Dissociation of tau pathology and neuronal hypometabolism within the ATN framework of Alzheimer’s disease

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Alzheimer’s disease (AD) is defined by amyloid (A) and tau (T) pathologies, with T better correlated to neurodegeneration (N). However, T and N have complex regional relationships in part related to non-AD factors that influence N. With machine learning, we assessed heterogeneity in 18F-flortaucipir vs. 18F-fluorodeoxyglucose positron emission tomography as markers of T and neuronal hypometabolism (NM) in 289 symptomatic patients from the Alzheimer’s Disease Neuroimaging Initiative. We identified six T/NM clusters with differing limbic and cortical patterns. The canonical group was defined as the T/NM pattern with lowest regression residuals. Groups resilient to T had less hypometabolism than expected relative to T and displayed better cognition than the canonical group. Groups susceptible to T had more hypometabolism than expected given T and exhibited worse cognitive decline, with imaging and clinical measures concordant with non-AD copathologies. Together, T/NM mismatch reveals distinct imaging signatures with pathobiological and prognostic implications for AD.
Alzheimer’s disease (AD) causes cognitive impairment with substantial between-patient variability in clinical presentation as well as the burden and distribution of pathology. This clinicopathologic heterogeneity is both a challenge and opportunity for systematic, biomarker-based studies to refine our understanding of AD biology, diagnosis and management. AD hallmark pathologies begin with accumulation of amyloid (A) plaques, followed by deposition of tau (T) tangles and subsequent neuronal injury/neurodegeneration (N). A and T aggregates are bound by specialized radiotracers for in vivo positron emission tomography (PET) imaging (such as 18F-Florbetapir for T tangles). N may be assessed via neuronal hypometabolism (NM) with 18F-fluorodeoxyglucose (18F-FDG) PET or structural atrophy (N) with magnetic resonance imaging (MRI). Additional polypathologies contribute to clinical progression in AD, including vascular and inflammatory etiologies, α-synucleinopathy and TAR DNA-binding protein-43 (TDP-43) diseases, many of which do not currently have specific in vivo measures.

To address this complexity and provide a biological, rather than clinical, definition of AD, the National Institute on Aging and Alzheimer’s Association proposed the ATN research framework. These criteria designate the global presence (+) or absence (−) of three AD dimensions: A, T and N. Patients with A+ status are included in the Alzheimer’s continuum while a research diagnosis of AD necessitates both A+ and T+. Consistent with the definition of AD neuropathologic change on autopsy. This model consolidates various pathological interactions in the Alzheimer’s continuum to classify heterogeneous groups by a panel of dichotomized biomarkers. Such categorical approach has already shed light on differential rates of memory decline and clinical risks/outcomes in patients with certain ATN combinations.

Neurodegeneration in AD is largely thought to be driven by T neurofibrillary tangles and neuronal hypometabolism (NM), a relative decoupling of T and NM (NM ~ T), a relatively decoupling of the relationship between T and NM, and subsequent neuronal injury/neurodegeneration (N). A and T aggregates are bound by specialized radiotracers for in vivo positron emission tomography (PET) imaging (such as 18F-Florbetapir for T tangles). N may be assessed via neuronal hypometabolism (NM) with 18F-fluorodeoxyglucose (18F-FDG) PET or structural atrophy (N) with magnetic resonance imaging (MRI). Additional polypathologies contribute to clinical progression in AD, including vascular and inflammatory etiologies, α-synucleinopathy and TAR DNA-binding protein-43 (TDP-43) diseases, many of which do not currently have specific in vivo measures.

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Here, we developed a machine learning-based clustering method to identify mismatch between T and NM using symptomatic patients from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort. We posited that mismatch analyses from PET markers of T and NM would reveal imaging signatures of patient groups including a typical or canonical T/NM relationship as well as unique patterns of resilience and susceptibility to T. We hypothesized for a given level of T, susceptible patients with greater than expected NM have worse cognitive decline compared to participants with canonical T/NM relationships, potentially due to more concomitant non-AD pathologies than the canonical group (Fig. 1a). Given that AD autopsy studies reveal widespread prevalence of non-AD copathology, we predicted that some of the dissociation between T and NM is attributable to a spectrum of mixed disease burden. The NM > T scenario may encompass patients with metabolic vulnerability to T along with the presence of non-AD copathologies such as α-synuclein and TDP-43 that contribute to NM independently of T and at levels greater than the canonical group. Moreover, we expected that the canonical group likely has some intermediate amount of mixed disease, while resilient groups may have less copathology and slower cognitive decline.

To this end, we evaluated T/NM mismatch and its relation to clinical features, cognitive progression and supportive evidence for copathologies. Since non-AD pathologies and risk factors are expected to be present in both A+ and A− individuals, we performed post hoc analyses in the whole cohort and A+ or A− groups. Our findings were replicated with a cohort of cognitively normal older adults in the Harvard Aging Brain Study (HABS). Overall, we demonstrate the utility of T/NM mismatch in modeling AD heterogeneity, predicting progression and providing pathophysiological insight for cognitive impairment.

Results

T/NM mismatch defines groups by regional residual patterns. We measured the relationship between T and NM (Fig. 1a) by regressions of 18F-FDG vs. tau standardized uptake value ratios (SUVRs) for each region-of-interest (ROI) and individual. Within our ADNI cohort (n = 289, Supplementary Table 1), clustering on T/NM regression residuals resulted in six groups with sizes ranging from 16 to 89 members. These groups were labeled based on the relative spatial pattern of metabolic resilience or vulnerability to T, which we describe below. As an example, group identity (the cluster to which a participant belongs) was mapped onto graphs for regions such as inferior temporal gyrus (Fig. 1b).

