UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Cognitive phenotypes: A novel taxonomy to studying the heterogeneity in temporal lobe epilepsy, associated neural correlates, and contributions of non-epilepsy factors

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Anny Reyes

Committee in charge:

University of California San Diego

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2022

The Dissertation of Anny Reyes is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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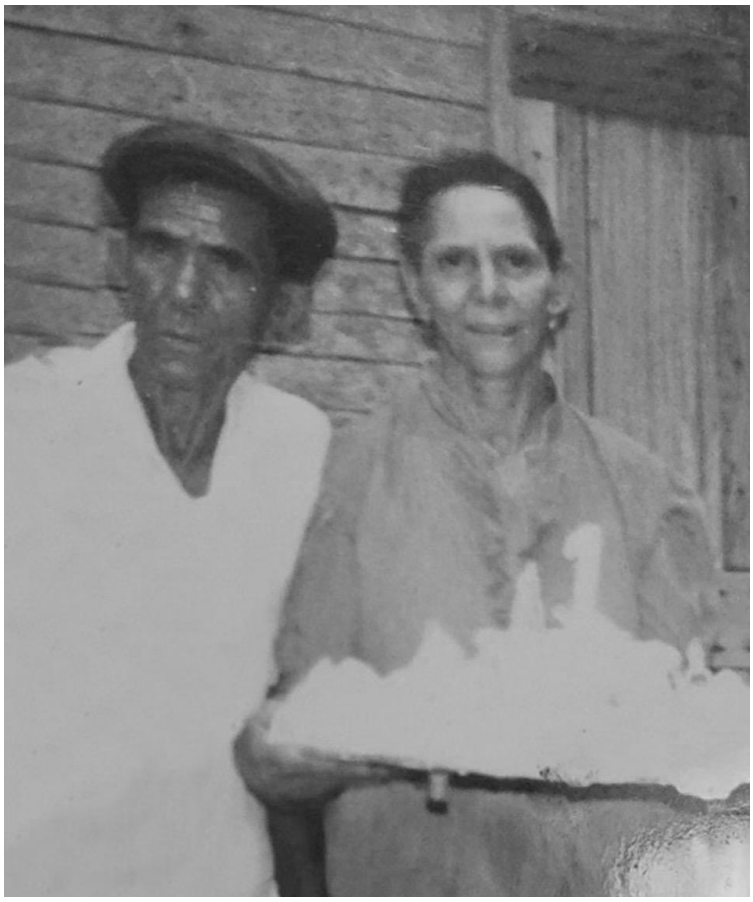
Chair

University of California San Diego
San Diego State University
2022

Dedication

I dedicate my dissertation and my doctoral degree to my grandparents Emilio Gomez and Enemencia Galvez Concepcion, who were not given the human right to an education. To my grandfather who I never had the honor to meet because we lost him to health disparities and to my grandmother who always protected me and loved me unconditionally, I hope that I carry the family legacy as the first member of our extended family to receive a PhD. You have inspired my commitment to improving the lives of those impacted by disease and disparities.



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If you want to go quickly, go alone. If you want to go far, go together -African Proverb

It takes a village to raise a child – African Proverb

Chapter 2, in full, is a reprint of the material as it appears in *Neurology* 2019, American Academy of Neurology; Chapter 3, in full, is a reprint of the material as it appears in *Epilepsia* 2020, Wiley-Blackwell on behalf of the International League Against Epilepsy; Chapter 4 contains materials that are under review in Brain Communications.

VITA

EDUCATION

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San Diego State University/University of California San Diego
Major area of study: Neuropsychology | Emphasis: Quantitative Methods

2016-2018 Master of Science in Clinical Psychology
San Diego State University

2014-2016 Master of Arts in General Psychology
Department of Psychology at New York University
Specialization: Neuropsychology

2007-2011 Bachelor of Science in Biology, Cum Laude
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GRANTS

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PEER REVIEWED PUBLICATIONS

Pubmed bibliography: https://www.ncbi.nlm.nih.gov/myncbi/anny.reyes.1/bibliography/public/
* Denotes shared first authorship | $^{+}$ Denotes lead or co-lead statistical analyses

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3. Hermann, B.P., Struck, A.F., Busch, R.M., **Reyes, A.,** Kaestner, E., & McDonald, C. R. (*2021)*. Moving Toward a Precision-Based Taxonomy of the Neurobehavioral Comorbidities of Epilepsy. *Nature Review Neurology; 731-746.* https://pubmed.ncbi.nlm.nih.gov/34552218/
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23. **Reyes, A.,** Kaestner, E., Bahrami, N., Balachandra, A., Hegde, M., Paul, B. M., Hermann, B.P., & McDonald, C. R. (*2019*). Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities. *Neurology, 92*(17): e1957-e1968. https://doi.org/10.1212/WNL.0000000000007370
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24. Erlich, T.*, **Reyes, A**.*, Paul, B., Uttarwar, V., Hartman, S., Mathur, K., Chang, Y.H.A., Hegde, M., Shih, J.J. & McDonald, C. R. (2019). Beyond depression: The impact of executive functioning on quality of life in patients with temporal lobe epilepsy. *Epilepsy Research, 149:*30-36. https://doi.org/10.1016/j.eplepsyres.2018.11.004
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27. Chang, Y. H. A., Javadi, S. S., Bahrami, N., Uttarwar, V. S., **Reyes, A.,** & McDonald, C. R. (2018). Mapping lexical-semantic networks and determining hemispheric language dominance: Do task design, sex, age, and language performance make a difference? *Brain and language*, *179:*42-50. https://doi.org/10.1016/j.bandl.2018.02.005
28. **Reyes, A.,** Holden, H. M., Chang, Y. H. A., Uttarwar, V. S., Sheppard, D. P., DeFord, N. E., DeJesus, S.Y., Kansal, L., Gilbert, P.E., McDonald, C. R. (2018). Impaired spatial pattern separation performance in temporal lobe epilepsy is associated with visuospatial memory deficits and hippocampal volume loss. *Neuropsychologia*, *111:*209-215. https://doi.org/10.1016/j.neuropsychologia.2018.02.009
29. **Reyes, A.,** Uttarwar, V. S., Chang, Y. H. A., Balachandra, A. R., Pung, C. J., Hagler Jr, D. J., Paul, B.M., McDonald, C. R. (2018). Decreased neurite density within frontostriatal networks

is associated with executive dysfunction in temporal lobe epilepsy. *Epilepsy & Behavior*, *78:187*-193. https://doi.org/10.1016/j.yebeh.2017.09.012

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32. Schaafsma, S.M., Gagnidze, K., **Reyes, A.,** Norstedt, N., Månsson, K., Francis, K., & Pfaff, D.W. (2017). Sex-specific gene-environment interactions underlying ASD-like behaviors. *Proceedings of the Academy of Sciences of the USA*. *114*(6):1383-1388. https://doi.org/10.1073/pnas.1619312114
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PUBLICATIONS UNDER REVIEW

35. Stasenko, A., Schadler, A., Kaestner, E., **Reyes, A**., Díaz-Santos, M., Połczyńska, M., & McDonald, C. R. (*Under review in Epilepsia*). Can Bilingualism Increase Neuroplasticity of Language Networks in Epilepsy?
36. Arrotta, K., **Reyes, A.**[+]**,** Kaestner, E., Barr, W.B., Hermann, B.P., McDonald, C. R. & Busch, R.M. (*Under review in Epilepsia*). Identifying Cognitive Phenotypes in Frontal Lobe Epilepsy: Moving Towards Precision Neuropsychology.

PUBLICATIONS IN PREPARATION

37. **Reyes,** Anny, Hermann, Bruce P., Busch, Robyn, Drane, D., Barr, William B., Hamberger, Marla J., Roesch, Scott, & McDonald, Carrie R. (*in preparation*). Moving towards a taxonomy of cognitive impairments in epilepsy: Application of latent profile analysis to 1,178 patients with temporal lobe epilepsy.
38. Ikanga, J., **Reyes, A.,** Tawo, Z., Zhao, L., Hill-Jarret, T., Epenge, E., Esambo, H., Esilakoy, C., Kavugho, I., Gikelekele, G., Alonso, A. Stringer, A., & Robinson-Lane, S. G. (*in preparation*). Predictors of Caregiver burden in primary caregiver of elderly Congolese with Suspected Alzheimer's Disease.
39. **Reyes, A**., Salinas, L., Busch, R. M., Block, C., Hessen, E., Loring D., Wilson, S. J., Baxendale, S., Hermann, McDonald, C. R., & Barr W., B. P. for the IC-CoDE Task Force. (*in preparation*). Cultural Considerations for the IC-CoDE: Implementing the Sociocultural Framework in the Diagnosis of Cognitive Disorders in Epilepsy.

ORAL PRESENTATIONS | SYMPOSIUMS

1. **Reyes, A. (Only Presenter).** (2022). *Cultural Considerations for the IC-CoDE: Implementing the Sociocultural Framework in the Diagnosis of Cognitive Disorders in Epilepsy.* As part of a symposium: International Classification of Cognitive Disorders in Epilepsy (IC-CoDE). International Neuropsychological Society Annual Meeting.
2. **Reyes, A. (Only Presenter).** (2021). *Cognitive phenotypes in Epilepsy: Implications for the study of brain-behavior relationships across epilepsy syndromes.* As part of Investigator Workshop: Multi-disciplinary Approaches for Cognitive and Affective Fingerprinting in Epilepsy. American Epilepsy Society Annual Meeting.
3. **Reyes, A.** (**Only Presenter**). (2021). *Integration of Diversity, Inclusion, and Equity Issues in Virtual Learning in Neuropsychology.* As part of a symposium: Training and Education in an Evolving Landscape- An Innovative Virtual Platform. Presentation at the American Psychological Association Annual Convention. Virtual Conference.
4. **Reyes, A.** (**Presenter**). (2021). *Discussion: Mentorship and Sponsorship of BIPOC Women/Non-Binary Gender Neuropsychology Trainees*. Presentation at the American Psychological Association Annual Convention. Virtual Conference.
5. **Reyes, A.** (**Only Presenter**). (2021). *Social Media: A Tool to Advance your Mission.* As part of a symposium: Social Media and Virtual Networking as a Trainee. Presentation at the American Psychological Association Annual Convention. Virtual Conference.
6. **Reyes, A.** (**Only Presenter**). (2021). *Retention of BIPOC Trainees and Creation of BIPOC Community Forum.* Presentation at UC San Diego Health Sciences Equity, Diversity, and Inclusion Community Fair.
7. **Reyes, A.** (**Only Presenter**). (2021). *Diagnostic Classification of Cognitive Disorders in Older Adults with Temporal Lobe Epilepsy.* As part of a symposium: Competing Models of Cognitive Decline and Dementia in Epilepsy. Presentation at the International Neuropsychological Society Annual Meeting. Virtual Conference.
8. Busch, R. M., Hogue, O., Miller M., Ferguson, L., McAndrews M.P., Hamberger, M.J., Kim, M., McDonald C.R., **Reyes, A.,** Drane, D. L., Hermann, B., Bingaman, W., Najm, I. M., Kattan, M. W., Jehi L., (2021). *Nomograms to Predict Memory Outcomes After Temporal Lobe Resection in Adults with Epilepsy.* Paper presentation at the International Neuropsychological Society Annual Meeting. Virtual Conference.
9. Arrotta, K., **Reyes, A.,** Kaestner E., Barr, W. B., Hermann, B., McDonald, C. R., Busch, R. M., (2021). *Identifying Cognitive Phenotypes in Frontal Lobe Epilepsy: Moving Towards Precision Neuropsychology.* Paper presentation at the International Neuropsychological Society Annual Meeting. Virtual Conference.
10. Carrasco, J. & **Reyes, A. (Presenter).** (2020). *Retention Strategies for Clinical Psychology Programs through Mental Health Lens*. As part of a symposium: Beyond Recruitment—Supporting the Success of Diverse Individuals in Neuropsychology. Presentation at the American Psychological Association Annual Convention.
11. **Reyes, A. (Only Presenter),** Kaestner, E., Ferguson, L., Jones, J., Seidenberg, M., Busch, R.M., Hermann, B.P., & McDonald, C. R. (2020*). Cognitive phenotyping in temporal lobe epilepsy: A comparison between clinical and data-driven approaches in 407 patients with refractory epilepsy.* Presentation at the 48th Annual Meeting of the International Neuropsychological Society.
    This abstract was selected for the INS Student Liaison Committee research award as one of the top abstract submitted by a graduate student.

12. **Reyes, A.** (**Presenter**) & Madore, M. (2019). *Integrating clinically relevant cultural information in assessments.* Presentation at the American Psychological Association Annual Convention.
13. **Reyes, A. (Only Presenter),** Paul, B.M., Marshall, A., Chang,Y.A, Bahrami, N., Gollan T.H., & McDonald, C.R. (2018). *Does bilingualism increase brain reserve or cognitive reserve in patients with temporal lobe epilepsy?* Presentation at the 46th Annual Meeting of the International Neuropsychological Society, Washington DC.
14. Santos, O. A., Love, C. E., Dumas, K., Scott, T. M., **Reyes, A. (Presenter),** Summers, A., Vogel, R., & Tureson, K. (2017). *Diversifying Neuropsychology from the Undergraduate Level to Board Certification.* Presentation at the 15th Annual Meeting of the American Academy of Clinical Neuropsychology in Boston, Massachusetts.

INVITED PRESENTATIONS| LECTURES | COLLOQUIA

1. **Reyes, A.,** (2021). *Cognitive phenotypes in Epilepsy: Moving Towards Precision Neuropsychology.* Presentation as part of Early Career BIPOC Scholars Neuropsychology Lecture Series at The Ohio State University.
2. **Reyes, A.** (2021). *Introduction to Neuropsychology.* Department of Social Sciences. Miami Dade College.
3. Skillings, J.L. **& Reyes, A**. (2021). *Psychologists as Leaders: An Important Professional Identity for New Challenges Ahead.* Presentation at American Psychological Association Practice Leadership Conference.
4. **Reyes, A.,** & Medina, L.D. *La Salud Mental en Pacientes con Epilepsia* (2021). Epilepsy Foundation of Colorado.
5. **Reyes, A.,** (2020). *Cognitive phenotypes in Epilepsy: Moving Towards Precision Neuropsychology.* Presentation as part of Connectomics in Epilepsy Workshop. Virtual workshop.
6. **Reyes, A.,** (2020). *Graduate School Funding: Before, During, and After.* Summer of Translational Aging Research for Undergraduates Program. Department of Neurology, Columbia University Medical Center.
7. **Reyes, A.,** (2020). *The Debt of Brain Science to the Epilepsies.* Psychological Sciences. University of San Diego.

POSTERS AND PUBLISHED ABSTRACTS

1. **Reyes, A.,** McBride, W. F., Anderson, K. M., Montgomery V., & Ray C., (2021). Closing the Gap in the Neuropsychology Pipeline via Mentorship Focusing on African American Students. National Academy of Neuropsychology Annual Meeting. Virtual Conference.
2. Whitlow, L., Beltran-Najera, I., **Reyes, A.,** Lerner, D., Dumas, K., Doriciak, K., Peraza, J., & Satos. O.A. (2021). *Barriers to Board Certification in Clinical Neuropsychology in a Diverse Sample of Trainees*. American Academy of Clinical Neuropsychology Annual Meeting. Virtual Conference.
3. Santos, O. A., **Reyes, A.,** Torres, S., Maietta, J., Tan, A., McBride W., Fox-Fuller, J.T., & Duggan, E.C. (2021). *Clinical Neuropsychology Trainee Forum: A Proposal for Impactful Student/Trainee Advocacy.* International Neuropsychological Society Annual Meeting. Virtual conference.
4. **Reyes, A.,** Lalani, S., Kaestner, E., Hooper, K. Chen A., Macari, A.C., Paul, B. M., Hermann, B.P., & McDonald, C. R. (2019). *The impact of cerebrovascular risk factors on postoperative*

memory decline in patients with left temporal lobe epilepsy. American Epilepsy Society, Baltimore, MD, USA.

5. Hermann, B., Conant, L.L , Cook, C., Hwang, G., Dabbs, K., Nair, V. A., Mathis, J., Rivera Bonet, C.N., Allen, L., Almane, D. N., Arkush, K., Birn, R., DeYoe, E. A., Felton, E., Maganti, R., Nencka, A., M., Raghavan, M., Sosa, V.N., Struck, A.R., Ustine, C., McDonald, C.R., Ustine, C., **Reyes, A.,** Kaestner, E. Prabhakaran, V., R. Binder, J.R., Meyerand, M.E. (20129). *Cognitive Phenotypes in Epilepsy are Associated with Unique Functional Connectivity Profiles: Findings from the Epilepsy Connectome Project.* American Epilepsy Society, Baltimore, MD, USA.
6. Balachandra, A., Kaestner, E., Bahrami, N., **Reyes, A.,** Lalani, S., Bonilha. L., & McDonald, C. R. (2019). *Predicting Verbal Memory Impairment Using Structural Connectomics in Drug-Resistant Temporal Lobe Epilepsy*. American Epilepsy Society, Baltimore, MD, USA.
7. Kaestner, E., Balachandra, A., Bahrami, N., **Reyes, A.,** Lalani, S., Bonilha. L., & McDonald, C. R. *The White Matter Connectome as an Individualized Biomarker of Language Impairment in Temporal Lobe Epilepsy.* American Epilepsy Society, Baltimore, MD, USA.
8. Tibs, M.D., Huynh-Le, M., **Reyes, A.,** Macari, A.C, Karunamuni, R., Tringale, K., Burkeen, J., Marshall, D., McDonald, C.R., & Hattangadi, J.A. (2019). *Longitudinal Analysis of Depression and Anxiety Symptoms as Independent Predictors of Neurocognitive Function: Prospective Trial of Brain Tumor Patients Receiving Radiotherapy [RT*]. American Society for Radiation Oncology Annual Meeting, Chicago, IL, USA. International Journal of Radiation OncologyBiologyPhysics. 105(1):S80 DOI: 10.1016/j.ijrobp.2019.06.543
9. Tibbs, M.D., Huynh-Le, M.P., **Reyes, A**., Macari, A.C., Karunamuni, R., Tringale, K.R., Burkeen, J., Marshall, D.C., McDonald, C.R., Hattangadi-Gluth, J.A. (2019). *Microstructural Injury to Perisylvian White Matter Predicts Language Decline after Brain Radiotherapy [RT]: Quantitative Analysis of a Prospective Trial.* American Society for Radiation Oncology Annual Meeting. Chicago, IL, USA. International Journal of Radiation OncologyBiologyPhysics 105(1): S79-S80. DOI: 10.1016/j.ijrobp.2019.06.542
10. Huynh-Le, M.P., Tibs, M.D., Karunamuni, R., Tringale, K., **Reyes, A.,** Connor M., Moiseenko, V., McDonald, C.R., & Hattangadi, J.A. (2019). *Diffusion Imaging Biomarkers of Corpus Callosum Injury and Dose-Dependent Volumetric Changes Correlate with Attention and Processing Speed Changes after Brain Radiotherapy*. American Society for Radiation Oncology Annual Meeting. Chicago, IL, USA. International Journal of Radiation OncologyBiologyPhysics. 105(1): S79. DOI:10.1016/j.ijrobp.2019.06.541
11. **Reyes, A.,** Tureson, K., Arias, J., Peraza, J., Gonzalez, D., Lerner, D., & Santos, O. (2019). *Barriers and Concerns Regarding Board Certification in Clinical Neuropsychology: A Program Evaluation.* Hispanic Neuropsychological Society Conference, New York, NY, USA.
12. **Reyes, A**., Cervantes, V., Hooper, K., Paul, B.M., & McDonald, C. R. (2019). *Differential impact of cerebrovascular risk factors on processing speed and executive function in patients with temporal lobe epilepsy.* International Neuropsychological Society Annual Meeting, New York, NY, USA.
13. **Reyes, A**., Marshall, A., Balachandra, A. R., Hegde, M., Paul, B. M., & McDonald, C. R. (2018). *Differential pattern of white matter network abnormalities across cognitive phenotypes in temporal lobe epilepsy.* American Epilepsy Society Annual Meeting, New Orleans, LA.

This abstract was selected for the AES Grass Young Investigator Award, which recognizes outstanding young investigators conducting research in basic or clinical neuroscience related to epilepsy.

14. **Reyes, A**., Uttarwar, V. S., Chang, Y. H. A., Balachandra, A. R., Pung, C. J., Hagler Jr, D. J., Paul, B. M., McDonald, C. R. (2018). *Decreased neurite density within frontostriatal networks is associated with executive dysfunction in temporal lobe epilepsy.* American Academy of Clinical Neuropsychology Annual Meeting.
15. Scott, T. M., **Reyes,** A., Summers, A., Vogel, R., Tureson, K., Dumas, K., Love, C. E., & Santos, O. (2018). *Diversifying neuropsychology from the bottom up: Outcomes from a student pipeline workshop.* International Neuropsychological Society Conference, Washington, D.C., USA.
16. **Reyes, A.,** Holden, H. M., Chang,Y. A., Uttarwar, V. S., Sheppard, D. P., DeFord, N. E., DeJesus, S. Y., Kansal, L., Gilbert, P. E., & McDonald, C.R. (2017*). Impaired spatial pattern separation in temporal lobe epilepsy is associated with visuospatial memory deficits and hippocampal volume loss.* American Psychological Association Annual Convention.
17. **Reyes, A.**, Theses, T., Kuzniecky, R., Devinsky, O., McDonald, C., Jackson, G., Vaughan, D., & Blackmon, K. (2017). *Amygdala enlargement: Temporal lobe epilepsy subtype or nonspecific finding*? American Academy of Clinical Neuropsychology Annual Meeting. Boston, MA, USA.
18. **Reyes, A.**, Theses, T., William, B., Morrison, C., McDonald, C., Kuzniecky, R., Devinsky, O., & Blackmon, K. (2017). *Reduced frontal lobe neuronal activity at rest contributes to executive function decrements in patients with temporal lobe epilepsy.* International Neuropsychological Society Annual Meeting.

    This abstract was selected for the INS Student Liaison Committee research award as one of the top abstract submitted by a graduate student.
19. Chang, Y.-H. A., Kemmotsu, N., Leyden, K. M., Kucukboyaci, N. E., Iragui, V. J., Tecoma, E. S., Kansal, L., Norman, M. A., Compton, R., Ehrlich, T. J., Uttarwar, V. S., **Reyes, A.**, Paul, B. M., & McDonald, C. R. (2016). *Integrating Structural, Functional, and Diffusion MRI to Explain Language Impairment in Patients with Left Temporal Lobe Epilepsy.* 4th Annual Postdoctoral Research Symposium, University of California - San Diego.
20. **Reyes, A**., LaBode-Richman, V., & Barr, W. B. (2016). *The WHO-AVLT recognition trial: Validation for a new malingering index for Spanish-speaking patients.* National Academy of Neuropsychology Annual Conference.
21. **Reyes, A**., Thesen, T., Wang, X., Hahn, D., Yoo, D., Kuzniecky, R., Devinsky, O., & Blackmon, K. (2016). *The fractional amplitude of low-frequency fluctuation on resting state fMRI differentiates temporal lobe epilepsy with and without mesial temporal sclerosis*. International Neuropsychological Society Annual Meeting.
22. **Reyes, A.**, Gagnidze, K., Norstedt, N., Månsson, K., Pfaff, D.W., & Schaafsma, S.M. (2015). *Prenatal stress sex specifically affects social recognition and ultrasonic vocalization in a mouse model for autism spectrum disorders.* American Psychological Association Annual Convention.
23. **Reyes, A.**, Gagnidze, K., Norstedt, N., Månsson, K., Pfaff, D.W., & Schaafsma, S. M. (2015). *Prenatal stress-sex specifically affects social recognition in a mouse model for autism spectrum disorders*. Association for Psychological Sciences Annual Convention.

24. **Reyes, A.,** Barr, W., Devinsky, O., Kuzniecky, R., Thesen, T., & Blackmon, K. (2015). *Neuroanatomical basis of anxiety in temporal lobe epilepsy.* New York University Department of Psychology MA Research Conference.
25. **Reyes, A.,** Lee, A. W., & Pfaff, D. W. (2008). *Effects of Estrogen, Thyroid Hormone, and Progesterone on Gene Expression. Leadership* Alliance: National Symposium.

TEXT CHAPTERS & BOOK REVIEWS

1. **Reyes, A.** Being a Woman of Color in Graduate School. In: Helms J, Rogers D, eds. *Majoring in Psychology.* Hoboken, NJ: Wiley & Sons; 2021.

DIVERSITY-RELATED LEADERSHIP & PROFESSIONAL SERVICE

2021-Present Early-Stage Social Engagement Leader for the Alzheimer's Association San Diego/Imperial Valley
2021-Present Bilingual Community Educator for the Alzheimer's Association San. Diego/Imperial Valley Chapter
2021-Present International League Against Epilepsy- Diversity, Equity, & Inclusion Taskforce **Student Representative**
2021-Present New2Neuropsychology- **Advisor**
2020-Present AACN Relevance 2050 Peer Consultation Network subcommittee
2021-Present Emory University Diversity & Inclusion Committee
2021 UCSD Department of Psychiatry Strategic Planning for Hiring URM Faculty
2021 Dr. Jennifer Kelly's Presidential Taskforce- Health Equity Roundtable
2021-Present Women in Neuropsychology-Adhoc Special Project Committee
2020-Present Society for Black Neuropsychology – **Co-chair of Mentoring, Education, & Training Committee**
2020-Present Hispanic Neuropsychological Society Student Association Committee
2020-Present Cultural Neuropsychology Council (CNC)- **Co-founder**
2020-Present UC San Diego Department of Psychiatry Anti-Racism Working Group
2020-Present Clinical and Counseling Graduate Students for Diversity, Equity, and Inclusion
2020 Invited to the NIH/NINDS Training and Diversity Discussion Panel
2019- Present SDSU/UC San Diego Joint Doctoral Program Diversity Committee
2020-2021 Hispanic Neuropsychological Society Science Task Force
2020-2021 APA Division 40, EMA Mentoring Program – **Mentor**
2019- 2020 Hispanic Neuropsychological Society Mentoring Program- **Mentor**
2018- 2020 APA Division 40 Public Interest Advisory Committee- Ethnic Minority Affairs Subcommittee | **Student Representative**
2016- Present American Academy of Clinical Neuropsychology's Relevance 2050 Student Pipeline Subcommittee | **Founding Member & Student Representative**
2016- 2021 Member of UC San Diego Department of Psychiatry Diversity Committee

PROFESSIONAL SERVICE

2021 UCSD Department of Psychiatry County Psych Project Development
2021 Curing the Epilepsies Conference/NINDS Epilepsy Research Benchmarks- Volunteer
2020 SDSU/ UC San Diego Joint Doctoral Program Student Selection Committee
2020-2021 UC San Diego/VA Clinical Neuropsychology Seminar Planning Committee

2020-Present Co-director of SCN Student Leadership Development Program
2020-Present Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment | **Journal Club Moderator**
2020-Present Co-founder and committee member of "KnowNeuropsychology Didactic Series"
2020-2021 National Academy of Neuropsychology Clinical Research Grants Committee
2019 SDSU/UC San Diego Joint Doctoral Program Student Selection Committee
2018- 20211 Epilepsy-Neuropsychology Organization- INS Special Interest Group **Trainee Liaison**
2016- 2019 APA Division 40, Association of Neuropsychology Students & Trainees (ANST) **Professional Development Officer**
2015-2016 APA Division 40, Association of Neuropsychology Students & Trainees (ANST) **Interest Group Representative New York University**
2014-2016 Association for Psychological Science **Student Caucus Campus Representative**
2014-2016 NYSPA, Neuropsychology Division **| Student Representative**
2014-2015 APAGS Advocacy Coordinating Team | **Campus Representative**

PROFESSIONAL AFFILIATIONS AND MEMBERSHIPS

2020- Present Association of Black Psychologists
2020- Present Asian Neuropsychological Association
2020- Present Society for Black Neuropsychology
2019- Present National Academy of Neuropsychology
2016- Present Society for Science of Clinical Psychology
2015- Present International Neuropsychological Society
2015- Present Society for Neuroscience
2015- Present Hispanic Neuropsychological Society
2014- Present Association for Psychological Science
2014- Present American Psychological Association and Division 40
2014- 2016 New York Psychological Association

EDITORIAL BOARDS & REVIEWER EXPERIENCE

Ad Hoc Reviewer– *Journal of Neuroradiology; Epilepsy & Behavior Reports; Frontiers in Neurology; Epilepsy Research; Archives of Clinical Neuropsychology; Brain Imaging & Behavior; The Clinical Neuropsychologist; Epilepsia; Epiletic Disorders; Epilepsy & Behavior; Frontiers in Psychology; Neuropsychology Review; Seizure European Journal of Epilepsy; Neuropsychology; Journal for the International Neuropsychological Society*

ABSTRACT OF THE DISSERTATION

Cognitive phenotypes: A novel taxonomy to studying the heterogeneity in temporal lobe epilepsy, associated neural correlates, and contributions of non-epilepsy factors

by

Anny Reyes

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2022
San Diego State University, 2022

Professor Carrie R. McDonald, Chair

Temporal lobe epilepsy (TLE) is characterized by debilitating and progressive cognitive impairment, but there is significant variability in the nature and severity of impairment across patients. Cognitive phenotyping is a promising approach for understanding the heterogeneity within TLE. This 3-paper dissertation aimed to identify the neural correlates associated with cognitive phenotypes, investigate methods for defining phenotypes, and examine epilepsy and health-related factors associated with each phenotype. Study 1 (Reyes et al., 2019) identified four distinct cognitive phenotypes in TLE (N = 70; 36.14 average age; 13.34 average education; 52% female) based on neuropsychological measures of memory and language. Each phenotype was associated with a unique pattern of white matter (WM) abnormalities. Patients with generalized impairment demonstrated widespread WM alterations, those with domain-specific impairment

demonstrated regional WM alterations, and those with no impairment demonstrated WM patterns similar to controls. Study 2 (N = 407; 36.36 average age; 13.22 average education; 55% female; Reyes et al., 2020) compared phenotype classifications based on a neuropsychological approach (clinically-driven) versus cluster analysis (data-driven). Both approaches identified three unique cognitive phenotypes with strong agreement (kappa=.716); however, cluster analysis misclassified 12% of impaired patients as having normal cognition. These findings led to the question: could a more robust, person-centered, data-driven approach improve phenotyping? Study 3 (N = 1,178; 37.76 average age; 13.94 average education; 57% female; Reyes et al., under review) used latent profile analysis (LPA) to test several models of cognitive phenotyping and adjudicate the impact of missing data to identify the "best" taxonomy. LPA revealed that the three-class model was the optimal solution (entropy=.816) and the most robust to missing data with a 98.98% agreement with an imputed dataset (kappa=.983). Preliminary analyses revealed lower subcortical volumes in patients with generalized impairment and higher intracranial volumes in those with an intact profile. There was a differential association between hyperlipidemia and cognitive performance across phenotypes. These studies demonstrate unique cognitive phenotypes exist within TLE that are stable across investigations and approaches and are characterized by distinct neural signatures. Knowledge of these phenotypes could drive cognitive and neuroanatomical taxonomies in epilepsy and enhance individualized prediction of cognitive trajectories.

Chapter 1:

Introduction

Epilepsy

Epilepsy is the fourth most common neurological disorder following migraine, dementia, and stroke, affecting approximately 50 million people worldwide (G. S. Bell, Neligan, & Sander, 2014). Epilepsy is defined as "*a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition*" (Fisher et al., 2005). Thus, the epilepsy-related comorbidities associated with cognition, psychiatric health, vascular health, and psychosocial outcomes are now part of the definition of epilepsy (Keezer, Sisodiya, & Sander, 2016). Given that cognitive impairment has been associated with poorer quality of life, decreases in functional independence, lower educational and occupational attainment, and overall significant life burden (Mitchell, Kemp, Benito-León, & Reuber, 2010), understanding the impact of epilepsy and epilepsy treatment on cognition has been an area of research inquiry for over a century. Specifically, the **National Institute of Neurological Disorders and Stroke** has developed benchmarks for epilepsy research and one of these benchmarks is to "*Limit or prevent adverse consequences of seizures and their treatment across the lifespan"* (Poduri & Whittemore, 2020). Although significant progress has been made in our understanding of the cognitive comorbidities of epilepsy, patients with epilepsy continue to be impacted by cognitive dysfunction. As such this area of research continues to be a priority in order to inform clinical care and outcomes and improve the quality of life of individuals living with epilepsy.

