UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

The Relationship Between Subjective Cognitive Decline and Objective Cognitive Performance Within Three Different Older Adult Samples

A Dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Clinical Psychology

by

Marina Zaher Nakhla

Committee in charge:

University of California San Diego

Professor Zvinka Z. Zlatar, Chair
Professor Dawn M. Schiehser, Co-Chair
Professor David Salmon

San Diego State University
Professor Paul E. Gilbert
Professor Scott Roesch

2024

The dissertation of Marina Zaher Nakhla is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

Chair

Co-Chair

University of California San Diego

San Diego State University

2024

DEDICATION

I dedicate this dissertation to my family, particularly my mom, dad, and sister. My parents had immigrated to the United States from Egypt for religious freedom and in hopes of providing a plethora of opportunities for their future family. They ceaselessly emphasized the importance of education throughout my childhood, stating, "Education is the key to success." They have always encouraged and supported me in all aspects of my life, including my personal, spiritual, and academic/professional endeavors. Words cannot express my gratitude for my family's unconditional encouragement, support, and love. They are my primary source of motivation and the reason for my accomplishments. I also dedicate this dissertation to my best friends, cohort, and peers. Thank you for your support, advice, and feedback. I have enjoyed having the company of my friends and peers while studying and working through my Ph.D. program.

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ACKNOWLEDGEMENTS

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Second, I would like to thank the rest of my Dissertation Committee. To Dr. Scott Roesch, thank you for providing me with beneficial feedback in regard to enhancing statistical analyses for my manuscripts, alternative methods for when the analyses did not pan out in the way I expected them, and clarifications for concepts that I was unclear about. To Dr. David Salmon, thank you for your immense involvement in my research projects involving Hispanics/Latinos including feedback on manuscripts and posters. To Dr. Paul Gilbert, thank you for your involvement on my Guidance Committee in addition to my Dissertation Committee. I am grateful for your encouragement, mentorship, and support as I progressed through the program.

Third, I would like to thank everyone at the JDP who has supported me in the process, including Drs. Vanessa Malcarne, Lauren Brookman-Frazee, and Bob Heaton, as well as Lynsey Miller and Kristin Deveraux. Last but not least, I would like to thank my mom, Hayam, my sister, Christina, and my dad, Zaher. They have been my rock since day #1. I love you all.

Chapter 1, in full, is a reprint of the material as it appears in the *Journal of the International Neuropsychological Society.* **Nakhla, M. Z.,** Bangen, K. J., Schiehser, D. M., Roesch, S., & Zlatar, Z. Z. (2024), *30,* 1-10. Chapter 2, in full, is a reprint of the material as it appears in the *Journal of Clinical and Experimental Neuropsychology*. **Nakhla, M. Z.,** Cohen, L., Salmon, D. P., Smirnov, D. S., Marquine, M. J., Moore, A. A., Schiehser, D. M., & Zlatar, Z. Z. (2021), *43*(7), 663-676. Chapter 3, in full, is a reprint of the material as it appears in the *Journal of the International Neuropsychological Society*. **Nakhla, M. Z.,** Holiday, K. A., Filoteo, J. V., Zlatar, Z. Z., Malcarne, V., Lessig, S., Litvan, I., & Schiehser, D. M. (2021), *27*(5), 439-449. The dissertation author was the primary investigator and author for each of these papers.

VITA

EDUCATION

San Diego State University/University of California San Diego
Joint Doctoral Program (JDP) in Clinical Psychology – APA-Accredited
Ph.D. Clinical Psychology – Major Area of Study: Neuropsychology 2024

San Diego State University
M.S. Clinical Psychology 2020

California State University, Northridge
M.A. Clinical Psychology 2018
B.A. Psychology Honors 2016

AWARDS

American Psychological Foundation: National Register Internship Travel Scholarship | 2023

UCSD Graduate Division, Strategic Enhancement of Excellence through Diversity (SEED) Fellowship | 2018-2024

Certificate of Recognition, Egyptians United USA | 2023

Young Leadership Award, Egyptian American Organization | 2022

SDSU/UCSD Joint Doctoral Program's Contribution to Diversity Award | 2022

UCSD's 27th Annual Inclusive Excellence Award | 2022

Women in Neuropsychology: Inclusion, Diversity, Equity, and Advocacy Award – Honorable Mention | 2021

Sally Casanova Pre-Doctoral Scholar | 2017-2018

NIH Research Initiative for Scientific Enhancement Graduate Scholar, CSUN | 2016-2018

NIH Research Initiative for Scientific Enhancement Undergraduate Scholar, CSUN | 2015-2016

Disability Resources and Educational Services (DRES) Recognition Award, CSUN | 2018

DRES Jane Small Scholarship for Advocates for People with Disabilities, CSUN | 2018

Scholar/Practitioner Award in Clinical Psychology, Department of Psychology, CSUN | 2018

PEER-REVIEWED PUBLICATIONS

Nakhla, M. Z., Bangen, K. J., Schiehser, D. M., Roesch, S., & Zlatar, Z. Z. (2024). Greater subjective cognitive decline severity is associated with worse memory performance and lower entorhinal cerebral blood flow in healthy older adults. *Journal of the International Neuropsychological Society, 30,* 1-10. doi:10.1017/S1355617723000115

Nakhla, M. Z., Banuelos, D., Pagan, C., Gavarrete Olvera, A., & Razani, J. (2022). Differences between episodic and semantic memory in predicting observation-based activities of daily living in mild cognitive impairment and Alzheimer's disease. *Applied Neuropsychology: Adult, 29*(6), 1499-1510. doi:10.1080/23279095.2021.1893172

Pluim, C. F., **Nakhla, M. Z.,** Split, M., Filoteo, J. V., Litvan, I., Moore, R. C., Lessig, S., & Schiehser, D. M. (2022). Changes in self- and informant-reported frontal behaviors in Parkinson's disease: A longitudinal study. *Journal of Geriatric Psychiatry and Neurology, 35*(1) 89-101. doi:0891988720964257

Nakhla, M. Z., Cohen, L., Salmon, D. P., Smirnov, D. S., Marquine, M. J., Moore, A. A., Schiehser, D. M., & Zlatar, Z. Z. (2021). Self-reported subjective cognitive decline is associated with global cognition in a community sample of Latinos/as/x living in the United States, *43*(7), 663-676. *Journal of Clinical and Experimental Neuropsychology*. doi: 10.1080/13803395.2021.1989381.

Nakhla, M. Z., Holiday, K. A., Filoteo, J. V., Zlatar, Z. Z., Malcarne, V., Lessig, S., Litvan, I., & Schiehser, D. M. (2021) Informant-reported cognitive decline is associated with objective cognitive performance in Parkinson's disease. *Journal of the International Neuropsychological Society, 27*(5), 439-449. doi:10.1017/S1355617720001137

Laganá, L., Balian, O., **Nakhla, M. Z.,** Zizumbo, J., & Greenberg, S. (2021). A preliminary model of health regarding sexual and ethnic minority older adults. *Culture, Health, & Sexuality, 23*(3), 333-348. doi:10.1080/13691058.2019.1710566

Holiday, K. A., Clark, A. L., Merrit, V. C., **Nakhla, M. Z.,** Sorg, S., Delano-Wood, L., & Schiehser, D. M. (2020). Response inhibition in Veterans with a history of mild traumatic brain injury: The role of self-reported complaints in objective performance. *Journal of Clinical and Experimental Neuropsychology, 42*(6), 556-568. doi:10.1080/13803395.2020.1776847

Mahmood, Z., Van Patten, R., **Nakhla, M. Z.,** Twamley, E. W., Filoteo, J. V., & Schiehser, D. M. (2020). REM sleep behavior disorder in Parkinson's disease: Effects on cognitive, psychiatric, and functional outcomes. *Journal of the International Neuropsychological Society, 26*(9), 894-905. doi:10.1017/S1355617720000430

Kaufmann, C. N., **Nakhla, M. Z.,** Lee, E. E. Yoon, H. K., Wing, D., Depp, C. A., & Eyler, L. T. (2019). Inaccuracy between subjective reports and objective measures of sleep duration and clinical correlates. *Journal of Affective Disorders, 250,* 226-230. doi: 10.1016/j.jad.2019.03.014

Lara-Ruiz, J., Kauzor, K., Gonzalez, K., **Nakhla, M. Z.,** Banuelos, D., Woo, E., Apostolova, L. G., & Razani, J. (2019). Functional ability of MCI and Alzheimer's patients predicts caregiver burden. *Journal of Gerontopsychology and Geriatric Psychiatry, 32(1),* 31-39. doi:10.1024/1662-9647/a000200

Laganá, L., Sosa, G., **Nakhla, M. Z.,** & Toscano, D. (2018). Cognitive gains from video game use in older age: A review of the literature corroborating them. *International Journal of Family and Community Medicine, 2(1),* 11-17. doi:10.15406/ijfcm.2018.02.00029

POSTER PRESENTATIONS

Zlatar, Z. Z., **Nakhla, M. Z.,** Marquine, M. J., Galasko, D., Tarraf, W., Duara, R., Barker, W., Gonzalez Pineiro, Y., Velasquez De Lopez, K., & Salmon, D. (2024, February). *Differences in objective cognitive performance among Latinx older adults with and without subjective cognitive decline.* Poster presented at the International Neuropsychological Society, New York, NY.

