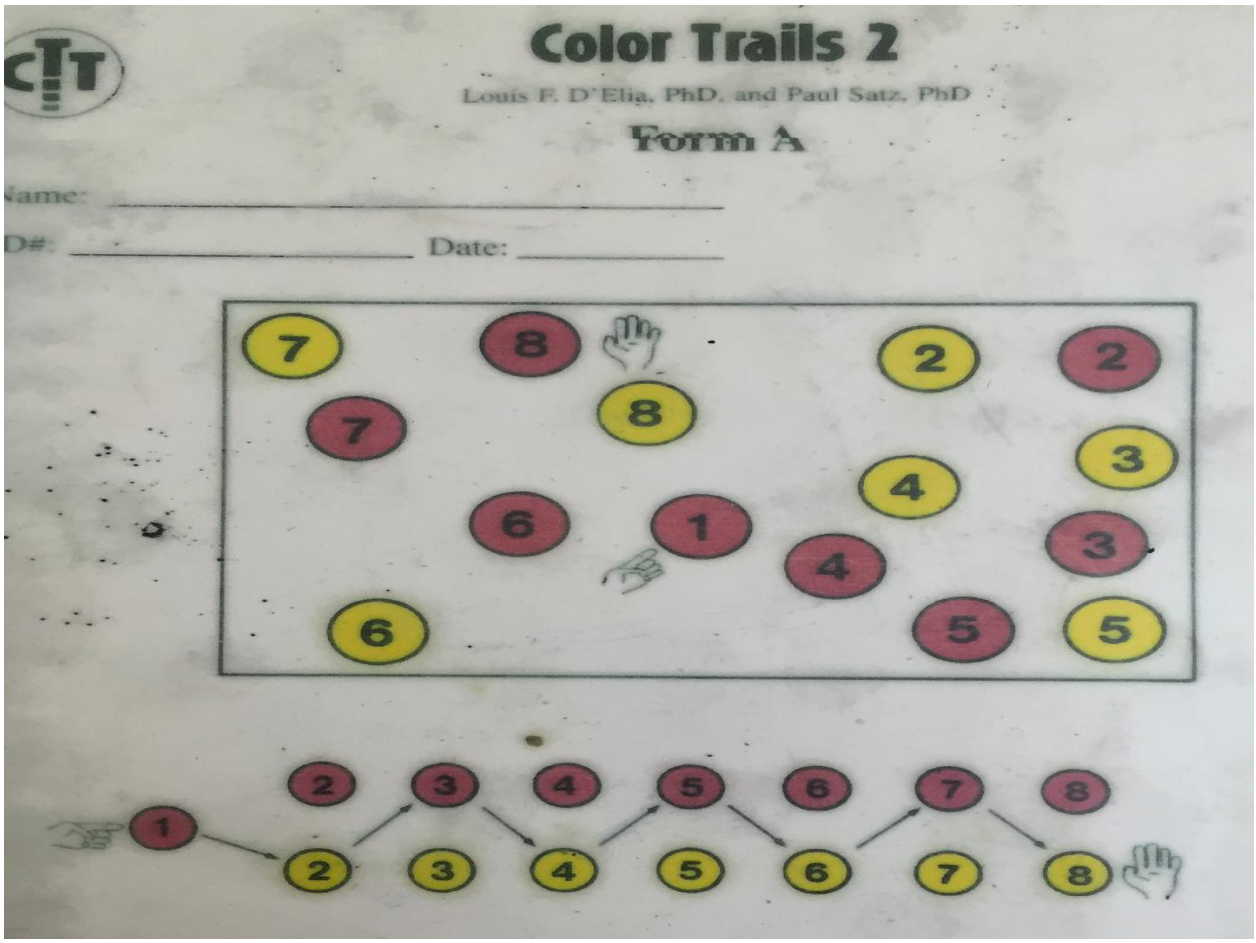
Procedure: Color trails 1 – It has a practice sheet and a test sheet. In practice session 1-8 number are randomly spread in a square box .The odd numbers are printed in pink and even numbers are printed in yellow in a circle. Below the box series of numbers are arranged in an order, the subject is asked to connect these numbers in ascending order. The subject is asked to point the numbers in ascending order.



Color trail 2 – It has a practice sheet and a test sheet. All numbers 2 to 8 are printed twice - one in pink and another in yellow circle. Numbers are arranged below the box in ascending orders, first row consists of numbers printed in pink and another row of

numbers printed in yellow and arrow pointing on alternating pink and yellow circles.

Scoring: The time taken to complete both the task are noted down.It approximately takes 10 minutes.



Digit vigilance test.

Digit vigilance test (Lezak, 1995) used mainly for sustained attention and it consists of a sheet containing numbers one to nine randomly ordered and placed in rows on a page. There are 30 digits per row and 50 rows in a test sheet. The subject has to focus on target digits six and nine amongst other distracter digits. Inability to sustain and focus attention leads to increased time to complete the test.

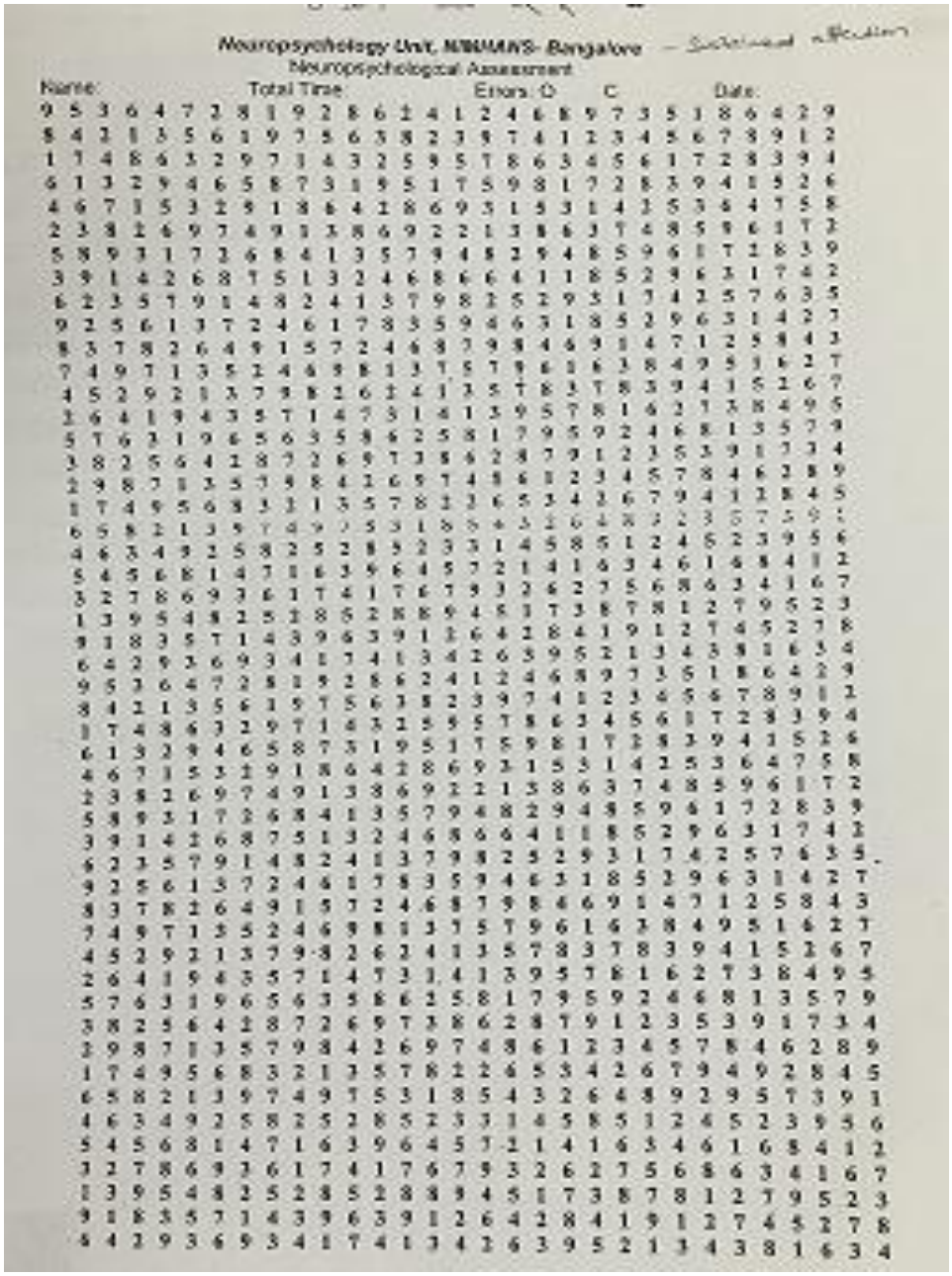
Administration.

The subject was seated comfortably and the test sheet was placed in front of the subject. The subject was asked to scan the sheet and cancel the target numbers six and nine (by drawing a mark on them) as fast as possible without missing the targets or canceling other numbers.

Scoring

The time taken to complete the test formed the score; the longer the time taken, poorer the performance. Error score – It the sum of the numbers of omissions. Durations takes about 15 minutes.

Digit vigilance test.



