

Featured Article

Magnetic resonance imaging measures of brain atrophy from the EXPEDITION3 trial in mild Alzheimer's disease

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Abstract

Introduction: Solanezumab is a humanized monoclonal antibody that preferentially binds to soluble amyloid β and promotes its clearance from the brain in preclinical studies. The objective of this study was to assess the effect of solanezumab in slowing global and anatomically localized brain atrophy as measured by volumetric magnetic resonance imaging (MRI).

Methods: In the EXPEDITION3 phase 3 trial, participants with mild Alzheimer's disease were randomized to receive intravenous infusions of either 400 mg of solanezumab or placebo every 4 weeks for 76 weeks. Volumetric MRI scans were acquired at baseline and at 80 weeks from 275 MRI facilities using a standardized imaging protocol. A subset of 1462 patients who completed both MRI and 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale assessments at both time points were selected for analysis. Longitudinal MRI volume changes were analyzed centrally by tensor-based morphometry with a standard FreeSurfer brain parcellation. Prespecified volumetric measures, including whole brain and ventricles, along with anatomically localized regions in the temporal, parietal, and frontal lobes were evaluated in those participants.

Results: Group-mean differences in brain atrophy rates were directionally consistent across a number of brain regions but small in magnitude (1.3–6.9% slowing) and not statistically significant when corrected for multiple comparisons. The annualized rates of change of the volumetric measures and the correlation of these changes with cognitive changes in placebo-treated subjects were similar to those reported previously.

Discussion: In the EXPEDITION3 trial, solanezumab did not significantly slow down rates of global or anatomically localized brain atrophy. Brain volume changes and their relationship to cognition were consistent with previous reports.

Declarations of interest: A.J.S., K.L.S., A.C., M.G.C., R.K.J., M.J.P., and E.R.S. are employees and minor stockholders of Eli Lilly and Company (or were when the work was undertaken), which owns patent rights to solanezumab, the drug that was used in this study. E.R.S. is currently the President of Siemers Integration LLC. and has been a consultant for Acelot Inc., Acumen Pharmaceuticals Inc., Cortexyme Inc., Gates Ventures, Partner Therapeutics Inc., Takeda, Vaccinex Inc., Washington University (St. Louis), Westin Foundation, Servier, and F. Hoffmann-La Roche Ltd. B.C.D. has been a consultant for Merck, Biogen, Piramal, and Eli Lilly

and Company and received royalties from Oxford University Press, Cambridge University Press, and Elsevier. A.J.S. is currently an employee of Takeda Pharmaceuticals. K.L.S. is currently an employee of B2S Life Sciences. R.K.J. is currently an employee of GSK Vaccines GmbH. L.B., D.S., J.O., and J.S. have nothing to report.

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Keywords: Solanezumab; Amyloid; Volumetric magnetic resonance imaging; MRI; Alzheimer disease; Atrophy; Cognition

1. Introduction

Solanezumab is a humanized monoclonal antibody that preferentially binds soluble amyloid β ($A\beta$) and was designed to slow Alzheimer's disease (AD) progression by increasing soluble $A\beta$ clearance from brain [1,2]. Initial phase 3, double-blind clinical trials of solanezumab, at a dose of 400 mg every 4 weeks for 76 weeks, in patients with clinically defined mild-to-moderate (baseline Mini-Mental State Examination [MMSE] score 16–26) AD (EXPEDITION and EXPEDITION2) failed to show a treatment benefit for solanezumab [3]. However, in a predefined secondary analysis of subjects with mild (baseline MMSE score 20–26) AD only, pooled across both trials, solanezumab-treated subjects declined more slowly on cognitive and functional measures than placebo-treated subjects [4]. No evidence of slowing of cognitive or functional decline was seen in subjects with moderate (baseline MMSE score 16–19) disease. Amyloid positron emission tomography imaging, performed in a small subset ($N = 251$) of the EXPEDITION and EXPEDITION2 participants with mild AD, revealed that approximately 25% of those subjects were amyloid negative and, in the placebo arm, did not show typical disease progression over the trial duration [5,6]. Analysis of brain atrophy measured via three-dimensional T1 (3DT1) volumetric magnetic resonance imaging (vMRI) scans did not show a difference between treatment groups in these studies [3,4].

A third double-blind, phase 3 trial (EXPEDITION3), intended to confirm the secondary efficacy analyses from the EXPEDITION and EXPEDITION2 studies, was conducted. Patients with mild AD who demonstrated biomarker evidence of amyloid pathology were randomized to either placebo or solanezumab. As reported in detail elsewhere [7], although directionally consistent with the secondary analyses of EXPEDITION and EXPEDITION2, there was no statistically significant difference at the endpoint (week 80) between solanezumab- and placebo-treated patients on the primary outcome scale, the 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog14) ($P = .095$). Secondary cognitive and functional measures consistently demonstrated slowing of decline in solanezumab-treated patients, often reaching nominal statistical significance at endpoint, although the treatment effect was consistently smaller than that seen in the secondary analyses of EXPEDITION and EXPEDITION2.

In EXPEDITION3, 3DT1 vMRI scans were scheduled at baseline and at the end of the double-blinded treatment period (week 80) with the aim of assessing solanezumab's

effects on longitudinal rates of brain atrophy. Here, we present an analysis of the vMRI data from the EXPEDITION3 trial. Most previous therapeutic trials, including EXPEDITION and EXPEDITION2, have reported findings relating to well-established vMRI endpoints such as hippocampus, ventricles, and whole-brain atrophy [4,8–10]. However, recent research has shown that subjects with AD exhibit patterns of brain atrophy that also involve regions of the temporal, parietal, and frontal lobes [11,12] and that changes in different cognitive tests are associated with specific patterns of brain atrophy [13]. Here, using an image-processing pipeline enabling parcellation of the cerebral cortex, we report atrophy profiles and treatment effects from the EXPEDITION3 trial across a wider range of brain regions than those that have been typically reported for late-phase drug-development trials.

