**Sex modifies predictive effects of imaging and CSF biomarkers on Alzheimer’s disease cognitive outcomes**

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**1. Introduction**

Previous studies showed sex differences in Alzheimer’s Disease (AD) risk potentially attributable to differences in life expectancy, the APOE ε4 genotype, and other factors. To date, no data model or biological paradigm fully explains this disparity, necessitating novel approaches for studying AD-related fluid biomarkers, imaging and cognitive data. Understanding these pathological differences help train fair models for AD that allow for the equally accurate prediction, diagnosis, and treatment of AD in men and women.

**2. Materials and Methods**

Participants included 1,479 subjects from the ADNI cohort with sixteen AD quantitative measures available over four time points (Figure 1). Chow tests were performed to understand the possible underlying biological mechanisms of sex-modified AD biomarker differences. Results of these tests show whether measures of each of 11 AD imaging and cerebrospinal fluid (CSF) markers predicted one of five AD cognitive outcomes with varying slopes when stratifying upon sex. Effects at each time point were evaluated separately. To determine the direction of the differential effects for each biomarker predictor, additional bootstrapped (n=599) Chow tests were conducted. A Bonferroni correction (p < 2.94E-4) was used to control for multiple comparisons.

**3. Results**

Multiple imaging and CSF biomarkers predicted AD cognitive scores with differing regression coefficients between men and women over four time points (Figure 1). The strongest signals involved the volumetric measures of the mid-temporal cortex, hippocampus, and fusiform gyrus respectively predicting the ADAS-13 score using baseline and month 24 data. Bootstrapped regression analyses showed effects on the medial-temporal-lobe and hippocampus were uniformly statistically significant, whereas effects in the P-tau biomarker were not (Figures 2-3).

**4. Conclusions**

While prior studies mainly investigated sex effects on AD biomarkers, this work examined how sex modified the predictive effects of imaging and CSF biomarkers on AD cognitive outcomes. It warrants further investigation to study if sex modifies multivariate biomarker-based predictive effects on cognitive outcomes. While consistent with prior results showing significant sex differences in brain volumetric and AD tau-based biomarkers, our findings can create fair sex-stratified predictive models to promote precision medicine and help elucidate how biological factors drive the sex-based pathological disparity in AD.

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Slow motor neurons resist pathological TDP-43 and mediate motor recovery in the rNLS8 model of amyotrophic lateral sclerosis.

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Abstract

In the intermediate stages of amyotrophic lateral sclerosis (ALS), surviving motor neurons (MNs) that show resistance to TDP-43 proteinopathy can partially compensate for the loss of their more disease-susceptible counterparts. Elucidating the mechanisms of this compensation may reveal approaches for attenuating motor dysfunction in ALS patients. In the rNLS8 model of ALS-like pathology driven by dihydrozone-regulated expression of hTDP-43 in neurons, slow MNs are more resistant to disease than fast-failing (FF) MNs and can mediate recovery following transgene suppression. In the present study, we use a viral tracing strategy to show that disease-resistant slow MNs quickly reinnervate motor emigrant subsets of target muscles vacated by degenerated FF-MNs. Moreover, we find that neuromuscular junctions within fast-twitch skeletal muscle (tibialis anterior, TA) reinnervated by rNLS-positive slow MNs acquire resistance to axonal dieback when challenged with a second insult of hTDP-43 rNLS pathology. Using a nerve crush followed by reinnervation surgery, we show that TA reinnervated by FF-MNs remains disease-susceptible, whereas contralateral reinnervation by slow MNs confers resistance to subsequent hTDP-43 insult. Collectively, these findings demonstrate that MN identity, rather than muscle fiber type, dictates the susceptibility of neuromuscular junctions to ALS pathology and that junctions reinnervated by slow MNs are remarkably resilient to disease.

Significance

Genetic models could help disease processes in motor neurons (MNs) of subsets of amyotrophic lateral sclerosis (ALS) patients, but patients are rarely diagnosed until well into disease so it is important to understand how surviving MNs compensate and impact motor function. Here, we show that slow (S) motor units and their associated target muscles are more resistant to disease than fast-failing (FF) motor units and may mediate recovery following transgene suppression. When the motor ends of “fast” muscles are reinnervated by FF-MNs, but not by the slow MNs, the neuromuscular junctions (NMJs) are susceptible to neuronal death. These findings suggest that if disease etiology can be directly targeted in ALS patients, the plasticity of the lower motor neuron system allows for the recovery of lost function.

1. Using rNLS8 mice to model selective vulnerability of motor neurons

Advantages for studying ALS-relevant selective neuronal vulnerability:

1) the transgene is induced by removing Doxycycline (DOX) from the animals’ diet and suppressed by reintroducing it and as a result the disease has a modifiable timeline to allow for the detection of subtle changes;
2) the regulation is temporally reproducible;
3) the disease is triggered by the major pathological hallmark of ALS, TDP-43, rather than a specific familial mutation.

2. rNLS8 mice can recover motor function following Dox reintroduction via reinnervated motor units.

(a) Experimental timeline to investigate the consequences of transgene expression after rescue. (b) Representative images of the lumbar MNs (KCNQ1, red) expressing high levels of completeness hTDP-43 (green) during both the first and second disease courses. Scale bar: 50microns. (c) rNLS8 mice lose one-third of lumbar MNs during the first disease course, but only lose an additional 2% per ventral horn during an additional 6 wk of Dox. (d) Representative immunofluorescence images show that during the second disease course, the amplitude does not decrease. (e) Max CMAP amplitude remains high through the second disease course, compared to the decline in the first disease course. (f) k-Intact MNs decline through 6 wk of Dox, and after recovery remains intact through the second disease course.

5. Muscle reinnervation by fast MNs does not change the TA muscle’s susceptibility to axonal dieback in the presence of pathological TDP-43.

(a) Schematic representation of unilateral sciatic nerve crush. (b) Representative images of the TA muscle before and after nerve crush showing intact MNs before nerve crush [note overlap between nerve endings labeled with WNT111, red, and motor endplate, labeled with a FITC-GFP, green], but not after (Scale bar: 200 microns). (c) Representative images of TA reinnervating MNs from rNLS8 mice bilaterally crushed with CTB 544 on the crushed side (left), and CTB 488 on the contralateral side (right). Green: Scale bar: 200 microns. (d) The size of the MNs after recovery is different from the contralateral TA MNs and is consistent with the size of FF (fast-failing) MNs

3. Tracing MNs that innervate the TA muscle before and after disease suggests that MNs from adjacent pools innervate new muscles.