Cognitive dysfunction in temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and it is characterized by seizures originating from the temporal lobes with the most common pathology being mesial temporal sclerosis (MTS; atrophy and gliosis of the hippocampus) (Engel Jr, 1996). TLE is the most refractory to antiseizure medications (ASM) which means that a large proportion of patients experience recurrent seizures, making TLE a chronic neurological condition (Tellez-Zenteno & Hernandez-Ronquillo, 2012). For many of these patients, epilepsy surgery which consists of resection of the epileptogenic brain tissue is a treatment option to ameliorate seizure frequency (Choi et al., 2008).

Cognitive dysfunction is a highly prevalent and debilitating comorbidity in patients with TLE (B. Bell, Lin, Seidenberg, & Hermann, 2011; Saling, 2009; Stretton & Thompson, 2012). For example, up to 80% of patients with TLE demonstrate impairments in at least one cognitive domain including language, memory, and executive function, with a subset of patients demonstrating progressive cognitive deterioration (C. Helmstaedter, Hermann, B., Lassonde, M., Kahane, P., & Arzimanoglou, A, 2011; C. Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003; B. P. Hermann et al., 2006). Furthermore, TLE is associated with accelerated brain and cognitive aging, placing patients are increased risk for developing dementia later in life, including Alzheimer's disease (Sen, Capelli, & Husain, 2018). In addition, patients with TLE who undergo unilateral anterior temporal lobectomy (ATL) or other surgical procedures to reduce seizure frequency are at risk for additional cognitive decline (C. Helmstaedter, 2013; C. Helmstaedter et al., 2003).

Beyond the Lesion/localization Model

The lesion model which assumes a direct relationship between brain structure and behavior has been the predominant approach to studying cognition in epilepsy (B. P. Hermann et al., 2021). This approach presumes that for the focal epilepsies (i.e., seizures originating from a specific area

in the brain) the effects of seizures on brain structure and function are restricted to the epileptogenic zone (Hennric Jokeit & Schacher, 2004). This approach yielded syndrome-specific cognitive profiles based on the location of the seizure origin (Figure 1.1). For example, in TLE cognitive impairments were predicted to be restricted to domains associated with temporal structures such as episodic memory (Saling, 2009). Other syndrome-specific cognitive profiles include executive dysfunction in frontal lobe epilepsy (FLE; Milner, 1975), visuospatial and constructive disorders in parietal lobe epilepsy (Hennric Jokeit & Schacher, 2004), and visuoperceptual and spatial impairments in occipital epilepsy (Germanò et al., 2005). The lesion model approach has been important for the fields of neuropsychology and neuroscience, as the study of brain-behavior relationships arose from lesion studies. For example, patient H.M. the most studied individual in the fields of neuropsychology and neuroscience, received bilateral ATL (i.e., removal of both hippocampi) to ameliorate his seizures due to TLE, however, this led to profound amnesia (Squire, 2009). Through H.M.'s unfortunate outcome the field has established key principles on memory organization and many other lesion studies have provided important insights into brain organization and function.

However, decades of research in the neuropsychology of epilepsy have demonstrated that the cognitive impairment in the focal epilepsies are more generalized and widespread than hypothesized by the lesion/localization model. For example, patients with TLE also demonstrate impairments in language and executive function (B. Bell et al., 2011; Sherman et al., 2011; Stretton & Thompson, 2012) and those with FLE demonstrate deficits in language (Arrotta et al., 2021; Stretton & Thompson, 2012), all cognitive abilities associated with brain structures beyond the temporal and frontal lobes, respectively. Furthermore, patients with seizures originating from the non-dominant hemisphere (i.e., hemisphere not critical for language function) also demonstrate

deficits in the domain of language (B. P. Hermann, Seidenberg, Schoenfeld, & Davies, 1997; Kaestner et al., 2019). There is also considerable variability in the nature and severity of cognitive impairments observed across patients with the same epilepsy disorder with some demonstrating generalized impairment and others showing relatively normal cognitive profiles (Arrotta et al., 2021; Dabbs, Jones, Seidenberg, & Hermann, 2009; B. Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; B. P. Hermann et al., 1997). Lastly, there are overlapping features in the neuropsychology profiles observed across epilepsy disorders despite patients demonstrating very different clinical syndromes (B. P. Hermann et al., 2021). These findings highlight that the lesion model fails to capture the heterogeneity in cognitive and behavioral disturbance observed across a range of epilepsy syndromes.

Underlying neurobiological networks in epilepsy

Perhaps the most compelling evidence that the lesion/localization model may no longer be applicable in the study of the neurobehavioral comorbidities of epilepsy, are neuroimaging and neuropathological findings demonstrating brain abnormalities beyond the epileptogenic focus in the focal epilepsies (Allone et al., 2017; Hatton et al., 2020; B. P. Hermann et al., 2021; Christopher D Whelan et al., 2018). For example, TLE is now understood to represent a network disorder given the brain abnormalities observed that extend far beyond the temporal lobe (B. Bell et al., 2011; Bernasconi et al., 2004; Leyden et al., 2015; C. D. Whelan et al., 2018). Specifically, patients with TLE demonstrate widespread alterations in white matter (WM) (Hatton et al., 2020; Leyden et al., 2015), cortical thinning (McDonald et al., 2008; Mueller et al., 2009; C. D. Whelan et al., 2018), reduced regional brain activity (Reyes et al., 2016), and glucose hypometabolism (Arnold et al., 1996). Neuropathological studies have also demonstrated extratemporal pathology in postmortem brains of patients with TLE, including the prefrontal and orbitofrontal cortices (Blanc et al., 2011).

Importantly, studies of structure-function relationships in TLE have also shown that these diffuse brain abnormalities are associated with a wide range of cognitive deficits (Allone et al., 2017; Leyden et al., 2015). Similar widespread neuroimaging findings have been found in other focal epilepsies and a series of investigations through the Enhancing NeuroImaging and Genetics through Meta- Analysis (ENIGMA- Epilepsy) initiative have demonstrated shared similarities in brain abnormalities across a range of epilepsy disorders (Hatton et al., 2020; C. D. Whelan et al., 2018). Although advanced neuroimaging has enhanced our understanding of the extent of epileptogenic networks in the brain, the relationship between these network alterations and the heterogeneity in cognitive impairment observed across epilepsy disorders is less understood.

Cognitive Phenotyping: Towards a New Taxonomy

An alternative approach to studying the neurobehavioral comorbidities of epilepsy is to aggregate patients with the same epilepsy syndrome into distinct groups based on their patterns of cognitive impairment (B. P. Hermann et al., 2021). In this approach, *latent groups* or *cognitive phenotypes* are identified by either data-driven methods such as cluster analyses or by utilizing a clinical cognitive criteria where patients are assigned to groups based on *a priori* defined classification (e.g., patients with impairments in memory). The relationships between epilepsy-related clinical features, cognition, and neuroimaging correlates are then examined within each unique phenotype (Figure 2.1). Inferences from the distinct phenotypes can then be applied to individual patients that demonstrate similar cognitive profiles. This innovative approach aligns with *precision medicine* which is defined as "*an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person*" (Josephson & Wiebe, 2021). Importantly, this approach allows for the integration of other factors known to impact cognition (e.g., vascular risk factors, cognitive reserve factors, social

determinants of health) providing a method to holistically study the heterogeneity of cognitive impairment in epilepsy which can inform the development of interventions aimed at reducing the negative impact of cognitive decline on quality of life and functional independence (Figure 1.3).

The study of cognitive phenotypes in epilepsy was pioneered by Dr. Bruce Hermann, and in his first study, he and his colleagues identified three major cognitive phenotypes in a group of patients with TLE (B. P. Hermann et al., 2006). These cognitive phenotypes included a group of patients with *generalized* impairment (i.e., impairment across multiple cognitive domains assessed), a group of patients with domain-specific impairments (i.e., language and memory), and a minimally impaired group. They also demonstrated that patients with generalized impairments were older, had longer disease duration, and were taking more anti-seizure medications (ASMs) relative to patients with minimally impaired profiles. These patients also showed abnormal brain volumes and had the most cognitive progression over a four-year course. Thus, a greater disease burden was associated with widespread cognitive deficits and brain abnormalities. In a follow-up study, these same cognitive phenotypes demonstrated unique patterns of cortical thinning, with patients with generalized cognitive impairment exhibiting the most cortical thinning and atrophy in subcortical structures relative to healthy controls (Dabbs et al., 2009). Interestingly, patients with minimally impaired profiles showed the least cortical thinning and atrophy. These findings highlight that aggregating patients into one group based on their epilepsy syndrome may obscure important neuroanatomical correlates that are more evident when patients are grouped based on their cognitive profiles. Given the role of neuroimaging in epilepsy surgical decision making, identifying unique neuroanatomical signatures within each phenotype can inform treatment decisions and the prediction of clinical postoperative outcomes.

Looking Beyond Epilepsy: Utilizing Phenotyping to Identify Unique Factors Impacting Cognition

As mentioned above, the phenotype approach provides a framework that incorporates other risk and protective factors known to impact cognition rather than attributing the cognitive deficits to the epilepsy syndrome alone (B. P. Hermann et al., 2021). The epilepsy literature has identified several clinical factors that are associated with cognitive dysfunction in epilepsy, including the presence of MTS or other structural pathology on MRI (Wieser & Epilepsy, 2004), the type and frequency of seizures (C. Helmstaedter et al., 2003; Majak & Pitkanen, 2004), age of seizure onset (B. Hermann et al., 2002), duration of disease (Oyegbile et al., 2004), and the effects of ASM (Meador, 2002). However, very little is known about other health-related or individual factors that may contribute to the variability observed in the neuropsychological syndrome of TLE. Via the phenotyping approach researchers can identify both the risk and protective factors associated with cognitive functioning within each phenotype, providing more precise information on cognitive risk for each individual patient. For example, one can hypothesize that patients with *generalized* impairments may present with health-related risk factors that are further exacerbating the epilepsy burden and those with relatively *intact* cognitive profiles may present with increased cognitive or brain reserve, mitigating the impact of epilepsy on cognition.

There is a growing literature focused on identifying risk factors for cognitive decline in healthy individuals and clinical populations. Specifically, vascular, inflammatory, and metabolic biomarkers have been shown to be associated with accelerated cognitive aging and dementia (Barnes & Yaffe, 2011; Baumgart et al., 2015; Daviglus et al., 2010; Knopman et al., 2001; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Despite some evidence that patients with TLE are at increased risk for progressive neurophysiological and structural brain changes that result in

reduced brain health and early cognitive decline (B. P. Hermann et al., 2006; H. Jokeit & Ebner, 1999), the effects of important health-related risk factors on cognition are rarely examined in TLE or epilepsy in general (Baxendale et al., 2015; Hamed, 2014; B. Hermann, Loring, & Wilson, 2017; B. P. Hermann, Sager, Koscik, Young, & Nakamura, 2017). Hermann et al. (B. P. Hermann et al., 2017) found that aging adults with chronic epilepsy demonstrate abnormalities in vascular, inflammatory, and metabolic biomarkers that are associated with poorer performance on neuropsychological measures of memory, psychomotor speed, and working memory. The authors emphasized that although the available literature has focused on epilepsy-specific factors that impact cognition, research should shift attention to health-related risk factors that are modifiable in nature. There is an emerging interest in understanding the effects of modifiable factors such as hypertension, obesity (Beydoun, Beydoun, & Wang, 2008; Sellbom & Gunstad, 2012), physical inactivity (Hamer & Chida, 2009; Rolland, Abellan van Kan, & Vellas, 2008), and smoking (Anstey, von Sanden, Salim, & O'Kearney, 2007; Zhong, Wang, Zhang, Guo, & Zhao, 2015) on accelerated cognitive aging in the general population and other neurological disorders. These factors would not only improve overall health and cognition but could also improve patients' quality of life.

In a postoperative study, I demonstrated that cerebrovascular risk factors (CVRFs) were associated with greater postoperative verbal memory decline in a group of patients with TLE (Reyes, Lalani, et al., 2020). Specifically, we showed that higher body mass index (BMI) was associated with greater memory deficits across different dimensions of memory and that BMI mediated the relationship between hippocampal volume and memory performance. Obesity is one of the modifiable risk factors that has been shown to directly impact brain structure leading to lower hippocampal volumes (Fotuhi, Do, & Jack, 2012). As such, these findings suggest that

targeted patient interventions may benefit from the inclusion of modifiable health-related risk factors such as weight management, healthy eating, and physical activity that may improve cognitive health and reduce the risk for further cognitive decline. In another study of older adults with TLE, we demonstrated that patients that met criteria for a cognitive disorder of aging had elevated CVRFs including hypertension, diabetes, hyperlipidemia, and abnormal white matter changes on brain imaging (Reyes et al., 2021). To date, no studies have utilized the phenotype approach to examine if there are unique health-related risk factors associated with different cognitive profiles across cognitive phenotypes in epilepsy. Given that several investigations have identified cognitive phenotypes with unique clinical and sociodemographic profiles, it is possible that these patients also present with unique comorbidities that may be further exacerbating the epilepsy burden.

There is a burgeoning literature exploring protective factors that can alter the response to pathology and influence the relationship between brain pathology and clinical phenotypes. The concept of *cognitive reserve* refers to a protective mechanism that allows individuals to cope with brain pathology by using residual brain resources more efficiently (Stern, 2002). Several factors have been identified to be related to cognitive reserve, including pre-morbid intelligent quotient (IQ), high education, complex occupational attainment, and bilingualism (Ghaffar, Fiati, & Feinstein, 2012; Guzman-Velez & Tranel, 2015; Whalley, Deary, Appleton, & Starr, 2004). Despite the well-established cognitive impairments found in TLE, surprisingly few studies have examined cognitive reserve in this clinical population. Jokeit et al. (H. Jokeit & Ebner, 1999), found that higher educational attainment in patients with TLE was an indicator of higher cognitive reserve, delaying the onset of cognitive decline. Oyegbile et al. (Oyegbile et al., 2004) also found that the effects of the duration of epilepsy on cognitive function were less apparent for individuals

with higher education, thus higher education appeared to be protective against epilepsy-related cognitive dysfunction. Additionally, bilingualism has been associated with enhanced executive functioning in healthy individuals as well as delayed onset of clinical symptoms associated with Alzheimer's disease (AD) and cognitive decline in aging (Guzman-Velez & Tranel, 2015). The cognitive advantage that bilingualism may confer has been most commonly studied with respect to executive functioning, wherein executive control abilities observed in bilinguals are thought to result from the strengthening of the executive control system, which is continuously recruited to manage attention to the target language and simultaneously inhibit the non-target language (Bialystok, Craik, Green, & Gollan, 2009; Grundy, Anderson, & Bialystok, 2017; Guzman-Velez & Tranel, 2015). My own work has provided initial support for bilingualism as a protective factor in TLE, demonstrating enhanced executive functions in bilinguals with TLE despite increased levels of frontotemporal white matter pathology (Reyes et al., 2018). However, investigations of protective factors in cognitive phenotypes remain to be explored. Examining protective factors in patients that demonstrate intact cognitive profiles despite having chronic epilepsy, can provide insight into the brain's resilience to epilepsy pathology.

Overall Approach to Dissertation

This staple dissertation will be the first to integrate neuroimaging data, cognitive data, and health-related risk factors and protective factors in an effort to unravel the heterogeneity of cognitive impairment in TLE (Figure 1.4). Previous findings in cognitive phenotypes and my own work on health-related risk and protective factors in epilepsy lay the groundwork for the current studies to examine (1) how regional and network-based measures of brain pathology can help to delineate cognitive phenotypes in TLE; (2) which methodology provides the most robust and rigorous approach to cognitive phenotyping; and (3) whether and how unique risk and protective

factors contribute to cognitive functioning in TLE phenotypes. Findings from this dissertation will provide greater insight into the heterogeneity observed across patients and will therefore inform clinical diagnostic frameworks, treatment approaches across epilepsy subtypes, and individualized interventions targeted at reducing risk for cognitive decline. Furthermore, this work can inform the identification of cognitive phenotypes in other neurological disorders.

Rationale for Study 1

Only three studies prior to Study 1 of this staple dissertation project have focused on identifying the neuroanatomical correlates of cognitive phenotypes in TLE (Dabbs et al., 2009; B. Hermann et al., 2007; Rodriguez-Cruces et al., 2018). These studies revealed that patients with generalized cognitive impairment demonstrate widespread cortical thinning (Dabbs et al., 2009) and decreased diffuse WM integrity (Rodriguez-Cruces et al., 2018), whereas patients with relatively normal cognitive profiles demonstrate the least structural abnormalities. The aim of **Study 1** was to identify cognitive phenotypes in a group of patients with TLE and examine the underlying brain network changes that are associated with each cognitive phenotype. A clinical approach was used to derive the cognitive phenotypes based on neuropsychological measures of memory and language. These actuarial neuropsychology criteria consists of *a priori* definition of impairment and patients are assigned to phenotypes based on their patterns of impairment. Defining cognitive phenotypes based on individual performance has been widely used within the Alzheimer's and dementia literature, given its clinical utility and comparability across different studies (Edmonds et al., 2016; Snowden et al., 2007). Although prior work has examined the WM integrity across cognitive phenotypes (Rodriguez-Cruces et al., 2018), this was done at the regional level and within conventional white matter tracks. The present study adds to the literature by examining both regional and network WM changes, including alterations in microstructure within

the superficial WM, which has been shown to be critical for cortico-cortical connectivity (Nazeri et al., 2015). Given that TLE is now considered a network disorder, examining network abnormalities within cognitive phenotypes can provide greater insight into subtle differences in neuroanatomical correlates across phenotypes that may not otherwise be observed with more traditional metrics of WM integrity.

Rationale for Study 2

There has been variability across cognitive phenotypes studies, including the number and nature of the phenotypes identified and the clinical and neuroimaging characteristics associated with each phenotype (B. P. Hermann et al., 2021). This may, in part, be due to single-site studies, the methodology used to derive the phenotypes, and variability in the assessments employed. Most of the phenotype literature has utilized data-driven approaches such as cluster analysis which has its advantages as it identifies groups from the data without restrictions imposed by the user. However, utilizing a specific neuropsychological criterion such as the one used in **Study 1** can inform the translation of these phenotypes into clinical diagnostic criteria given its clinical utility (Edmonds et al., 2016; Snowden et al., 2007). In order to derive clinically significant phenotypes that are interpretable and comparable across different studies, consensus on the appropriate method to phenotyping is needed. In **Study 2**, we compare clinically-driven and data-driven methods in a sample of 407 patients with TLE, test the utility and reproducibility of each method, and expand on **Study 1** by including tests of verbal memory, language, executive function, and psychomotor speed.

Rationale for Study 3

Findings from **Study 2** demonstrated that there was good concordance between cluster analysis and the clinical criteria, however, cluster analyses misclassed 12% of patients with clinically-defined impairment as having normal cognition (Reyes, Kaestner, et al., 2020). This misclassification may impact clinical care, as false negatives can prevent the identification of patients that are at increased risk for cognitive progression. Furthermore, cognitive phenotypes have been shown to be useful in predicting postoperative cognitive outcomes (Baxendale & Thompson, 2020). The prediction and evaluation of postoperative cognitive decline has been a critical component of epilepsy care and one that continues to evolve. As such, identifying the most rigorous and robust clustering methodology will be imperative for the translation of cognitive phenotypes into clinical care. **Study 3** aims to address the disadvantages and pitfalls of cluster analysis, by utilizing latent profile analyses, a person-centered approach that 1) identifies groups with a greater level of certainty, 2) handles missing data, and 3) provides the probability of group membership. We also adjudicate the impact of invariably missing data in order to identify the "best" taxonomy using the most rigorous clustering method. Furthermore, **Study 3** represents the largest investigation of cognitive phenotypes across the entire epilepsy literature with a sample of 1,178 patients with TLE. Lastly, the overarching aim of **Study 3** is to inform future phenotyping investigations in epilepsy and other neurological disorders.

Rationale for Preliminary Analyses for Future Study

One of the aims of the staple dissertation was to examine the effects of modifiable risk factors and protective factors on cognition and brain structure across phenotypes. Due to recruitment issues as a result of the COVID-19 pandemic, the prospective collection of modifiable risk factors and protective factors came to a halt. Furthermore, we were able to amass the largest sample of patients with TLE across multiple epilepsy centers which address the lack of

generalizability from single-site data. However, many of these patients did not have health-related vascular or neuroimaging data available at the time of analyses, and acquisition and collection of data are still ongoing. The current sample with available data includes 205 patients (17.4% of Study 3 sample) with neuroimaging data, 196 patients (16.6% of Study 3 sample) with health-related vascular data, and 390 patients (33.1% of Study 3 sample) with language information available to ascertain bilingualism status. As such, additional analyses with these data were not included in Study 3 to keep the focus on examining the methodology in a more comprehensive manner. Rather, I provide preliminary analyses that will inform the preparation of a future manuscript.

Acknowledgments

Chapter 2 contains material as a reprint that was published in *Neurology*, 2019.

Chapter 3 contains material as a reprint that was published in *Epilepsia*, 2020.

Chapter 3 contains material that is under review in *Brain Communications*. The dissertation author was the primary investigator and author of this material. Co-authors at this point include: Bruce P. Hermann, Robyn M. Busch, William B. Barr, Daniel L. Drane, Marla Hamberger, Scott C. Roesch, and Carrie. R. McDonald.

Chapter 4 contains preliminary analyses that are anticipated to be incorporated into a future manuscript.

Figures

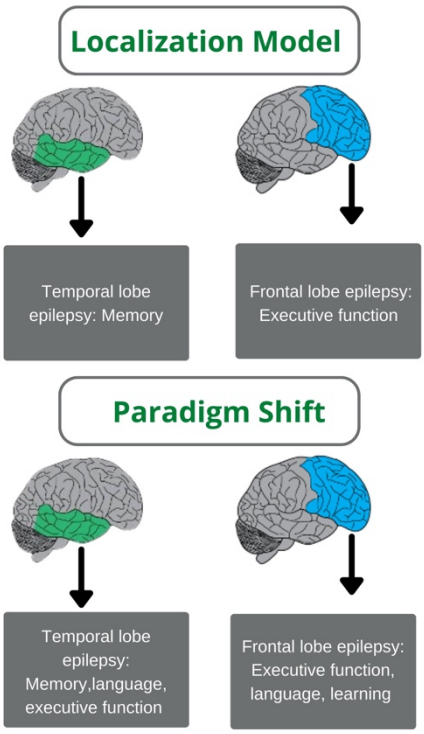

Figure 1.1: *Paradigm shift in the localization model of cognition in epilepsy.* Historically, the lesion-model or localization approach hypothesized that there was a direct relationship between the focal epilepsy syndrome and expected cognitive dysfunction. Specifically, the lesion-model presumed that cognitive dysfunction was restricted to the epileptogenic zone. This approach yielded syndrome-specific cognitive profiles based on the location of the seizure origin. For example, patients with temporal lobe epilepsy were thought to have deficits in memory and those with frontal lobe epilepsy were expected to have deficits in executive function. This direct relationship between seizure origin and cognitive function has been challenged by a plethora of investigation demonstrating that the cognitive dysfunction in the focal epilepsies are more widespread than hypothesized. For example, patients with TLE present with impairments in language and executive function, and those with FLE show deficits in language and learning.

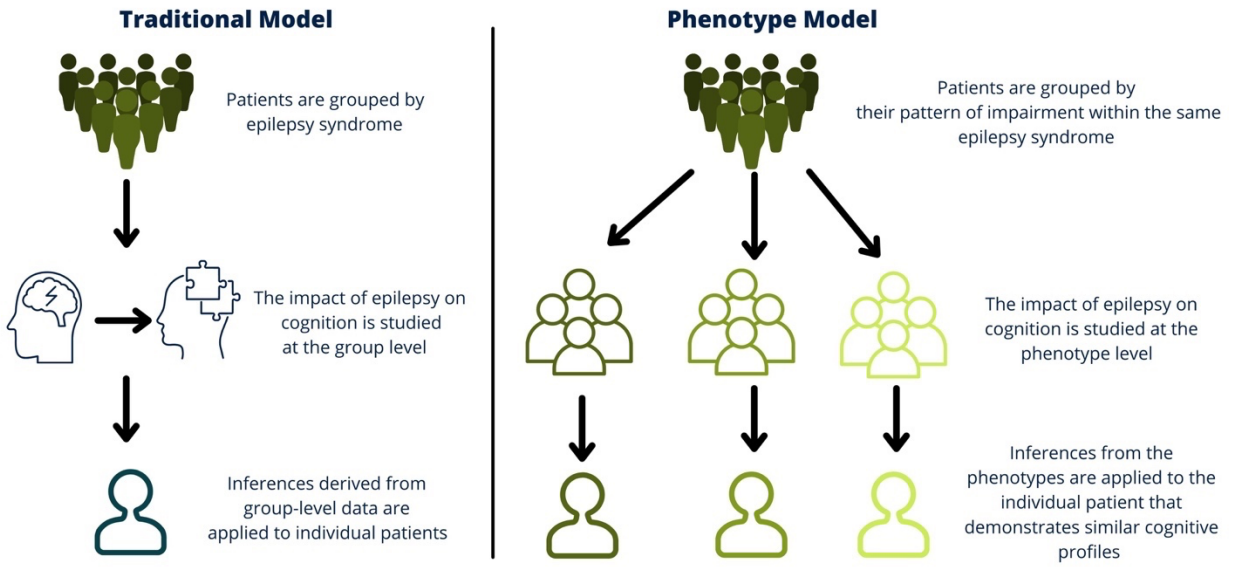

Figure 1.2: *Traditional versus phenotype model to study cognition in epilepsy.* In the traditional lesion-model, patients are aggregated into a group based on their epilepsy syndrome, and the impact of epilepsy and epilepsy treatment on brain structure and function is examined at the group level. Inferences from these investigations are then applied to individual patients. By contrast, in the phenotype model, patients are first grouped into *classes* or *phenotypes* based on their pattern of cognitive impairment. The impact of epilepsy on brain structure and function is examined within each phenotype and across phenotypes. In this approach, findings for each phenotype can then be applied to individual patients that demonstrate similar cognitive profiles.

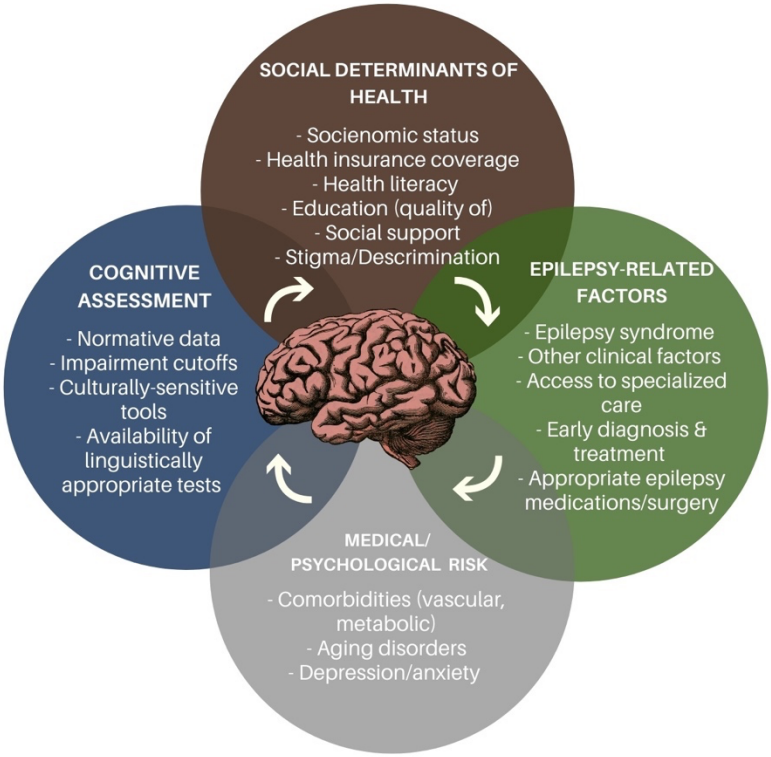

Figure 1.3: *Beyond the epilepsy: Examining factors that impact cognition.* The phenotype approach places cognitive dysfunction at the forefront of investigations. This, in turn, allows researchers to investigate other factors that may be impacting cognitive abilities in patients with epilepsy. Specifically, by identifying subgroups of patients with unique cognitive profiles, researchers can examine factors contributing to cognitive dysfunction at the phenotype level. Factors for investigation can include examining medical and psychological risk (e.g., health-related comorbidities, depression/anxiety), social determinants of health (e.g., economic deprivation, impact of education), and determining the impact of cognitive assessment methods. This approach aligns with *precision medicine* and provides a method to develop patient-centered interventions.

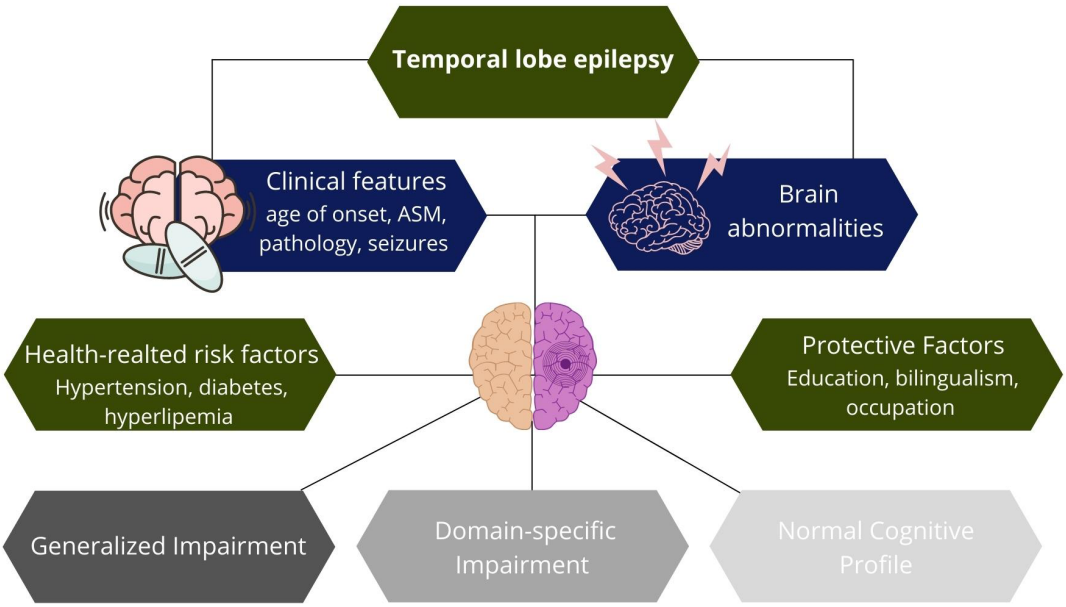

Figure 1.4: *Hypothesized model to cognitive phenotypes in epilepsy.* This dissertation aimed to investigate the factors associated with different cognitive profiles in temporal lobe epilepsy. In addition to investigating the clinical features associated with cognitive dysfunction, brain abnormalities, health-related risk factors, and protective factors were examined at the phenotype level. This approach improved the identification of unique brain signatures within each phenotype that better map onto the cognitive dysfunction observed. Other factors that may be moderating or mediating the brain-behavior relationship were also examined, arriving at patient-centered cognitive risk.

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Chapter 2:

Study 1

The content within this section, titled "Chapter 2: Study 1," reflects material from a paper that has been published in Neurology. The proper citation is as follows:

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Abstract

Objective: To identify distinct cognitive phenotypes in temporal lobe epilepsy (TLE) and evaluate patterns of white matter (WM) network alterations associated with each phenotype.

Methods: Seventy patients with TLE were characterized into four distinct cognitive phenotypes based on patterns of impairment in language and verbal memory measures (Language & Memory Impaired, Memory Impaired only, Language Impaired only, No Impairment). Diffusion tensor imaging was obtained in all patients and in 46 healthy controls (HC). Fractional anisotropy (FA) and mean diffusivity (MD) of the WM directly beneath neocortex (i.e., superficial WM; SWM) and of deep WM tracts associated with memory and language were calculated for each phenotype. Regional and network-based SWM analyses were performed across phenotypes.