This ROI is involved in early symptomatic stages of AD progression and is a representative of between-group differences in T/NM relationships. We assessed the consistency of our clustering across different visualization methods. A principal component analysis (PCA) (Fig. 1c) and t-distributed stochastic neighbor embedding (t-SNE) method (Supplementary Fig. 1) map the 104 ROI dimensions onto two axes and both corroborated the between-group separation of clusters. A dendrogram visualized the within-group similarity across clustered patients (Fig. 1d). Therefore, the consistency of these groups across several dimensionality reduction methods substantiates this clustering approach.

There was no significant between-group difference in A status. Despite this lack of statistically significant difference, some groups appeared more enriched in A+ individuals, so we covaried by A status, as well as for sex, age, education level and T burden in the inferior temporal gyrus in subsequent omnibus and between-group analyses. There were between-group differences, including significant differences in sex and education, across all participants (Table 1) and specifically among A+ (Table 2) or A− patients (Supplementary Table 2). There were no significant differences in age. The groups had similar average tau SUVRs across all regions; the distribution of individuals with regional T patterns that correspond to AD Braak stages were also similar across groups for all participants (Fig. 2). Hence, these groups likely do not depict distinct stages of AD progression but instead appear to represent unique spatial patterns of the relationship between T pathology and its functional consequences.

Herein, we characterize our six T/NM mismatch groups. The largest group of individuals (89/289) were found close to the regression line across most regions, with the smallest residuals. This canonical group defines the condition where relative NM was statistically commensurate to the level of T (NM ~ T). The other five groups were compared to the canonical group by T/NM residuals in three- and two-dimensional regional maps across all participants (Fig. 2a), visualizing regions where NM is greater or less than what is observed in the canonical group given the T level. Groups derived from clustering all participants showed...
Fig. 1 T/NM mismatch by clustering of the whole cohort. a Schematic of proposed relationship between tau (T) and neurodegeneration (N) by neuronal hypometabolism (N\textsubscript{NM}). b Regression model of 18F-FDG vs. log tau SUVR in the inferior temporal gyrus, a typical tau staging region in AD. Solid line represents the model, with dashed lines denoting standard deviation-based thresholds (n = 289 participants). N\textsubscript{NM} < T denotes points above the line and N\textsubscript{NM} > T depicts points below the line. Circles are A+; Diamonds are A− participants. Source data are provided as a Source Data file. Consistent clustering by T/NM mismatch of all regional and patient residuals is visually demonstrated by (c) principal component analysis and (d) dendrogram.

distinct neuroanatomical patterns; these patterns were similar across subcohorts of A+ patients (Fig. 2b) and A− patients (Supplementary Fig. 3).

There were 3 groups with less N relative to their T level compared to the canonical group (positive residuals), thus classified as resilient to T (Fig. 2). The resilient groups had relative differences in spatial patterns of T/NM mismatch corresponding to prominent regions either throughout the cerebral cortex, termed the cortical resilient groups, or limbic areas, termed the limbic resilient group. Cortical resilient patterns stratified into two groups based on either high or low magnitude residuals. The high cortical resilient group (50/289) had higher T/ N\textsubscript{NM} residuals across most cortical and limbic ROIs compared to the canonical group and was the first group to split in clustering (Fig. 1d). The low cortical resilient group (62/289) had positive residuals throughout the cortex compared to the canonical or limbic resilient groups. While both cortical resilient groups had similar T levels (Supplementary Fig. 2), the high cortical resilient group had greater T/N\textsubscript{NM} residuals (Fig. 2). Both high and low cortical resilient groups had similar distributions of positive residuals but the low cortical resilient group had lower magnitude residuals, especially in limbic structures. The limbic resilient group (16/289) had high positive T/N\textsubscript{NM} residuals localized to the medial temporal lobe (MTL), anterior temporal and orbitofrontal regions compared to the canonical or other resilient groups, while other cortical regions had lower residuals here relative to the canonical group.

Two groups had worse N than typical for their level of T (negative residuals) and were considered susceptible to T (Fig. 2). These groups also had a relative predition for spatial patterns involving predominantly cortical or limbic regions, though these regional distributions were less distinct compared to those in the resilient groups. The cortical susceptible group (47/289) had lower residuals generally in cortical regions, with lesser extent in limbic regions than other groups. The limbic susceptible group (25/289) had a pattern of low residuals in primarily limbic and anterior frontotemporal areas.

T/NM groups have differences in N but not T markers. We evaluated whether clustering in T/N\textsubscript{NM} residuals was generally driven by either tau or 18F-FDG SUVR. Notably, our groups did not significantly vary by T burden (Supplementary Fig. 2), indicating that residual-based clustering was more influenced by between-group 18F-FDG SUVR differences, even after covarying for sex, age, education, A status and T level. Among resilient groups, T/N\textsubscript{NM} residual patterns (Fig. 2) were not linked to regional differences in tau SUVR (Fig. 3a), but rather 18F-FDG SUVR (Fig. 3b). The high cortical resilient group had significantly higher covariate-adjusted 18F-FDG SUVR across several representative regions compared to the canonical and other resilient groups (p’s < 0.005). Significant differences between covariate-adjusted 18F-FDG SUVR in the limbic and low cortical resilient groups matched the group differences in T/N\textsubscript{NM} residuals. Compared to the canonical group, the limbic resilient group had significantly higher 18F-FDG SUVR in MTL structures while the low cortical resilient group had elevated 18F-FDG SUVR throughout the cortex (p’s < 0.005). Likewise, across susceptible groups, there were no regional differences in tau SUVR (Fig. 3c), but instead 18F-FDG SUVR (Fig. 3d). Compared to the canonical group, the limbic susceptible group had lower 18F-FDG SUVR in limbic areas while the cortical susceptible group had worse 18F-FDG SUVR in other cortical regions (p’s < 0.005). Regional resilience and susceptibility patterns across the cohort (Fig. 3a–d) were replicated in subgroups of A+ patients (Fig. 3e–h) and A− patients (Supplementary Fig. 4).