2. Methods

2.1. Study participants

The EXPEDITION3 trial design and methodology, along with results of primary outcome measures and descriptions of adverse events and participant disposition, are described in detail elsewhere [7]. Briefly, participants were male or female, were 55 to 90 years of age, and met the diagnostic criteria for probable AD from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [14]. Unlike EXPEDITION and EXPEDITION2, EXPEDITION3 included only patients with mild AD and only those who showed biomarker evidence of amyloid pathology as determined by either a florbetapir positron emission tomography scan or cerebrospinal fluid $A\beta_{1-42}$ measurements.

Patients were randomized in a double-blind fashion to receive intravenous infusions of either 400 mg of solanezumab ($N = 1057$) or placebo ($N = 1072$) every 4 weeks up to and including week 76. Stable, concomitant drug and nondrug treatments were allowed to ensure patients continued to receive AD standard of care. MRI assessments were scheduled at baseline and at 80 weeks (4 weeks after the last solanezumab or placebo treatment) or early discontinuation. Cognitive and functional performance (including ADAS-Cog14, Clinical Dementia Rating scale: Sum of Boxes [CDR-SB], and MMSE) was also assessed at baseline and endpoint. A subset of 1462 subjects ($N = 721$ for placebo, $N = 741$ for solanezumab) who completed both

MRI and ADAS-Cog14 assessments at both time points were selected for analysis in this study.

The primary objective of EXPEDITION3 was to test the hypothesis that solanezumab would slow the progression of cognitive decline of AD, as compared with placebo, in patients with mild dementia due to AD, based on changes in ADAS-Cog14. The EXPEDITION3 study protocol was approved by ethical and institutional review boards at all sites. All study participants provided written informed consent before participation in the study.

2.2. Magnetic resonance imaging

A total of 275 imaging sites contributed to the sample and were located in the United States/Canada (61.45%), Europe (28%), Australia (4.36%), and Japan (6.18 %). All MRI facilities were trained on study procedures by the central imaging laboratory and implemented a standardized imaging protocol on their MRI scanner. Both 1.5T and 3T scanners were allowed, representing 75% and 25% of the subjects scanned, respectively. Scanners were manufactured by General Electric (28.9% of subjects), Philips (18.6%), Siemens (52.4%), or Toshiba (0.1%). Scanner performance was assessed during site qualification and monitored throughout the trial using American College of Radiology phantoms. Only study participants whose baseline and follow-up scans were obtained on the same MRI scanner were included in the present quantitative analysis.

The 3DT1 data consisted of sagittal 3D magnetization-prepared rapid gradient-echo (Siemens), sagittal 3D turbo field echo (Philips), coronal 3D fast spoiled gradient recalled (General Electric), or sagittal 3D field echo (Toshiba) sequences with 1.2-mm-thick slices and a 1.25×1.25 -mm² in-plane resolution.

The vMRI scans were assessed by tensor-based morphometry, which captures volume changes within the deformation fields resulting from applying a symmetric deformable registration technique [15,16] between a pair of MRI scans by a nonlinear symmetric log-demons deformation technique [15] and robust cross-correlation metric [16] to ensure invertibility of the transformation. The determinant of the Jacobian matrix of the deformation field then provides a measure of local volume change. Integration of the determinant over a prespecified brain region provides an estimation of its change in volume. The images were parcellated using FreeSurfer and the Desikan atlas [17] for region-of-interest definition.

Hippocampus, entorhinal cortex, ventricle, and whole-brain volumes were prespecified as the primary vMRI variables of interest for analysis of treatment effects on brain volume changes. In addition, to explore a wider neuroanatomical profile of the baseline brain structure and longitudinal change, volumes of the following brain regions were also calculated: isthmus cingulate, precuneus, inferior parietal lobule, and superior temporal gyrus as individual structures; lateral parietal cortex (comprising supramarginal gyrus,

inferior parietal lobule, and superior parietal lobule); lateral prefrontal cortex (comprising caudal middle frontal gyrus, rostral middle frontal gyrus, pars opercularis, and pars triangularis); medial temporal lobe (comprising parahippocampal gyrus, entorhinal cortex, hippocampus, and amygdala); and whole temporal lobe (comprising superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, transverse temporal gyrus, banks of the superior temporal sulcus, parahippocampal gyrus, fusiform gyrus, entorhinal cortex, and temporal pole). These regions are illustrated in Fig. 1. To assess treatment effects in distributed “AD signature” patterns, two additional combinations of regions were also calculated from the aforementioned predefined set of brain structures, informed by literature reports [11,18]. A small region combination comprised the entorhinal cortex, precuneus, isthmus cingulate, and inferior parietal lobule, and a large region combination comprised the lateral parietal cortex, lateral prefrontal cortex, and whole temporal lobe. All volumes were calculated in mm³.

2.3. Statistical analysis

Analysis of covariance models were applied (per brain region) with change from baseline in the vMRI parameter as the dependent variable and independent terms comprising vMRI baseline value, pooled investigator, treatment arm, and baseline age. Primary analyses were performed on the bilateral sum of left and right hemisphere volumes. Analyses were also performed with the participants split by sex. Annualized least squares (LS) mean percentage change relates the 80-week LS mean change to the average baseline volume (within each treatment arm) and normalizes the fraction to 52 weeks. Relative slowing was determined by taking the difference between the (annualized) LS mean changes (solanezumab LS mean change – placebo LS mean change) relative to the (annualized) LS mean change in the placebo arm.

Spearman correlation between the 80-week change in each vMRI region and each clinical scale (ADAS-Cog14, CDR-SB, and MMSE) was calculated by treatment. The relationship between whole temporal lobe atrophy and change in ADAS-Cog14 was further explored via linear regression models. All *P* values are reported as uncorrected.

To achieve largely consistent longitudinal analysis populations across approaches, for each region separately, analysis populations were restricted to intent-to-treat patients with change values of the corresponding MRI measurements (atrophy) as well as change values of the ADAS-Cog14 measurement (both changes from baseline to endpoint at week-80 visit).