Results: The Language & Memory Impaired group and the Memory Impaired group showed distinct patterns of microstructural abnormalities in SWM relative to HC. In addition, the Language & Memory Impaired group showed widespread alterations in WM tracts and altered global SWM network topology. Patients with isolated language impairment exhibited poor network structure within perisylvian cortex, despite relatively intact global SWM network structure, whereas patients with no impairment appeared similar to HC across all measures.

Conclusions: These findings demonstrate a differential pattern of WM microstructural abnormalities across distinct cognitive phenotypes in TLE that can be appreciated at both the regional and network levels. These findings not only help to unravel the underlying neurobiology associated with cognitive impairment in TLE, but they could also aid in establishing cognitive taxonomies and/or in the prediction of cognitive course in TLE.

Introduction

Cognitive dysfunction is a highly prevalent and debilitating comorbidity in patients with temporal lobe epilepsy (TLE; Bell, Lin, Seidenberg, & Hermann, 2011; Saling, 2009). Up to 80% of TLE patients demonstrate impairments in at least one cognitive domain, most frequently in language and/or memory (C. Helmstaedter, Hermann, B., Lassonde, M., Kahane, P., & Arzimanoglou, A, 2011; C. Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003; B. P. Hermann et al., 2006). Despite the high prevalence of cognitive dysfunction in TLE, there is considerable variability in the nature and severity of impairments observed across patients, some demonstrating generalized impairment, some specific cognitive deficits, and others with normal cognition (Oyegbile et al., 2004).

Recently, studies have attempted to understand the heterogeneity in TLE by identifying cognitive phenotypes and examining the neuroanatomical correlates associated with each subtype (Dabbs, Jones, Seidenberg, & Hermann, 2009; B. Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; Rodriguez-Cruces et al., 2018). These studies have revealed that patients with generalized cognitive impairment demonstrate widespread cortical thinning (Dabbs et al., 2009), subcortical atrophy (B. Hermann et al., 2007), and diffuse white matter (WM) compromise (Rodriguez-Cruces et al., 2018), whereas patients with normal cognitive profiles demonstrate minimal structural abnormalities. These studies revealed that the type and degree of cognitive impairment are associated with the extent of brain abnormalities in TLE. However, more precise characterization of patients according to domain-specific cognitive impairment is warranted and could provide new insights into the neuroanatomical substrates of cognitive dysfunction in TLE.

In this study, we identify unique *cognitive phenotypes* in TLE based on patterns of language and memory impairment and examine microstructural alterations associated with each phenotype.

We accomplish this by evaluating patterns of WM disruption within deep, long-range association tracts and within the WM directly beneath the cortex, using both a regional and a network-based approach. We hypothesize that distinct cognitive phenotypes can be identified with unique patterns of network disruption that underlie the neuropsychological heterogeneity of TLE. Specifically, patients with isolated memory or language impairment will demonstrate significant mesial versus lateral temporal pathology, respectively, whereas those with impairment in both domains will demonstrate widespread fronto-temporal pathology that is more pronounced within the left hemisphere. Finally, we anticipate patients with no impairment will show minimal regional or network-based pathology.

Methods

Participants

This study was approved by the Institutional Review Boards at UC San Diego and UC San Francisco, and informed consent was collected from all participants. Seventy patients with TLE and 46 healthy controls (HC) met inclusion/exclusion criteria for the study. All patients were recruited through referral from the UC San Diego or UC San Francisco Epilepsy Centers. Inclusion criteria for patients included a TLE diagnosis by a board-certified neurologist with expertise in epileptology, in accordance with the criteria defined by the International League Against Epilepsy, and based on video-EEG telemetry, seizure semiology, and neuroimaging evaluation. The presence of mesial temporal sclerosis (MTS) was determined by inspection of MRI images by a board-certified neuroradiologist. In 35 patients, MRI findings suggested the presence of ipsilateral MTS and the remaining patients demonstrated normal MRI. Patients were excluded if there was evidence on video-EEG of extratemporal seizure onset or the presence of a mass lesion on MRI. HC were included if they were between the ages of 18 and 65 and had no reported history of neurological or psychiatric disease.

Neuropsychological measures

Neuropsychological data were available for all patients and HC. Verbal memory was evaluated with the California Verbal Learning Test-Second Edition (CVLT-II; Delis, Kramer J. H. , Kaplan E., & Ober, 2000) long delayed free recall (CVLT- LDFR) and the Wechsler Memory Scale-Third Edition (WMS-III) Logical Memory delayed (LM Delayed) and Verbal Paired Associates delayed (VPA Delayed; Wechsler, 1997). Language ability was also evaluated with the Boston Naming Test (BNT; Kaplan, 2001), Auditory Naming Test (ANT; Hamberger & Seidel, 2003), and Category Fluency subtest of the Delis-Kaplan Executive Function System (D-KEFS; delis, Kaplan, & Kramer, 2001).

Cognitive Phenotyping

The cognitive phenotypes were derived using the three measures of verbal memory and three measures of language described above. Raw scores for all patients' neuropsychological data were converted into z-scores based on the mean of the HC data. Impairment was defined as 1.5 standard deviations below the mean of the HC. According to procedures outlined by Edmonds et al. (Edmonds et al., 2016), patients were determined to be impaired in a given domain (i.e., memory or language) if two or more of the three cognitive tests fell within the impairment range. Four distinct cognitive phenotypes were derived: 1) patients impaired on both language and memory measures (*Language & Memory Impaired*); 2) patients impaired on memory measures only (*Memory Impaired*); 3) patients impaired on language measures only (*Language Impaired*); and 4) patients with no evidence of impairment on language or memory measures (*No Impairment*) (Fig 1). Twenty-four percent of patients were impaired in both language and memory, 20% were impaired in memory only, 29% were impaired in language measures only, and 27% were not impaired in either domain.

MRI acquisition

MRI data were collected on a General Electric (GE) Discovery MR750 3T scanner with an 8-channel phased-array head coil at the Center for Functional MRI at UC San Diego or the Surbeck Laboratory for Advanced Imaging at UC San Francisco. Image acquisitions on the 3T scanner were identical at both centers and included a conventional three-plane localizer, GE calibration scan, a T1-weighted 3D customized FSPGR structural sequence (TR = 8.08 ms, TE = 3.16 ms, TI = 600 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 x 192, slice thickness = 1.2 mm), and for diffusion MRI, a single-shot pulse-field gradient spin-echo EPI sequence (TR = 8000 ms, TE = 82.9 ms, flip angle = 90°, FOV = 240 mm, matrix = 96 x 96m, slice thickness = 2.5 mm, echo-spacing = 588 ms). Diffusion data used for the DTI analysis were acquired with b-value= 0 and 1,000 s/mm^2 with 30 unique gradient directions. For use in nonlinear B_0 distortion correction, two additional b=0 volumes were acquired with either forward or reverse phase-encode polarity.

DTI Processing

Preprocessing of the diffusion data included corrections for distortions due to magnetic susceptibility (B_0), eddy currents, and gradient nonlinearities, head motion correction and registration to the T1-weighted structural image. For B0 distortion correction, a reverse gradient method was used (Holland, Kuperman, & Dale, 2010). A detailed description of the image processing is provided elsewhere (McDonald et al., 2014). DTI-derived fractional anisotropy (FA) and mean diffusivity (MD) were calculated based on a tensor fit to the b = 1,000 data.

SWM calculations

Individual T1-weighted MRIs were used for cortical surface reconstruction and parcellation using *FreeSurfer, 5.3.0* (Dale, Fischl, & Sereno, 1999). FA and MD for the SWM

were calculated by sampling 1 mm below the pial surface normal at each vertex. To improve signal-to-noise ratio, all surface-based measures were smoothed on the average surface using a 20-mm full width at half maximum Gaussian kernel. Vertex-wise maps of FA and MD for the SWM were created for each individual and then averaged into a spherical representation to align sulcal and gyral features allowing for accurate matching of FA and MD measurement locations at the individual level, while minimizing metric distortion (Fischl, Sereno, & Dale, 1999).

Fiber tract calculations

Fiber tract FA and MD values were derived using a probabilistic diffusion tensor atlas that was developed using in-house software written in MATLAB, which has been validated in HC and patients with TLE (Hagler et al., 2009). For each participant, T1-weighted images were used to nonlinearly register the brain to a common space, and diffusion tensor orientation estimates were compared to the fiber tract atlas to obtain a map of the relative probability of a voxel belonging to a particular fiber tract, given the location and similarity of diffusion orientations. Voxels identified with FreeSurfer as cerebrospinal fluid or cortical gray matter were excluded from the fiber regions of interest (ROIs). Fiber tracts were segmented in this way for each individual, and mean FA and MD values were calculated based on that participant's diffusion data. A full description of the atlas is described elsewhere (Hagler et al., 2009). In the current study, the method described above was used to reconstruct the following tracts because they are among the most frequently implicated in verbal memory and language processing and are often reported to be compromised in TLE (Allone et al., 2017; Leyden et al., 2015): arcuate fasciculus (ARC), uncinate fasciculus (UNC), fornix (FX), inferior longitudinal fasciculus (ILF) and parahippocampal cingulum (PHC) (Figure 2.2). Furthermore, decreases in FA and increases in MD within these tracts have been associated with impairment in language and memory in TLE and are sensitive to axonal loss and demyelination,

respectively (Allone et al., 2017; Leyden et al., 2015; Song et al., 2003).

Network Analysis

Due to evidence that patients with TLE show less efficient network integration and over-segregation of cortical and subcortical networks relative to HC (Bernhardt, Bonilha, & Gross, 2015), graph theoretical analysis was applied to the SWM data to determine whether cognitive phenotypes differ in their network microstructure covariance (Bahrami et al., 2017; Bernhardt, Chen, He, Evans, & Bernasconi, 2011; Carmeli, Fornari, Jalili, Meuli, & Knyazeva, 2014). Estimates of FA were measured within 33 gyral-based ROIs per hemisphere (Desikan et al., 2006) that were based on average estimates obtained from the unsmoothed data at each vertex within a given SWM ROI. A 66 x 66 symmetric-weighted matrix of the structural connectivity in the whole brain was constructed using Pearson Correlations for each phenotype group and the HC as well as for the pooled group of all TLE patients. Each correlation value in this matrix represents the covariance strength between two related nodes (i.e., ROIs).

For this study, we analyzed differences in four network-based measures: *global efficiency, local efficiency, transitivity,* and *modularity*, due to evidence that these measures are (1) sensitive to global and local network-changes in TLE (Bernhardt et al., 2015; Bernhardt et al., 2011) or (2) implicated in cognitive functioning (Brier et al., 2014; de Haan et al., 2012). Group differences in each measure were tested over a wide range of network densities, $0.1 \leq S_{thr} \leq 0.5$, with the threshold incremented by 0.05, using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010). Global efficiency is a measure of global network integration and is defined as the average inverse shortest path length (Latora & Marchiori, 2001). Local efficiency is calculated using the global efficiency from the adjacent subgraph of the node and can be interpreted as local network connectivity representing regional topological changes (Rubinov & Sporns, 2010); the local efficiencies across

all nodes are then averaged to estimate the total network local efficiency. Transitivity is a measure of network segregation, such that greater transitivity indicates a tendency for nodes to be highly integrated within their local cluster (Newman, 2003). This measure is similar to *clustering coefficient*. However, unlike clustering coefficient, transitivity is normalized collectively for all nodes and therefore is not influenced by the number of nodes in the network (Rubinov & Sporns, 2010). Finally, modularity describes the degree to which a network may be divided into nonoverlapping groups with a high number of within-module connections and a low number of between-module connections (de Haan et al., 2012; Newman, 2006). A detailed description of these graph theoretic measures, as well as the toolbox used to calculate them are described in a review by Rubinov and Sporns (Rubinov & Sporns, 2010).

Statistical analysis

Independent *t*-tests and Fisher's tests were used to test differences in demographic variables between patients and HC. Analysis of variance (ANOVA) was conducted to compare clinical and demographic variables across the four cognitive phenotypes. Vertex-wise *t*-tests were used for surface-based comparisons between each cognitive phenotype group and HC and corrected for multiple comparisons using a false discovery rate (FDR). ANOVA was conducted to compare FA and MD of fiber tracts across the four cognitive phenotypes and HC, correcting for multiple comparisons using FDR. When results from the ANOVA were significant, group contrasts were assessed using post-hoc pairwise tests with Bonferroni correction.

For the graph theoretic measures, a sub-sampling methodology (Bahrami et al., 2017) was used to estimate a spread of values for the HC group for each measure at each network density level. Patient group values outside of the .0005 and .9995 percentile range (corresponding to a *p*-value of .001) were considered significantly different from HC. Because the individual phenotype

groups had less patients per group than the number of HC, to create the HC spread of values, a sub-sample of 18 HC, corresponding to the average size of the phenotype groups, was sampled 4000 times.

Data Availability Statement

Authors have full access to all study data and participant consent forms and take full responsibility for the data, the conduct of the research, the analysis and interpretation of the data, and the right to publish all data.

Results

Demographics and patient clinical variables

There were no differences in age [t (114) = -.020, p = .984] or sex distribution (Fisher's Exact = .383, p = .571) between patients with TLE and HC; however, as expected, HC had more years of education [t (114) = -5.715, p < .001] (Table 2.1). There were no differences in age (F (3, 66) = .869, p = .462), education (F (3, 66) = .329, p = .805), sex distribution (Fisher's Exact = 4.087, p = .699), handedness (Fisher's Exact = 6.61, p = .083), duration of epilepsy (F (3, 66) = 2.15, p = .102), seizure frequency (F (3, 61) = 1.308, p = .280), number of antiepileptic drugs (AEDs; F (3, 66) = 1.73, p = .169), MTS status (Fisher's Exact = 2.162, p = .533) or side of seizure onset (Fisher's Exact= 3.975, p = .707) across the four cognitive phenotype groups. However, there were differences in age of seizure onset (F (3, 66) = 7.02, p < .001), with the Memory Impaired group demonstrating an older age of seizure onset relative to the Language & Memory (p = .023) and the Language Impaired (p < .001) groups.

Surface-based SWM abnormalities across Cognitive Phenotypes

The results of the surface maps for SWM FA and MD are presented in Figure 2.3. Relative to HC, the Language & Memory group showed widespread reductions in FA in lateral temporal,

parietal, frontocentral/cingulate, and lateral prefrontal regions bilaterally, coupled with highly left lateralized increases in MD that were pronounced within lateral temporal and orbitofrontal SWM. In the Memory Impaired group, higher MD was observed in the inferior and medial temporal lobe regions bilaterally, including parahippocampal, entorhinal, fusiform, and temporal pole, as well as the cingulate cortices (Figure 2.3A). The Language Impaired and the No Impairment group (not depicted) showed no differences in SWM FA or MD relative to HC that survived FDR-correction. Post-hoc comparisons across the cognitive subgroups revealed higher MD in the Language & Memory group compared to the No Impairment group within left lateral temporo-parietal regions (Figure 2.3B).

Differences in FA/MD of deep white matter fiber tracts

ANOVA revealed group differences in FA and MD of the ARC and ILF bilaterally and in FA of the left UNC (Table 2.2). Pairwise comparisons revealed that the Language & Memory group had lower FA of the left and right ARC (Left ARC: $p = .004$; Right ARC: $p = .018$), the left and right ILF (Left ILF: $p = .005$; Right ILF: $p = .011$), and the left UNC ($p < .01$) relative to HC. They also showed higher MD of the left ILF relative to HC ($p = .002$). The Memory Impaired group showed higher MD of the right ILF relative to HC ($p = .034$) and the Language Impaired group demonstrated lower FA of right ILF relative to HC ($p = .045$).

Post-hoc comparisons across the patient subgroups showed that the Language & Memory group had lower FA of the left UNC relative to the Language Impaired group ($p = .013$). This group also showed higher MD of the left ARC relative to the No Impairment group ($p = .024$), and a trend for higher MD of the left ILF relative to the No Impairment group ($p = .062$). Given that patients in the Memory Impaired group had an older age of seizure onset and a trend for a longer duration of disease, we conducted a secondary analysis controlling for age of seizure onset and

disease duration for WM tracts that were significant in the primary analysis. Similar results were obtained in this analysis, with the exception that the finding of higher MD of the left ARC in the Language & Memory Impaired relative to the No Impairment Group only approached significance ($p = .064$). No other patient subgroups comparisons were significant.

Global and local network analysis

Whole-group analysis

When treated as a single group, patients with TLE showed decreased global efficiency across a consecutive range of network densities (10-to-35; $p < .001$), as well as increased transitivity (network densities: 15-to-50; $p < .001$) and decreased modularity (network densities: 10-to-20; $p < .001$) relative to HC (Fig 2.4A).

Cognitive phenotypes analysis

When analyzing the data separately for each cognitive phenotype, only the Language & Memory and Memory Impaired groups showed significant differences from HC. The Language & Memory group showed decreased global efficiency (network densities: 10-to-45; $p < .001$), increased transitivity (network densities: 15-to-50; $p < .001$), and decreased modularity (network densities: 10-to-30; $p < .001$). The Memory Impaired group demonstrated decreased global efficiency relative to HC at a network density of 30 ($p < .001$). Neither the No Impairment nor the Language Impaired group displayed any significant differences in global network structure from HC.

Given that the Language Impaired group failed to show any differences in the regional or global network SWM analyses, a post-hoc sub-network analysis was performed to determine if the Language Impaired group differed in their network structure within classic language (i.e.,

perisylvian) regions. For this analysis, local efficiency was selected and tested within the pars triangularis (pTRI)/pars opercularis (pOPC), superior temporal gyrus (STG), and supramarginal gyrus. One region, the STG, displayed significantly decreased local efficiency for the Language Impaired group, bilaterally ($p < .05$; Figure 2.5A-B). No other group differed from HC across perisylvian regions.

Discussion

In this study, we identify four distinct cognitive phenotypes within TLE and demonstrate that each phenotype is associated with a unique pattern of WM abnormalities. Specifically, we show that patients in the *Language & Memory* and *Memory Impaired* groups show pronounced microstructural changes within widespread SWM regions and deep WM association tracts implicated in language and memory (Leyden et al., 2015). These findings were particularly pronounced for those in the *Language & Memory Impaired* group at both the regional and global network levels. Finally, we show that patients in the *Language Impaired* group show abnormal network structure within perisylvian SWM, despite relatively intact global network structure. Collectively, our findings suggest that distinct cognitive phenotypes exist in TLE that are not differentiated or explained by known clinical characteristics. Rather, these different phenotypes appear to be characterized by underlying neurobiological differences in their regional WM microstructure and network topology.

Cognitive dysfunction is the most common comorbidity in TLE, with impairments in language and memory accounting for a majority of this comorbidity (Bell et al., 2011; B. P. Hermann et al., 2006; Oyegbile et al., 2004; Saling, 2009; Stretton & Thompson, 2012). A number of factors have been identified as playing a pivotal role in the cognitive dysfunction observed in TLE, including the presence of MTS (Wieser & Epilepsy, 2004), the type and frequency of seizures

(C. Helmstaedter et al., 2003) , age of seizure onset (B. Hermann et al., 2002), duration of disease (Oyegbile et al., 2004), and the effects of AEDs (Meador, 2002). Interestingly, not all patients with TLE demonstrate cognitive dysfunction, even when they share similar clinical characteristics to those that do. In our study, 1/4 of the patients were impaired in both language and memory, while approximately one half of the sample had isolated memory or language impairment and the remaining patient sample demonstrated a relatively normal cognitive profile. In particular, patients who were impaired in both language and memory showed the poorest performance across all measures, indicating more pervasive cognitive dysfunction relative to those with domain-specific impairments (i.e., *Memory Impair*ed and *Language Impaired*). This group of patients may reflect those described as having "generalized impairment" in Hermann et al. (B. Hermann et al., 2007), where approximately 29% of patients in their study demonstrated impairment in memory, language, executive function, and processing speed. Of interest, this patient group was at risk for cognitive progression over a 4-year interval, whereas their other groups (i.e., *memory impaired, minimally impaired*) showed minimal progression over time. In addition, we replicate their prior findings of a subgroup of patients with isolated memory deficits (20%) and of a sizable group with no significant impairments (27%). Importantly, we expand this literature by further characterizing cognitive profiles in a large cohort of patients using *a priori* neuropsychological criteria that have been shown to produce meaningful cognitive subtypes in other neurological disorders (Edmonds et al., 2016; Snowden et al., 2007). By doing so, we were able to identify a unique group (*Language Impaired*) that constituted 29% of our sample and may be best described as harboring a significant anomia (see Figure 2.1). Despite the range in cognitive performances across the four phenotypes, our groups demonstrated relatively similar clinical features (Table 2.1). Therefore, we purport that the nature and extent of cognitive dysfunction observed in TLE cannot be fully explained by

common clinical characteristics (i.e., MTS, side of onset, AEDs), and that treating patients with TLE as a single group may obscure important cognitive and neuroanatomical variability across patient samples. In addition, given the evidence that different cognitive phenotypes may be at differential risk for cognitive progression (B. Hermann et al., 2007), the cognitive course of patients with normal cognitive profiles or with generalized impairments may not be fully appreciated when comparing these patients to the "average" cognitive profile described in the TLE literature. Therefore, a finer characterization of cognitive phenotypes is warranted and could aid in the prediction of individual cognitive trajectories.

The white matter directly beneath the cortex (i.e., the *SWM*) has been shown to be particularly important for cognition given its key role in maintaining cortico-cortical connectivity (Nazeri et al., 2013; Nazeri et al., 2015; Ouyang, Kang, Detre, Roberts, & Huang, 2017). Furthermore, there is evidence that the SWM is highly sensitive to TLE-related pathology and may be an important predictor of post-operative outcomes (Liu et al., 2016). Here, we demonstrate a differential pattern of SWM alterations across unique cognitive phenotypes. Specifically, the *Language & Memory Impaired* group showed decreases in FA throughout frontocentral and lateral temporal regions bilaterally, coupled with highly left lateralized increases in MD that were pronounced within lateral temporal and orbitofrontal SWM. Conversely, the *Memory Impaired* group showed increased MD that was particularly pronounced within the cingulate and medial temporal lobes, bilaterally. Notably, a dissociative pattern emerged between these groups, where impairments in both language and memory were associated with SWM alterations that encompassed perisylvian regions, whereas isolated memory impairments were associated with changes in SWM within medial temporal structures critical to memory (Squire & Zola-Morgan, 1991). An unexpected finding was the lack of regional changes in SWM microstructure in patients

with isolated language impairment. Interestingly, this group did not differ from the other groups in the number of AEDs or other identifiable clinical characteristics. A post-hoc analysis also demonstrated that this group of patients was not more likely to be bilingual (25%), nor were they more likely to be on topiramate (10%) or zonisamide (10%) (all chi-square *p*-values > .05)—all of which may contribute to language impairments in TLE (Gollan, Montoya, Fennema-Notestine, & Morris, 2005; Ojemann et al., 2001). Rather, results from a sub-network analysis (discussed below) indicate that the *Language Impaired* group may harbor subtle changes within perisylvian network structure that are not apparent in traditional regional analysis. As anticipated, we found no significant changes in SWM microstructure in patients with normal cognitive profiles. Despite a prolonged course of epilepsy and having a clinical profile known to affect cognition, the patients in the *No Impairment* group showed a similar neuropsychological and microstructural profile to HC. Altogether, these findings further highlight the importance of the SWM to cognition and reveal that cognitive phenotypes in TLE have unique SWM signatures.

Alterations in deep WM tracts are often associated with impairments in memory and language in TLE (Allone et al., 2017; Leyden et al., 2015). In our study, patients demonstrating impairment in both language and memory showed reductions in FA of the ARC and ILF bilaterally, and left UNC, and increases in MD of the left ARC and ILF. These findings suggest that a worse cognitive phenotype is associated with widespread WM alterations in both short-range U-shaped fibers connecting adjacent gyri (Ouyang et al., 2017) and long-range association tracts connecting distal cortical regions. Interestingly, the *Memory Impaired* group showed minimal alterations in deep WM tracts relative to HC despite showing diffuse SWM MD changes within inferior and mesial temporal structures. Although several studies have found an association between compromise to our selected frontotemporal and medial temporal lobe tracts and both language *and*

memory impairment in TLE (McDonald et al., 2008; McDonald et al., 2014), it is possible that microstructural loss restricted to the SWM within the medial temporal lobe is more likely to result in an isolated memory impairment. In particular, the SWM beneath the entorhinal cortex includes the perforant path, which provides afferent input to the hippocampus (CA3/dentate) (Witter, 2007) and is known to be critical to verbal memory, but not necessarily to language (McDonald et al., 2014; Yassa, Mattfeld, Stark, & Stark, 2011). Therefore, while we found more restricted alterations in deep WM tracts in the domain-specific groups, it is possible that damage to multiple deep association tracts leads to impairment in both cognitive domains.

Given that TLE is now understood to represent a network disorder with alterations in whole-brain network topology (Bernhardt et al., 2015), we applied a graph theory approach to explore whether distinct cognitive phenotypes demonstrate unique SWM network organization. First, we replicate previous findings (Bernhardt et al., 2015; Bernhardt et al., 2011) demonstrating that patients with TLE display disrupted integration (i.e., lower global efficiency) and increased segregation (i.e., increased transitivity) at the whole group level. However, our subgroup analysis revealed that these topological differences were primarily driven by the *Language & Memory Impaired* group, with minimal differences observed in the other groups at the global network level. These findings mirror the regional analysis and indicate that more pervasive cognitive deficits are associated with pronounced alterations of SWM network structure.

Previous studies using network analyses in TLE have found consistent increases in path length and clustering coefficient (Bernhardt et al., 2015; Bernhardt et al., 2011), suggesting a more regularized network configuration that may be less resilient to epilepsy-related pathology. In our study, we found decreases in global efficiency (i.e*., increased path length)* in patients with language and memory impairment, as well as increases in transitivity (i.e., *increased coefficient*).

These alterations in global topology have been characterized as reflecting a "lattice-like" network configuration (Bernhardt et al., 2011) that may lead to reduced efficiency in information transfer, contributing to the cognitive dysfunction in this clinical population. Thus, the broad cognitive impairment observed in the *Language & Memory Impaired* group may, in part, be due to an altered global topology within SWM networks. We also found decreases in modularity and increases in transitivity in patients in the *Language & Memory Impaired* group relative to HC. Modularity describes the extent to which networks are organized into smaller sub-groups (Bullmore & Sporns, 2009; de Haan et al., 2012). A highly modular brain may offer a high level of local specialization needed for the demands of different cognitive processes. In support of this, De Haan et al. (de Haan et al., 2012) found decreases in modularity to be associated with poorer language and memory performances in patients with Alzheimer's Disease (AD). Decreases in modularity have also been linked to more advanced clinical status in AD (Brier et al., 2014). Our results in the *Language & Memory Impaired* group provide further evidence that decreases in modularity may result in disruption in intermodular communication and lead to pervasive cognitive deficits in TLE.

As described above, patients with isolated language impairment showed intact global network structure but decreased local efficiency within the left and right STG, suggesting less integration of the STG with other brain regions. Given that the STG is a critical node within the perisylvian network, a less well integrated STG may lead to isolated language impairment in some patients in the absence of other cognitive or microstructural changes and suggests avenues for further inquiry. Collectively, these results demonstrate unique changes in network organization within specific cognitive phenotypes. Specifically, more pervasive language and memory impairments are associated with widespread WM pathology that leads to altered segregation and

integration of WM networks, whereas isolated language impairment may be associated with disruption of local nodes within perisylvian networks.

Our study has several important limitations that should be noted. First, we only included neuropsychological measures of language and memory. While impairments in language and memory account for the most pervasive and problematic cognitive comorbidities in patients with TLE (Bell et al., 2011), impairments in executive function and processing speed are also present in some patients and could help to further subdivide our phenotypes. Future studies with a broader examination of different cognitive domains are warranted. Second, we used specific neuropsychological criteria to define impairment and to derive our phenotypes, whereas previous studies (Dabbs et al., 2009; B. Hermann et al., 2007; Rodriguez-Cruces et al., 2018) in TLE have relied on a data-driven approach (i.e., cluster analysis). Defining cognitive phenotypes based on individual test performance has been widely used within the mild cognitive impairment and AD literature, given its clinical utility, interpretability, and comparability across different studies (Edmonds et al., 2016; Snowden et al., 2007). However, a comparison of clinically-driven and data-driven methods is needed to test the utility and reproducibility of each method. Nonetheless, our study adds to an emerging literature demonstrating that TLE is associated with distinct cognitive phenotypes with unique underlying neuroanatomical signatures. Knowledge of these phenotypes not only helps to improve cognitive and neuroanatomical taxonomies in TLE, but it may also enhance individualized prediction of cognitive trajectories and yields a different perspective on the cognitive consequences of the TLE. Additional longitudinal studies such as Hermann et al. (B. Hermann et al., 2007) will improve our understanding of whether these distinct phenotypes portend differential patterns of cognitive impairment progression and whether epilepsy-related clinical variables (e.g., seizure frequency, number and type of AEDs) impact such

progression. Furthermore, knowledge about these phenotypes and their underlying neurobiology could be used in combination with clinical data to help predict risk for cognitive decline associated with aging or medical/surgical interventions in TLE. As the field of epilepsy is moving towards establishing more meaningful cognitive and neurobehavioral taxonomies, identifying syndrome-dependent and syndrome-independent phenotypes and understanding their accompanying neurobiology could improve our ability to match patients to treatments and improve a range of epilepsy-related outcomes.

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Figures

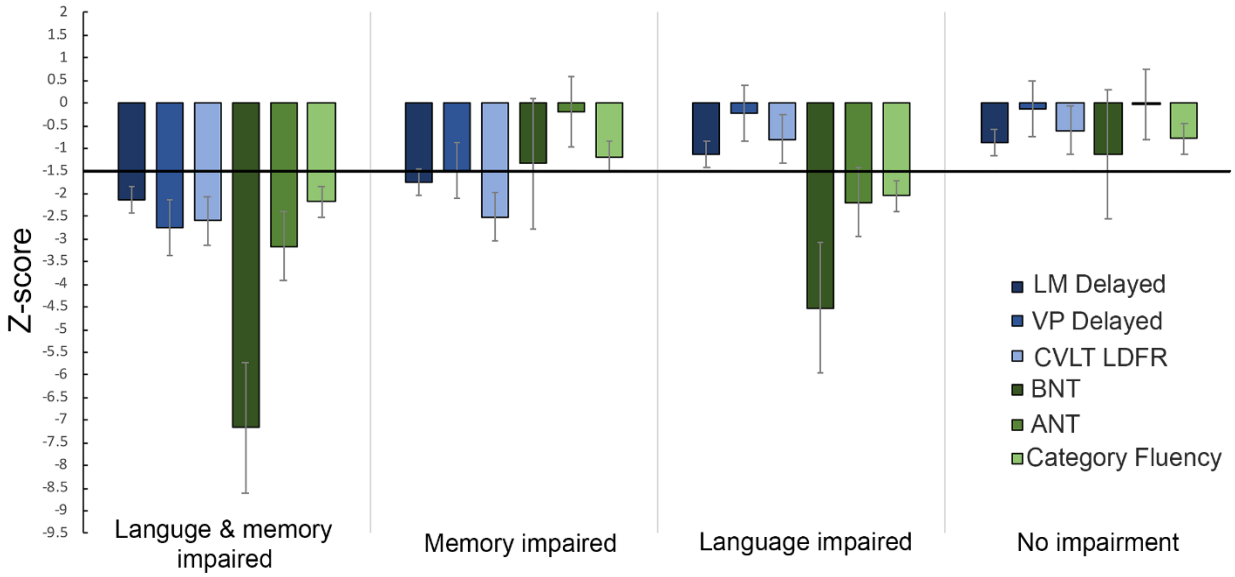

Figure 2.1: *Distribution of language and memory performance across cognitive phenotypes.* Mean z-scores on measures of language and memory across cognitive phenotypes. Error bars represent standard deviations. Impairment was defined as 1.5 SD below the mean of HC (represented as horizontal black line). LM= logical memory; VP= verbal paired associates; CVLT LDFR= California Verbal Learning Test—Long delayed free recall; BNT= Boston Naming Test; ANT= Auditory Naming Test.