Pantoja, E., **Nakhla, M. Z.,** Gutierrez Aceves, R., Salmon, D., Marquine, M. J., Gonzalez, Y., Duara, R., Barker, W., Tarraf, W., & Zlatar, Z. Z. (2023, April). *Self and informant reports of subjective cognitive decline are associated with acculturation levels in Hispanic/Latinx older adults.* Poster presented at UC San Diego's Judd Symposium, San Diego, CA.

Paredes, D., Dang, T., **Nakhla, M. Z.,** Moore, R. C., Lessig, S., Litvan, I., Bayram, E., Filoteo, J. V., & Schiehser, D. M. (2023, February). *Grit predicts lower cognitive fatigue in persons with Parkinson's disease independent of cognitive status*. Poster presented at the International Neuropsychological Society, San Diego, CA.

Cabrera Tuazon, A. E., **Nakhla, M. Z.,** Almklov, E., Moore, R. C., Filoteo, J. V., Bayram, E., Lessig, S., Litvan, I., Schiehser, D. M. (2022, February). *The relationship between resilience and quality of life in individuals with Parkinson's disease.* Poster presented at the International Neuropsychological Society [remote].

McMann, T., **Nakhla, M. Z.,** Whiteley, N., Ton-Loy, A., Vannini, M., Litvan, I., Lessig, S., Filoteo, V. F., & Schiehser, D. M. (2020, February). *Antidepressants exacerbate cognitive dysfunction in Parkinson's disease.* Poster session presented at the International Neuropsychological Society [remote].

Nakhla, M. Z., Martinez, M. Balian, O., Chaves, S., Morain, K., & Lagana, L. (2020, October). *A review of the physical and psychosocial challenges faced by individuals living with a physical disability*. Poster session presented at the Western Psychological Association [remote].

Laganà, L., Balian, O., **Nakhla, M. Z.,** Zizumbo, J., & Greenberg, S. (2020, October). *A preliminary model of risk and protective factors impacting the well-being of older adults with sexual, gender, and racial/ethnic minority identities.* Poster session presented at the Western Psychological Association [remote].

Nakhla, M. Z., Cohen, L., Knight, C. R., Williams, A., Pulido, B., Salcedo-Borrego, C. G., Schiehser, D. M., Salmon, D., Marquine, M. J., Moore, A. A., & Zlatar, Z. Z. (2020, February). *Relationship between self- and informant-reports of subjective cognitive decline with Dementia Rating Scale scores in Hispanics: A preliminary study.* Poster session presented at the International Neuropsychological Society, Denver, CO.

Nakhla, M. Z., Holiday, K. A., Whiteley, N., Cabrera Tuazon, A. E., Mahmood, Z., Filoteo, J. V., Zlatar, Z. Z., & Schiehser, D. M. (2020, February). *Parkinson's disease performance-based activities of daily living are associated with caregiver, not patient reports.* Poster session presented at the International Neuropsychological Society, Denver, CO.

Mahmood, Z., Van Patten, R., **Nakhla, M. Z.,** Twamley, E. W., Filoteo, J. V., & Schiehser, D. M. (2020, February). *REM sleep behavior disorder in non-demented Parkinson's disease is related to poorer cognitive performance.* Poster session presented at the International Neuropsychological Society, Denver, CO.

Bashor, K. L., Cabrera Tuazon, A. E., **Nakhla, M. Z.,** Whiteley, N., McMann, T., Almklov, E., Litvan, I., Filoteo, J. V., and Schiehser, D. M. (2020, February). *Differential impact of HRT in Parkinson's disease compared to healthy women: A preliminary study*. Poster session presented at the International Neuropsychological Society, Denver, CO.

Whiteley, N., Bashor, K. L., Holiday, K. A., Cabrera Tuazon, A. E., **Nakhla, M. Z.,** Das, A., Filoteo, J. V., & Schiehser, D. M. (2020, February). *Is fatigue associated with cognitive performance in Parkinson's disease?.* Poster session presented at the International Neuropsychological Society, Denver, CO.

Nakhla, M. Z., Filoteo, J. V., Pluim, C. F., Cabrera Tuazon, A. E., Whiteley, N., Zlatar, Z. Z., Lessig, S., Litvan, I., & Schiehser, D. M. (2019, November). *Executive functioning best predicts performance-based financial skills in non-demented Parkinson's disease.* Poster session presented at the National Academy of Neuropsychology, San Diego, CA.

Whiteley, N., King, H., Cabrera Tuazon, A. E., Pluim, C. F., **Nakhla, M. Z.,** Mills, P, & Schiehser, D. M. (2019, November). *Osteopathic manipulative treatment improves non-motor symptoms in Parkinson's disease: A preliminary study*. Poster session presented at the National Academy of Neuropsychology, San Diego, CA.

Mahmood, Z., Van Patten, R., **Nakhla, M. Z.,** Twamley, E. W., Filoteo, J. V., & Schiehser, D. M. (2019, November). *REM sleep behavior disorder in non-demented Parkinson's disease is related to poorer cognitive performance.* Poster session presented at the National Academy of Neuropsychology, San Diego, CA.

Holiday, K. A., Clark, A. L., Sorg, S., Merritt, V. C., **Nakhla, M. Z.,** Delano-Wood, L., & Schiehser, D. M. (2019, November). *The relationship between subjective and objective disinhibition in mild-moderate traumatic brain injury.* Poster session presented at the National Academy of Neuropsychology, San Diego, CA.

Nakhla, M. Z., Pulido, B., Salcedo-Borrego, C. G., Lewis, J. D., Cohen, L., Yassai-Gonzalez, D., Marquine, M., Schiehser, D. M., Salmon, D., Moore, A., & Zlatar, Z. Z. (2019, June). *Subjective cognitive decline and neurocognition in Hispanics/Latinos: A pilot study.* Poster session presented at the UCLA RCMAR Center for Health Improvement of Minority Elderly (CHIME), Los Angeles, CA.

Nakhla, M. Z., Pulido, B., Salcedo-Borrego, C. G., Lewis, J. D., Cohen, L., Yassai-Gonzalez, D., Marquine, M., Schiehser, D. M., Salmon, D., & Zlatar, Z. Z. (2019, February). *Subjective cognitive decline predicts concurrent cognition in Hispanics, but not in Non-Hispanic Whites: A pilot study.* Poster session presented at the Hispanic Neuropsychological Society, New York, NY.

Nakhla, M. Z., Pluim, C. F., Zlatar, Z. Z., Filoteo, J. V., Cabrera Tuazon, A. E., Whiteley, N., Lessig, S., Litvan, I., & Schiehser, D. M. (2019, February). *Attention abilities best predict medication management in Parkinson's disease*. Poster session presented at the International Neuropsychological Society, New York, NY.

Pluim, C. F., Whiteley, N., Cabrera Tuazon, A. E., **Nakhla, M. Z.,** McMann, T., Moore, R. C., Lessig, S., Litvan, I., Filoteo, J. V., & Schiehser, D. M. (2019, February). *Do subjective complaints of dysexecutive behavior predict future neuropsychological test performance in Parkinson's disease?*. Poster session presented at the International Neuropsychological Society, New York, NY.

Tuazon, A. E. C., Pluim, C. F., Pirogovsky-Turk, E. Whiteley, N., **Nakhla, M. Z.,** Filoteo, J. V., Lessig, S., Litvan, I., & Schiehser, D. M. (2019, February). *Apathy predicts cognitive decline in individuals with Parkinson's disease*. Poster session presented at the International Neuropsychological Society, New York, NY.

Banuelos, D., **Nakhla, M. Z.,** Gavarrete Olvera, A., & Razani, J. (2019, February). *Different CVLT subscales predict shopping skills in Alzheimer's disease and mild cognitive impairment.* Poster session presented at the International Neuropsychological Society, New York, NY.

Toscano, D., Balian, O., Laganá, L., **Nakhla, M. Z.,** Zizumbo, J., & Santana, E. (2018, August). *A literature review on the multiple psychosocial challenges often faced by older LGBTQ individuals.* Poster session presented at the American Psychological Association, San Francisco, CA.

Nakhla, M. Z., Banuelos, B., Gavarrete Olvera, A., Herrera, J. D., & Razani, J. (2018, June). *Semantic memory mediates the relationship between episodic memory and shopping skills in Alzheimer's disease and mild cognitive impairment compared to healthy controls.* Poster session presented at the American Academy of Clinical Neuropsychology, San Diego, CA.

Gavarrete Olvera, A., **Nakhla, M. Z.,** Banuelos, D., Gonzalez, K., & Razani J. (2018, June). *Working memory differences between Hispanics and Caucasians with possible associations to acculturation.* Poster session presented at the American Academy of Clinical Neuropsychology, San Diego, CA.

Kaufmann, C. N., Sutherland, A., **Nakhla, M. Z.,** Yoon, H., Soontornniyomkij, B., & Eyler, L.T. (2018, June). *Sleep and inflammatory profiles in bipolar disorder*. Poster session presented at the convention of SLEEP 2018, Baltimore, MD.

Laganá, L., **Nakhla, M. Z.,** Chavez, S., Balian, O., Grewe, D., & Pajulas, A. (2018, April). *A literature review on how to improve attitudes towards individuals with physical impairments.* Poster session presented at the Western Psychological Association, Portland, OR.

