PROJECT COMPLETION REPORT - DST/CSRI/2018/11
August 26,2019

1. **Title of the project:** Resting state functional magnetic resonance imaging and its cognitive correlates in patients with intracranial dural arteriovenous fistulas before and after interventional therapy.
2. **Principal Investigator(s) and Co-Investigator(s):**

PI Name & Organization

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Date of Birth: 25-09-1978

3. **Implementing Institution(s) and other collaborating Institution(s):**

Sree Chitra Tirunal Institute for Medical Sciences and Technology, Medical College PO, Thiruvananthapuram, Kerala, India. Pin: 695011

4. **Date of commencement:** 07-January-2020

5. **Planned date of completion:** 06-January-2023 (extended up to 06-July-2023)

6. **Actual date of completion:** 06-July-2023

7. **Objectives as stated in the project proposal:**

   i. Identification of resting state fMRI functional connectivity changes in patients with intra-cranial dural arteriovenous fistulas before and after embolization via functional connectivity analysis in comparison with normal healthy controls.

   ii. Defining the role of functional connectivity changes in the evaluation of cognitive impairment in dural arteriovenous fistulas patients in comparison with age matched cognitively normal healthy controls.

8. **Deviation made from original objectives if any, while implementing the project and reasons thereof:**

   Nil

9. **Experimental work giving full details of experimental set up, methods adopted, data collected supported by necessary table, charts, diagrams & photographs:**

During the three-year time (07-01-2020 to 06-07-2023) staff recruitment, equipment procurement, standardization of the procedure, data collection, analysis of data and publishing the results in international journals were done. A total of 20 DAVF patients and 20 age and gender matched healthy controls have been recruited after obtained IEC clearance. Baseline Neuropsychology and rsfMRI evaluations were done for all subjects. After one month of embolization therapy, 20 DAVF patients underwent both resting state fMRI and neuropsychological evaluation. One-year post embolization evaluation of 20 DAVF patients were also performed with similar protocol. Functional connectivity and neuropsychology correlative analyses were carried out using the obtained dataset. Data quality assessment was performed first. Functional connectivity analysis was done using group independent component analysis (ICA) and seed to voxel analysis. Neuropsychology scores of patients were compared with that of healthy controls and correlated with functional connectivity changes. Results were presented in various national and international conferences and published in reputed journals like JMRI and Neuroradiology. Apart from this, evaluated the low-frequency oscillations of the brain in intracranial DAVF patients using amplitude of low-frequency fluctuation (ALFF) and fractional ALFF (fALFF), in comparison to healthy controls. Disrupted low-frequency oscillation amplitude was found in multiple brain regions in dural fistula patients, with altered amplitude distributed over the frontal, temporal, parietal, and occipital regions. The results were presented as conference abstract at the Annual Conference of India Society of Neuroradiology (ISNR 2023) and is under review for publication. Also analysed the cognitive impairment subclassification of DAVF based on fractal analysis of resting state fMRI data, found that the machine learning classifiers are capable of subclassification of cognitive impairment from the resting state connectivity pattern, which were presented as conference abstract at the Annual

Conference of Cognitive Science (ACCS9) and is also under preparation of manuscript for publication. Also, using machine learning algorithms, developed a Convolution Neural Network model for identification and classification of intracranial dural arteriovenous fistula from susceptibility weighted images, which was presented at the International Society for Magnetic Resonance in Medicine (ISMRM) 2022 at London, UK.

Methodology

In this prospective functional connectivity study, consecutive DAVF patients fulfilling the inclusion criteria attending the Intervention Radiology outpatient / ward of Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), were screened for eligibility and willingness to participate and 20 patients were finally recruited. An equal number of age and gender matched healthy controls were also recruited for the study. The study had been approved by the Institute Ethics Committee (IEC) of SCTIMST. A written informed consent was obtained from each participant. Patients and controls underwent a thorough neurological examination and neuropsychological evaluation for cognitive assessment. All subjects underwent resting state fMRI study with a 3 Tesla MRI machine (Discovery 750w, GE Healthcare, Milwaukie, USA) as early as possible within 1 week of cognitive evaluation. The fMRI was done with eyes closed while being calm and mind not focusing on anything, without falling asleep. A high-resolution structural MRI was also acquired for anatomic reference using the three-dimensional T1-weighted magnetization prepared rapid acquisition gradient-echo sequence. After embolization of DAVf, patients had undergone follow up resting state fMRI, neuropsychological evaluation after one month and one year.

