Supporting Information

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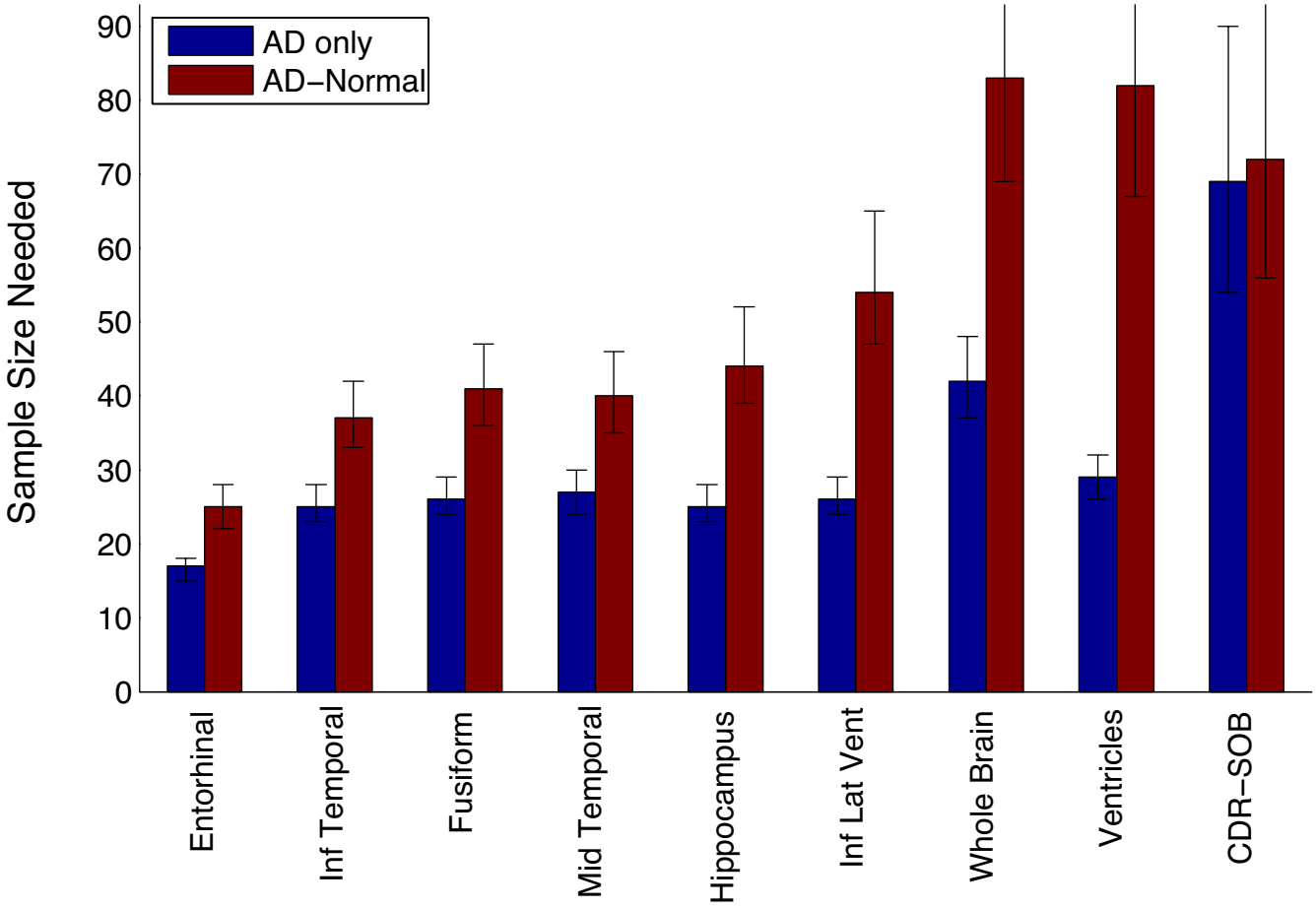

Fig. S1. Sample size estimates for AD from a linear random-effects model (not incorporating random slopes). The bars, with 95% confidence intervals, indicate the expected number of subjects needed per arm to detect a 25% reduction in rate of change at the $P < 0.05$ level with 80% power, assuming a 24-month trial with scans every 6 months. Results for Model T are in blue, and results for Model D are in red; numerical values are in Table S1.