Experimental timeline to compare the identity of the lumbar MNs that reinnervate the TA muscle before the first recovery (TA2) compared to the original motor pool (TA1) using retrograde neuronal tracers with different fluorophores (Alexa488 or Cy3). (a) Representative microscopic images of rNLS8 TA2 MNs are labeled by CTB 488 during both the first and second disease course. Scale bar: 30 microns. (b) Quantification of labeled neurons shows that approximately 15% of TA2 MNs were not part of the TA1 motor pool.

6. Cross-reinnervation surgery manipulates slow (S) MNs to innervate TA muscle instead of fast fatigue (FF) MNs.

CTD-disease rNLS8 TA mice with or without proviral insertions were surgically debrided to cross reinnervate the TA muscle. (a) Representative retrograde neuronal tracers with different fluorophores (CTB 488 vs. 594 on the crushed side (top, native fluorescence), while a subset of rNLS8 TA MNs are labeled by CTB 488 only after cell death followed by TDP-suppression-induced muscle reinnervation (bottom, fluorescent). Scale bar: 30 microns. (b) Quantification of labeled neurons shows that approximately 15% of TA2 MNs were not part of the TA1 motor pool.

7. Slower motor units are disease resistant during mutant hTDP-43 expression, even after innervating a traditionally “fast” muscle.

(a) Experimental timeline to test if recovery after unilateral nerve crush in thalamus could be halted on re-inervation events during transgene expression. (b) There is no difference between hTDP-43 on the unilateral crushed vs. contralateral side after six weeks of Dox, suggesting that the reinnervation process itself does not confer disease resistance. (c) There is no difference between the average number of lumbar MNs on the ipsilateral vs. contralateral side after six weeks of Dox.

8. Conclusion

• Naturally disease-resistant MNs mediate the functional motor recovery of rNLS mice.
• Reinnervated MNs are resistant to subsequent TDP-43 insults.
• Injury-induced phenotypic changes do not drive the resistance of reinnervated motor units to disease.
• Motor unit resistance is driven by slow MNs.

9. Significance

• Particularly exciting given recent advances in ALS clinical programs aimed at targeting genetic drivers of disease.
• These early results in this novel model of TDP-43 proteinopathy offer hope that in the future, if disease progression could be halted on re-inervation events during transgene expression.
• Slower motor units could be a target in ALS treatments, offering hope that in the future, if disease progression could be halted on re-inervation events during transgene expression.
• Slower motor units could be a target in ALS treatments, offering hope that in the future, if disease progression could be halted on re-inervation events during transgene expression.
**NIA Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS): 2021 Update**

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Improving Neuropathological Analysis in IHC through Starburst Artifact Detection

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**Background**
- Semi-Automated Neuropathological Analysis (SANA) is a tool-kit currently in development, which allows for the efficient analysis of post-mortem human brain tissue. It provides predictive models for semi-automated segmentation of objects such as neurons, plaques, and tangles, as well as various modules which measure the degree of pathology or the amount of degeneration in the cytoarchitecture.
- However, artifacts in the tissue affect the accuracy of these predictive models and cause inaccuracies in the measurements of pathology and/or degeneration.

**Object Detection**
- 9 ATB stained slides from FTLD patients were selected for analysis. These slides cover various regions from the brain: ANG, HH, CNG, MFC, WERN and OFC.
- From these slides, 89 regions of interest (ROIs) were randomly selected for the dataset.
- The ROIs were manually created as annotations in QuPath 2.0 bioimage analysis software and exported as JSON files.

**Image Processing**
- The Artifact Detection module is developed in Python, along with the rest of the SANA architecture.
- Pre-Processing:
  1. Load ROI Frame into memory.
  2. Separate the DAB stain from the Frame through color deconvolution.
  3. Apply Anisotropic Diffusion filtering to smooth inconsistencies in the DAB staining.
  4. Perform Stain Thresholding to remove insignificant background staining.
  5. Apply Morphological Opening filtering to further remove background staining and simplify objects in the stained image.

**Dataset**
- Figure 1: Representative Starburst Artifact in ATB Stained Tissue
  - (A) Shows a starburst artifact while (B) show true pathology
- Figure 2: Representative ROIs
  - ROIs containing starburst artifacts (top row) and ROIs with no starburst artifacts (bottom row)

**Template Matching**
- The Image Processing step provides a segmentation for each object in the stained image.
- A Template Matching algorithm is performed on each segmentation, which yields a confidence value -- the probability that said segmentation is a starburst artifact.
- The Template used is a 2D Gaussian Probability Density Function (PDF) Kernel.

**Results**
- Positive detections are considered True or False based on the IOU (intersection over union) score between itself and any given manual annotation.
- Scoring of this object detection software is done via Precision-Recall (PR) Curves, as well as Average Precision (AP) values.

**Conclusion**
- The developed artifact detection software provides high Precision and Recall at low IOU.
- SANA will require this performance at higher IOU’s before being implemented in the full processing pipeline.
- Detection of starburst artifacts could improve pathological and degeneration measures.

**Future Directions**
- Run the system on SANA’s large datasets to test performance in more difficult scenarios.
- Optimize image processing parameters and techniques.
- Expand the system to include tissue tears, blood vessels, and other important artifacts.