3. Results

3.1. Study sample

A summary of baseline patient characteristics and selected imaging metrics is provided in Table 1 for the population with both temporal lobe volume measures and ADAS-Cog14 at

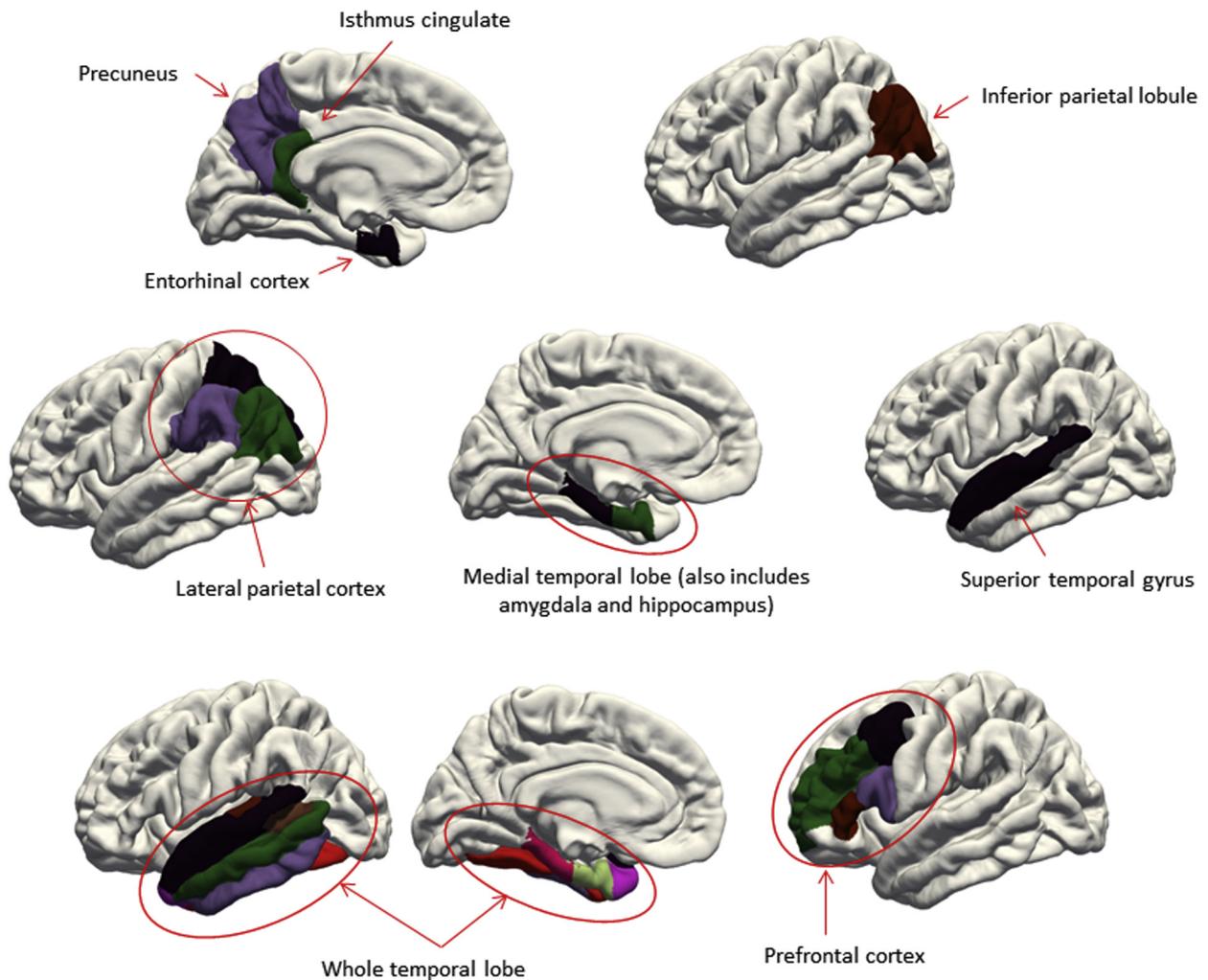


Fig. 1. Anatomical visualization of prespecified brain regions used for the analysis of atrophy (in addition to ventricular volume and whole brain).

both baseline and week-80 visit. In general, characteristics were very similar for the populations with both baseline and week-80 visit data from other vMRI metrics and representative of both the larger set of subjects with any baseline MRI assessment as well (data not shown) and the full EXPEDITION3 trial population [7]. There were no clinically meaningful differences between the treatment arms in age, cognitive scores, percentage of APOE $\epsilon 4$ carriers, concomitant medication use, or baseline vMRI metrics.

3.2. Effect of solanezumab on rates of brain atrophy

Longitudinal absolute changes in all vMRI parameters were nominally smaller in the solanezumab arm relative to the placebo arm, as shown in Table 2 and illustrated graphically in Fig. 2. For the prespecified primary vMRI parameters, the relative difference (or slowing of atrophy) in the solanezumab arm relative to the placebo arm was 4.1% for the hippocampus ($P = .082$), 4.0% for the entorhinal cortex ($P = .09$), 4.3% for the whole brain ($P = .097$), and 3.9% for the ventricles ($P = .196$). None of the differences was statistically significant after Bonferroni correction for multiple comparisons

(critical P value = .0036) or using the Benjamini-Hochberg method with a false discovery rate of 5%.

The exploration of other cortical areas revealed results consistent with those of the primary vMRI measures, with the isthmus cingulate (6.9%, $P = .023$) and temporal lobe (5.1%, $P = .015$) showing nominally larger relative differences than the primary vMRI measures. Over all the vMRI outcome measures assessed, the average relative difference in annualized atrophy was 3.8%.

When split by sex, there was no systematic bias toward increased slowing of atrophy in either men or women (Supplementary Table S2). Five of the outcome measures favored women, and nine outcome measures favored men; none of the tests survived correction for multiple comparisons at the $P = .05$ level.