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Additionally, mean cortical thickness differed among groups (Tables 1 and 2). In the whole cohort, thickness was greater in the low cortical resilient (2.10 mm, \( p = 0.01 \), unadjusted) and high cortical resilient group (2.09 mm, \( p = 0.04 \), unadjusted) compared to the canonical group (1.87 mm).

**T/NM clustering shows consistency across internal and external validation.** We aimed to internally validate our clustering approach within those participants demonstrating AD pathologic change. We performed clustering on A+ participants only, who overall also demonstrate higher T burden (since 87% of A+ participants were T+). Indeed, groups generated from A+ participants alone resembled groups formed from clustering all participants, in overall patterns and group identity (Supplementary Fig. 5). Then, we compared the robustness of clustering on subsets of 150 randomly selected participants over ten folds. Clustering was stable across folds (Supplementary Fig. 6). About 90% of participants had a match between their original group identity and the group identity endorsed by a majority of folds, while 9% of participants had group identity shift in the same residual direction (such as between high and low cortical resilience). These experiments demonstrate the robustness of our clustering.

Because clustering was similar across A+ and A− cognitively impaired ADNI participants, next we corroborated clustering in the external HABS cohort of cognitively normal older adults with lower levels of A and T pathology (Supplementary Tables 3 and 4). Six T/NM groups were generated from the whole HABS cohort, demonstrating similar regional patterns to those found in symptomatic ADNI participants: canonical, high and low cortical resilience, limbic resilience, cortical susceptibility and limbic-susceptible participants. These results were replicated with additional global cognitive measures (Mini-Mental Status Exam (MMSE) and Clinical Dementia Rating sum of boxes (CDR-SOB)). For cross-sectional assessments, both ADAS-Cog and Dementia Rating sum of boxes (CDR-SOB) were noted between the canonical and low cortical resilient groups (2.10, 2.09 mm, respectively). Though ADAS-Cog slopes in resilient groups did not significantly differ from the canonical group, the high cortical

**T/NM groups exhibit different cognitive trajectories.** We hypothesized that relative hypometabolism for a given level of T may be associated with differences in cross-sectional and longitudinal cognitive measures. Although T and N markers both strongly associate with cognitive impairment, we predicted that susceptible participants may have additional copathologies contributing to N and leading to greater cognitive decline than predicted by T. We found significant cross-sectional group differences across the cohort for various cognitive tests at the time of 18F-FDG scan even after controlling for covariates such as sex, age, education, baseline cognition, A status and T level (Table 1). In absolute terms, the canonical group had mid-range impaired ADAS-Cog (22.9), while resilient groups had better scores (25.6, 26.0). These results were replicated with additional global cognitive measures (Mini-Mental Status Exam (MMSE) and Clinical Dementia Rating sum of boxes (CDR-SOB)). For cross-sectional covariance-adjusted pairwise comparisons, significant differences were noted between the canonical and low cortical resilient groups on the ADAS-Cog (\( p = 0.0003 \)) and MMSE (\( p = 0.002 \)). Such differences were also seen in the A+ cohort (Table 2).

Then, we compared longitudinal cognitive trajectories by linear mixed effects models with covariates (Fig. 4 and Supplementary Table 5). Across groups, the canonical group had mid-range decline on ADAS-Cog (+0.8 points/year) (Fig. 4a). The resilient groups (high cortical, limbic, low cortical) had the slowest progression on ADAS-Cog (−0.07, +0.6, +0.6 points/year, respectively). Though ADAS-Cog slopes in resilient groups did not significantly differ from the canonical group, the high cortical

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**Table 1** T/NM mismatch clustering across all participants.

| Group | Cognition | ADAS-Cog | CDR-SOB | MMSE | CDR-SOB
|-------|-----------|----------|---------|------|---------|
| MCI/+ | 27.8 (2.6) | 27.8 (2.6) | 16.3 (2.6) | 7.4 (1.7) | 0.001 |
| MCI−/ | 20.3 (7.6) | 17.7 (2.0) | 16.3 (2.6) | 7.4 (1.7) | 0.001 |
| Limbic + | 22.9 (8.8) | 25.1 (3.0) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
| Limbic − | 26.0 (8.4) | 25.1 (3.0) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
| Cortical + | 33.5 (5.6) | 26.0 (8.4) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
| Cortical − | 32.0 (8.4) | 25.1 (3.0) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |

**Table 2** Mismatch clustering across all participants.

| Group | Cognition | ADAS-Cog | CDR-SOB | MMSE | CDR-SOB
|-------|-----------|----------|---------|------|---------|
| MCI/+ | 27.8 (2.6) | 27.8 (2.6) | 16.3 (2.6) | 7.4 (1.7) | 0.001 |
| MCI−/ | 20.3 (7.6) | 17.7 (2.0) | 16.3 (2.6) | 7.4 (1.7) | 0.001 |
| Limbic + | 22.9 (8.8) | 25.1 (3.0) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
| Limbic − | 26.0 (8.4) | 25.1 (3.0) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
| Cortical + | 33.5 (5.6) | 26.0 (8.4) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
| Cortical − | 32.0 (8.4) | 25.1 (3.0) | 16.5 (2.6) | 7.4 (1.7) | 0.001 |
### Table 2 T/N_M mismatch clustering across A+ patients.