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**References**

5. OpenCV. (2020). https://docs.opencv.org/master/d4/d86/group__imgproc__filter.html#ga67493776e3ad1a3df63883829375201f
6. https://docs.opencv.org/3.4.2/d4/d86/group__imgproc__filter.html#ga67493776e3ad1a3df63883829375201f

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**Regulation of multiple genes by an enhancer encompassing MAPT rs242557**

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**KEY TAKE AWAY:** rs242557 is part of an enhancer that regulates expression of:-
1. **MAPT, KANSL1, NSF, CRHR1, KANSL1 AS-1, LRRC37A, LRRC37A2, and LRRC37A3 transcripts, and**
2. **KANSL1, NSF and CRHR1 proteins in microglial cells**

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**INTRODUCTION**

- Microtubule associated protein tau (MAPT) helps in assembly and stabilization of microtubules.
- Mutated or misfolded tau aggregates in frontotemporal dementia (FTD), Progressive supranuclear palsy (PSP), Corticobasal degeneration (CBD) or with another protein like amyloid beta as in Alzheimer’s disease (AD).
- MAPT H1 haplotype and intronic SNP rs242557 are the top two risk signals in chromosome 17 for PSP [1, 2, 3], CBD [1, 2, 3, 4, 5] and PD [Parkinson’s disease] (6, 7).
- rs242557 is part of a FANTOMS enhancer in eye and brain evolutionarily conserved from humans to amphidipids.
- Strong, independent signals from MAPT neighbouring genes KANSL, NSF, LRRTM1 and WNT3 have also been noted in some of these diseases.

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**METHODS**

- **A. Expression of immediate neighboring genes of MAPT are altered**
  - **B. Significant reduction in MAPT transcripts**
  - **C. No off target effect of the guide RNA pair used**

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**RESULTS (continued)**

**CONCLUSIONS**

- Role of rs242557 (if any) in activated microglia.
- Investigate if manipulation of the function of rs242557 or the enhancer as a whole can restore regular expression of MAPT and its neighboring genes in diseased state.

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**REFERENCES**


**Funding:** CoreNet (P50 2020-01); U54 NS100693, U24 NS104105

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**Table 1: Patient demographics and pathology characteristics.**

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**Supplementary figure 1:** Table showing patient demographics and pathology characteristics.

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**Supplementary figure 2:** Illustration of different layers of the brain, with annotations indicating pathology distribution.

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**Supplementary figure 3:** Heatmap visualizing the correlation between TDP-43 and tau pathology across different brain regions.

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**Supplementary figure 4:** Comparison of pathology distribution between TDP-43 and tauopathies, highlighting significant differences.

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**Supplementary figure 5:** Flowchart outlining the methodology and data analysis process.

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**Supplementary figure 6:** Graphical representation of the main findings, including statistical significance levels.

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**Supplementary figure 7:** Additional validation data from independent cohorts, supporting the robustness of the findings.

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**Supplementary figure 8:** Detailed imaging analysis showing the spatial distribution of tau and TDP-43 pathology.

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**Supplementary figure 9:** Image showing the integration of clinical and pathological data, highlighting the correlation with cognitive impairment.

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**Supplementary figure 10:** Comparison of tau and TDP-43 pathology across different age groups, noting the progression patterns.

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**Supplementary figure 11:** Graphs illustrating the temporal dynamics of tau and TDP-43 accumulation over time, showing distinct trends.

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**Supplementary figure 12:** Additional pathological markers indicating the presence of tau and TDP-43 in various brain regions.

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**Supplementary figure 13:** Detailed analysis of the correlation between different pathological markers, emphasizing the specificity of the findings.

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**Supplementary figure 14:** Flowchart summarizing the key steps and results of the study, guiding further research directions.

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**Supplementary figure 15:** Graphs showing the progression of pathology in different patient groups, indicating the impact of genetic factors.

---

**Supplementary figure 16:** Comparison of tau and TDP-43 pathology across different pathological stages, highlighting the progression patterns.

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**Supplementary figure 17:** Additional validation data from independent cohorts, supporting the robustness of the findings.

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**Supplementary figure 18:** Graphical representation of the main findings, including statistical significance levels.

---

**Supplementary figure 19:** Flowchart outlining the methodology and data analysis process.

---

**Supplementary figure 20:** Image showing the integration of clinical and pathological data, highlighting the correlation with cognitive impairment.

---

**Supplementary figure 21:** Detailed imaging analysis showing the spatial distribution of tau and TDP-43 pathology.

---

**Supplementary figure 22:** Comparison of tau and TDP-43 pathology across different age groups, noting the progression patterns.

---

**Supplementary figure 23:** Graphs illustrating the temporal dynamics of tau and TDP-43 accumulation over time, showing distinct trends.

---

**Supplementary figure 24:** Detailed analysis of the correlation between different pathological markers, emphasizing the specificity of the findings.

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**Supplementary figure 25:** Flowchart summarizing the key steps and results of the study, guiding further research directions.

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**Supplementary figure 26:** Graphs showing the progression of pathology in different patient groups, indicating the impact of genetic factors.
Engineered nuclear import receptor Karyopherin-β2 chaperones ALS-associated mutant cargo

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Background

FUS is an RNA-binding protein with a non-canonical proline-tyrosine nuclear localization signal (PY-NLS).

Mutations to the PY-NLS, including P525L, cause cytoplasmic mislocalization and are associated with severe juvenile amyotrophic lateral sclerosis (ALS).

Karyopherin-β2 (Kap2) is a nuclear import receptor that chaperones cargo with a PY-NLS.

The chaperone activity of Kap2 is severely impaired against P525L FUS, suggesting that Kap2 activity is important for preventing disease.

Goal: Introduce mutations into Kap2 to recover chaperone activity against P525L FUS.

Approach

Strategy One: Target cargo-facing residues

Using structural data and protein modeling computational software, we generated a set of nine point-mutations predicted to increase the stability of the mutant FUS-Kap2 complex.

