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Supplementary Data

New MRI Markers for Alzheimer's Disease: A Meta-Analysis of Diffusion Tensor Imaging and a Comparison with Medial Temporal Lobe Measurements

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Supplementary Table 1
Technical details of the medial temporal lobe studies included in the meta-analysis

Study	Total *n*	Field strength (Tesla)	Slice thickness (in mm)	Volumetric measurement of MTL structures
Pitkänen et al. [1]	131	1.5	1.5	Manual tracing
Convit et al. [2]	76	1.5	4.0	Manual tracing
Kaye et al. [3]	30	1.5	2.5	Manual tracing
Mori et al. [4]	58	1.5	1.5	Semi-automated tracing
Jack et al. [5]	48	1.5	1.60	Manual tracing
Juottonen et al. [6]	62	1.5	1.75	Manual tracing
Krasuski et al. [7]	34	1.5	0.50	Manual tracing
Laakso et al. [8]	139	1.5	1.50	Manual tracing
Visser et al. [9]	25	0.6	5.00	Manual tracing
Barber et al. [10]	48	1.0	1.0	Manual tracing
de Toledo-Morrell [11]	48	1.5	5.00	Manual tracing
Laakso et al. [12]	60	1.5	2.00	Manual tracing
Xu et al. [13]	90	1.5	1.60	Manual tracing
Du et al. [14]	105	1.5	1.40	Manual tracing
De Santi et al. [15]	38	1.5	1.3	Manual tracing
Goncharova et al. [16]	50	1.4	5.0	Manual tracing
Wolf et al. [17]	39	1.5	1.5	Manual tracing
Bottino et al. [18]	59	1.5	0.6	Manual tracing
Hsu et al. [19]	60	1.5	1.0	Manual tracing
Killiany et al. [20]	138	1.5	1.50	Manual tracing
Mega et al. [21]	20	1.5	1.50	Manual tracing
Pantel et al. [22]	55	1.5	–	Manual tracing
Du et al. [23]	44	1.5	1.40	Manual tracing
Du et al. [24]	45	1.5	1.40	Manual tracing
Pennanen et al. [25]	172	1.5	2.00	Manual tracing
Testa et al. [26]	52	1.5	1.30	VBM + manual tracing
Müller et al. [27]	36	1.5	1.00	Manual tracing
Bastos-Leite et al. [28]	36	1.5	1.50	N.A.
Kalus et al. [29]	30	1.5	1.00	Manual tracing
Teipel et al. [30]	56	1.5	1.20	Manual tracing
Uotani et al. [31]	60	–	5.00	Manual tracing
van de Pol et al. [32]	176	1.5	1.50	Manual tracing
Barnes et al. [33]	30	1.5	1.5	Manual tracing
Meyer et al. [34]	101	1.5	–	Manual tracing
Ridha et al. [35]	73	1.5	1.50	Manual tracing
Slavin et al. [36]	35	4.0	1.50	Manual tracing
Colliot et al. [37]	74	1.5	1.5	Automated segmentation
Delano-Wood [38]	40	1.5	3.8	Manual tracing
Duara et al. [39]	261	1.5	1.50	N.A.
Kenny et al. [40]	63	1.5	1.6	Manual tracing
Appel et al. [41]	192	1.5	1.5	N.A.
Bai et al. [42]	62	1.5	2.00	VBM + semi-automated tracing
Cho et al. [43]	60	1.5	–	N.A.
Feczko et al. [44]	76	1.5	1.25	Automated segmentation
Ferrarini et al. [45]	130	1.0	1.3	Manual tracing
Henneman et al. [46]	75	1.5	1.50	N.A.
Henneman et al. [47]	142	1.5	1.50	Automated segmentation
Hyun et al. [48]	60	1.5	–	N.A.
Jauhiainen et al. [49]	50	1.5	1.00	Manual tracing
Lee et al. [50]	215	1.5	–	Semi-automated tracing
Loewenstein et al. [51]	234	1.5	1.50	N.A.
Morra et al. [52]	400	1.5	1.20	Automated segmentation
Rogalski et al. [53]	28	1.5	1.60	Manual tracing
Bird et al. [54]	38	1.5	1.50	N.A.
Bouwman et al. [55]	348	1.0	1.50	N.A.
Cherubini et al. [56]	90	3.0	1.00	Automated segmentation
Choo et al. [57]	56	3.0	1.40	Manual tracing
Desikan et al. [58]	724	1.5	–	Automated segmentation
Jhoo et al. [59]	51	3.0	1.40	Manual tracing
Johnson et al. [60]	59	3.0	1.00	Automated segmentation
Lehmann et al. [61]	20	1.5	1.50	Manual tracing

