Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/xf8wn381

PREFERENTIAL ANTERIOR INSULA INVOLVEMENT BY TDP-43 PATHOLOGY IN LATE-NC AND ALS: A NEUROPATHOLOGICAL STUDY

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ABSTRACT
We investigated whether the anterior insula stands as a primary spot for TDP-43 pathology progression in LATE-NC by taking into account its relation to the amygdala via anatomical position and functional and neural connections. An analysis of phospho-TDP (pTDP) aggregate pathology based on matched anterior and posterior insula tissue from 105 autopsied patients with Alzheimer's disease, Lewy body disease, hippocampal sclerosis among LATE-NC patients, amyotrophic lateral sclerosis (ALS) and additional conditions took place without considering clinical or neuropathologic information. Among all subjects, pTDP pathology existed in 34.3% of cases and researchers discovered this pathology as cluster formations inside lamina II neurons as well as short neuritic structures inside lamina II and subpial formations resembling amygdala pTDP pathology. Among cases with positive pTDP pathology the protein distribution extended to the anterior insula in 41.7% of cases but was also found in both anterior and posterior insula in 58.3% of cases; anterior insula showed higher pTDP pathology burden in all diagnostic conditions ($p < .001$). pTDP pathology occurred in 46.7% of ALS cases although protein pathology was generally minimal. The presence of pTDP-43 appeared in 30.4% of LATE-NC patients (mainly stage 2 and 3) when it appeared alongside basal forebrain disease and HS thus suggesting this phase marks the key stage when pathology spreads away from temporal brain regions.

KEY WORDS : Agranular insula, Amygdala, Amyotrophic lateral sclerosis (ALS), lower motor neuron, Anterior insula, Limbic-predominant age-related TDP-43 encephalopathy (LATE), Posterior insula, TAR DNA-binding protein 43 kDa (TDP-43)

INTRODUCTION
Pathological abnormalities of TDP-43 affect over forty percent of elderly individuals according to recent studies (1). The neuropathological change termed limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) occurs frequently with advanced Alzheimer's disease and Lewy body disease but has also been identified in patients with mild AD-like dementia and hippocampal sclerosis and limited other brain pathologies (4). A specific group of LATE patients who display low to intermediate AD pathology together with TDP-43 deposits and hippocampal sclerosis has received different diagnoses including "hippocampal sclerosis of aging" (5, 6) or "hippocampal sclerosis dementia" (7). TDP-43 aggregation spreads throughout the brain tissue regardless of AD

neuropathology severity in HS-Aging patients. TDP-43 deposition in the basal forebrain proved present during dementia assessments whose pathological evidence demonstrated stronger correlation to HS-Aging than AD or LBD (8). Researcher-defined stages of TDP-43 pathology in LATE include involvement of the amygdala region at stage I followed by hippocampal involvement at stage II then middle frontal gyrus at stage III (9). Research models have linked pathologic stages to basal forebrain involvement in addition to levels 1 and 3 (10). Future biomarker development depends heavily on complete mapping of TDP-43 pathology distribution since it helps define clinical traits while enabling tool development. Recent research illustrates that LATE patients often present with neuropsychiatric symptoms including apathy together with personality changes and disinhibition when they show low to intermediate-grade AD pathology (12). The clinical manifestations of frontal-subcortical cognitive impairment found in amyotrophic lateral sclerosis (13) also appear among patients with LATE even when they do not have frontotemporal dementia (FTD). The research findings indicate that diffuse TDP-43 pathology in LATE causes more than a simple gradual deterioration of memory since it affects clinical manifestations as well. This research assessed TDP-43 pathology occurrence throughout the anterior insula of patients with LATE because this region shows anatomical interconnections to the amygdala which acts as the initial site in LATE-NC development (14). TDP-43 pathology affects emotional response regulation and mood regulation through its involvement in the "forebrain circuit" together with the amygdala and anterior frontotemporal cortex and ventromedial basal ganglia and basal forebrain (15). The anterior section of the insula proves essential for processing emotional and social information more than its neighboring insular regions (16). The clinical characteristics of LATE-NC can be influenced by TDP-43 pathology which affects areas beyond memory deficits within this region. The proposed extension of TDP-43 pathology from the amygdala to the anterior insula happens during LATE-NC disease progression due to their shared anatomical and functional connections. The research confirmed frontotemporal lobar degeneration (17) begins with TDP-43 pathology in the early stages thus we predicted anterior insular TDP-43 pathology would appear in ALS patients who lacked FTLD parallel diagnosis. The study examined TDP-43 pathology between the anterior and posterior (granular) insula regions for both the ALS cases and the LATE-NC group. The researchers assessed these assumptions by performing phospho-TDP (pTDP) immunohistochemical tests on brain tissue obtained from deceased persons who had LATE and ALS and AD neuropathologic change and LBD diagnoses. We collected tissues from anterior and posterior insular cortices which we obtained according to positions matching both the nucleus accumbens and thalamus areas. Independent researchers who were ignorant about clinical and neuropathological data performed all pathological evaluations.