Strategy Two: Perturb the interactions that drive FUS self-assembly

FUS self-assembly is driven, in part, bycation-π interactions between Tyr residues in its PrLD and Arg residues in its RGG domains. We hypothesized that introducing Arg residues to the surface of Kap2 would allow Kap2 to more efficiently access FUS structures.
Utilizing RNA to prevent TDP-43 aggregation

Numerous bait RNAs strongly prevent aggregation of WT TDP-43

Bait RNAs differentially prevent aggregation of patient TDP-43 missense variants

Relative differences exist in the efficacy of bait RNAs against aggregation of patient TDP-43 missense variants

Conclusions and future directions

Acknowledgements

Developing RNA therapeutics for TDP-43 proteinopathy in ALS/FTD

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Developing RNA therapeutics for TDP-43 proteinopathy in ALS/FTD

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Utilizing RNA to prevent TDP-43 aggregation

Does not cause TDP

length TDP

TDP

43 protein with C

aggregation assay

Specific bait RNA sequences dose-dependent aggregation of WT TDP-43. A. Turbidity measurements demonstrate a correlation between bait and no RNA in various concentrations of bait RNA, normalized to the maximum of no-RNA control. Relative-normalized area under the curve of turbidity measurements. Right Normalized area under the curve plotted against bait RNA concentration, with the IC50 noted. B. (RNA[TDP-43]): n=4, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. C. Normalized area under the curve of turbidity measurements demonstrate that (AC)RNA does not prevent aggregation (Cu[TDP-43]: n=4, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

Bait RNA potency differs for WT versus select ALS/FTD patient TDP-43 missense variants. A. Heat map of the IC50 values for each bait RNA against WT and patient missense mutants of TDP-43 (Cu[TDP-43]: n=3-6). B. Heat map of the rank ordering of the IC50 values for each TDP-43 variant. C. Heat map of the hit rates for aggregation prevention by each bait RNA for each TDP-43 variant. D. For each bait RNA and TDP-43 variant pair, the corresponding IC50 and hit rates values are plotted against each other, demonstrating a strong correlation (Pearson correlation).

The ability of bait RNAs to prevent aggregation of select patient TDP-43 missense mutants differs across RNA concentration ranges. A. Heat maps of the normalized area under the curve for each bait RNA against WT and patient missense mutants of TDP-43 (Cu[TDP-43]): n=4, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. B. (AC)RNA significantly prevents aggregation of two tested TDP-43 missense mutants (Cu[TDP-43]: 1:4[RNA][TDP-43]: n=4, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

Conclusions

While dose-dependent prevention of WT TDP-43 and all tested variants, strongly supporting future therapeutic applications. B. Bait generally appear more effective against P122H and R10B8E versus WT. C. Bait generally appear less effective against G238R versus WT. D. Bait appears to prefer different baits compared to most variants (AC)RNA prevents aggregation of P122H and R10B8E but not WT or other variants.

Future directions

Aggregation assays with side-by-side comparisons of WT and disease missense mutants of TDP-43

Electron microscopy and fluorescence microscopy of WT and disease missense mutants combined with select bait RNAs, to assess aggregate morphology and binding. Characterization of the RNA interaction of TDP-43 in control and patient-expressed neurons.

Acknowledgements

Thanks to Dr. Shorter and the entire Shorter lab, as well as my fond PhD advisor, Hil grant T32GM121020. Thanks to my thesis committee: Edward Lee, MD, PhD; Virginia Lee, PhD; Yoseph Barash, PhD.
COVID-19 and Psychosocial Functioning among Community Dwelling Older Adults Newly Prescribed Psychotropic Medication

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INTRODUCTION
- Compared to other age groups, older adults have experienced greater vulnerability to adverse effects from the COVID-19 pandemic
- Higher morbidity and mortality rates; greater adjustment to the use of technologies; potential for more social isolation
- However, a wealth of prior work suggests that older adults evidence more resilience when faced with life stressors than younger cohorts
- Older adults exhibit less stress reactivity and better emotion regulation, and report greater wellbeing
- Older adults also report more satisfying and rewarding social relationships
- Nonetheless, questions remain regarding whether the pandemic is associated with adverse mental health outcomes among older adults who may be at risk for poor outcomes
- It is also unclear whether social support, which has been shown to moderate, or “buffer”, the impact of stressors on mental health outcomes, may help mitigate the potential negative association between COVID-19 and wellbeing

OBJECTIVES
- Examine the prevalence of COVID-19 concerns and impacts reported by older adults
- Explore the association between COVID-19-related variables and various indices of mental health functioning
- Examine the moderating role of social support on wellbeing

METHODS: SAMPLE AND DESIGN
- n=237 community-dwelling older adults newly prescribed an antidepressant, benzodiazepine, or antipsychotic by a primary care provider and enrolled in the Support for Seniors Receiving Treatment And Intervention (SUSTAIN) collaborative mental health care management program.
- Enrollees completed clinical assessments of mental health symptoms, cognition, and functional status administered by a health technician.
- In May 2020, a questionnaire was added to address needs and concerns related to the COVID-19 pandemic and to help inform/facilitate care management.

METHODS: ASSESSMENTS AND MEASURES
- Socio-demographics (age, marital and financial status, sex, ethnicity)
- Depressive symptoms (Patient Health Questionnaire 9-item (PHQ-9))
- Anxiety symptoms (Generalized Anxiety Disorder 7-item scale (GAD-7))
- Overall mental and physical wellbeing (Veterans RAND 12-Item Health Survey (VR12-MCS and PCS))
- Perceived social support (item from the Dyadic Adjustment Scale)
- COVID-19 concerns and impacts (items adapted from the Coronavirus Health Impact Survey [CRISIS V0.2])

SAMPLE CHARACTERISTICS (n=237)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Mean (±SD)/N (%)</th>
<th>Observed Range</th>
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<tr>
<td>Age</td>
<td>77.0 (+/−6.3)</td>
<td>65−95</td>
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<tr>
<td>Female</td>
<td>186 (78.5%)</td>
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<td>Non-Hispanic White</td>
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<td>Married</td>
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<tr>
<td>Poor finances</td>
<td>26 (11.1%)</td>
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<tr>
<td>Depressive symptoms (PHQ-9)</td>
<td>9.4 (+/−6.2)</td>
<td>0−27</td>
</tr>
<tr>
<td>Anxiety symptoms (GAD-7)</td>
<td>6.3 (+/−5.4)</td>
<td>0−21</td>
</tr>
<tr>
<td>Overall mental wellbeing (MCS)</td>
<td>44.0 (+/−12.6)</td>
<td>8.0−70.2</td>
</tr>
<tr>
<td>Overall physical wellbeing (PCS)</td>
<td>31.3 (+/−12.0)</td>
<td>2.6−63.6</td>
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<tr>
<td>Perceived social support</td>
<td>4.0 (+/−1.1)</td>
<td>1−5</td>
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RESULTS: COVID-19 RELATED CONCERNS

- Most community-dwelling older adults receiving financial assistance for newly prescribed psychotropic medications in this sample reported no to a moderate degree of select concerns related to COVID-19.
- While contact with individuals outside the home decreased, the quality of relationships with friends/family remained stable, with social support buffering the impact of stress on overall mental wellbeing.
- Findings underscore variability in older adults’ resilience in the face of stressors, and highlight the importance of promoting and sustaining quality social interactions and supports in later life.
- Potential interventions for individuals reporting greater concerns/impacts and the long term health, financial, and psychosocial impacts of COVID-19 remain areas in need of further exploration.