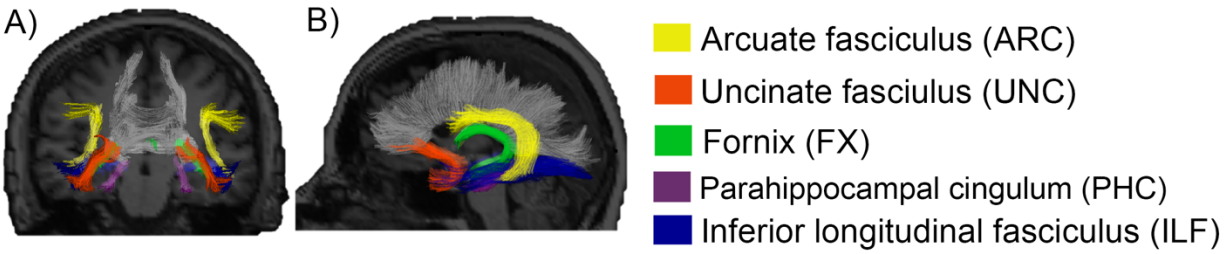

Figure 2.2: *Deep white matter tracts of interest*. A) Coronal and B) Sagittal rendering of the arcuate fasciculus (ARC), uncinate fasciculus (UNC), fornix (FX), parahippocampal cingulum (PHC), and inferior longitudinal fasciculus (ILF) derived from AtlasTrack projected onto a T1-weighted image for a single individual. The corpus callosum is portrayed in light gray in order to provide additional spatial information.

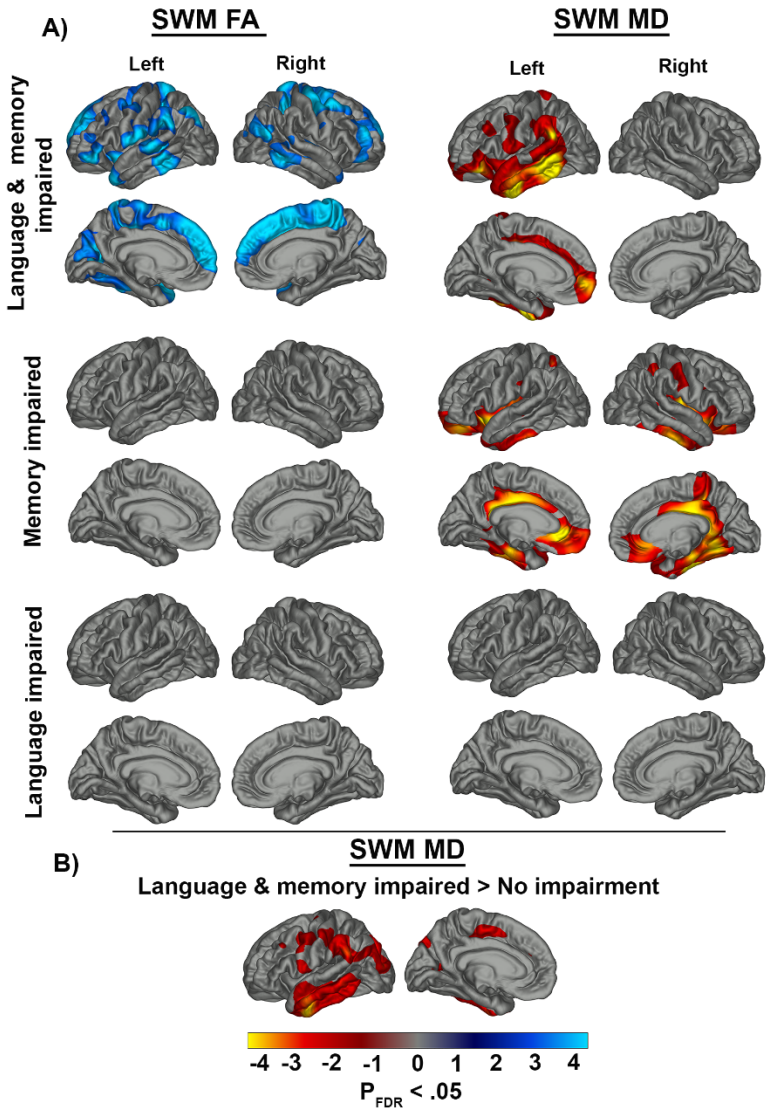

Figure 2.3: *Surface-based superficial white matter abnormalities across cognitive phenotypes.* A) Surface-based mapping of SWM FA and MD differences across cognitive phenotypes relative to HC after correcting for multiple comparisons, $P_{FDR} < .05$. The color bar shows patients with either lower values than controls in blue/cyan, or greater value than HC in red/yellow. B) Post-hoc comparison between the Language & Memory impaired group and the No Impairment group in SWM MD. Increases in MD in the Language & Memory group are shown in red/yellow.

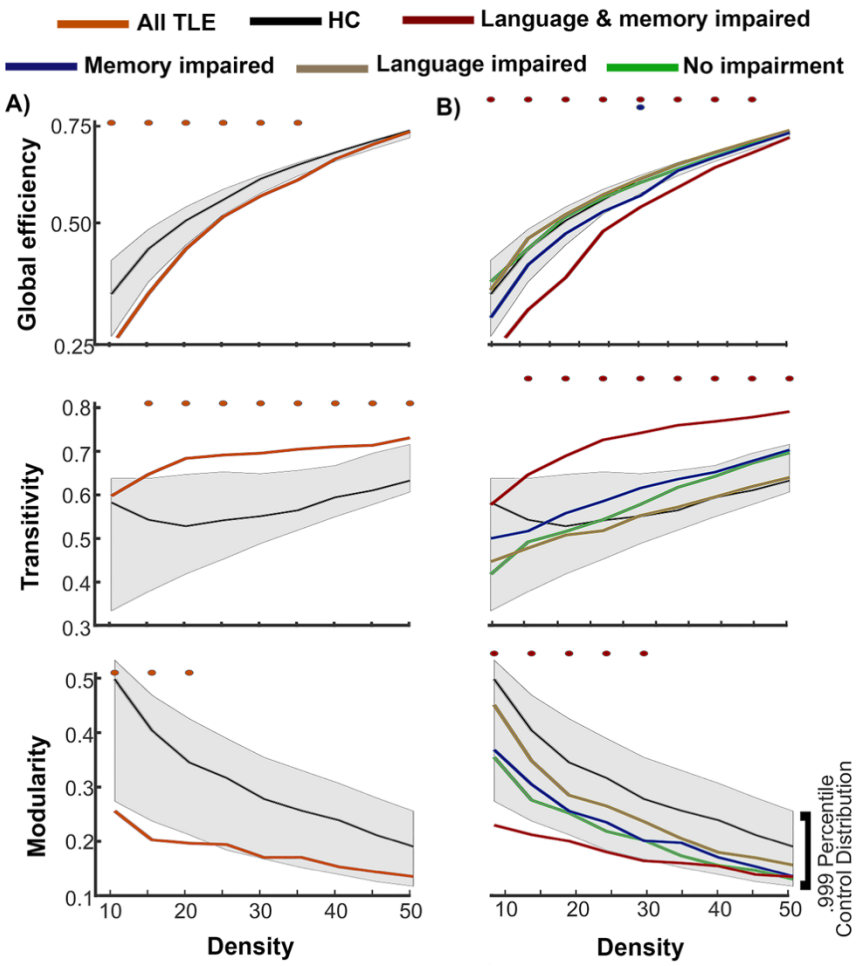

Figure 2.4: *Global network measures.* A) Plots show differences in global efficiency, transitivity, and modularity between healthy controls (HC) and the whole TLE group across network densities. Shaded areas represent the upper and lower bounds of each measure in HC. B) Differences in global efficiency, transitivity, and modularity between HC and each cognitive phenotype. Colored circles represent significant difference between HC and patients.

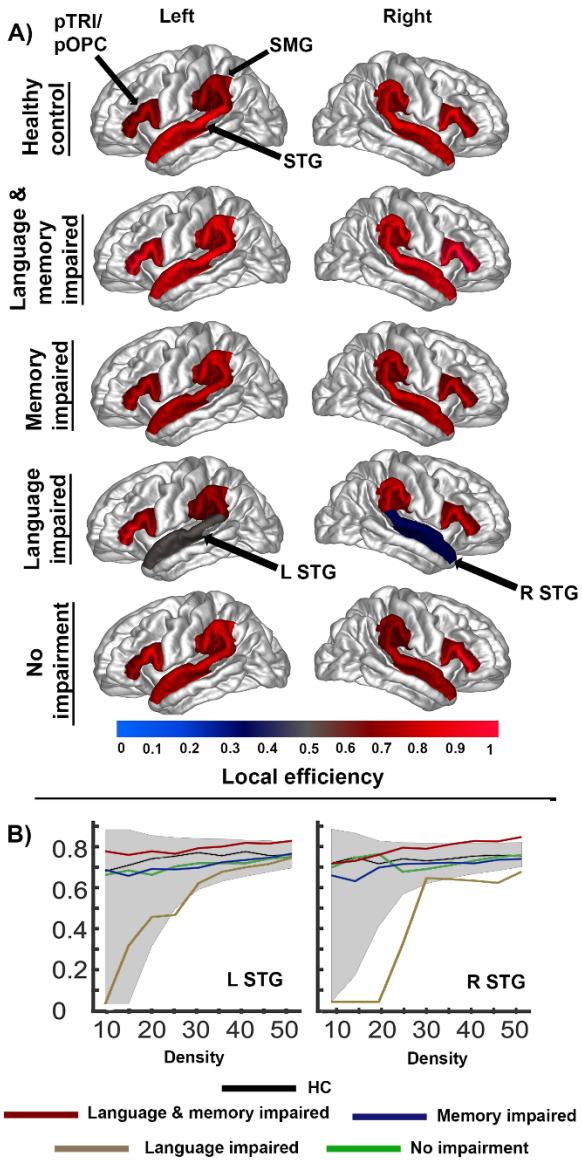

Figure 2.5: *Local efficiency differences within perisylvian regions.* A) Local efficiency differences between HC and each cognitive phenotype in pars triangularis (pTRI)/pars opercularis (pOPC), superior temporal gyrus (STG), and supramarginal gyrus (SMG). Significant differences from HC are depicted in gray/blue within each region of interest. B) Differences in local efficiency within the left and right STG between HC and each cognitive phenotype across different network densities. Shaded areas represent the upper and lower bounds in local efficiency for HC.

Tables

Table 2.1: *Demographics and clinical variables*

	TLE		HC	
N	70		46	
Age	36.14 (13.66)		36.19 (14.13)	
Education	13.34 (2.26)		15.80 (2.33)	
Sex: M/F	33/37		19/27	
	Language & Memory Impaired	Memory Impaired	Language Impaired	No Impairment
N	17	14	20	19
Age (years)	36.06 (15.51)	40.14 (14.56)	32.60 (13.06)	37.00 (11.86)
Education (Years)	13.00 (2.85)	13.71 (2.19)	13.15 (2.28)	13.58 (1.57)
Sex: M/F	8/9	10/4	10/10	5/14
Handedness: L/R/A	2/14/1	2/11/1	1/19	2/17
MTS: Yes/No	11/6	8/6	8/11	9/10
Side: L/R/Bilateral	8/8/1	7/7	8/9/3	8/10
Age of Onset	17.82 (12.08)	32.07 (16.50)	11.25 (12.12)	20.68 (14.17)
Duration (years)	18.24 (19.22)	8.07 (8.87)	21.35 (13.47)	16.32 (16.89)
Number of AEDs	1.88 (.857)	2.35 (.633)	2.45 (.887)	2.36 (.83)
Seizure frequency*	6.10 (5.72)	6.83 (5.63)	4.47 (4.23)	4.05 (2.34)

TLE: temporal lobe epilepsy; F: females; M: males; L: left; R: right; A: ambidextrous; MTS: mesial temporal sclerosis; AEDs: antiepileptic drugs; standard deviations are presented inside the parentheses
* Number of seizures per month. Patients with 2 standard deviations above the mean of the entire TLE group were removed from analysis

Table 2.2: *FA and MD group comparisons*

		Language & Memory Impaired	Memory Impaired	Language Impaired	No Impairment	HC	ANOVA	
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*F*-value	*p*-value
ARC								
Left								
	FA	**0.449 (0.044)**	**0.473 (0.028)**	**0.467 (0.031)**	**0.466 (0.029)**	**0.480 (0.024)**	**3.600**	**0.008**
	MD	**0.762 (0.030)**	**0.757 (0.025)**	**0.735 (0.025)**	**0.720 (0.082)**	**0.732 (0.025)**	**3.478**	**0.010**
Right								
	FA	**0.436 (0.033)**	**0.459 (0.029)**	**0.448 (0.039)**	**0.448 (0.024)**	**0.462 (0.023)**	**3.147**	**0.017**
	MD	0.740 (0.049)	0.747 (0.036)	0.737 (0.040)	0.718 (0.089)	0.725 (0.030)	1.063	0.378
UNC								
Left								
	FA	**0.380 (0.062)**	**0.416 (0.033)**	**0.423 (0.031)**	**0.408 (0.046)**	**0.431 (0.028)**	**5.663**	**<0.001**
	MD	0.832 (0.088)	0.815 (0.028)	0.795 (0.038)	0.793 (0.085)	0.779 (0.046)	2.858	0.027
Right								
	FA	0.388 (0.049)	0.409 (0.027)	0.398 (0.030)	0.396 (0.039)	0.414 (0.255)	2.553	0.044
	MD	0.778 (0.098)	0.816 (0.032)	0.793 (0.060)	0.787 (0.111)	0.777 (0.064)	0.821	0.515
FX								
Left								
	FA	0.304 (0.037)	0.295 (0.037)	0.291 (0.039)	0.297 (0.043)	0.307 (0.030)	0.876	0.481
	MD	1.216 (0.346)	1.33 (0.357)	1.259 (0.261)	1.212 (0.197)	1.187 (0.231)	0.964	0.430
Right								
	FA	0.314 (0.080)	0.318 (0.037)	0.290 (0.050)	0.298 (0.032)	0.313 (0.033)	1.336	0.261
	MD	1.147 (0.333)	1.332 (0.355)	1.233 (0.262)	1.226 (0.189)	1.234 (0.250)	0.902	0.466
PHC								
Left								
	FA	0.326 (0.085)	0.347 (0.063)	0.342 (0.046)	0.327 (0.056)	0.367 (0.051)	2.488	0.047
	MD	0.876 (0.241)	0.846 (0.062)	0.802 (0.088)	0.811 (0.121)	0.777 (0.111)	2.038	0.094
Right								
	FA	0.332 (0.112)	0.330 (0.046)	0.337 (0.079)	0.327 (0.079)	0.370 (0.075)	1.597	0.180
	MD	0.870 (0.265)	0.889 (0.067)	0.800 (0.146)	0.804 (0.185)	0.755 (0.173)	2.248	0.068
ILF								
Left								
	FA	**0.440 (0.029)**	**0.459 (0.037)**	**0.454 (0.034)**	**0.462 (0.036)**	**0.471 (0.022)**	**3.623**	**0.008**
	MD	**0.853 (0.050)**	**0.847 (0.027)**	**0.827 (0.044)**	**0.805 (0.091)**	**0.797 (0.056)**	**5.361**	**0.001**
Right								
	FA	**0.438 (0.027)**	**0.451 (0.022)**	**0.445 (0.029)**	**0.449 (0.029)**	**0.463 (0.022)**	**3.703**	**0.007**
	MD	**0.809 (0.066)**	**0.840 (0.022)**	**0.820 (0.076)**	**0.784 (0.097)**	**0.782 (0.044)**	**3.196**	**0.016**

HC= healthy controls; ARC= arcuate; UNC= uncinate fasciculus; FX= fornix; PHC= parahippocampal cingulum; ILF = inferior longitudinal fasciculus; FA= fractional anisotropy; MD= mean diffusivity; SD= standard deviation
Bold signifies significance at an FDR correction of q*= 0.02

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Chapter 3:

Study 2

The content within this section, titled "Chapter 3: Study 2," reflects material from a paper that has been published in Epilepsia. The proper citation is as follows:

Reyes, Anny, Kaestner, Erik, Ferguson, Lisa, Jones, Jana E., Seidenberg, Michael, Barr, William B., Busch, Robyn M., Hermann, Bruce P. & McDonald, Carrie R. (2020). Cognitive phenotypes in temporal lobe epilepsy utilizing data-and clinically driven approaches: Moving toward a new taxonomy. Epilepsia, 61(6), 1211-1220.

Objective: To identify cognitive phenotypes in temporal lobe epilepsy (TLE) and test their reproducibility in a large, multisite cohort of patients using both data-driven and clinically-driven approaches.

Method: Four-hundred and seven patients with TLE who underwent a comprehensive neuropsychological evaluation at one of four epilepsy centers were included. Scores on tests of verbal memory, naming, fluency, executive function, and psychomotor speed were converted into z-scores based on 151 healthy controls (HC). For the data-driven method, cluster analysis (k-means) was used to determine the optimal number of clusters. For the clinically-driven method, impairment was defined as greater than 1.5 standard deviations below the mean of the HC, and patients were classified into groups based on the pattern of impairment.

Results: Cluster analysis revealed a 3-cluster solution characterized by 1) generalized impairment (29%), 2) language and memory impairment (28%), and no impairment (43%). Based on the clinical criteria, the same broad categories were identified, but with a different distribution; 1) generalized impairment (37%), 2) language and memory impairment (30%), and 3) no impairment (33%). There was an 82.6% concordance rate with good agreement (kappa=.716) between the methods. Forty-eight patients classified as having a normal profile based on cluster analysis, were classified as having generalized impairment (n=16) or an isolated language/memory impairment (n=32) based on the clinical criteria. Patients with generalized impairment had a longer disease duration and patients with no impairment had more years of education. However, patients demonstrating the classic TLE profile (i.e., language & memory impairment) were not more likely to have an earlier age of onset or mesial temporal sclerosis.

Significance: We validate previous findings from single-site studies that have identified three unique cognitive phenotypes in TLE and offer a means of translating the patterns into a clinical diagnostic criteria, representing a novel taxonomy of neuropsychological status in TLE.

Key Words: cognitive phenotypes, epilepsy, taxonomy

Key Points

- In a large, multi-site study of 407 patients with TLE, we validate smaller single-site studies identifying three unique cognitive phenotypes in TLE.
- We demonstrate that these phenotypes are robust to the methods employed, including clinically-driven and data-driven approaches.
- The data-driven approach misclassified 12% of the patients with clinically-defined significant impairment as having normal cognition.
- Both approaches produce groups that differed in important clinical and demographic characteristics known to impact cognition.
- Cognitive phenotypes offer a new classification framework that considers the individual variability observed within and across epilepsy syndromes.

Introduction

Cognitive impairment is the most prevalent comorbidity in patients with temporal lobe epilepsy (TLE), with many patients demonstrating impairments in language, memory, and executive function (Bell, Lin, Seidenberg, & Hermann, 2011; Saling, 2009; Stretton & Thompson, 2012). In a subset of patients, these impairments have been shown to be progressive in nature (C. Helmstaedter, Hermann, B., Lassonde, M., Kahane, P., & Arzimanoglou, A, 2011; C. Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003; B. P. Hermann et al., 2006; Thompson & Duncan, 2005). Furthermore, patients with TLE who undergo unilateral anterior temporal lobectomy (ATL) or other surgical procedures are at risk for additional cognitive decline (C. Helmstaedter, 2013; C. Helmstaedter et al., 2003). Despite patients with focal TLE having seizures arising from temporal lobe regions, there is variability in the nature and severity of cognitive impairment observed across patients, with some demonstrating generalized impairment, some showing a profile of focal cognitive deficits, and others showing relatively intact cognitive profiles (Elverman et al., 2019; B. Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; Reyes et al., 2019).

In efforts to unravel the heterogeneity of cognitive impairment in TLE, studies have shifted from examining TLE patients in aggregate to identifying latent profiles, or *cognitive phenotypes*, within TLE (Dabbs, Jones, Seidenberg, & Hermann, 2009; Elverman et al., 2019; B. Hermann et al., 2007; Kaestner et al., 2019; Reyes et al., 2019; Rodriguez-Cruces et al., 2018). The first study of its kind identified three distinct cognitive phenotypes using cluster analysis, which included a group of patients with isolated memory impairment, a second group with minimal impairment, and a third group with more generalized and pervasive impairment (B. Hermann et al., 2007). Follow-up studies have identified similar cognitive phenotypes and shown that these phenotypes are associated with unique patterns of structural and functional abnormalities, with more pervasive

cognitive impairment associated with distributed brain abnormalities and isolated deficits associated with restricted regions of brain dysfunction (Dabbs et al., 2009; B. Hermann et al., 2007; Bruce P. Hermann et al., 2019; Reyes et al., 2019; Rodriguez-Cruces et al., 2018). However, there is some variability in the phenotypes described across studies, as well as the clinical characteristics and neuroimaging findings associated with each phenotype. This may be due to characteristics of single site data, methods used to derive the phenotypes, the limited sample sizes available, and/or the extent of the cognitive assessment employed (limited versus extensive), and the variability in tests administered across studies. As this literature continues to develop, it is critical to further validate the clinical utility of the *cognitive phenotypes* derived from data-driven approaches by establishing diagnostic criteria that can be used in clinical practice.

The neuropsychological approach to determining cognitive impairment in clinical practice includes a comprehensive review of all test scores with the operational definition of impairment typically ranging from 1 to 2 standard deviations (SD) below normative means. This approach is employed in presurgical evaluations aimed at estimating risk for postoperative cognitive decline and for determining overall cognitive trajectories in TLE. Recently, our group has utilized a modified clinically-driven method adopted from the mild cognitive impairment (MCI) literature (Kaestner et al., 2019; Reyes et al., 2019) where phenotypes are derived by considering impairment profiles across multiple tests within each cognitive domain. In this approach, impairment is defined as greater than 1-1.5 SD below the normative mean on two or more measures within each domain and patients are grouped into phenotypes based on the pattern of impairment. Conversely, the most common approach in research studies of phenotyping in TLE has been to derive groups based on cluster analysis (Dabbs et al., 2009; Elverman et al., 2019; B. Hermann et al., 2007; Rodriguez-Cruces et al., 2018), a data-driven method where objects (e.g., individuals) are portioned into

groups based only on information found in the data. The goal of this method is to produce empirically meaningful groups that share common characteristics without restrictions imposed by the user (e.g., clinician).

Given the common use of data-driven approaches in research, we sought to validate the cognitive phenotypes reported in the literature using cluster analysis and then to determine whether the derived data-driven phenotypes are concordant with those identified using a neuropsychological diagnostic approach commonly used in clinical practice. We test both approaches in a large, multi-center cohort of patients with TLE and identify the clinical profiles associated with each phenotype for each approach. Second, we compare the concordance rate between our data-driven and clinical approaches. Based on the existing literature, we predicted that both approaches would yield three phenotypes including a group of patients with generalized impairment, a group with primarily verbal memory and/or language deficits, and third group with normal cognition.

Methods

Participants

This study was approved by the Institutional Review Boards at UC San Diego, UC San Francisco, University of Wisconsin Madison, and Cleveland Clinic. Informed consent was collected from patients and healthy controls (HC) at UC San Diego, UC San Francisco, and University of Wisconsin Madison. At Cleveland Clinic, data were collected as part of an IRB-approved data registry. Four-hundred ninety-four patients with TLE and 150 HC met inclusion criteria for the study. Patients were included in the study if they had a diagnosis of TLE by a board-certified neurologist with expertise in epileptology, in accordance with the criteria defined by the International League Against Epilepsy, and based on video-EEG telemetry, seizure semiology,

and/or neuroimaging evaluation. The presence of mesial temporal sclerosis (MTS) was determined by inspection of MRI images by a board-certified neuroradiologist. Healthy controls were recruited through community and patient networks were included if they were between the ages of 18 and 65 and had no reported history of neurological or psychiatric disease.

Neuropsychological measures

All patients and HC completed neuropsychological testing. The following tests were common across the sites and were selected based on recommendations from the National Institute of Neurological Disorders and Stroke (NINDS) Epilepsy Common Data Elements (CDE; Loring et al., 2011) and the ILAE Neuropsychology Task Force Diagnostic Methods Commission (Baxendale et al., 2019). In addition, measures of motor dexterity and processing speed were included based on previous studies demonstrating that these skills are often impaired in TLE patients with generalized impairment (Elverman et al., 2019; B. Hermann et al., 2007). Verbal memory was evaluated with Wechsler Memory Scale-Third Edition (WMS-III) Logical Memory (LM) and Verbal Paired Associates (VPA; Wechsler, 1997); language ability was evaluated with the Boston Naming Test (BNT; Kaplan, 2001) and letter fluency; executive function was measured with the Trail Making Test B (TMT-B); processing speed was measured with TMT-A; fine motor dexterity was measured with Grooved Pegboard [Peg dominant (PegD) and non-dominant hand (PegND)]. Age-corrected scaled scores were calculated for LM and VPA based on normative data provided by the test manual. Age, education, and sex-corrected T-scores were calculated for the BNT, letter fluency, TMT-A, TMT-B, and the Grooved Pegboard based on normative data from expanded Halstead-Reitan Battery (Heaton, Miller, Taylor, & Grant-Isibor, 2004). Although letter fluency has both a language and an executive function component, in our sample letter fluency scores showed a stronger correlation with BNT scores ($r = .499$, $p < .0001$) than TMTB ($r = .353$,

$p < .001$); therefore, we included letter fluency in the language domain. For verbal memory, immediate and delayed memory indices were created by summing the scaled scores for LM I and VPA I immediate total recall scores and LM II and VPA II for delayed total recall, respectively. From a total of 494 TLE patients, 87 patients had missing individual data points on the neuropsychological battery and were therefore excluded from analysis. Case-wise exclusion of patients was necessary given that cluster analysis cannot accommodate missing data. We compared important demographic and clinical variables between the 87 patients that were excluded and the remaining 407 patients. There were no differences in education, age, age of onset, duration of epilepsy, presence of MTS or seizure side (all p-values >.05). Scores for the remaining 407 patients were converted into z-scores based on the HC data. No patients were removed based on outlier detection.

Data-driven: Cluster analysis

Patients' z-scores were subjected to k-means clustering, an algorithm that defines groups in terms of a centroid, which is typically the mean of a group of points (e.g., cognitive test scores). We tested whether a 3-cluster solution from Hermann et al. (B. Hermann et al., 2007) was optimal in our dataset by using the NbClust R package (Charrad M, 2013), which provides 23 indices for determining the number of clusters and proposes the optimal number of clusters from the different results obtained by varying all combinations of number of clusters, distance measures, and clustering methods. To further evaluate the clustering algorithm, the Dunn Index was calculated (Dunn, 1973; Dunn†, 1974). The Dunn Index is the ratio of the smallest distance between observations not in the same cluster to the largest intra-cluster distance. The Dunn Index has a value between zero and infinity, with a higher value indicating better clustering.

Clinically-driven: Neuropsychological criteria

For the clinical approach, we defined impairment as greater than 1.5 standard deviations below the mean of the HC for each test. This impairment cut-off has been shown to be sensitive enough to detect impairment while maintaining specificity (Jak et al., 2009). Second, patients were grouped into phenotypes based on the number of impaired tests and the pattern of impairment, which based on the previous literature was hypothesized to fit three diagnostic cognitive patterns (B. P. Hermann et al., 2006). *Generalized impairment* was defined as having impairment in at least four of the seven tests, with at least one test per cognitive domain impaired. The *domain-specific* group was defined as having impairment in verbal memory and/or language, with impairment in either the two tests of verbal memory (i.e., immediate and delayed memory) or the two tests of language (i.e., BNT, letter fluency); for patients with impairment in both domains, they had to be impaired in at least three out of the four tests of verbal memory and language. The *normal cognitive profile* included patients who met impairment criteria on only one or none of the 7 measures. Several studies have demonstrated that impairment on one test is common among individuals with no neurological or psychiatric disorders (Binder, Iverson, & Brooks, 2009).

Statistical Analysis

Independent *t*-tests and Fisher's Exact tests were used to test for differences in demographic variables between patients and HC. An analysis of agreement using the Cohen's Kappa statistic was performed to determine the consistency of impairment classification between the two approaches. To determine if the two approaches yield different clinical profiles, analysis of variance (ANOVAs) were conducted to compare clinical and demographic variables across the clinical phenotypes and the clusters, respectively. Benjamini-Hochberg false discovery rate was used to correct for the multiple comparisons across the ANOVAs conducted.

Results

Demographics and patient clinical variables

There were no differences in age [t (555) = .88, p = .38] or sex distribution (Fisher's Exact = 1.29, p = .289) between patients with TLE and HC; however, as expected, HC had more years of education [t (555) = -6.01, p < .001] (Table 3.1).

Cluster analysis

Ten out of the 23 indices from NbClust R package indicated that a 3-cluster solution was an optimal number of clusters for portioning the data. The DI for a 3-cluster solution was DI= 0.098. *Cluster 1* was comprised of 29% of patients, *Cluster 2* included 28% of the patients, and *Cluster 3* was comprised of 43% of the patients (Figure 3.1). Regarding the pattern of impairment within clusters, patients in *Cluster 1* demonstrated impairments across all domains (*Cluster-Gen),* patients in *Cluster 2* showed predominantly impairments in language and/or verbal memory (*Cluster-LM*), and patients in *Cluster 3* demonstrated minimal impairment at the group level (*Cluster-MI*). Table 3.2A shows differences in clinical and demographic variables across the clusters. Patients in the *Cluster-LM* were younger than patients in the *Cluster-MI* (p<.001) and *Cluster-Gen* groups (p<.001). Patients in the *Cluster-MI* had more education relative to the *Cluster-LM* (p<.001) and the *Cluster-Gen* (p=.004) groups. Patients in the *Cluster-MI* also had an older age of seizure onset compared to the *Cluster-LM* (p <.001), but not with the *Cluster-Gen*. Patients in the *Cluster-Gen* had a longer disease duration relative to the *Cluster-MI* (p=.011) and *Cluster-LM* (p=.018). The *Cluster-MI group* had a comparable number of right and left TLE patients, while the *Cluster-LM and Cluster-Gen* groups both had a greater number left TLE patients.

Clinical criteria

Based on the clinical approach, 37% percent of patients met diagnostic criteria for having a generalized impairment profile (*Generalized*), 30% were impaired on verbal memory and/or language measures (*Language & Verbal Memory*), and 33% did not meet criteria for impairment and were classified in the no impairment group (*No Impairment*). No patients showed isolated executive function or processing speed impairments. Out of those patients in the *No Impairment* group, 52 patients had impairment on one test and 70 patients did not demonstrate impairment on any test. Table 3.2B shows differences in clinical and demographic variables across the clinically-derived phenotypes. Patients in the *No Impairment* group had greater years of education relative to the *Language & Verbal Memory* (p=.001) and *Generalized* groups (p=.040). Patients in the *No Impairment* group also had an older age of seizure onset compared to the *Language & Verbal Memory* (p =.040) and *Generalized* groups (p= .004). There was a trend for patients in the *Generalized* group to have a longer disease duration relative to the *No Impairment* group (p=.050). Information on MTS status was available for 77% of the patient sample. There was a trend for patients in the *No Impairment* group to have fewer patients with MTS (40%) relative to the other two patient groups.

Concordance

Cohen's Kappa statistic revealed moderate agreement between the two approaches (κ = .716 p < .001), with an 82.6% concordance rate. Forty-eight patients classified into *Cluster-MI* (i.e., minimal impairment) met clinical criteria for having verbal memory and language impairment (n=32) or generalized impairment (n=16) (Figure 3.2). Table 3 shows the clinical characteristics of the *clinically-impaired* patients that were classified as *Cluster-MI* with cluster analysis. As expected, these patients demonstrated more subtle or circumscribed impairments across the tests. Specifically, the *mis-classified* Verbal Memory & Language impaired patients tended to show

subthreshold impairment in immediate (z = -1.16) and delayed (z = -1.23) memory rather than in naming (-1.18) or fluency (-.86) (i.e., an isolated verbal memory deficit), and the *mis-classified* Generalized impairment patients showed impairment in executive functioning (z= -1.85), with more subtle deficits in other domains.