MATERIALS AND METHODS

Case Identification

The analyzed postmortem samples originated from patients who received autopsy examinations at Houston Methodist Hospital. The procedure of pathologic assessment took place for every case through the examination of board-certified neuropathologists at Houston Methodist. The patients' next of kin provided written consent along with permission for research uses. The study received authorization from the Institutional Review Board of Houston Methodist Hospital (IRB Pro00010377). The research implemented convenience sampling for its subject selection to study TDP-43 proteinopathies among ALS patients together with those diagnosed with LATE-NC. Neuropathologic pathology examinations were performed during diagnosis for neurodegenerative diseases while tissue preservation enabled insular cortex harvesting for all studied cases. Different categories of neurodegenerative diseases appeared in this study. All participants featured complete clinical data with information about clinical diagnosis together with whole-brain autopsy findings that tracked Alzheimer's disease neuropathologic change (ADNC) levels. Prion disease specimens as well as those with significant diffuse hypoxic/ischaemic damage were removed from analysis alongside cases that did not have appropriate areas for assessment.

Neuropathologic Sampling

Standardised brain autopsy sections were obtained after brain removal when samples underwent minimum one-week formalin-fixation in 20% formalin solution. The assessment process involved three brainstem levels as well as the amygdala and hippocampal regions together with thalamus, basal ganglia with basal forebrain and anterior cingulate and frontal, parietal, temporal, and occipital neocortices. The researchers acquired “Anterior” and “Posterior” insula samples directly from formalin-fixed “wet” tissue according to section preparation from the coronal plane. Histological evaluation of "anterior" insula sections sampled at the nucleus accumbens plane with H&E and LFB/PAS staining showed complete lack of fully matured layers 2 and 4 within insular cortex. Research has already shown that these areas consisted of both dysgranular and agranular cortex (18). The “posterior” insula sections measured at the dorsomedial thalamic nucleus level displayed granular insular cortex since both layers 2 and 4 showed distinct characteristics. The insula contains three cytoarchitectonic zones which run from dorsal to ventral instead of extending from rostral to caudal (19). The researchers omitted any assessment of the individual subfields because they integrated them as one entity. A sampling pairing operation was used to place anterior and posterior insula tissue together inside one block that permitted blinded pathological examination of the tissue pairs.

Neuropathologic Evaluation

All specimen testing employed the TDP-43 N-terminal antibody from Proteintech (10782-2-AP rabbit polyclonal 1:200) together with Dako tau (Glostrup Denmark 1:40,000) and phospho-tau AT8 clone alongside Dako beta-amyloid 6F/3D post-formic acid processing and α-synuclein antibody. All cases underwent assessments for Braak and Braak stages of neurofibrillary tangles along with amyloid distribution patterns, neuritic plaque densities, TDP-43 pathology, α-synuclein pathology and hippocampal sclerosis according to NIA/AA guidelines (2012) (20). Doctors evaluated arteriosclerosis extent through qualitative grading on a scale of absent, mild, moderate and severe. The research used established diagnostic criteria to detect argyrophilic grain disease and aging-related tau astrogliopathy.