MRI data acquisition and protocol

Discovery MR750W 3.0 T MRI scanner (GE Health care, Milwaukee) with 24 channel phased array head coil was used to acquire structural and rs-fMRI images from each subject. These were acquired using following parameters: TR/ TE= 2500/ 30 ms, voxel size =3.31 x 3.31 x 4 mm3, FOV= 21.2 cm, slice thickness = 3.2 mm, matrix 64 x 64. A high-resolution reference axial 3D brain volume imaging sequence (BRAVO) with TR/TE = 7/2.98 ms, slice thickness = 1mm, flip angle = 12o, matrix size = 256 x 256, voxel size = 1 mm x 1mm x 1mm was collected for anatomical reference. All the participants were instructed to close their eyes and relax while inside the scanner while conducting the task-free resting-state fMRI acquisition.

Post processing

Post-processing of images was performed using the FC toolbox (CONN, version 18.b; https:// www.nitrc.org/projects/conn) running in SPM12. The steps included functional realignment (subject

motion estimation and correction), functional outlier detection (artifact detection tool-based identification of outlier scans for scrubbing), functional direct coregistration to structural body (rigid body transformation), structural segmentation (gray/white/CSF tissue estimation), functional direct segmentation and normalization (simultaneous gray/white/CSF segmentation and MNI normalization), and functional smoothing (spatial convolution with Gaussian kernel). The images were smoothed using an 8-mm full-width-at-half-maximum (FMWH) Gaussian kernel. Linear de-spiking was performed on the RS-fMRI data. Potential confounding effects used in CONN's default de-noising pipeline, such as noise components from cerebral white matter and cerebrospinal fluid areas, estimated subject-motion parameters, and identified outlier scans, or scrubbing, were used in this study (overall blood oxygen level dependent [BOLD] signal percentage variance threshold was set at 0.25). Component-based noise reduction method (CompCor) in CONN was used to remove principal components from noise regions of interest. The motion parameters were used as first-level covariates for the analysis. The bandpass filter of 0.008 to 0.09 was applied to data to reduce noise effects and low frequency drift.

Also, evaluated the amplitude of low-frequency oscillations of the brain in intracranial dAVF patients using amplitude of low-frequency fluctuation (ALFF) and fractional ALFF (fALFF) and correlated with the cognitive impairment subclassification of dAVF based on fractal analysis of resting state fMRI data. We also used Machine Learning approaches for the identification of intracranial DAVF on susceptibility-weighted images (SWI) with convolutional neural network (CNN) to determine whether intracranial DAVF could be reliably identified on susceptibility-weighted images (SWI), that help physicians on imaging diagnosis.

10. **Detailed analysis of results indicating contributions made towards increasing the state of knowledge in the subject:**

(i)All the structural and resting state fMRI were converted to NIFTY images. Anterior commissure and posterior commissure alignment are done for all structural and functional images. Check registration option of spm8 was used to make it clear that structural and functional images are in same alignment. Resting state fMRI images were processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and Conn toolbox (https://www.nitrc.org/projects/conn/).

(ii) Resting state fMRI images were subjected to functional realignment, functional segmentation, and normalization to MNI space (Montreal Neurological Institute). Smoothing was done by spatial convolution with Gaussian kernel of 8mm full width half maximum. To correct physiological noise, the inbuilt Compcor method (Component based noise correction) in Conn tool box was used. Nuisance

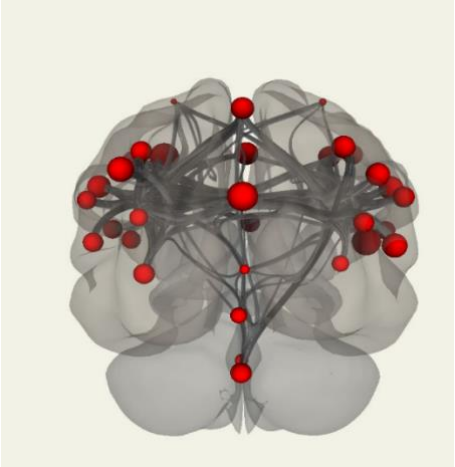
covariates regression was used to regress out the BOLD signal obtaining from white matter and cerebrospinal fluid signals.

(iii) During first level model for reducing residual motion effects, Realignment parameter was added as a covariate. The resulting signal was band pass filtered using a cut off frequency of 0.008-0.09Hz. After the pre-processing, denoising was done. First level and second level analysis were conducted in conn toolbox to extract the final results.