Alternative clusters

In a more recent paper, Elverman et al. (Elverman et al., 2019) found a 4-cluster solution to be clinically meaningful, where two groups of patients with focal impairment emerged. Therefore, we also tested the robustness of a 4-cluster solution to examine whether we could identify sub-groups of patients with more focal impairments (see supplemental Figure available online). The 4-cluster solution produced one group that was minimally impaired (26%), one group that showed only language and/or verbal memory impairment (21%), and two groups that showed generalized impairment, but with one disproportionately impaired in language & verbal memory relative to the other (34% and 19%, respectively). However, the latter two groups showed overlapping patterns across most tests. Therefore, the 3-cluster solution produced more distinct, interpretable phenotypes.

Discussion

In a large, multi-site study of 407 patients, we validate previous findings from single-site studies that have identified unique cognitive phenotypes in TLE. We add to this literature by demonstrating the robustness of these phenotypes across data-driven and clinically-driven approaches and, for the first time, show how established neuropsychological criteria can be applied to identify phenotypic impairment at the individual patient level. Previous studies have identified the same general pattern of impairment across phenotypes in TLE: a group with domain-specific impairments in verbal memory and language, a group of patients with broad and pervasive

impairment, and a group of patients with intact cognition (Elverman et al., 2019; B. Hermann et al., 2007; Reyes et al., 2019). While these studies have been pivotal for discovering these phenotypes in independent datasets, they have not offered a means of translating the patterns into the clinical diagnostic setting. Here, we demonstrate that both approaches identified the same broad phenotypes with moderate agreement. Overall, these findings offer validation that 1) cognitive phenotypes are stable across TLE samples and 2) specific neuropsychological criteria can be applied to re-create these clusters and diagnose impairment profiles at the individual patient level.

Implications of a network disorder in cognitive taxonomy

The traditional view of TLE as characterized by focal, often unilateral, medial temporal lobe dysfunction has been replaced by one that appreciates TLE as a network disorder with widespread abnormalities, including bilateral temporal and extra-temporal cortical thinning (Lin et al., 2007; McDonald et al., 2008; Whelan et al., 2018), widespread alterations in deep white matter tracks (Leyden et al., 2015; Otte et al., 2012) and superficial white matter (Chang et al., 2019; Liu et al., 2016; Reyes et al., 2019), and increased large-scale network disruption (Bernhardt, Chen, He, Evans, & Bernasconi, 2011; van Diessen et al., 2014). More importantly, studies of structure-function relationships in TLE have shown that these diffuse brain abnormalities are associated with a wide range of cognitive deficits (Allone et al., 2017; Bell et al., 2011; Leyden et al., 2015). However, there are inconsistencies across neuroimaging studies in the nature and strength of these associations which may, in part, reflect studies aggregating all patients into one group. We replicate smaller studies that have identified three major cognitive phenotypes within the syndrome of TLE (Dabbs et al., 2009; Elverman et al., 2019; B. Hermann et al., 2007; Reyes et al., 2019). Studies examining the neural correlates associated with each phenotype have found

that patients with generalized impairment have brain abnormalities that are widespread in nature, those with syndrome-specific memory and language deficits have circumscribed alterations within the temporal lobes, and patients with intact cognition have brains comparable to healthy controls (Reyes et al., 2019; Rodriguez-Cruces et al., 2018). Therefore, treating all patients with TLE as a single group may obscure important cognitive and neuroanatomical variability across patient samples that are important for our understanding of the impact of TLE on cognition, which may hamper *precision neuropsychology*---the diagnosis and treatment of cognitive impairment in patients with epilepsy at the individual patient level.

Clinical features associated with cognitive phenotypes

Approximately 25% of patients across recent phenotype studies have demonstrated specific impairments in memory and/or language (Dabbs et al., 2009; Elverman et al., 2019; B. Hermann et al., 2007; Reyes et al., 2019). We found that both approaches identified a similar proportion of patients with language and verbal memory impairment, with cluster analysis classifying 28% of patients and the clinical criteria identifying 30% as language/verbal memory impaired. Despite these patients demonstrating the traditional cognitive profile associated with TLE, they comprised the smallest group across both approaches. Furthermore, these patients did not demonstrate the traditional *clinical* profile associated with TLE; for example, they were not more likely to have an earlier age of seizure onset or a greater proportion of patients with MTS than the other groups. Our generalized group represented 40% of the patients when classified with the clinical criteria. These patients had longer disease duration (20 years on average) relative to patients with isolated verbal memory and language impairment and those with minimally impaired profiles. Longer disease duration has been associated with worse cognition and adverse long-term cognitive outcomes (C. Helmstaedter & Elger, 2009; C. Helmstaedter et al., 2003; B. P. Hermann et al.,

2006). Hermann et al. (B. Hermann et al., 2007) demonstrated that patients with generalized impairment and longer disease duration were at increased risk for an abnormal cognitive trajectory compared to patients with domain-specific impairment over a 4-year interval. These findings suggest that cognitive phenotyping may not only explain the underlying neurobiology, but may also be important for predicting clinical course. However, disease duration alone may not explain the pervasive cognitive dysfunction observed in these patients given that other studies have not found this association (Elverman et al., 2019; Reyes et al., 2019). Given some evidence that patients with TLE are at increased risk for progressive neurophysiological and structural brain changes, it is possible that patients with generalized impairment represent a group of patients with co-morbid non-epilepsy pathology, elevated health-related risk factors, greater generalized tonic-clinic seizures or low brain reserve. Finally, patients with minimally impaired profiles may represent a group of individuals with higher brain reserve given their intact cognition despite having similar clinical features to those with cognitive dysfunction. In our study, these patients had greater years of education, which has been hypothesized to be protective against epilepsy-related cognitive dysfunction (Jokeit & Ebner, 1999; Oyegbile et al., 2004). Importantly, both approaches produce groups that differed in important clinical and demographic characteristics known to impact cognition.

Misclassification

Although cluster analysis was able to correctly classify 82% of the patients based on their clinically-identified profiles, approximately 12% of patients with clinically significant impairment were classified as having a minimally impaired profile. These patients at the group level had more subthreshold anomalies than those who were classified into the other two groups. These results suggest that cluster analysis may be less sensitive for detecting complex patterns of impairment

within smaller samples. It is also possible that given our limited number of tests per domain, we were not able to capture the full pattern of impairment of these patients across all cognitive domains. Notably, cluster analysis is very sample-dependent given that it portions the data based on the information that is available and therefore, it is possible that these patients could have been classified into different solutions if we had a more comprehensive test battery. By contrast, the clinical criteria employed in our study are uniform in nature and are robust to different samples.

Given that Elverman et al. (Elverman et al., 2019) identified two subgroups of patients with isolated language and memory impairment and isolated executive function and processing speed, respectively, we ran a 4-cluster solution to determine whether these groups would emerge from those patients that were miss-classified. From our 4-cluster solution, two groups of patients with generalized impairment emerged, with one group demonstrating greater impairment in verbal memory relative to the other group. However, all other tests scores were highly overlapping, limiting the distinctness of these groups. The other two groups identified in the 4-cluster solution were similar to those identified in the 3-cluster solution, which included a group with isolated verbal memory and language impairment and a group with minimal impairment. A potential explanation for the discrepancy between the two studies is that the patients in our study were more impaired, on average, compared to the patients in Elverman et al. In fact, the phenotypes in their study were not clinically impaired but overall demonstrated low scores across multiple domains.

Limitations

There are several limitations to our study. First, we had an appropriate but somewhat limited number of tests per domain and therefore we could not further divide the patients into finer subgroups (i.e., verbal memory only, language only). Second, we did not have common visual memory and visuospatial tests across all three sites and therefore could not include these two

domains in our analyses. We recognize that not including a non-verbal memory test in the characterization of TLE phenotypes limits the generalizability of our findings. However, available non-verbal memory tests have shown poor sensitivity to right medial temporal lobe dysfunction in epilepsy (Barr, 1997; Barr et al., 1997; Saling, 2009; Vaz, 2004). This poor sensitivity of non-verbal memory measures is reflected in the NINDS Epilepsy CDEs, which do not recommend any specific tests for this domain. Furthermore, the visuospatial domain is included as an optional domain to include and is very seldom impaired in TLE (Barr, 1997; Tallarita, Parente, & Giovagnoli, 2019; Vaz, 2004), even in patients with generalized impairment (Elverman et al., 2019; B. Hermann et al., 2007). However, future research incorporating protocols that include multiple non-verbal tests that are sensitive to non-dominant hemisphere dysfunction could help to refine cognitive phenotypes in TLE and other epilepsy syndromes. Third, we did not have neuroimaging data on our patients and therefore could not explore brain abnormalities associated with each phenotype. Future studies of brain-behavior relationships with large samples such as ours are warranted to replicate the findings in the literature on a large scale. Fourth, we had to remove 87 patients from the analysis given that cluster analysis does not handle missing data. In the future, we plan to explore the misclassification patterns of cluster analysis by comparing this method to other data-driven approaches robust to missing data. Fifth, our patient group consisted of mostly drug-resistant TLE, which may not generalize to all patients with TLE. However, the stability of these three phenotypes has recently been identified in a cohort of patients with mostly well-controlled TLE (Bruce P. Hermann et al., 2019). Finally, there are other epilepsy-related clinical variables (i.e., number and types of seizures, life-time number of GTC seizures, history of AEDs) that were not available in our dataset that may further differentiate the phenotypes identified.

Conclusion

We demonstrate the clinical translation of more than a decade of research into cognitive phenotypes in TLE. Specifically, in a large, multi-center sample, we propose a diagnostic approach for characterizing phenotypic patterns of impairment at the individual patient level. This classification framework not only helps to establish more meaningful cognitive and neurobehavioral taxonomies, but it could improve our ability to predict individual cognitive trajectories and/or match patients to individual treatments in order to improve a range of epilepsy-related outcomes. While studying cognitive dysfunction based on epilepsy syndromes has expanded our understanding of the impact of epilepsy-related pathology on cognition, the phenotyping approach has offered a new classification framework that considers the individual variability observed within and across epilepsy syndromes. Further studies evaluating cognitive phenotypes in other epilepsy syndromes (e.g., frontal lobe epilepsy, genetic generalized epilepsy, juvenile myoclonic epilepsy) are needed in order to identify syndrome-dependent and syndrome-independent phenotypes that could improve our ability to match patients to treatments and improve epilepsy-related outcomes.

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Disclosure of conflicts of interest/ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflicts of interest to disclose.

Dissertation Author's Acknowledgements

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Figures

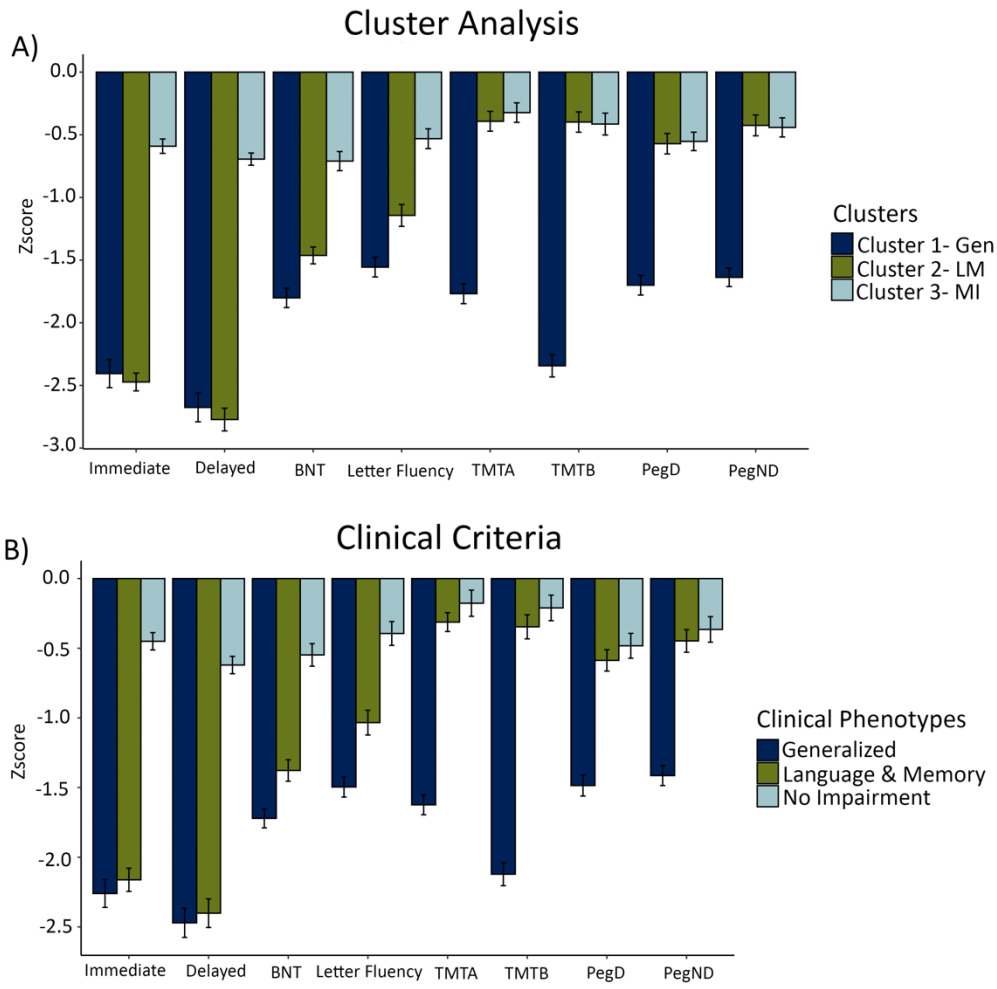

Figure 3.1: *Distribution of cognitive scores across groups for the cluster analysis and clinical criteria.* Scores are represented as mean z-scores and error bars represent standard deviations.

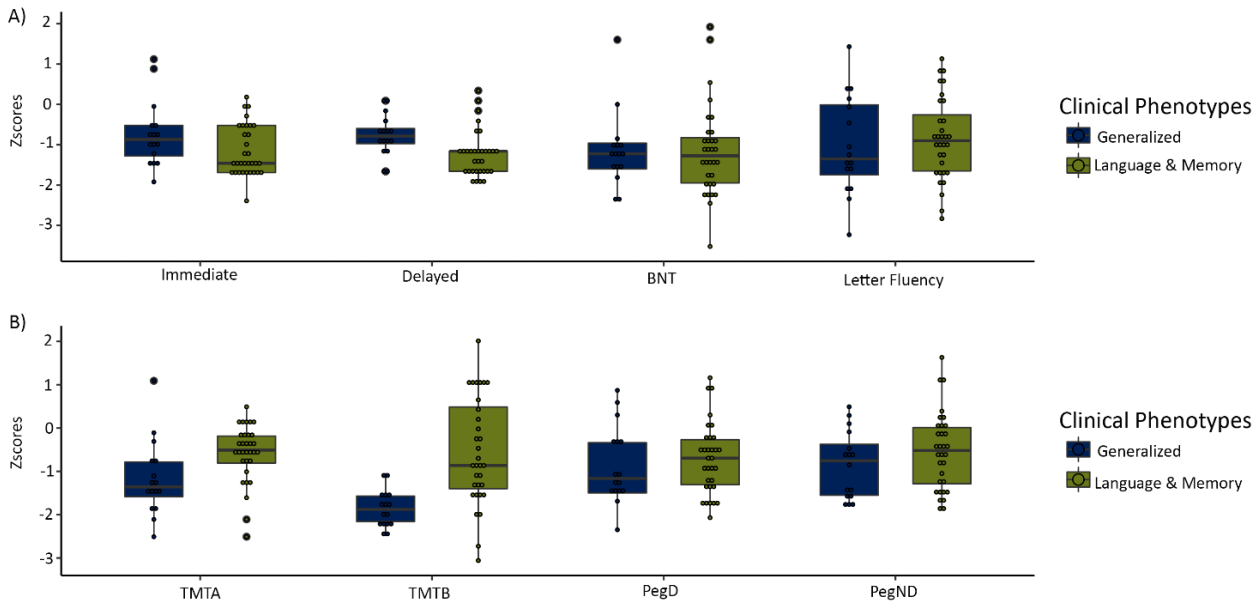

Figure 3.2: *Distribution of z-scores for patients that were mis-classified as having minimal impairment based on cluster analysis*.

Tables

Table 3.1: *Demographics and clinical variables*

	All TLE	HC
N	407	150
Age	36.36 (12.29)	35.31 (13.26)
Education	13.22 (2.4)	14.61 (2.5)
Sex: M/F	182/225	59/91

TLE: temporal lobe epilepsy; F: females; M: males; L: standard deviations are presented inside the parentheses

Table 3.2: *Demographics and clinical variables clusters and clinical phenotypes*

A) Demographics and clinical variables across clusters					
	Cluster 1-Gen	Cluster 2-LM	Cluster 3-MI		
n	118	113	176	ANOVA	*p*-value
Age (years)	36.15 (12.44)	34.92 (11.68)	37.43 (12.29)	1.467	.232
Education (Years)	12.97 (2.39)	12.76 (2.19)	13.67 (2.43)	**6.012**	**.003**
Age of Onset	15.54 (12.66)	16.89 (12.88)	19.97 (13.91)	**4.322**	**.014**
Duration (years)	20.59 (12.82)	18.01 (12.16)	17.43 (12.83)	2.316	.100
				Fisher's Exact	*p*-value
Sex: M/F	48/70	60/53	74/102	4.46	.109
Handedness: L/R/A	17/97/3	17/92/4	22/148/6	3.15	.909
Side: L/R/Bilateral	68/35/4	69/32/4	77/67/7	6.89	.135
MTS: Yes/No	53/39	54/41	48/74	**9.43**	**.009**
B) Demographics and clinical variables across clinical phenotypes					
	No Impairment	Language & Verbal Memory	Generalized		
n	133	121	153	ANOVA	*p*-value
Age (years)	37.53 (12.65)	35.56 (12.17)	35.98 (12.09)	.928	.396
Education (Years)	13.80 (2.43)	12.72 (2.16)	13.10 (2.4)	**6.95**	**.001**
Age of Onset	20.99 (13.67)	16.86 (13.61)	15.86 (12.51)	**5.81**	**.003**
Duration (years)	16.51 (12.12)	18.69 (12.76)	20.11 (12.94)	*2.905*	*.056*
				Fisher's Exact	*p*-value
Sex: M/F	61/72	60/61	61/92	2.69	.254
Handedness: L/R/A	20/108/5	15/102/4	21/127/4	2.39	.975
Side: L/R/Bilateral	58/49/3	68/41/4	88/44/8	5.29	.257
MTS: Yes/No	36/54	58/45	61/55	*5.53*	*.063*

F: females; M: males; L: left; R: right; A: ambidextrous; MTS: mesial temporal sclerosis; MI: minimal impairment; LM: language & memory; Gen: generalized; standard deviations are presented inside the parentheses
Bold: significant with FDR correction

Table 3.3: *Demographics and clinical variables across clinically impaired patients classified as having a normal profile with cluster analysis*

	Language & Verbal Memory	Generalized
N	32	16
Age (years)	36.09 (13.19)	37.82 (10.66)
Education (Years)	13.13 (2.34)	14.00 (2.556)
Age of Onset	17.00 (13.82)	16.81 (14.15)
Duration (years)	19.09 (14.27)	21.01 (14.02)
Sex: M/F	13/19	3/13
Handedness: L/R/A	1/30/1	1/14/1
Side: L/R/Bilateral	15/13/2	7/6/2
MTS: Yes/No/Unknown	9/17/6	4/6/6
Neuropsychological Profile		
Immediate Memory	-1.16 (.626)	-.74 (.816)
Delayed Memory	-1.23 (.571)	-.771 (.515)
BNT	-1.18 (.1.12)	-1.15 (.928)
Letter Fluency	-.861 (1.09)	-1.02 (1.22)
TMT-A	-.568 (.663)	-1.16 (.867)
TMT-B	-.546 (1.24)	-1.85 (.428)
Peg Dominant	-.714 (.828)	-.865 (.901)
Peg Non-Dominant	-.538 (.898)	-.849 (.777)

F: females; M: males; L: left; R: right; A: ambidextrous; MTS: mesial temporal sclerosis; BNT: Boston Naming Test; TMT-A: Trail Making Test condition A; TMT-B: Trail Making Test condition B; Peg: Grooved Pegboard; standard deviations are presented inside the parentheses

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Chapter 4:

Study 3

The content within this section reflects material from a paper that is under review in Brain Communications. The dissertation author was the primary investigator and author of this material. Reyes, Anny, Hermann, Bruce P., Busch, Robyn, Drane, D., Barr, William B., Hamberger, Marla J., Roesch, Scott, & McDonald, Carrie R. Moving towards a taxonomy of cognitive impairments in epilepsy: Application of latent profile analysis to 1,178 patients with temporal lobe epilepsy.

Abstract

Background: Utilize latent profile analysis (LPA) to test several models of cognitive phenotypes in a large multicenter sample of patients with temporal lobe epilepsy (TLE) and evaluate their demographic and clinical profiles. To examine the added value of replacing missing data and examine factors that may be contributing to missingness.

Method: A sample of 1,178 participants met inclusion criteria for the study, which included a diagnosis of TLE and availability of comprehensive neuropsychological data. Models with 2-5 classes were examined using LPA and the optimal model was selected based on fit indices, posterior probabilities, and proportion of sample sizes. The models were also examined with imputed data to investigate the impact of missing data on model selection.

Results: Based on the fit indices, posterior probability, and distinctiveness of the latent classes, a 3-class solution was the optimal solution. This 3-class solution was comprised of a group of patients with multidomain impairments, a group with impairments predominantly in language, and a group with no impairments. Overall, the *Multidomain* group demonstrated a worse clinical profile and was comprised of a greater proportion of patients with mesial temporal sclerosis, longer disease duration, and higher number of antiseizure medications. The 4-Class and 5-Class solutions demonstrated the lowest probabilities of group membership. Analyses with imputed data demonstrated that the 4-Class solution was the optimal solution; however, there was weak agreement between the missing and imputed datasets for the 4-Class solutions ($\kappa = .288$, $p < .001$).

Conclusions: This study represents the first to use LPA to test and compare multiple models of cognitive phenotypes in TLE, and to determine the impact of missing data on model fit. We found that the three-phenotype model was the most meaningful based on several fit indices and produced phenotypes with unique demographic and clinical profiles. Our findings demonstrate that LPA is

a rigorous method to identify phenotypes in large, heterogeneous epilepsy samples. Furthermore, this study highlights the importance of examining the impact of missing data in phenotyping methods. Our LPA-derived phenotypes can inform future studies aimed at identifying cognitive phenotypes in other neurological disorders.

Abbreviated summary: Reyes et al. utilize latent profile analyses to derive cognitive phenotypes in a large, multi-site study of 1,178 patients with temporal lobe epilepsy. The authors found that the three-phenotype model was the most meaningful based on several fit indices, the most robust to missing data, and produced phenotypes with unique demographic and clinical profiles.

Key words: temporal lobe epilepsy, cognitive phenotype, taxonomy, latent profile analyses, data-driven approach, memory, language

Running title: Utility of latent profile analyses

Introduction

The cognitive comorbidities of epilepsy have been an area of research inquiry for over a century (David W Loring, 2010) and are now part of the formal definition of epilepsy *(Robert S Fisher et al., 2005)*. Historically, the lesion model has been used to examine the relationship between epilepsy pathology and cognition, yielding syndrome-specific cognitive profiles (B. P. Hermann et al., 2021). However, a myriad of studies have demonstrated that cognitive impairments in epilepsy are more widespread and generalized than hypothesized by the lesion model (Allone et al., 2017; B. Bell, J. J. Lin, M. Seidenberg, & B. Hermann, 2011). For example, patients with temporal lobe epilepsy (TLE) demonstrate impairments in domains that are not typically associated with temporal lobe damage (i.e., executive function), and those with frontal lobe epilepsy demonstrate impairments in "non-frontal" functions (i.e., memory) (Arrotta et al., 2021; Centeno, Thompson, Koepp, Helmstaedter, & Duncan, 2010; Helmstaedter, Kemper, & Elger, 1996; Stretton & Thompson, 2012). Further, there is significant variability within epilepsy syndromes with some patients demonstrating generalized impairment while others have minimally impaired profiles despite having similar clinical features (Arrotta et al., 2021; B. Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; B. P. Hermann et al., 2021; Reyes et al., 2019; Reyes et al., 2020).

In efforts to better understand the cognitive heterogeneity within and across epilepsy syndromes, an emerging taxonomy has been proposed and validated in several independent samples. The phenotyping approach identifies *latent groups* or *phenotypes* that share similar patterns of performance across a series of neuropsychological tests. To date, 18 studies have identified phenotypes based on objective or subjective cognitive impairments across a range of epilepsy disorders (for a review see B. P. Hermann et al., 2021). Several of these studies have also

found neuroimaging correlates that are unique to each phenotype and more directly map on to the pattern of cognitive impairment that is otherwise obscured by the lesion-based model (Dabbs, Jones, Seidenberg, & Hermann, 2009; B. Hermann et al., 2020; Reyes et al., 2019; Rodríguez-Cruces, Bernhardt, & Concha, 2020; Rodriguez-Cruces et al., 2018). Furthermore, this approach has been shown to be useful in examining cognitive progression (B. Hermann et al., 2007) and postoperative cognitive decline (Baxendale & Thompson, 2020). Importantly, this new taxonomy allows for the integration of non-epilepsy factors that are known to impact cognition and exacerbate existing neurological disorders and may further explain the heterogeneity in cognitive impairment observed within epilepsy syndromes (B. P. Hermann et al., 2021).

In TLE specifically, 3-5 phenotypes have been identified, with three consistent groups across studies: a group of patients with generalized impairment, a group with a more domain-specific profile (e.g., memory and language), and a subgroup with minimally impaired cognitive profiles (Elverman et al., 2019; Garcia-Ramos et al., 2021; B. Hermann et al., 2020; B. Hermann et al., 2007; Reyes et al., 2019; Reyes et al., 2020; Rodriguez-Cruces et al., 2018). The generalized and intact phenotypes have been uniformly described across studies, however, there has been substantial variability in the number and nature of the "focal" or domain-specific phenotypes across investigations. Thus, a final or definitive taxonomy remains to be determined. The variability in the domain-specific group may in part be due to differences in the methodology used across investigations. Methods to cognitive phenotyping have included data-driven approaches such as cluster analysis as well as actuarial approaches, which consist of establishing and applying *a priori* criteria for impairment. Our group has demonstrated that there is high concordance between phenotypes derived from cluster analysis and actuarial neuropsychology criteria; however, cluster analysis tends to misclassify patients with clinically-defined cognitive

impairments as having intact cognition (Reyes et al., 2020). Furthermore, many of the phenotype studies have been conducted in single epilepsy centers with modest samples sizes which could have impacted the number and nature of the derived phenotypes. We argue that studies with large samples and rigorous methodology are needed in order to derive at a definitive taxonomy, particularly as we are to translate these research-based phenotypes into clinical practice or deploy our model for international use.

The utility of the cognitive phenotyping approach has been evaluated in other neurological, developmental, and psychiatric disorders including multiple sclerosis (De Meo et al., 2021; Leavitt, Tosto, & Riley, 2018), Parkinson's disease (Barvas et al., 2021; Kenney et al., 2022), Autism Spectrum Disorder (Charman et al., 2011), and childhood psychiatric disorders (Kavanaugh et al., 2016). These studies have demonstrated that deriving more clinically meaningful cognitive phenotypes leads to a better understanding of the pathophysiological mechanisms underlying these conditions. Importantly, cognitive phenotyping is a patient-centered approach that could eventually inform personalized treatments for a variety of neurological, psychiatric, and developmental disorders.

Although several phenotype models have been reported in the epilepsy literature, this represents the first study to use latent profile analyses (LPA) to consider and compare multiple models. LPA is a person-centered statistical technique that classifies individuals into groups based on their patterns of responses to a set of observed variables (Conte, Heffner, Roesch, & Aasen, 2017; Spurk, Hirschi, Wang, Valero, & Kauffeld, 2020). The primary goal of LPA is to maximize both the homogeneity within groups and the heterogeneity among groups. The selection of the optimal number of groups or *classes* is based on probabilities and objective and rigorous fit indices. Unlike other data-driven approaches, such as cluster analysis, that assign an individual to one

group only, LPA examines the probability of membership to each cluster or class. Thus, LPA can inform the definition of mutually exclusive taxonomies with a greater level of certainty. First, we test several models and use a variety of fit indices to derive with the most meaningful model. Second, we test the added value of replacing missing data and examine factors that may contribute to missingness. Finally, we examine the demographic and clinical profiles of the cognitive phenotypes. Epilepsy syndromes offer an opportunity to examine methods of cognitive phenotyping as they represent a neurological condition with both focal and generalized pathology, thus providing insight into brain-behavior relationships within phenotypes. As such, information gained from this study can be applied to other neurological conditions that may have underlying cognitive phenotypes.

Materials and Methods

Participants

This study was approved by the Institutional Review Boards at UC San Diego, UC San Francisco, University of Wisconsin Madison, Cleveland Clinic, Emory University, Columbia University, and New York University. Informed consent was collected from patients at UC San Diego, UC San Francisco, Emory University, Columbia University, and University of Wisconsin Madison. At Cleveland Clinic and New York University, data were collected as part of IRB-approved data registries. Patients were included in the study if they had a diagnosis of TLE including unilateral and bilateral TLE by a board-certified neurologist with expertise in epileptology, in accordance with the criteria defined by the International League Against Epilepsy (R. S. Fisher et al., 2017), and based on video-EEG telemetry, seizure semiology, and/or neuroimaging evaluation. The presence of mesial temporal sclerosis (MTS) was determined by inspection of MRI images by a board-certified neuroradiologist. Information on other types of

pathology was not systematically available across sites and therefore excluded from analyses. One-thousand four-hundred and twenty-five patients with TLE met inclusion criteria for the study. Although LPA handles missing data, a cut-off of 6 out of the 8 neuropsychological tests was used to minimize the number of missing data points per patient. This resulted in the inclusion of 1,178 patients for the final analysis (72%= 8 tests, 24% = 7 tests, 4%= 6 tests). There were no differences in demographic or clinical variables between the included and excluded cases (all p-values >.05). Average age of the final sample was 37.76 (SD=12.14), average education 13.94 (SD= 2.806); the sample was 57% female; and self-identified race distribution was as follow: 79.6% Non-Hispanic White, 9.3% Non-Hispanic Black, 2.9% Asian, 0.3% Native American, 1.9% Multiracial, and 5.9% unknown/not reported. Approximately 2.3% of the total sample self-identified as Hispanic/Latinx.

Neuropsychological measures

The following tests were common across the sites and were selected based on recommendations from the National Institute of Neurological Disorders and Stroke Epilepsy Common Data Elements (CDE; D. W. Loring et al., 2011) and the ILAE Neuropsychology Task Force Diagnostic Methods Commission (Baxendale et al., 2019). In addition, measures of motor dexterity and processing speed were included based on previous studies demonstrating that these skills are often impaired in TLE patients with generalized impairment (Elverman et al., 2019; B. Hermann et al., 2007). Verbal memory was evaluated with the Wechsler Memory Scale-Third or Fourth Edition Logical Memory (LM) immediate (LM1) and delayed recall (LM2) (Wechsler, 1997). The CDE recommends list learning measures to assess verbal memory, however, there was variability in the tests administered across sites and therefore list learning was not included in this study. Language ability was evaluated with the Boston Naming Test (BNT; Kaplan, 2001) and

letter (F-A-S) and animal fluency; mental flexibility/set-shifting was measured with the Trail Making Test B (TMT-B); processing speed was measured with TMT-A; fine motor dexterity was measured with the Grooved Pegboard to obtain a proxy for medication effect (Eddy, Rickards, & Cavanna, 2011; David W Loring, Marino, & Meador, 2007). There were limited common visuospatial tests across sites, which has been a limitation across other multi-center studies in cognitive phenotypes (McDonald et al., 2022; Reyes et al., 2020). Given that the scores for the dominant and non-dominant hands were highly correlated (r=.532, p<.001) in our sample, scores from the dominant hand were selected to reduce collinearity. Although letter fluency has both a language and an executive function component, it showed a strong correlation with BNT (r= .395, p <.001) and animal fluency performance (r= .605, p <.001) at the TLE group level. Age-corrected scaled scores were calculated for LM1 and LM2 based on normative data provided by the test manual. Race, age, education, and sex-corrected T-scores were calculated for the BNT, letter fluency, animal fluency, TMT-A, TMT-B, and PegD based on normative data from the expanded Halstead-Reitan Battery (Heaton, Miller, Taylor, & Grant-Isibor, 2004). All scores were converted to T-scores for interpretability. The distribution of missing data across tests was animal fluency (n=209), letter fluency (n=63), PegD (n=39), TMT-B (n=24), BNT (n=13), TMT-A (n=8), LM2 (n=6), and LM1 (n=5).