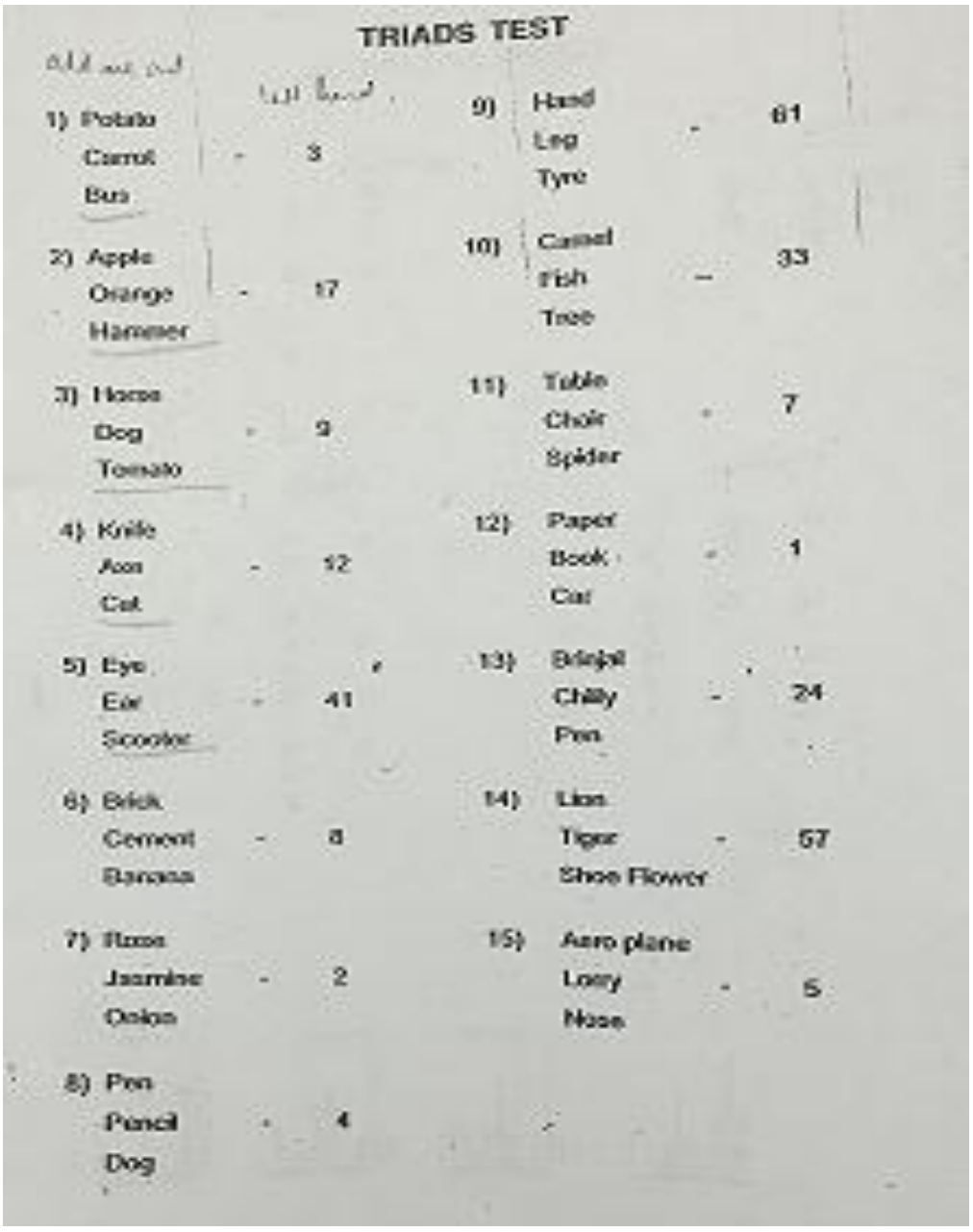
Triads Test:

Triads Test was developed at NIMHANS and mainly indicates division of attention. It is performed by using two different task performing at the same time. It includes auditory, visual and touch sensation related tests are performed. It depends on stimulus modality and processing of stimulus mainly verbal response. If there is overlap in response between the stimulus and processing it denotes the division of attention.

Administration:

The subject is explained in detail about each task, here two tasks are performed. First task verbal triad, the subject id asked to call out one word which does not belong to the other category. The other task a sample digit is written on the non-dominant hand on the palm and asked to call out the digit. In each triad of verbal one are grouped, in that two words are similar words and other one does not belong to that group. The subject is asked to pronounce the odd words out. Simultaneously the number is written slowly on the non-dominant palm.

Score: Errors committed in each task is counted. The types of errors namely word and number errors. Duration taken is about seven minutes.



TRIADS TEST

1)	Potato Carrot Bus	-	3	9)	Hand Leg Tyre	-	61
2)	Apple Orange Hammer	-	17	10)	Camel Fish Tree	–	33
3)	Horse Dog Tomato	-	9	11)	Table Chair Spider	-	7
4)	Knife Axe Cat	-	12	12)	Paper Book Car	-	1
5)	Eye Ear Scooter	-	41	13)	Brinjal Chilly Pen	-	24
6)	Brick Cement Banana	-	8	14)	Lion Tiger Shoe Flower	-	57
7)	Rose Jasmine Onion	-	2	15)	Aero plane Lorry Nose	-	5
8)	Pen Pencil Dog	-	4				

Tests of executive function:

Executive function consists of different modalities of performance like anticipation, goal selection, planning and monitoring (Stuss & Benson 1986). On other words defined as the 'ability to maintain an appropriate problem solving set for the attainment of future goals.

Executive functions involve an intention to inhibit a response or to defer it to a later time, a plan of action sequence , mental representation of task, stimulus information into memory and future goal'(Pennigton & Ozonoff 1996). Executive functions include fluency, working memory,set-shifting ability, set maintenance, planning, response inhibition, error detection, abstraction and organization.

Fluency refers to mental flexibility. It exhibits spontaneous verbal and visual fluency. Many studies have shown that verbal fluency activates frontal lobes, design fluency bilateral prefrontal activation (Pujol et al 1996). Phonemic fluency occurs when there is damage to left frontal lobe (Benton & Hamsher 1989). Category fluency involves the temporal lobe (Frith et al 1989).The former is known as phonemic fluency and the latter is known as category fluency.

Controlled oral word association test (COWA).

The Controlled oral word association test (Benton & Hamsher, 1989) is a measure of phonemic fluency. In this test, the subject generates words based on phonetic similarity of words. The subject is required to generate words beginning with the letters F, A, and S for one minute. Proper nouns and names should be excluded.

The same word should not be repeated with a different suffix. Subjects who do not know the English language were asked to generate words in their own mother tongue commencing with ‘ka’, ‘pa’, ‘ma’. The subject was asked to generate words for one minute in case of each letter starting with F, going unto A and ending with S or with ‘ka’, going on to ‘pa’ and ending with ‘ma’ as the case may be.

Administration.

The subject was seated comfortably and told that he or she has to generate words beginning with a letter, which will be provided by the tester. A practice trial was given with the letter other than the ones used in the test. The subject was asked to generate as many words as possible for one minute in the case of each letter, and not to repeat the same words or give names of persons and places, and also not to say different deviations of the same word (e.g., ask, asking, asked). After each one-minute test, the subject was

given a short rest pause before commencing the next test with a different letter.

Scoring

The total number of acceptable new words produced in one minute was noted down for each consonant. The average of the new words generated over the three tasks formed the score; the higher the score, better the performance. Duration usually takes about 5 minutes.

Animal names test

Animal names test is a measure of category fluency (Lezak, 1995). Category fluency is another form of verbal fluency. In this test, it is the content of the words rather than the phonetic similarity of the words, which is regulated. The subject generates words which belong to a particular semantic category. The Animal names test requires the subject to generate names of animals but it should not include birds, marine, reptiles and should be worked out for one minute.

Administration

The subject was asked to generate the names of as many animals as possible in one minute. He or she has to exclude the names of fish, birds and snakes.

Scoring.

The total number of new words generated formed the score; the higher the score, better the performance. It approximately should take three minutes.

Design Fluency Test:

Visual fluency is the capacity to generate new visual forms. It is a mechanism of thinking with visual imagery and visual forms. Design fluency means testing the visual fluency. It was designed by Jones- Gotman & Milner 1977. It measures to produce designs and it should not represent actual objects or namable abstract form, example not to use geometrical figures. There are two types of free and fixed condition.

