Original Article

# Hippocampal Volume in Children with Attention Deficit Hyperactivity Disorder and Speech and Language Delay

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## Abstract

**Introduction:** Hippocampus is a complex brain structure located deep in the temporal lobes of the brain. The structure has been implicated in several disorders related to cognition. Reports are emerging of its involvement in attention deficit hyperactivity disorder (ADHD). The current study was planned to assess the volume of the hippocampus in children with ADHD and speech and language delay with normal birth history using magnetic resonance imaging (MRI) of the brain. **Material and Methods:** MRI brain of 12 children (age range = 3–6 years) and 22 controls with clinical diagnosis of ADHD as per Diagnostic and Statistical Manual-5 were obtained in oblique coronal sequence (T1 weighted). The entire hippocampus formation was outlined manually using Image-J software available freely from www.freesurfer.com. Results were expressed as volume cubic millimeters ± SD. **Results:** Volumes of the hippocampi of children with ADHD were 2450.2 ± 667 $mm^3$ (R) and 2505.8 ± 878.5 $mm^3$ (L), respectively. The mean volume (bilateral) of the cases was 2478 ± 772.75 $mm^3$. The right hippocampal volume of the controls was 3255.8 ± 1374.3 $mm^3$ (R) and that of the left side was 3159.3 ± 1451 (L) $mm^3$, respectively. **Conclusion:** Current study reported a substantial shrinkage (23%) of the left and right hippocampus in children with ADHD compared to controls.

**Keywords:** Atrophy, attention deficit hyperactivity disorder, hippocampus

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder affecting millions. Prevalence of ADHD ranges from 5.4% to 6% in the world[1]; prevalence in India[2] has been reported to be 11% in primary school children. Children with ADHD were present with deficient attention and/or hyperactivity due to which tasks involving mental abilities become challenging for them. In cases with hyperactivity, issues in playing quietly, and symptoms such as excessive talking, interruption, or intrusion of other children occur. The contribution of the hippocampus to attention deficit in ADHD is likely since attention and memory are complimentary and synergistic brain functions and are localized hippocampus as a neural substrate.[3] This is exemplified by the fact that most patients with ADHD have language or speech problems perhaps caused by the inability to focus attention and by impulsive speech or behavior.

Hippocampus is a complex brain structure located in the temporal lobes of the brain.[1,2] The structure has been implicated in several disorders related to cognition. Reports[3] are emerging of its involvement in ADHD. Attention and memory are interlinked and complimentary by nature and are predominant hippocampal functions. It looks plausible to assume that the involvement of the hippocampus could be contributing to encoding and retrieval dysfunction seen in children with ADHD. Also, there seem to have neural mechanisms used by the brain in service of memory and language involving hippocampi.

ADHD[4-7] is classified into three distinct subtypes: inattentive, hyperactive-impulsive, and combined types. Each type has distinct symptoms and corresponding treatments. However, the most common is the combined type, when patients have symptoms of both inattentive and hyperactive-impulsive subtypes. Speech and language delay is common in children with ADHD affecting up to 30–50% of cases.

Limbic structures have been implicated in the genesis of ADHD by the presence of mood and cognitive disturbances (e.g., poor attention, memory, executive dysfunction, etc.) in affected individuals and by elevated rates of mood disorders in family members of probands with ADHD. The current study was planned to assess the volume of the hippocampus in children with ADHD with speech and language delay and normal birth history using magnetic resonance imaging of the brain.

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## Material and Methods

MRI brains of the children with a clinical diagnosis of ADHD as per Diagnostic and Statistical Manual-V were obtained in oblique coronal sequence (T1-weighted). The entire hippocampus formation was outlined manually using Image-J software available freely from www.freesurfer.com. Results were expressed as volume cubic centimeters.