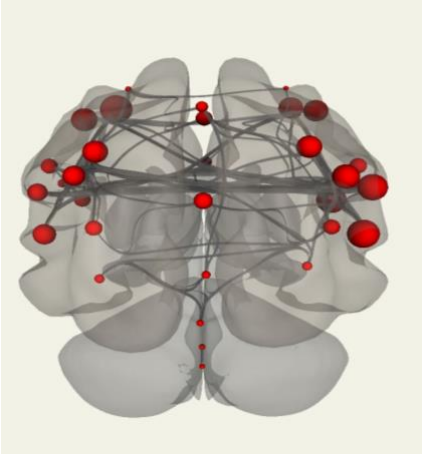
(iv) The functional connectivity analysis between the region of interest (ROI) was done using group independent component analysis (ICA) and ROI to ROI analysis (pFDR corrected < 0.05).
(vi) Second level functional connectivity analysis was conducted by the effect of dAVF patients over healthy controls settings.
(v) Also, second level functional connectivity analysis was conducted by the effect of dAVF patients over post embolization dAVF patients on month and twelve month follow up.

Results of analysis:

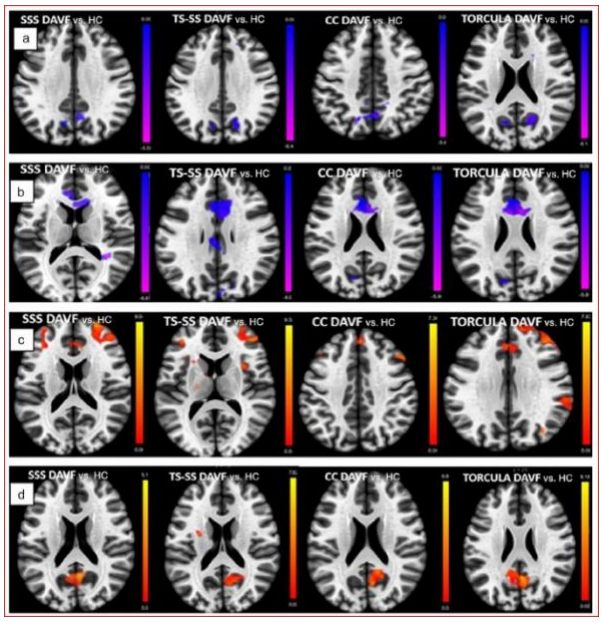
The following connectivity figures show the graphical network analysis in DAVF patients compared to healthy control and post embolization. The results obtained from a preliminary in-house funded project and the current project are published in Journal of Magnetic Resonance Imaging JMRI ("Alterations in Resting-State Functional MRI Connectivity Related to Cognitive Changes in Intracranial Dural Arteriovenous Fistulas Before and After Embolization Treatment". J Magn Reson Imaging. 2022;55(4):1183-1199.) and in Neuroradiology ("Impaired intrinsic functional connectivity among medial temporal lobe and sub-regions related to memory deficits in intracranial dural arteriovenous fistula" Neuroradiology.2021 ;63(10):1679-1687).



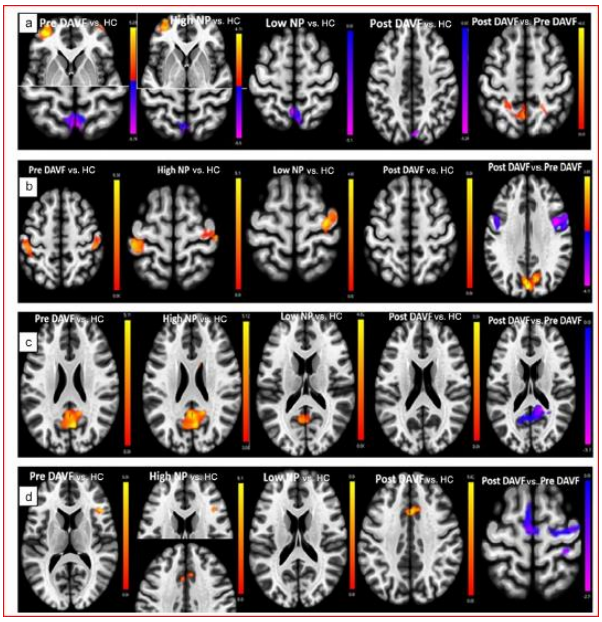
Pre DAVF patient vs Healthy control



Pre DAVF patient vs Post embolization



Group ICA functional connectivity analysis



Seed to voxel functional connectivity analysis

11. **Conclusions summarizing the achievements and indication of scope for future work:**

Dural arterio- venous fistula (DAVF) can produce hemorrhagic and non- hemorrhagic complications in the human brain. While embolization treatment strategies are currently aimed at reducing hemorrhagic risk, it should be noted that DAVF is also a cause for preventable dementia, if diagnosed and intervened early. This project looked at the resting state connectivity analysis and their cognitive correlates in patients with DAVF before and after treatment. The data analysis showed promising results which help to predict the cognitive outcome in such patients.