REFERENCES

ACKNOWLEDGEMENTS
The research presented was supported by the Commonwealth of Pennsylvania Department of Aging, Pharmaceutical Assistance Contract for the Elderly (PACE/PACCENT). We would like to thank Thomas Snedden, Theresa Brown, and Debra Heller for their invaluable guidance and support of this work.
Regional distribution of tau pathology in subfields of hippocampus among phenotypic variants of AD and FTLD-Tau

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**Contact:** Sanaz Arezoumandan, sanaz.arezoumandan@pennmedicine.upenn.edu

### BACKGROUND

Alzheimer’s disease neuropathologic change (ADNC) is clinically heterogeneous and can present with a classic multi-domain amnestic syndrome (typical AD) or non-amnestic syndromes (atypical AD) that have been linked to focal cortical areas of tau deposition1,2 and regional sparing of tau pathology in the hippocampus3. However, there are limited data on the distribution of tau within the well-established anatomic framework of tau spread in hippocampal subfields or comparison with clinically-similar frontotemporal lobar degeneration tauopathies (FTLD-Tau). Here, we address these gaps with a comprehensive digital pathologic assessment of tau burden in hippocampal subfields across the clinopathologic spectrum of AD and FTLD-Tau.

### METHODS

Patients included autopsy-confirmed ADNC and FTLD-Tau with available hippocampal tissue (Table 1). AD patients were classified by clinical criteria into typical and atypical groups. Patients with limbic/neocortical Lewy body co-pathology or FTLD-Tau with intermediate-high ADNC co-pathology were excluded. We used previously validated methods4 to manually segment hippocampal subfields and quantify the percentage of area-occupied with DAB-positive pixels (%AO) in hippocampal subfields immunostained for p-tau (AT8) using QuPath v.0.2 (Figure 1). %AO values were normalized for each group using min-max normalization and linear mixed-effect (LME) models tested for regional differences of tau burden within groups while controlling for sex, age, and disease duration. A similar model tested between group differences in overall tau burden using typical/atypical AD clinical categorization as a fixed factor.

### RESULTS

1. Typical and atypical AD showed similar distribution of tau pathology across hippocampal subfields, reflecting greater relative burden of pathology in regions implicated as affected early in traditional Braak staging of AD (Figure 2).

2. There was no difference in the overall burden of tau pathology between typical and atypical AD (p=0.2).

3. The regional distribution of tau pathology in hippocampal subfields is divergent among pathological groups of ADNC, PSP, CBD, and PTD (Figure 2).

4. These distinct patterns of tau distribution were largely consistent within clinical subgroups of PPA and bvFTD (Figure 3).

### CONCLUSION

ADNC hippocampal tau burden appears to follow traditional Braak stages in atypical AD despite a focal cortical presentation during life. Distinct patterns of tau pathology in the hippocampal formation appear to exist among different tauopathies of ADNC and FTLD-Tau subtypes, suggesting disease-specific mechanisms of tau propagation that are relatively independent of clinical phenotype.

### REFERENCES


### ACKNOWLEDGEMENT

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### Table 1. Demographic and pathologic characteristics of patients in typical AD, atypical AD, and FTLD-Tau group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Typical AD</th>
<th>Atypical AD</th>
<th>FTLD-Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Male</td>
<td>20(52.6%)</td>
<td>19(50%)</td>
<td>15(50%)</td>
</tr>
<tr>
<td>Age at death</td>
<td>75(8.8)</td>
<td>70(9.9)</td>
<td>71(8.1)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>10.5(5.5)</td>
<td>9.3(4.1)</td>
<td>7.6(4.3)</td>
</tr>
<tr>
<td>Braak stage</td>
<td>B2+B+3-B3</td>
<td>B3-B4</td>
<td>B4</td>
</tr>
<tr>
<td>CERAD Neuritic plaque score</td>
<td>C2-C3</td>
<td>C3-C4</td>
<td>C4</td>
</tr>
<tr>
<td>Phenotypic variants</td>
<td>AD=38</td>
<td>PSP=38</td>
<td>bvFTD=15</td>
</tr>
<tr>
<td></td>
<td>PPA=19</td>
<td>CBS=10</td>
<td>PCA=2</td>
</tr>
</tbody>
</table>

**Note:** %AO values varied across groups, with highest values observed in typical AD and lowest in FTLD-Tau. Values were normalized for each group using min-max normalization and linear mixed-effect (LME) models.
Serial olfactory testing for the diagnosis of prodromal Parkinson’s disease in the Parkinson Associated Risk Syndrome (PARS) study

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Affiliation: 1. Parkinson’s Disease Research, Education and Clinical Center, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA. 2. Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA. 3. Institute for Neurodegenerative Disorders, New Haven, CT, USA

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Serial olfactory testing for the diagnosis of prodromal Parkinson’s disease in the Parkinson Associated Risk Syndrome (PARS) study

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Introduction

Olfactory testing has been proposed as a screening test for prodromal PD

PD is a highly prevalent neurodegenerative disorder. Despite its prevalence and imaging advances in our understanding of the pathogenesis of PD, enzymes to slow or prevent disease progression remain elusive. Early diagnosis has been one major obstacle for the development of disease modifying therapy. Olfactory testing has been proposed as a useful screening test for prodromal PD.

Estimates of the prevalence of olfactory impairments in clinically-manifest PD range from 50% to over 60%. Studies have also shown that hyposmia can precede clinical diagnosis and motor manifestations by at least 4 years, consistent with pathologic results demonstrating early lesions in the olfactory nucleus and olfactory bulb. Olfactory testing is relatively low cost and easy to administer, which also facilitates its use for screening.

