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Featured Article

Meta-analysis of synaptic pathology in Alzheimer's disease reveals selective molecular vesicular machinery vulnerability

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Abstract

Introduction: Loss of synapses best correlates to cognitive deficits in Alzheimer's disease (AD) in which oligomeric neurotoxic species of amyloid-β appears to contribute synaptic pathology. Although a number of clinical pathologic studies have been performed with limited sample size, there are no systematic studies encompassing large samples. Therefore, we performed a meta-analysis study.
Methods: We identified 417 publications reporting postmortem synapse and synaptic marker loss from AD patients. Two meta-analyses were performed using a single database of subselected publications and calculating the standard mean differences.
Results: Meta-analysis confirmed synaptic loss in selected brain regions is an early event in AD pathogenesis. The second meta-analysis of 57 synaptic markers revealed that presynaptic makers were affected more than postsynaptic markers.
Discussion: The present meta-analysis study showed a consistent synaptic loss across brain regions and that molecular machinery including endosomal pathways, vesicular assembly mechanisms, glutamate receptors, and axonal transport are often affected.

Keywords: Alzheimer's disease; Endosomal/lysosomal pathway; Meta-analysis; Synapse markers; Synapse number

1. Introduction

Synaptic damage has been extensively studied in Alzheimer's disease (AD; reviewed by [1]) because in this neurodegenerative disorder the loss of synapses is the best correlate to the cognitive deficits [2,3]. Moreover, amyloid beta (Aβ) oligomers appear to be formed and transported at the synapses and interfere with glutamate receptors [4,5] and synaptic functioning by interactions with presynaptic and postsynaptic receptors such as EphA [6], EphB2 [7], PrPc [8], mGluR5 [9], NMDA-R [10], frizzled, insulin-R, and nerve growth factor receptor among others [11].

The loss of synapses in AD and other neurodegenerative disorders is most likely part of a spectrum of alterations and pathogenic molecular cascades which begins with alterations in the synaptic vesicle machinery and glutamate receptors, progressing to mitochondrial dysfunction, reduced axonal flow, and loss of neurotrophic support [12]. Together, these alterations might manifest at early stages as synaptic dysfunction that could be reversible; however, as the process advances and alterations become irreversible, damage to synapses and spines might occur resulting eventually in synaptic and neuronal loss.

In the very early stages of AD, clinically manifested as amnestic mild cognitive impairment [13], there is sprouting and expansion of presynaptic terminals, probably as a compensatory mechanism, that is followed by a 15%–25% loss of

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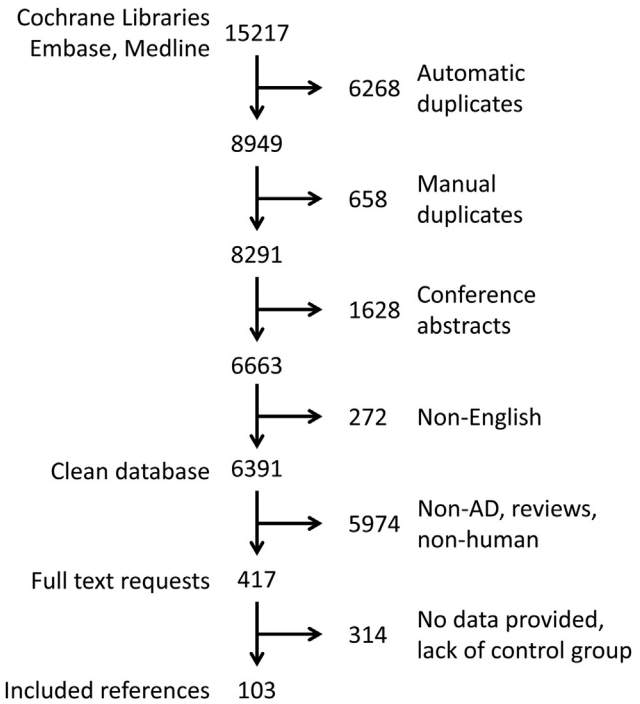

Fig. 1. Breakdown of publication selection. Schematic illustrating the subselection of articles for meta-analysis. Abbreviation: AD, Alzheimer's disease.

synapses in the frontal cortex and limbic system [14,15]. Specifically, a significant reduction in synapse numbers in the CA1 region of the hippocampus and the inferior temporal cortex has been demonstrated by electron microscopy [16,17]. Moreover, recent studies found a decrease in the dendritic proteins PSD-95 and drebrin in the hippocampus and superior temporal cortex [18–20], whereas synaptophysin was relatively preserved in these regions but reduced in the dentate gyrus and frontal cortex [15]. In more advanced forms of AD, there is a more severe loss of synapses in the neocortex and limbic system varying from 20 to 40%, depending on the methods to estimate synaptic alterations [15,21–26] and reviewed by Scheff et al. [1].