12. **S&T benefits accrued:**

i. (a) **List of Research publications**

Sr.	Authors	Title of paper	Name of the Journal	Volume	Pages	Year
1	Sekar S, Kannath SK, Ramachandran S, Menon RN, Thomas B.	Alterations in Resting-State Functional MRI Connectivity Related to Cognitive Changes in Intracranial Dural	Journal of Magnetic Resonance Imaging	Volume 55, Issue 4	957-1272	2022

		Arteriovenous Fistulas Before and After Embolization Treatment.				
2	Joseph JE, Sekar S, Kannath SK, Menon RN, Thomas B.	Impaired intrinsic functional connectivity among medial temporal lobe and sub-regions related to memory deficits in intracranial dural arteriovenous fistula.	Neuroradiology	Volume 63	1679–1687	2021
3	Jithin S S, S Kannath, S Ramachandran R S N Menon, BThomas,	Cognitive impairment subclassification using various machine learning approaches on fractal analysis of resting state functional MRI data	Brain Imaging and Behavior	Submitted (Under review)		2023
4	Amplitude of low-frequency fluctuation (ALFF) and fractional ALFF in intracranial dural fistula patients using resting-state functional MRI	Jithin S S, S Kannath, S Ramachandran R S N Menon, BThomas,		Manuscript under preparation		2023

(**b) Papers published in Conference Proceedings**

1. Cerebral Circulation Time Related DMN Connectivity in Intracranial Dural Arterio-Venous Fistula before and after treatment. Bejoy Thomas, Jithin S S, Sabarish S Sekar, Santhosh Kannath, Ramshekhar N Menon. Annual Virtual Conference of International Society for Magnetic Resonance in Medicine (ISMRM), May 15- 20, 2021.

2. Frequency Dependent Altered Functional Connectivity of Declarative Memory Networks in Patients with Dural Arterio Venous Fistula. Bejoy Thomas, Josline Elsa Joseph, Sabarish S Sekar, Santhosh Kannath, Ramshekhar N Menon. Annual Virtual Conference of International Society for Magnetic Resonance in Medicine (ISMRM), May 15- 20, 2021.

3. Machine learning for detecting intracranial dural arteriovenous fistula on susceptibility weighted image using a convolutional neural network. Bejoy Thomas, Jithin S S, Ajimi mol Anzar, and Santhosh Kannath. Annual Virtual Conference of International Society for Magnetic Resonance in Medicine (ISMRM), May 07-12 May 2022.

4. Resting state functional MRI connectivity alterations related to cognitive changes in intracranial dural arteriovenous fistulas before and after embolization treatment. Sabarish S Sekar, Santhosh Kannath, Sushama Ramachandran, Ramshekhar N Menon and Bejoy Thomas.8 th Annual Conference of Cognitive Science (ACCS8), 20th – 22 nd January 2022.
5. Cognitive impairment subclassification using various machine learning approaches on fractal analysis of resting state functional MRI data. Jithin S. S., Santhosh Kumar K., Ramshekhar N. Menon and Bejoy Thomas.9th Annual Conference of Cognitive Science (ACCS9), 8th – 10th December 2022.

6. Amplitude of low-frequency fluctuation (ALFF) and fractional ALFF in intracranial dural fistula patients using resting-state functional MRI. Jithin S. S., Santhosh Kumar K. and Bejoy Thomas, 24th Annual Conference of India Society of Neuroradiology (ISNR 2023), 24th– 26thFeb 2023.

7. Cognitive Improvement Post-Endovascular Treatment of Intracranial Dural Arteriovenous Fistula:A Prospective Study. Bejoy Thomas, Dewansh Mishra, Santhosh Kumar K. 14th Asian Oceanian Congress of Neuroradiology (AOCNR), Singapore, 18- 20/Aug2023

ii. **Manpower trained on the project**

a) **Research Scientists or Research Associates:** Senior Research Fellow
b) **No. of Ph.D. produced:** Nil
c) **Other Technical Personnel trained:** Research Fellows 2, DM students-3

iii. **Patents taken, if any*:*** Nil

13. **Financial Position:**

Sr.	Budget Head	Funds Sanctioned	Expenditure	% of Total cost
1.	Manpower	1086160	1086160	100%
2.	Consumables	300000	300000	100%
3.	Contingencies	43096	43096	100%
4.	Travel	45097	15097	33.47%

5.	Overhead Expenses	120000	120000	100%
6.	Equipment	149200	127246	85.28 %
7.	Others, if any	-	-	-
	Total	1743553	1691599	97.02 %
Bank interest earned Rs.16147/- is remitted vide Bharatkosh				

14. **Procurement/Usage of Equipment**

a)

Sr.	Name of Equipment	Make/ Model	Cost (FE/ Rs.)	Date of Installation	Utilization Rate (%)	Remarks regarding maintenance/ breakdown
1	Dell OptiPlex 7070 MT	2020	1,27,246.00/-	02-07-2020	85.29 %	Nil