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Featured Article

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

Martijn C. de Wilde[a,1], Cassia R. Overk[b,1], John W. Sijben[a], Eliezer Masliah[b,c,*]

[a]Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands
[b]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA
[c]Department of Pathology, University of California, San Diego, La Jolla, CA, USA

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

None of the authors report a conflict of interest.
[1]Co-first author.
*Corresponding author. Tel.: +1-858-534-8992; Fax: +1-858-534-6232.
E-mail address: emasliah@ucsd.edu

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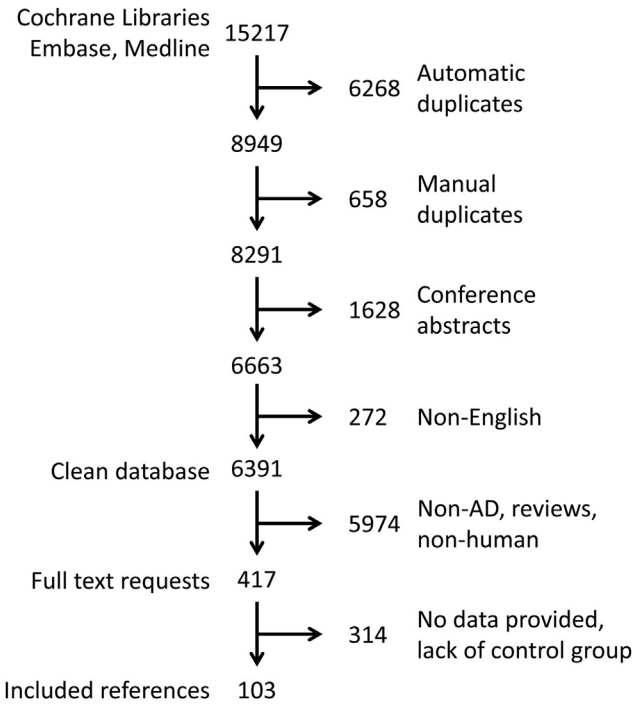

Fig. 1. Breakdown of publication selection. Schematic illustrating the subselection of articles for meta-analysis. Abbreviation: AD, Alzheimer's disease.

