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Volumetric analysis of hippocampal sub-regions in late onset depression: A 3 tesla magnetic resonance imaging study

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ABSTRACT

Background: While many studies have reported reduced volume of hippocampus in late onset depression (LOD), the status of hippocampus sub-regions (anterior/posterior) is yet to be explored. Evaluating hippocampal sub-regions might facilitate better elucidation of the neurobiological basis of LOD.
Methods: Twenty five elderly subjects with LOD (mean age = 65.28 yr, SD = 5.73, 15 females) and 20 healthy controls (mean age = 65.35 yr, SD = 5.67, 7 females) were examined using 3-tesla magnetic resonance imaging (MRI). They were also evaluated with Montgomery Asberg Depression Rating Scale (MADRS) and Hindi Mental State Examination (HMSE). We examined the difference in volume of Hippocampal sub-regions between the LOD group and control group controlling for the age, sex and intracranial volume.
Results: Left posterior hippocampus volume was significantly smaller in LOD group than the control group (1.01 ± 0.19 ml vs 1.16 ± 0.25 ml, $F = 7.50$, $p = 0.009$). There was a similar trend for the right posterior hippocampus (1.08 ± 0.19 ml vs 1.18 ± 0.27 ml, $F = 3.18$, $p = 0.082$). Depression severity (mean MADRS score = 20.64 ± 8.99) had a significant negative correlation with volumes of right posterior hippocampus ($r = -0.37$, $p = 0.012$) and left posterior hippocampus ($r = -0.46$, $p = 0.001$) in the LOD group.
Conclusions: Specific reduction of posterior hippocampus volume and its relationship with depression severity indicates sub region specific hippocampal volumetric abnormalities in LOD. Future studies need to evaluate sub region specific hippocampal volume in LOD longitudinally for better understanding of the pathogenesis of LOD in view of the functional differences between anterior and posterior hippocampus.

1. Introduction

Depression is associated with structural brain changes in the form of reduced volume in areas like hippocampus, caudate, putamen, anterior cingulate cortex, orbito-frontal cortex and thalamus (Kempton et al., 2011; Koolschijn et al., 2009). Several studies and meta-analysis have shown reduced hippocampal volume in depression (Campbell et al., 2004; Kempton et al., 2011; McKinnon et al., 2009; Videbech and Ravnkilde, 2004). However there are several inconsistencies in the correlates associated with reduced hippocampal volume in depression. Factors like age group of subjects, subtypes based on age of onset of first episode (early vs late), duration of illness, recurrence, severity and measurement of sub-regions of hippocampus are some of the important correlates that are likely to determine the association of hippocampal volume with depression(Eker and Gonul, 2010). There are only limited numbers of studies evaluating hippocampal volume in elderly with depression. A recent meta-analysis of studies in late life depression reported significantly reduced hippocampal volume but of small effect size. However, there were many individual comparison studies (8 out of 15) that did not show significant reduction of hippocampal volume in late life depression (Sexton et al., 2013).

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Some studies have suggested that hippocampal volume is reduced in elderly with early onset depression (Gerritsen et al., 2011; Janssen et al., 2007). Abnormality in hypothalamic–pituitary–adrenal (HPA) axis leading to glucocorticoid toxicity has been proposed as the mechanism behind hippocampal volume reduction in early onset depression. On the contrary, studies evaluating this cortisol mediated pathway did not establish this mechanism conclusively (Gerritsen et al., 2011; O'Brien et al., 2004). Also some studies have shown that hippocampal volume is reduced in patients with late onset depression (LOD) (Hickie et al., 2005; Lloyd et al., 2004). Sharing of pathophysiology between LOD and Alzheimer's Dementia (AD) has been proposed as the underlying mechanism, based on the evidence for elevated risk for AD with history of LOD (Jorm et al., 1991). Hippocampal volume is reduced in phenotypically heterogeneous conditions like schizophrenia and depression. Hippocampal subfields (dentate gyrus, CA1, CA3 and subiculum) and sub-regions along longitudinal axis (anterior and posterior) appears to have functional heterogeneity (Small et al., 2011; Strange and Dolan, 1999). Hence measurement of total hippocampus volume might reduce the effect due to specific sub-regional hippocampal volume change. Recent studies on adults with depression have suggested reduced volume in the posterior hippocampal sub-region (Maller et al., 2007; Neumeister et al., 2005). Volumetric analysis of hippocampal sub-region has not been adequately studied in elderly with LOD.

In this study, we evaluated the difference in volume of hippocampal sub-regions between elderly subjects with LOD and healthy control group. We hypothesized that elderly with LOD will have reduced hippocampal volume, particularly in the posterior hippocampal sub-region based on the results of previous studies (as summarized above) in depression.