Additional histologic procedures

Scientists obtained sections of 6 μm from Formalin-fixed, Paraffin-embedded (FFPE) tissue blocks that included paired anterior and posterior insular regions. These sections were later mounted onto charged stationary glass slides. The slides spent an overnight period at 60°C to dry. The researchers applied Luxol fast blue/periodic acid–Schiff staining along with phospho-TDP-43 (pTDP) immunohistochemistry to consecutively-cut sections using a rabbit polyclonal antibody at a dilution of 1:500 from Proteintech (catalogue ID 22309-1-AP). The prepared study sections displayed proper orientation without evidence of hypoxic/ischemic damage or any additional artifacts that could affect the results. The study evaluated insular cortex pathology independently from prior knowledge about TDP-43 distribution in all cases.

Assessment of pTDP pathology in insular cortex

Independent evaluation of paired insular pTDP-43 pathology was conducted by two authors including R.L. and M.D.C. who both evaluated the sections without knowledge of patient data or LATE-NC extent in other cortical areas. Research analysts documented pTDP immunostaining status individually for anterior and posterior insular specimens before classifying them as either positive or negative. Each case obtained one of four pTDP status classifications based on whether pTDP appeared only in anterior insula or posterior insula or both regions or neither region at all. The research logged the particular inclusion pathology patterns within each positive case (e.g., “subpial processes only”). The research team assigned independent semiquantitative pTDP burden grades to anterior and posterior insula regions through a scale ranging from 0 (no pTDP detected) to 4 (pathology resembling FTLD patterns). The monitoring of pTDP-43 inclusions in positive sections involved counting 1 to 30 inclusions per field at 400× magnification until reaching the maximum rating of 30 in cases with severe involvement. Our former study proved that this non-

quantitative pTDP-43 inclusion grading method shows good agreement with pTDP-43 immunohistochemistry analysis using images from ALS tissue samples (23).

Single-nucleotide polymorphisms genotyping

Sample genotyping of SNPs from APOE and TMEM106B genetic variants took place for all specimens. The QIAamp DSP DNA FFPE Tissue Kit obtained from Qiagen (Catalogue ID 60404, Hilden, Germany) provided the DNA extraction method that followed standard manufacturer guidelines to extract DNA from FFPE tissues. The investigators conducted SNP analysis by applying TaqMan assays for APOE rs429358/rs7412 alongside TMEM106B rs1990622 (Thermo Fisher Scientific, Waltham, MA) through the Bio-Rad CFX96 Real-Time PCR System (Bio-Rad, Hercules, CA) as per previous report (14). The CFX Maestro Software (Bio-Rad) enabled evaluation of genotypes through its Allelic Discrimination module.

Statistical methods

The statistical analysis used Wilcoxon ranked-sum tests and chi-square ($\chi 2$) testing in the program R version 2.4 (24) as needed. Two-sided testing of statistics produced results with significance at p levels below 0.05. This high number of samples prevented the assessment of genotype associations which led to reporting only the important frequency data instead.