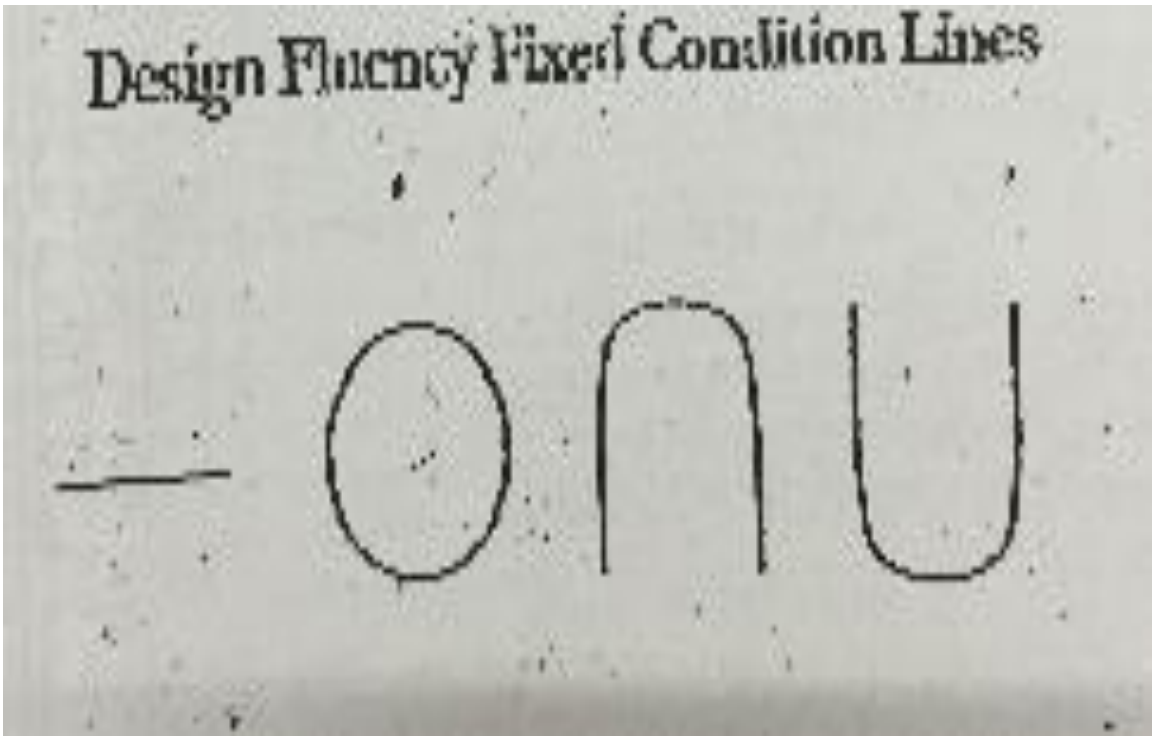
Administration:

The subject is asked to draw as many new forms of design in a given period of time.The subject is instructed to drawa design and each design should be different from the previous one. In free condition the subject is instructed to draw in in a sheet of paper and pencil different form of design and give examples how to draw and should be performed within 5minutes. In fixed condition in another sheet of paper with time interval of four minutes ask them to design using 4 lines as shown in the figure below. Each design should be different from each other. Straight line, semicircle, circle will count as one line.

Scoring:

Scoring is done for free and fixed design depending upon the number of design drawn.

Timing of twelve minutes is taken as maximum time limits.



Working memory:

Concept have been illustrated by Baddeley in 1986, it mainly refers to the capacity to hold and manipulate information for an ongoing processes. It is associated with long term memory. There are three major types of working memory named as verbal working memory, spatial working memory and a central executive memory.

Verbal N back test.

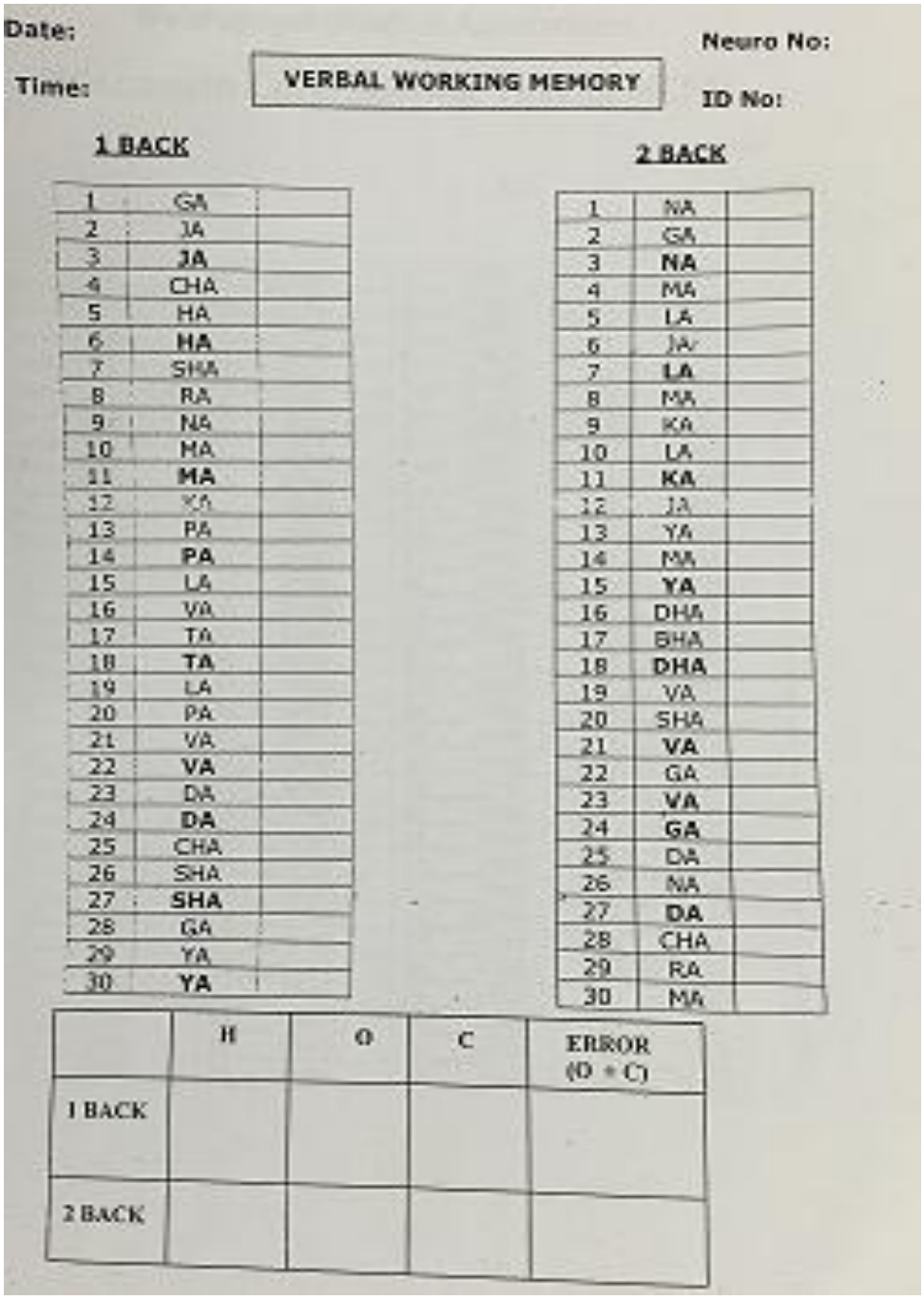
The 1 back and 2 back versions of the N back test (Smith & Joindes, 1999) assess verbal working memory. The 1 back version requires verbal storage and rehearsal while the 2 back version requires in addition to the above, manipulation of information. Therefore, the 1 back version would involve the articulatory loop in the verbal modality and the visuo-spatial sketchpad in the visual modality. The 2 back would involve the central executive in both the modalities.

Administration.

Thirty randomly ordered consonants common to multiple Indian languages are presented auditory communication at the rate of one per second. Nine of the 30 consonants are repeated. The consonants which are repeated are randomly chosen. In the 1 back test the subject has to respond by tapping the table whenever a consonant was repeated consecutively. Example the subject hears 'MA' "RA" "RA", ask the patient to listen carefully and respond by tapping the table, if the words are repeated. In the 2 back test, the subject has to respond by tapping the table whenever a consonant was 112 repeated after an intervening consonant. That means, in this test there will be an intervening consonant after which the consonant might repeat. Therefore, the subject was instructed to remember each consonant till the consonant is over. A practice trial was given for the subject with four consonants wherein 1 consonant is repeated.

Scoring.

The number of correct responses formed the score in each test; the higher the score, better the performance. It approximately takes twelve minutes time.



Date:

Neuro No:

Time:

VERBAL WORKING MEMORY

ID No:

1 BACK

1	GA	
2	JA	
3	**JA**	
4	CHA	
5	HA	
6	**HA**	
7	SHA	
8	RA	
9	NA	
10	MA	
11	**MA**	
12	KA	
13	PA	
14	**PA**	
15	LA	
16	VA	
17	TA	
18	**TA**	
19	LA	
20	PA	
21	VA	
22	**VA**	
23	DA	
24	**DA**	
25	CHA	
26	SHA	
27	**SHA**	
28	GA	
29	YA	
30	**YA**	

2 BACK

1	NA	
2	GA	
3	**NA**	
4	MA	
5	LA	
6	JA	
7	**LA**	
8	MA	
9	KA	
10	LA	
11	**KA**	
12	JA	
13	YA	
14	MA	
15	**YA**	
16	DHA	
17	BHA	
18	**DHA**	
19	VA	
20	SHA	
21	**VA**	
22	GA	
23	**VA**	
24	**GA**	
25	DA	
26	NA	
27	**DA**	
28	CHA	
29	RA	
30	MA	

	H	O	C	ERROR (O + C)
1 BACK				
2 BACK				

Tower of London Test:

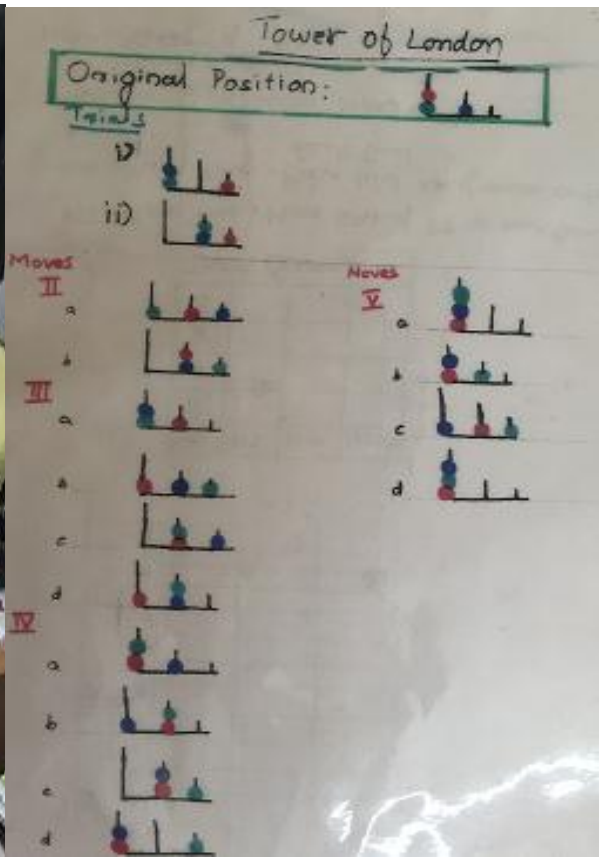
This test is involves the planning evaluation proposed by Shallice 1982. The test evaluates subject's mental ability to plan and perform the activities. The test consists of two identical wooden boards. Board measuring 38cms long and 13cms wide and each board is fitted with 3 round pegs of different sizes. These three woods have metal balls painted red green and blue respectively.

Administration:

The subject is made to sit opposite to the examiner and patient is instructed such that two wooden boards which are identical kept near to each other. The subject is made to observe the arrangement of balls and asked to reproduce in the same way. The subject should not hold the ball in hand and can lift only one at a time and place it when the examiner does and should follow the instructions by examiner.

Scoring:

The average time is noted for 2, 3, 4, 5 moves and the mean is calculated. The overall score is calculated wit number of moves. Finally the results are obtained by totaling the number of problems with minimum number of moves in each category of problem. Duration time is about thirty minutes.



Winson card sorting test:

Winson card sorting test proposed by Milner, 1963. It mainly used to test set shifting ability. This is performed to know the concept formation, abstracting reasoning and the ability to alter the cognition effect change in response to changing environment. The test consistsof 128 cards. The stimuli on the card vary in color, form and number.

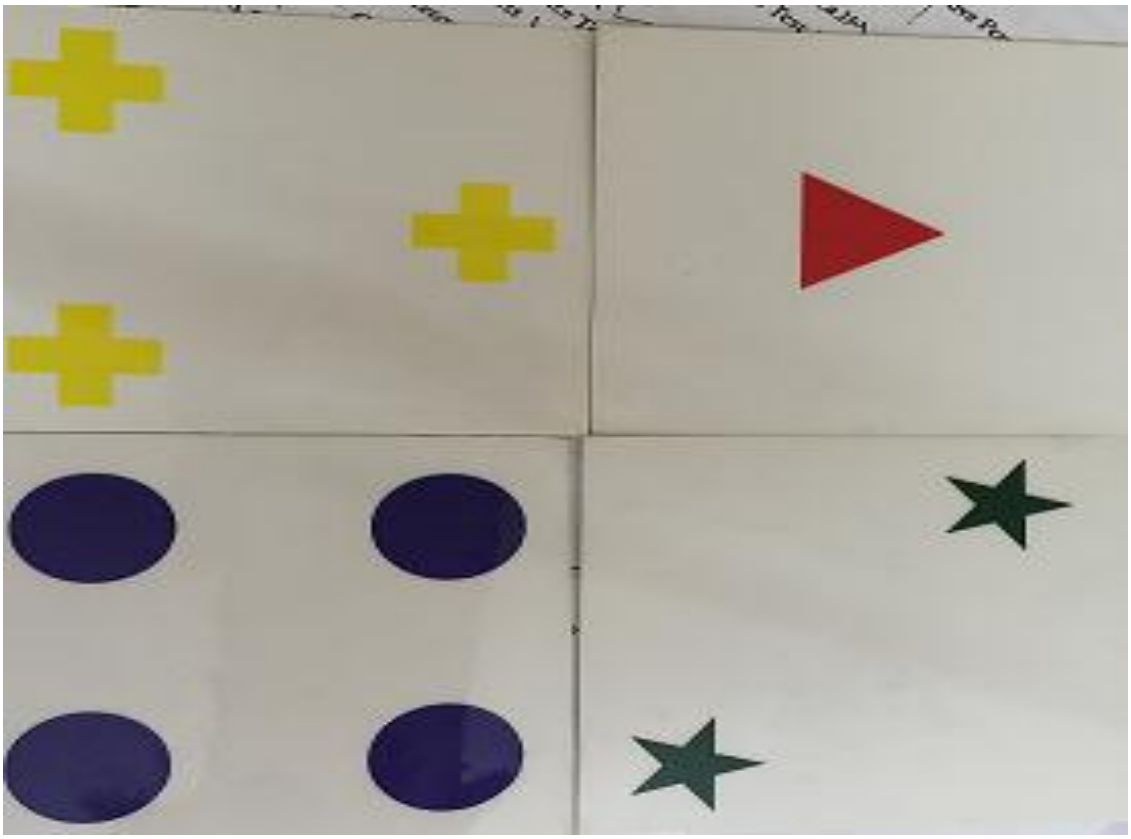
The stimuli are geometrical figures consisting different forms of triangle, star, cross, circle with different colors red, green, yellow, blue and with different numbersone, two, three, four. Out of 128 cards, 4 stimulus cards are used. Out of four stimulus cards, first card consist if red triangle, second consists of green starts, three yellow cases and the fourth blue circles.

Administration:

The four stimulus cards are placed in front of the patient and arranged in a series. The subject is instructed to study the cards and match each successive cards from the pack to one or four stimulus. The first principle is to match the color, followed by the form and the finally by the number.

Scoring:

Scoring is done based on ambiguous – unambiguous responses- If two or more characteristics matches its correct response and another is based on preservative- non preservative errors. Duration time is approximately thirty minutes.



Stroop test:

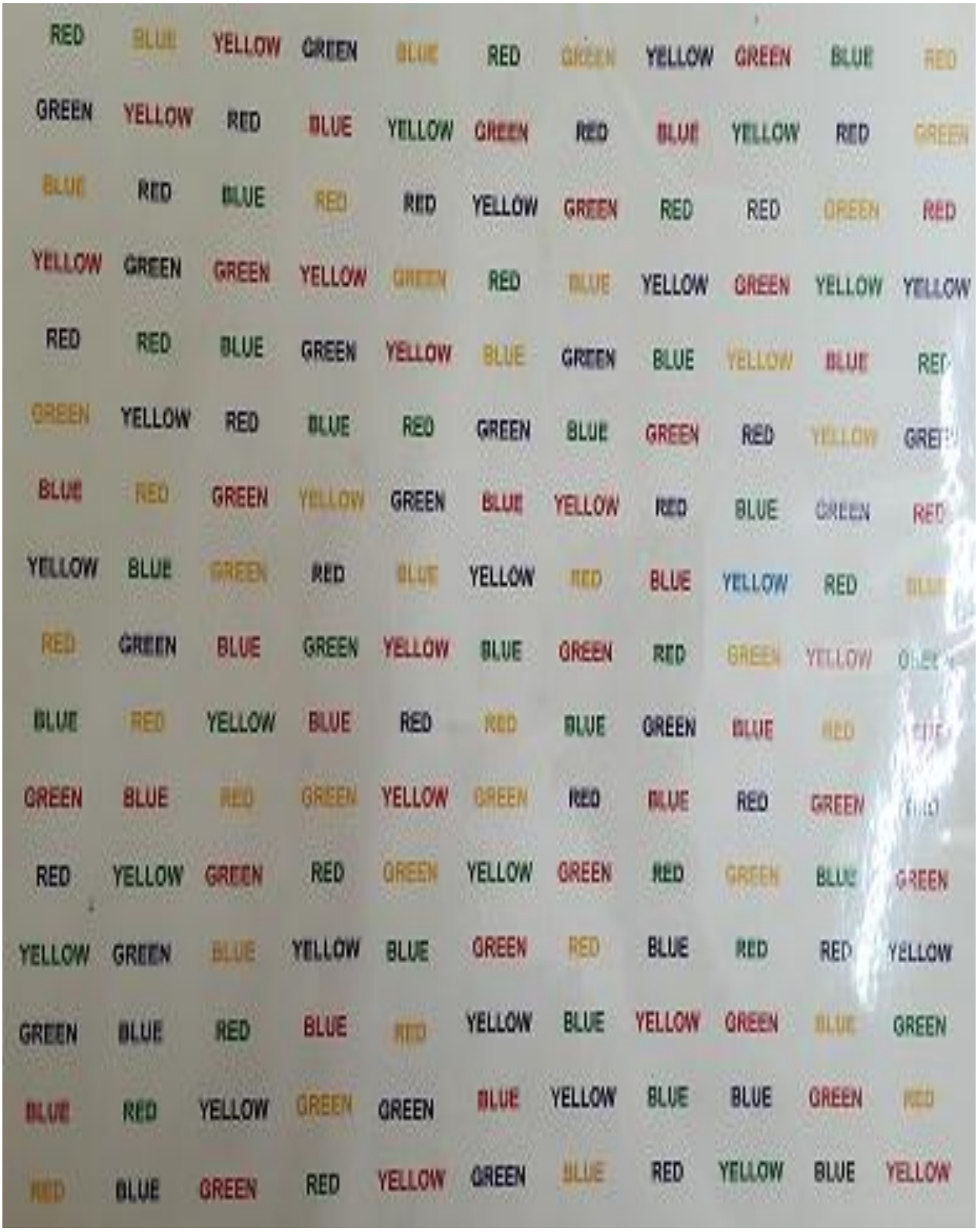
Stroop test measures response inhibition (Benson & Struss, 1986). It measures the ease with which a perceptual set can be shifted both to conjoin demands and suppressing a habitual response in favor of an unusual one. The prefrontal areas are essential for response inhibition. In this test, the color names ‘blue’, ‘green’, ‘red’, and ‘yellow’ are printed in capital letters on a paper.The color of the print occasionally corresponds with the color designated by the word. The words are printed in 16 rows and 11 columns.