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

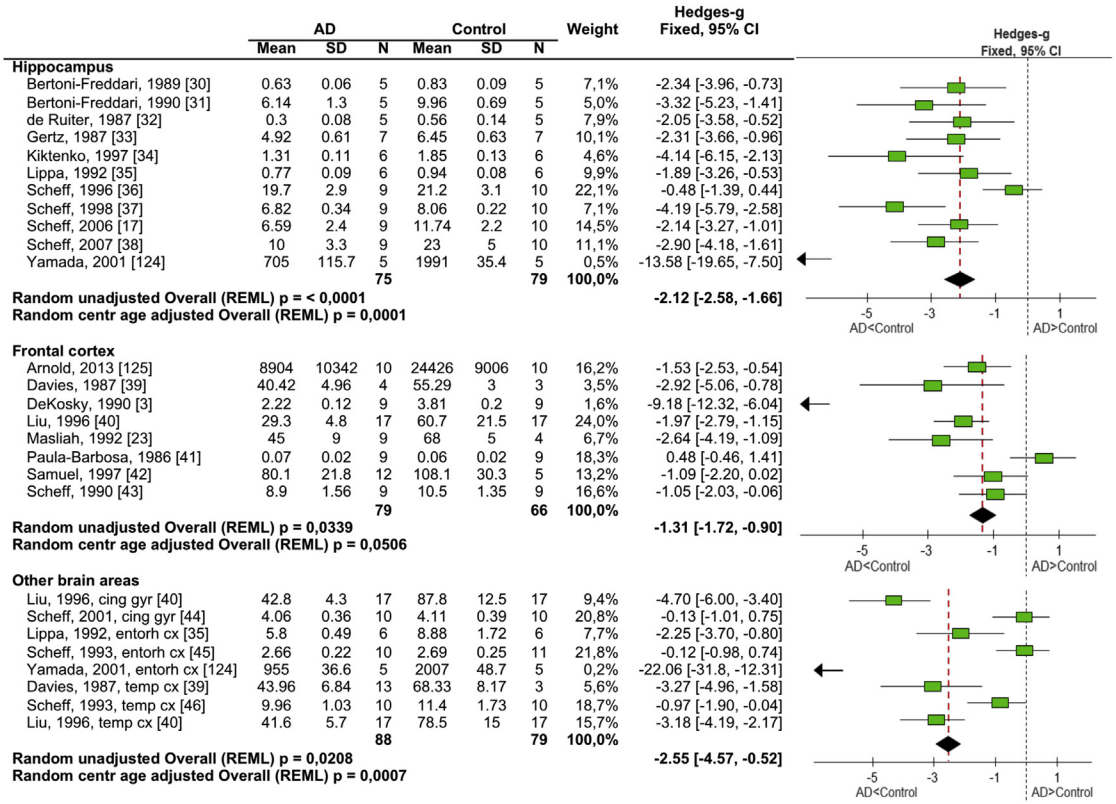

Fig. 2. Meta-analyses of synapse numbers in the hippocampus, frontal cortex, and C,E,T. Information extracted from the articles for the meta-analysis of synapse numbers in the different brain regions along with the forest plot of the standard mean differences. Abbreviations: C,E,T, cingulate gyrus, entorhinal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

Table 1
List of individual synaptic markers obtained from the included publications

Function	Presynaptic	Postsynaptic	Presynaptic and postsynaptic
Adhesion			Catenin beta
			N-cadherin
			NCAM
Calcium buffer	Parvalbumin		Calbindin
			Calretinin
Calcium sensor	Synaptotagmin		
Calmodulin-binding protein		Neurogranin	
Cytoskeleton	Septin 5	Drebrin	Actin
	Septin 7	Drebrin/actin	
		IRSp53	
		MAP2	
		SAPAP 1/GKAP	
		Synaptopodin	
Endocytosis	AP180		
	Dynamin 1		
"Growth" or "plasticity" protein		GAP43	
Neuroendocrine secretory proteins	Chromogranin A		
	Secretogranin 2		
Neurotransmitter synthesis	ChAT		
Protein phosphatase		Spinophilin	Calcineurin
Ras GTPase-activating protein SynGAP		SynGAP	
Receptor		G-0a	TrkA
		G-b	
		GBR1 GABAB receptor R1	
		G-ia	
		G-ia.1	
		G-protein a q/11	
		G-protein b common	
		G-sa	
		G-sa_s	
		Muscarinic M1	
		Muscarinic M4	
		NR1	
		NR2A	
		NR2B	
Redox proteins			Thioredoxin
Signaling		CaMKIIa	
		CaMKIIb	
		pCaMKII	
		PSD95	
		TotalCaMKII	
Small GTPase	Rab3a		
	Rab5		
	Rab7		
SNARE	Complexin 1		
	Complexin 2		
	SNAP25		
	Synaptobrevin		
	Synaptobrevin 2		
	Syntaxin		
	Syntaxin 1		
	Syntaxin 1A		
	Syntaxin 1B		
	VAMP2		
	VAMP2/3		
Tethering	Synapsin-1		
Transporter		ZnT1	
Vesicular	SV2		
	Synaptophysin		
	VGLUT1		
	VGLUT2		

Table 2
Detailed summary of the standard mean differences of the meta-analysis for presynaptic and postsynaptic markers by brain region