| Group                  | MCI/Dem | F/M  | Age (y)     | Educ (y) | Cognition          | Cortical thickness (mm) |
|------------------------|---------|------|-------------|----------|---------------------|-------------------------|
| High cortical resilient| 19/4    | 11/12| 74.5 (6.8)  | 16.5 (2.5)| 22.5 (8.6) 2.0      | 27.1 (3.4) 2.05         |
| Limbic resilient       | 5/2     | 4/3  | 70.4 (11.5) | 15.6 (2.3)| 23.5 (9.0) 2.4     | 24.7 (4.7) 1.95         |
| Low cortical resilient | 31/5    | 20/16| 73.4 (7.4)  | 15.0 (2.1)| 20.7 (5.8)** 2.0**  | 27.1 (2.2)** 2.08**     |
| Canonical              | 26/23   | 19/30| 75.6 (7.4)  | 16.6 (3.6)| 26.5 (8.4) 3.0     | 25.6 (3.1) 1.77         |
| Cortical susceptible   | 14/17   | 10/21| 74.3 (15.6)| 15.6 (3.1)| 28.4 (8.4) 4.0     | 24.2 (3.6) 1.78         |
| Limbic susceptible     | 7/11    | 11/7 | 78.8 (5.3)  | 15.7 (2.2)| 28.0 (9.6) 3.3     | 24.7 (4.4) 1.64         |
| Group p val            | 0.03    | 0.01 |             |          |                     | <0.0001 0.01 <0.05 0.005|

Diagnosis (MCI/dementia) and sex (F/M) are in frequencies. Mean (standard deviation) values are shown for age/education (years), ADAS-Cog, CDR-SOB, MMSE, and global cortical thickness (mm). The last row depicts group difference p values by likelihood ratio tests after adjusting for covariates. Significant differences in pairwise comparisons between a non-canonical and canonical group with covariate adjustment are annotated. For pairwise comparisons, ** denotes p < 0.005 after multiple tests adjustment and + denotes p < 0.05 before multiple tests adjustment. Covariates include sex, age, education and inferior temporal gyrus tau SUVR. Sample sizes and p values are listed in Supplementary Data 1.

### Fig. 2 Brain maps visualize T/N_M mismatch relationships and spatial patterns.
Three- and two-dimensional renderings of mean T/N_M relation regional residuals are shown for a all participants and b A+ patients. Compared to the canonical (N_M ~ T) group, resilient (N_M < T) and susceptible (N_M > T) groups have limbic vs. cortical involvement (arrowheads). Color scale represents the mean T/N_M residual (in 18F-FDG SUVR). R right, L left, A anterior, P posterior.
resilient group showed less decline on CDR-SOB than the canonical group ($p = 0.04$, uncorrected). In contrast, there was significantly steeper decline on ADAS-Cog in the cortical susceptible ($+2.4$ points/year, $p = 0.002$) and limbic susceptible groups ($+3.9$ points/year, $p < 0.0005$) than the canonical group (Fig. 4a). Significant differences between canonical and susceptible trajectories were also found for CDR-SOB and MMSE (Fig. 4b,c). Among A+ participants (Fig. 4d–f) and A− patients only (Supplementary Fig. 8), between-group differences in cognitive progression rates were comparable to the whole cohort.

Akin to cognitively impaired ADNI participants, cognitively normal HABS participants had a significant group difference in...
Fig. 4 Differential cognitive decline based on T/NF mismatch. Longitudinal cognitive trajectories differ by group identities among (a-c) all participants and (d-f) A+ participants. Decline rates are shown for (a, d) AD Assessment Scale Cognitive 13 item (ADAS-Cog, higher score is worse), (b, e) Clinical Dementia Rating Sum of Boxes (CDR-SOB, higher is worse) and (c, f) Mini-Mental Status Exam (MMSE, lower is worse) by linear mixed effects models with amyloid status, baseline score, education, sex, age and T level as covariates. Lines show the mixed effect model and error bands show ±1 propagated standard error. Significant differences in pairwise comparisons of cognitive decline between a non-canonical and canonical group by linear mixed effects analysis with multiple test (Benjamini–Hochberg) adjustment are denoted as *p < 0.05, **p < 0.005. + denotes p < 0.05 before multiple test adjustment. Sample sizes and p values are provided in Supplementary Data 1. Source data are provided as a Source Data file.
cross-sectional MMSE ($p = 0.008$) (Supplementary Table 4). On MMSE, groups corresponding to T/N_M susceptibility had significantly lower baseline scores. Together, our data suggests that the decoupling of T and N_M may relate to factors affecting cognitive outcomes in both symptomatic and asymptomatic individuals across the distribution of T level.

**Exploratory analysis of copathology factors driving T/N_M mismatch.** Since susceptible groups had greater N than expected given their T and faster cognitive progression, we considered potential roles of copathology in driving advanced N (Fig. 5a). The cortical and limbic susceptible groups had significantly greater number of vascular clinical risk factors than the canonical group ($p = 0.0003$, $p = 0.04$, respectively) (Fig. 5b). The limbic susceptible group had significantly higher average subcortical infarct burden than the canonical group ($p = 0.04$) (Fig. 5c). White matter hyperintensity (WMH) volumes were higher in susceptible groups compared to the canonical group though such trends were not significant (Supplementary Fig. 9A). We also explored APOE, a gene harboring a common variant linked to dementia. APOE4 risk allele frequency was higher in the susceptible groups than other groups but not significantly different than the canonical group (Supplementary Fig. 9B).

Next, we studied how mixed proteinopathies may contribute to susceptible groups. While there are no definitive imaging or cognitive markers for the presence of α-synuclein or TDP-43, we assessed the consilience of several suggestive imaging and...
cognitive tests to provide some indication for what additional copathologies may be present in the setting of T/NM mismatch.