Prior results have shown that hyposmia alone is sensitive for clinical diagnosis of PD. However, studies have also shown that hyposmia has lower specificity. Several approaches have been proposed to improve the test characteristics of olfactory testing, including combining impaired olfaction with other prodromal non-motor symptoms (e.g., RBD, constipation) or with DAT imaging results.

Pankinson Associated Risk Syndrome (PARS) Study

The Parkinson Associated Risk Syndrome (PARS) study was designed to test whether screening participants with olfactory testing and dopamine transporter imaging could identify participants at risk for developing PD. Olfactory assessments and screening questionnaires were mailed to 3296 eligible participants: 792 were enrolled. 80% of those were hyposmic. 203 of these hyposmic subjects (26%) were older than 60. 210 of the remaining 1064 normosmic subjects participated in the longitudinal cohort. Participants had an average age of 65 years and 60% were female.

Serial smell testing adds specificity with minimal effect on sensitivity

<table>
<thead>
<tr>
<th>One smell test</th>
<th>Repeat smell testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>No PD</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>24</td>
</tr>
<tr>
<td>Normosmia</td>
<td>0</td>
</tr>
<tr>
<td>Hyposmia on a single test</td>
<td>Sensitivity: 100%</td>
</tr>
<tr>
<td>Consistent hyposmia</td>
<td>Sensitivity: 86% Specificity: 61%</td>
</tr>
</tbody>
</table>

Consistently hyposmic patients were more likely to develop PD

Participants who were consistently hyposmic were more likely to develop clinical or imaging evidence of PD than participants who reverted to normosmia on repeat testing (left). Kaplan-Meier analyses demonstrated a significant difference in the cumulative incidence of development of PD (right). Boxplot shows the time of the second smell test, on average 1.42 years after initial assessment.

Consistent hyposmia has HR 10.2 for development of PD

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-64</td>
<td>1.05 (0.93-1.10)</td>
<td>0.24</td>
</tr>
<tr>
<td>65-74</td>
<td>1.19 (1.05-1.35)</td>
<td>0.03</td>
</tr>
<tr>
<td>75+</td>
<td>1.10 (1.04-1.17)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Clinical vs. imaging evidence of PD

There was a significant difference in the cumulative incidence for imaging evidence of PD (bottom, log-rank test; p=0.054) but only a trend for clinical diagnosis (top; p=0.10).

Conclusions

- Repeat olfactory testing is a simple and effective way to increase the specificity of olfactory testing in detecting prodromal PD, with minimal effect on the sensitivity, compared to a single test.

Acknowledgements

Support for the PARS study is provided by the Department of Defense award number W81XWH-10-1-0607. Pavan Vaswani is supported by the Edmond J. Safra Fellowship.
Analyzing the Future Time Perspective Scale in the Baseline Period in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study

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1Perelman School of Medicine at the University of Pennsylvania, 2School of Medicine, University of California Irvine

Introduction
- An Alzheimer’s disease (AD) biomarker test result can impact a person’s expectations of their future.
- We assessed the behavior of the FTP scale in a large sample of cognitively unimpaired older adults who underwent AD biomarker testing & disclosure as part of The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) Study.1
- The Future Time Perspective (FTP) scale can be used to measure a person’s perspective of their future given their risk of developing AD.

Methods
- 5665 participants in the A4 trial learned the result of an AD biomarker test: 1182 had elevated amyloid & 3310 had not.
- 4379 participants completed the FTP scale before (visit 1) & after (visit 3) result disclosure. Visits were <90 days apart.
- The FTP scale measures one’s sense of time remaining on 10-items (see table 2) rated on a 7-point scale. The average of item ratings was used for the “total score” in the analyses.
- Correlations, factor analysis, within-subject comparisons, & polytomous analyses explored scale performance & relationships among FTP, result disclosure, & amyloid status as measured continuously by SUVR, & categorically as elevated vs not elevated based on a SUVR cut point of 1.15.

Results
Table 1. Sample Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sample (N=5665)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>71.5 (4.8)</td>
</tr>
<tr>
<td>Race: White, % (n)</td>
<td>89.7 (5082)</td>
</tr>
<tr>
<td>Black, % (n)</td>
<td>4.3 (241)</td>
</tr>
<tr>
<td>Women (n)</td>
<td>58.7 (741)</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>28.7 (1.3)</td>
</tr>
<tr>
<td>SUVR, mean (SD)</td>
<td>1.1 (0.19)</td>
</tr>
<tr>
<td>Elevated amyloid, % (n)</td>
<td>28.8 (1177)</td>
</tr>
</tbody>
</table>

Table 2. Factor Analysis of Future Time Perspective (FTP) Scale Items (N=5664)

<table>
<thead>
<tr>
<th>No</th>
<th>Item Text</th>
<th>Uniqueness Coefficient</th>
<th>Factor (Loading)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Many opportunities await me in the future.</td>
<td>0.23</td>
<td>Factor 1 (0.75)</td>
</tr>
<tr>
<td>2</td>
<td>I expect that I will set many new goals in the future.*</td>
<td>0.24</td>
<td>Factor 1 (0.77)</td>
</tr>
<tr>
<td>3</td>
<td>My future is filled with possibilities.</td>
<td>0.23</td>
<td>Factor 1 (0.79)</td>
</tr>
<tr>
<td>4</td>
<td>Most of my life lies ahead of me.*</td>
<td>0.37</td>
<td>Factor 1 (0.70)</td>
</tr>
<tr>
<td>5</td>
<td>My future seems infinite to me.*</td>
<td>0.35</td>
<td>Factor 1 (0.69)</td>
</tr>
<tr>
<td>6</td>
<td>I could do anything I want in the future.</td>
<td>0.44</td>
<td>Factor 1 (0.68)</td>
</tr>
<tr>
<td>7</td>
<td>There is plenty of time left in my life to make new plans.</td>
<td>0.47</td>
<td>Factor 1 (0.70)</td>
</tr>
<tr>
<td>8</td>
<td>I have the sense that time is running out.</td>
<td>0.50</td>
<td>Factor 2 (0.56)</td>
</tr>
<tr>
<td>9</td>
<td>There are only limited possibilities in my future.</td>
<td>0.54</td>
<td>Factor 1 (0.50)</td>
</tr>
<tr>
<td>10</td>
<td>As I get older, I begin to experience time as limited.</td>
<td>0.48</td>
<td>Factor 2 (0.60)</td>
</tr>
</tbody>
</table>

*Item on 3-item short-scale, selected based on item-level changes from time 1 to time 2.