Administration.

The stimulus sheet was placed in front of the subject. The subject was asked to read the printed words column-wise as fast as possible. The time taken to read all the 11 columns was noted down. Next, the subject was asked to read the colour in which the words were printed. The time taken to read all colours was noted down. The words were presented in the mother tongue of the subject. The test takes about 20 minutes.

Scoring

The time taken to read the printed words and the time taken to read the colour of the printed words were converted into seconds. The time taken to read the printed words was subtracted from the time taken to read the colour to get the Stroop effect score; the higher the score, poorer the performance.


RED BLUE YELLOW GREEN BLUE RED GREEN YELLOW GREEN BLUE RED
GREEN YELLOW RED BLUE YELLOW GREEN RED BLUE YELLOW RED GREEN
BLUE RED BLUE RED RED YELLOW GREEN RED RED GREEN RED
YELLOW GREEN GREEN YELLOW GREEN RED BLUE YELLOW GREEN YELLOW YELLOW
RED RED BLUE GREEN YELLOW BLUE GREEN BLUE YELLOW BLUE RED
GREEN YELLOW RED BLUE RED GREEN BLUE GREEN RED YELLOW
BLUE RED GREEN YELLOW GREEN BLUE YELLOW RED BLUE GREEN RED
YELLOW BLUE GREEN RED BLUE YELLOW RED BLUE YELLOW RED
RED GREEN BLUE GREEN YELLOW BLUE GREEN RED GREEN YELLOW
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GREEN BLUE RED GREEN YELLOW GREEN RED BLUE RED GREEN
RED YELLOW GREEN RED GREEN YELLOW GREEN RED GREEN BLUE GREEN
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BLUE RED YELLOW GREEN GREEN BLUE YELLOW BLUE BLUE GREEN RED
RED BLUE GREEN RED YELLOW GREEN BLUE RED YELLOW BLUE YELLOW

Token Test:

Token test is a verbal comprehension test in which the ability to understand spoken speech. Wernicke's area mediates verbal comprehension (Joseph, 1996) the test involves of tokens differing in color, size and shape. The test involves capacity to know verbal acquiring capability.

Administration:

The token contains different subsets of squares and circles of two different sizes and called as tokens. Each tokens is placed in order for example if large tokens are placed first and then follow small tokens. The subject is instructed to see colored bits and instruction have to be given and tell to follow the instructions and arrange accordingly.

Scoring:

Scoring is given each time with a score of one and score of half is detected for every repetitions. If the subject fails to follow the instruction, score of zero is given. Maximum score of 36 is maximum.

Token Test Arrangement of Tokens in front of Subject

Row 1

Large circles in order: red, blue, yellow, white, green

Row 2

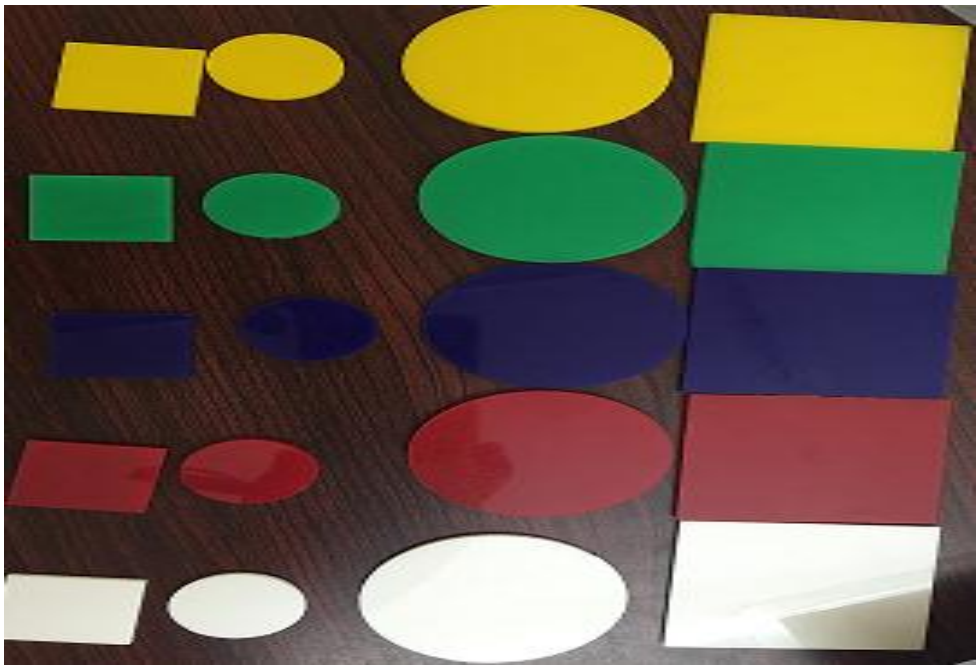
Large squares in order: blue, red, white, green, yellow

Row 3

Small circles in order: white, blue, yellow, red, green

Row 4

Small squares in order: yellow, green, red, blue, white



Tests of learning and memory.

Learning is the process of acquiring new information about the environment and the process of memory retaining it. Learning and memory are dependent process. Memory are divided into short term and short term memories. Long term memory means capability of retaining memory of lifetime of an individual. Memory for events, figures, words, scenes and facts are considered as domain explicit memory. Retrieval of personally experienced events is known as episodic memory. Knowledge of facts and concepts is known as semantic memory. So therefore learning and memory for verbal and visual domain are two main factors of explicit memory.

Rey's auditory verbal learning test (AVLT).

The Rey's Auditory Verbal Learning Test (Schmidt, 1996) adapted for different cultures by WHO (Maj et al., 1994) was adapted to suit conditions in India. Rey originally developed the test in 1996. It consists of words designating familiar objects like vehicles, tools, animals and body parts. There are two lists A and B, with 15 different words in each list. The words were translated into the five Indian languages-Kannada, Tamil, Telugu, Hindi, and Malayalam. Word lists in the different languages are given in appendix. The words in list A were presented at the rate of one word per second in five successive trials.

The words were presented in the same order in every trial. Each trial consisted of the presentation of all 15 words, immediately followed by recall of the same. In each trial, after the presentation of the words the subject was asked to recall the words in any order. The examiner noted down the responses verbatim in the order in which the subject gives them. On an average, recall in each trial takes about 2 minutes. After the completion of all the five trials of list A, words in list B were presented once and an immediate recall was taken for the same. This is followed by the immediate recall from list A.

The subject was given a brief rest of a few minutes and then the Stroop test which does not involve the task of recall was given. After a lapse of 20 minutes from the completion of the last recall of list A, a delayed recall of words was taken. Following delayed recall, recognition of the words in list A was tested. In recognition trial, the examiner presented the words form the recognition list one by one at the rate of one word per second and the subject was asked to identify the words from list A by saying “yes” or “no”. The number of words correctly identified formed the hits. The test takes about 30 minutes.

Scoring.

The number of words correctly recalled in each of the 5 trials of list A as well as the total number of words recalled over all the five trials formed the AVLT- Total score. The number of words recalled correctly in the immediate recall trial, delayed recall trial and

the recognition trial formed the memory. In the recognition trial, the hits or the correct response were scored separately .The other score was Long Term Percent Retention, which was calculated by the formula: Delayed Recall Score / Trial 5 score x100; the higher the score, better the performance.

9. Auditory Verbal Learning Test-English Version (AVLT)

List "A"	A1	A2	A3	A4	A5	List "B"	B1	IR	DR	Recognition-Hits
1.Hand						Shoes				Mirror
2.Cat						Monkey				**Hammer**
3.Axe						Bowl				**Knife**
4.Plane						Cow				Candle
5.Bed						Finger				Bike
6.Ear						Dress				**Axe**
7.Dog						Spider				Clock
8.Hammer						Cup				**Chair**
9.Horse						Bee				**Plane**
10.Eyes						Foot				Turtle
11.Chair						Hat				Leg
12.Car						Butterfly				**Dog**
13.Knife						Kettle				Table
14.Clock						House				**Cat**
15.Bike						Arm				Lips
										Tree
										Hand
										Nose
										Sun
										Truck
										Eye
										Fish
										Ear
										Horse
										Bike
										Stool
										Bus
										Bed
										Car

Scores

1	2	3	4	5	Total Leaning	List B	IR-A	DR-A	RECOGNITION
									Hits
									Omission
									Commission

Logical memory:

Logical memory is used to assess the immediate and delayed recall of a meaningful sentences. The test consist of a short story is narrated and an immediate recall is done and after a delay of 30 minutes a delayed recall is taken.