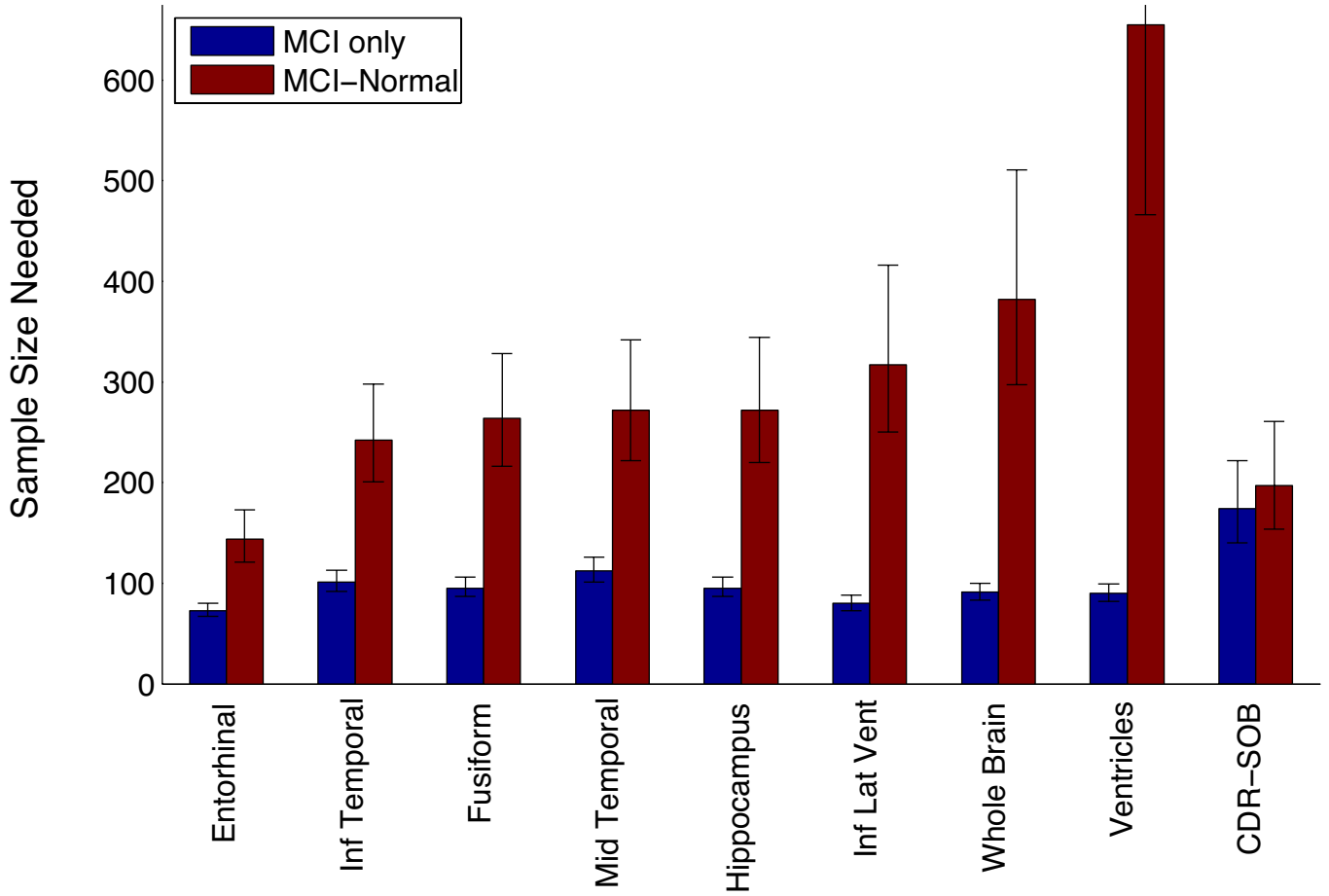

Fig. S2. Sample size estimates for MCI from a linear random-effects model (not incorporating random slopes). See Fig. S1 for description. Numerical values are in Table S2.