Statistical Analysis

Latent profile analysis

Latent profile analysis was conducted using Mplus Version 8 (Muthén & Muthén, 2010). The following continuous variables were included in the model: LM1, LM2, BNT, animal fluency, letter fluency, TMT-A, TMT-B, and PegD. Although LPA handles missing data, the models were also evaluated with imputed data using multiple imputations in SPSS (Nie, Bent, & Hull, 1975;

van Ginkel & van der Ark, 2005). Missing scores were replaced with the average score across five imputed datasets. There were 853 (73%) patients with a complete dataset. There were differences in missingness across the sites (Fisher's Exact= 496.27, p<.001), with UCSF, Cleveland Clinic, and UCSD having the most missing data. There were differences in age [t (523.39) =1.996, p=.023] and education [t (681.16) = -6.479, p<.001] between the patients with complete data and those with missing data. Patients with complete data were younger in age (Mean= 37.26, SD= 12.59) and had greater years of education (Mean=14.25, SD = 2.87) relative to patients with missing data (Age mean= 39.17, SD=14.40; Education mean= 13.16, SD=2.45). However, effects sizes calculated with Cohen's *d* were in the small range (Age *d*=.138; Education *d*=.394). There were no differences in the distribution of sex, age of epilepsy onset, and duration of disease (all p-values > .05).

The following model indices were evaluated to determine the optimal number of classes/profiles: Lo–Mendell–Ruben Adjusted Likelihood Ratio Test (LMRT; Lo, Mendell, & Rubin, 2001), Bootstrapped Likelihood Ratio Test (BLRT; Arminger, Stein, & Wittenberg, 1999; McLachlan, Lee, & Rathnayake, 2019; Ramaswamy, DeSarbo, Reibstein, & Robinson, 1993), Akaike Information Criteria (AIC; Akaike, 1974), Bayesian Information Criterion (BIC; Schwarz, 1978), sample size-adjusted BIC (Schwarz, 1978), and entropy (Ramaswamy et al., 1993). The LMRT provides an indication of statistically significant improvement by comparing the solution being evaluated with a more complex solution; significant LMRT indicates that a more complex solution (e.g., 4-class) provides better fit relative to a less complex model (e.g., 3-class). Similar to the LMRT, the BLRT statistically compares a more complex model to a less complex one by using repeated sampling methods. The AIC, BIC, and size-adjusted BIC are each based on the log likelihood function for each individual model and lower values indicate better relative fit. Entropy

is a measure on how well the classes/profiles can be distinguished and is calculated from the posterior probabilities. Each individual is assigned a posterior probability for each class rather than being assigned to one and only one class. Entropy is therefore the aggregate of the posterior probabilities and it ranges from 0 to 1, with higher values (>.80) indicating that the classes can be highly distinguished. In addition to the indices described above, each class sample size was evaluated. The interpretability of each class was evaluated to determine if a specific class solution was consistent with previous research.

An analysis of agreement using the Cohen's Kappa statistic was performed to determine the consistency of impairment classification between missing data and imputed data. Discriminant function analyses (DFA) were conducted to further validate the distinctiveness of the latent classes. The R3Step approach in MPlus was used to compare categorical and continuous sociodemographic and clinical variables associated with class membership (Asparouhov & Muthén, 2014; Collier & Leite, 2017). This approach simultaneously estimates the best-fitting solution while evaluating the associations between class membership and variables of interest, thus accounting for potential misclassification in class membership. The DCON command was used for continuous variables and DCAT for continuous variables. Analysis of covariance (ANCOVA), controlling for age, sex, and education were conducted to compare neuropsychological performance (T-scores) across groups. When results from the ANCOVA were significant, group contrasts were assessed using post-hoc pairwise tests with Bonferroni correction. Multiple comparisons were corrected using Benjamini-Hochberg false discovery rate (Benjamini & Hochberg, 1995).

Data Availability Statement

Authors have full access to all study data and participant consent forms and take full responsibility for the data, the conduct of the research, the analysis and interpretation of the data, and the right to publish all data.

Results

Latent Profile Analysis

Table I demonstrates the fit indices and sample sizes across the different class solutions for both the missing data and imputed data. For the dataset with missing data (Table 1A), the best fitting and most substantively meaningful solution had 3 classes based on entropy, fit statistics, and pattern of scores. For the 3-Class solution, entropy was .816 but dropped below .80 when increasing to a 4-Class solution; and LMRT test went from significant with the 3-class solution ($p<.01$) to non-significant when moving to the 4-class solution ($p=.116$). Figure 1 shows the pattern of impairment for each class without the imputed data. Impairment was defined as one standard deviation below the mean (T-score<40). For the 3-Class solution, Class 1 demonstrated impairments across most tests (7/8 tests) with predominant memory and language impairments, Class 2 demonstrated predominantly impairments in language and Class 3 demonstrated no impairments at the group level with relatively high scores in memory. The models were also tested with the sample that had at least 7 out of the 8 tests available and the results were consistent with the above sample.

For the imputed dataset (Table 2B), the 4-Class solution was the best fitting given that entropy was the highest and the LMRT was significant when moving to a 4-Class solution from a 3-Class solution, but non-significant when moving to a 5-Class solution. Figure 2A shows the pattern of impairment for each class across the 4-Class solution based on the imputed data. Class 1 demonstrated impairment across most tests (7/8) with predominant deficits in memory and

language; Class 2 demonstrated impairments in language and borderline impairments delayed memory; Class 3 showed mainly impairments in naming (BNT); and Class 4 had an overall intact profile. Fine motor dexterity was impaired across Classes 1-3. Given that the language measures had the most missing data, the distribution of scores were plotted for BNT (Fig 2B), animal (Fig 2C), letter fluency (Fig 2D), with individual data points coded by whether they were raw values versus imputed values.

Agreement between missing data and imputed data

Cohen's Kappa statistic revealed an almost perfect agreement between the dataset with missing data and the imputed data for the 2-Class ($\kappa = .985$, $p < .001$; 99.23% concordance rate) and 3-Class ($\kappa = .983$ $p < .001$; 98.98% concordance rate) solutions. A weak agreement was found for the 4-Class ($\kappa = .288$, $p < .001$; 47.37% concordance rate) and the 5-Class ($\kappa = .120$, $p < .001$; 28.9% concordance rate) solutions. Further examination of the 4-Class solutions demonstrated that misclassification was mostly between Class 2 (49% misclassified as Class 3 with the imputed data) and Class 3 (50% misclassified as Class 2 with the imputed data). Subsequent analyses were conducted on the dataset with missing data points to demonstrate the utility of LPA with handling missing data.

Probability of group membership

Figure 3 shows the distribution of probability of group membership for each class solution. Average probabilities were as follows: 2-Class (mean=.933, SD= .121; range= .51-1); 3-Class (mean=.914, SD= .129; range= .51-1); 4-Class (mean=.848, SD= .173; range= .35-1); 5-Class (mean=.877, SD= .149; range= .36-1). A cut-off of above 80% was considered good probability of group membership. The percentage of patients with a probability lower than 80% was the lowest

for the 2-Class solution (12.8%), followed by 3-Class (17.1%), 5-Class (24.9%) and highest in the 4-Class solution (32.2%).

Discriminant function analysis

To further validate the distinctiveness of the latent classes, DFA was performed with the cognitive scores as predictors of latent class membership. The DFA indicated that 97.9% of cases were correctly classified in the 2-Class solution; 96.2% for the 3-Class solution; 95.9% for the 4-Class solution; and 95.8% for the 5-Class solution. Figure 4 shows the scatter plots of individuals on the discriminant dimensions for the 3-, 4-, and 5-Class solutions.

Selection of most meaningful solution

Based on the fit indices, posterior probability, and distinctiveness of the latent classes, a 3-class solution was selected. This was further supported by the patterns of cognitive impairment observed, which were similar to what has been reported on prior literature on cognitive phenotypes in TLE (Elverman et al., 2019; Garcia-Ramos et al., 2021; B. Hermann et al., 2020; B. Hermann et al., 2007; Reyes et al., 2019; Reyes et al., 2020). As described, patients in Class 1 demonstrate a profile characterized by impairments across most tests with prominent impairments in verbal learning and memory and language and are labeled the *Multidomain* phenotype hereafter. Class 2 showed a predominantly language impaired profile and will be labeled *Language* phenotype hereafter. Patients in Class 3 showed a profile characterized by no measurable impairments across tests and are labeled the *No Impairment* phenotype.

Differences in demographics, clinical, and neuropsychological variables

Table 2 shows differences in demographic and clinical variables across phenotypes for the 3-Class solution and table 3 shows the follow-up group contrasts. There were differences in age, education, age at onset of epilepsy, disease duration, and number of antiseizure medications

(ASM) across phenotypes. The *Multidomain* group had a younger age, lower years of education, younger age of epilepsy onset, and longer disease duration relative to the *Language Impaired* and the *No Impairment* phenotypes. The *Multidomain* phenotype also had a greater number of ASMs relative to the *No Impairment* phenotype. The *Language* phenotype had a younger age, lower years of education, younger age of epilepsy onset, longer duration, and a greater number of ASM relative to the *No Impairment* phenotype. There were differences in the presence of MTS, with the *No Impairment* group having fewer patients with MTS (26.4%) relative to the *Multidomain* (38.5%) and *Language* phenotype (35.9%). There were no other differences across phenotypes.

There were differences across all neuropsychological measures (Table 4A). Group contrasts revealed significant differences between phenotypes for all test except for TMT-A. For TMT-A there were no differences between the *Language* and *No Impairment* groups (p=.079). Cohen's *d* effect sizes were calculated to determine the difference in magnitude between groups (Table 4B). Effect sizes between groups ranged from small to large and the pattern of effect sizes was consistent across groups.

Discussion

This study utilized a robust and rigorous statistical method to derive cognitive phenotypes in a large, multi-site study of 1,178 patients with TLE in order to adjudicate among published findings which have produced variable results, and to arrive at a definitive taxonomy of neuropsychological status in this common and problematic epilepsy syndrome. First, we found that the three-phenotype model was the most meaningful based on several fit indices and pattern of impairment; it was the most robust to missing data; and the demographic and clinical profiles were consistent with prior literature. Second, we demonstrated the importance of examining the factors associated with missing data and determined whether different phenotype models are

robust to the missingness. Third, we provide methods to examining the stability of the phenotypes including examining the probability of group membership provided by LPA. As the cognitive phenotyping approach continues to gain traction in the neuropsychology literature, utilizing rigorous, person-centered methods such as LPA will inform the generalizability of the phenotypes and the translation of the cognitive phenotypes into clinical diagnostic criteria.

Determining the Optimal Solution

An advantage of LPA is that individuals are assigned into classes based upon membership probabilities estimated directly from the model (Spurk et al., 2020). Further, LPA provides several fit indices that can help the researcher determine the optimal solution with a greater level of certainty. In our study, we tested five solutions (2-5 classes) based on prior literature with and without imputed data. Based on the fit indices described above, the 3-Class solution was the optimal solution with the raw dataset. We also examined the posterior probabilities, which provide information on the probability of an individual belonging to the group to which they were assigned. We found that for models with multiple classes (e.g., 4-Class and 5-Class), the probability of group membership decreases. In fact, for the 4-Class solution approximately 4% of the sample had a probability of group membership below 50% and Class 3 and 4 within this model had a large proportion of patients with poor probability of group membership. This may suggest that with finer characterization of phenotypes (e.g., domain-specific) it is more difficult to distinguish the groups as individual patients may have overlapping features across classes. Given that we had a limited number of tests per cognitive domain, it is possible that with a more comprehensive battery (i.e., more tests per domain) or potentially more sensitive measures (i.e., list learning instead of story recall) LPA will be able to classify individuals with greater level of certainty. We also used discriminant function analysis to further examine the distinctiveness of the groups and again we

found that correct classification using the cognitive scores only was lower for the 4-Class and 5-Class models. Overall, this suggests that in order to further divide patients into finer subgroups using data-driven approaches (i.e., verbal memory only, language only), large samples with comprehensive batteries of tests may be required. Notably, using clinical criteria may allow for the characterization of finer groups such as the single-domain impaired phenotype described in harmonized, actuarial approaches, such as the International Classification of Cognitive Disorder in Epilepsy (IC-CoDE) framework (McDonald et al., 2022; Norman et al., 2021).

The Impact of Missing Data

Given the nature of clinical research, missing neuropsychological data may be unavoidable. However, missing data may lead to bias and loss of information when utilizing data-driven approaches and this is particularly important for the phenotyping literature as groups are derived based on the data that are available (Ibrahim, Chu, & Chen, 2012; Sterne et al., 2009). Although it is difficult to determine if neuropsychological data are missing at random or not at random, systematically examining the characteristics of the samples may provide valuable information and inform the generalizability of the findings. In our sample, there were no significant differences in demographic and clinical variables between the final sample (N=1,178) and the patients that were excluded due to missing a substantial amount of data (N=247). When examining the final sample, the patients with incomplete data had fewer years of education and were older in age. Notably, although this was statistically significant, the magnitude of the difference was small and not clinically meaningful. Interestingly, post-hoc analyses revealed differences in the proportion of patients with incomplete data across the 3-Class solution (FE= 14.44, p=<.001), with the *No Impairment* phenotype having fewer patients with missing data (17%) relative to the *Multidomain* (30%) and *Language* (30%) phenotypes. Therefore, it is possible that older age and fewer years of

education were contributing factors to the missing data or that greater cognitive impairment led to incomplete testing. Although it is not possible to determine whether these factors truly explain the missing data, this suggests that the data are not missing at random and that there may be factors (e.g., patient or study-specific) explaining the missingness. Therefore, future studies in cognitive phenotyping should examine contributing factors to missing data given their potential impact on the generalizability of the phenotypes.

Unlike cluster analysis, which cannot handle missing data, missing data in latent class indicators is generally acceptable in LPA. To address any pitfalls in our analyses, we replaced missing values with values imputed from the data that were available and ran the models with the imputed datasets. Results from these analyses suggested that the 4-Class solution was the most meaningful solution. The groups in this solution were less distinct based on the clinical interpretation of their cognitive profiles. Based on prior literature (Elverman et al., 2019; Reyes et al., 2020), the pattern of impairment with four groups or more are less consistent across studies and this may be due to the number and type of tests selected, the degree of cognitive impairment across patient samples, and the method used to derive the phenotypes. Further, there was perfect agreement between the missing and imputed datasets for the 2-Class and 3-Class but weak agreement for the 4-Class and 5-Class solutions. Further examination of the 4-Class solutions demonstrated that misclassification was most common between Classes 2 and 3, which shared similar features in their cognitive profiles. Thus, the imputed data had a greater impact when deriving finer characterizations of cognitive phenotypes and thus future studies must consider the impact of missing data and the methods for replacing the missing data when examining more than three phenotypes. Lastly, these findings suggest that the three cognitive phenotypes described

across several studies are relatively stable and are more robust to missing data compared to models with four or more classes.

Optimal solution

Similar to prior studies (B. Hermann et al., 2020; B. Hermann et al., 2007; B. P. Hermann et al., 2021; Reyes et al., 2020; Rodriguez-Cruces et al., 2018), the 3-Class model consisted of a group of patients with multidomain impairments (30%), a sizable group with focal deficits in language (53%), and a third group with relatively intact cognitive profile (16%). The proportion of patients in the *Multidomain* and *Language* phenotypes fell within the range reported in the literature for generalized impairment (9-29%) and focal deficits (24-54%) (B. P. Hermann et al., 2021). Surprisingly, the *No Impairment* group was relativity smaller compared to other investigations reporting 27 to 54% of their samples with intact profiles. Most recently, the cognitive phenotyping literature has informed the development of the IC-CoDE initiative aimed at developing a consensus-based classification system for cognitive disorders in epilepsy(Norman et al., 2021). The IC-CoDE leveraged results from the cognitive phenotyping and neuropsychology literature more broadly, to develop a framework for diagnostic decisions that utilizes the *number* of impaired domains to derive cognitive phenotypes. This framework includes four cognitive phenotypes: 1) generalized impairment (i.e., 3 more domains impaired), 2) bi-domain, 3) single-domain, 4) cognitively intact (McDonald et al., 2022). However, given that the initial purpose of the IC-CoDE was to provide a framework for research, more rigorous methods and external validation will be needed to determine its clinical utility and LPA provides a promising methodology to achieve this goal.

A major interest in the phenotype literature is relating the derived clusters or classes to sociodemographic and clinical variables, neural correlates, and treatment outcomes. We used a

robust method to examine differences in demographic and clinical variables across phenotypes, which reduces bias by accounting for the uncertainty of the best-fitting class solution (Asparouhov & Muthén, 2014). These analyses revealed that the *No Impairment* phenotype had more years of education, which has been shown to serve as a protective factor against epilepsy-related pathology (Jokeit & Ebner, 1999; Oyegbile et al., 2004). This group also demonstrated less disease burden relative to the other two groups including less duration of disease, fewer ASMs, and fewer patients with MTS. All of these factors have been associated with increased risk of cognitive impairment (Brian Bell, Jack J Lin, Michael Seidenberg, & Bruce Hermann, 2011; Elger, Helmstaedter, & Kurthen, 2004; B. P. Hermann et al., 2021). Thus, this smaller subgroup of patients in our sample may represent a group with a combination of protective factors and less disease burden. Notably, our sample consisted of mostly drug-resistant TLE, which based on the epilepsy literature is associated with poorer cognitive profiles than those who are drug-responsive (Brian Bell et al., 2011; B. P. Hermann et al., 2021). However, given that most neuropsychological studies in epilepsy aggregate all patients into one group, patients with drug-resistant epilepsy, but with intact cognitive profiles have not been well characterized until recently.

Further, the *Multidomain* group is another unexpected phenotype based on the lesion-model that has been hypothesized to represent a group of patients with potential co-morbid non-epilepsy pathology, elevated health-related risk factors, greater generalized tonic-clinic seizures or lower brain reserve (B. P. Hermann et al., 2021). In our study, this group had less years of education, younger onset of epilepsy, longer duration of disease, were taking more ASMs, and had a greater proportion of patients with MTS. Other studies have also found that phenotypes with generalized impairment have less years of education (Elverman et al., 2019; Rodriguez-Cruces et al., 2018), younger age of onset (Elverman et al., 2019; Reyes et al., 2020; Rodriguez-Cruces et

al., 2018), longer disease duration (B. Hermann et al., 2007), were taking more ASMs (B. Hermann et al., 2007), and had greater portion of patients with MTS (Rodriguez-Cruces et al., 2018). In more benign forms of TLE (B. Hermann et al., 2020), patients with multidomain impairments had lower years of education as did their parent, which has been suggested to be a potential socioeconomic indicator. Finally, the *Language* phenotype also demonstrated greater disease burden relative to the *No Impairment* phenotype. It is noteworthy to mention that there were no differences in the side of seizure onset across the phenotypes, which has been a consistent finding across studies (B. Hermann et al., 2007; Reyes et al., 2019; Reyes et al., 2020; Rodriguez-Cruces et al., 2018). Although this may at first appear surprising, this complements a growing literature that demonstrates a pattern of bilateral and often widespread brain abnormalities in patients with drug-resistant TLE, likely leading to a "non-lateralized" pattern of impairment even in patients with a unilateral seizure onset. This again highlights how a simple lesion-model fails to capture the complexity of cognitive impairments experienced by patients with TLE and lends support for network-based approach. However, we did not have information on hemispheric language dominance and therefore could not determine if patients had epilepsy in the dominant hemisphere which warrants further investigation. Lastly, it is possible that our tests of language lack the sensitivity to capture subtle lateralizing deficits in language (i.e., those that would reveal greater deficits in patients with left or language-dominant TLE) or that there are other factors (e.g., number and type of ASM, bilingualism) explaining the language deficits in patients with non-dominant hemisphere epilepsy.

When examining the extent of the cognitive impairments, differences among the three groups were greater in the areas of memory and language regardless of group membership. In fact, patients in the *No Impairment* group had scores in immediate and delayed memory that were

approximately one standard deviation above the mean of a healthy normative sample. Although this group had the least number of patients with MTS, we tested memory with prose recall, which has been shown to be less sensitive to memory impairments relative to list-learning (McDonald et al., 2022). In the IC-CoDE application study, the base rates of impairment ranged from 22-24% for prose recall (i.e., LM1 and LM2) but were higher for list learning and memory (27-43%) depending on the test and impairment threshold used. Thus, it is possible that the high scores in the *No Impairment* group reflect the lower sensitivity of prose recall in detecting memory impairments in TLE. Furthermore, it is possible that finer phenotypes could emerge with the use of more sensitive tests, by considering specific test indices (e.g., recognition scores for memory, reaction times for naming), or by further deconstructing test impairment patterns (e.g., impact of ASMs).

The *Multidomain* phenotype had impaired scores in language tests that were lower than the *Language* phenotype, suggesting that this group represents patients with more pervasive impairment that may be explained by factors beyond epilepsy-related pathology (e.g., ASMs). The pattern of impairment for the *Language* phenotype was surprising given that focal or domain-specific phenotypes have been described to have impairments in both memory and language (B. P. Hermann et al., 2021; Reyes et al., 2020). Although we did not have comprehensive EEG data, information on other types of pathology, or detailed ASM information available, this group of patients may represent a group with greater pathology in the lateral temporal lobe or those taking ASMs known to affect language function such as topiramate or zonisamide (Ojemann et al., 2001). Furthermore, it is possible that due to the lower sensitivity of logical memory we did not capture many patients with both language and more subtle memory impairments within this focal group.

Interestingly, naming had the lowest scores across all three groups regardless of the level of impairment, which is consistent with findings in the IC-CoDE validation study which included a subset of the patients from this study (McDonald et al., 2022). In the IC-CoDE study, deficits in BNT were the most commonly observed with 53-67% of the patients demonstrating impairments depending on the impairment cutoff applied. Lastly, the pattern of scores across tests of processing speed, mental flexibility/set-shifting, and fine motor dexterity were similar across groups, contributing less to the distinctiveness of the phenotypes.

Strengths and Limitations

This study represents the first and largest investigation of cognitive phenotypes in TLE utilizing LPA. We provide a detailed description of LPA and apply additional statistical tests that investigators in this area can use to validate the stability of cognitive phenotypes in other neurological disorders. We also examined the utility of different metrics provided by LPA, which can inform future studies in cognitive phenotyping across the neuropsychology literature. Lastly, we explore the missing data in our sample as this could have an impact on the development and applicability of cognitive phenotypes.

Nonetheless, there are several limitations to our study that should be addressed in future investigations. First, given the multicenter aspect of our study, we had a limited number of tests per domain and did not include tests in visual memory and visuospatial domains. The lack of visual memory and visuospatial tests has been a limitation across many studies in epilepsy phenotyping given a) variability across tests given within these domains, 2) poor sensitivity of these tests in detecting right hemisphere and right medial temporal dysfunction (Vaz, 2004), and 3) base rates of impairment across these domains are lower relative to other domains. The application of the IC-CoDE which includes a subset of the patients from this study, included a

visuospatial domain and demonstrated that this domain was less commonly available across six major epilepsy centers in the U.S, with many cases missing visuospatial data. Furthermore, the visuospatial domain was the least impaired across a sample of 2,485 with drug-resistant TLE. Nonetheless, it is possible that the *Multidomain* phenotype in our study had intact or minimally impaired visuospatial abilities, representing a phenotype with primarily verbal-based impairments.

Second, we did not include measures of list learning, which have been shown to be sensitive to medial temporal dysfunction. In the IC-CoDE study, there were differences across sites on the type of measure given for list learning, with some sites utilizing the California Verbal Memory Test (CVLT) and other sites the Rey Auditory Verbal Learning test (RAVLT). It has been shown that standard scores for the CVLT are significantly lower relative to the RAVLT (Stallings, Boake, & Sherer, 1995) and therefore harmonizing methods between these two tests are needed to reduce the missingness in future studies. Third, we excluded 247 patients due to having a significant amount of missing data. Our study demonstrated that there were some differences in demographic and clinical characteristics between patients with complete data and those missing tests. This suggest that there is a subset of patients that are not being captured in the cognitive phenotyping literature due to missing data and therefore findings from these studies may not be applicable to this subset of patients. Fourth, we did not have comprehensive information on other non-epilepsy comorbidities or language status (i.e., bilingualism) that may further explain the heterogeneity observed as proposed by other studies. Determining the impact of bilingualism on these phenotypes will be important given the heavy verbal demands of the tests used to determine the phenotypes. Finally, although our sample was somewhat diverse in terms of race/ethnicity, we did not have the power to examine the phenotypes within each group separately to determine if there are unique demographic and clinical characteristics that may explain the extent of cognitive

impairment for each population. Future work in this area should validate the cognitive phenotypes in large, more racially/ethnically and linguistically diverse samples to improve the generalizability of the findings. Furthermore, the cognitive phenotypes should be examine utilizing different clinical neuropsychological measures testing similar constructs to address the generalizability of the findings and its international applicability**.**

Conclusion

The process of cognitive phenotyping based on heterogeneous tests is not intended to replace single or multi-cohort studies that are designed to dissect the neuroanatomy of TLE. Rather, cognitive phenotyping leads to an improved understanding of the presence and frequency of *combinations* of impairments that characterize TLE and the opportunity to determine the underlying factors that drive phenotypic membership. The cognitive phenotype approach can also help to provide a framework for large-scale collaborative efforts that will have to rely on different tests and languages, and address cross-cultures issues in the neuropsychology of epilepsy.

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Figures

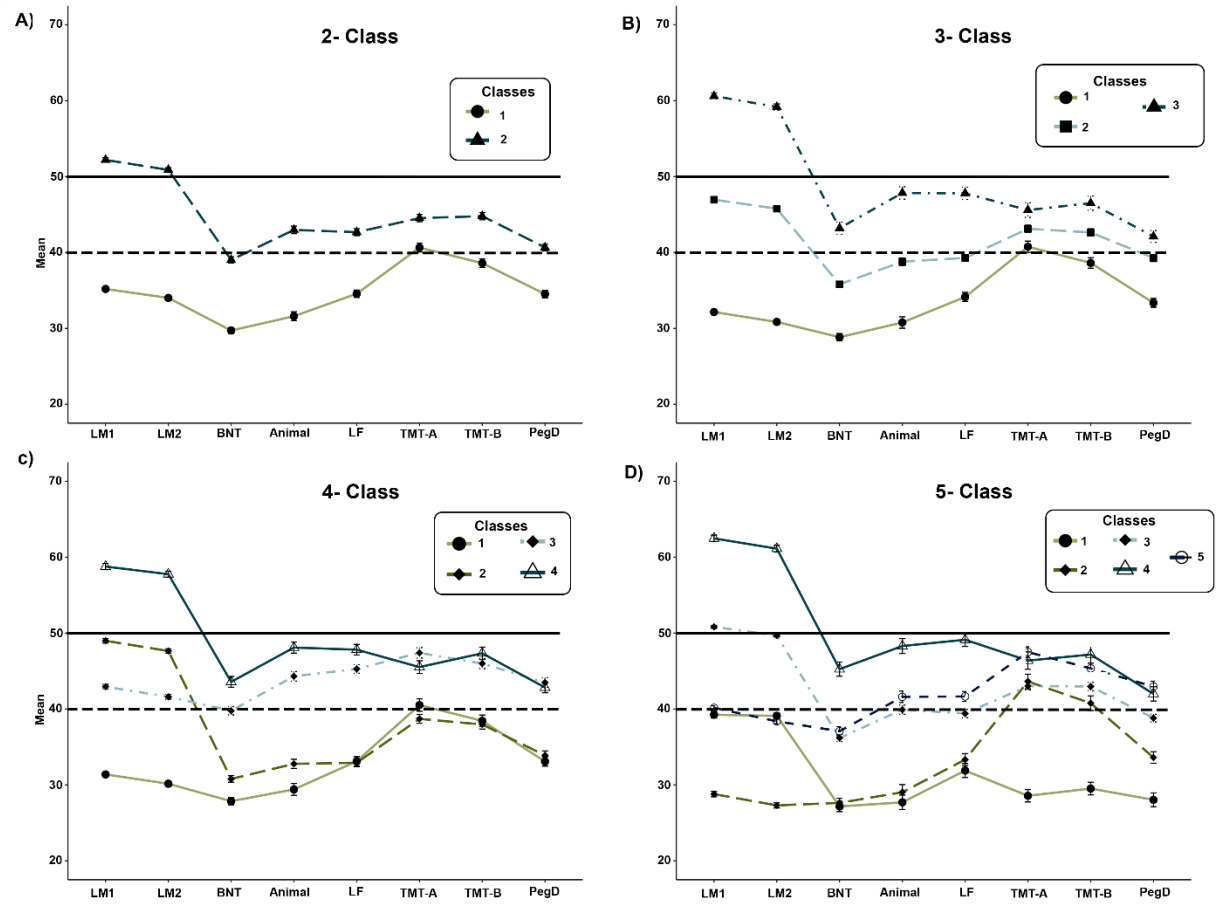

Figure 4.1: *Cognitive scores across class solutions.* Each panel shows the average T-scores across tests for each class. The solid line represents average scores and the dashed line represents impairment at one standard deviation below the mean of a healthy normative sample. Abbreviations: LM1: Logical Memory Immediate Recall; LM2: Logical Memory Delayed Recall; BNT: Boston Naming Test; LF: Letter Fluency; TMT-A: Trail Making Test condition A; TMT-B: Trail Making Test condition B; PegD: Grooved Pegboard dominant hand

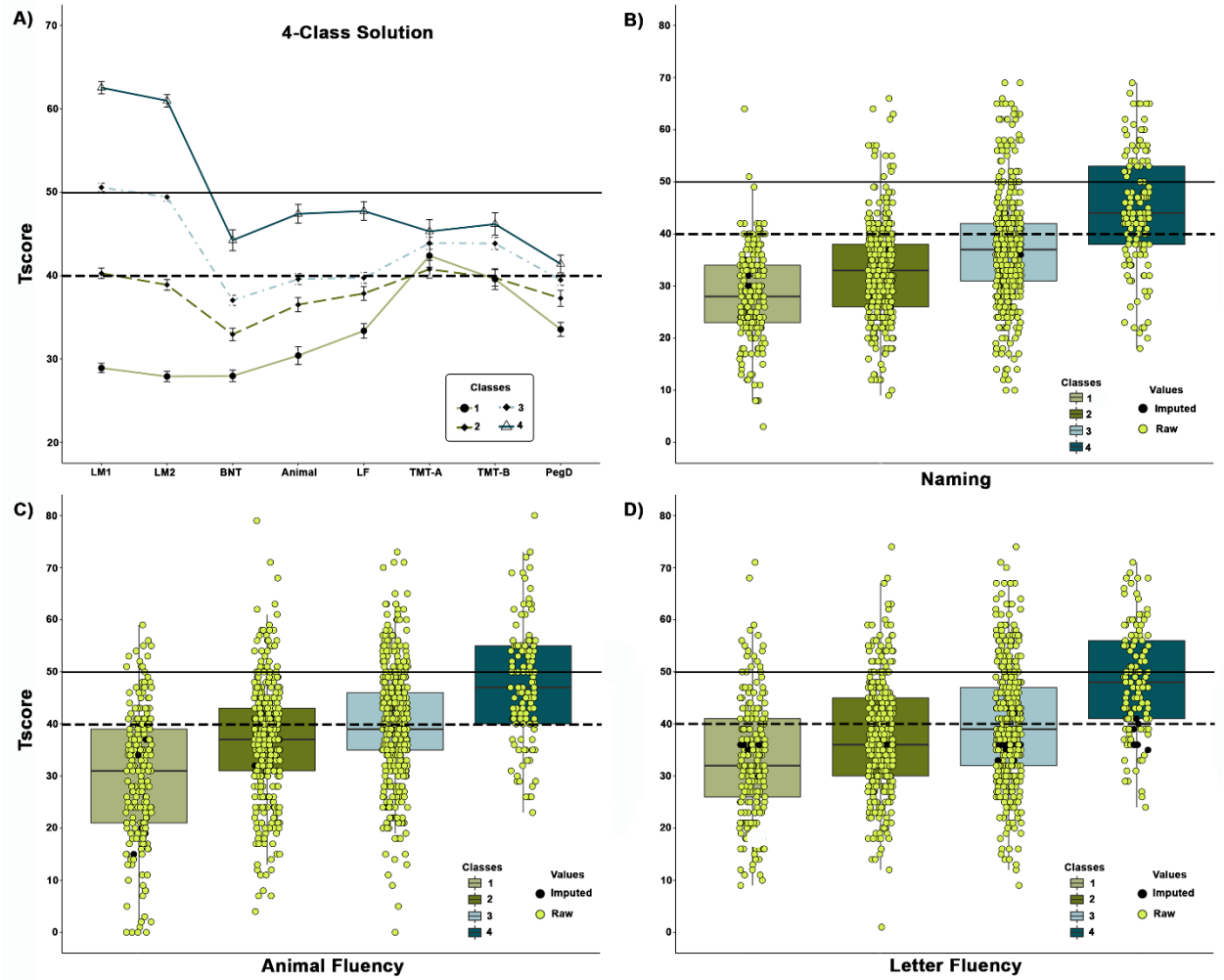

Figure 4.2: *Class-4 solution with imputed data.* Panel A shows the average T-scores across tests for each class utilizing the imputed data. Panels B-D shows the distribution of scores for measures of language for each class within the 4-Class Solution. The raw data points are colored in bright yellow-green and imputed data points are colored in black. The solid line represents average scores and the dashed line represents impairment at one standard deviation below the mean of a healthy normative sample. Abbreviations: LM1: Logical Memory Immediate Recall; LM2: Logical Memory Delayed Recall; BNT: Boston Naming Test; LF: Letter Fluency; TMT-A: Trail Making Test condition A; TMT-B: Trail Making Test condition B; PegD: Grooved Pegboard dominant hand