RESULTS

Clinical and pathologic characteristics of the study sample

Table 1. Clinical and pathologic features of groups in the autopsy cohort

Group	N	Age (years) †	Male/Female	NFT †	APOE ε4 (%)	TMEM106B (%)	HS (%)	TDP-43 ‡ (%)	Anterior Insula pTDP (%)
Common ADRDs *	72	82 (15)	32/40	4 (1.5)	52.8	64.3	22	55	32.5
ALS	18	63 (12)	10/8	1 (0.5)	11.1	61.1	0	100	50.0
PSP-CBD	12	69 (10)	7/5	2 (0.5)	41.7	66.7	0	50	25.0
FTLD	6	73 (11.5)	4/2	2 (1)	33.3	50.0	67	83.3§	83.3§
Neuromusc.	3	74 (NA)	2/1	0 (NA)	33.3	33.3	0	0	0

Table 2. Common ADRD study samples with and without insula pTDP pathology

	Insula pTDP+	Insula pTDP−	p-Value
N	24	45	–
Male/Female	12/12	21/24	–
Age (years) *	84 (n = 12)	79 (n = 14)	.02
Braak NFT stage *	5 (n = 2)	4 (n = 1)	NS
Hippocampal sclerosis (HS)	50.0%	8.9%	.0001
TDP-43 (LATE-NC †)	87.5%	40.0%	.0012
No known LATE-NC	12.5%‡	60.0%	–
Stage 1 LATE-NC	8.3%	17.8%	–
Stage 2 LATE-NC	54.2%	22.2%	–
Stage 3 LATE-NC	25.0%	0.0%	–
Lewy body disease §	29.2%	31.1%	NS
APOE ε4 carrier	50.0%	58.0%	–
TMEM106B risk	70.8%	62.2%	–

