SUPPLEMENTARY MATERIAL

Detailed statistical methods for main linear mixed effects model

The general framework for our statistical approach can be found in the main manuscript. All analyses were based on linear mixed effects regression models[1] and fit using version 1.1-12 of the *lme4* package for the R statistical computing environment.

Below we describe in detail our primary analysis comparing rates of hippocampal atrophy for different pathologically defined groups. Other models used in our analyses follow a similar approach.

Our main model involved fitting a model with an interaction between time, neurofibrillary tangle stage (B1, B2, or B3), and TDP (Stage 0, Stage 1, and Stage ≥2). The model also allowed for an individual's rate of atrophy to depend on his or her age at death via a time × age-at-death interaction. To control for variation due to different field strengths and head sizes we included these terms in the model as well. Heterogeneity across individuals and intraclass correlation due to repeated measurements of an individual were accounted for by including subject-specific random intercepts and slopes.

In the *lmer* package syntax, the model was specified as follows:

```
R> library("lme4")
R> fit1 <- lmer(log(hippvol) ~ time*tdp*tau + time*agedeath +
+                  tiv + fieldstr + (1 + time | subj),
+              data = pathdata)
```

The terms in this main model are described in Supplementary Table 1 below.

Supplementary Table 1: Terms in the main linear mixed effects model

Term	Description
log(hippvol)	Natural logarithm of hippocampal volume in cm^3
time	Time in years with zero corresponding to death. An MRI five years prior to death would be coded as −5.
tdp	TDP-43 stage with levels Stage 0 (reference), Stage 1, and Stage ≥2
tau	Neurofibrillary tangle stage with levels B1 (reference), B2, and B3
agedeath	Age at death centered at 80 and divided by 10 so that units are in decades
tiv	Total intracranial volume expressed in L centered at 1.4L
fieldstr	MRI field strength with levels of 1.5T (reference) and 3T
subj	Randomly assigned unique participant identifier

The summary output from the model is shown below in Supplementary Table 2. Since the response is log-transformed, the coefficients can be multiplied by 100 and interpreted as approximate percentage differences.

Supplementary Table 2: Summary output from the main linear mixed effects model

```
Linear mixed model fit by REML ['lmerMod']
Formula:
log(hippvol) ~ time * tdp * tau + time * agedeath + tiv + fieldstr +
    (1 + time | subj)
   Data: pathdata

REML criterion at convergence: -1828

Scaled residuals:
   Min     1Q Median     3Q    Max
-3.328 -0.350  0.006  0.378  4.180
```

```
Random effects:
 Groups   Name        Variance Std.Dev. Corr
 subj     (Intercept) 0.032452 0.1801
          time        0.000159 0.0126   0.44
 Residual             0.000836 0.0289
Number of obs: 816, groups:  subj, 298

Fixed effects:
                       Estimate Std. Error t value
(Intercept)             2.009837   0.036937    54.4
time                   -0.011775   0.004633    -2.5
tdpStage 1             -0.024292   0.079431    -0.3
tdpStage 2+            -0.042784   0.098942    -0.4
tauB2                  -0.098681   0.048420    -2.0
tauB3                  -0.205837   0.042157    -4.9
agedeath               -0.078308   0.012149    -6.4
tiv                     0.005914   0.002731     2.2
fieldstr3              -0.077980   0.009033    -8.6
time:tdpStage 1        -0.003902   0.008113    -0.5
time:tdpStage 2+       -0.012252   0.014016    -0.9
time:tauB2             -0.004520   0.005986    -0.8
time:tauB3             -0.019324   0.005112    -3.8
tdpStage 1:tauB2        0.040029   0.113086     0.4
tdpStage 2+:tauB2      -0.122567   0.112891    -1.1
tdpStage 1:tauB3       -0.008933   0.091379    -0.1
tdpStage 2+:tauB3      -0.113832   0.102236    -1.1
time:agedeath           0.003547   0.001372     2.6
time:tdpStage 1:tauB2   0.002188   0.010834     0.2
time:tdpStage 2+:tauB2 -0.012015   0.015347    -0.8
time:tdpStage 1:tauB3   0.002094   0.009356     0.2
time:tdpStage 2+:tauB3 -0.000557   0.014301     0.0
```

Interpretations of the regression parameters can be found below in Supplementary Table 3.