Laganá, L., **Nakhla, M. Z.,** Toscano, D., Sosa, G., Baris, J., & Ginoyan, V. (2018, April). *Videogame interventions aimed at improving cognitive functioning in older adults: A literature review*. Poster session presented at the Western Psychological Association, Portland, OR.

Laganá L., Balian, O., **Nakhla, M. Z.,** Zizumbo, J., Grewe, D., & Santana, E. (2018, April). *A literature review on interventions aimed at supporting older LGBTQ individuals.* Poster session presented at the Western Psychological Association, Portland, OR.

Nakhla, M. Z., Gavarrete Olvera, A., Arce, S., Banuelos, D., & Razani, J. (2018, April). *Time spent in the U.S. as a sensitive predictor of full scale intelligence quotient in middle easterners.* Poster session presented at CSUN's 22nd Annual Student Research & Creative Works Symposium, Northridge, CA.

Gavarrete Olvera, A., **Nakhla, M. Z.,** Banuelos, D., Gonzalez, K., & Razani, J. (2018, April). *Different factors predict phonemic fluency performance in varied ethnic groups.* Poster session presented at CSUN's 22nd Annual Student Research & Creative Works Symposium, Northridge, CA.

Arce, S., **Nakhla, M. Z.,** & Razani, J. (2018, April). *Differences in nonverbal neuropsychological test performance across various ethnic groups.* Poster session presented at CSUN's 22nd Annual Student Research & Creative Works Symposium, Northridge, CA.

Escobar, Y., Chavez, S., **Nakhla, M. Z.,** Balian, O., Martinez, M., Morain, K., & Laganá, L. (2018, April). *The multiple challenges related to living with a physical disability: A literature review*. Poster session presented at CSUN's 22nd Annual Student Research & Creative Works Symposium, Northridge, CA.

Santana, E., Toscano, D., **Nakhla, M. Z.,** Sosa, G., Balian, O., Morain, K., & Laganá, L. (2018, April). *The cognitive and psychological challenges associated with older age: A literature review*. Poster session presented at CSUN's 22nd Annual Student Research & Creative Works Symposium, Northridge, CA.

Nakhla, M. Z., Kaufmann, C., Yoon, H., Sutherland, A., & Eyler, L. T. (2018, February). *Gender differences in social cognition in bipolar disorder with possible links to inflammation.* Poster session presented at the International Neuropsychological Society, Washington, D. C.

Nakhla, M. Z., Herrera, J., Banuelos, D., Gonzalez, K., & Razani, J. (2018, February). *The differences between semantic and episodic memory predicting shopping skills in Alzheimer's*

disease and mild cognitive impairment. Poster session presented at the International Neuropsychological Society, Washington, D.C.

Nakhla, M. Z., Banuelos, D., Alostaz, J., Herrera, J., Gonzalez, K., Woo, E., Apostolova, L., & Razani, J. (2017, June). *The effect of episodic and semantic memory dysfunction on activities of daily living in Alzheimer's disease and mild cognitive impairment*. Poster session presented at the American Academy of Clinical Neuropsychology Conference, Boston, MA.

Nakhla, M. Z., Alostaz, J., & Razani, J. (2017, April). *Episodic memory predicting activities of daily living in mild cognitive impairment and Alzheimer's disease.* Poster session presented at the Western Psychological Association, Sacramento, CA.

Herrera, J., **Nakhla, M. Z.,** & Razani, J. (2017, April). *Executive functioning in Alzheimer's disease and mild cognitive impairment compared to normal control.* Poster session presented at CSUN's 21st Annual Student Research & Creative Works Symposium, Northridge, CA.

Lara-Ruiz, J., Kauzor, K., Castillo, G., Banuelos, D., **Nakhla, M. Z.,** & Razani, J. (2017, February). *The impact of PTSD symptoms and cognitive performance on student veterans' academic achievement.* Poster session presented at the annual convention of the International Neuropsychological Society, New Orleans, LA.

Banuelos, D., Gonzalez, K., Kauzor, K., **Nakhla, M. Z.,** & Razani, J. (2017, February). *The relationship between verbal and nonverbal neuropsychological tests and aspects of English fluency in ethnically diverse individuals.* Poster session presented at the International Neuropsychological Society, New Orleans, LA.

Kauzor, K., Flowers, A., Castillo, G., **Nakhla, M. Z.,** Herrera, J. Banuelos, D., & Razani, J. (2017, February). *Hispanic performance on verbal and non-verbal neuropsychological tests.* Poster session presented at the International Neuropsychological Society, New Orleans, LA.

Nakhla, M. Z., Alostaz, J., & Razani, J. (2017, January). *Episodic memory predicting activities of daily living in mild cognitive impairment and Alzheimer's disease.* Poster session presented at the Council of University Directors of Clinical Psychology: 2017 Diversifying Clinical Psychology Networking Event, San Diego, CA.

Nakhla, M. Z., Finzi, D., & Aron, A. (2016, October). *The effects of surprise on visuospatial working memory*. Poster session presented at the annual convention of the Society for Advancing Chicanos/Hispanics & Native Americans in Science Conference, Long Beach, CA.

Lara-Ruiz, J., Kauzor, K., Castillo, G., Banuelos, D., Flowers, A., Alostaz, J., **Nakhla, M. Z.,** & Razani, J. (2016, May). *Ethnic differences in neuropsychological verbal and non-verbal test performance.* Poster presented at the annual convention of the Association for Psychological Science, Chicago, IL.

Kauzor, K., Lara-Ruiz, J., Castillo, G., Banuelos, D., Flowers, A., Alostaz, J., **Nakhla, M. Z.,** & Razani, J. (2016, May). *Effects of acculturation on attention test in ethnically diverse*

populations. Poster presented at the annual convention of the Association for Psychological Science, Chicago, IL.

Nakhla, M. Z., Banuelos, D., Kauzor, K., & Razani, J. (2016, April) *Performance of Alzheimer's disease patients on MMSE and DAFS*. Poster session presented at the annual convention of the Western Psychological Association, Long Beach, CA.

ORAL PRESENTATIONS

Nakhla, M. Z. (2018, April). Executive functioning mediates the relationship between semantic memory and financial skills in cognitively impaired patients. In J. Razani (Chair), *Predicting various functional abilities with neuropsychological tasks that assess semantic and episodic memory tasks.* Symposium conducted at the Western Psychological Association, Portland, OR.

Nakhla, M. Z., Kaufmann, C. N., Sutherland, A., & Eyler, L. T. (2017, August). *Short-term temporal relationships between inflammation, sleep variability, and attentional performance in bipolar disorder and healthy individuals*. Symposium conducted at the 2017 Summer Research Conference at UCSD, San Diego, CA.

Nakhla, M. Z., Finzi, D., & Aron, A. (2016, August). *The effects of surprise on visuospatial working memory*. Symposium conducted at the UCSD Summer Research Conference, San Diego, CA.

CLINICAL EXPERIENCE

APA-Accredited Predoctoral Internship in Clinical Psychology

West Los Angeles VA Healthcare Center | 2023-Present

Neuropsychological Assessment Experience

UC San Diego Brain Health and Memory Disorders Clinic | UC San Diego Healthcare System | 2022-2023

Neuropsychological Assessment Unit | VA San Diego Healthcare System | 2021-2022

UC San Diego Shiley-Marcos Alzheimer's Disease Research Center | UC San Diego | 2019-2022

UC San Diego Wellness Initiative for Senior Enrichment Lab | UC San Diego | 2018-2019

Psychodiagnostic Assessment and Psychotherapy Intervention Experience

UC San Diego Medical Center Hillcrest Psychiatry Consultation-Liaison Service | UC San Diego Healthcare System | 2022-Present

SDSU Psychology Clinic | SDSU | 2019-2020

Inpatient Brief Cognitive Assessment and Psychotherapy Intervention Experience

Community Living Center | VA San Diego Healthcare System | 2020-2021

Other Assessment Experience

Diagnostic Assessment Program | CSU Northridge | 2016-2017

PROFESSIONAL AND ACADEMIC SERVICE

Committees

Student President | Delta Alpha Pi International Honor Society | UC San Diego | 2020-2022

Student Member | Disability Subcommittee, Diversity Committee | Department of Psychiatry | UC San Diego | 2019-2023

Student Member | SDSU/UC San Diego JDP Justice, Equity, Diversity, and Inclusion Committee | 2019-2021

Team Leader | Mental Health Awareness Team | Coptic Health | 2020-Present

Patient Advocate and Ambassador | Hanger Clinic: Prosthetics and Orthotics | 2018-Present

PROFESSIONAL MEMBERSHIPS

APA Division 40: Society for Clinical Neuropsychology | Student Member

National Academy of Neuropsychology | Student Member

American Arab, Middle Eastern, and North African Psychological Association | Student Member

ABSTRACT OF THE DISSERTATION

Relationship Between Subjective Cognitive Decline and Objective Cognitive Performance Within Three Different Older Adult Samples

by

Marina Zaher Nakhla

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2024
San Diego State University, 2024

Professor Zvinka Z. Zlatar, Chair
Professor Dawn M. Schiehser, Co-chair

Older adults, including Non-Hispanic Whites (NHWs), Hispanics/Latinos, and those with neurodegenerative diseases (e.g., Parkinson's Disease: PD), are at risk for dementia. Subjective cognitive decline (SCD; perceived cognitive difficulties) may be an early risk marker of

dementia. However, its neural correlates and utility to predict concurrent objective cognition across these different risk groups remain understudied. This 3-paper dissertation investigated associations of SCD with concurrent objective cognition across older adults at risk for dementia: 1) mostly NHWs (87% Caucasian) (age= 72.90), 2) Hispanics/Latinos (age= 73.97) versus NHWs (age= 71.81), and 3) PD (age= 67.56). Study 2 augmented Study 1 by examining ethnic differences in SCD reporting between NHWs and Hispanics/Latinos, while Study 3 expanded findings to neurodegenerative disease. Archival data was used from the UCSD WISE Lab, Shiley Marcos Alzheimer's Disease Research Center, and VA San Diego Healthcare System.