a. Enrolment: Preschool children (3 to 6 years) coming to the outpatient pediatrics department of a tertiary care institute in Western India with speech and language delay and normal birth history were assessed using DSM-V criteria for diagnosis of attention deficit hyperactivity disorder (n = 12). The majority of the patients were from rural backgrounds. Controls were (n = 22; age = 2–12 years; M:F = 15:7) children with headaches, generalized seizures where neuroimaging was done as a routine diagnostic workup. Additional T1-weighted sequences, perpendicular to the long axis of the hippocampus, were taken for measurement of hippocampal volumes for these children. Preschool children (3–6 years) with a diagnosis of attention deficit hyperactivity disorder with speech and language delay, who had undergone magnetic resonance imaging of the brain, were taken into the study. ADHD children with abnormal birth history or having autistic features were excluded. Also, those with a history of abnormal birth history and abnormal T2 FLAIR images (e.g., malformation, birth trauma, etc.) were excluded from the current study. Serum B12 and Vitamin-D3 were measured in all cases.
b. Magnetic resonance brain scans: MRI brain of children who have met the diagnostic criteria for ADHD with speech and language delay as per the Diagnostic and Statistical Manual of Mental Disorders-5 was acquired by a trained radiologist using MPRAGE sequence (Epilepsy protocol). T1-weighted inversion recovery coronal images obtained in the oblique coronal plain were taken.
c. Image parameters: High-resolution T1-weighted images of the brain using an MPRAGE pulse sequence [repetition time (TR) = 1900 ms; echo time (TE) =3.13 ms; flip angle = 9°; matrix size = 256 × 256; field of view (FOV) = 230 × 230 $mm^2$; thickness = 0.9 mm] were obtained. Foam pads to minimize head motion-related artifacts during brain scanning were used.
d. Hippocampal volume measurement process: Measurement of hippocampal volumes using MRI brain images was done using a standard measurement protocol as described previously.[8] After getting the Coronal Oblique MRI Brain Images in Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE sequences), they were opened in DICOM viewer to examine any gross structural brain abnormalities. The images were then transferred to Image-J, a software designed by the National Institute of Health J (Available freely from https://imagej.nih.gov/ij/download.html). Images were transferred to Image-j from DICOM viewer, and measurement was done. Process followed was manual delineation of the hippocampus starting from the head of the hippocampus. Boundaries between the hippocampus and the amygdala were identified anteriorly, and the head of the hippocampus was used as the anterior boundary and tail as the posterior boundary. Likewise, the cortical boundary section between entorhinal cortex and hippocampus was used as the lateral boundary of the left and right hippocampus. The area was summed up and multiplied by the inter-slice gap to get the entire volume as per standard protocol. Non-normal hippocampal volumes have been calculated in this study. Study was approved by Institute Ethics Committee, ICMR-NIIRNCD Jodhpur (Rajasthan), vide letter no ICMR-NIIRNCD IEC/2022/PG/3.

## Results

The volume of hippocampus in children with ADHD was 2450.2 ± 667 $mm^3$ (R) and 2505.8 ± 878.5 $mm^3$ (L). The mean volume (bilateral) was 2478 ± 772.75 $mm^3$. Right hippocampal volume of the control was 3255.8 ± 1374.3 $mm^3$ (R) and 3159.3 ± 1451 $mm^3$, respectively. The bilateral mean of the cases was 3207.5 ± 1397.6 $mm^3$. There was a mean volume loss of about 23% in children with ADHD compared to controls [Figure 1]. Comparison of cases and controls hippocampal volume in the current study are given in Table 1.

Serum B12 was normal in all children and Vitamin-D3 was normal in all except one child in the control group where vitamin D deficiency was noted. Details of the cases are given below in Table 1.

## Discussion

ADHD is currently diagnosed clinically and does not have any biomarker (laboratory or radiological) that can help confirm the clinical diagnosis. Neuropsychological tests have low sensitivity for diagnosing the disorder. Therefore, evaluation of the patient is done using different scales and corroboration by informants (e.g., parents/or teachers) is required.

Hippocampus has long been recognized as a site for learning and memory.[3,8] Since neurocognitive deficits are prominent among children with ADHD, hippocampal measurement

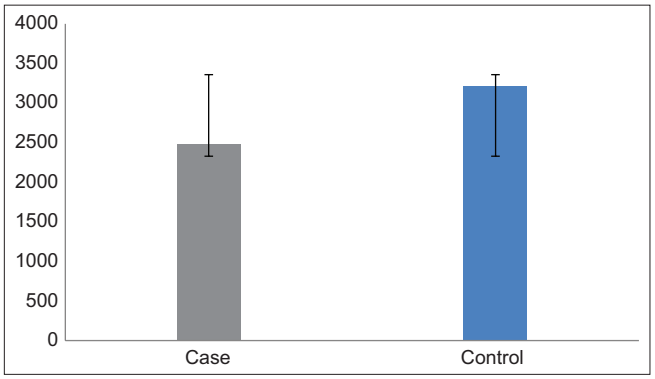


**Figure 1:** Comparison of cases and controls hippocampal volumes (total) in the current study

**Table 1: Hippocampal volume measurements of patients with attention deficit hyperactivity disorders in the current study along with clinical details and 3D maps of hippocampal areas**