Marker	Hippocampus	Frontal cortex	C,E,T	Cingulate gyrus	Entorhinal cortex	Temporal cortex	Amygdala
Presynaptic							
Vesicle-related proteins [2,20,21, 47–87,124,125]	−1.56	−1.49	−2.06	−0.59	−3.45	−1.51	
Cell adhesion [78,88,89]	0.14	−2.79	−1.62			−1.62	
Calcium buffer [90–97]	−3.74	−5.11	−1.84			−1.84	
Calcium sensor [20,55,63,72,77,98]	−1.07	−0.46	−1.45		−1.19	−1.7	
Cytoskeleton [21,89,99]	1.89	−0.95	−0.33			−0.33	
Endocytosis [52,78]	−1.2	−0.44	−1.39		−2.2	−0.74	
Neuroendocrine secretory proteins [63,80]		−0.28	0.22			0.22	
Neurotransmitter synthesis [97]							
Protein phosphatase [100]							
Receptor [101,102]		−1.59	−1.53	−1.63		−1.42	
Redox proteins [103]	−1.23	−0.85					−1.16
Small GTPase [55,72,77,104–106]	0.01	0.18	−1.28		−1.28		
SNARE [19,21,67,72,77,78,85,107,108]	−0.15	−1.31	−1.18		−0.79	−1.56	
Tethering [19,77,109–112]	−0.87	−0.79	0.15	0.49	−0.14	0.11	
Overall presynaptic markers	−1.21	−1.35	−1.62	−0.58	−2.47	−1.34	−1.16
Postsynaptic							
Cell adhesion [78,88,89]	0.14	−2.79	−1.62			−1.62	
Calcium buffer [91,93–97]		−5.11	−2.21			−2.21	
Calmodulin-binding protein [55,72]	−0.62	−0.36					
Cytoskeleton [20,54,64,65,72,89,99]	−1.02	−0.86	−1.74	−1.99	−1.34	−1.77	
Growth factor related [55,72,113–115]	−1.05	−0.42					
Protein phosphatase [64,65,100,116]	−1.66	−1.08	−0.44		−0.44		
Ras GTPase-activating protein SynGAP [89]							
Receptor [101,102,117–121]	−0.2	0.18	−1.88	−1.63	−2.83	−1.51	
Redox proteins [103]	−1.23	−0.85					−1.16
Signaling [19,64,65,67,86,89,122]		0.13	0.61	0.22	2.74	−0.72	
Transporter [123]	4.04	−3.29					3.23
Overall postsynaptic markers	−0.33	−1.06	−1.54	−0.8	−1.25	−1.76	1.04
Overall synaptic markers	−1.04	−1.12	−1.56	−0.55	−2.2	−1.4	3.23

Abbreviation: C,E,T, cingulate gyrus, entorhinal cortex, and temporal cortex.

reported means and standard deviations for each measured parameter in each study. The present meta-analysis study showed a consistent synaptic loss across brain regions and that the molecular machinery involved in endosomal pathways, vesicular assembly mechanisms, glutamate receptors, and axonal transport are often affected.

2. Methods

2.1. Search strategy and selection criteria

Literature published from 1980 to February, 15th 2015 was systematically screened in the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase electronic databases according to PRISMA guidelines [27] using the following search terms in the title, abstract, or descriptors:

$$[(\text{Alzheimer}*\ \text{OR dement}*)\text{AND}(\text{synap}*\ \text{OR spine}*\ \text{OR bouton})]$$

The search resulted in 15,217 results that were imported into EndNote. Duplicate references (6268) were automatically removed, followed by manual examination, which retrieved another 658 duplicate references (Fig. 1). Conference abstracts (1628) and non-English publications (272) were also excluded from the database (Fig. 1). The title and abstract of the remaining 6391 publications were evaluated according to predefined inclusion (AD population; synaptic marker levels, synapse and/or dendritic spine counts) exclusion (non-AD population, non-human data, review/opinion articles) criteria.

We retrieved 417 publications reporting synapse counts or levels of synaptic proteins in patients with AD and cognitively intact elderly, even if not explicitly mentioned in the abstract. The full-text of these publications were analyzed according to the following inclusion criteria: contained AD patient population according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria [28] and/or the Diagnostic and Statistical Manual for Mental Disorders [29] criteria for AD and mentioned the use of a cognitively intact elderly control group, mean and standard deviation or standard error for synapse counts and/or synaptic proteins levels, number of AD patients and

Basal forebrain	Basal ganglia	Cerebellum	Cortex	Insular	Mesencephalon	Motor cortex	Neocortex	Occipital cortex	Parietal cortex	Thalamus
	−0.03	0.85	−5.58			−0.4	−2.65	−0.87	−2.06	0.28
			−4.15					0.54		
−0.43										
	−0.12							−0.26	0.08	
		−0.64	0.59							
								−0.33		
−7.27										
		0.5						−0.24		
−8.62								−0.48	−1.93	
1.27	0.15	−0.01						0.09	−1.22	
	−0.48			−0.71				−0.54	−0.88	
	0.51				−0.04			0.21		
−1.46	0.02	0.12	−3.32	−0.71	−0.04	−0.4	−2.65	−0.55	−1.57	0.28
			−4.15					0.54		
−0.43										
									−0.37	
		−0.9	−2.42					−2.44	0.03	
		0.43							−0.27	
		0.5						−0.24		
			−0.35							
−8.62	−1.15							−0.84	−0.83	
			−1.21				−1.55		−1.08	
									3.05	
−3.16	−1.15	−0.22	−2.14				−1.55	−0.79	−0.36	
−1.46	−0.13	−0.05	−2.21	−0.71	−0.04	−0.04	−2.38	−0.65	−1.21	0.28

controls, and mean age or age range of AD and control groups. The following publications were excluded: those reporting on gene expression, messenger RNA expression, and receptor binding studies (Fig. 1).