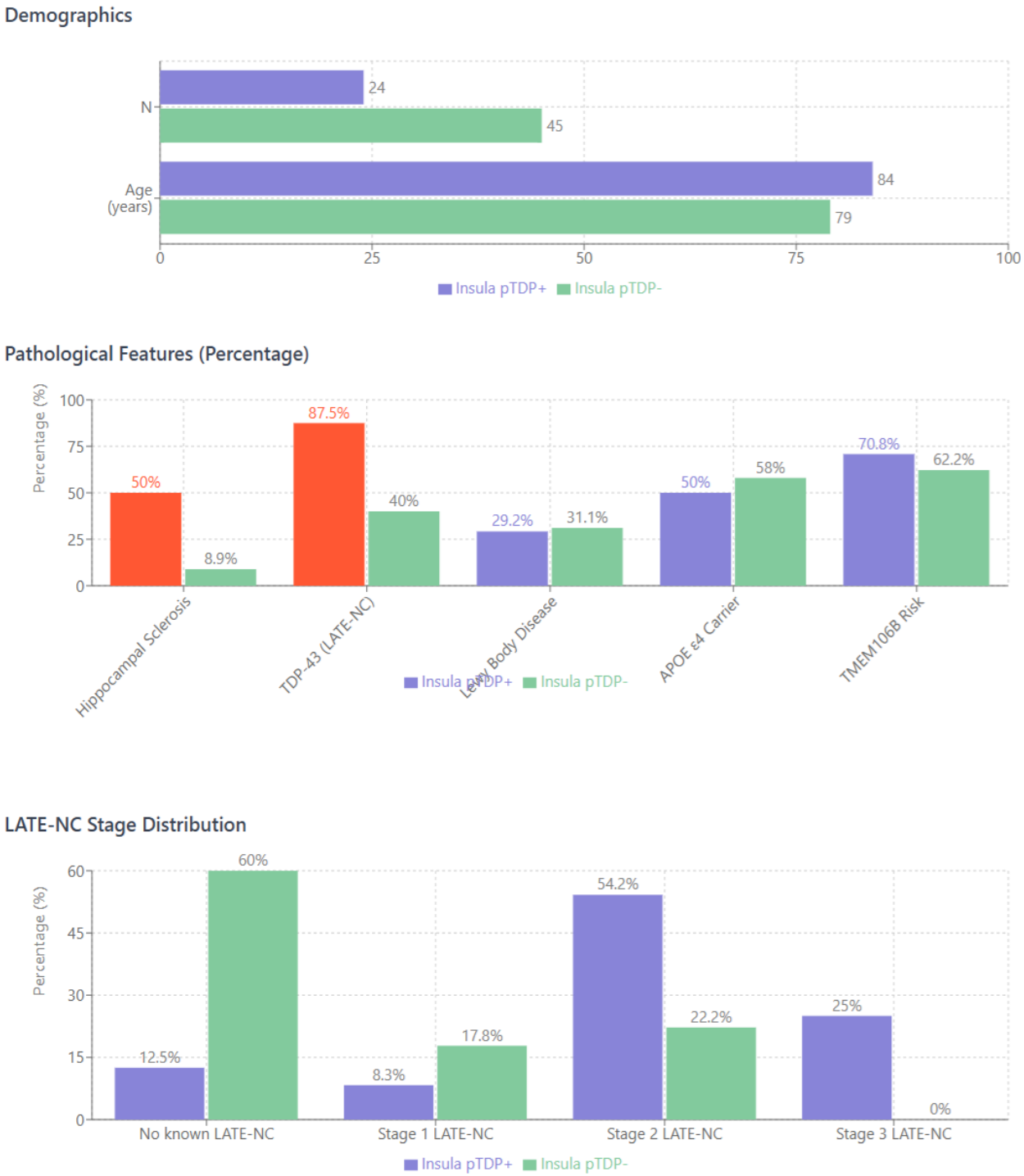

Figure 1. ADRD Study Samples: Comparison Between Insula pTDP+ and pTDP- Groups

Autopsy patients demonstrate their clinical and pathological features as presented in Table 1. The Common ADRDs group included seventy-two participants as its largest group followed by ALS patients who had an average age of sixty-three. A balance of male and female participants existed throughout the different study groups. The stages of Neurofibrillary tangle (NFT) remained minimal throughout all examined groups. The Common ADRDs subjects displayed the highest share of APOE ε4 genetic carriers at 52.8% among tested groups but ALS patients possessed the least APOE ε4 allele frequency at 11.1%. Concerning TMEM106B risk allele frequency the data was stable among different groups with values between 33.3% and 66.7%. The brain pathology of hippocampal sclerosis existed in 22% of subjects with Common ADRDs and in 67% of those with FTLD while it was not observed in patients with ALS and PSP-CBD and Neuromuscular conditions. The TDP-43 pathology showed its highest frequency in patients with ALS since every case had it while FTLD

presented an 83.3% level of positive cases. The frequency of anterior insula pTDP positivity reached its highest levels in FTLD patients with 83.3% cases and in ALS patients with 50.0% of cases. Table 2 analyzes Common ADRD participants according to whether insular pTDP pathology exists or not exists. Participants with positive insular pTDP showed an average age of 84 years which exceeded the age of 79 years recorded for the pTDP-negative cluster at a statistically meaningful level (p=0.02). Among all participants, pTDP-positive patients exhibited increased rates of hippocampal sclerosis (50% compared to 8.9%) and LATE-NC pathology (87.5% compared to 40.0%) with statistical significance (p=0.0001 and p=0.0012 respectively). Stage 2 and Stage 3 LATE-NC disease stages prevalently occurred in participants with pTDP-43 pathology in the insula but not in other regions. The frequencies of Lewy body disease pathology along with APOE ε4 carriers matched between patient groups. The research shows that TDP-43 pathology in the insula relates to both hippocampal sclerosis and severe Lesion-associated neurodegenerative disease with tau neurodegeneration.