Over the past 30 years, there have been over 400 publications focusing on analyzing synapses and synaptic marker loss in postmortem tissues from patients with AD and control subjects. To provide a systematic overview of synapse loss and the loss of synaptic markers in AD, 22 publications provided data on synapse numbers and 83 publications provided data on synaptic marker levels suitable for meta-analyses. The advantage of using meta-analysis is that it offers a way to compare a variety of parameters of synaptic pathology with each other without requiring those parameters to use the same scales or units of measurements. To facilitate such comparisons, a database was built by calculating the standard mean difference (SMD) using the

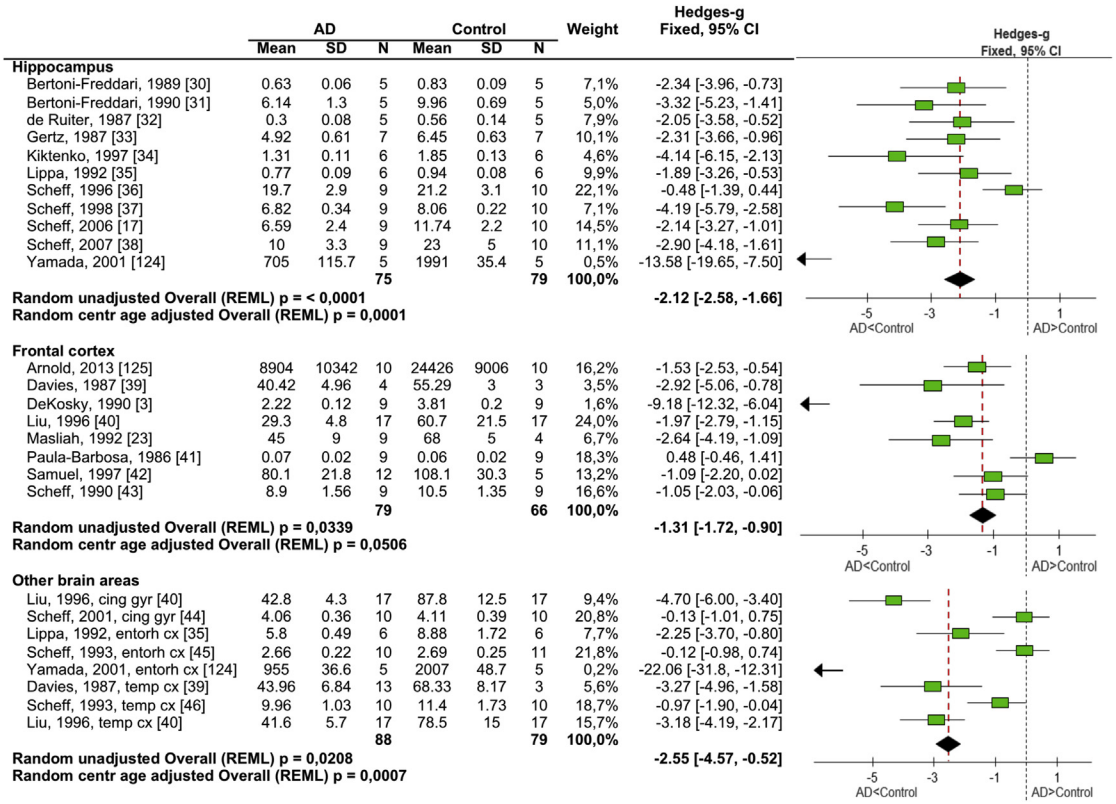

Fig. 2. Meta-analyses of synapse numbers in the hippocampus, frontal cortex, and C,E,T. Information extracted from the articles for the meta-analysis of synapse numbers in the different brain regions along with the forest plot of the standard mean differences. Abbreviations: C,E,T, cingulate gyrus, entorhinal cortex, and temporal cortex; AD, Alzheimer's disease; SD, standard deviation; CI, confidence interval; REML, restricted maximum likelihood.