Administration:

The subject had to listen carefully a story narrated and after reading the story asked to narrate the story. The subject is again asked to narrate the story after thirty minutes and this is referred to as delayed recall.

Scoring:

The facts that have been recalled immediately is called immediate recall score and the number of facts correctly correlating later is called delayed recall score. The duration takes about 10 minutes for both recalls together.

Complex figure test (CFT).

The complex figure test (Meyers & Meyers, 1995) consists of a complex design which is abstract in nature and cannot be named easily. This test measures visuo-constructive ability and visual learning and memory. The115 figure from the complex figure is copied and subsequently recalled. Immediate and delayed memory scores are obtained.

Administration.

An 8.5 inch by 11 inch card containing the complex figure is placed in front of the subject. A paper of the same size of the complex figure card was placed in front of the subject. The subject was asked to copy the figure on the paper and he or she was not allowed to use rulers to draw lines, but rather draw it freehand. The subject was allowed to use eraser. The subject was asked to recall the figure twice: the first time was an immediate recall three minutes after the copying was completed, and the second time was a delayed recall 30 minutes later.

For the intervening three minutes, after the subject finished copying the design and before the immediate recall, another task such as one measuring verbal fluency was given to the subject. After the lapse of three minutes another sheet of paper was placed in front of the subject and then the subject was again asked to draw the design. Following this, during the thirty minutes before the delayed recall was given, the subject was given another task and he/she was not told that the design has to be drawn after this delayed period. After thirty minutes have elapsed, another sheet of paper was placed in front of the subject and the subject was asked to draw the design again from memory.

Scoring.

On each of the copy, immediate recall and delayed recall trials, a score of 0, 0.5, 1 or 2 was assigned to each unit of the figure based on the accuracy and placement criteria. The correctness of reproduction is assessed according to the scoring system given in the test manual; the higher the score, better the performance.

Design learning test:

Thedesign learning test (Jones- Gottman et al 1997) is used to assess the visual learning and memory. These includes two different kinds of phases learning phase and delayed recall phase. In the learning phase, the subject has to copy each design drawn by the instructor after ten second and after four hours asked to repeat again and this is called as delayed recall.

Scoring:

Each pattern is given a maximum of 4 points. The tests takes about one hour.

Sensitivity and Specificity

In NIMHANS battery, the subjects who score below the 15th percentile on the scores of accuracy are considered to have a deficit. A score above the 85th percentile is considered as a deficit for time and error scores. So the 15^{th} and 85th percentiles are taken as cut-off scores to identify deficits as these represent mean plus and minus 1 standard deviation.

RESULTS & ANALYSIS:

In this Randomized Prospective study assessment of neurocognitive is performed by comparing with the 40 patients who is treated with IMRT (with Cisplatin based Chemotherapy) during the same period. Study Arm contains patients who receive dose to hippocampal region, eg- in nasopharynx, hypopharynx, oropharynx, unknown primary. The control arm are the patients who doesn't receive dose to hippocampal region, eg- tongue, cheek, floor of mouth, larynx. NIMHANS neuropsychological battery have been used to assess the performance for each individual.

40 Patients those who meets both the inclusion & exclusion criteria, as mentioned above, are allowed for this study after obtaining their written informed consent. Each patient have been assessed with NIMHANS neuropsychological battery before the start of treatment and 2months after the end of treatment. Each test was explained clearly in detail before the start process and based on timing basis the results are calculated. Here the hippocampus have been contoured and dose receiving to hippocampal are have been studied and analyzed.

DETAILS OF PATIENTS INCLUDED IN THE STUDY ARM (ARM-A): HIPPOCAMPUS NOT SPARED

SITE	HYPO-PHARYNX	ORO-PHARYNX	UNKNOWN PRIMARY	NASO-PHARYNX
No. Patients	6	6	4	4
STAGE	II -IVA	II-IVA	II-IVA	III-IV
RT DOSE	60Gy	60-66Gy	66Gy	66Gy
HIPPPO	13.77Gy	11.89Gy	13.49Gy	14.25Gy

DETAILS OF PATIENTS INCLUDED IN THE CONTROL ARM (ARM-B): HIPPOCAMPUS SPARED

SITE	TONGUE	BUCCAL MUCOSA	LIP	GINGIVUM
No. Patients	8	6	3	3
STAGE	II -IVA	II-IVA	III-IVA	III-IV
RT DOSE	60-66Gy	60-66Gy	60Gy	60Gy
HIPPPO	1O.63Gy	10.26Gy	8.76Gy	9.67Gy

DETAILS OF TARGET VOLUME & ORGAN AT RISK:

SITE	HIPPOCAMPUS NOT SPARED	HIPPOCAMPUS SPARED
TARGET VOLUME	Primary and nodal regions.	Primary and nodal regions.
TOTAL DOSE	60-66Gy	60-66Gy
ORGAN AT RISK	Spinal cord, Parotids, Brainstem.	Spinal cord, Parotids, Brainstem.

S.No	Tests		HIPPOCAMPUS NOT - SPARED			
			Pre		Post	
			Score	Percentile	Score	Percentile
1	Digit Symbol Substitution Test		534	15-18	604	8
2	Color Trails Test	1	58	88-91	127	9-12
		2	158	72	294	7-9
3	Digit Vigilance Test	1	979	13-15	1114	7-9
		2	4	95	97	<2
4	Triads Test	1	12	53	10	47
		2	10		10	
5	COWA Test		5.66	30-40	NA	NA
6	Animal Names Test		8	10 TO 15	NA	NA
7	Design Fluency Test	1	5	70	8	60-70
		2	2	5	2	5
8	N Back Tests	1	5	40	6	25
		2	3	20	6	10
9	Tower of London Test	1	2	100	2	100
		2	3	100	3	100
		3	2	26.34	3	66-100
		4	0	0	2	65
10	Wisconsin Card Sorting Test		12	20	4	40 -75
11	Stroop Test		163	46-49	NA	NA
12	Token Test		34	40-50	32	40
13	Logical Memory Test		8	25-30	2	5
14	Complex Figure Test	C	29	30-35	6	30-35
		IR	18	25-30	3	7
		DR	17	40	1	3
15	Design Learning Test		26	80-85	10	50

S.No	Tests		HIPPOCAMPUS SPARED			
			Pre		Post	
			Score	Percentile	Score	Percentile
1	Digit Symbol Substitution Test		512	21-24	489	32
2	Color Trails Test	1	161	12-Oct	102	37
		2	288	15	233	32
3	Digit Vigilance Test	1	NA	NA	NA	NA
		2	NA	NA	NA	NA
4	Triads Test	1	14	81	11	11
		2	12		9	
5	COWA Test		NA	NA	NA	NA
6	Animal Names Test		NA	NA	NA	NA
7	Design Fluency Test	1	10	40	10	40
		2	8	25-40	6	15
8	N Back Tests	1	7	25-30	9	80-95
		2	6	20-50	9	85-90
9	Tower of London Test	1	2	100	2	100
		2	4	85	2	100
		3	4	100	4	100
		4	7	52.57	12	8
10	Wisconsin Card Sorting Test		3	15	5	2
11	Stroop Test		NA	NA	NA	NA
12	Token Test		34	60-70	36	90-95
13	Logical Memory Test		7	20	4	10
14	Complex Figure Test	C	29	30-35	32	95
		IR	18	25-30	15	20
		DR	17	40	12	10
15	Design Learning Test		18	95	19	95

Neurocognitive function assessment after chemo radiation for the study arm and control arm in head and neck cancers have shown significant variation. The study arm contains hippocampal non spared region, that is minimal dose has been received to hippocampal region.

The study arm contains patient of different subsets including hypopharynx which included 6 patients in which dose received to hippocampal region varies around 12.77Gy and oropharynx which included 6 patients and dose received to hippocampal region varies around 11.89Gy, in unknown primary which included 4 patients and dose received to hippocampal region 13.49Gy and nasopharynx included 4 patients and dose to hippocampal region is about 14.25Gy.

These are considered as hippocampal non spared region because there is always a minimum amount of radiation dose affecting the hippocampal region. The normal hippocampus **tolerance maximum dose 11Gy.**

The control arm is taken as hippocampus spared region containing different subsets of head and neck patients which includes tongue 8 patients and dose receiving to hippocampus region 10.63Gy, buccal mucosa 6 patients

receiving dose to hippocampal region is about 10.26Gy, lip 3 patients and dose to hippocampal region is about 8.76Gy and gingivum 3 patients hippocampus region dose is about 9.67Gy.The hippocampus dose when compared to study arm is lower and is below the normal dose constraints as the planning target volume varies.

Contouring to hippocampus region and dose received have been only monitored. On an analysis study arm has received dose above the normal dose constraints to hippocampus more than 11 Gy when compared to those patients in the control arm.