DISCUSSION

Research in insular TDP-43 pathology involvement among various neurodegenerative disorders yielded multiple notable outcomes. Research showed that anterior insula damage affects patients with LATE-NC at all disease stages including low and intermediate ADNC levels from Stage 1 and primarily Stages 2 and 3 of current classifications (9). Previous studies confirm that the insula serves as a TDP-43 pathology target in AD cases while also identifying it as the primary staging component ("Stage 4") in alternate staging proposals (10). Insular involvement rates in the past research study which showed less than 20% frequency stood lower than the 30.4% observed in our ADRD syndromes likely resulted from dissimilar methods used for insula regions study. The anterior section of the insula showed high vulnerability to damage in subjects diagnosed with ALS regardless of their TDP-43 pathologic status or presence of overlapping FTLD-TDP. Most of the TDP-43-positive insula clinical cases were found in ALS patients demonstrating "TDP-43-limited" or "TDP-43-moderate" pathological involvement (25). An automatic early appearance of TDP-43 pathology occurred in the anterior insula before the posterior insula and produced denser TDP-43 inclusions in the anterior section when both areas presented TDP-43 pathology. The differentiation between these regions holds special importance because standard autopsy methods fail to collect anterior insula tissue but they do obtain posterior insula tissue by thalamic level sampling. The analysis of pTDP pathology in the anterior insula should include sections taken through the nucleus accumbens. A fourth essential observation demonstrates that TDP-43 proteinopathy spreads from basal forebrain areas and anterior insula cortex in LATE/HS-Aging before reaching full neocortical development (8, 10). Research implies anterior insula pathologic conditions create an important bridge from the beginning stage to the end stage of TDP-43 disease development in AD and aging individuals. Research findings demonstrated that patients with hippocampal sclerosis frequently experienced this pathology while avoiding pathologic involvement of amygdala or hippocampus. Additional research must combine longitudinal imaging assessments with cognitive tests that measure pathology within both anterior insula and basal forebrain tissues for more precise study of LATE disease processes. Medical science groups the anterior insula as one of several "paralimbic" brain regions together with the parahippocampal gyrus, orbitofrontal cortex, retrosplenial cortex, cingulate cortex, temporal pole, and subcallosal area (18). The human brain applies paralimbic areas to connect allocortical regions with neocortical structures in their three- and six-layer development respectively (18, 26). Additional research indicates that the paralimbic networks develop TDP-43 pathology before amygdala and hippocampus during the disease process. Research has shown that entorhinal cortex paralimbic areas establish pre-amygdala pathology in certain cases of LATE-NC and early TDP-43 pathology occurs at paralimbic temporal pole regions during normal aging and AD progression (14, 27). Evidence shows tauopathies including PART and AD display paralimbic vulnerability yet TDP-43 pathologies involving LATE-NC and ALS require more investigation regarding their paralimbic vulnerability. The anterior insula's connectivity with limbic structures such as the entorhinal cortex, transentorhinal cortex, and amygdala (19) likely contributes to its