We tested imaging and clinical markers of α-synuclein (Lewy body) pathology in the cortical susceptible group. A well-studied, potential indicator of Lewy Body Disease (LBD) is the cingulate island sign in the posterior cingulate cortex relative to precuneus and cuneus. There was significantly higher cingulate island ratio in the cortical susceptible group compared to the limbic susceptible and canonical groups ($p < 0.005$, Fig 5a). Differences were also significant in A+ and A− cohorts. We also assessed cognitive features linked to LBD, such as visuospatial impairment17. Compared to the canonical group, the cortical susceptible group had significantly worse copathology-adjusted Clock Drawing scores ($p = 0.03$) and other visuospatial markers (Fig 5e and Supplementary Fig. 9C) and trended toward higher proportion of patients with hallucinations on the Neuropsychiatric Inventory (NPI) and worse visuospatial z-scores (Fig 5f, g). Thus, these imaging and cognitive results suggest potential α-synuclein pathology in the cortical susceptible group.

We analyzed the possibility of Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) copathology in the limbic susceptible group given a pattern of severe anterior temporal/MTL hypometabolism relative to T (Figs 2 and 5a). We utilized the I/MTL/FSO ratio, defined as worse MTL and frontal supraorbital (FSO) hypometabolism relative to inferior temporal gyrus (I). Higher I/MTL/FSO ratio signifies worse MTL hypometabolism and correlates to LATE in clinicopathologic studies. The limbic susceptible group had significantly higher MTL asymmetry in 18F-FDG SUVR and thickness (Fig 5i, j). We further evaluated memory phenotypes linked to LATE compared to the canonical group, the limbic susceptible group had worse semantic memory with significant copathology-adjusted differences in category fluency ($p = 0.02$) (Fig 5k), Multilingual Naming Test ($p = 0.008$) (Supplementary Fig. 9D) and ADNI domain z-scores for language and memory ($p's < 0.05$) (Fig 5l, m). These imaging and cognitive profiles imply possible TDP-43 pathology in the limbic susceptible group.

Overall, these findings suggest that symptomatic susceptible groups had more copathology-related factors than the canonical group. Cognitively normal groups resembling T/NM susceptible patterns in the HABS cohort also demonstrate copathology-adjusted biomarker elevations consistent with greater non-AD pathology (Supplementary Fig. 10). When we evaluate the same biomarkers of copathology in the resilient groups, we generally observed less evidence of mixed pathology burden than the canonical group, particularly the cingulate island ratio as well as I/MTL/FSO ratio and MTL thickness asymmetry (Supplementary Fig. 11). Overall, non-AD pathology biomarkers convey higher burden in susceptible groups and lower burden in resilient groups compared to the canonical group, indicating that relative levels of mixed copathologies contribute to T/NM mismatch and that canonical patients have some degree of copathology concordant with their commonality in autopsy series.

**Discussion**

We leveraged paired tau and 18F-FDG PET studies to assess the in vivo dissociation of T and N M relationships in cognitively impaired individuals in the ADNI dataset. Clustering identified six groups of patients, including a canonical group that defines the expected relationship between T and N M (N M ≈ T) and additional groups that were either more resilient (N M < T) or susceptible (N M > T) to T, defined by less or greater N M than expected for a given level of T, respectively. We also clustered residuals from the T/NM relationship across ten folds on random subsets of participants, and with A+ participants only, which did not impact overall clustering. Groups resembling our six T/NM groups in symptomatic ADNI participants appeared in the asymptomatic HABS cohort, further validating the spatial patterns presented here.

Our T/NM groups had significant differences in 18F-FDG and not tau SUVR at a group level (Fig 3). This fact does not necessarily signify that T/NM clustering was solely driven by 18F-FDG, but rather that clustering depends on variation in 18F-FDG relative to tau SUVR at an individual level. Certain participants can be identified with similar cortical 18F-FDG SUVR, but vastly different tau SUVR. For instance, a patient with high tau SUVR may have lower N M (more metabolism) than expected given their level of T and may be placed in the low cortical resilient group, whereas a patient with low tau SUVR may have higher N M (less metabolism) than expected given their T and may fall in the cortical susceptible group. Compared to clustering on just N M, T/NM clustering enables regional and relative comparisons of N M given a level of T and promotes the evaluation of factors beyond AD stage or pathology that may not be captured from N M alone.

Relative to the canonical group, the resilient groups had better baseline cognitive scores whereas susceptible groups had faster cognitive decline over time. Metabolic and cognitive phenotypes in the T/NM resilient and susceptible groups were shared across A+ and A− cohorts. The observations of impaired cognition and hypometabolism in A− susceptible groups strengthen the notion that factors influencing the T/NM relationship in AD (like copathology) are also present in non-AD symptomatic patients. In other words, the A+ group may reflect AD plus additional factors, including copathologies, whereas the A− group may have these non-AD factors alone affecting this clustering. Our results support the use of T/NM mismatch as a complement to direct measures of ATN biomarkers to study disorders of AD and non-AD pathology.

It is important to note that T/NM groups also differed with regard to cortical atrophy (Tables 1 and 2). Since N S and N M are linked, it is reasonable to predict that T/N S and T/N M relationships are also associated. Indeed, clustering with T/N S approaches yields groups with relative resilience or vulnerability to T25. The median regional correlation coefficient between T/N S and T/N M residuals was 0.29, suggesting that while T/N S and T/N M relationships are similar, they may provide some unique information. For example, metabolism may be more sensitive to Lewy body pathology than structure18,19. Likewise, metabolism may reflect aspects of functional reserve and synaptic activity not captured by structural markers while, alternatively, structure may be less affected by non-disease related functional variability than metabolism. Thus, it is likely the case that T/N S and T/N M mismatch each offer complementary, yet unique characterizations.