2.2. Data collection

Of 417 publications, 103 publications met all inclusion criteria (Fig. 1); 20 publications reported counts of synapses [3,17,23,30–46], 81 publications reported synaptic protein levels [2,19–21,47–123], and two publications reported both [124,125]. Collectively, the 83 publications [2,19–21,47–125] reported 67 different synapse-related proteins in 17 different brain areas. Because not every possible combination of a synapse protein and brain area has been studied or reported usable data to allow inclusion to the meta-analyses, approximately 35% of these possible combinations were available and provided data suitable for meta-analyses.

Data from the identified publications were extracted on synapse counts and/or synapse protein levels, number of subjects, and average age of the AD and control groups. SMDs were calculated based on the difference between the control and the AD groups took into account the variation within the groups and the number of subjects per group. For publications where more than one measurement was performed, this resulted in more than one SMD, e.g., when synaptophysin was measured in hippocampus, temporal cortex, and entorhinal cortex, three different SMDs were calculated.

2.3. Statistical analysis

All reported comparisons of synapse counts and synapse protein levels in AD patients and controls were integrated and summarized into a final result per brain area-synaptic protein combination, using meta-analysis (regression) methods [126], according to the PRISMA statement [27]. For meta-analysis, a minimum of four publications was required [127,128]. Comparison across studies did not require conversion to the same unit because our analysis was based on the difference between groups, i.e., not on the absolute value. These data were analyzed using the random-effects meta-analysis model [126] fitted by

Table 3
Further summarization of the standard mean differences for presynaptic and postsynaptic markers in different brain areas

Marker	Hippocampus	Frontal cortex	C,E,T
Presynaptic			
Calcium regulation [90,92–96]	−3.74	−5.11	−1.84
Cytoskeleton [21,99]	1.89	−0.95	−0.33
Vesicular organization [2,19–21,47–81,98,104,105,108–112,124,125]	−1.03	−1.15	−1.61
Grand total presynaptic	−1.21	−1.35	−1.62
Cell adhesion [78,88]	0.14	−2.79	−1.62
Postsynaptic			
Calcium regulation [55,72,93–96,122]	−0.62	−2.39	−1.67
Cytoskeleton [20,54,64,65,72,99,116]	−1.45	−0.92	−1.55
Intracellular signaling [19,55,64,65,67,72,113,115]	−1.05	−0.08	1.01
Neurotransmission [117–121]	−0.2	0.63	−1.96
Grand total postsynaptic	−0.33	−1.06	−1.54
Overall effect	−1.04	−1.12	−1.56

Abbreviation: C,E,T, cingulate gyrus, entorhinal cortex, and temporal cortex.

restricted maximum likelihood using the program metareg from Stata (Statistical Software: Release 12.1; StataCorp 2001, College Station, TX, USA). As synapse numbers and synaptic proteins were also affected by aging, meta-analyses were conducted with and without a correction by meta-regression for differences in mean age between AD patients and controls.

2.4. Analysis of bias

According to the PRISMA statement [27], the quality of a systematic review depends on the quality of the individual publications and the absence of bias for their inclusion. The quality of the studies was assessed by several inclusion and exclusion criteria (listed in section 2.1, Search strategy and selection criteria). Furthermore, results of the meta-analyses were statistically analyzed for possible bias because meta-analyses that are based on small studies reporting larger (smaller) effects may tend to overestimate (underestimate) the actual outcome. Funnel plots, which plot the standard error against the reported mean difference for each publication, can indicate the overestimation or underestimation of the actual difference occurring in the meta-analysis. Therefore, we used Egger's test as implemented in the Stata program meta-bias [129] to test the association between standard error and effect size in the funnel plot. For this analysis, a minimum of eight publications is generally recognized to be required [127,128].