early involvement in LATE-NC. The links between orbitofrontal cortex together with the medial temporal cortex and temporal pole brains' physical pathways explain why the structure is vulnerable. The clinical manifestations which result from anterior insula TDP-43 pathology are most commonly observed in cases of FTLD-TDP but scientists remain uncertain about their impact in LATE-NC and ALS patients. According to studies the insula serves as an organ that enables sensory processing while generating gustatory and language output and processing emotions and controlling autonomic functions while supporting higher-level cognitive tasks (19). Various functional networks such as sensorimotor together with gustatory and social-emotional and cognitive circuits are integrated within the insula (16). Studies combining data from multiple investigations demonstrate that the social-emotional activation activates the anterior and ventral parts of the insula while somatosensory stimuli primarily activate the posterior section. The LATE-NC clinical stage showed anterior insula pTDP pathology that occurred jointly with basal forebrain damage before pathology spread to posterior insula and neocortical areas. Total diffusion of TDP-43 pathology specifically in early stages of basal forebrains and basal ganglia occurs commonly in ALS patients (25, 18). A well-established observation in ALS shows that patients usually avoid FTLD diagnosis even though they exhibit tiny yet recognizable dysfunctions within frontal-subcortical networks leading to "frontal dysexecutive syndrome" manifestations regarding mental inflexibility and perseverative behavior and psychomotor slowness (13, 26). The relation between anterior insular atrophy and progressive nonfluent aphasia has been shown in high-resolution imaging studies yet widespread inferior frontal atrophy seen in FTD remains underreported in LATE-NC subjects. LATE-NC presents as a mild amnestic syndrome where the combination of AD and LBD makes it difficult to identify early frontal-subcortical dysfunction in small patient groups. The NACC database demonstrates apathy and behavioural disinhibition occur more often in LATE-NC cases that show low ADNC burden (12) which supports the early paralimbic pattern. The anterior insula works as part of a “forebrain circuit” including amygdala, anterior insula, nucleus accumbens and ventromedial frontal cortex that controls emotional processing and mood regulation according to experimental animal research (15). Research is needed to determine if circuit dysfunction causes symptoms in patients with late neurodegenerative disease without Alzheimer dementia. The pathology of FTLD-TDP features distinct patterns of anterior insula atrophy that correspond to various clinical syndromes as described in research by (28). The study verifies anterior insula shows greater damage compared to posterior insula while examining LATE-NC, ALS, and related disorders but additional research must reveal the identity of weak cells in this region. Insula follows a dorsoventral organizational pattern through its three cortices of agranular, dysgranular and granular rather than a rostral-caudal axis organization (19, 30). Scientists included two anterior insula divisions as part of their analysis which correspond to areas IA in von Economo's classification. Research shows that cortical subtypes differ by their development of laminar structure and myelin formation and their responses to acetylcholinesterase (18, 19). Researchers have determined that dysgranular cortex comprises the anterior half area of the insular surface. Research groups have generated probability maps for cortical subdivisions that MRI studies match to human brain structures. Research confirms that the anterior insula section studied corresponds with area "IA" of von Economo while being located near fronto-insular transition factors "IC" and "FJ" (30). These brain locations hold von Economo neurons which seem to help process sophisticated social and emotional functions (19). Scattered appearances of these neurons emerged in our samples (~33% of cases) but pTDP proteins never exclusively targeted them in LATE-NC patients thus demanding future research.

CONCLUSION

The research findings show that pTDP pathology selects the anterior insula as a preferred target in both LATE-NC and ALS. The aggregation of pathological elements was consistently greater in anterior portions of the insular cortex compared to posterior regions when both parts became participated. Apart from anterior insula involvement researchers have found that pathology spreads to basal forebrain and paralimbic areas before affecting widespread neocortical tissue. Early-stage LATE-NC neuropathological evaluation should focus on anterior insula with basal forebrain and

ventral striatum because these specific areas provide crucial information. Longitudinal research needs to determine if fronto-subcortical mental changes similar to those seen in ALS develop from this specific insular cortex pathology in patients with TDP-43 proteinopathies and their complete clinical impact.