Intriguingly, both resilient and susceptible groups appeared to divide along patterns roughly involving either limbic or cortical regions. Several studies demonstrate similar spatial separation. For example, heterogeneity in either T or N alone has been examined by regional involvement and disease trajectories. Here, we investigate the variability in relationships between T and N M biomarkers with an integrative approach that evinces consistent patterns of neuroimaging and cognitive measures within the disentangling of N M relative to T. To some extent, this dividing line between limbic vs. cortical involvement perhaps parallels the dissociable MTL networks described by29–32. This previous work supports the existence of the anterior temporal network, most akin to the limbic regions described here, and a
posterior-medial network that largely conforms to the default mode network. Prior research has also suggested differential changes within these networks across the AD continuum.\textsuperscript{39,33,34} Non-AD pathologies, such as TDP-43, might also split along this anterior-posterior axis.\textsuperscript{35} Though we observed two cortical resilient groups (high and low), it is unclear what factors beyond metabolism distinguish high and low cortical resilience. These T/NM differences were enough for these groups to strongly cluster separately since the high cortical resilient group was the first group to separate in terms of dendrogram distance (Fig. 1d). That said, these two groups may reflect a continuum of cortical resilience. Together, our findings may indicate differentially connected networks harbor not only dissociable vulnerabilities to accumulation of different pathologies, but also relative resiliencies to these pathological states.

We probed several factors that may influence the link between T and NM, including association of surrogate markers for three copathologies (vascular disease, \textalpha-synuclein and TDP-43). While our groups did not differ in mean tau SUVR burden or inferred Braak stage distribution (Fig. 3 and Supplementary Fig. 2), they did separate in terms of cognitive profiles, progression, and copathology-associated markers, suggesting that non-AD pathologies contribute to the dissociation of T and NM and, thus, to the cognitive trajectory beyond Braak stage. In fact, longitudinal group differences were found even when covarying for baseline tau SUVR, which further suppresses effects of AD severity. Other aspects of resilience or vulnerability outside copathology also may influence outcomes beyond Braak staging. To this point, there was evidence of greater burden of vascular disease, a common copathology in AD,\textsuperscript{3} in the susceptible patients, suggesting that the elevated levels of cerebrovascular disease compared to the canonical group are a factor in their relative vulnerability.

AD can present with multiple proteinopathies, including \textalpha-synuclein\textsuperscript{18} and TDP-43 inclusions.\textsuperscript{23} While there are not yet well-established biomarkers for these pathologies, \textsuperscript{18}F-FDG PET studies have provided patterns probabilistically related to both entities.\textsuperscript{19–22} We emphasize that this analysis was exploratory and requires further comprehensive validation. The cortical susceptible group harbored higher cingulate island ratio and worse visuospatial processing and trended toward greater frequency of episodic memory impairment associated with TDP-43 pathology.\textsuperscript{36–38} The limbic susceptible group had the worst categorical and naming fluency. While these features are correlative and not comprehensive, the convergence of imaging, cognitive and clinical evidence support a potential contribution of copathology to susceptible groups with greater hypometabolism than expected given their level of T.

Resilience and susceptibility as defined here by NM > T and NM < T, respectively, may be thought of as a combination of separate yet related factors, including relative levels of copathology and factors that directly influence the neuronal and glial responses to T pathology. Currently, it is more straightforward to assess the former, but the latter may reflect intrinsic resilience or vulnerability to T, perhaps related to genetic/epigenetic factors. Our copathology analyses suggest that susceptible groups have mixed cognitive impairment with more evidence of copathologies than the canonical group to contribute to hypometabolism not accounted for by T alone. Given the frequency of mixed disease on autopsy,\textsuperscript{16} non-AD pathologies may represent an orthogonal axis along which canonical groups have intermediate levels of copathology, while resilient and susceptible groups have less or more mixed pathology, respectively (Fig. 5 and Supplementary Fig. 11). In the context of AD, these copathologies may be synergistic as non-AD proteinopathies can influence how neurons and glia respond to T.\textsuperscript{39–42} Additional differences in non-disease related genetic, lifestyle and environmental factors also decouple the T/NM relationship, representing attributes that affect how neurons respond to injury perhaps related to or distinct from copathology. The metabolic and cognitive profiles in resilient and susceptible groups were shared across A+ and A−cohorts and in symptomatic and asymptomatic patients. The observations of similar patterns of T/NM mismatch and impaired cognition between A+ and A−susceptible groups are expected, as factors influencing the T/NM relationship in AD may also be present in non-AD symptomatic patients. Given current constraints of in vivo biomarkers, autopsy data must confirm these hypotheses regarding specific copathology.

The study had several limitations. First, neuropathological validation is important for this work, but currently no datasets with tau PET, \textsuperscript{18}F-FDG PET and autopsy were available to us. Analyses in symptomatic individuals were performed on one cohort (ADNI) which includes multiple sites but with well-established data harmonization methods. Given the ADNI inclusion/exclusion criteria, this sample may not be representative of the broader population of cognitively impaired patients that harbor more mixed pathology, particularly vascular disease. A more heterogeneous sample might show more phenotypes/groups. However, the HABS dataset offers corresponding evidence of T/NM dissociation patterns in cognitively normal older adults known to harbor significant regional relationships between tau and \textsuperscript{18}F-FDG PET.\textsuperscript{42} Notably, these similar T/NM groups arose with use of two distinct processing methods (ANTs for ADNI data and FreeSurfer for HABS data), indicating robustness of clustering to specific processing pipelines. Despite this, the separation of susceptible groups by imaging and cognitive factors associated with copathology highlight the non-trivial amount of copathology in ADNI participants. To this point, autopsy study of an ADNI subset demonstrated that \textalpha-synuclein and TDP-43 polypathology are frequently present in ADNI patients and correlate with antemortem imaging markers.\textsuperscript{16} The canonical group is a statistical designation and does not quantify the absolute amount of AD vs. non-AD pathology. However, the canonical group does provide a relative benchmark for the population. While there was not much available data to study resilience-related factors, our initial analysis of resilient and susceptible groups supports the continued search for genetic, epigenetic and pathophysiological features that influence these relationships. Note that resilient groups had significantly higher APOE2 carrier frequency and the susceptible groups trended toward higher APOE4 frequency, though these differences were not seen after adjusting for A status (Supplementary Fig. 9B). Investigations into additional AD-associated features, such as glial and immune cell-mediated inflammation as well as blood brain barrier dysfunction, may also be warranted.\textsuperscript{4,43,44}

Despite these limitations, the T/NM mismatch approach may hold utility for biomedical research, specifically allowing clinical trials to measure heterogeneity across the Alzheimer’s continuum. For instance, the group of NM > T susceptible patients may have mixed pathologies, which could reduce study power and complicate the assessment of investigational treatments designed to target single pathways. Consequently, future trials for anti-amyloid or anti-tau therapies might intentionally recruit patients or stratify findings based on T/NM groups.