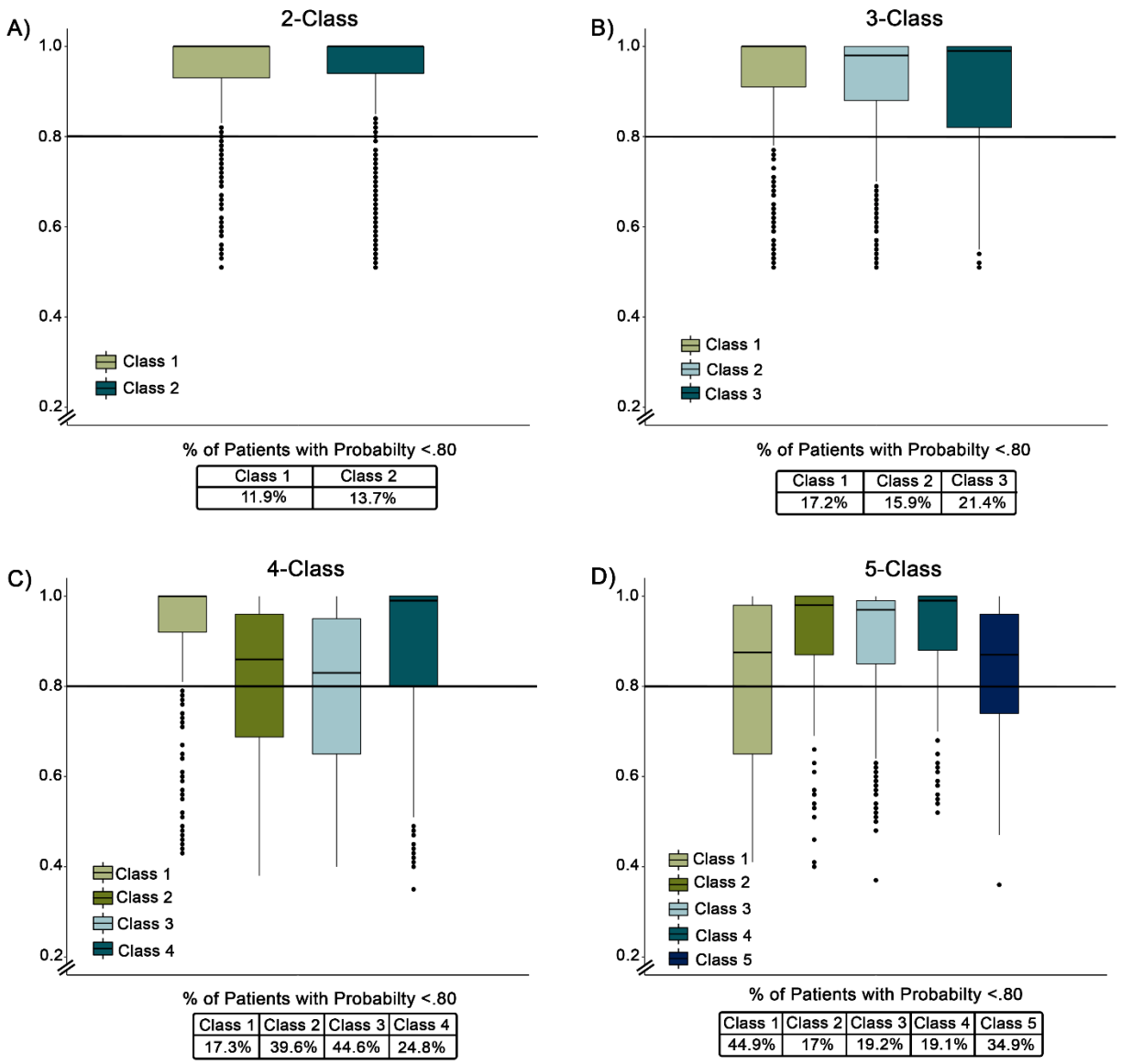

Figure 4.3: *Distribution of probability of group membership.* For each class solution, the probability of group membership is shown for each class. The solid line represents a probability of group membership below 0.80.

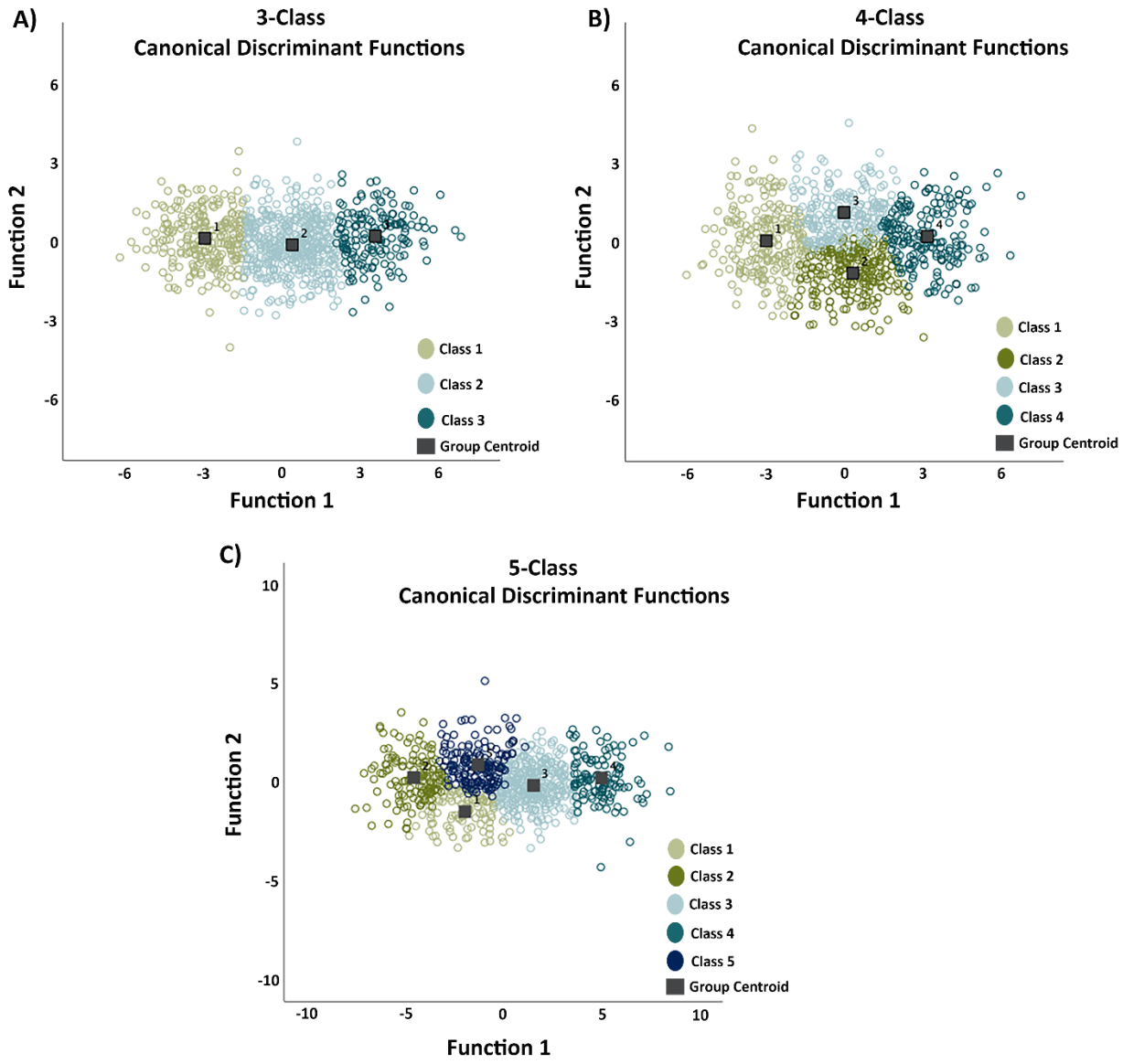

Figure 4.4: *Scatterplot of canonical discriminant function analysis*. A) 3-Class Solution, B) 4-Class Solution, and C) 5-Class Solution.

Table 4.1: *Fit indices across class solutions*

Table 1A: Fit indices across class solutions with missing data

	AIC	BIC	sBIC	Entropy	LMRT (p)	BLRT	Sample per class
2- Classes	69278.61	69405.40	69325.99	0.775	1269 (<.001)	<.001	1=528; 2=650
3- Classes	**68803.56**	**68976.01**	**68868.01**	**0.816**	**485 (<.001)**	**<.001**	**1=361; 2=630; 3=187**
4- Classes	68570.14	68788.21	68651.63	0.737	247 (.116)	<.001	1=312; 2=328; 3=312; 4=226
5- Classes	68289.12	68552.84	68387.67	0.807	225 (.35)	<.001	1=136; 2=206; 3=447; 4=131; 5=258

Table 1B: Fit indices across class solutions with imputed data

	AIC	BIC	sBIC	Entropy	LMRT (p)	BLRT	Sample per class
2- Classes	71859.50	71986.29	71906.88	0.776	1260 (<.001)	<.001	1=527; 2=651
3- Classes	71363.22	71535.66	71427.66	0.823	506 (<.001)	<.001	1=358; 2=638; 3=182
4- Classes	**71059.93**	**71278.01**	**71141.42**	**0.834**	**316 (<.001)**	**<.001**	**1=217; 2=380; 3=448; 4=133**
5- Classes	70857.37	71121.09	70955.92	0.807	217 (.23)	<.001	1=138; 2=207; 3=254; 4=450; 5=129

AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; sBIC: size-adjusted-Bayesian Information Criterion; LMRT: Lo–Mendell–Ruben Adjusted Likelihood Ratio Test; BLRT: Bootstrapped Likelihood Ratio Test

Table 4.2: *Clinical and demographic characteristics across phenotypes for the 3-Class Solution*

	Multidomain	Language	No Impairment	p-value
N	361	630	187	-
Percent of Sample	30%	53%	16%	-
Age	35.56 (.66)	38.13 ()	40.57 (.96)	**<.001**
Education	12.84 (.13)	13.93 (.10)	15.84 (.23)	**<.001**
Age of Onset	15.14 (.65)	20.76 (.61)	26.63 (1.22)	**<.001**
Duration (years)	20.37 (.76)	17.44 (.54)	13.69 (.86)	**<.001**
Current # of ASMs*	2.19 (.06)	2.07 (.05)	1.79 (.07)	**<.001**
				p-value
Sex				.317
Male	163 (45%)	264 (42%)	80 (43%)	
Female	198 (55%)	366 (58%)	107 (57%)	
Handedness				.267
Left	46 (13%)	77 (12%)	26 (14%)	
Right	309 (86%)	535 (85%)	154 (82%)	
Ambidextrous	5 (1%)	16 (3%)	7 (4%)	
Mesial temporal sclerosis				**.040**
Yes	124 (39%)	199 (36%)	39 (26%)	
No	198 (61%)	355 (64%)	109 (74%)	
Onset Side	202/107/40	365/182/54	113/46/15	.431
Left	202 (58%)	365 (61%)	113 (65%)	
Right	107 (31%)	182 (30%)	46 (26%)	
Bilateral	40 (11%)	54 (9%)	15 (9%)	

ASM: antiseizure medications
Standard deviations are presented inside the parentheses
* More than 20% of data is missing
Bold signifies statistical significance using the R3Step approach

Table 4.3: *Group contrasts for demographic and clinical variables using R3Step approach*

	Multidomain vs Language	Multidomain v No Impairment	Language vs No Impairment
Age	.002	<.001	.025
Education	<.001	<.001	<.001
Onset	<.001	<.001	<.001
Duration	.002	<.001	<.001
Current # of ASMs	.155	<.001	.002
MTS	.655	.015	.025

ASM: anti-seizure medications; MTS: mesial temporal sclerosis

Table 4.4: *Neuropsychological differences across phenotypes for the 3-Class solution (4A) and Cohen's D effect sizes across phenotypes (4B)*

Table 4A: Neuropsychological differences across phenotypes for the 3-Class solution

	Multidomain	Language	No Impairment	ANCOVA	p-value
LM1	**32.13 (6.15)**	46.95 (5.49)	60.61 (5.48)	1445.94	<.001
LM2	**30.85 (6.29)**	45.76 (5.55)	59.17 (5.51)	1387.49	<.001
BNT	**28.79 (9.09)**	**35.79 (9.88)**	43.20 (11.03)	135.43	<.001
Animal Fluency	**30.71 (13.1)**	**38.78 (11.4)**	47.84 (10.8)	108.21	<.001
LF	**34.14 (11.2)**	**39.28 (10.9)**	47.79 (10.6)	69.53	<.001
TMT-A	40.74 (14.1)	43.12 (11.9)	45.58 (13.2)	7.82	<.001
TMT-B	**38.82 (13.1)**	42.63 (12.1)	46.50 (12.6)	28.09	<.001
PegD	**33.34 (10.8)**	**39.26 (11.7)**	42.10 (10.6)	36.75	<.001

Table 4B: Cohen's D effect sizes across phenotypes

	Multidomain vs Language	Multidomain v No Impairment	Language vs No Impairment
LM1	2.58	4.80	2.49
LM2	2.56	4.70	2.42
BNT	.73	1.46	.73
Animal Fluency	.67	1.39	.81
LF	.47	1.25	.78
TMT-A	.18	.35	.20
TMT-B	.32	.61	.48
PegD	.52	.82	.41

Estimated marginal means and standard error with covariates of education, age, and sex
Bold signifies average T-score below the impairment cut-off (<40)

Covariates: age, education, sex

Cohen's D effect sizes: small= .2; medium= .5; large= .8

LM1: Logical Memory Immediate Recall; LM2: Logical Memory Delayed Recall; BNT: Boston Naming Test; LF: Letter Fluency; TMT-A: Trail Making Test condition A; TMT-B: Trail Making Test condition B; PegD: Grooved Pegboard dominant hand

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Chapter 5:

Preliminary Analyses for Future Study

Rationale

Given the chronic nature of epilepsy, many patients with epilepsy present with an accumulation of health-related risk factors including cerebrovascular risk factors (CVRFs), comorbid neurologic conditions (e.g., migraines), altered lifestyle (e.g., sedentary lifestyle), psychiatric conditions (e.g., depression, anxiety), somatic disorders, among others (Keezer, Sisodiya, & Sander, 2016; Seidenberg, Pulsipher, & Hermann, 2009). In fact, approximately 50% of adults living with epilepsy have at least one comorbid medical condition (Forsgren, 1992; Keezer et al., 2016). Prospective studies have demonstrated altered cognitive trajectories in patients with chronic TLE that are not well explained by traditional epilepsy-related factors, suggesting that other factors may be explaining the extent and severity of cognitive dysfunction (Hermann et al., 2008). Despite the high prevalence of comorbid disorders in epilepsy, many known to impact cognition, the impact of these comorbid disorders on cognitive trajectories or their mediating effect on epilepsy burden are not well understood.

Furthermore, there are fewer investigations identifying factors that increase the brain's resilience to epilepsy-related pathology. The aging literature has demonstrated that the identification of resilience or *protective* factors is crucial for intervention and prevention (Montine et al., 2019). My work on the protective effects of bilingualism in TLE is one of the few studies in epilepsy examining the concepts of brain and cognitive reserve in epilepsy (Reyes et al., 2018). Other identified factors include higher global ability (Rzezak, Guimarães, Guerreiro, & Valente, 2017) and education (Jokeit & Ebner, 1999; Oyegbile et al., 2004).

I propose that using the cognitive phenotype approach can provide an avenue to investigate the impact of the health-related factors on cognitive risk and whether and how they further exacerbate epilepsy burden. Furthermore, this approach can also aid in the identification of protective factors mitigating the impact of epilepsy on cognitive trajectories. Specifically, examining these factors at the cognitive phenotype level rather than at the syndrome level (i.e., all patients with TLE) can delineate the factors unique to each cognitive profile. For example, patients with *Multidomain* impairments may present with other comorbidities that are leading to widespread cognitive dysfunction, and patients with *No Impairment* profiles may present with protective factors that are increasing their cognitive or brain reserve (Figure 5.1).

As previously mentioned, examining the impact of health-related risk factors and protective factors on cognition across phenotypes was one of the aims of the dissertation. However, due to issues with data collection and acquisition, these analyses were excluded from Study 3 as the current sample with these data available ranged from 16% to 42% of the original sample. Importantly, given that this study can inform patient-tailored interventions, examining these factors in a large and representative sample will have a greater impact on clinical outcomes. Here, I provide preliminary analyses examining 1) structural brain changes across phenotypes, 2) the presence of CVRFs across phenotypes, and 3) the contribution of CVRFs and bilingualism to cognitive performance. Mood (e.g., depression and anxiety) has been shown to have an adverse effect on cognitive function in patients with epilepsy (Paradiso, Hermann, Blumer, Davies, & Robinson, 2001). However, the impact of mood on cognition has not been investigated at the cognitive phenotype level. As such, I also examine both depressive and anxiety symptoms across cognitive phenotypes.

Methods

Cerebrovascular risk factors, mood, and bilingualism

For all TLE patients, epilepsy-related clinical variables (i.e., age of seizure onset, duration of disease, antiseizure medication: ASM, mesial temporal sclerosis: MTS) and CVRFs were collected during a standard clinical examination. CVRFs included diagnoses of hypertension, hyperlipidemia, diabetes mellitus, and/or obesity defined by a body mass index (BMI; mass [kg]/ height $[m]^2$) ≥ 30. Bilingualism status was obtained during the neuropsychological evaluation. For the purpose of these analyses, patients were considered bilinguals if their first language was another language other than English. Patients with mood assessments available completed the Beck Depression Inventory second edition (BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). The BDI-II is a 21-item self-report measure of common depressive symptoms, with higher scores indicating a greater number and severity of depressive symptoms. Scores ranging from 0-13 indicate minimal symptoms; 14-19 indicate mild symptoms; 20-28 indicate moderate symptoms, and 29-63 indicate severe symptoms of depression. The BAI is a 21-item self-report measure of common anxiety-related symptoms. Scores ranging from 0 - 7 indicate minimal symptoms; 8 – 15 indicate mild symptoms; 16 - 25 as moderate; and 26 - 63 severe symptoms.

Imaging acquisition

A subset of patients (n=205, 17.4% of original sample) had imaging data available. All TLE T1 MRI data were acquired without gadolinium contrast at each of the 4 epilepsy centers. Healthy control MRI data were collected at UC San Diego. The typical scan at UC San Diego was T1-weighted 3D customized FSPGR structural sequence, at 1.5T the scan parameters were TR = 10.73 ms, TE = 4.87 ms, TI = 1000 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 x 192, slice thickness = 1.0 mm and at 3T the scan parameters were TR = 8.08 ms, TE = 3.16 ms, TI = 600

ms, flip angle = 8°, FOV = 256 mm, matrix = 256 x 192, slice thickness = 1.0 mm. The typical Cleveland Clinic scan parameters at 3T were TR = 1,860 ms, TE = 3.4 ms, TI = 1,10ms, flip angle = 10°, matrix = 256 x 256, slice thickness = 0.94 mm and at 1.5T the scan parameters were TR = 11 ms, TE = 4.6 ms, flip angle = 20°, matrix = 256 x 256, slice thickness = 1.25 mm. The typical scan at Emory University at 3T scan parameters were TR = 2300 ms, TE = 3 ms, TI = 1100 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 x 240, slice thickness = 1 mm.

Cortical and Subcortical MRI Procedures

All image processing and analyses were performed at the Center for Multimodal Imaging and Genetics Laboratory at UC San Diego using the exact same imaging analysis stream. *FreeSurfer v5.3* software was used to obtain cortical thickness estimates and subcortical volumes, using validated procedures as previously described (Desikan et al., 2006; Fischl & Dale, 2000). The cortical surface was reconstructed and parcellated using *FreeSurfer*. A local quality check was performed by visual inspection of all images to identify topological defects, which were subsequently edited using established software guidelines. Quantification of cortical thickness estimates was determined by measurement of the distance between the white matter and the pial surfaces at each vertex. The cortical surface was then parcellated into regions of interest (ROIs) using the Desikan-Killiany atlas (Desikan et al., 2006), and average thickness was calculated within each ROI. Cortical thickness estimates were computed point-by-point across the cortical mantle, then averaged to create gyral-based ROIs. In order to control for differences in brain size, subcortical volumes were represented as a ratio to total intracranial volume.

Image harmonization

The batch-effect correction tool, ComBat, was used to harmonize the MRI data, adjusting for between-site variations in cortical thickness and volume across the epilepsy centers. The

ComBat method globally rescales the data for each site using a z-score transformation map common to all features, as described in (Fortin et al., 2017). ComBat uses an empirical Bayes framework to improve the variance of the parameter estimates (Johnson, Li, & Rabinovic, 2007), assuming that all ROIs share the same common distribution. Therefore, all ROIs are used to inform the statistical properties of the site effects. Site was used as the batch effect. The ComBat approach has proven effective for harmonizing T1-weighted MRIs in multi-national imaging collectives such as ENIGMA (Radua et al., 2020) and has been used in TLE imaging data (Kaestner et al., 2021).

Statistical analyses

Analysis of covariance (ANCOVA) were conducted to test for differences in mood symptoms (i.e., BDI-II and BIA scores) across phenotypes. Given differences in sample sizes, nonparametric tests were conducted to test for differences in test performance between monolingual and bilingual patients for each phenotype. Multiple stepwise linear regressions were conducted to evaluate the contribution of demographic, epilepsy-related clinical variables, and CVRFs to cognitive performance across phenotypes. ANCOVAs controlling for age, sex, field strength were conducted to compared ROI across groups (i.e., healthy controls, Generalized, Language, Minimally Impaired). Multiple comparisons were corrected using Benjamini-Hochberg false discovery rate (Benjamini & Hochberg, 1995) for left and right hemisphere ROIs, respectively. When results from the ANCOVA were significant, group contrasts were assessed using post-hoc pairwise tests with Bonferroni correction.

Preliminary Results

Health-related risk and protective factors

There were cerebrovascular risk factors (CVRFs) data available on a subset of patients (n=196) from Study 3. Table 5.1 shows the proportion of patients with hypertension, hyperlipidemia, diabetes, a history of smoking, and a BMI higher than 30. There was no significant difference in the proportion of patients with CVRFs across phenotypes.

Approximately 26 to 42% (BDI-II n=499; BAI n=316) of the original Study 3 sample had BDI-II and BAI data available. Table 5.1 shows the percentage of patients with minimal to severe symptoms of depression and anxiety across phenotypes. There were differences in severity of depressive symptoms across phenotypes, with patients in the *Multidomain* phenotype endorsing more moderate to severe symptoms relative to the *Language* and *No Impairment* phenotypes. When examining the BDI-II and BAI scores as continuous variables, there were differences across phenotypes after controlling for age, education, and sex $F(2, 493) = 4.84$, p=.008. The *Multidomain* phenotype had higher BDI-II scores (Mean=14.94; Standard deviation (SD)= 10.78) relative to the *Language* phenotype (Mean=11.91; SD= 8.97); and higher scores compared to the *No Impairment* (Mean=12.63; SD= 9.29). There were no differences on BAI scores across the phenotypes $F(2, 310) = .776$, p=.461, [*Multidomain (*Mean=12.90; SD= 11.69); *Language (*Mean=11.10; SD= 10.06); *No Impairment (*Mean=10.76; SD= 8.172)].

Regarding bilingualism, of the 390 patients with language information available, 22.1% of this sample was bilingual with Spanish being the most common language (51% of the bilingual subsample). There were no significant differences in the proportion of patients that were bilingual across phenotypes (Fisher's Exact= 4.39, p=.109), however, within the *Multidomain* phenotype 27.4% were bilingual, 22.3% within the *Language* phenotype, and 14.6% within the *No Impairment* group. Further examination revealed that 46.2% of the bilinguals in the *Multidomain*

group spoke Spanish, 61% of bilinguals in the *Language* phenotype spoke Spanish, and 70% of the bilinguals in the *No Impairment* phenotype were Spanish speakers.

Differences in performance between monolingual and bilingual patients

For the *Multidomain* phenotype, there were no differences across cognitive scores between monolingual and bilingual patients (all p-values >.05). For the *Language* phenotype, Mann-Whitney U revealed differences in BNT (U = 6021, *p*=<.001) and letter fluency (U = 4248, *p*=.017) scores between monolingual and bilingual patients. Bilingual patients (n=45) had lower BNT (Mean= 24.17, SD= 7.62) and letter fluency (Mean= 37.58, SD=12.73) scores. For the *No Impairment* phenotype there were differences in BNT scores (U = 566.5, *p*=.012) with the bilingual patients (n=11) demonstrating lower scores (Mean= 32.73, SD= 16.46).

Contribution of demographic, clinical, CVRFs to cognitive impairment across phenotypes

To reduce the number of variables included in the model, we conducted stepwise regressions to examine the differential contribution of demographics, epilepsy-related clinical variables, and CVRFs to each neuropsychological test performance. Models were conducted for each phenotype individually to identify factors that uniquely contribute to cognitive performance in each group. For *Multidomain* phenotype, female sex was associated with better performance in immediate memory (LM1) and set-shifting (TMT-B); and a higher number of ASMs and the presence of hyperlipidemia was associated with worse fine motor dexterity and speed (PegD). For the *Language* phenotype, female sex was associated with better performance in immediate (LM1) and delayed memory (LM2), and set-shifting (TMT-B); more years of education was associated with better performance in delayed memory (LM2) and fine motor dexterity and speed (PegD); hyperlipidemia was associated with worse performance in delayed memory (LM2); longer duration of disease was associated with poorer naming performance (BNT); and higher number of

ASM was associated with worse fine motor dexterity and speed (PegD). For the *No Impairment* phenotype, the presence of MTS was associated with poorer delayed memory (LM2); higher number of ASM was associated with worse processing speed (TMT-A); hyperlipidemia was associated with worse performance in set-shifting (TMT-B); and older age was associated with worse fine motor dexterity and speed (PegD).

Cortical and volumetric differences across groups

There was a trend towards differences in intracranial volume (ICV) across groups F (3, 252) = 2.621, p=.051 with the *No Impairment* demonstrating higher ICVs compared to the *Multidomain* phenotype (p=.075) and the *Language* phenotype (p=.065). Figure 5.1 shows the distribution of ICVs across groups. Cohen's *d* revealed a medium effect size between the *Multidomain* and the *No Impairment* (d=.59) phenotypes after controlling for sex, age, education, and scanner strength. There was also a medium effect size between the *Language* and *No Impairment* (d=.56) phenotypes.

Table 5.3 shows significant differences in cortical regions across groups. After controlling for age, sex, education, and scanner strength, 11 left hemisphere ROIs and 15 right hemisphere ROIs were significantly different across groups. For all regions, healthy controls had thicker cortex relative to the phenotypes. The only significant difference between patient groups was between the *Language* and *No Impairment* phenotypes, with the Language group showing thicker cortex within right lateral occipital (p= .043) and right parahippocampal gyri (p= .033).

Table 5.4 shows comparisons in subcortical structures across groups. There were significant differences in the right amygdala, left and right putamen, left and right thalamus, and right pallidum, with patients having lower volumes relative to healthy controls. The *Multidomain* phenotype had reduced volumes relative to healthy controls in the right amygdala, left putamen,

left and right thalami, and right pallidum. The *Language* phenotype had reduced volumes compared to healthy controls in left and right putamen and left and right thalami. The *No Impairment* phenotype had lower volumes relative to healthy controls in left and right putamen. The *Multidomain* phenotype showed lower right amygdala volume relative to the *No Impairment* group.

Summary

These preliminary analyses demonstrate 1) greater depressive symptoms in patients with *Multidomain* impairment; 2) differential contribution of demographic, clinical, and CVRFs to cognitive performance across phenotypes, with the presence of hyperlipidemia associated with worse cognitive performance; 3) lower language scores in bilingual patients across the *Language* and *No Impairment* phenotypes; 4) cortical thinning and subcortical atrophy compared to HC across phenotypes; 5) a pattern of lower subcortical volumes in the *Multidomain* phenotype; and 6) although not statistically significant, higher ICVs in patients in the *No Impairment* group.

Depression has been associated with worse performance across a range of neuropsychological tests in TLE (Paradiso et al., 2001). These preliminary analyses revealed that patients with generalized impairment had more severe symptoms of depression with approximately 13% of the patients endorsing severe symptoms. In TLE, depression has also been associated with poorer quality of life (Ehrlich et al., 2019) and mood outcomes after epilepsy surgery have been variable, with some studies reporting improvements in depressive symptoms (Blumer, Wakhlu, Davies, & Hermann, 1998; Reuber, Andersen, Elger, & Helmstaedter, 2004), while others reporting worsening of symptoms (Altshuler, Rausch, Delrahim, Kay, & Crandall, 1999; Glosser, Zwil, Glosser, O'Connor, & Sperling, 2000). Furthermore, it has been hypothesized that there is a bidirectional relationship between depression and epilepsy with shared underlying mechanisms

(Kanner, 2011). Given the prevalence of depressive disorders in epilepsy and this proposed bidirectional relationship, the treatment of depression has been a priority in epilepsy care (Cardamone, Salzberg, O'brien, & Jones, 2013). However, identifying patients at increased risk for postoperative depression or worsening of existing depressive symptoms has been more challenging. Efforts are underway to provide clinicians with tools to identify patients at increased risk (Doherty et al., 2021). Given that patients with *Multidomain* impairments demonstrated the most severe symptoms, studies are needed to systematically examine whether treating depression improves the cognitive impairments in this subgroup of patients.

These preliminary analyses also demonstrated a differential contribution of CVRFs to cognitive performance across phenotypes. Specifically, hyperlipidemia was associated with worse performance in all three phenotypes, however, the association was different for each phenotype. This suggests that there may be patient factors that are moderating or mediating the impact of these CVRFs on cognition. Given that the sample with CVRFs was modest, studies with large samples are needed to better delineate these patient factors. Furthermore, longitudinal studies examining whether treating the CVRFs improves cognition and/or reduces postoperative cognitive decline are warranted. Nonetheless, these findings highlight that the relationship between health-related risk factors and cognition in epilepsy may not be uniform across patient groups.

In the current sample, bilingual patients had poorer language scores within the *Language* and *No Impairment* phenotypes. Although this is an expected finding, as bilinguals tend to have lower language scores due to the competing demands of both languages (Gollan, Montoya, Fennema-Notestine, & Morris, 2005; Sandoval, Gollan, Ferreira, & Salmon, 2010), this association was not present in bilingual patients with the *Multidomain* phenotype. Assessing language in bilingual patients with TLE has been a challenge given that it is difficult to tease apart

the contribution of epilepsy pathology on language from the nonpathological effects of bilingualism (Gooding, Cole, & Hamberger, 2018). These preliminary findings may suggest that for patients with generalized impairment, the bilingual disadvantage on language may be attenuated by other factors impacting cognition. We did not find a bilingual advantage on measures of executive function (i.e., TMT-B) which has been previously found in TLE (Reyes et al., 2018). It is possible that we need more comprehensive tests to examine the possible advantage of bilingualism on different aspects of executive function across phenotypes.