Supplementary Table 3: Interpretation of the regression coefficients of the main mixed effects model

Coefficient	Interpretation
(Intercept)	Mean *y* when all categorical terms are at their reference level and continuous terms set to zero
time	Mean annual change in *y* for an individual in NFT stage B1 and TDP-43 Stage 0 assuming age of death of 80 years
tdpStage 1	Mean difference in *y* between TDP-43 Stage 1 and Stage 0 assuming NFT stage B1 and other terms set to their reference level or zero
tdpStage 2+	Mean difference in *y* between TDP-43 Stage ≥2 and Stage 0 assuming NFT stage B1 and other terms set to their reference level or zero
tauB2	Mean difference in *y* between NFT stage B2 and Stage B1 assuming TDP-43 Stage 0 and other terms set to their reference level or zero
tauB3	Mean difference in *y* between NFT stage B3 and Stage B1 assuming TDP-43 Stage 0 and other terms set to their reference level or zero
agedeath	Mean difference in *y* for a decade difference in age at death
tiv	Mean difference in *y* for a 1L increase in total intracranial volume
fieldstr3	Mean difference in *y* for MRI fieldstrength of 3T versus 1.5T
time:tdpStage 1	Mean difference in annual change in *y* between TDP-43 Stage 1 and Stage 0 assuming NFT stage B1 and age of death of 80 years
time:tdpStage 2+	Mean difference in annual change in *y* between TDP-43 ≥2 and Stage 0 assuming NFT stage B1 and age of death of 80 years
time:tauB2	Mean difference in annual change in *y* between NFT stage B2 and B1 assuming TDP-43 Stage 0 and age of death of 80 years

time:tauB3	Mean difference in annual change in *y* between NFT stage B3 and B1 assuming TDP-43 Stage 0 and age of death of 80 years
tdpStage 1:tauB2	A contrast of the mean differences in *y* for TDP-43 Stage 1 versus 0 for NFT stage B2 compared to B1
tdpStage 2+:tauB2	A contrast of the mean differences in *y* for TDP-43 Stage ≥2 versus 0 for NFT stage B2 compared to B1
tdpStage 1:tauB3	A contrast of the mean differences in *y* for TDP-43 Stage 1 versus 0 for NFT stage B3 compared to B1
tdpStage 2+:tauB3	A contrast of the mean differences in *y* for TDP-43 Stage ≥2 versus 0 for NFT stage B3 compared to B1
time:agedeath	Mean difference in annual change in *y* for a 1-decade increase in age at death assuming TDP-43 Stage 0 and NFT stage B1
time:tdpStage 1:tauB2	A contrast in the annual changes in *y* for TDP-43 Stage 1 versus 0 for NFT stage B2 compared to B1
time:tdpStage 2+:tauB2	A contrast in the annual changes in *y* for TDP-43 Stage ≥2 versus 0 for NFT stage B2 compared to B1
time:tdpStage 1:tauB3	A contrast in the annual changes in *y* for TDP-43 Stage 1 versus 0 for NFT stage B3 compared to B1
time:tdpStage 2+:tauB3	A contrast in the annual changes in *y* for TDP-43 Stage ≥2 versus 0 for NFT stage B3 compared to B1

In the above parameterization, linear combinations of coefficients can be calculated to estimate annual change for a given pathologically defined group. For example the estimated annual change among individuals with NFT stage B0 and TDP-43 stage 1 is the sum of the "time" and "time:tdpStage 1" coefficients. Similarly, linear combinations of the coefficients can be used to contrast rates of change in one group compared to another.

