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Review

A systematic review and meta-analysis of longitudinal hippocampal atrophy in healthy human ageing☆,☆☆,★,★★

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ABSTRACT

Introduction: This review aimed to produce hippocampal atrophy rate estimates from healthy ageing studies as well as control samples from observational studies across the adult lifespan which can be used as benchmarks to evaluate abnormal changes in pathological conditions.

Methods: The review followed PRISMA guidelines. PUBMED (to February 2014) was searched for longitudinal MRI studies reporting hippocampal atrophy or volume change in cognitively healthy individuals. Titles were screened and non-English, duplicate or irrelevant entries were excluded. Remaining record abstracts were reviewed to identify studies for full text retrieval. Full text was retrieved and screened against inclusion/exclusion criteria. Bibliographies and previous reviews were examined to identify additional studies. Data were summarised using meta-analysis and age, segmentation technique and study type were tested as potential moderators using meta-regression. It was hypothesised that population studies would produce higher atrophy rates than clinical observational studies.

Results: The systematic search identified 4410 entries and 119 studies were retrieved with 58 failing selection or quality criteria, 30 were excluded as multiple reports and 3 studies were unsuitable for meta-analysis. The remaining 28 studies were included in the meta-analysis, n = 3422, 44.65% male, 11,735 person-years of follow-up, mean age was 24.50 to 83 years. Mean total hippocampal atrophy for the entire sample was 0.85% per year (95% CI 0.63, 1.07). Age based atrophy rates were 0.38% per year (CI 0.14, 0.62) for studies with mean age <55 years (n = 413), 0.98% (CI 0.27, 1.70) for 55 to <70 years (n = 426), and 1.12% (CI 0.86, 1.38) for ≥70 years (n = 2583). Meta-regression indicated age was associated with increased atrophy rates of 0.0263% (CI 0.0146, 0.0379) per year and automated segmentation approaches were associated with a reduced atrophy rate of −0.466% (CI −0.841, −0.090). Population studies were not associated with a significant effect on atrophy. Analyses of 11 studies separately measuring left and right hippocampal atrophy (n = 1142) provided little evidence of laterality effects. While no study separately reported atrophy by gender, a number tested for gender effects and 2 studies reported higher atrophy in males.

Conclusions: Hippocampal atrophy rates increase with age with the largest increases occurring from midlife onwards. Manual segmentation approaches result in higher measured atrophy rates.

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Contents

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Introduction

The hippocampus plays an essential role in memory function, goal selection, and mood regulation. Hippocampal volume changes have been associated with neurological conditions including Alzheimer's disease (Jack et al., 2000; West et al., 1994), Parkinson's disease (Camicioli et al., 2003), Huntington's disease (Majid et al., 2011), epilepsy (Liu et al., 2001), schizophrenia (Wang et al., 2008), and depression (Arnone et al., 2012; Steffens et al., 2011). Hippocampal volume changes also occur across the typical adult lifespan (Raz et al., 2010). However, the magnitude of normal hippocampal age related change is unclear and this presents a challenge when evaluating abnormal changes in pathological conditions such as Alzheimer's disease.

In order to accurately estimate hippocampal change in pathological conditions it is critical that reliable and precise estimates be available for generally healthy populations of different ages. This review has focused on estimates from longitudinal studies in preference to cross-sectional estimates because cross-sectional estimates can be confounded by individual subject baseline volumes. Studies where both longitudinal and cross-sectional analyses were used indicate that cross-sectional studies are less able to detect hippocampal volume change effects (Du et al., 2006; Raz et al., 2005; Ridha et al., 2006).

There is now a substantial body of research investigating longitudinal hippocampal volume change across multiple domains encompassing the entire adult lifespan. The domain covering younger individuals focuses on neurodegenerative conditions that become apparent in adolescence or young adulthood such as schizophrenia, temporal lobe epilepsy and mood disorders (Geuze et al., 2005). The studies in these younger age groups tend to have small sample sizes and small effect sizes (<0.5% annualised atrophy). A second domain of research focuses on conditions that become apparent later in life including AD, other forms of dementia, Parkinson's disease, Huntington's disease and other age related pathologies (Geuze et al., 2005). Hippocampal atrophy rates increase prior to the appearance of AD symptoms and continue to increase as the disease progresses (Fox et al., 2001; Ridha et al., 2006; Whitwell et al., 2007). Given that the incidence of dementia is increasing as populations worldwide age (Fratiglioni et al., 1999), a growing body of research on dementia with many large samples primarily focused on people over 50 years of age has emerged. In a review of AD studies, Barnes et al. (2009) estimated annualised atrophy rates of 4.66% per year (95% CI 3.92, 5.40) for AD subjects and 1.41% per year (95% CI 0.52, 2.30) for healthy elderly controls. A third domain investigates changes in healthy ageing in normal individuals. Available evidence suggests that hippocampal volumes change throughout adult life in a non-linear manner (Raz et al., 2010), with hippocampal volume being relatively stable in young adulthood. There appears to be a critical point after 50 years of age when the rate of hippocampal atrophy accelerates to 0.8–0.9% per year with hippocampal volumes declining steadily thereafter with age (Fjell et al., 2013; Schuff et al., 2012).

The aim of this review was firstly to provide age-specific data on the rates of hippocampal atrophy across the adult lifespan which are as representative as possible of the normal population. The second aim was to investigate the effects of segmentation techniques on atrophy measurements. Thirdly, we sought to investigate the impact of study design on measured atrophy rates. It was hypothesised that population studies would produce higher atrophy rates due to less restrictive health-based exclusion criteria than control groups used in clinical investigations. Our final goal was to summarise other findings pertinent to normal ageing such as gender and laterality effects.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines without prior publication of the review protocol (Moher et al., 2009). The literature search was based on predetermined search terms, inclusion, exclusion and quality criteria that included the assessment of bias at the study level. The approach used for data collection, confirmation and data simplifications are fully described. The risk of bias across studies was assessed and the post hoc analyses are clearly identified.

Search strategy

PUBMED (1950 to February 2014) was searched using the terms: "(hippocampus or hippocamp*) and (longitudinal or atrophy or change or volume or volumetry or volumetric) and humans and (magnetic resonance imaging or MRI or neuroimaging)". All returned titles were screened and any non-English, duplicate or clearly irrelevant entries were excluded. Next, the remaining record abstracts were reviewed to identify studies for full text review. Full text and supplementary material of potential studies were retrieved for screening against inclusion and exclusion criteria. Bibliographies of retrieved reports and previous reviews covering hippocampal atrophy were examined to identify additional studies for inclusion.

Inclusion and exclusion criteria

Published studies were included if they met the following criteria: (1) were an empirical study; (2) measured adult human hippocampal volume from in-vivo structural MRI images at more than one time

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