3.3. Relationship between regional atrophy rates and change in cognitive scales

In the placebo arm, the longitudinal changes in vMRI metrics were correlated with longitudinal changes in global

Table 1
Demographics and study sample

Variable, statistic	Placebo arm	Solanezumab arm
Enrolled with at least one MRI at baseline or endpoint, N	1043	1038
Population with change values for both ADAS-Cog14 and whole temporal lobe volumes from baseline to week 80, N	721	741
Age in years (SD)	72.6 (7.76)	72.3 (7.62)
Baseline MMSE score (SD)*	22.9 (2.87)	23.0 (2.69)
Baseline ADAS-Cog14 score (SD)	28.8 (8.16)	28.5 (7.97)
APOE ϵ 4 carriers, %*	66.7	69.0
AChEI/memantine use, %	81.1	78.5
Baseline hippocampal volume (left + right), mm ³ (SD) [†]	6021.8 (1038.59)	6018.7 (1075.39)
Baseline entorhinal cortex volume (left + right), mm ³ (SD) [†]	2684.9 (673.40)	2683.4 (648.44)
Baseline whole-brain volume, mm ³ (SD) [†]	974,424.6 (101,470.01)	977,383.1 (106,014.61)
Baseline ventricular volume, mm ³ (SD) [†]	48,151.8 (21,599.14)	48,448.5 (22,023.68)
Baseline CSF t-tau, pg/mL (SD) [‡]	353 (165)	364 (145)
Baseline CSF p-tau, pg/mL (SD) [§]	35.8 (18)	37.3 (18)

Abbreviations: AChEI, acetylcholinesterase inhibitor; ADAS-Cog14, 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale; APOE, apolipoprotein E; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SD, standard deviation.

*Based on patients with baseline MMSE (placebo N = 697; solanezumab N = 723), based on available APOE status (placebo N = 703; solanezumab N = 728) within the analysis population (second data row).

[†]Based on patients as selected for the presented analysis population but requiring the applicable region atrophy instead of the whole temporal lobe atrophy (hippocampus: N = 723, N = 744; entorhinal cortex: N = 723, N = 744; whole brain: N = 721, N = 741; ventricles: N = 722, N = 743). Small differences in numbers reflect MRI analysis QC fails. See [Supplementary Table S1](#) for additional brain regions.

[‡]Based on patients with available baseline CSF t-tau (placebo N = 103; solanezumab N = 119).

[§]Based on patients with available baseline CSF p-tau (placebo N = 105; solanezumab N = 120).

cognitive scales in a region-specific manner ([Table 3](#)). Changes in ADAS-Cog14, CDR-SB, and MMSE correlated most strongly with regional volume changes in the large region combination, the whole brain, and in the superior temporal gyrus and whole temporal lobe ($0.38 \leq |r| \leq 0.48$).

Changes in these scales were also correlated with atrophy rates in the precuneus and ventricles ($0.35 \leq |r| \leq 0.44$) and, to a slightly lesser extent, with lateral parietal cortex, prefrontal cortex, and small region combination ($0.29 \leq |r| \leq 0.43$). The relationships were weaker for medial

Table 2
vMRI results from EXPEDITION3 (analysis population with MRI and ADAS-Cog14 change values)

Region*	80-Week LS mean change, mm ³ (placebo)	Annualized LS mean % change (placebo) [†]	80-Week LS mean change, mm ³ (sola)	Annualized LS mean % change (sola) [†]	Relative slowing (sola vs. placebo) [‡]	p (sola vs. placebo)
Hippocampus	-307.4	-3.32%	-294.7	-3.18%	4.1%	0.082
Entorhinal cortex	-178.8	-4.33%	-171.5	-4.15%	4.0%	0.090
Whole brain	-23,620.9	-1.58%	-22,668.1	-1.51%	4.3%	0.097
Ventricles	7289.1	9.84%	7051.1	9.46%	3.9%	0.196
Temporal lobe	-3882.5	-2.97%	-3684.0	-2.82%	5.1%	0.015
Lateral parietal cortex	-1978.4	-2.14%	-1955.3	-2.11%	1.3%	0.662
Prefrontal cortex	-1616.3	-2.1%	-1572.6	-2.03%	3.3%	0.394
Medial temporal lobe	-771.8	-3.55%	-745.6	-3.43%	3.5%	0.086
Isthmus cingulate	-143.5	-2.36%	-134.1	-2.20%	6.9%	0.023
Precuneus	-657.5	-2.76%	-642.4	-2.67%	3.2%	0.418
Superior temporal gyrus	-732.3	-2.45%	-705.7	-2.36%	3.6%	0.171
Inferior parietal lobule	-755.7	-2.33%	-737.9	-2.27%	2.7%	0.414
Small region combination	-1735.6	-2.61%	-1687.2	-2.53%	3.3%	0.238
Large region combination	-7475.2	-2.49%	-7213.9	-2.40%	3.7%	0.115

NOTE: For vMRI results from EXPEDITION3 (analysis population with MRI and ADAS-Cog14 change values) split by sex, see [Supplementary Table S2](#). Abbreviations: ADAS-Cog14, 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale; LS, least squares; sola, solanezumab; vMRI, volumetric magnetic resonance imaging.

*All regions reported as the sum of left and right hemisphere volumes in each subject.

[†]Annualized LS mean percentage change relates the 80-week LS mean change to the corresponding average baseline volume and normalizes the fraction to 52 weeks (rounded results are presented).

[‡]Relative slowing is the difference of (annualized) LS mean percentage change of placebo minus solanezumab divided by the (annualized) LS mean percentage change of placebo. (Calculations use full precision numbers, then presented as rounded results in percent).