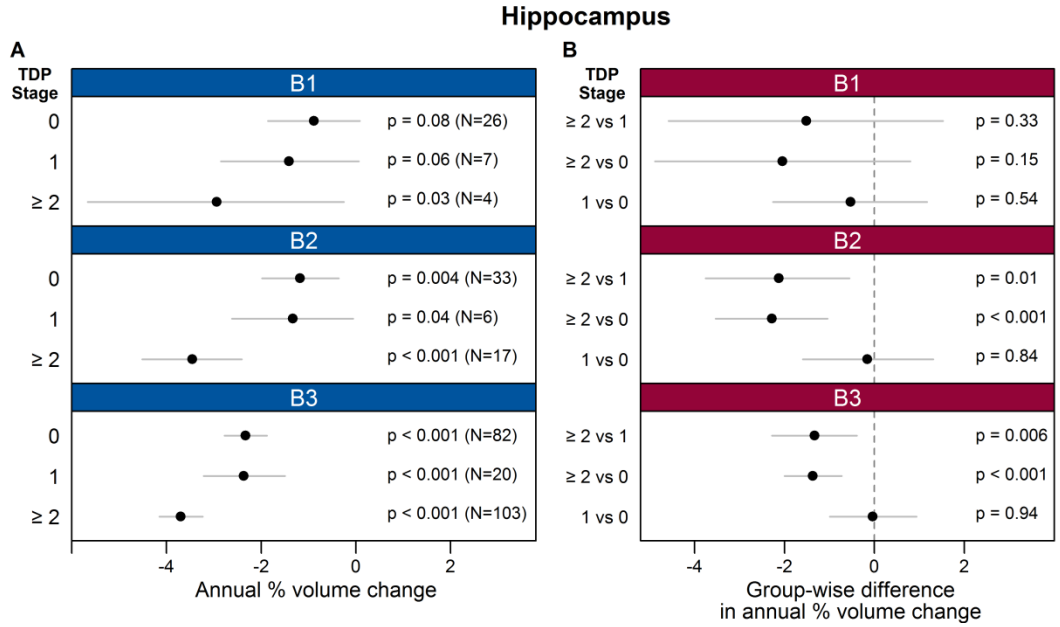
We used the *arm* package to obtain 10,000 parametric bootstrap replicates[2] of the coefficients. We report 95% confidence intervals based on calculating the 2.5th and 97.5th percentiles of the quantity of interest. We report p-values for contrasts of interest based on the duality between confidence intervals and hypothesis tests. In the same way that a 95% confidence interval that does not include the null value (typically zero) indicates $p<0.05$, we report p-values by calculating the widest percentile based confidence interval that excludes the null value.

References

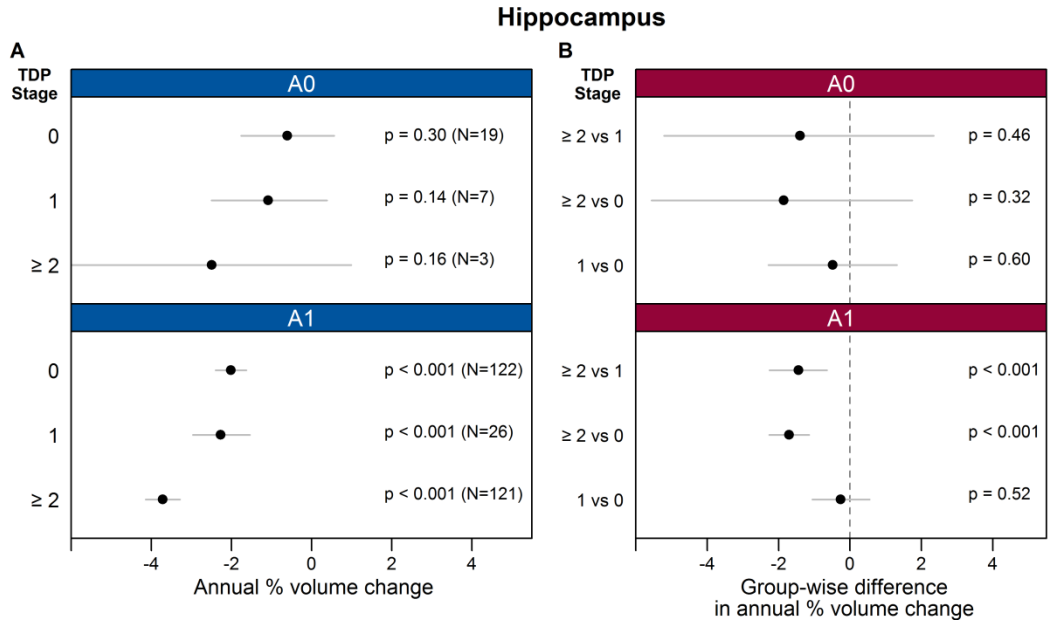
1. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. Hoboken, N.J: Wiley-Interscience; 2004.
2. Gelman A, Hill J. Data analysis using regression and multilevel/hierarchical models. Cambridge; New York: Cambridge University Press; 2007.