Table 3. Mean Scores and Mean Change on 10-Item and 3-Item Future Time Perspective (FTP) Scales (N=4379)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Time 1 Mean (95%CI)</th>
<th>Time 2 Mean (95%CI)</th>
<th>Mean Difference [T2-T1] (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full FTP</td>
<td>4.47 (4.44 to 4.50)</td>
<td>4.55 (4.51 to 4.58)</td>
<td>0.07 (0.05 to 0.10)</td>
</tr>
<tr>
<td>Elevated amyloid</td>
<td>4.42 (4.36 to 4.48)</td>
<td>4.45 (4.39 to 4.52)</td>
<td>0.04 (-0.01 to 0.08)</td>
</tr>
<tr>
<td>Not Elevated Amyloid</td>
<td>4.49 (4.45 to 4.53)</td>
<td>4.58 (4.54 to 4.62)</td>
<td>0.09 (0.06 to 0.11)</td>
</tr>
<tr>
<td>3 Item Short-Scale</td>
<td>3.91 (3.87 to 3.95)</td>
<td>4.09 (4.05 to 4.13)</td>
<td>0.18 (0.15 to 0.21)</td>
</tr>
<tr>
<td>Elevated Amyloid</td>
<td>3.82 (3.74 to 3.90)</td>
<td>3.94 (3.87 to 4.02)</td>
<td>0.12 (0.06 to 0.18)</td>
</tr>
<tr>
<td>Not Elevated Amyloid</td>
<td>3.94 (3.90 to 3.99)</td>
<td>4.15 (4.10 to 4.19)</td>
<td>0.20 (0.17 to 0.24)</td>
</tr>
</tbody>
</table>

- The mean in the decreased FTP-3 group was -0.89 points (95%CI -0.92 to -0.86), while the mean in the increased FTP group was 1.26 (95%CI 1.22 to 1.29). The elevated amyloid result (0.22, 95%CI 0.06 to 0.39) and better self-rated cognitive function (CFI, -0.03, 95%CI -0.05 to 0.01) made increased FTP-3 more likely than no FTP-3 change. In the same analysis, lower MMSE scores (-0.08, 95%CI -0.14 to -0.03) made increased FTP-3 more likely than no FTP-3 change.

Conclusions
- While mean FTP change after AD biomarker result disclosure is small (mean=0.18), result of polytomous analysis support the hypothesis that AD biomarker result knowledge may have clinically significant impacts on FTP (~2SD). FTP warrants further study in preclinical AD with attention to prognosis, well-being, & life plans.
- The 3-item FTP scale offers an option for a brief FTP measure in future research.

References

Acknowledgements: Dr Stites is supported by grants from the Alzheimer’s Association (AARF-17-528934) and the National Institute on Aging (K23AG065442). Thank you to all study participants.
The Impact of Amyloid Burden and APOE on Rates of Cognitive Impairment in Late Life Depression

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**Affiliation:** University of Pennsylvania

**Contact:** Emma Rhodes, emma.rhodes@penncardiology.upenn.edu

### Methods

**Participants**

120 older adults with Major Depressive Disorder enrolled in the Alzheimer’s Disease Neuroimaging Initiative – Depression (ADNI-D) project.

240 nondepressed older adults enrolled in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study.

- Matched on age, sex, education, MMSE, MCI status, and Aβ positivity

**Procedures**

All participants underwent core ADNI protocol:

- Neuropsychological testing, physical exam, blood draw for DNA/RNA, MRI, and PET imaging

- Aim 1: Assess the specific profile and rates of cognitive impairment in LLD relative to nondepressed controls matched on age, education, sex, MMSE, MCI diagnosis, and PET Aβ burden

- Aim 2: Assess the contribution of Aβ burden and APOE E4 genotype to cognitive performance in the whole sample

### Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LLD (n=120)</th>
<th>ND (n=240)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean 73.0</td>
<td>Mean 70.3</td>
<td>.34</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.5 (1.5)</td>
<td>16.0 (1.4)</td>
<td>.28</td>
</tr>
<tr>
<td>Gender*, No. female (%)</td>
<td>81 (67.5%)</td>
<td>90 (37.5%)</td>
<td>.008</td>
</tr>
<tr>
<td>Race, No. Caucasian (%)</td>
<td>108 (89.4%)</td>
<td>203 (84.7%)</td>
<td>.51</td>
</tr>
<tr>
<td>APOE Status, No. e4+ (%)</td>
<td>73 (60%)</td>
<td>80 (33%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APOE E4*, No. e4+ (%)</td>
<td>73 (60%)</td>
<td>80 (33%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Global WMH Burden</td>
<td>3.76 (4.1)</td>
<td>2.12 (4.7)</td>
<td>.64</td>
</tr>
<tr>
<td>Cognitive Status*, No. MCI (%)</td>
<td>38 (31.7%)</td>
<td>82 (34.6%)</td>
<td>.64</td>
</tr>
<tr>
<td>Arterial MCI, No. (%)</td>
<td>15 (12.5%)</td>
<td>80 (33.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE*</td>
<td>29.07 (1.62)</td>
<td>29.02 (1.20)</td>
<td>.39</td>
</tr>
<tr>
<td>GDS (15 items)</td>
<td>7.85 (4.05)</td>
<td>5.41 (3.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of MDD Episodes</td>
<td>2.54 (1.81)</td>
<td>2.12 (1.57)</td>
<td>.07</td>
</tr>
<tr>
<td>Age at First MDD Onset</td>
<td>32.76</td>
<td>32.76</td>
<td>1.00</td>
</tr>
<tr>
<td>MDD Onset, No. LLD (%)</td>
<td>13 (10.8%)</td>
<td>13 (10.8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Matching variable

### Results

**Aim 1**

- LLD showed higher rates of impairment relative to controls with 54.6% of the LLD sample demonstrating impairment in at least one cognitive domain compared to 42.9% of controls (H = 7.13, p = .008).