Study 1 (Nakhla et al., 2024) investigated the relationship of self-reported SCD with objective cognition and cerebral blood flow (CBF) in a cognitively normal sample (N=52) with varying stroke risk status. Greater SCD severity was significantly associated with lower memory and entorhinal CBF in the total sample and in those with higher stroke risk (n=31). **Study 2** (Nakhla et al., 2021) investigated if the relationship between self-reported SCD and objective cognition varies as a function of ethnicity [Hispanics/Latinos (N= 35) vs NHWs (N= 48)]. Higher self-reported SCD was associated with lower global cognition in Hispanics/Latinos, but not in NHWs. **Study 3** (Nakhla et al., 2021) investigated the relationship between informant-reported SCD and objective cognition in a confirmed neurodegenerative disease sample, i.e., PD, (N= 139). Higher informant-reported SCD was significantly associated with poorer objective cognition (attention, learning, delayed recall, executive function).

Collectively, these studies contributed to the literature by further characterizing SCD in three different and understudied older adult samples at risk for dementia: mostly NHWs, Hispanics/Latinos, and neurodegenerative disease (i.e., PD). Findings inform clinical practice by

advancing our understanding of how SCD relates to objective cognition in different samples and provide evidence that SCD is related to early risk markers of dementia.

INTEGRATED INTRODUCTION

The worldwide older adult population continues to grow steadily each year, and this growth is accompanied by increasing prevalence rates of various chronic conditions (Tkatch et al., 2016) and diseases such as Parkinson's disease (**PD**; Pringsheim, Jette, Frolkis, & Steeves, 2014) and Alzheimer's disease and related dementias (**ADRD**; Barnes & Yaffe, 2011). There are approximately 50 million individuals currently diagnosed with ADRD worldwide, and it is estimated that 152 million will be diagnosed by 2050 due to longer life expectancy and demographic changes (World Health Organization, 2019). Mild cognitive impairment (**MCI**) is a stage of subtle cognitive decline that occurs between typical aging and ADRD, which increases a person's chances to progress to ADRD. Those with MCI convert to ADRD (most often Alzheimer's disease dementia) at a rate of 10-15% each year (Farias et al., 2009; Petersen, 2011). Similarly, PD is the second most common neurodegenerative disorder after Alzheimer's disease (Aarsland & Kurz, 2010), with a PD-MCI to PD dementia conversion rate of 19-62% per 2 to 5 years following diagnosis (Wood et al., 2016).

Although it is widely known that advanced age is the greatest risk factor for ADRD (Guerreiro & Bras, 2015), individuals of underrepresented ethnic groups (i.e., Hispanics/Latinos) (Manly et al., 2008; Mayeda et al., 2016) and with confirmed neurodegenerative diseases (i.e., Parkinson's disease) (Hindle et al., 2013; Litvan et al., 2012), are also at higher risk for dementia. As there is currently no cure for dementia (Patnaik, 2015), the comprehensive understanding of early risk markers in cognitively normal and MCI groups is a critical goal for healthcare professionals to accurately detect cognitive impairment and implement early interventions prior to ADRD symptom manifestation.

A plethora of research has found that subjective cognitive decline (**SCD**), defined as the experienced self- or informant-based perception of cognitive decline compared to a previous state, may be an early risk marker of MCI or dementia (Jessen, 2014; Molinuevo et al., 2017). In fact, SCD – specifically self-reported concerns and even informant confirmation of these worries – may be considered as the first clinical indication of MCI (Studart Neto & Nitrini, 2016) and dementia (Kielb et al., 2017; Lee et al., 2020). However, there are several factors that must be accounted for in the association between SCD and objective cognitive performance, such as the type of respondent (e.g., self vs informant) (Molinuevo et al., 2017), disease stage (i.e., cognitively normal, MCI) (Rabin et al., 2017), mood (e.g., depression, anxiety), cultural factors (i.e., Hispanic/Latino culture) (Sayegh & Knight, 2013), as well as the presence of neurodegenerative diseases (Molinuevo et al., 2017). Cognitively normal older individuals (i.e., healthy older adults) who self-endorse SCD are at an increased risk of higher and more rapid rates of objective cognitive impairment compared to older individuals who do not endorse SCD (Reisberg et al., 2010). Informant reports of SCD in cognitively normal and MCI older adults are associated with lower global cognition (Gifford et al., 2015), and have also seemed useful in predicting diagnostic progression to dementia (Gifford et al., 2015; Jessen et al., 2014). With the aforementioned points in mind, both self- and informant- reported SCD may be useful early risk markers of cognitive decline. In addition to older age (Guerreiro & Bras, 2015), other groups are at higher risk for experiencing SCD and objective cognitive deficits than the normative population including those from certain ethnic backgrounds (i.e., Hispanics/Latinos) and with neurodegenerative conditions (i.e., Parkinson's disease). Given that the cost of neuropsychological evaluation may restrict easy accessibility to these services (Rivera Mindt et al., 2010), research must explore the utility of self and informant SCD measures as *screening*

tools to identify individuals at risk and in need of definitive, objective comprehensive cognitive testing.

SCD in a mostly Non-Hispanic White older adult sample (Study 1)

Given that older age is the most significant risk factor for dementia (Guerreiro & Bras, 2015) and that SCD reporting may detect those at risk early in the disease process, it is important to understand the relationship between self-reported SCD with objective cognitive performance and determine if SCD is associated with the neural signature of AD in older adults. A growing body of literature suggests that SCD is linked to brain abnormalities consistent with Alzheimer's disease pathology (Jessen et al., 2014). In cognitively normal older adults, SCD has been associated with cortical thinning in the entorhinal, fusiform, posterior cingulate, and inferior parietal cortices, increased amyloid-beta levels in the brain, and higher levels of white matter hyperintensities (Amariglio et al., 2012; Schultz et al., 2015). Moreover, SCD has been linked to reduced left hippocampal and bilateral entorhinal cortex volume (Rabin et al., 2017) and abnormalities in the middle temporal lobe, an important substrate for memory functions (Rabin et al., 2017). However, research studying the association of SCD with cerebral blood flow (**CBF**), an important marker of brain health and an early risk marker of AD (Wierenga et al., 2014), is lacking. One study found evidence of neurovascular dysregulation in cognitively normal older individuals who self-report SCD; whereby higher CBF (thought to be good for cognition) was associated with worse memory performance, indicating that increased CBF may no longer support cognitive performance in those with SCD (Hays et al., 2018). Given the importance of CBF to maintain brain health and its role as a potential early risk marker of cognitive decline (Hays et al., 2016; Rabin et al., 2017; Wierenga et al., 2014), research is needed to determine if SCD is associated with CBF in at-risk older adults. In addition to CBF

changes, cardiovascular risk factors – such as obesity, hypertension, and stroke risk (Hasnain & Vieweg, 2014) – increase the risk of progressing to ADRD (Chen et al., 2014). However, there is limited research investigating the relationship between SCD and memory performance accounting for markers of cardiovascular burden (Uiterwijk et al., 2014), such as stroke risk, particularly in healthy older adults. A couple of recent studies have found that higher SCD was associated with lower objective memory performance above and beyond vascular risk factors in healthy older adults (Tyndall et al., 2020; Zlatar et al., 2022). However, depression may be a risk factor for vascular risk (Aizenstein et al., 2016), which may influence SCD reporting in individuals with high vascular burden (Humphreys et al., 2007). Therefore, more research is needed to elucidate the relationship between SCD and objective cognition while adjusting for mood *and* measures of cardiovascular burden (i.e., stroke risk).

SCD in a Hispanic/Latino older adult sample (Study 2)

Another group at high risk for dementia and with high SCD reporting rates are older Hispanics/Latinos. Research suggests that Hispanics/Latinos are at greater risk of developing MCI and dementia (i.e., ADRD) compared to Non-Hispanic Whites (**NHWs**; Black et al., 1999; Manly et al., 2008; Mayeda, Glymour, Quesenberry, & Whitmer, 2016), with one study revealing that older Mexican American adults have higher rates of neurocognitive impairment and decline compared to NHWs (Nguyen et al., 2002). In addition, Hispanics/Latinos living in the U.S. are, on average, four years younger when diagnosed with dementia (Fitten et al., 2014) and tend to seek care later in the course of the disease (Chin et al., 2011) compared to NHWs.