Supplementary Figures

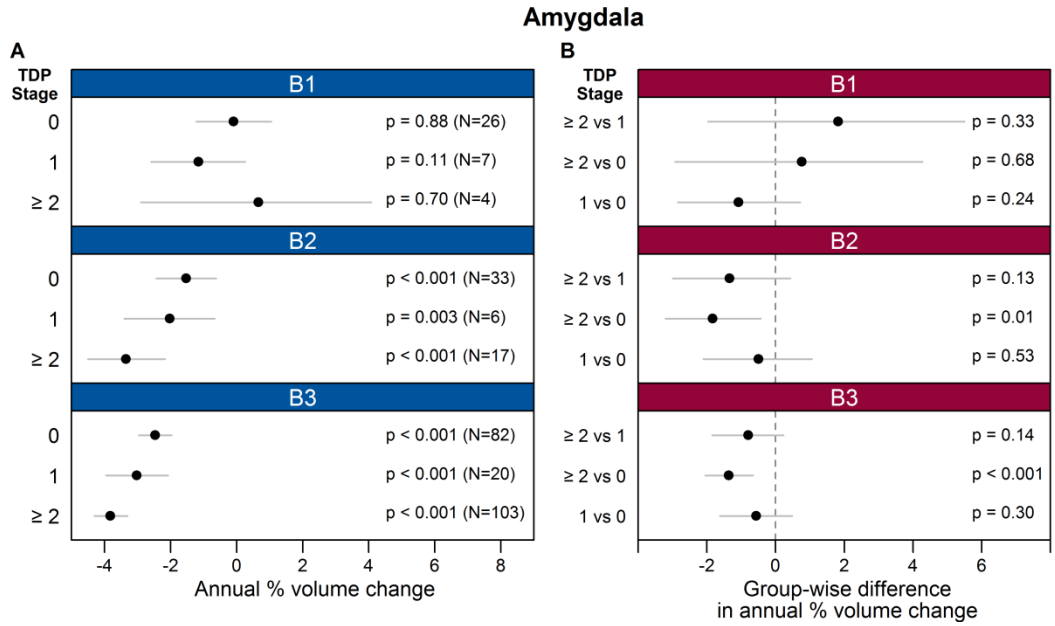
Supplementary Figure 1: Analyses of TBM-SyN hippocampal atrophy rates by TDP-43 and neurofibrillary tangle stages based on linear mixed effects regression modeling. (A) Shows hippocampal atrophy rates, expressed as an annual percent volume change, by TDP-43 stage separately for neurofibrillary tangles stages B1, B2, and B3. (B) Compares the rates of hippocampal atrophy, expressed as differences in annual percent volume change, between TDP-43 stages for each of the three neurofibrillary tangle stages.



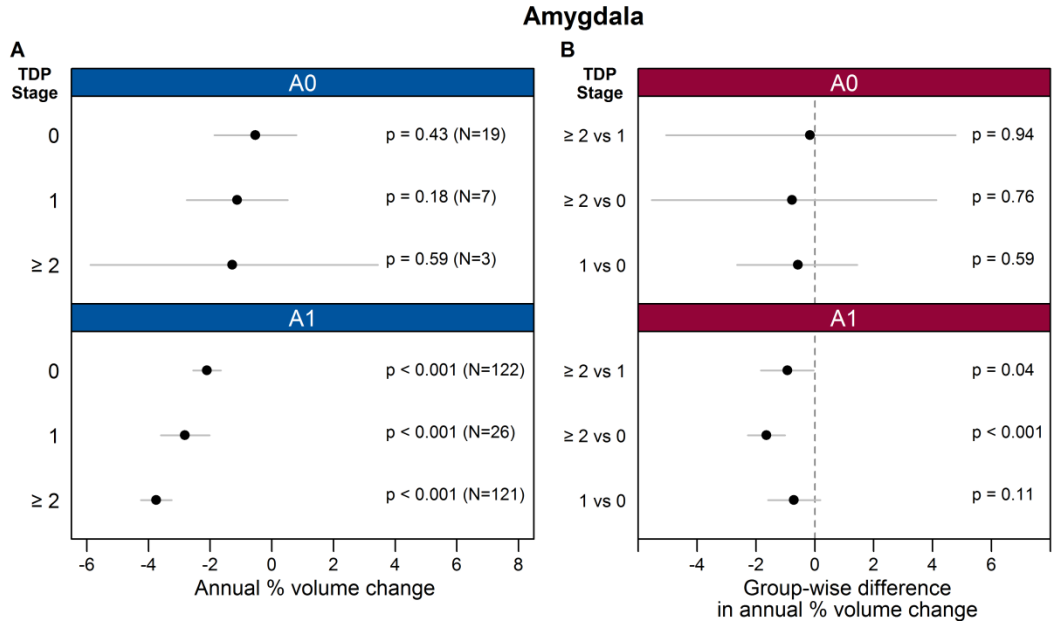
Supplementary Figure 2: Analyses of TBM-SyN hippocampal atrophy rates by TDP-43 and amyloid stage (amyloid- (A0), and amyloid + (A1)) based on linear mixed effects regression modeling. (A) Shows hippocampal atrophy rates, expressed as an annual percent volume change, by TDP-43 stage in amyloid- and amyloid+. (B) Compares the rates of hippocampal atrophy, expressed as differences in annual percent volume change, between TDP-43 stages in amyloid- and amyloid+.