Supplementary Table 1
(*Continued*)

Study	Total *n*	Field strength (Tesla)	Slice thickness (in mm)	Volumetric measurement of MTL structures
Liu et al. [62]	291	1.5	1.20	Automated segmentation
Luckhaus et al. [63]	57	1.5	1.80	Manual tracing
Mueller et al. [64]	91	4.0	2.0	Manual tracing
Pengas et al. [65]	52	1.5	1.8	Manual tracing
Ryu et al. [66]	37	1.5	1.0	Automated segmentation
Sanchez-Benavides et al. [67]	78	1.5	1.5	Semi-automated tracing
Schott et al. [68]	677	1.5	–	Semi-automated tracing
Westman et al. [69]	300	1.5	1.20	Manual tracing
Yakushev et al. [70]	38	1.5	1.00	Manual tracing
Zarei et al. [71]	38	1.5	1.00	Automated segmentation
Echavarri et al. [72]	54	3.0	1.00	Manual tracing
Jacobs et al. [73]	74	1.5	1.5	Semi-automated tracing
Prestia et al. [74]	39	1.0	1.3	Manual tracing
Zhang et al. [75]	389	3.0	1.0	Automated segmentation

MTL: Medial Temporal Lobe; VBM: Voxel Based Morphometry. N.A.: not applicable (only qualitative MTA-rating was provided in the study).

Supplementary Table 2
Technical details of diffusion tensor imaging studies included in the meta-analysis

Study	Total *n*	Field strength (Tesla)	Number of directions	Voxel size (mm)	b-value (s/mm^2)	NEX	DTI modality
Rose et al. [76]	20	1.5	6	$1.2 \times 2.3 \times 6.0$	875	1	Manual placement of standard ROIs
Bozzali et al. [77]	26	1.5	8	$2.0 \times 2.0 \times 5.0$	1044	1	Automated segmentation
Stahl et al. [78]	19	1.5	6	$1.8 \times 1.8 \times 3.6$	1000	10	VBM
Fellgiebel et al. [79]	43	1.5	6	Slice thickness 5.0	900	6	Manual placement of standard ROIs
Head et al. [80]	50	1.5	7	$2.5 \times 2.5 \times 4.0$	1005	4	Manual tracing
Sugihara et al. [81]	30	1.5	6	Slice thickness 5.0	1000	1	Manual placement of standard ROIs
Choi et al. [82]	20	1.5	6	$1.9 \times 1.9 \times 5.0$	1000	4	Manual placement of standard ROIs
Fellgiebel et al. [83]	63	1.5	6	$1.8 \times 1.8 \times 5.0$	900	4	Tractography
Duan et al. [84]	28	1.5	25	$1.9 \times 1.9 \times 5.0$	1000	1	Manual placement of standard ROIs
Naggara et al. [85]	24	1.5	25	$1.8 \times 1.8 \times 3.0$	1000	2	Manual placement of standard ROIs
Rose et al. [86]	34	1.5	6	Slice thickness 2.5	1100	1	VBM
Taoka et al. [87]	30	1.5	6	$1.8 \times 1.8 \times 6.3$	1000	6	Tractography
Chen et al. [88]	20	1.5	25	$1.9 \times 1.9 \times 3.0$	1000	1	Automated segmentation
Firbank et al. [89]	30	1.5	6	$2.6 \times 1.9 \times 6.0$	4000	1	Manual placement of standard ROIs
Huang and Auchus [90]	18	1.5	12	$1.9 \times 1.9 \times 3.0$	1000	1	Manual placement of standard ROIs
Müller et al. [91]	36	1.5	6	$1.8 \times 1.8 \times 5.0$	900	1	Manual placement of standard ROIs
Stahl et al. [92]	50	1.5	6	$1.8 \times 1.8 \times 3.6$	1000	10	Manual placement of standard ROIs
Zhang et al. [93]	52	1.5	6	$2.3 \times 2.3 \times 5.0$	1000	1	Manual placement of standard ROIs
Cho et al. [94]	22	1.5	25	$2.0 \times 2.0 \times 4.0$	1000	1	Manual placement of standard ROIs
Delano-Wood [38]	40	1.5	42	$3.8 \times 3.8 \times 2.8$	1990	7	Tractography + manual placement of ROIs
Ding et al. [95]	37	1.5	25	$1.9 \times 1.9 \times 5.0$	1000	1	Manual placement of standard ROIs
Fujie et al. [96]	32	3.0	12	$1.8 \times 1.8 \times 3.0$	700	1	Tractography
Parente et al. [97]	61	1.5	6	$1.8 \times 1.8 \times 6.5$	1000	3	Manual placement of standard ROIs
Shim et al. [98]	38	1.5	25	$2.0 \times 2.0 \times 5.0$	1000	1	Manual placement of standard ROIs
Ukmar et al. [99]	47	1.5	6	$2.5 \times 1.9 \times 6.0$	1000	1	Manual placement of standard ROIs
Yasmin et al. [100]	38	1.0	12	$1.8 \times 1.8 \times 3.0$	700	6	Tractography
Bai et al. [101]	44	1.5	25	$1.9 \times 1.9 \times 4.0$	1000	2	Manual placement of standard ROIs
Chen et al. [102]	40	1.5	25	$1.9 \times 1.9 \times 5.0$	1000	2	Manual placement of standard ROIs
Chen et al. [103]	60	1.5	25	$1.9 \times 1.9 \times 5.0$	1000	2	Manual placement of standard ROIs
Kiuchi et al. [104]	49	1.5	6	$1.8 \times 1.8 \times 3.0$	1000	6	Tractography
Liu et al. [105]	63	1.5	30	$1.7 \times 1.7 \times 5.0$	1000	1	TBSS + manual placement of ROIs
Mielke et al. [106]	75	3.0	32	$2.2 \times 2.2 \times 2.2$	700	2	Tractography + manual tracing
Nakata et al. [107]	41	1.0	12	$1.8 \times 1.8 \times 3.0$	700	6	Tractography
Rogalski [53]	28	1.5	24	$2.0 \times 2.0 \times 3.0$	800	6	Manual placement of standard ROIs
Stricker et al. [108]	30	3.0	15	$1.9 \times 1.9 \times 3.0$	1500	4	TBSS + manual placement of ROIs
Wang et al. [109]	20	3.0	16	$1.9 \times 1.9 \times 2.0$	1000	1	Manual placement of standard ROIs
Zarei et al. [110]	38	1.5	60	$2.0 \times 2.0 \times 2.0$	700	1	TBSS, tractography