A Longitudinal changes in placebo and solanezumab arms by vMRI parameter

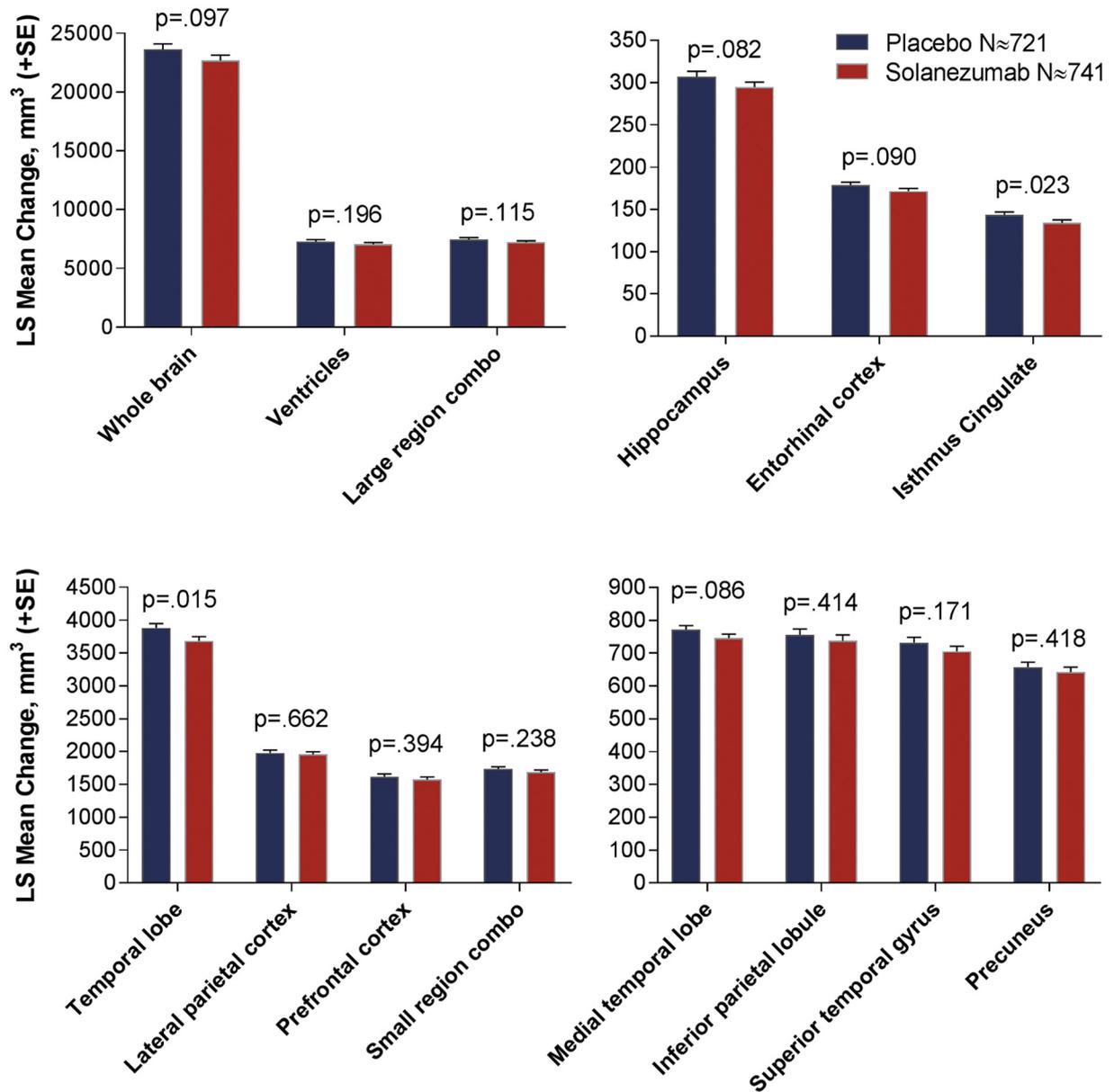


Fig. 2. (A) Absolute LS mean changes in vMRI parameters for placebo- and solanezumab-treated groups. Error bar represents standard error. Small differences in numbers (N) across regions are due to MRI analysis QC fails (cf. Table 1, Note [B]). (B) Between-group differences in longitudinal changes between the solanezumab arm and the placebo arm, expressed as a percentage of the change in the placebo arm. Blue bars represent predefined primary vMRI parameters, red bars represent lobar composite regions, orange represents a medial temporal lobe composite region (including the hippocampus and entorhinal cortex, and partially overlapping with the whole temporal lobe composite region), green represents preselected individual atlas regions, and gray represents combination regions. All regions reported as the sum of left and right hemisphere volumes in each participant. Abbreviations: LS, least squares; SE, standard error; vMRI, volumetric magnetic resonance imaging.

temporal regions ($0.19 \leq |r| \leq 0.23$). While the anatomical profiles of these associations were similar for each of these instruments, the correlations were stronger overall for ADAS-Cog14 and MMSE than for CDR-SB. Results for the solanezumab arm were similar (Supplementary Table S3).

Because the whole temporal lobe exhibited a strong association with changes in ADAS-Cog14 ($r = -0.46$) and one of the largest treatment effects (Table 2), we focused further on the relationship between temporal lobe atrophy and changes in ADAS-Cog14. The relationship between individual longitudinal changes in temporal lobe volume