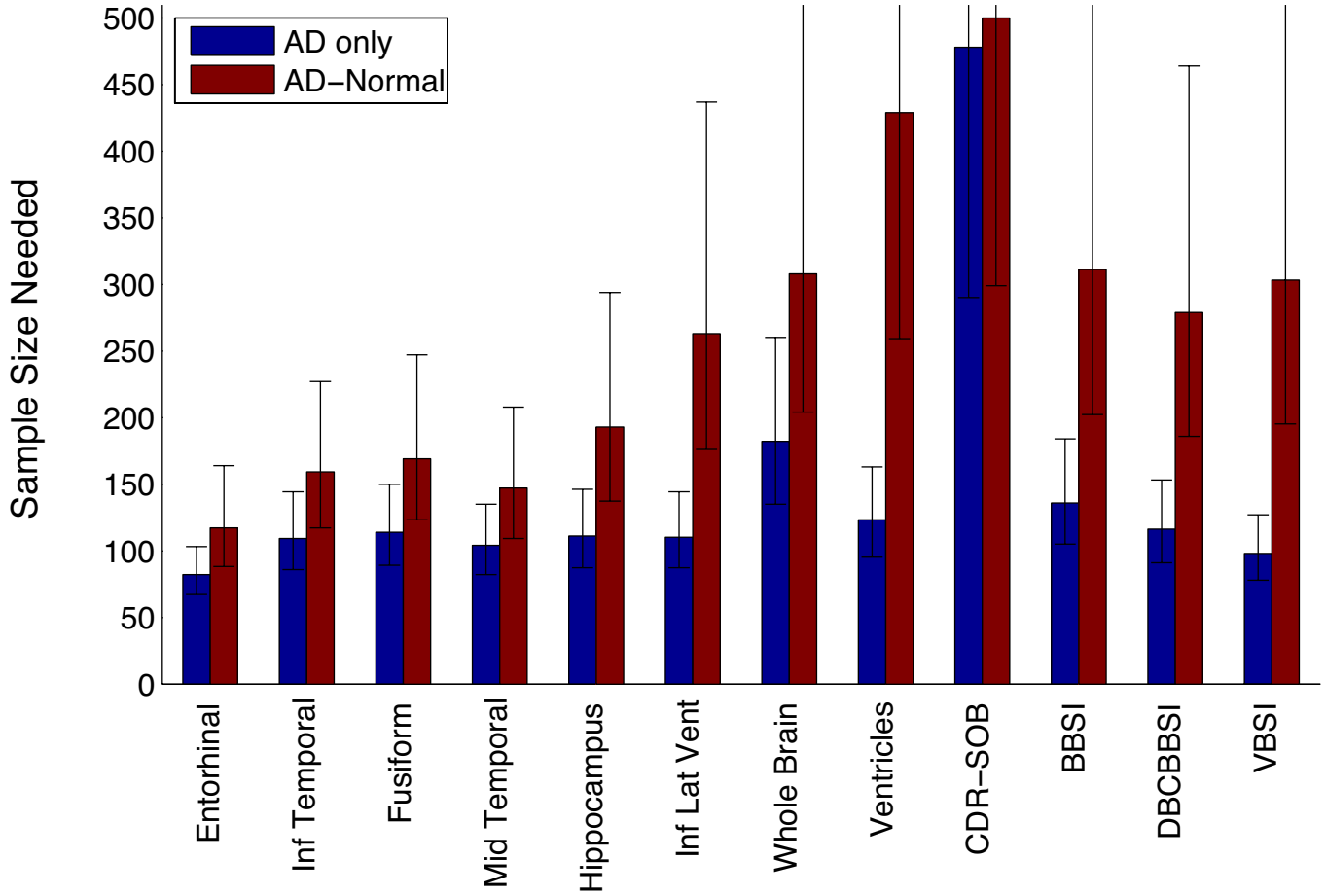

Fig. S3. Sample size estimates for AD from a linear mixed-effects model with random slopes, comparing the current method, a cognitive measure, and boundary shift integral (BSI). The bars, with 95% confidence intervals, indicate the expected number of subjects needed per arm to detect a 25% reduction in rate of change at the $P < 0.05$ level, with 80% power assuming a 12-month trial with scans every 6 months. Results for Model T are in blue, and results for Model D are in red; numerical values are in Table S3.