2. Methods

2.1. Participants

Subjects with LOD ($N = 25$) were recruited from the geriatric clinic and services at the National Institute of Mental Health and Neurosciences (NIMHANS). All subjects in the LOD group had diagnosis of major depression according to Diagnostic Statistical Manual (DSM) IV. Diagnosis was done by trained research fellow after administering structured diagnostic evaluation with Mini International Neuropsychiatric Interview Plus (MINI Plus) (Sheehan et al., 1998). Subsequently the diagnosis was confirmed by a consultant psychiatrist through independent evaluation. Other inclusion criteria for subjects in the LOD group were age above 60 years and onset of first depressive episode after 50 years of age. Subjects were excluded from the study if they had psychotic symptoms, dementia, stroke, Parkinson's disease, epilepsy, significant head injury, treatment with electroconvulsive therapy, regular substance use other than nicotine and any other major comorbid psychiatric, neurological or general medical illness likely to interfere with participation in the study. The control group ($N = 20$) were recruited from volunteers in the community by word of mouth. They were matched for age and sex with LOD group. They were screened to rule out psychiatric illness and other neurological illness like dementia, stroke etc. by administering MINI plus structured interview and comprehensive clinical evaluation. Also a detailed family history assessment was done to exclude those with history of psychiatric illness in first degree relatives from the control group. All the subjects in both LOD and control group were right handed individuals.

Subjects fulfilling the above mentioned criteria were recruited for the study after written informed consent. The study was approved regarding ethical aspects by NIMHANS Ethics committee.

2.2. Assessments

The socio-demography and details of other relevant history were collected through a semi-structured questionnaire. Specifically age of onset of first episode of depression in LOD group was clarified by interviewing patient, reliable informant and review of available records. Depression severity was assessed with Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Cognitive function was assessed with Hindi Mental State Examination (HMSE) (Ganguli et al., 1995), which is the Indian adaptation of Mini Mental state Examination (MMSE). Assessment of vascular risk factors was done based on the presence of diabetes, hypertension, ischemic heart disease, dyslipidaemia and smoking/chewing nicotine. Information from history, physical examination, use of medications for treatment of the above conditions, review of medical records and blood investigations were considered for deciding the presence of vascular risk factors. Vascular risk score was calculated by adding up the above mentioned five risk factors. The segmentation of hippocampus anterior and posterior sub divisions was done at the level of uncal sulcus as shown in Fig. 1

2.3. MRI scan

All subjects underwent 3 tesla magnetic resonance imaging (MRI) brain scan. T1 weighted images (with capability for 3-dimensional reconstruction) were acquired using the following parameters: TR = 8.1 ms, TE = 3.7 ms, nutation angle = 8 degree, FOV = 256 mm, slice thickness = 1 mm without interslice gap, NEX = 1, matrix = 256 × 256. The scans were aligned in a consistent fashion so that the long axis of the hippocampus was comparable across the subjects. The images were transferred on to a personal computer (PC) platform. They were archived with coded identification. MRI Scans were reviewed by experienced neuroradiologist for any gross structural abnormalities. Anterior and posterior sub-region hippocampal volumes were measured using 3D Slicer software as per established guidelines.

2.3.1. Hippocampus Volumetry

Bilateral hippocampi with anterior-posterior sub-divisions were measured using MRI scans with the software '3D Slicer 3.4' (http://www.slicer.org). The structure was outlined by the rater who was blind to the diagnostic group status of the subjects using the computer mouse controlled pointer and measured using manual three-dimensional interactive method. The gray matter area was marked in each consecutive coronal slice along the anterior to posterior using anatomical landmarks validated using review of literature (Konrad et al., 2009). Anteriorly, first appearance of alveus was identified to reliably differentiate hippocampus from amygdale (MacQueen et al., 2003). Superior border of hippocampus is covered by the alveus and adjoins to cerebrospinal fluid while the inferior border was identified by the white matter of the parahippocampal gyrus below the subiculum. The lateral ventricle CSF was used as an external landmark to define the lateral extent. Medial border was defined superiorly by the CSF of the cisterna ambiens and inferiorly by vertical arbitrary line placed at the dorsomedial tip of the white matter of the parahippocampal gyrus (Neumeister et al., 2005). In the coronal slice, where an ovoid gray matter starts to appear inferiomedially to the trigone of the lateral ventricle marked the posterior end (Narr et al., 2004).

Hippocampal sub-divisions namely anterior hippocampus (AHc, hippocampal head) and posterior hippocampus (PHc, hippocampal body & tail) were obtained along the longitudinal axis (Weiss et al., 2005). Similar attempt of mapping hippocampal sub-divisions namely—the anterior as well as posterior has been done in previous report on hippocampal volumetry in patients with depression although not in geriatric age ranges