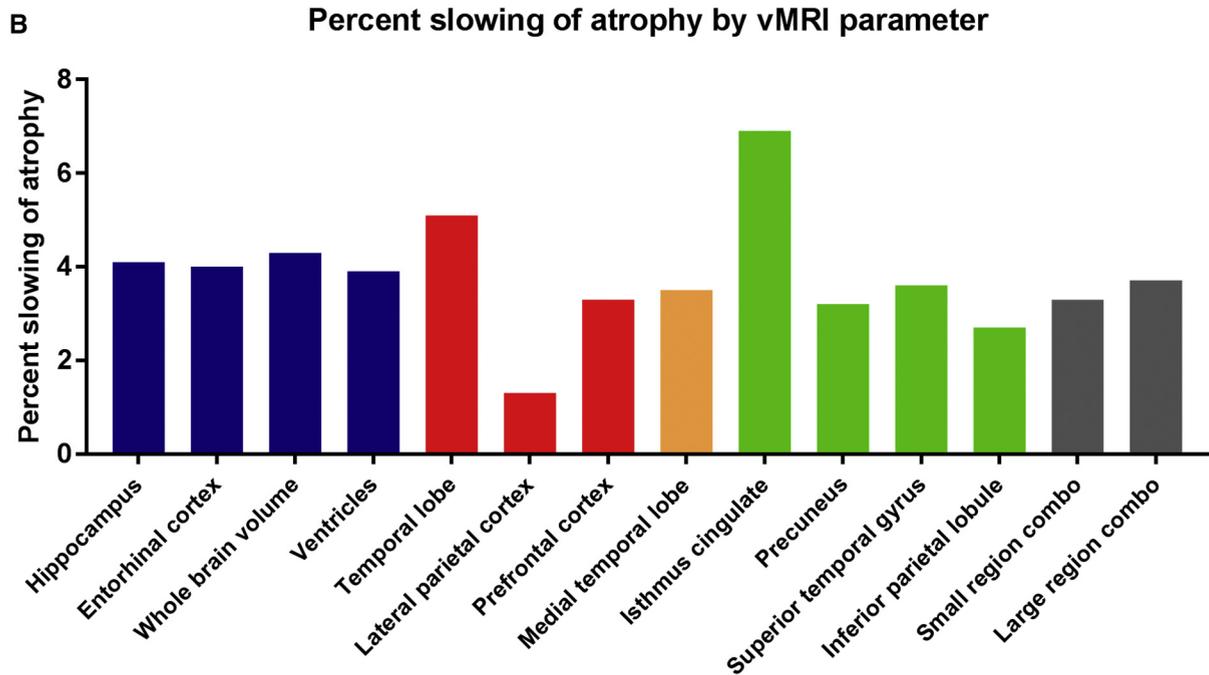


Fig. 2. (continued).

and in ADAS-Cog14 is shown in Fig. 3A. The observed relationship was comparable in both placebo- and solanezumab-treated populations, with a slope of $-75 \text{ mm}^3/\text{point}$ and $-77 \text{ mm}^3/\text{point}$, respectively. The observed difference between the LS mean change in temporal lobe volume between the two treatment arms was 198.5 mm^3 (5.1% of the LS mean change of 3882.5 mm^3 in the placebo arm) (Fig 3B).

Table 3

Correlations (Spearman) between absolute longitudinal change in vMRI regions and longitudinal change in cognitive instruments in the placebo arm

Region*	ADAS-Cog14	CDR-SB	MMSE
Hippocampus	-0.106	-0.147	0.158
Entorhinal cortex	-0.135	-0.133	0.143
Medial temporal lobe	-0.192	-0.224	0.230
Superior temporal gyrus	-0.442	-0.386	0.451
Temporal lobe	-0.459	-0.386	0.475
Isthmus cingulate	-0.337	-0.282	0.350
Precuneus	-0.414	-0.358	0.412
Inferior parietal lobule	-0.362	-0.235	0.347
Lateral parietal cortex	-0.418	-0.295	0.375
Prefrontal cortex	-0.412	-0.343	0.399
Whole brain	-0.473	-0.403	0.451
Ventricles	0.431	0.384	-0.434
Small region combination	-0.424	-0.321	0.413
Large region combination	-0.478	-0.382	0.469

Abbreviations: ADAS-Cog14, 14-item Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating scale: Sum of Boxes; MMSE, Mini-Mental State Examination; vMRI, volumetric magnetic resonance imaging.

*All regions reported as the sum of left and right hemisphere volumes in each subject.

4. Discussion

Annualized rates of change for whole-brain and ventricular volumes in the placebo arm (1.58%/y and 9.84%/y, respectively) were similar to those previously observed in the pooled mild AD sample from the EXPEDITION and EXPEDITION2 trials (1.3%/y and 9.6%/y, respectively) [4] despite the use of different image quantitation algorithms for those studies. Differences in the rates of atrophy between the treatment arms in EXPEDITION3 were directionally consistent, with all regions showing a nominally slower rate of atrophy in the solanezumab arm relative to the placebo arm. However, the changes were overall weak in magnitude (1.3–6.9% slowing; average 3.8%) and not statistically significant if corrected for multiple comparisons across the different regions assessed. The slowing of brain atrophy observed in the pooled mild AD sample from the EXPEDITION and EXPEDITION2 trials was 2.3% for the whole brain and 5.6% for ventricular volume [4], in contrast to the values 4.3% and 3.9% observed for those metrics in EXPEDITION3. The treatment effects were thus directionally consistent and of similar overall magnitude between EXPEDITION/EXPEDITION2 and EXPEDITION3 trials. There was no clear evidence of a greater treatment effect on female or male participants when analyzed separately.

The directionality of the vMRI findings observed with solanezumab in the EXPEDITION trials is in contrast to results reported from the AN1792 A β active immunization trial, in which patients clinically defined as probable AD who exhibited an active antibody response to treatment had a substantial and significant increase in their