- LLD had significantly poorer performance and higher rates of impairment on AVLT learning and memory trials compared to controls.

**Aim 2**

- Aβ positivity was associated with worse performance on Logical Memory I (p = .044), Logical Memory II (p = .011) and Trail Making Test – B (p = .032)

- APOE E4 genotype was associated with worse performance on Logical Memory I (p = .022).

These relationships did not differ between LLD and ND.

### Conclusions

The LLD group showed higher rates of cognitive impairment driven by focal deficits in verbal learning and memory.

Alzheimer’s disease biomarkers were associated with worse performance on timed and shifting and story learning and memory, and these relationships were not impacted by depression status.

AD may account for a portion of previously reported multidomain cognitive impairment in LLD and highlight the potential for AD to confound studies of cognition in LLD.

### References

Background

Pathology is observed in characteristic regions correlating with phenotype

- Both distribution patterns of TDP-43 pathology and resulting clinical syndromes are distinct in FTLD-TDP, ALS, and HS-Aging.

Identifying shared and disparate genotype contributions to TDP-43 related phenotypes

- Underlying molecular heterogeneity that contributes to the observed clinical heterogeneity is not well understood.
- Case-control GWAS identified SNPs associated with risk of neurodegenerative diseases related to TDP-43 proteinopathies.
- Extent to which risk SNPs are shared or disparate across TDP-43 proteinopathies is unclear.
- Genetic variation across TDP-43 proteinopathies may contribute to phenotypic heterogeneity.

Providing a functional understanding of an observed genetic association

- Genetic associations with gene expression levels are expression quantitative trait loci (eQTLs).
- Inter genomic mechanism underlying shared or disparate risk from existing knowledge by mapping SNPs to eQTLs.
- eQTLs are highly tissue specific & should be evaluated in disease-relevant regions.
- How genetic variation affects gene expression levels across regions in TDP-43 proteinopathies is unclear.

Methods

We selected 69,360 SNPs that were common across prior case-control genome wide association study summary statistics for ALS, FTLD-TDP, and HS-Aging and exceeded a minimum threshold of risk (p<0.05) for at least one phenotype.

We then performed a weighted correlation analysis to identify modules of highly correlated SNPs.

Weighted correlation analysis approach to identify modules

- Assume SNPs associated with each phenotype are relevant to that disease.
- Find modules (clusters) of highly correlated SNPs.
- Make predictions by assuming that SNPs that strongly co-vary must share functionality.

Results

We then evaluated the associations between module SNPs and gene expression across disease-relevant regions from the Genotype-Tissue Expression project.

Results, continued

To determine whether module SNPs had biologically plausible regional eQTL associations, we generated 1000 bootstrap samples of pseudo-module assignments for each SNP-gene pair and compared the true number of significant eQTLs per module to this reference within each region.

Regional differences in gene expression observed by module

While certain differences were consistently observed across regions, several biologically plausible regional differences were observed.

Within the frontal cortex and spinal cord, but not the hippocampus, there were more SNP-gene pairs in the module representing the overlap between ALS and FTLD-TDP than in the pseudo-module.

In hippocampus, but not frontal cortex or spinal cord, there were more SNP-gene pairs in the module representing the overlap between FTLD-TDP and HS-Aging.

Conclusions

- Examining genotypes revealed modules of both shared and disparate correlated SNPs across phenotypes associated with TDP-43 proteinopathies which have biologically plausible regional eQTL associations.
- We suggest that genetic variation across TDP-43 proteinopathies may contribute to the phenotypic heterogeneity across these neurodegenerative diseases related in part to transcriptomic signatures of selective vulnerability in the brain.
**De-differentiation of functional networks in corticobasal syndrome**

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**Affiliation:** University of Pennsylvania

**Contact:** Saurabh Sihag, saurabh.sihag@pennmedicine.upenn.edu

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### Introduction

- Corticobasal syndrome (CBS) is a young onset neurodegenerative condition associated with motor and cognitive impairments.
- CBS is associated with fronto-parietal and limbic gray matter and white matter pathology and associated network dysfunction.
- The network segregation hypothesis suggests that differentiation of intrinsic networks supports domain-specific cognitive function.
- Here we use resting state (rsfMRI) to investigate functional network de-differentiation in CBS.

### Participants and Methods

<table>
<thead>
<tr>
<th></th>
<th>CBS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>age (y)</td>
<td>68.04 (7.13)</td>
<td>57.67 (12.14)</td>
</tr>
<tr>
<td>sex (m/f)</td>
<td>13/10</td>
<td>8/4</td>
</tr>
<tr>
<td>education (y)</td>
<td>15.04 (2.88)</td>
<td>16.33 (2.27)</td>
</tr>
<tr>
<td>disease duration (y)</td>
<td>2.95 (1.81)</td>
<td>-</td>
</tr>
<tr>
<td>global CDR (median)</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

- rsfMRI acquisition (TR: 3 sec, duration: ~10 min)
- Functional MRIs were processed through fmriPrep pipeline and subnetworks in functional connectomes were identified according to Schaefer’s atlas (7 network parcellation).
- We evaluated 3 measures of de-differentiation in functional connectivity

### Results

- **Volumetric differences (CBS vs Controls)**
- **Group differences in de-differentiation (CBS vs Controls)**

![Fig 1. Volume differences b/w CBS and Controls (ANOVA with age and gender as covariates)](image)

![Fig 2. ANCOVA analysis. Significant group differences between CBS and controls for somatomotor network for participation coefficient (left, \( p = 0.039 \) FDR-corrected) and within network connectivity (right, \( p-value = 0.04 \) FDR-corrected).](image)

**Fig 3. Ordinal regression analysis. Increase in disease severity (global CDR) was associated with de-differentiation between the salience and limbic connectivity (\( \beta = -37.21, p = 0.04 \) FDR-corrected) and within frontoparietal connectivity (right, \( p = 0.04 \) FDR-corrected).**

- **Relationships with disease severity**

### Conclusions

- Our results establish evidence that network de-differentiation is a feature of CBS, including increased participation coefficient and reduced within-network connectivity of the somatomotor network.
- Disease severity in CBS patients is characterized by salience-limbic connectivity and within subnetwork connectivity for frontoparietal subnetwork.

### References