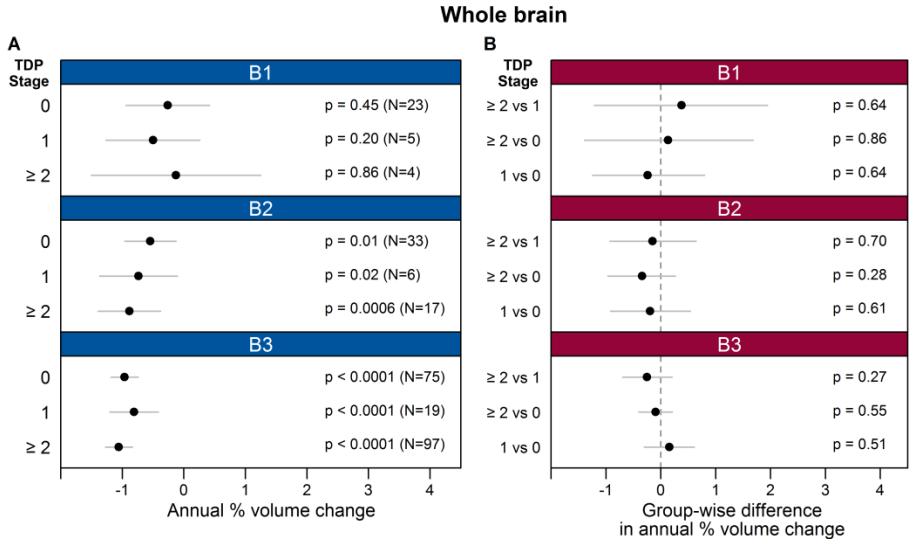
Supplementary Figure 3: Analyses of FreeSurfer amygdala atrophy rates by TDP-43 and neurofibrillary tangle stages. (A) Shows amygdala atrophy rates, expressed as an annual percent volume change, by TDP-43 stage separately for neurofibrillary tangles stages B1, B2, and B3. (B) Compares the rates of amygdala atrophy, expressed as differences in annual percent volume change, between TDP-43 stages for each of the three neurofibrillary tangle stages.