Overall, we define PET-based T/NM mismatch measurements to evaluate the varying relationships of neuronal metabolism to T pathology in participants with cognitive decline. Dissociation in
the T/NM relationship demonstrates distinct groups with some showing resilience and others depicting susceptibility to T in terms of regional distributions of hypometabolism, cognition and pathological factors. T/NM mismatch provides a quantitative spatial approach to assess neuroanatomical patterns of metabolic states affected by T pathology. This may improve our understanding of the biology and prognostication of subgroups in the Alzheimer’s and non-AD continuums. Additional studies may elucidate the heterogeneity of cellular metabolic responses to AD features as a step toward the successful implementation of precision medicine in AD.

Methods

Patient cohort. From the ADNI cohort database (http://adni.loni.usc.edu), we included participants with a 18F-flortaucipir (tau) PET and 18F-FDG PET performed within 1 year of each other, along with a measure of amyloid (A) status and a MRI scan (within about 1 year of PET scans). Of these, 289 participants with a diagnosis of mild cognitive impairment (MCI) or dementia were found. Evaluation of A status utilized 18F-flortaucipir (n = 182) or 18F-florbetaben (n = 105) amyloid PET or Eccoli cerebrospinal fluid (CSF) Aβ assay (n = 2). Median time between 18F-FDG vs. tau PET in the cohort was 12 days. Stratification by A was based on Aβ positivity in the ADNI cohort (n = 164) and those with likely non-AD (n = 125) pathology. Additional cohort details are listed in Supplementary Table 1. In the cognitively normal HABS cohort (data release 2.0; https://habs.mgh.harvard.edu/)45, we included 115 participants with tau PET. 18F-FDG PET, 11C-Pittsburgh compound B (amyloid) PET and MRI with the same criteria as above. Median time between 18F-FDG vs. tau PET in the HABS sample was 105 days (63% of cases within 5 months). See details in Supplementary Table 3. For the ADNI data, human subjects approval was obtained by the ADNI investigators to compile with the Institutional Review Board; a complete listing of ADNI sites is provided at the end of the article file. All ADNI participants provided written informed consent. ADNI data was accessed according to the policies of the ADNI data sharing and publications committee. For the HABS data, HABS protocols were approved by the Partners Human Research Committee, the Institutional Review Board for the Massachusetts General Hospital and Brigham and Women’s Hospital, and all participants gave informed consent. HABS data was accessed according to the policies of the HABS data committee.

Imaging data. Post-processed PET images from the ADNI data archive (http://adni.loni.usc.edu/data-samples/access-data/) were obtained46. Tau PET imaging was original performed using the ADNI protocol with 30-min brain scans (six 5-min frames) starting 75 min after intravenous administration of ~10.0 mCi 18F-Flortaucipir. 18F-FDG PET imaging consisted of a 30-min scan (six 5-min frames) at 30 min after 5.0 mCi 18F-FDG injection. For amyloid PET, a 20-min brain scan (four 5-min frames) was performed 50 min after ~10.0 mCi 18F-Florbetapir or 90 min following ~8.1 mCi 18F-Florbetaben injection. Processed PET images with uniform isotropic resolution (8 mm full-width-at-half-maximum) were obtained. All ADNI PET images used in this publication were obtained from the ADNI database archive described in Supplementary Note 2. Post-processed PET images were generated in SPM12 and 3D Slicer. PET images were aligned in 3D space and processed using the ANTs (v2) pipeline47 for inhomogeneity correction, brain extraction, template Size, Uniform Resolution. ADNI MRI included a T1-weighted structural scan (ADNI_UCD_WMTH_DICT_09_01_20, accessed 1/2021). Apolipoprotein E (ApoE) e4 allele frequency was analyzed (APOE2, accessed 7/2021). In follow-up analyses, we calculated 18F-FDG PET measures which are thought to map to different non-AD pathologies. The cerebellar island sign represents metabolic sparing of posterior cingulate cortex relative to precuneus and cuneus and has been associated with a synuclein pathology. It was quantified as the ratio of posterior cingulate/precuneus/cuneus 18F-FDG SUVR; higher cingulate SUVR ratio is linked to α-synucleinopathy19,20. The presence of TDP-43 pathology has been associated with reduced TMTL and FSOG SUVRs in frontal and temporal lobes (I). The UMTL/FSO ratio was calculated as the ratio of inferior temporal gyrus/MTL/ECOgyrus SUVR. Higher UMTL/FSO ratio is associated with TDP-43 disease11,22. An MTL asymmetry index was calculated as [left−right]−(left−right) for 18F-FDG SUVR and cortical thickness as23 an additional potential marker of TDP-43 pathology2.