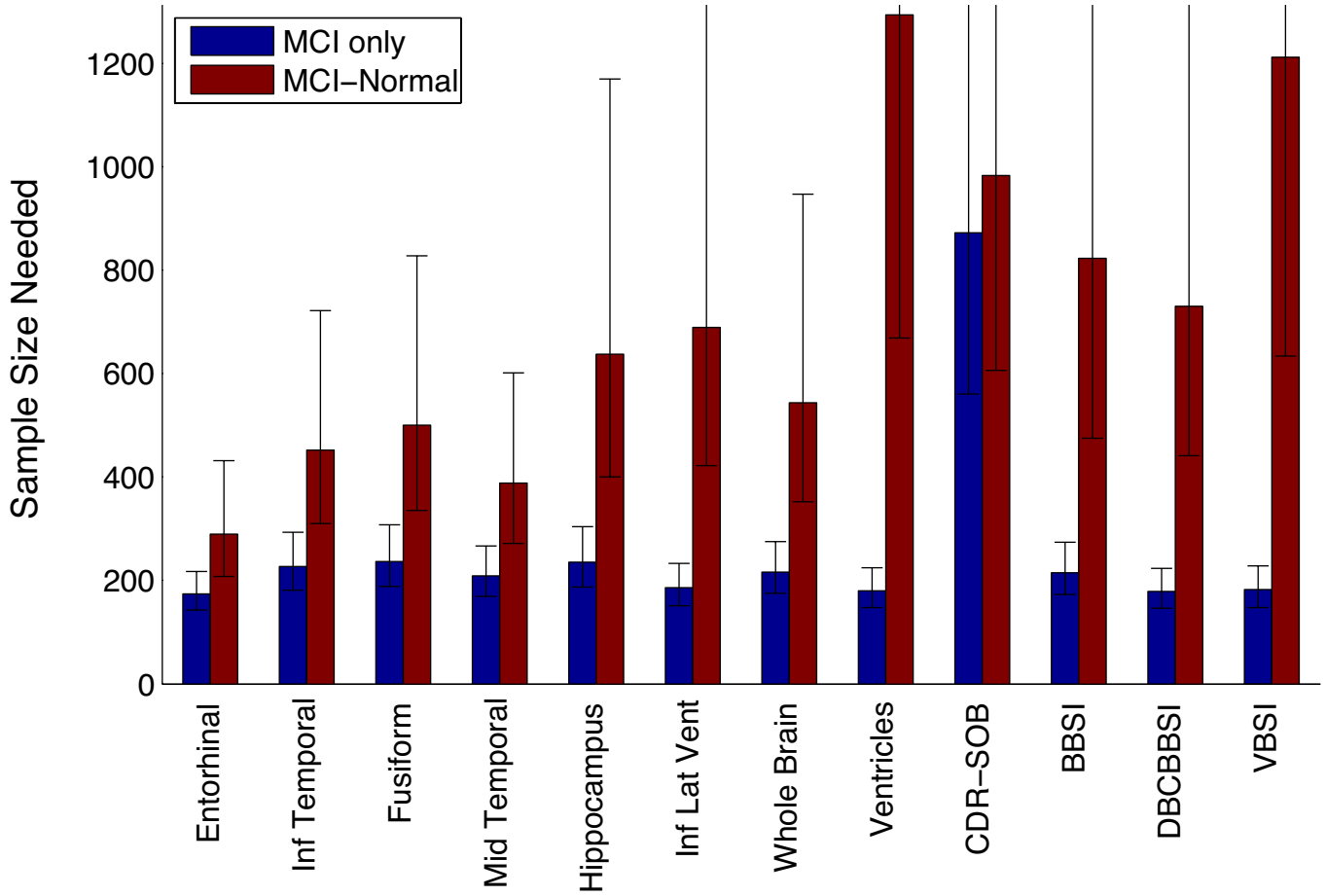

Fig. S4. Sample size estimates for MCI from a linear mixed-effects model with random slopes, comparing the current method, a cognitive measure, and BSI. See Fig. S3 for description. Numerical values are in Table S4.