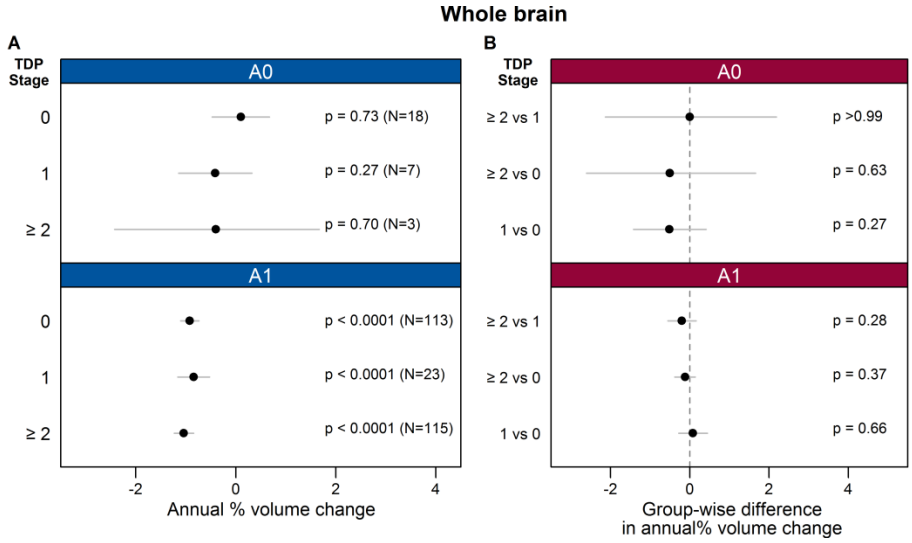
Supplementary Figure 4: Analyses of FreeSurfer amygdala atrophy rates by TDP-43 and amyloid positivity (amyloid- (A0), and amyloid + (A1)). (A) Shows amygdala atrophy rates, expressed as an annual percent volume change, by TDP-43 stage in amyloid- and amyloid+. (B) Compares the rates of amygdala atrophy, expressed as differences in annual percent volume change, between TDP-43 stages in amyloid- and amyloid+.



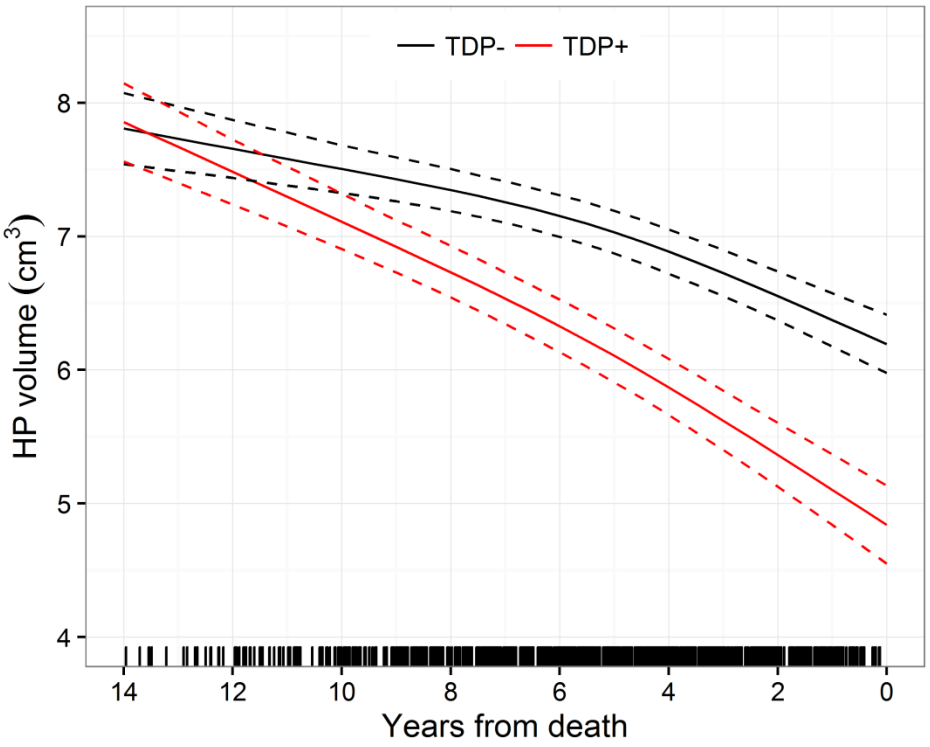
Supplementary Figure 5: Analyses of FreeSurfer whole brain rates by TDP-43 and neurofibrillary tangle stages. (A) Shows whole brain atrophy rates, expressed as an annual percent volume change, by TDP-43 stage separately for neurofibrillary tangles stages B1, B2, and B3. (B) Compares the rates of whole brain atrophy, expressed as differences in annual percent volume change, between TDP-43 stages for each of the three neurofibrillary tangle stages. We performed this analysis in all subjects as well as in subjects with 1.5T scans based on an inspection of the data and finding an apparent incompatibility between change estimates among those with 1.5T versus those with 3T scans. Regional structures did not exhibit any signs of field strength discrepancies after statistical adjustment. Regardless, TDP-43 was not associated with whole brain rates in the whole cohort or in the 1.5T subset (shown below).