Despite the fact that Hispanics/Latinos are expected to comprise over 28% of the U.S. population by the year 2060 (Colby & Ortman, 2015), and that they have higher rates of neurocognitive impairment compared to NHWs (Mehta & Yeo, 2017; Nguyen et al., 2002),

there is sparse literature examining the relationship between SCD and objective cognition in this group. The few studies investigating SCD in this group suggest that older Hispanics/Latinos in the U.S. are more likely to report SCD compared to older NHWs (Alzheimer's Association, 2018; Burnam et al., 1987; Harwood, Barker, Ownby, & Duara, 1998; Taylor, Bouldin, & McGuire, 2018). This may be explained by different factors, such as the influence of family responsibilities and perceived societal roles (Cuevas & Zuñiga, 2020), lower levels of education, and less engagement in cognitively stimulating activities (e.g., access to a newspaper/magazine subscription, encyclopedia, or dictionary) compared to NHWs (Marquine et al., 2012).

A majority of SCD studies with older Hispanic/Latino adults have been conducted in Spain and Brazil, finding conflicting evidence regarding the utility of self- and informant-reported SCD (refer to Alegret et al., 2015; Fernandez-Blazquez, Ávila-Villanueva, Maestú, & Medina, 2016; Minett, Da Silva, Ortiz, & Bertolucci, 2008; Sánchez-Benavides et al., 2018; Valech et al., 2015, 2018). These studies cannot be generalized to Hispanics/Latinos in the U.S. due to various cultural factors that can impact SCD reporting, such as the perception of what is normal versus pathological aging, potential distrust of the healthcare system, religious beliefs, and even access to healthcare services (Chin et al., 2011).

SCD in a sample of older adults with Parkinson's Disease (Study 3)

Other vulnerable groups, such as those with a neurodegenerative disorder, are at higher risk for dementia and elevated levels of SCD. PD, the second-most prevalent neurodegenerative disease in the U.S. (Kowal et al., 2013), is characterized by motor and cognitive deficits in learning, attention, executive function, and visuospatial function (Kehagia et al., 2013; Kowal et al., 2013; Svenningsson et al., 2012) and has the most prevalent age of onset at or above 65 years of age (Caslake et al., 2013; Pringsheim et al., 2014). Cognitive deficits often present early on in

the disease, and can manifest as MCI (Litvan et al., 2011) or dementia (Hindle et al., 2013), yet are largely under-recognized in clinical practice (Barone et al., 2011). Thus, the criteria for PD-MCI have recently been developed to better identify those with cognitive impairment and understand the course of disease progression, as well as to assist with the development of specific treatments (Litvan et al., 2012). The criteria for PD-MCI require subjective cognitive complaints (i.e., SCD), which can come from the patient, informant, or clinician. Importantly, the presence of SCD has been found to be a risk factor for later development of PD-dementia (Galtier et al., 2019).

Self-reports of SCD may be unreliable due to PD patients' lack of awareness, minimization of symptoms, and/or even motivation to conceal desirable information (Papay et al., 2011), particularly with worsening objective cognitive deficits (Lehrner et al., 2015). Furthermore, the unreliability of self-reports has been referenced as a rationale for the exclusion of SCD from prior PD-MCI criteria (Copeland et al., 2016). As such, informant reports have been recommended to provide clinically relevant information about a PD patient's cognitive decline status, as these reports are potentially sensitive to subtle changes in cognition (Naismith et al., 2011; Tsang et al., 2012). However, there is limited research examining the relationship between the accuracy of informant-reported SCD and objective cognition in nondemented PD (Copeland et al., 2016). PD caregivers assist with administrating complicated medication regimens, making medication decisions, and carrying out activities of daily living, and they also provide emotional and social support (Goldman et al., 2018). This suggests that informants may supply healthcare providers with useful information about changes in the patient's cognitive status that may otherwise be unavailable. On the other hand, informant reports may be biased due to informants' own symptoms of depression and anxiety (Kudlicka et al., 2011; Morrell et

al., 2019). Thus, the accuracy of informant-reported SCD in PD remains unclear. Examining the relationship between informant-reported SCD and objective cognitive performance would not only improve our understanding of the utility of informant-reported SCD in PD patients without dementia, but would also inform our characterization of SCD as a useful (or not) criteria for PD-MCI diagnosis.

Summary

Our studies will follow recommendations from the SCD Initiative (SCD-I) Working Group (Molinuevo et al., 2017) by studying SCD within the context of different clinical groups (Study 3), including more diverse racial and ethnic backgrounds in SCD research (Study 2), identifying the potential biomarkers of SCD (Study 1), accurately describing the recruitment strategy and setting (e.g., memory clinic/medical help-seeking samples, volunteer sample, or community-based cohort) (Studies 1-3), selecting the most appropriate measures for the target population (Studies 1-3), and including both informant (Studies 2 and 3) and self (Studies 1 and 2) reports of SCD to improve measurement accuracy (Jessen et al., 2014; Molinuevo et al., 2017). In conclusion, evaluating the relationship of subjective and objective cognition in older adults at risk of dementia with different clinical diagnoses (i.e., cognitively normal, MCI, PD, and PD-MCI), and from different cultural/ethnic groups (i.e., Hispanics/Latinos and NHWs), is essential to establish the utility and validity of SCD as an early risk marker of ADRD. The goal of this 3-paper dissertation is to address several of the aforementioned gaps in the literature and advance the research on SCD as a potential early risk marker of ADRD.

General Aims

This 3-paper dissertation aims to:

- Study 1: Investigate the relationship between self-reported SCD and objective memory performance across older adult groups at risk for ADRD by virtue of cardiovascular burden (i.e., stroke risk status) and determine if SCD is related to cerebral blood flow in the medial temporal lobe in the entire sample and within stroke risk groups.
- Study 2: Investigate if the association of self-reported SCD with objective cognition in older adults is moderated by ethnic background (Hispanic/Latino compared to NHWs) and determine if self- and/or informant-reported SCD are correlated with objective global cognition in community-dwelling Hispanics/Latinos.
- Study 3: Investigate the relationship between informant-reported SCD and objective cognitive performance across different domains of cognitive functioning (i.e., global cognition, learning, delayed recall, attention, executive function, language) in older PD patients with normal cognition and MCI.

Summary of 3-paper Dissertation Project.

STUDY 1	STUDY 2	STUDY 3
Utility of self-reported SCD with objective cognition and cerebral blood flow in the MTL in mostly older adult NHWs	Utility of self and informant reported SCD with objective cognition in Hispanics/Latinos within the U.S.	Utility of informant reported SCD with objective cognition in Parkinson's disease
Cognitively normal older adults only	Cognitively normal and MCI older adults	PD with normal cognition and MCI (older adults)
SCD measurement: Everyday Cognition Scale	SCD measurement: Subjective Cognitive Decline Questionnaire	SCD measurement: Informant Questionnaire on Cognitive Decline in the Elderly
Cognition: -Memory	Cognition: -Global Cognition	Cognition: -Global Cognition -Executive Function -Language -Learning -Delayed Recall -Attention -Visuospatial Function

Chapter 1 : STUDY 1

The content within this section, titled “Chapter 1: Study 1,” reflects material from a paper that has been published in the *Journal of the International Neuropsychological Society*. The proper citation is as follows:

Nakhla, M. Z., Bangen, K. J., Schiehser, D. M., Roesch, S., & Zlatar, Z. Z. (2024). Greater subjective cognitive decline severity is associated with worse memory performance and lower entorhinal cerebral blood flow in healthy older adults. *Journal of the International Neuropsychological Society, 30,* 1-10. doi:10.1017/S1355617723000115

Abstract

Subjective cognitive decline (SCD) is a potential early risk marker for Alzheimer's disease (AD), but its utility may vary across individuals. We investigated the relationship of SCD severity with memory function and cerebral blood flow (CBF) in areas of the middle temporal lobe (MTL) in a cognitively normal and overall healthy sample of older adults. Exploratory analyses examined if the association of SCD severity with memory and MTL CBF was different in those with lower and higher cardiovascular disease (CVD) risk status. Fifty-two community-dwelling older adults underwent magnetic resonance imaging, neuropsychological testing, and were administered the Everyday Cognition Scale (ECog) to measure SCD. Regression models investigated whether ECog scores were associated with memory performance and MTL CBF, followed by similar exploratory regressions stratified by CVD risk status (i.e., lower vs higher stroke risk). Higher ECog scores were associated with lower objective memory performance and lower entorhinal cortex CBF after adjusting for demographics and mood. In exploratory stratified analyses, these associations remained significant in the higher stroke risk group only. Our preliminary findings suggest that SCD severity is associated with cognition and brain markers of preclinical AD in otherwise healthy older adults with overall low CVD burden and that this relationship may be stronger for individuals with higher stroke risk, although larger studies with more diverse samples are needed to confirm these findings. Our results shed light on individual characteristics that may increase the utility of SCD as an early risk marker of cognitive decline.

Introduction

The worldwide older adult population continues to grow steadily each year, and this growth is accompanied by increasing prevalence rates of various chronic conditions (Tkatch et al., 2016) and Alzheimer's disease (AD) and related dementias (ADRD) (Barnes & Yaffe, 2011). There are approximately 50 million individuals currently diagnosed with dementia of various etiologies worldwide, and it is estimated that 139 million will be diagnosed by 2050 due to longer life expectancy and demographic changes (World Health Organization, 2022).