Supplementary Table 2
(*Continued*)

Study	Total *n*	Field strength (Tesla)	Number of directions	Voxel size (mm)	b-value (s/mm^2)	NEX	DTI modality
Zhang et al. [111]	37	4.0	6	$2.0 \times 2.0 \times 3.0$	800	4	Tractography
Catheline et al. [112]	30	1.5	6	$2.4 \times 2.4 \times 2.5$	800	1	Tractography
Cherubini et al. [56]	90	3.0	12	$1.5 \times 1.5 \times 2.0$	1000	1	Automated segmentation
Choo et al. [57]	56	3.0	25	$0.94 \times 0.94 \times 0.94$	1000	1	Tractography, manual placement of VOI's
Hong et al. [113]	30	1.5	25	Slice thickness 4.0	1000	1	Manual placement of standard ROIs
Jhoo et al. [59]	51	3.0	25	$0.94 \times 0.94 \times 0.94$	1000	1	Tractography, manual placement of VOI's
Johnson et al. [60]	59	3.0	12	Slice thickness 3.0	1000	1	Manual placement of standard ROIs
Kantarci et al. [114]	90	3.0	21	Slice thickness 3.3	1000	1	Automated segmentation
Pievani et al. [115]	59	1.5	12	Slice thickness 2.5	1000	1	Tractography
Pitel et al. [116]	45	1.5	6	Slice thickness 4.0	860	1	Semi-automated ROIs
Scola et al. [117]	60	1.5	8	Slice thickness 5.0	1044	1	Manual placement of standard ROIs
Sexton et al. [118]	23	1.5	51	Slice thickness 2.8	1000	1	Manual placement of standard ROIs
Sjöbeck et al. [119]	30	3.0	12	Slice thickness 5.0	1000	1	Manual placement of standard ROIs
Yakushev et al. [70]	38	1.5	6	$1.8 \times 1.8 \times 3.0$	1000	1	Manual placement of standard ROIs
Zarei et al. [71]	38	1.5	60	$2.0 \times 2.0 \times 2.0$	700	1	Tractography
Zhang et al. [75]	60	3.0	15	Slice thickness 2.0	800	1	Manual placement of standard ROIs
Thillainadesan et al., unpublished data	396	3.0	6	$1.95 \times 1.95 \times 3.5$	1000		Manual placement of standard ROIs

DTI: Diffusion Tensor Imaging; NEX: Number of excitations; VBM: Voxel Based Morphometry; ROI: Region of interest; VOI: Volume of Interest; TBSS: Tract-based Spatial Statistics.