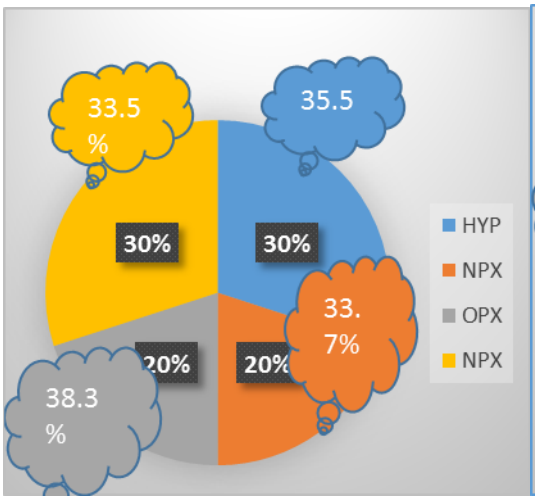
Neurocognitive function assessment has been done using NIMHANS neuropsychological battery. These contains of about 15 tests which is implemented on each subject before start of treatment. Each test have been clearly explained to the subject. Initial patient selection criteria is been selected based on mini mental scale assessment and a score 25-30 are included in this assessment.

The assessment is based on motor speed, focused attention, sustained attention, division of attention, executive functions mainly involving the verbal fluency, categorized fluency test, design fluency test, planning and solving a problem,

thinking capability, understanding the spoken speech, immediate and delayed recall of memory, visual memory.

Test of speed- DIGITAL SYMBOL SUBSTITUTON TEST

BEFORE



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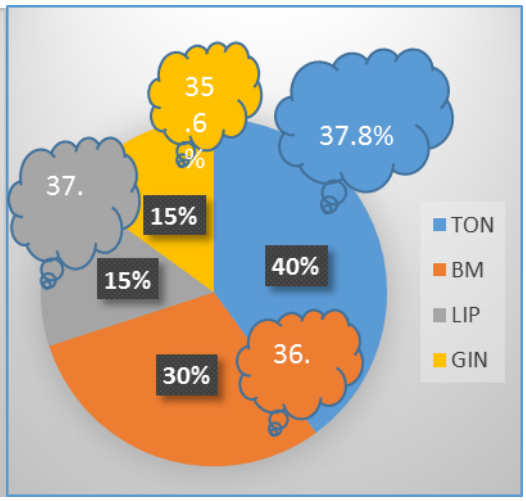

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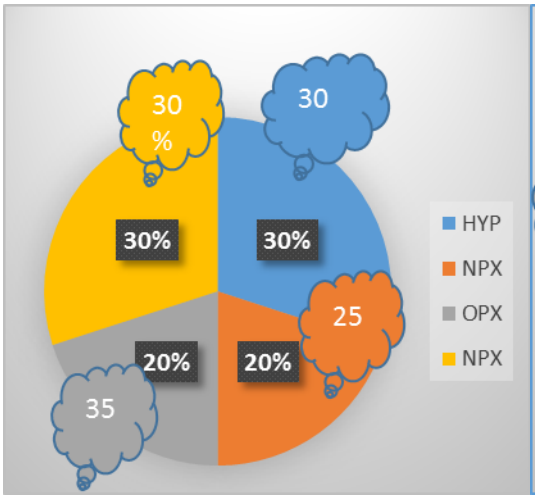

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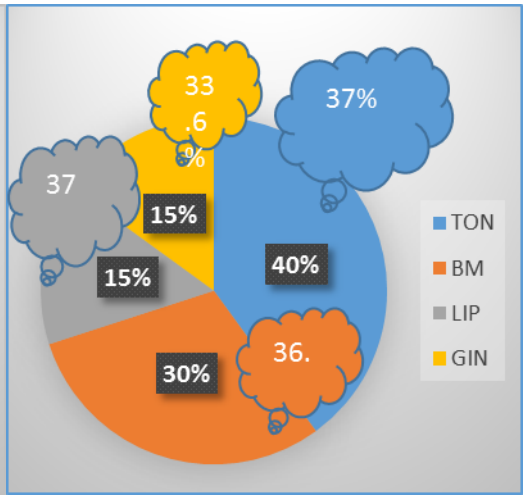

Test of attention–a. Color Trails Test

b. Digit Vigilance Test

c. Triads Test

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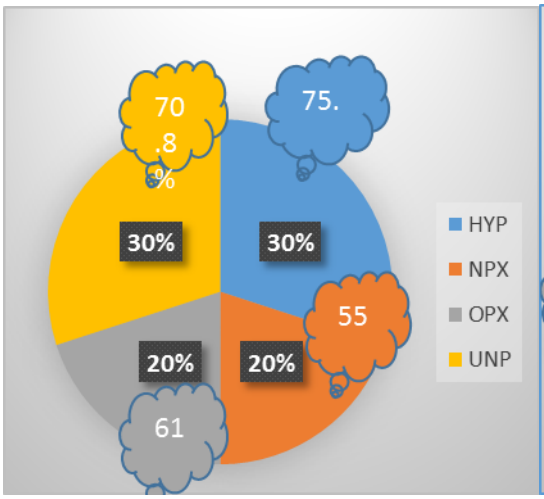

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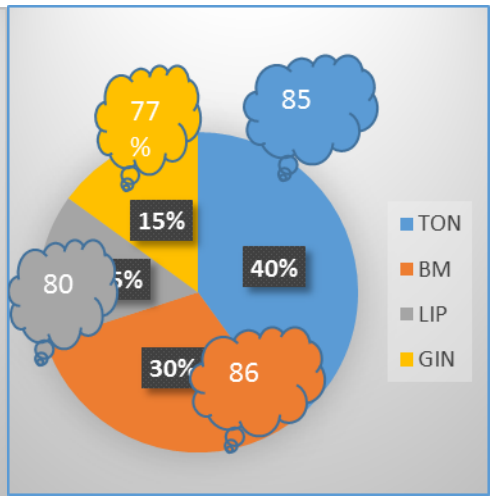

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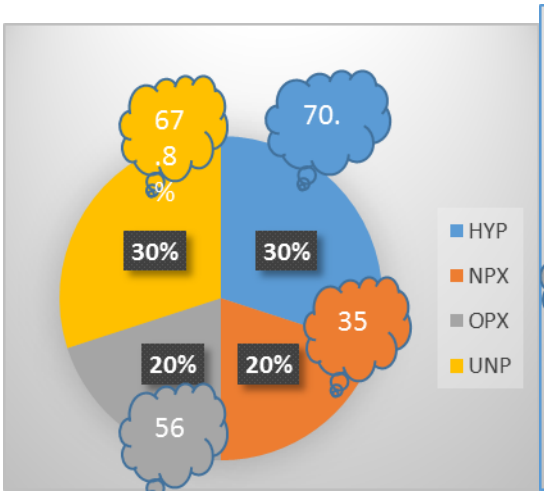

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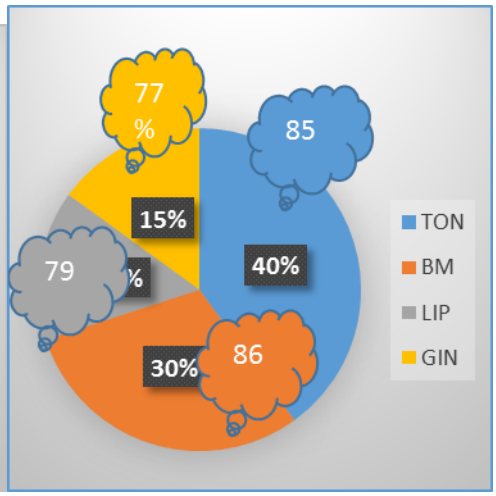
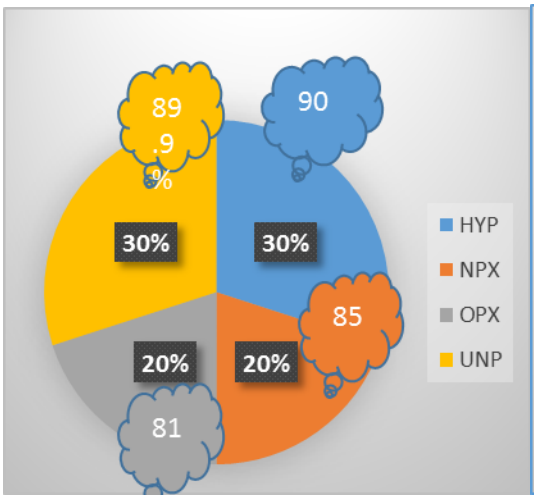


Test of Comprehension–Token Test

BEFORE



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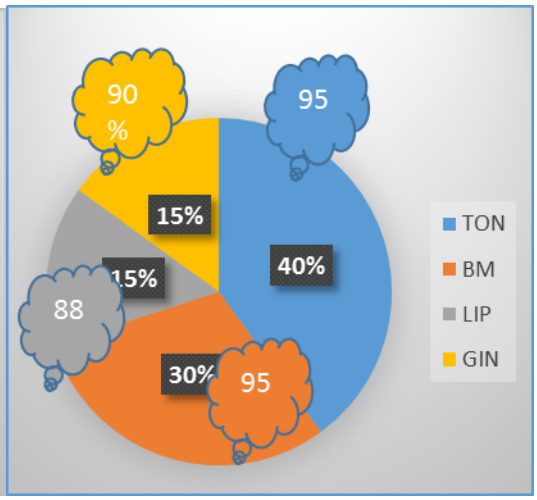