A comprehensive understanding of early risk markers in cognitively normal individuals is critical to accurately detect those at risk for ADRD and implement early interventions prior to symptom manifestation. A plethora of research has found that subjective cognitive decline (SCD), defined as the self-experienced perception of decline in one or more cognitive domains compared to a previous state, may be an early risk marker of AD (Jessen, 2014; Molinuevo et al., 2017), and is related to brain abnormalities consistent with AD pathology (Amariglio et al., 2012; Jessen et al., 2014; Jia et al., 2021; Rabin et al., 2017; Schwarz et al., 2021; Zhao et al., 2019). Since many individuals may report SCD for reasons other than preclinical AD (e.g., depression and other mood disturbances, poor physical health) (Molinuevo et al., 2017; Rabin et al., 2017), a deeper understanding of the individual characteristics that strengthen the ability of SCD severity to predict cognition and AD biomarkers is needed.

Several studies have demonstrated that higher SCD reporting is associated with lower objective cognition in various community-based older adult samples (Blom et al., 2019; Burmester et al., 2016; Corlier et al., 2020; Jessen, 2014; Kielb et al., 2017; Nakhla et al., 2021;

Rabin et al., 2020; Studart Neto & Nitrini, 2016; Zlatar et al., 2022) and increases the risk of progressing to dementia (Mazzeo et al., 2020; Mendonça et al., 2016; Mitchell et al., 2014). However, other studies have shown that SCD may be related more closely to depression than objective cognition (Molinuevo et al., 2017; Slavin et al., 2010; Zlatar et al., 2014). Given conflicting findings, it is important to study if the severity of SCD reporting is sensitive to cognitive abilities and markers of brain health in non-clinic-based community samples, while accounting for depressive symptoms (Jessen et al., 2014, 2020; Rabin et al., 2020).

AD pathology is linked to preclinical changes in cerebrovascular function and cardiovascular disease (CVD) risk factors such as hypertension, hyperlipidemia, diabetes, and metabolic syndrome, which increase the risk of developing dementia (Knopman & Roberts, 2010). The two-hit vascular hypothesis of AD (Zlokovic, 2011) posits that damage to the brain's microcirculation (hit one) initiates a cascade of vascular-related neuronal dysfunction, mediated by changes in blood-brain barrier function and reductions in cerebral blood flow (CBF). These vascular changes lead to a second hit, which arises from increased amyloid-β accumulation and impaired amyloid-β clearance mechanisms, which exert neurotoxic effects on the brain leading to degeneration and dementia. Given the involvement of cerebrovascular dysfunction in preclinical AD, and more specifically decreased CBF, it is important to study if SCD severity relates to CBF in cognitively normal individuals.

However, research studying the association of SCD with CBF is sparse. One study found that greater CBF did not support memory performance in those with SCD, whereas greater CBF was associated with better memory performance in those without SCD, suggesting neurovascular dysregulation in those with SCD (Hays et al., 2018). Another community-based study also found higher CBF in the left parahippocampal gyrus of individuals with SCD compared to those

without SCD (Wenyi Li et al., 2022), suggestive of neurovascular dysregulation (Hays et al., 2016; Østergaard et al., 2013; Wierenga et al., 2014). Moreover, a longitudinal study showed that baseline SCD (measured as a continuous variable in a community-based sample) was associated with reduced global CBF in older adults over a 3.8 year follow-up period (Kresge et al., 2020). Given the importance of CBF to maintaining brain health and supporting cognitive function, and its role as a potential early marker of cognitive decline (Hays et al., 2016; Rabin et al., 2017; Wierenga et al., 2014), research is needed to better understand if SCD is associated with CBF in older adults.

We examined if SCD severity (with SCD as a continuous variable rather than a diagnostic criterion) is associated with memory performance and with CBF in areas of the middle temporal lobe (MTL) that are implicated in preclinical AD. We hypothesized that greater SCD severity would be associated with worse memory performance and lower CBF in the MTL, adjusting for demographics and mood. To identify individual characteristics that may increase the likelihood that SCD reporting may be due to preclinical AD rather than other mood or health characteristics, we explored if those with greater CVD risk showed a stronger association of SCD severity with memory performance and CBF in the MTL.

Methods

Participants

Participants were 52 community-dwelling research volunteers from the community with normal cognition and who were overall healthy, with mostly low CVD risk. They were recruited from ongoing aging studies at the UC San Diego's (UCSD) Wellness Initiative for Senior

Enrichment (WISE) Lab and Veteran Affairs San Diego Healthcare System (VASDHS). Participants were recruited from Research Match, registries, word of mouth, and community outreach. Study protocols were approved by UCSD or VASDHS Institutional Review Boards, and all participants provided written informed consent. Research was completed in accordance with the Helsinki Declaration.

Inclusion criteria for this sample consisted of individuals between the ages of 65 to 85 years, who are English-speaking as needed to complete cognitive testing, have no contraindications for magnetic resonance imaging, and ambulate independently. Exclusionary criteria included a pre-existing diagnosis of MCI or dementia, history of vascular events (e.g., myocardial infarction, transient ischemic attacks, stroke), diabetes, chronic psychiatric conditions, major neurologic disorders, history of falls resulting in hospitalization in the past two years, and poorly controlled chronic conditions. Cognitive impairment for exclusion was based on comprehensive neuropsychological testing and followed the recommendation outlined by Jak and colleagues, which was defined by performance greater than one standard deviation below the norm on at least two measures within the same cognitive domain (Jak et al., 2009).

Subjective Cognitive Decline Measurement

SCD severity was measured as a continuous variable with the Everyday Cognition Scale (ECog) (Farias et al., 2008), a questionnaire of perceived cognitive decline compared to ten years inquiring about the loss in cognitively mediated functional abilities (e.g., remembering recent events, communicating thoughts, planning a shopping trip, multitasking). The ECog has been validated in older adults with normal cognition, MCI, and dementia and has the following subscales: Global Function, Memory, Language/Semantic, Visuospatial, and Executive: Planning, Organization, Divided Attention (Farias et al., 2008). The questionnaire consists of 39

items each scored on a scale of 1-4 (1= better or no change, 2= questionable/occasionally worse; 3= consistently a little worse; 4= consistently much worse) (Farias et al., 2008). Total raw scores range from 39 to 156 points, with higher scores reflecting perception of more severe cognitive decline.

Memory Assessment

All participants completed a comprehensive neuropsychological battery. A Memory Composite Score was calculated based on *a priori* tests of immediate and delayed verbal recall by averaging across z-scores derived from each tests' raw score. The memory tests included in the composite were: Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM)-I immediate recall (Wechsler, 1987); WMS-R LM-II delayed recall (Wechsler, 1987); RAVLT – Trials 1-5 Total (Schmidt, 1996) [OR] CVLT – Trials 1-5 Total (Delis et al., 2000); RAVLT – Short Delay Free Recall (Schmidt, 1996) [OR] CVLT – Short Delay Free Recall (Delis et al., 2000); RAVLT – Long Delay Free Recall (Schmidt, 1996) [OR] CVLT – Long Delay Free Recall (Delis et al., 2000). Participants from the WISE Lab (n = 39) were administered the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996), and participants from the VASDHS Lab (n = 13) were administered the California Verbal Learning Test (CVLT-II) 2nd Edition (Delis et al., 2000). Given that the CVLT and RAVLT differ in word list length, we standardized the raw scores based on the means and standard deviations of each test prior to creating the memory composite. Previous research has supported the comparability between the CVLT and RAVLT (Beier et al., 2019; Grimes et al., 2017; Samudra et al., 2020; Stallings et al., 1995), particularly for raw scores (Stallings et al., 1995; Wiens et al., 1994).

Assessment of Depression

Depressive symptomatology was assessed with the Geriatric Depression Scale (**GDS**) – a 30-item, self-report questionnaire, with higher scores reflecting worse depressive symptoms (Yesavage et al., 1982). Total scores of 0-4 suggest no depression, 5-8 suggest mild depression, 9-11 suggest moderate depression, and 12-15 suggest severe depression (Greenberg, 2012). Since the GDS contains cognitive items (Montorio & Izal, 1996) that may increase the shared variance with the ECog, we created a modified GDS score by removing the following items from our total score: *item 14* "Do you feel like you have more problems with memory than most?; *item 26:* "Do you have trouble concentrating?"; *item 29:* "Is it easy for you to make decisions?". The modified GDS score (m-GDS) was used as a covariate in all analyses.

CVD Risk Assessment

The Framingham Stroke Risk Profile (FSRP) (D'Agostino et al., 1994) is a scale that evaluates the probability [percentage] of stroke occurrence over a 10-year period in adults ages 55 and older. FSRP scores of less than 10% suggest low stroke risk, 10-19% suggest moderate stroke risk, and 20% or more suggest high stroke risk (Bosomworth, 2011; D'Agostino et al., 1994). The FSRP is corrected for sex and accounts for several risk factors: age (in years), systolic blood pressure (mm Hg), history of cardiovascular disease (e.g., myocardial infarction, coronary insufficiency, congestive heart failure), left ventricular hypertrophy, and/or atrial fibrillation, diabetes mellitus, cigarette smoking, and use of antihypertensive medications.