| Age, Gender | Left HPV ($mm^3$) | Right HPV ($mm^3$) |
|---|---|---|
| 5 years/female | 2916.3 | 2702.2 |
| 3 years/male | 2730 | 2715 |
| 5 years/male | 1719 | 1863 |
| 4 years/male | 2211 | 2706 |
| 4 years/female | 1309.7 | 2076 |
| 3 years/male | 1535.2 | 1397 |
| 8 years/male | 2845.5 | 1930.8 |
| 3 years/male | 3195 | 3329.4 |
| 5 years/male | 4101.3 | 3744 |
| 4 years/male | 1946.7 | 1944 |
| 7 years/male | 3672.6 | 2747.1 |
| 8 years/male | 1887.6 | 2248.8 |

was chosen for the current study as a putative radiological biomarker. Also seizure disorder is an associated factor for hippocampal volume loss; children with ADHD have an increased risk of seizures, with approximately 14% of children with ADHD, clinical subtypes related to hippocampal volume loss. ADHD is the most common co-occurring disorder in children with epilepsy. However, the children enrolled in the current study as cases who were selected to undergo an MRI brain were free from seizures. Control children had generalized seizures, but they had a normal birth and neurodevelopmental history and had no structural lesion on the MRI brain.

A recent study found a significant reduction of total hippocampal volume in the combined ADHD group compared to healthy controls. This reduction was due to the atrophy of regions of the hippocampus, that is, CA1, CA4, molecular layer, granule cell layers of the dentate gyrus, presubiculum, subiculum, and hippocampal tail.[3] Atrophy of the hippocampus was present in all the areas of the hippocampus, for example, CA1, CA4, molecular layer, granule cell layers of the dentate gyrus, presubiculum, subiculum, and hippocampal tail. The current study has taken children diagnosed with speech and language delay with ADHD using DSM-5 but having the normal birth history and no autistic spectrum disorder.

ADHD is characterized by age-inappropriate symptoms of inattention and/or hyperactivity-impulsivity that interfere with cognitive functioning and development hinting at hippocampal involvement. Despite its high prevalence and impact, neural mechanisms underlying ADHD remain unclear[4-8]; hence, a clinically useful biomarker is not available.[4-8]

Several observations have emerged in hippocampal volume loss seen in earlier studies, for example, reduction of hippocampal subfields could account for hippocampal volume loss. Also, the volume loss is related to the combined phenotypes of attention deficit hyperkinetic children.[3] The same has been documented in children taking high doses of medication.[9]

ADHD is a typical disorder associated with attention deficit; there have been inconsistencies between the findings regarding the changes in the hippocampal volume in children and adolescents diagnosed with ADHD in published studies.[10] Brain dysfunction is key to patients with ADHD,[11] which could have been the reason behind the reduced hippocampal volume seen in current study. It has been examined that methylphenidate, the main drug acting on hippocampal neurons, has an impact on its neurovascular unit and functions.[12] The current study has excluded children with abnormal birth history as neonatal hypoxia has been shown to cause ADHD in later life.[13] This points toward the reduction in hippocampal volume in perhaps being the causative factor associated with brain pathology related to loss.

It has been demonstrated that attention is associated with hippocampal functions because adults who were better at recalling working memory demonstrated higher activation in the hippocampus during the encoding stage. The same association of hippocampal volume with attention during childhood and adolescence is less examined. It has now been realized that in ADHD with comorbid conditions, there are changes in brain morphology other than the hippocampus as well.[14] The same correlations between hippocampal volume and adult patients have been observed.[15,16] The role of hippocampus in ADHD seems to be growing,[10,17,18] and a recent study has linked the disease severity of ADHD with the hippocampus and amygdaloidal involvement.[17]

While enlargement of the head of the hippocampus has been reported in the hippocampal head,[19,20] the children in the study belonged to the older age group (6–18 years). The current study reports shrinkage among young children (preschool) of whole hippocampal volume which is the usual age group for patients with ADHD. Moreover, findings of hippocampus enlargement are not very stable across different samples of patients with ADHD. Contradictory findings may be related to the different locations of alterations along the complex circuits responsible for the different symptoms of ADHD. Further studies involving larger samples of adult patients with ADHD and using multimodal designs are needed.[20,21] Though the current study has reported the volumes of hippocampi in patients with attention deficit disorders as reduced, the small sample size is an obvious limitation, which can be addressed using an adequately powered study involving a larger sample size. An additional limitation is non-normalized, non-correlated volumes, and non-significant differences between the two groups. Notwithstanding the limitations, this is the first study from the Indian subcontinent and only study to be the best of our knowledge that has measured hippocampal volume in children with ADHD and speech and language delay with normal birth history. The study proposes hippocampal volume as a surrogate marker for diagnosing patients with ADHD with speech and language delay subjected to confirmation of results in a larger subset of patients.

## Conclusion

The current study reported a substantial shrinkage hippocampus in children with attention deficit hyperkinetic disorders with speech and language delay.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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