3. Results

Of 103 references that met all inclusion criterion, 22 references were used to evaluate the extent to which changes in synapse numbers occurred in different brain regions that are affected in AD. A meta-analysis of the number of synapses was performed in the hippocampus, frontal cortex, and in the combined regions of the cingulate gyrus, entorhinal cortext, and temporal cortex (C,E,T). Data analysis of patients with AD revealed consistently lower synapse numbers in the hippocampus, the frontal cortex, and in the C,E,T (Fig. 2) compared with those in the control group. Synapse numbers were most affected in the hippocampus (SMD −2.12) followed by the C,E,T (SMD −2.55) and the frontal cortex (SMD −1.31 Fig. 2), using the SMD method.

Because synapse numbers were reduced in the hippocampus, C,E,T, and frontal cortex, we performed a second meta-analysis of the effect of AD on 67 presynaptic and postsynaptic markers to determine if specific molecular pathways in the synapse were selectively affected in AD (Table 1). The most widely analyzed synaptic marker in the brains of AD patients is the synaptic vesicle protein synaptophysin [1,12]; however, several other synaptic proteins have been shown to be altered in the brains of patients with AD including synaptobrevin [19,72,77], SNAP25 [19,21,77,108], synaptotagmin [20,55,63,72,77,98], syntaxin [19,21,67,77], Rab3a [55,72,77,104], synapsin I [19,77,109–112], and the postsynaptic proteins PSD-95 [19,64,65,67], Homer, and IRSp53 [89]. The 83 publications reported at least one synaptic marker level and combined provided information on 67 different markers (Table 1). Combining results together in one comparison shows on which markers and brain areas research has focused and which markers and brain areas are underrepresented in the overview (Table 2). Using the SMD allowed us to pool 67 different synaptic markers into a single overall database for comparison [19–21,52,55,63–65,67,72,77,78,80,85,86,88–123]. Irrespective of the brain area, these synaptic markers can be divided into 28 presynaptic markers in 10 functional categories, 30 postsynaptic markers in eight functional categories, and nine markers in six functional categories without specific presynaptic or postsynaptic localization (Table 2).

After the combination of the 67 synaptic markers from all brain regions into one database, we used the same regional division of the brain into hippocampus, frontal cortex, and C,E,T. As a result, we evaluated 57 different synaptic markers retrieved from a selection of 70 publications which reported results for the brain regions of interest: hippocampus, frontal cortex, and C,E,T (Table 3). These