Brain Imaging Acquisition

Magnetic resonance imaging (MRI) data were acquired on a GE Discovery MR 750 3T whole-body system with a body transmit coil and an 8-channel receive-only head coil at the UCSD's Center for functional MRI. The structural brain sequence was a high-resolution T1-weighted Fast Spoiled Gradient Recall (3DFSPGR) scan: 172 1mm contiguous sagittal slices,

field of view (FOV)=25 cm, repetition time (TR)=8 ms, echo time (TE)=3.1 ms, flip angle=12, inversion time (TI)=600 ms, 256×192 matrix, Bandwidth=31.25 kHz, frequency direction=S-I, NEX=1, scan time=8 min and 13 s. T1-weighted images were processed using FreeSurfer 6.0 software. The images underwent skull stripping, B1 bias field correction, gray matter-white matter segmentation, reconstruction of cortical surface models, and parcellation and labeling of cortical surface regions and subcortical structures (Dale et al., 1999; Fischl et al., 2002).

CBF was assessed with a 2D Pseudo Continuous Arterial Spin Labeling (ASL) MRI (2DPCASL) sequence; TR=4500 ms, TE=3.2 ms, FOV=24 cm, labeling duration=1800 ms, post-labeling delay=2000 ms, with a single shot spiral acquisition and a total scan time of 4:30 min plus a 40.5 s calibration scan. The calibration scan was acquired immediately after the ASL scan using a spiral readout with TR=4.5 s and TE=3.2 ms with 8 dummy radiofrequency (RF) pulses (amplitude set to zero) to generate a 36 s delay followed by a 90-degree RF pulse in the last repetition interval to generate proton density-weighted contrast. Two field map scans were collected for off-line field map correction for signal bunching and dropouts in the frontal/medial temporal lobes.

CBF quantification was conducted using the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) database and analysis pipeline (Shin et al., 2013). CBFBIRN quantifies CBF and adjusts for partial volume effects (Shin et al., 2013) by using a combination of custom MATLAB (MathWorks, 1996) routines and various Analysis of Functional Neuroimages (AFNI) (Cox, 1996) and FMRIB Software Library (FSL) (Smith et al., 2004) functions (Zlatar et al., 2019). We used MATLAB to form a mean ASL image from the average difference of the control and tag images. For CBF calibration, we used a proton density image for conversion of the ASL difference signal into physiological units (ml/100g/min). Slice

timing delays were accounted for, making the post-labeling delay slice specific. Skull stripping of the high-resolution T1-weighted image was performed using AFNI's 3dSkullStrip. We used FSL's Automated Segmentation Tool (FAST) algorithm to define cerebrospinal fluid, gray matter, and white matter regions. To correct CBF for partial volume effects and ensure that CBF values were not influenced by known decreased perfusion in the white matter or increased volume of cerebrospinal fluid, we used a linear regression method (Asllani et al., 2008) with a 5x5 regression kernel to obtain corrected gray matter CBF measurements. For each participant's partial volume corrected quantified CBF map (in units of ml/100 g tissue/min), voxels with negative intensities were replaced with zero.

We used FreeSurfer 6.0 software to create anatomical ROIs for the CBF data. For each participant, using AFNI's @SUMA_AlignToExperiment program, the FreeSurfer formatted T1-weighted brain volume was registered to the ASL CBF-aligned T1-weighted anatomical image which was derived from CBFBIRN. The resulting co-registration matrix was used to align the FreeSurfer aparc+aseg segmentation volume to the ASL CBF-aligned T1-weighted image using AFNI's 3dAllineate program. The CBF-aligned FreeSurfer volumes were visually inspected to ensure proper alignment and were then downsampled to the resolution of the CBF ASL image using AFNI's 3dfractionize program. Mean CBF was extracted for each FreeSurfer ROI, for each participant, which were entered as outcome variables in our models. We focused on investigating average CBF in AD-related regions of the MTL (hippocampal, parahippocampal, and entorhinal cortex) to determine their association with ECog total scores.

ASL MRI studies of older adults show similar patterns of regional CBF compared to studies using fluorodeoxyglucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) (Chen et al., 2011; Takahashi et al., 2014). ASL has

advantages over PET and SPECT given its use of a non-invasive, endogenous tracer rather than an intravenously administered contrast agent and also allows quantification of cerebral perfusion (in milliliters per 100 g of tissue per minute). Notably, the use of ASL in older adult populations may give rise to unique challenges given that the signal to noise ratio (SNR) may be lower due to reduced CBF and potential vascular changes with aging. Age-related partial volume effects due to tissue atrophy and prolonged transport time from the labeling position to the tissue (i.e., arterial transient time) due to factors such as internal carotid stenosis or vessel tortuosity may affect the ASL signal and lead to underestimation or overestimation of CBF (Kilroy et al., 2014). To minimize the effects of these potential issues, we followed the white paper recommendations for the implementation of ASL published by the International Society for Magnetic Resonance in Medicine (ISMRM) and the European Consortium for ASL in Dementia including a PCASL labeling approach and a relatively long post labeling delay (i.e., 2,000 ms in older adults rather than the standard 1,800 ms) (Alsop et al., 2015). Future studies using angiograms to improve tagging efficiency and quantifying arterial transit time delays may improve quantification of CBF among older adults (Alsop et al., 2015).

Statistical Analyses

Analyses were conducted using IBM SPSS Version 28.0 (IBM, 2021). Data were screened for normality by inspecting skewness and kurtosis limits (Field, 2009), and no significant outliers were detected for the memory outcome variable. There was one outlier for the ECog total scores (>4 standard deviations above the mean), which was removed.

We removed one participant that had CBF values (i.e., entorhinal) outside of the expected physiological range (<10 or >150 ml/100g/min) (Bangen et al., 2014). There were also three statistical outliers in the dataset with mean regional CBF values within the range that our group

has considered physiologically plausible (i.e., >10 and <150; Bangen et al., 2014, 2018), but were excluded given statistical considerations (>3 standard deviations above the mean). This is not uncommon since several studies have shown that older adults at risk for cognitive decline demonstrate elevated CBF, which may represent a compensatory mechanism and/or neurovascular dysregulation (Bangen et al., 2012; Thomas et al., 2022). Altogether, a total of 5 outliers (1 Ecog + 4 CBF) were removed, which resulted in a final sample of 52 participants for all analyses.

Pearson correlations between the predictor variables were within acceptable limits (all *rs* < .6). For all regression models, tolerance levels were >.1 and variance inflation factors <.2, indicating no evidence of multicollinearity (Field, 2009). Covariates of interest were theoretically selected based on the SCD literature and following best practices (Jessen et al., 2014; Molinuevo et al., 2017). As such, we included age, sex, years of education, and m-GDS scores in all regression models.

Relationship between ECog, Objective Memory, and CBF in the total sample (n=52): Linear regression models were conducted to determine the association of continuous ECog scores with 1) memory composite scores, 2) CBF in the hippocampus, 3) CBF in the parahippocampal gyrus, 4) and CBF in the entorhinal cortex. All models were adjusted for age, sex, years of education, and m-GDS scores.

Exploratory Analysis: ECog, Objective Memory, and CBF Stratified by CVD Risk: Linear regression models stratified by FSRP scores were conducted to determine if the association of ECog with memory and CBF was higher in those with greater FSRP scores. We dichotomized the continuous FSRP% Stroke Risk variable into “lower FSRP scores” (n=21) and “higher FSRP scores” (n=31) groups based on a median split (median value= 6%). Only 14

participants in the sample had FSRP scores ≥10, suggestive of medium to high stroke risk (Bosomworth, 2011; D'Agostino et al., 1994), which was too small to dichotomize groups based on this criteria. Since we are studying a healthy sample of older adults, and our strict inclusion criteria excluded individuals with very high CVD risk, results are interpreted in the context of those with overall low CVD risk. *T*-tests and chi-square analyses explored differences in demographics and mood, FSRP scores, blood pressure, CBF, and memory performance between lower and higher FSRP score groups. We adjusted for demographic characteristics (age, sex, education) and mood (m-GDS scores).

Results

Participants' characteristics are displayed in Table 1.1. They were, on average, 72.9 years old (range=65-83 years), mostly female (69%), relatively well-educated (mean=16.98 years, SD= 2.28 years), predominantly Caucasian/White (87%), and with overall low CVD risk status as indicated by FSRP scores (mean=8.12, SD=5.34).

Relationship Between ECog, Objective Memory, and CBF in the total sample (n=52): Fully adjusted linear regression models (Table 1.2 & Figures 1.1 and 1.2) revealed that higher ECog total scores were significantly correlated with lower memory performance after adjusting for age, sex, education, and m-GDS. Similarly, higher ECog total scores were associated with lower CBF in the entorhinal cortex after adjusting for age, sex, education, and m-GDS. Results did not change when using the total GDS scores instead of the m-GDS scores as a covariate.

Exploratory Analysis: ECog, Objective Memory, and CBF Stratified by CVD Risk: Lower and higher FSRP score groups did not significantly differ in years of education, m-GDS scores, memory performance, ECog total scores, or CBF (hippocampal, parahippocampal, entorhinal). The sex distribution and age were statistically different between the lower and higher

FSRP score groups. The higher FSRP score group had significantly greater FSRP% stroke risk scores and systolic blood pressure (Table 1.3). There was a significant association of greater ECog scores with lower memory performance and entorhinal CBF only for those in the higher FSRP score group. Memory performance and entorhinal CBF were not associated with ECog scores in the lower FSRP score group (Table 1.4 and Figure 1.3). Results did not change when using the total GDS scores instead of the m-GDS scores as a covariate.