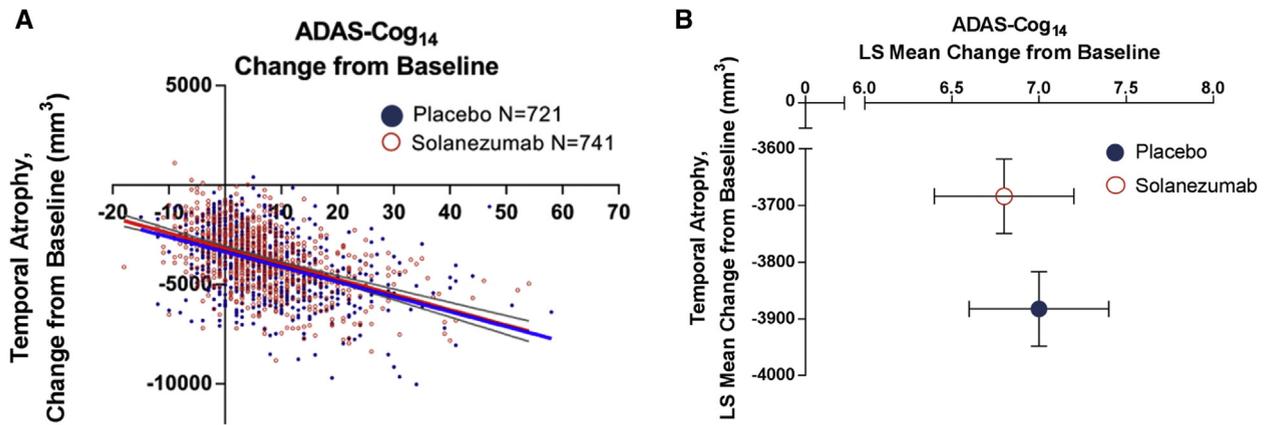


Fig. 3. (A) Scatter plots and regression lines with 95% confidence intervals between change in temporal lobe volume (mm^3) and change in ADAS-Cog14 score for the analysis population in placebo and solanezumab arms. Changes were calculated at 80 weeks, and the regression model was calculated independently for each arm. The slopes of the regression lines ($-75 \text{ mm}^3/\text{unit score}$ for placebo and $-77 \text{ mm}^3/\text{unit score}$ for solanezumab) were not substantially different. Spearman Rank Correlation Coefficients, P values, and slopes of the regression lines for each regional change in brain volume against change in ADAS-Cog14 are included in [Supplementary Table S2](#). (B) LS mean change in ADAS-Cog14 plotted against LS mean change in temporal lobe volume for each arm of the analysis population. Error bars denote standard error. Abbreviations: ADAS-Cog₁₄, 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale; LS, least squares.

rate of atrophy, compared with placebo-treated individuals, for whole-brain and ventricular boundary shift integral measures but not for hippocampal volume [10]. The group sizes in that study were small ($N = 38\text{--}57$ evaluable, depending on the measure) but similar to that which was targeted ($N = 75$) based on power calculations for a 30% reduction in whole-brain atrophy. In the bapineuzumab studies, no significant difference in whole-brain atrophy between treated and placebo groups was observed in any of the four phase 3 trials [8,9] nor in a meta-analysis of six phase 2 and 3 trials [19]. Moreover, no relationship between brain boundary shift integral and drug exposure levels was observed in an analysis of two of the phase 3 trials [20]. Directionally, the differences between bapineuzumab and placebo arms were not consistent across arms and trials, favoring bapineuzumab in some cases and placebo in others. Because statistical significance of group differences is dependent on the sample size, it is also worthwhile considering the magnitude of between-group differences observed in these studies. For whole-brain volume change, the difference between treated and placebo groups in the 18-month change in the first two phase 3 bapineuzumab trials reported ranged from a 1.9% decrease to a 8.6% increase in atrophy [8] compared with a 4.3% decrease in atrophy observed in EXPEDITION3 and a 2.5% decrease in atrophy observed in the pooled mild AD sample from EXPEDITION/EXPEDITION2 [4]. In the AN1792 trial, the group difference in whole-brain volume change was substantially larger, equating to a 49.5% increase in atrophy in the antibody responders [10].

In EXPEDITION3, the anatomical patterns of correlation between changes in brain volumes and changes in clinical scales were consistent for all the scales of global

cognition or function, with the whole temporal lobe and measures of global atrophy correlating most strongly and medial temporal structures notably more weakly. This anatomical pattern is consistent with that obtained in a vertex-wise whole-brain analysis of cortical thinning in relation to CDR-SB change in subjects with mild cognitive impairment [13], although medial temporal structures were more strongly associated with CDR-SB decline in that study. Medial temporal structures are affected early during the course of the disease [21], and so, cognitive decline might be more closely associated with atrophy in those regions in earlier disease stages. Consistent with this notion, significant negative correlations between CDR-SB and medial temporal lobe cortical thickness were reported in a study of subjects with mild cognitive impairment ($r = -0.36$, $P < .01$) [22], whereas significant negative correlations between cortical thickness and CDR box scores in the parietal, but not in the temporal, lobe was found in patients with AD [23]. The relationship between changes in whole-brain atrophy and in scales of global cognition ($0.40 \leq |r| \leq 0.48$) in the present analysis is comparable to reported relationships ($0.48 \leq r \leq 0.56$) between changes in ADAS-Cog11 and brain boundary shift integral, a measure of whole-brain atrophy, reported across several vMRI substudies on mild-to-moderate AD in the bapineuzumab trials [24].

The relative magnitude of changes in imaging markers relative to changes in clinical instruments could be an important consideration in AD studies. Many studies comparing the relative statistical power of imaging and cognitive outcome measures have assumed the same rate of slowing (e.g., 25%) as a putative treatment effect [25,26]. However, the results of the present study suggest that a given

slowing of clinical decline may be accompanied by a smaller relative degree of slowing in brain atrophy. The regression relationship between the change in ADAS-Cog14 and change in temporal lobe volume in individual participants was similar for both placebo and solanezumab groups. The larger differences in treatment-effect magnitudes (percentage change in slowing) than absolute atrophy rates between the previous trials and EXPEDITION3 and the fact that the treatment effects were overall small and nonsignificant are limitations in drawing too strong a conclusion from the specific relationship between magnitudes of treatment effect from these data. Nevertheless, the notion that the relative effect size of interventional treatments on brain atrophy measures might be different from that of cognitive outcomes is an important consideration when powering clinical trials for biomarker and/or clinical changes.

A limitation of this study is that a range of scanner manufacturers, hardware and software versions, and a mix of 1.5T and 3T scanners were included. While this likely contributes additional variability in the imaging data, it is intrinsic to large, global, multisite trials. We attempted to mitigate the effects of this via centralized management of acquisition parameter harmonization, scanner qualification, imaging site training, and data quality control and analysis. Moreover, any subject whose baseline and follow-up scans were obtained on different scanners (e.g., due to an unavoidable site scanner upgrade) was excluded from the present quantitative vMRI analysis.