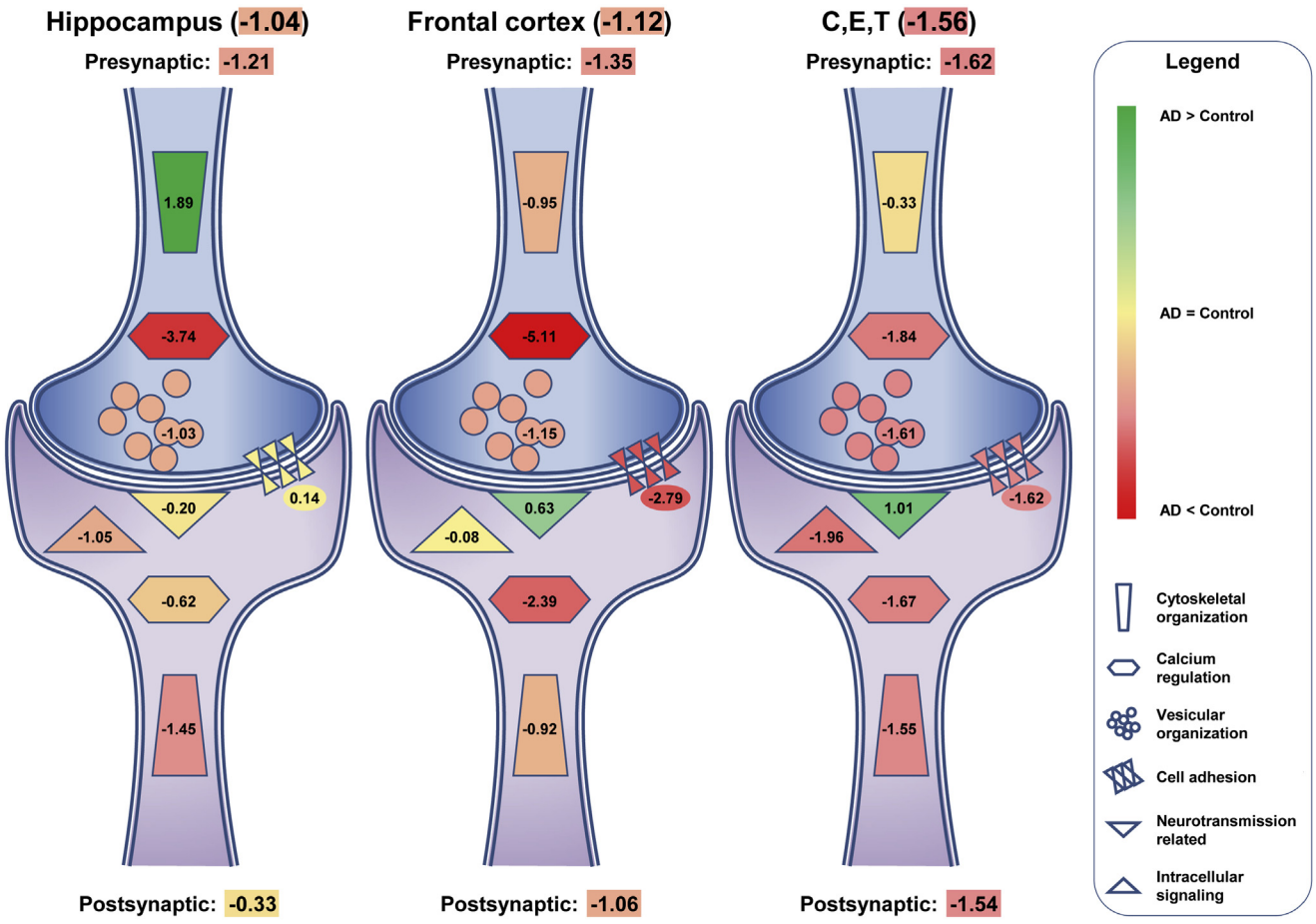

Fig. 3. Presynaptic and postsynaptic marker changes in different brain areas. Schematic representation of the standard mean differences (SMD) for presynaptic and postsynaptic markers in the hippocampus, the frontal cortex, C,E,T (cingulate gyrus, entorhinal cortex, and temporal cortex), and the remaining. Presynaptic markers are more affected by AD than the postsynaptic markers in all areas observed. These differences vary by brain area with the hippocampus showing the greatest difference and the C,E,T showing the smallest difference. SMD's are listed in each summarizing structure, for the overall presynaptic and postsynaptic change and for the overall change per brain area. Green-to-red color change depicts an increase or decrease of synaptic markers in comparison with healthy controls, where more green indicates stronger increase and more red stronger decrease. Abbreviations: C,E,T, cingulate gyrus, entorhinal cortex, and temporal cortex; AD, Alzheimer's disease.

markers can be divided into 24 presynaptic markers in nine functional categories, 25 postsynaptic markers in seven functional categories, and seven markers in five functional categories without specific presynaptic or postsynaptic localization (Table 3). Irrespective of the synaptic markers, the hippocampus and the frontal cortex showed equal reduction of synaptic markers with SMDs of −1.04 and −1.12, respectively (Table 3). The C,E,T were affected slightly more with a SMD of −1.56. In the three evaluated brain areas, presynaptic markers were affected more than postsynaptic markers; however, this difference was stronger in the hippocampus (pre-SMD −1.21 vs. post-SMD −0.33) than in the frontal cortex (pre-SMD −1.35 vs. post-SMD −1.06) and the C,E,T (pre-SMD −1.62 vs. post-SMD −1.54).

Summarizing the data further showed that some aspects of synaptic organization were affected to a similar extent across brain regions, whereas other aspects of synapse function were affected differently (Fig. 3). More specifically, calcium homeostasis was negatively affected both presynaptically and postsynaptically in all the brain regions. Vesicular organization was decreased in the hippocampus (SMD −1.03) and frontal cortex (SMD −1.15) and strongest in the C,E,T (SMD −1.61). Intracellular signaling was hardly affected in the frontal cortex (SMD −0.08), whereas it was negatively affected in the hippocampus (SMD −1.05) and C,E,T (SMD −1.96; Fig. 3 and Table 3). Similarly, postsynaptic cytoskeleton organization was decreased in all brain areas (hippocampus −1.45, frontal cortex −0.92, and C,E,T −1.55), whereas presynaptic cytoskeleton organization showed a reduced SMD of −0.95 in the frontal cortex and minor changes in the C,E,T (SMD of −0.33), although in the hippocampus, there was an increased SMD of 1.89 (Fig. 3). Another difference between the hippocampus and the other two brain regions, the frontal cortex, and the C,E,T, was the lack of changes in cell adhesion markers (SMD 0.14) in the

hippocampus, compared with the decreases in the frontal cortex (SMD −2.79) and the C,E,T (SMD −1.62; Fig. 3).