Lastly, there were differences in structural brain integrity, with all phenotypes demonstrating greater cortical thinning relative to healthy controls; patients in the *Multidomain* phenotype showing greater subcortical atrophy; and patients in the *No Impairment* group showing a trend towards greater ICVs. Regarding cortical thinning, there was no evident pattern across phenotypes. A previous study demonstrated that patients with generalized impairment showed the most cortical thinning (Dabbs, Jones, Seidenberg, & Hermann, 2009); thus in our sample, this pattern did not emerge. However, a pattern was observed across subcortical volumes, with patients with *Multidomain* impairments showing the most atrophy across several structures. This is consistent with the previous findings demonstrating that patients with generalized impairment had the most subcortical atrophy (Dabbs et al., 2009). Another interesting finding that emerged, although not statistically significant, was greater ICVs in patients with *No Impairment* profiles. ICV has historically been used as a *proxy* for brain reserve and greater ICV has been shown to be associated with better cognitive performance (Van Loenhoud, Groot, Vogel, Van Der Flier, & Ossenkoppele, 2018). Therefore, these preliminary findings suggest that patients with minimal impairments may present with higher brain reserve mitigating the impact of epilepsy burden on cognition. Although these initial neuroimaging findings are promising, larger samples are needed

to further examine the contribution of these neural correlates to cognitive impairment while maintaining power and controlling for multiple comparisons.

Next Steps

These preliminary findings highlight the need to examine health-related risk factors, resilience factors, mood, and neural correlates at the phenotype level rather than at the syndrome level (i.e., all TLE). As previously shown, aggregating patients into one group obscure subtle differences that can be appreciated at the phenotype level. Upon collection of the remainder of the data, these analyses will be replicated with the larger sample to achieve power, reduce type 1 and 2 errors, and systematically control for multiple comparisons. The contribution of these factors to cognitive performance will be examined with regression analyses. Mediation analyses will also be conducted to examine the mediating effects of health-related risk factors and protective factors on the relationship between neural correlates and cognitive impairment.

Figures

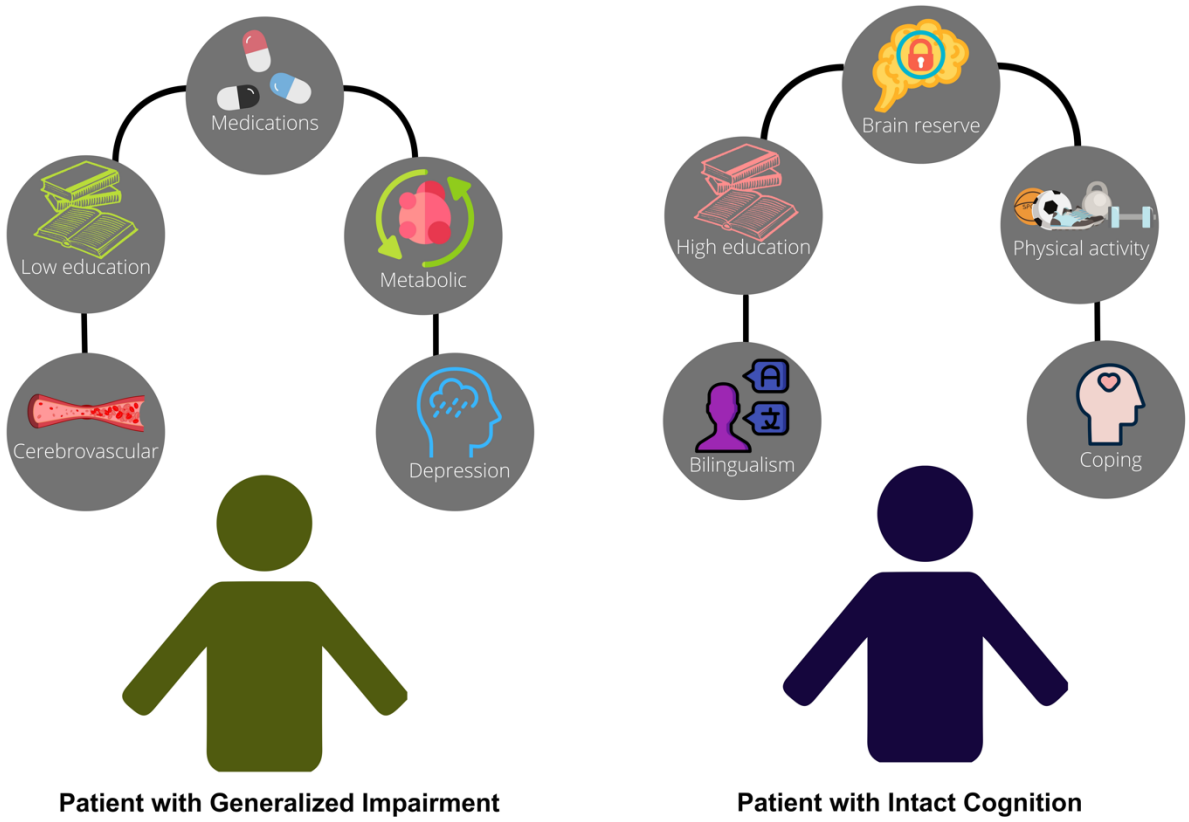

Figure 5.1: *Hypothetical model for patient-centered cognitive risk.* The phenotype approach can provide a mechanism to examine comorbidities and protective factors associated with cognitive risk. Rather than examining these factors at the syndrome level (i.e., all patients with TLE) which can obscure mediating effects, investigating these factors at the phenotype level (i.e., patients with generalized impairment vs patients with intact cognition) can provide patient-centered information on cognitive risk.

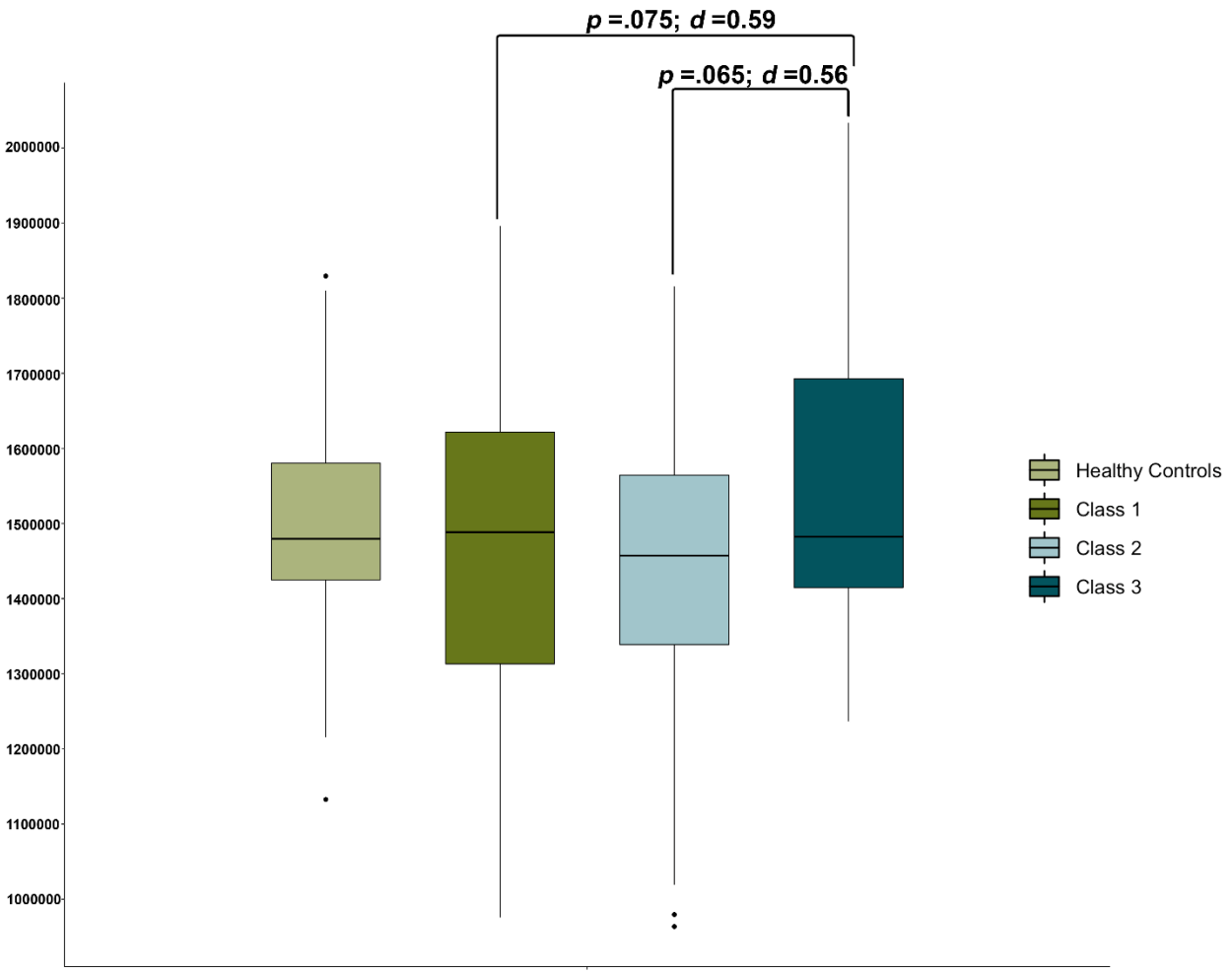

Figure 5.2: *Distribution of Intracranial volume (ICV) across groups.* Overall, the Multidomain (Class 1) and Language (Class 2) phenotypes demonstrated a wider distribution of ICV. Although not statistically significant, the Multidomain and Language phenotype had on average lower ICV relative to the No Impairment group with medium effects sizes calculated with Cohen's *d*.

Tables

Table 5.1: *Preliminary data on vascular risk factors and mood symptoms on a subset of patients from Study 3.* There were no significant differences across phenotypes in the percentage of patients with vascular risk factors are represented.

Cerebrovascular risk factors (n=196)					
	Class 1	Class 2	Class 3	Fisher's Exact	p-value
N	69	101	26		
Hypertension: Y/N	11/58	17/87	6/20	.898	.649
Hyperlipidemia: Y/N	6/47	12/69	4/19	.703	.664
Diabetes: Y/N	1/68	3/101	1/25	.947	.827
BMI Category: Y/N	43/25	57/40	15/10	.497	.813
Smoking History: Y/N	21/48	26/75	9/17	1.08	.602
Depressive (n=499) and Anxiety symptoms (n=316)					
Depression				**14.7**	**.021**
Minimal	50%	63.3%	58.9%	--	--
Mild	16.9%	19.1%	17.9%	--	--
Moderate	20%	11.3%	17.9%	--	--
Severe	13.1%	6.4%	5.4%	--	--
Anxiety				9.49	.143
Minimal	41.4%	45.5%	44.7%	--	--
Mild	24.3%	29.9%	26.3%	--	--
Moderate	17.1%	15.6%	26.3%	--	--
Severe	17.1%	9%	2.6%	--	--

Class 1: Multidomain; Class 2: Language; Class 3: No Impairment

BMI category: Body mass index higher than 30

BDI-II: Beck Depression Inventory Second Edition
Minimal: 0-13; Mild: 14-19; Moderate: 20-28; Severe: 29-63

BAI: Beck Anxiety Inventory
Minimal: 0-7; Mild: 8-15; Moderate: 16-25; Severe: 26-63

Table 5.2: *Contribution of demographic and clinical variables and CVRFs to cognitive impairment.* The regression models were conducted for each phenotype independently to identify unique factors that are contributing to cognitive impairment. Stepwise regressions were used to reduce the number of variables in the model and demographic, clinical, and CVRFs were entered in separate blocks.

Multidomain		Beta	R^2	R^2 change	F Change	p-value
LM1	Sex	3.61	.081	--	4.26	.044
TMT-B	Sex	6.63	.093	--	2.24	.030
PegD	ASM	-4.38	.204	--	11.8	.001
	Hyperlipidemia	-7.71	.272	.067	4.14	.048
Language						
LM1	Education	.852	.080	--	6.63	.012
	Sex	2.68	.131	.050	4.36	.040
LM2	Sex	4.60	.074	--	6.06	.016
	Education	.968	.151	.078	6.86	.011
	Hyperlipidemia	-4.18	.195	.044	4.04	.048
BNT	Duration	-.179	.059	--	4.77	.032
TMT-B	Sex	-6.63	.085	--	6.84	.011
PegD	Education	1.51	.103	--	7.77	.007
	ASM	-4.13	.186	.107	9.09	.004
No Impairment						
LM2	MTS	-4.52	.175	--	4.47	.047
TMT-A	ASM	-7.00	.147	--	4.81	.040
TMT-B	Hyperlipidemia	15.13	.270	--	7.78	.011
Peg-D	Age	.238	.264	--	7.18	.014

Model 1- Demographic: Age, education, sex (0=Male; 1=Female)
Model 2- Clinical Variables: Duration, antiseizure medication (ASM), mesial temporal sclerosis (MTS; (0=not present; 1=present)
Model 3- Cerebrovascular factors: Hypertension (0=not present; 1=present), hyperlipidemia (0=not present; 1=present), diabetes (0=not present; 1=present), body mass index (BMI; continuous)

LM1: Logical Memory Immediate Recall; LM2: Logical Memory Delayed Recall; BNT: Boston Naming Test; LF: Letter Fluency; TMT-A: Trail Making Test condition A; TMT-B: Trail Making Test condition B; PegD: Grooved Pegboard dominant hand

Table 5.3: *Differences in cortical thickness across groups*. A total of 32 cortical thickness ROIs were examined for each hemisphere. The table includes the ROIs that were significantly different across groups. False-discovery rate was used to correct for multiple comparisons for each hemisphere. Age, sex, education, and scanner strength were entered as covariates in the model.

	Class 1	Class 2	Class 3	HC	ANCOVA	Pairwise
	Estimated Mean (SE)	Estimated Mean (SE)	Estimated Mean (SE)	Estimated Mean (SE)	F (p-value)	
Left Hemisphere						
Entorhinal	3.23 (.054)	3.28 (.043)	3.15 (.090)	3.48 (.064)	4.33 (.005)	HC>1; HC>2; HC>3
Fusiform	2.66 (.022)	2.68 (.017)	2.57 (.036)	2.73 (.026)	4.49 (.004)	HC>3
Inferior parietal	2.45 (.022)	2.48 (.017)	2.40 (.036)	2.55 (.026)	4.54 (.004)	HC>1; HC>3
Isthmus cingulate	2.44 (.027)	2.45 (.021)	2.38 (.045)	2.65 (.032)	12.6 (<.001)	HC>1; HC>2; HC>3
Lateral occipital	2.11 (.020)	2.13 (.016)	2.04 (.034)	2.22 (.024)	7.26 (<.001)	HC>1; HC>2; HC>3
Lingual	1.90 (.019)	1.90 (.015)	1.86 (.031)	2.08 (.022)	16.7 (<.001)	HC>1; HC>2; HC>3
Pericalcarine	1.53 (.020)	1.54 (.016)	1.51 (.033)	1.64 (.024)	5.63 (<.001)	HC>1; HC>2; HC>3
Posterior cingulate	2.48 (.023)	2.53 (.018)	2.47 (.038)	2.66 (.027)	8.82 (<.001)	HC>1; HC>2; HC>3
Precuneus	2.32 (.020)	2.34 (.016)	2.29 (.033)	2.42 (.024)	4.69 (.003)	HC>1; HC>2; HC>3
Superior parietal	2.20 (.021)	2.19 (.016)	2.16 (.034)	2.29 (.024)	4.93 (.002)	HC>1; HC>2; HC>3
Frontal pole	2.80 (.037)	2.85 (.029)	2.83 (.061)	2.99 (.043)	3.29 (.009)	HC>1
Right hemisphere						
Entorhinal	3.37 (.061)	3.41 (.048)	3.18 (.101)	3.65 (.072)	5.46 (.001)	HC>1; HC>2; HC>3
Fusiform	2.65 (.023)	2.68 (.018)	2.57 (.038)	2.76 (.027)	6.26 (<.001)	HC>1; HC>3;
Inferior parietal	2.49 (.023)	2.50 (0.18)	2.44 (.039)	2.62 (.028)	6.08 (<.001)	HC>1; HC>2; HC>3
Isthmus cingulate	2.40 (.028)	2.45 (.022)	2.35 (.046)	2.51 (.033)	3.58 (.014)	HC>3
Lateral occipital	2.19 (.022)	2.22 (.017)	2.11 (.036)	2.31 (.026)	7.44 (<.001)	HC>1; HC> 2; HC>3; 2>3
Lingual	1.91 (.017)	1.96 (.014)	1.90 (.029)	2.06 (.021)	11.7 (<.001)	HC>1; HC>2; HC>3
Middle temporal	2.88 (.024)	2.87 (.019)	2.84 (.039)	2.98 (.028)	4.29 (.006)	HC>1; HC>2; HC>3
Parahippocampal	2.68 (.037)	2.69 (.029)	2.69 (.029)	2.79 (.044)	5.20 (.002)	HC>3; 2>3
Paracentral	2.30 (.023)	2.32 (.018)	2.33 (.038)	2.43 (.044)	3.97 (.009)	HC>1; HC>2
Posterior cingulate	2.46 (.021)	2.51 (.016)	2.42 (.034)	2.58 (.025)	5.89 (<.001)	HC>1; HC>3
Precentral	2.41 (.025)	2.45 (.019)	2.46 (.041)	2.45 (.029)	3.77 (.011)	HC>1
Precuneus	2.33 (.020)	2.34 (.016)	2.29 (.033)	2.44 (.023)	6.24 (<.001)	HC>1; HC>2; HC>3
Superior parietal	2.18 (.021)	2.18 (.017)	2.14 (.035)	2.29 (.025)	5.31 (.001)	HC>1; HC>2; HC>3
Transverse temporal	2.32 (.033)	2.39 (.026)	2.39 (.055)	2.49 (.039)	4.02 (.008)	HC>1; HC>2

Class 1: Multidomain; Class 2: Language; Class 3: No Impairment

Estimated means controlling for age, sex, education, and scanner strength

SE: standard error; HC: healthy controls; ANCOVA: analysis of covariance

False-discovery rate:
Left hemisphere comparisons FDR corrected p-value: .0171875
Right hemisphere comparisons FDR corrected p-value: .0234375

Table 5.4: *Comparison of subcortical structures across groups.* All subcortical volumes were corrected for intracranial volume to adjust for differences in brain size.

	ANCOVA	HC vs Class 1	HC vs Class 2	HC vs Class 3	Class 1 vs Class 2	Class 1 vs Class 3	Class 2 vs Class 3
	F (p-value)						
Left hippocampus	1.98 (.117)	1.00	.942	1.00	1.00	.317	.193
Right hippocampus	0.476 (.699)	1.00	1.00	1.00	1.00	1.00	1.00
Left amygdala	2.35 (.073)	.123	1.00	.329	.731	1.00	1.00
Right amygdala	**5.61 (<.001)**	**.018**	.597	1.00	.357	**.002**	.059
Left putamen	**6.41 (<.001)**	**.005**	**.003**	**<.001**	1.00	1.00	.776
Right putamen	**4.59 (.004)**	.264	**.048**	**.003**	1.00	.253	.423
Left caudate	0.55 (.649)	1.00	1.00	1.00	1.00	1.00	1.00
Right caudate	0.37 (.771)	1.00	1.00	1.00	1.00	1.00	1.00
Left thalamus	**4.14 (.007)**	**.006**	**.016**	.819	1.00	1.00	1.00
Right thalamus	**4.13 (.007)**	**.009**	**.021**	1.00	1.00	.583	1.00
Left pallidum	2.76 (.043)	.034	1.00	1.00	.304	.888	1.00
Right pallidum	**4.43 (.005)**	**.002**	.181	1.00	.252	.430	1.00

Class 1: Multidomain; Class 2: Language; Class 3: No Impairment

Covariates: age, sex, education, and scanner strength

HC: healthy controls; ANCOVA: analysis of covariance

Bold represents significance with a false-discovery rate correction of .025

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Chapter 6:

Integrated Discussion

As the field of medicine continues to move towards *precision medicine*, utilizing individualized approaches to studying neuropsychological syndromes will advance our understanding of brain-behavior relationships in the context of patient-specific factors. This staple dissertation 1) demonstrated that cognitive phenotypes in epilepsy are stable across studies; 2) provided detailed information on the most robust and rigorous methodology to phenotyping, thus informing future studies in this area; 3) demonstrated that cognitive phenotypes in temporal lobe epilepsy (TLE) have unique imaging signatures (i.e., WM, cortical thickness, subcortical volumes) that better explain the cognitive dysfunction observed within patient subtypes; and 4) demonstrated the utility of the phenotyping approach in studying the impact of health-related and protective factors on cognition. Work from this dissertation has informed international initiatives in this area and efforts are underway to continue expanding the findings from the current studies in larger, international, culturally, and linguistically diverse populations.

Study 1: Unmasking phenotype-specific white matter microstructural networks

Study 1 provided initial findings of unique WM signatures across cognitive phenotypes in TLE that could be appreciated both at the regional and network level. Here, we show that the phenotyping approach reveals WM changes that more directly map on to the cognitive profiles observed across patient groups. Further, we were able to identify patients with unique cognitive profiles not well represented across the epilepsy literature (e.g., patients with intact cognition). Importantly, the cognitive phenotypes were not well differentiated based on classic epilepsy characteristics (i.e., MTS, duration of epilepsy, seizure frequency, number of ASMs) but instead demonstrated distinct patterns of regional and network WM microstructural abnormalities. For

example, patients with both language and memory impairments showed changes in superficial WM (SWM) within lateral temporal lobes encompassing perisylvian regions involved in language processing (Catani, Jones, & Ffytche, 2005). Whereas patients with isolated memory impairments demonstrated changes in SWM within medial temporal structures critical to memory (Squire & Zola-Morgan, 1991). Despite all patients in this study having chronic epilepsy, a modest sample of patients did not demonstrate any cognitive deficits and their WM networks were similar to healthy controls. These findings illustrate that aggregating patients into one group may obscure changes in microstructural integrity that can better explain cognitive deficits and inform patient outcomes. Thus, I argue that in order to systematically delineate the brain abnormalities associated with cognitive deficits in epilepsy, the phenotype approach should be implemented to better characterize structural and functional alterations that are unique to patient subtypes. Global research initiatives such Enhancing NeuroImaging and Genetics through Meta-Analysis (ENIGMA- Epilepsy) can provide the infrastructure and resources needed to replicate these findings in large, representative samples. Furthermore, most investigations in cognitive phenotypes in epilepsy have been conducted in the U.S. (B. P. Hermann et al., 2021), thus there is a need to replicate these phenotypes in international cohorts.

Study 2: Examining the clinical utility of cognitive phenotypes

Although findings from Study 1 and other phenotype investigations (Sallie Baxendale & Pamela Thompson, 2020; Elverman et al., 2019; B. Hermann et al., 2020; B. Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; Rodríguez-Cruces et al., 2018) have identified a similar pattern of phenotypes (i.e., generalized group, focal group, and a minimally impaired group), there has been variability in the number and base rates of the phenotypes identified and the nature of the cognitive profiles. Importantly, the methods employed to derive the phenotypes have varied across studies.

Given that a major goal of this literature is to translate these cognitive phenotypes into clinical diagnostic criteria, determining the clinical utility of these phenotypes is paramount. As such, the aim of Study 2 was to conduct a head-to-head comparison between a data-driven approach and an actuarial clinical criterion that can be implemented into clinical diagnostic approaches. Specifically, I compare cluster analysis, one of the most commonly used data-driven clustering methods, to the clinical criteria used in Study 1. These clinical criteria are commonly used in the aging literature (Jak et al., 2009) and have been shown to derive cognitive subtypes in patients with mild cognitive impairment (MCI), the preclinical phase of Alzheimer's disease (E. C. Edmonds et al., 2016).

Study 2 revealed that there was a good agreement between cluster analysis and the clinical criterion, however, cluster analysis misclassified ~12% of patients with clinically defined impairments as having normal cognition. This can present an obstacle to the translation of these phenotypes into clinical diagnostic frameworks. The impact of false-negative diagnostic errors in neuropsychology can have a direct impact on clinical practice. Edmonds et al. (Emily C Edmonds et al., 2016) emphasized that false-negatives among cases of MCI can result in missed opportunities for interventions, can lead to exclusion from beneficial treatments (e.g., clinical trials), and can impact the recommendations provided to patients and their families. In epilepsy specifically, a patient's cognitive status has important implications for surgical decisions. Baxendale and Thompson (S. Baxendale & P. Thompson, 2020) utilized clinical criteria to ascertain risk for postoperative cognitive decline across cognitive phenotypes in TLE. In this study, they also identified a group of patients with generalized impairment, a second group with focal deficits in language and memory, and a group with intact cognitive function. They found that an intact phenotype was a risk for cognitive decline in visual learning. Although the authors did not

find associations between cognitive phenotypes and declines in other cognitive domains, these initial findings are promising and illustrate that cognitive phenotypes can provide another method to determining postoperative cognitive decline.

Study 3: Can we arrive at the most robust and rigorous clustering method?

Findings from Study 2 revealed some disadvantages to clustering analysis that can potentially impact the translation of cognitive phenotypes into clinical practice. These findings led to the question "*what is the optimal method for defining cognitive phenotypes across neuropsychological syndromes*?" Given that the cognitive phenotype literature is gaining attraction across several neurological disorders, the aim of Study 3 was two-fold: 1) to test several models (i.e., 2-5 groups) of cognitive phenotypes in TLE using latent profile analysis (LPA) and 2) demonstrate the utility of LPA to inform investigations of cognitive phenotypes across other neurological disorders. This study represents the largest, multicenter investigation with 1,178 patients with TLE, building upon Study 2 which had 407 patients. LPA is a person-centered clustering method that maximizes the homogeneity within groups and the heterogeneity across groups while providing the probability of group membership. Here, we demonstrate that a 3-class (i.e., 3 phenotypes) model was the optimal solution based on several fit indices and it was the most robust to missing data. We also adjudicate the impact of missing data, demonstrating that missing data impacts clustering models with multiple phenotypes (i.e., 4-5), particularly phenotypes that share similar cognitive features (e.g., focal language deficits). These findings demonstrate that LPA is a more rigorous and robust clustering method and we advocate for its use to avoid the pitfalls of clustering analysis or other clustering methods that 1) do not handle missing data, 2) do not test the probability of group memberships, and 3) do not provide the user with several fit indices to inform decision making.

Beyond the seizures: The neglected comorbidities in epilepsy

Although Study 3 had many strengths, there were some limitations that can inform future studies. First, the tests included had heavy verbal demands, and tests of visual memory and visuospatial abilities were not included due to lack of availability across epilepsy centers. A future study with a more comprehensive battery of tests is needed to determine if focal groups of patients with focal deficits in visual memory/abilities exist and whether patients with generalized impairments also have deficits in these domains. Second, we did not have comprehensive data on other factors that may explain the heterogeneity of the cognitive phenotypes which was an initial aim of the dissertation. An important feature of the cognitive phenotype approach is that it places the patient's cognitive status and risk at the center of care, allowing researchers and clinicians to examine other comorbidities that may be contributing to the patient's cognitive profile (see Figure 5.1). The classic lesion model attributed the cognitive deficits in epilepsy to the location of seizure origin and other epilepsy-related variables (e.g., antiseizure medications, seizure frequency, duration of epilepsy, surgery). And although the comorbidities of epilepsy (e.g., vascular, psychiatric) and associated psychosocial outcomes have been well documented (Keezer, Sisodiya, & Sander, 2016; Seidenberg, Pulsipher, & Hermann, 2009), their effects on cognition has been a neglected area in epilepsy research and care. Furthermore, *precision medicine* considers "individual variability in genes, environment, and lifestyle for each person" and thus the inherited variability in cognitive deficits in epilepsy suggests that there are individual factors beyond the epilepsy disorder that must be considered. In epilepsy specifically, Josephson and Wiebe argue that identifying phenotypes in epilepsy *"will, by nature, catalyze tailored treatments specific to individual, rather than population-level, traits"* (Josephson & Wiebe, 2021).

The preliminary findings (Chapter 5) included in this dissertation demonstrated: 1) unique contributions of cerebrovascular factors to cognitive impairment across phenotypes; 2) moderate to severe depressive symptoms in patients with generalized impairment; 3) an expected bilingual disadvantage in language measures across the *Language* and *No Impairment* phenotype that was not present in those with *Multidomain* impairments; 4) cortical thinning across phenotypes with the *Multidomain* phenotype demonstrating the greatest subcortical atrophy; and 5) higher intracranial volume (a proxy for brain reserve) in patients with *No Impairment.* Although these findings must be replicated in the entire sample from Study 3, it highlights that the phenotype approach can disentangle patient-specific factors that as Josephson and Wiebe proposed, can catalyze tailored treatments specific to the patient. For example, patients with *Multidomain* impairments may benefit from aggressive treatment of depression which has been associated with poorer surgery outcomes and reduced quality of life (Reuber, Andersen, Elger, & Helmstaedter, 2004).

What can we learn from the intact phenotype?

The *Intact* or *Minimally Impaired* phenotype has been an unexpected group across phenotype investigations, as these patients present with chronic epilepsy and in some studies have indistinguishable clinical profiles compared to patients with cognitive dysfunction (Elverman et al., 2019; Reyes et al., 2019; Reyes et al., 2020). The aging literature has coined the term "superager" or older individuals (>80 years) that demonstrate superior cognitive abilities and therefore may present with increases in brain and/or cognitive reserve mitigating nonpathological and pathological mechanisms of aging (De Godoy et al., 2021). Thus, the finding of an "Intact Phenotype" across studies raises the question "*Are there individuals with epilepsy that present with increased resilience to epilepsy-related pathology?"* Investigating this group of patients can help

identify factors that can inform interventions, treatments, and health policies. For example, education has been found to be a protective factor against epilepsy pathology (Jokeit & Ebner, 1999) and to reduce the risk of developing epilepsy (Wang et al., 2021). Patients in the *No Impairment* group (Study 3) had greater years of education and preliminary results (Chapter 5) demonstrated that greater years of education were associated with better performance across a range of tests. Patients with epilepsy, particularly those that are diagnosed in childhood or adolescence, present with lower educational and occupational attainment which has been shown to lead to poorer quality of life and lower socioeconomic status (Jennum, Debes, Ibsen, & Kjellberg, 2021). Thus, there is an opportunity to develop and implement programs aimed at providing individuals with epilepsy the resources (e.g., tutoring, early educational programs) needed to achieve higher educational attainment. Given that patients with intact cognition also present with minimal brain abnormalities and therefore potential indicators of higher brain reserve, longitudinal studies following individuals with newly onset epilepsy as they age can provide insights into the mitigating effects of brain reserve on both cognitive and seizure outcomes.

The future of epilepsy research and clinical care

Since the first cognitive phenotype publication in 2007, there have been over 17 publications examining cognitive and behavioral phenotypes in epilepsy. In a recent review published in *Nature Reviews Neurology*, our group provided compelling evidence supporting the use of this new taxonomy and a detailed rationale as to why the lesion-model fails to capture the cognitive heterogeneity observed across patients. Furthermore, findings from Studies 1 and 2, along with other phenotype investigations have informed the development of an international initiative — International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) — aimed at developing a consensus-based classification system for cognitive disorders in epilepsy that can

be used in research investigations (McDonald et al., 2022; Norman et al., 2021). The IC-CoDE provides a diagnostic framework for classifying patients into cognitive phenotypes based on actuarial neuropsychological criteria. This initiative will facilitate international communication and collaborations and move the field of epilepsy toward *precision neuropsychology*. Importantly, there is a need to replicate these cognitive phenotypes in ethnoracially and linguistically diverse populations. Current efforts are underway to test the IC-CoDE in a Spanish-speaking sample of patients with TLE (Reyes, 2022) with the goal of validating the framework across a range of ethnoracial and linguistically diverse samples.

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