In conclusion, the changes in brain volumetric measures between solanezumab-treated and placebo-treated participants were not statistically significant over 80 weeks in the EXPEDITION3 trial. The group-mean differences were directionally consistent across a number of brain regions but small in magnitude (equivalent to 1.3–6.9% slowing). The rates of atrophy and correlations between absolute volume changes and cognitive changes in placebo-treated subjects were similar to those reported previously.

Acknowledgments

The study was supported by Eli Lilly and Company, Indianapolis, Indiana, USA. Sreelatha Akkala, a full-time employee of Eli Lilly and Company, provided support with the preparation of the manuscript. We thank the patients, caregivers, and families who participated in this trial; the site investigators and personnel; the members of the steering committee; and the members of the trial team.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.trci.2019.05.007>.

RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Recent publications describing the results of experimental anti-amyloid therapies in late-phase clinical trials and their effects on brain atrophy are appropriately cited.
2. **Interpretation:** Our findings demonstrate a modest but consistent trend to slowing of brain atrophy across a number of brain regions in patients treated with solanezumab relative to placebo. Changes in temporal lobe volume across participants were strongly correlated with changes in ADAS-Cog14. These findings are consistent with the modest but consistent previously reported trend of slowing of cognitive decline in patients treated with solanezumab relative to placebo.
3. **Future directions:** The manuscript demonstrates an anatomical profile of treatment effects on brain atrophy beyond the traditionally reported hippocampus, ventricles, and whole brain and, hence, a framework for future studies of putative disease-modifying treatments in Alzheimer's disease to interrogate a wider range of brain structures.

References

- [1] DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-A beta antibody alters CNS and plasma A beta clearance and decreases brain A beta burden in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* 2001;98:8850–5.
- [2] Demattos RB, Bales KR, Cummins DJ, Paul SM, Holtzman DM. Brain to plasma amyloid-beta efflux: a measure of brain amyloid burden in a mouse model of Alzheimer's disease. *Science* 2002; 295:2264–7.
- [3] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *New Engl J Med* 2014;370:311–21.
- [4] Siemers ER, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, et al. Phase 3 solanezumab trials: secondary outcomes in mild Alzheimer's disease patients. *Alzheimer's Dement: J Alzheimer's Assoc* 2016;12:110–20.
- [5] Salloway S, Sperling R, Gregg K, Yu P, Joshi A, Lu M, et al. Incidence and clinical progression of placebo-treated amyloid-negative subjects with mild-to-moderate Alzheimer's disease (AD): results from the phase III PET substudies of bapineuzumab and solanezumab. *Alzheimer Dement* 2013;9:889.
- [6] Dean RA, Shaw LM, Waligorska T, Korecka M, Figurski M, Trojanowski JQ, et al. Inclusion of patients with Alzheimer's disease pathology in solanezumab EXPEDITION3 using florbetapir (18F) PET imaging or INNO-BIA AlzBio3 CSF Aβ1-42. *Alzheimer's Dement: J Alzheimer's Assoc* 2014;10:811.

- [7] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, et al. Solanezumab for mild dementia due to Alzheimer's disease. *New Engl J Med* 2018;378:321–30.
- [8] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *New Engl J Med* 2014;370:322–33.
- [9] Vandenberghe R, Rinne JO, Boada M, Katayama S, Scheltens P, Vellas B, et al. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. *Alzheimer's Res Ther* 2016;8:18.
- [10] Fox NC, Black RS, Gilman S, Rossor MN, Griffith SG, Jenkins L, et al. Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology* 2005;64:1563–72.
- [11] Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex* 2009;19:497–510.
- [12] Dickerson BC, Wolk DA. Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics. *J Neurol Neurosurg Psychiatry* 2011;82:45–51.
- [13] McDonald CR, Gharapetian L, McEvoy LK, Fennema-Notestine C, Hagler DJ Jr, Holland D, et al. Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. *Neurobiol Aging* 2012;33:242–53.
- [14] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
- [15] Vercauteren T, Pennec X, Perchant A, Ayache N. Symmetric log-domain diffeomorphic Registration: a demons-based approach. *Med Image Comput Assist Interv* 2008;11:754–61.
- [16] Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* 2008;12:26–41.
- [17] Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006;31:968–80.
- [18] Sabuncu MR, Desikan RS, Sepulcre J, Yeo BT, Liu H, Schmansky NJ, et al. The dynamics of cortical and hippocampal atrophy in Alzheimer disease. *Arch Neurol* 2011;68:1040–8.
- [19] Abushouk AI, Elmarazy A, Aglan A, Salama R, Fouda S, Fouda R, et al. Bapineuzumab for mild to moderate Alzheimer's disease: a meta-analysis of randomized controlled trials. *BMC Neurol* 2017;17:66.
- [20] Russu A, Samtani MN, Xu S, Adedokun OJ, Lu M, Ito K, et al. Biomarker exposure-response analysis in mild-to-moderate Alzheimer's disease trials of bapineuzumab. *J Alzheimer's Dis: JAD* 2016;53:535–46.
- [21] Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica* 1991;82:239–59.
- [22] Bakkour A, Morris JC, Dickerson BC. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. *Neurology* 2009;72:1048–55.
- [23] Du AT, Schuff N, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin K, et al. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain* 2007;130:1159–66.
- [24] Novak G, Einstein S, Lu Y, Tudor IC, Gregg K, Collins P, et al. Correlation of brain atrophy with clinical progression in mild-to-moderate Alzheimer's disease: results from the volumetric MRI substudies of two phase III trials with bapineuzumab. *Alzheimer's Dement* 2013;9:P289.
- [25] Holland D, McEvoy LK, Dale AM. Unbiased comparison of sample size estimates from longitudinal structural measures in ADNI. *Hum Brain Mapp* 2012;33:2586–602.
- [26] Beckett LA, Harvey DJ, Gamst A, Donohue M, Kornak J, Zhang H, et al. The Alzheimer's Disease Neuroimaging Initiative: annual change in biomarkers and clinical outcomes. *Alzheimer's Dement: J Alzheimer's Assoc* 2010;6:257–64.