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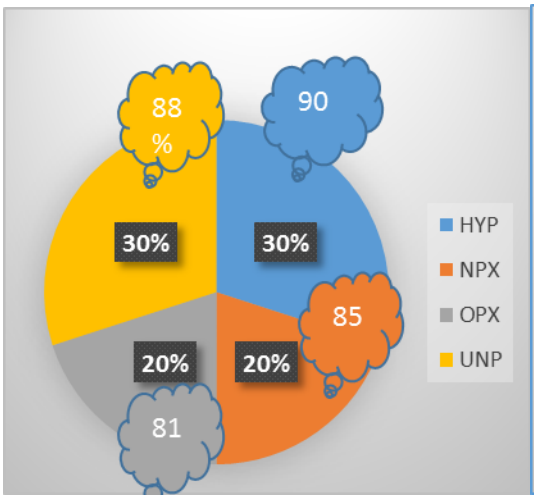

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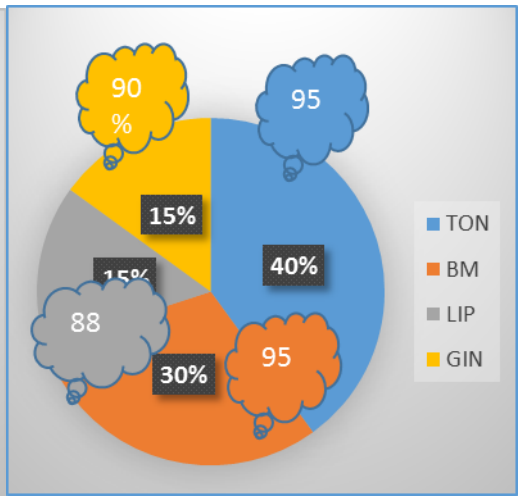


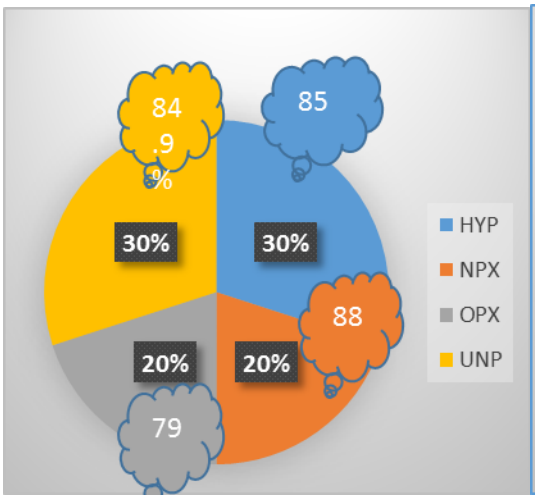
Tests of Learning and Memory– 1. Auditory Verbal Learning Test

2. Logical Memory Test

3. Complex Figure Test

4. Design Learning Test

BEFORE



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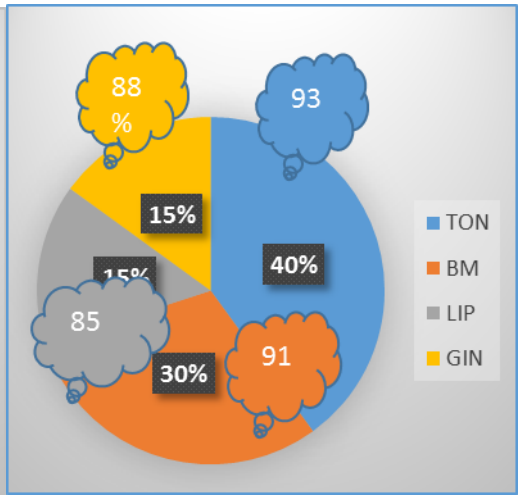

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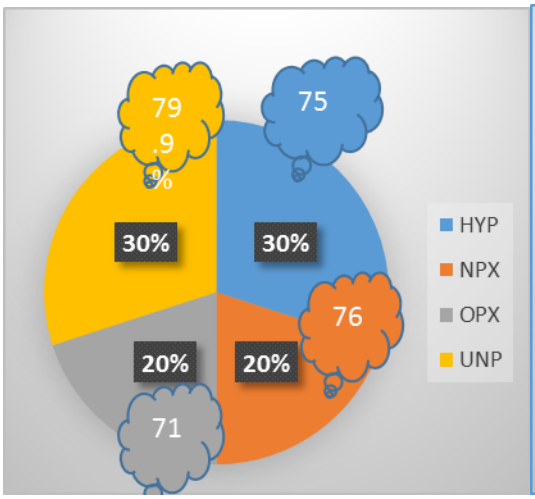

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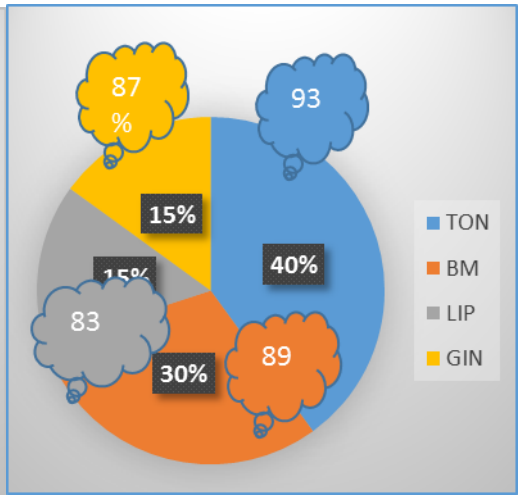

TEST	HIPPOCAMPUS NOT SPARED PRE Rx POST Rx		HIPPOCAMPUS SPARED PRE Rx POST Rx	
Speed	35.12%	33.4%	36.82%	36.74%
Attention	67%	65.7%	70.35%	69.55%
Comprehension	87.47%	86.96%	88.58%	88.03%
Learning and Memory	79.87%	73.43%	89.25%	88.34%

From the analysis it shows that there is much variation for learning and memory in study arm when compared to the control group. These indicate the dose to hippocampus patients are those who received more than 12Gy and these patients have neurocognitive deficit within 2 months from completion of treatment. It was found that in the control arm, the dose to the hippocampus was <11Gy (tolerance dose of hippocampus) for all the patients, whereas in the study arm, 7patients received >12Gy to the hippocampus region. After neuropsychological assessment, it was found that cognition impairment was present in 63-65% in study group for patients those who received >12Gy to the hippocampus and 36% for those who receive RT 10-12Gy. There was no significant variation in the control group**.**

DISCUSSUION:

Chemo-radiation plays in important role in the management of head and cancers. Radiation induced normal tissue injury occurs in the components of brain and results in cognitive deficit and on trends cognitive effect is being an important factor for an individual. This assessment done based on in order to reduce patient and clinical burden. It had alternate forms of the tests in order to reduce practice effects and therefore allow for repeated test administration. It had good psychometric properties such as validity, reliability, and population norms so that true changes in NCF above fluctuations due to situational factors can be detected. It had sensitive to changes in cognitive function. It had highly standardized and easy to administer so that no specialized psychological training is necessary in order to be able to administer the test battery. Most patients had completed the neurocognitive tests.

The Hopkins Verbal Learning Test (HVLT-R) test that has been used and validated in the phase III trial of motexafin gadolinium for patients with brain metastases. In this trial, compliance with NCF testing was 87% to 98% at baseline and 77% to 87% at 6 months (Meyers 2004). This is one of the study which have shown validated tool. In this study NIMHANS neuropsychological battery a validated tool have been used and analyzed with 15 subset of tests and results

reported as there is a decline in memory function which is related to hippocampal region.

The effect of medical interventions on neurocognitive function may also include chemotherapy, anticonvulsants, use of steroids and opioid analgesics have not been analyzed by the retrospective studies after radiotherapy. There are some data showing that an impaired pretreatment neurocognitive function may be significant problem for patients with head and cancers. Majority of head and neck cancers have an risk of alcoholic induced neurocognitive problem before the start of treatment, and these kind of patients definitely post treatment neurocognitive decline for alcohol dependency and alcoholic abuse.

On the other hand, Rogers et al retrospectively assessed alcohol use in a cohort of 58 patients with head and cancer and he found there is no association between alcoholic consumption and impaired neurocognitive function. Mostly treated patients have been mostly associated with depression. Results of this study have shown results of depression rates between 17 and 30% after completing the treatment. Although with depression symptoms they have reported that greater level of fatigue are those patients presented with neurocognitive function. Prospectively gathered data for treated head and cancer shown that should be compared with assessment of pretreatment baseline neurocognitive function.

This study have shown that there is decline in neurocognitive function for the hippocampus non spared group. Multifactorial approach have also been studied. The neurocognitive function not only based on only treatment approach, it depends upon the nature of person understanding towards the disease characteristics, treatment period, surrounding factors such as social well- being, intent of treatment of patients acceptance, personal hygiene, any habits, and how patient feels about the response of treatment. Neurocognitive deficit varies with the individual and performing capability, most neurocognitive function is related to more for the study group when compared to the control group.

CONCLUSION:

- Patients in whom base of skull is included in the radiation field as in cases of nasopharynx and hypopharynx,UNP, there is a significant dose received by hippocampus which in turn leads to impairment in cognition
- Cognition impairment can be seen from 2 months to 2 years post radiotherapy
- Hence, it is vital to spare hippocampal dose as much as possible to maintain a good quality of life.

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