Table S1. Sample size estimates (N) and annualized percent change for AD: Linear random-effects model not incorporating random slopes

Measure	AD only N	AD-HC N	AD % change*	HC % change*
Entorhinal	17 [15 18]	25 [22 28]	−3.94 [−4.10 −3.79]	−0.72 [−0.83 −0.61]
Inf temporal	25 [23 28]	37 [33 42]	−3.85 [−4.04 −3.66]	−0.67 [−0.74 −0.60]
Fusiform	26 [24 29]	41 [36 47]	−3.05 [−3.20 −2.89]	−0.61 [−0.66 −0.55]
Mid temporal	27 [24 30]	40 [35 46]	−3.65 [−3.84 −3.47]	−0.65 [−0.73 −0.57]
Hippocampus	25 [23 28]	44 [39 52]	−3.32 [−3.48 −3.15]	−0.82 [−0.90 −0.73]
Inf lat vent	26 [23 29]	54 [47 65]	16.22 [15.42 17.03]	4.99 [4.55 5.42]
Whole brain	42 [37 48]	83 [69 102]	−1.53 [−1.62 −1.43]	−0.44 [−0.48 −0.40]
Ventricles	29 [26 32]	82 [67 101]	11.32 [10.73 11.92]	4.56 [4.21 4.91]
CDR-SOB	69 [54 90]	72 [56 95]	1.81 [1.58 2.04]	0.04 [0.01 0.07]
ADAS-Cog†	88 [67 120]	78 [60 105]	5.10 [4.37 5.83]	−0.33 [−0.58 −0.08]
MMSE†	132 [96 193]	137 [98 205]	−2.42 [−2.84 −2.00]	−0.04 [−0.16 0.07]

Values in brackets are 95% confidence intervals. ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive; CDR-SOB, clinical dementia rating, sum of boxes; HC, healthy controls; MMSE, Mini-Mental State Examination.

*Annual percent change in volume for all entries except CDR-SOB, ADAS-Cog, and MMSE.

†Not shown in Fig. S1.

Table S2. Sample size estimates (N) and annualized percent change for MCI: Linear random-effects model not incorporating random slopes

Measure	MCI Only N	MCI-HC N	MCI % change*	HC† % change*
Entorhinal	73 [67 80]	144 [121 173]	−2.49 [−2.60 −2.38]	−0.72 [−0.83 −0.61]
Inf temporal	101 [92 113]	242 [201 298]	−1.89 [−1.99 −1.80]	−0.67 [−0.74 −0.60]
Fusiform	95 [87 106]	264 [216 328]	−1.52 [−1.60 −1.44]	−0.61 [−0.66 −0.55]
Mid temporal	112 [101 126]	272 [222 342]	−1.82 [−1.92 −1.72]	−0.65 [−0.73 −0.57]
Hippocampus	95 [87 106]	272 [220 344]	−2.00 [−2.10 −1.90]	−0.82 [−0.90 −0.73]
Inf lat vent	80 [73 88]	317 [250 416]	10.00 [9.54 10.46]	4.99 [4.55 5.42]
Whole brain	91 [83 100]	382 [297 511]	−0.86 [−0.90 −0.82]	−0.44 [−0.48 −0.40]
Ventricles	90 [82 99]	655 [466 986]	7.25 [6.90 7.60]	4.56 [4.21 4.91]
CDR-SOB	174 [140 222]	197 [154 261]	0.67 [0.59 0.75]	0.04 [0.01 0.07]
ADAS-Cog‡	603 [409 977]	397 [264 662]	1.41 [1.11 1.71]	−0.33 [−0.58 −0.08]
MMSE‡	474 [335 722]	526 [342 912]	−0.87 [−1.04 −0.71]	−0.04 [−0.16 0.07]

Values in brackets are 95% confidence intervals.
*Annual percent change in volume for all entries except CDR-SOB, ADAS-Cog, and MMSE.
†Normal values reproduced from Table S1.
‡Not shown in Fig. S2.

Table S3. Sample size estimates (N) and annualized percent change for AD: Comparison with BSI