Supplementary Figure 6: Analyses of FreeSurfer whole brain atrophy rates by TDP-43 and amyloid positivity (amyloid- (A0), and amyloid + (A1)). (A) Shows whole brain atrophy rates, expressed as an annual percent volume change, by TDP-43 stage in amyloid- and amyloid+. (B) Compares the rates of whole brain atrophy, expressed as differences in annual percent volume change, between TDP-43 stages in amyloid- and amyloid+. We performed this analysis in all subjects as well as in subjects with 1.5T scans based on an inspection of the data and finding an apparent incompatibility between change estimates among those with 1.5T versus those with 3T scans. Regional structures did not exhibit any signs of field strength discrepancies after statistical adjustment. Regardless, TDP-43 was not associated with whole brain rates in the whole cohort or in the 1.5T subset (shown below).



Supplementary Figure 7: Trajectories of TBM-SyN hippocampal volume for cases with and without hippocampal TDP-43. The prediction assumed age at death of 80, MRI scan field strength of 1.5T, and a total intracranial volume of 1.4L. Note that cases with TDP-43 in the hippocampus (TDP+) had faster rates of hippocampal atrophy compared to cases without TDP-43 in the hippocampus (TDP-). The separation of the confidence intervals of the trajectories appears roughly a decade prior to death. Tick marks on the x-axis indicate available MRI data points in terms of years from death.



Supplementary Tables

Supplementary Table 1: Annual percent volume changes (95% CI.) for Figures 1A and 2A

TDP stage	Braak			Amyloid	
	B1 (N=37)	B2 (N=56)	B3 (N=205)	A0 (N=29)	A1 (N=269)
0 (N=141)	-1.18 (-2.08, -0.28)	-1.63 (-2.43, -0.83)	-3.11 (-3.54, -2.68)	-1.46 (-2.60, -0.32)	-2.64 (-3.02, -2.27)
1 (N=33)	-1.56 (-2.90, -0.25)	-1.78 (-3.04, -0.55)	-3.29 (-4.11, -2.46)	-1.29 (-2.73, 0.14)	-3.06 (-3.75, -2.36)
≥ 2 (N=124)	-2.39 (-5.09, 0.20)	-4.05 (-5.09, -2.99)	-4.39 (-4.82, -3.95)	-2.27 (-5.79, 1.34)	-4.41 (-4.83, -3.99)

Supplementary Table 2: Group-wise difference in annual percent volume change (95% CI.) for Figures 1B and 2B

TDP stage	Braak			Amyloid	
	B1	B2	B3	A0	A1
≥ 2 vs 1	-0.83 (-3.76, 2.08)	-2.27 (-3.79, -0.67)	-1.10 (-2.02, -0.19)	-0.98 (-4.79, 2.86)	-1.35 (-2.14, -0.56)
≥ 2 vs 0	-1.21 (-4.02, 1.48)	-2.43 (-3.66, -1.18)	-1.28 (-1.88, -0.67)	-0.81 (-4.53, 2.96)	-1.76 (-2.31, -1.23)
1 vs 0	-0.38 (-1.97, 1.20)	-0.16 (-1.61, 1.25)	-0.18 (-1.11, 0.75)	0.17 (-1.63, 1.94)	-0.42 (-1.19, 0.37)

Supplementary Table 3: Group-wise difference in annual percent volume change (95% CI.) for Figure 4A

	Estimates (95% CI)
TDP Stage 0 (reference)	0 (0, 0)
TDP Stage 1	-0.21 (-0.87, 0.46)
TDP Stage ≥ 2	-1.16 (-1.73, -0.61)
NFT Stage B1 (reference)	0 (0, 0)
NFT Stage B2	-0.70 (-1.54, 0.15)
NFT Stage B3	-1.59 (-2.4, -0.77)
Amyloid Positive	-0.62 (-1.57, 0.33)
Hippocampal sclerosis	-0.90 (-1.52, -0.26)
Age at death, 10-year inc.	0.39 (0.14, 0.65)

Supplementary Table 4: Group-wise difference in annual percent volume change (95% CI.) for Braak NFT stage B3 vs B1/B2 for Figure 4B

	Estimates (95% CI)
TDP stage 0	-1.66 (-2.42, -0.91)
TDP stage 1	-1.61 (-2.81, -0.39)
TDP stage ≥ 2	-0.58 (-1.60, 0.45)