REFERENCES

1. Nelson PT, Brayne C, Flanagan ME, et al. Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: Combined data from 13 community-based or population-based autopsy cohorts. Acta Neuropathol 2022;144:27–44
2. Josephs KA, Murray ME, Whitwell JL, et al. Staging TDP-43 pathology in Alzheimer's disease. Acta Neuropathol 2014;127:441–50
3. Josephs KA, Whitwell JL, Weigand SD, et al. TDP-43 is a key player in the clinical features associated with Alzheimer's disease. Acta Neuropathol 2014;127:811–24
4. Cykowski MD, Powell SZ, Schulz PE, et al. Hippocampal sclerosis in older patients: Practical examples and guidance with a focus on cerebral age-related TDP-43 with sclerosis. Arch Pathol Lab Med 2017;141:1113–26
5. Amador-Ortiz C, Lin WL, Ahmed Z, et al. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol 2007;61:435–45
6. Nelson PT, Smith CD, Abner EL, et al. Hippocampal sclerosis of aging, a prevalent and high-morbidity brain disease. Acta Neuropathol 2013;126:161–77
7. Dickson DW, Davies P, Bevona C, et al. Hippocampal sclerosis: A common pathological feature of dementia in very old (> or = 80 years of age) humans. Acta Neuropathol 1994;88:212–21
8. Cykowski MD, Takei H, Van Eldik LJ, et al. Hippocampal sclerosis but not normal aging or Alzheimer disease is associated with TDP-43 pathology in the basal forebrain of aged persons. J Neuropathol Exp Neurol 2016;75:397–407
9. Nelson PT, Lee EB, Cykowski MD, et al. LATE-NC staging in routine neuropathologic diagnosis: An update. Acta Neuropathol 2023;145:159–73
10. Josephs KA, Murray ME, Whitwell JL, et al. Updated TDP-43 in Alzheimer's disease staging scheme. Acta Neuropathol 2016;131:571–85
11. Butler Pagnotti RM, Pudumjee SB, Cross CL, et al. Cognitive and clinical characteristics of patients with limbic-predominant age-related TDP-43 encephalopathy. Neurology 2023;100:e2027–35
12. Gauthreaux K, Mock C, Teylan MA, et al. Symptomatic profile and cognitive performance in autopsy-confirmed limbic-predominant age-related TDP-43 encephalopathy with comorbid Alzheimer disease. J Neuropathol Exp Neurol 2022;81:975–87
13. Ringholz GM, Appel SH, Bradshaw M, et al. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology 2005;65:586–90
14. Cykowski MD, Arumanayagam AS, Powell SZ, et al. Patterns of amygdala region pathology in LATE-NC: Subtypes that differ with regard to TDP-43 histopathology, genetic risk factors, and comorbid pathologies. Acta Neuropathol 2022;143:531–45
15. Price JL. Comparative aspects of amygdala connectivity. Ann N Y Acad Sci 2003;985:50–8
16. Kurth F, Zilles K, Fox PT, et al. A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct 2010;214:519–34
17. Seeley WW. Anterior insula degeneration in frontotemporal dementia. Brain Struct Funct 2010;214:465–75
18. Mesulam MM, Mufson EJ.. Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol 1982;212:1–22
19. Nieuwenhuys R. The insular cortex: A review. Prog Brain Res 2012;195:123–63

20. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1–13
21. Kovacs GG, Ferrer I, Grinberg LT, et al. Aging-related tau astrogliopathy (ARTAG): Harmonized evaluation strategy. Acta Neuropathol 2016;131:87–102
22. Jicha GA, Petersen RC, Knopman DS, et al. Argyrophilic grain disease in demented subjects presenting initially with amnestic mild cognitive impairment. J Neuropathol Exp Neurol 2006;65:602–9
23. Cathcart SJ, Appel SH, Peterson LE, et al. Fast progression in amyotrophic lateral sclerosis is associated with greater TDP-43 burden in spinal cord. J Neuropathol Exp Neurol 2021;80:754–63
24. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2021
25. Cykowski MD, Powell SZ, Peterson LE, et al. Clinical significance of TDP-43 neuropathology in amyotrophic lateral sclerosis. J Neuropathol Exp Neurol 2017;76:402–13
26. Braak H. Architectonics of the Human Telencephalic Cortex. Berlin; NY: Springer-Verlag; 1980
27. Nag S, Yu L, Boyle PA, et al. TDP-43 pathology in anterior temporal pole cortex in aging and Alzheimer's disease. Acta Neuropathol Commun 2018;6:33. [DOI] [PMC free article] [PubMed] [Google Scholar
28. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): A common pathology associated with human aging. Acta Neuropathol 2014;128:755–66 [DOI]
29. Braak H, Alafuzoff I, Arzberger T, et al. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 2006;112:389–404
30. Salameh JS, Brown RH Jr, Berry JD.. Amyotrophic lateral sclerosis: Review. Semin Neurol 2015;35:469–76