4. Discussion

The present study reviewed 417 references on synaptic pathology in AD and performed meta-analysis for synapse number (22 publications) and synaptic proteins in a subset of these references (83 publications). The benefits of using meta-analysis are clearly illustrated by the potential of a single database to bring together publications on synaptic pathology, which can grow when data from new publications and existing data (from publications not presenting means plus standard deviations) are added. An additional benefit of this approach is that it allows comparison of the collective results of 83 publications with proteomics studies. The current results are consistent with recent proteomics studies in synaptosomal preparations indicating that proteins such as Rabs, synaptotagmin, annexins, heat shock proteins, glutathione, and others that are involved in regulating energy and calcium metabolism and are dysregulated in AD, such as signal transduction, vesicle transport, and antioxidant activity [89,130,131].

Interestingly, more recent proteomics studies with postsynaptic density preparations from AD patients have shown that brain-specific angiogenesis inhibitor 1–associated protein 2 (IRSp53) was altered. IRSp53 belongs to a family of proteins harboring IRSp53–MIM domain that is associated with both actin and lipids [89]. This cluster of proteins regulates the spine cytoskeleton and membrane trafficking. IRSp53 interacts with postsynaptic density scaffold proteins (e.g., PSD-95 and chapsyn-110/PSD-95 and Rabs to modulate dendritic structure [89]). Thus, alterations observed in the brains of patients with AD might reflect defects in dendritic spine motility and disorganization of the postsynaptic scaffolds [19].

Although the earliest and most significant alterations in postmortem studies in AD and in APP tg models appear to be in proteins located in the presynaptic site, it is likely that both the presynaptic and postsynaptic compartments are affected because the soluble synaptotoxic hydrophobic Aβ oligomers diffuse rapidly between the axonal and dendritic partition [12,132]. Together, these studies suggest that at early stages of AD, soluble Aβ oligomers that diffuse from cell to cell might exert their toxic effects by locally affecting in the presynaptic site the SNARE machinery components, Rabs, calcium sensors, and antioxidant molecules and in the postsynaptic site glutamate receptors, postsynaptic density scaffold molecules, and mitochondria. Moreover, these oligomers might engage synaptic receptors that trigger neurotoxic signaling pathways (e.g., Fyn, CDK5, GSK3β) that merge in tau dependent and independent pathways [133–135].

A challenge of the current methodology is that most studies included in the meta-analysis approach consist of rather small studies. The average study population size is 10 subjects in the AD group versus 10 subjects in the healthy elderly control group. These small sample sizes carry the risk of publication bias, which is observed in the synapse count meta-analyses for hippocampus and frontal cortex. To overcome this problem, future research should aim for larger study populations, which will improve the intrinsic power of the individual study and also the overall power of meta-analysis approaches.

In conclusion, the present meta-analysis study showed a consistent synaptic loss across brain regions and that the molecular machinery involved endosomal pathways, vesicular assembly mechanisms, glutamate receptors, and axonal transport are often affected. Based on these findings, future research focusing on a set of crucial experiments that are designed to methodically test the hypothesis that synapse loss is due to soluble Aβ oligomers exerting their toxic effects by locally affecting the molecular machinery in the presynaptic site including the SNARE machinery components, Rabs, calcium sensors, and anti-oxidant molecules and in the post-synaptic site glutamate receptors, postsynaptic density scaffold molecules and mitochondria would greatly advance our scientific understanding of synapse loss in AD.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature on the molecular underpinnings and progression of synapse loss in Alzheimer's disease and found that although several studies have been published, but to date no meta-analysis that is inclusive of all the publications has been considered.
2. Interpretation: Our findings from the meta-analysis of close to 100 of the most important publications showed a consistent synaptic loss across brain regions and that the molecular machinery including endosomal pathways, vesicular assembly mechanisms, glutamate receptors, and axonal transport are often affected.
3. Future directions: The article synthesized data from over 100 articles on synaptic markers and synapse loss; however, owing to the small average sample sizes for both the control and Alzheimer's disease groups (n = 10), future research should aim for larger study populations, which will improve the intrinsic power of the individual study and also the overall power of meta-analysis approaches.

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