Supplementary Table 3

Significant univariate regressions for DTI effect sizes and technical parameters. Meta-regression indicated that a number of technical parameters were associated with effect size (ES). An increasing number of directions was associated with a higher ES. A possible explanation for this finding is that with an increasing number of directions contrast of FA/MD maps improves. The contrast-to-signal variance ratio between the main WM and the surrounding regions significantly increases as number of directions increases allowing a better delineation of the gray-white matter junction and thus a more precise FA determination [120, 121]. The ES of splenium FA seemed to increase with decreasing b-value and increasing field strength (MCI versus AD). This could be explained by the fact that a higher field strength provides better spatial and contrast resolution compared to a lower field strength. In one study FA values were significantly higher at 3.0 Tesla compared with 1.5 Tesla [122]. In general, a higher b-value leads to lower signal-to-noise levels and higher FA values [89, 123]. Our finding is therefore somewhat counterintuitive. However, there seems to be a lot of variability between studies regarding the effect of b-value on FA, since other studies found that FA values were not dependent on changes in b-value [124, 125]. The ES of parietal MD (controls versus MCI) and genu CC MD (MCI versus AD) seems to increase with increasing voxel size. The ES of hippocampal MD on the contrary, seems to increase with a decrease in voxel size. A possible explanation is that in broader structures (e.g., corpus callosum) a higher voxel size can clearly reveal possible differences whereas in smaller structures (e.g., hippocampus) a smaller voxel size is needed for better resolution. Current evidence indicates that in general, mean diffusivity values are not affected by voxel size [126]

		Effect size		Significant univariate regressions	
		Hedges g (CI)	*p*-value	DTI parameter	*p*-value
FA					
Controls versus AD	*n studies (n Controls nN AD)*				
Occipital Lobe	14 (298/244)	0.11 (−0.09; 0.32)	0.29	Directions	0.05
Total cingulum	5 (84/90)	**1.73 (0.22; 3.23)**	0.02	Field srength	0.008
ACC	3 (59/58)	1.37 (−0.30; 3.04)	0.11	Directions	0.04
				B-value (−)	0.04
Splenium CC	22 (467/417)	**1.10 (0.65; 1.55)**	<0.001	Directions	0.008
Controls versus MCI	*N studies (N Controls/N MCI)*				
PCC	10 (402/327)	**0.65 (0.32; 0.98)**	<0.001	Directions	0.006
MCI versus AD	*N studies (N MCI/N AD)*				
Splenium CC	12 (274/256)	**0.51 (0.11; 0.91)**	0.01	Field srength	0.03
				B-value (−)	0.01

Supplementary Table 3
(*Continued*)

		Effect size		Significant univariate regressions	
		Hedges g (CI)	*p*-value	DTI parameter	*p*-value
MD					
Controls versus AD	*N studies (N Controls/N AD)*				
Frontal Lobe	10 (165/176)	**−0.75 (−1.24; −0.27)**	0.002	Directions	0.053
Parietal Lobe	9 (155/166)	**−1.03 (−1.58; −0.49)**	<0.001	Directions	0.009
Splenium CC	12 (226/216)	**−0.94 (−1.53; −0.35)**	0.002	Directions	0.04
Internal capsule	7 (118/118)	**−0.66 (−1.19; −0.13)**	0.01	Directions	0.02
Controls versus MCI	*N studies (N Controls/N MCI)*				
Parietal Lobe	5 (77/786)	**−0.69 (−1.09; −0.28)**	0.01	Voxel size (+)	0.04
MCI versus AD	*N studies (N MCI/N AD)*				
Hippocampus	3 (68/70)	−0.33 (−0.77; −0.11)	0.14	Field strength	0.06
				Voxel size (−)	0.06
Genu CC	6 (89/113)	**−0.32 (−0.61; −0.03)**	0.03	Voxel size (+)	0.01

CI: Confidence interval; MCI: mild cognitive impairment; AD: Alzheimer's disease. Data shown in bold are statistically significant. PCC: posterior cingulum; PHC: parahippocampal cingulum; UF: uncinate fasciculus; SLF: superior longitudinal fasciculus. Regression: + or − = polarity ofregression coefficient/slope.

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