Measure	AD only N	AD-HC N	AD % change*	HC % change*
Entorhinal	82 [67 103]	117 [88 164]	−3.68 [−4.07 −3.28]	−0.61 [−0.86 −0.36]
Inf temporal	109 [86 144]	159 [117 227]	−3.54 [−4.00 −3.09]	−0.60 [−0.78 −0.42]
Fusiform	114 [89 150]	169 [123 247]	−2.80 [−3.16 −2.43]	−0.51 [−0.66 −0.35]
Mid temporal	104 [82 135]	147 [109 208]	−3.43 [−3.84 −3.00]	−0.55 [−0.72 −0.37]
Hippocampus	111 [87 146]	193 [137 294]	−3.42 [−3.85 −2.98]	−0.83 [−1.04 −0.61]
Inf lat vent	110 [87 144]	263 [176 437]	14.18 [12.39 15.98]	5.00 [4.00 6.01]
Whole brain	182 [135 260]	308 [204 517]	−1.49 [−1.73 −1.24]	−0.34 [−0.44 −0.25]
Ventricles	123 [95 163]	429 [259 839]	10.35 [8.97 11.73]	4.82 [4.05 5.58]
CDR-SOB	478 [290 934]	500 [299 1000]	1.60 [1.14 2.05]	0.04 [−0.01 0.08]
ADAS-Cog†	624 [355 1,368]	473 [278 982]	4.08 [2.76 5.41]	−0.60 [−1.15 −0.06]
MMSE†	1,056 [525 3,113]	1,103 [533 3,502]	−2.29 [−3.25 −1.34]	−0.05 [−0.28 0.18]
BBSI	136 [105 184]	311 [202 539]	1.80 [1.55 2.05]	0.61 [0.47 0.75]
DBCBBSI	116 [91 153]	279 [186 464]	1.63 [1.42 1.84]	0.58 [0.46 0.69]
VBSI	98 [78 127]	303 [195 532]	8.81 [7.75 9.86]	3.79 [3.16 4.43]

Twelve-month study with 102 AD subjects and 130 healthy controls: comparison with boundary-shift integral methods. Values in brackets are 95% confidence intervals. BBSI, boundary shift integral from baseline; DBCBBSI, differential bias corrected BSI from baseline; VBSI, ventricular BSI.
*Annual percent change in volume for all entries except CDR-SOB, ADAS-Cog, and MMSE.
†Not shown in Fig. S3.

Table S4. Sample size estimates (N) and annualized percent change for MCI: Comparison with BSI

Measure	MCI only N	MCI-HC N	MCI % change*	HC† % change*
Entorhinal	174 [143 217]	290 [208 432]	−2.71 [−2.99 −2.43]	−0.61 [−0.86 −0.36]
Inf temporal	227 [181 293]	452 [310 722]	−2.06 [−2.31 −1.82]	−0.60 [−0.78 −0.42]
Fusiform	237 [189 308]	500 [335 828]	−1.62 [−1.82 −1.43]	−0.51 [−0.66 −0.35]
Mid temporal	209 [169 267]	389 [272 602]	−2.04 [−2.28 −1.81]	−0.55 [−0.72 −0.37]
Hippocampus	235 [187 304]	638 [401 1,170]	−2.10 [−2.35 −1.85]	−0.83 [−1.04 −0.61]
Inf lat vent	186 [151 233]	690 [422 1,326]	10.39 [9.27 11.51]	5.00 [4.00 6.01]
Whole brain	216 [175 275]	544 [352 947]	−0.93 [−1.03 −0.82]	−0.34 [−0.44 −0.25]
Ventricles	180 [147 225]	1,294 [669 3,486]	7.68 [6.86 8.49]	4.82 [4.05 5.58]
CDR-SOB	872 [561 1,538]	983 [607 1,858]	0.63 [0.47 0.78]	0.04 [−0.01 0.08]
ADAS-Cog‡	4,167 [1,758 19,659]	1,831 [848 6,502]	1.19 [0.55 1.83]	−0.60 [−1.15 −0.06]
MMSE‡	3,091 [1440 10,805]	3,522 [1400 20,566]	−0.78 [−1.15 −0.42]	−0.05 [−0.28 0.18]
BBSI	215 [173 274]	823 [475 1,762]	1.24 [1.10 1.39]	0.61 [0.47 0.75]
DBCBBSI	179 [146 223]	731 [441 1,440]	1.14 [1.02 1.26]	0.58 [0.46 0.69]
VBSI	182 [148 228]	1,212 [634 3,179]	6.19 [5.53 6.85]	3.79 [3.16 4.43]

Twelve-month study with 236 MCI subjects and 130 healthy controls: comparison with BSI methods.
*Annual percent change in volume for all entries except CDR-SOB, ADAS-Cog, and MMSE.
†Normal values reproduced from Table S3.
‡Not shown in Fig. S4.