Statistical analysis. Statistical analysis was performed in R (v4.0.5). All statistical tests were two-sided. Comparisons for variables such as cognition or tau and 18F-FDG SUVRs were performed with likelihood ratio tests by linear regression. Covariates included sex, age, education, amyloid status (A+/A−) and tau SUVR in the inferior temporal gyri, a region where T correlates with disease severity3,17. Multiple test adjustment by Benjamini–Hochberg correction with false discovery rate (FDR) was conducted for pairwise comparisons with the canonical group. Box plots show the data points as dots, mean as an X symbol, median as the middle box line, first quartile (Q1) and third quartiles (Q3) as box edges (denoting the

Definition of regional T/NM mismatch by clustering. Spatial patterns of T/NM mismatch were investigated by clustering of the residuals on a regression model of 18F-FDG vs. tau SUVR. Robust linear regressions of individual 18F-FDG SUVR vs. a log transform of tau SUVR (to ameliorate effects of a skewed distribution of T) across all patients were performed in each of the 104 gray matter ROIs (Fig. 1) to yield T/NM mismatch residuals (in units of 18F-FDG SUVR). A bi-square weighting function minimized the influence of outliers in robust regression. To attempt to identify the effect of outliers on clustering regression residuals for tau ROI and individual were discretized into a vector based on whether the residual was greater than 0.6 SD from the regression line (a cutoff that identifies the farthest ~25% of points above or ~25% of points below the regression line) and if the residual was negative or positive, generating an array of 104 ROIs across 289 participants where each entry was −1, 0, or 1. Discretized residuals were inputs for Ward’s agglomerative hierarchical clustering48 with the hclust and cluster packages on R (v4.0.5) to create T/NM mismatch groups. The number of clusters was selected by elbow and silhouette analysis9, which both suggested that k = 6 clusters optimizes within-cluster similarity. These methods did not agree on lower values, which would appear to capture much broader variation in T/NM mismatch. Dimensionality reduction on discretized residuals was performed by PCA (Fig. 1) and t-SNE (Supplementary Fig. 1A). Regional mean residuals were visualized in cohort-based heatmaps, brain maps and three-dimensional renderings by ITK-SNAP49 and MRicroGL50. Clustering validation was performed across 10-folds of 10 randomly selected ADNI participants, which showed stable group patterns and identities.

Cognitive evaluation. ADNI and HABS performed cognitive testing using unified methodologies (accessed 8/2021 and 11/2021, respectively). We selected cognitive testing sessions closest to the 18F-FDG scan along with longitudinal follow-up testing. Global measures included AD Assessment Scale-Cognition 13 item (ADAS, higher score is worse)51, Clinical Dementia Rating sum of boxes (CDR-SOB, higher is worse)52 and Mini-Mental Status Exam (MMSE, lower is worse)53. Exploratory analysis was pursued with additional measures based on mismatch group findings and included the use of the Clock Drawing Test54, NPI56 item B for proportion of patients with hallucinations after scan, ADNI z-scores for visuospatial, language and memory domains57,58, categorical fluency of animals59, Everyday Cognition test60 and Multilingual Naming Test61.

Exploratory assessment of features associated with brain copathologies. Available vascular risk factors assessed at initial medical history were obtained from ADNI (INTIHEALTH, accessed 4/2021), including presence of hypertension, hyperlipidemia, type 2 diabetes, arrhythmia, cerebrovascular disease, endovascular management of head/neck vessels, coronary artery disease (angina or acute coronary), interventional coronaries (sten, bypass graft), heart failure, structural heart defects and peripheral artery disease. Number of subcortical infarcts (>3 mm in size) were centrally measured from MRI scans22 performed up to 18F-FDG scan (MRI INFARCTS_01_29_21, accessed 4/2021). Infarcts mostly localized to cerebral white matter, basal ganglia and cerebellum. White matter hyperintensity (WMH) volumes were measured from ADNI analysis of FLAIR MRIs73 (ADNI_UCD_WMH_DICT_09_01_20, accessed 1/2021). Apolipoprotein E (APOE) e4 allele frequency was analyzed (APOE2, accessed 7/2021).
interquartile range, IQR), whiskers as the minimum/maximum points and outliers based on thresholds $Q1 - 1.5(IQR)$ or $Q3 + 1.5(IQR)$. Exploratory analyses (such as for copathology biomarkers) were also performed without multiple test adjustment. Genotype frequency comparisons were performed with $\chi^2$ tests. Longitudinal cognitive trajectories were assessed with linear mixed effects models to account for participant-specific random intercepts with baseline cognitive score at scan, time from scan, cluster and cluster*time interaction as independent variables and sex, age, education and A status as covariates. Slopes of annual cognitive change for each cluster were defined as the sum of the time from scan slope and cluster*time interaction slope. Differences in decline rates were assessed by significance of the slope of the cluster*time interaction.

**Reporting summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

**Data availability**

The raw and processed data including the participant scans and spreadsheets described above are available on the data archives of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu) and the Harvard Aging Brain Study (https://habs.mgh.harvard.edu/). Supplementary Material is available online. Additional information can be provided by the authors upon reasonable request. Source data are provided with this paper.

**Code availability**

Relevant code can be found at: http://stnava.github.io/ANTs/. This includes links to scripts on brain extraction (https://github.com/ANTsX/ANTs/blob/master/ImageSegmentation) and segmentation (https://github.com/ANTsX/ANTs/tree/master/ImageRegistration) and registration (https://github.com/ANTsX/ANTs/tree/master/Tree/master). Additional information can be provided by the authors upon reasonable request.

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Author contributions

M.T.D., S.R.D., D.A.W. and I.M.N. conceptualized the study and developed the methods. M.T.D., S.R.D., X.L. and P.A.Y. processed the data. M.T.D. analyzed the data with statistical assistance from H.R. and S.X.X. M.T.D. wrote the initial manuscript with input and feedback from S.R.D., D.A.W. and I.M.N. M.T.D., S.R.D., D.A.W. and I.M.N. interpreted the findings. All authors revised the manuscript and provided critical feedback. D.A.W. and I.M.N. supervised the study.

Competing interests

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Additional information

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