Discussion

This study investigated the association of SCD severity with objective memory performance and CBF in areas implicated in preclinical AD in older cognitively normal research volunteers. We also explored if those with greater CVD risk severity showed a stronger correlation of ECog scores with memory performance and CBF. We found that greater SCD severity, measured with the ECog, was associated with lower memory performance in our sample of cognitively normal older adults, after controlling for demographic characteristics and mood. This is consistent with other studies (Brailean et al., 2019; Corlier et al., 2020; Farias et al., 2013; Kielb et al., 2017; Wei Li et al., 2022), and highlights that SCD severity in community-based samples may be sensitive to concurrent memory difficulties, even in individuals who are cognitively normal, non-medical help-seeking, and have overall low CVD risk profiles.

We also found an association between greater SCD severity and lower entorhinal CBF across the total sample, even after adjusting for demographics and mood. The entorhinal cortex is thought to be one of the first regions to be affected in AD and a strong predictor of disease progression from MCI to AD (Khan et al., 2014; Zhou et al., 2016). In fact, reduced CBF in the

MTL has been predictive of faster rates of cognitive decline, neurodegeneration and white matter hyperintensity progression (Bangen et al., 2021), and decline in daily functioning (i.e., instrumental activities of daily living) (Sanchez et al., 2020). Dysfunction in the entorhinal cortex is thought to precede dysfunction in the hippocampal circuit (Khan et al., 2014), a brain region that is associated with hallmark memory deficits observed in AD (Babcock et al., 2021; Chen et al., 2021; Setti et al., 2017). Reductions in CBF have been associated with increased Aβ production and are thought to be an early risk marker of AD (Hays et al., 2016; Korte et al., 2020; Park et al., 2019; Wierenga et al., 2014; Zlokovic, 2011). As such, our findings provide evidence that SCD severity is not only associated with objective memory, but also with one of the earliest brain signatures of AD in a cognitively normal, community-based sample. These findings are consistent with recent literature showing that CBF alterations in the MTL are an independent risk factor for SCD (Wenyi Li et al., 2022), and that, compared to healthy controls, those with SCD show lower CBF in areas of the MTL (Yang et al., 2021).

Consistent with our hypothesis, exploratory stratified analyses within FSRP score groups suggest that the relationship of SCD severity with memory performance and entorhinal CBF in our sample of cognitively normal older adults may be driven by those with higher risk for developing AD by virtue of their CVD burden. That is, the association of greater SCD severity with worse memory performance and lower entorhinal cortex CBF was only significant within the higher FSRP score group. As previously noted, SCD is associated with an increased risk for dementia (Jessen, 2014; Mendonça et al., 2016; Mitchell et al., 2014; Molinuevo et al., 2017) for some individuals. Similarly, those with greater CVD burden also have an increased risk of developing AD (Song et al., 2021). Our findings suggest that SCD severity in individuals with a higher CVD burden may be more closely associated with cognition and brain markers of

preclinical AD than in those with lower CVD burden. These exploratory results shed light on a potential variable that may help increase the clinical utility of SCD reporting in cognitively normal and overall healthy individuals, although larger studies with more diverse individuals (i.e., with greater CVD risk and from different ethnic and socioeconomic backgrounds) are needed to replicate these findings.

It is important to keep in mind that not everyone who reports SCD will progress to AD since SCD reporting may reflect other conditions such as depression, anxiety, or other neurologic conditions (Jessen et al., 2014; Molinuevo et al., 2017; Slavin et al., 2010; Zlatar et al., 2014). As such, finding individual characteristics that increase the clinical utility of SCD to predict preclinical AD and later progression warrants further study. Alternatively, our findings could also indicate that cognitively normal individuals with a higher CVD burden may also be more aware of subtle changes in their memory performance and/or may be at greater risk for memory difficulties.

Limitations of this study include a cognitively normal older adult community-based sample that was mostly Caucasian/White, female, and highly educated, limiting the generalizability of our findings. Individuals in our sample generally reported minimal to no depressive symptoms and reported low SCD severity. Similarly, we had strict inclusion criteria, excluding individuals with a history of vascular events (e.g., myocardial infarction, transient ischemic attacks, stroke) and diabetes, which are components of the FSRP score we used to characterize CVD risk. This resulted in an overall healthy sample with low CVD risk burden. Thus, our results cannot be generalized to individuals with high CVD burden, a diagnosis of SCD, and/or clinical samples seeking medical help for cognitive decline. Since CVD risk and other health conditions may influence SCD reporting (Gu et al., 2013; Molinuevo et al., 2017;

Rabin et al., 2017; Sajjad et al., 2015), future research with larger and more diverse samples, including individuals with high CVD risk burden is warranted. Moreover, our small sample size may have obscured potential associations of SCD with CBF in other MTL regions due to lack of power. Notably, this study was cross-sectional, and therefore, we cannot determine if SCD predicts changes in objective cognition or CBF over time. Future longitudinal studies would be beneficial in elucidating these important relationships. Lastly, inclusion of other measures of CVD risk (including relevant variables such as hyperlipidemia, hypercholesterolemia, body mass index, renal function) (Bosomworth, 2011) and other markers of brain health would be beneficial to increasing our understanding of how CVD risk may impact the relationship of SCD severity with memory and CBF.

In summary, findings provide evidence that SCD severity is associated with objectively measured cognition and CBF in regions implicated in preclinical AD, and further suggest that those with greater CVD risk may be driving this relationship. Findings are aligned with previous studies suggesting that the ECog can be used as a clinically valuable prescreening tool (Corlier et al., 2020; Farias et al., 2013; Rueda et al., 2015; Shokouhi et al., 2019). In this case, the ECog seems particularly sensitive to memory performance and neural markers of preclinical AD in individuals with greater CVD risk. Future studies should investigate if individuals who present with greater CVD burden and report greater SCD severity have a higher chance of progression to MCI and AD over time.

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Table 1.1. Descriptive and demographic information (n=52).

Abbreviations: SCD=subjective cognitive decline; ECog=Everyday Cognition Scale; m-GDS=modified Geriatric Depression Scale; CVD=cardiovascular (risk); CBF=cerebral blood flow; FSRP=Framingham Stroke Risk Profile; WMS=Wechsler Memory Scale; RAVLT=Rey Auditory Verbal Learning Test; CVLT=California Verbal Learning Test.
All values listed are means (standard deviations) unless otherwise indicated.

Demographic Characteristics	**M (SD)**
Age (years)	72.90 (4.53)
Education (years)	16.98 (2.28)
Males:Females (total)	16:36
Mood & SCD	
m-GDS Score	2.60 (2.86)
ECog Total	51.65 (10.42)
CVD Risk	
FSRP Score	8.12 (5.34)
Average CBF (ml/100g/min)	
Hippocampal	40.86 (9.72)
Parahippocampal	38.89 (9.61)
Entorhinal	39.24 (15.29)
Cognition	
Memory (z-scores)	.00 (.81)
Raw Scores	
WMS Logical Memory I [range 0-50]	28.79 (6.51)
WMS Logical Memory II [range 0-50]	26.13 (8.28)
RAVLT Trials 1-5 Total [range 0-75]	49.56 (10.09)
CVLT Trials 1-5 Total [range 0-80]	47.54 (10.50)
RAVLT Short Delay Free Recall [range 0-15]	10.92 (2.77)
CVLT Short Delay Free Recall [range 0-16]	10.77 (4.15)
RAVLT Long Delay Free Recall [range 0-15]	10.82 (2.94)
CVLT Long Delay Free Recall [range 0-16]	10.23 (4.83)

Table 1.2. Ecog Scores Predicting Memory and CBF in the Total Sample (n=52).

Note: All models were adjusted for age, sex, years of education, and modified GDS scores. B (SE) denotes unstandardized coefficient and corresponding standard error. β denotes the standardized coefficient.
Abbreviations: ECog=Everyday Cognition Scale; CBF=cerebral blood flow.
* $p < .05$, ** $p < .01$, *** $p < .001$.

					***95% Confidence Interval for* B**	
	B (SE)	**β**	***t***	***p***	**Lower Bound**	**Upper Bound**
Cognition						
Memory	-.03 (.01)	-.42	-2.51	.016*	-.06	-.01
Average CBF (ml/100g/min)						
Hippocampal	-.24 (.16)	-.26	-1.48	.146	-.57	.09
Parahippocampal	-.28 (.16)	-.31	-1.76	.085	-.61	.04
Entorhinal	-.68 (.23)	-.46	-2.95	.005**	-1.14	-.22

Table 1.3. Demographic characteristics of the lower (n=21) and higher (n=31) FSRP Score Groups.

P-values were derived from independent samples *t*-tests and χ^2 tests. All comparisons based on *df*=50. Abbreviations: CVD=cardiovascular (risk); m-GDS=modified Geriatric Depression Scale; FSRP= Framingham Stroke Risk Profile; CBF=cerebral blood flow; ECog=Everyday Cognition Scale.
All values listed are means (standard deviations) unless otherwise indicated.
* $p < .05$, ** $p < .01$, *** $p < .001$.

	Lower FSRP Score Group (n = 21) Mean (SD)	Higher FSRP Score Group (n = 31) Mean (SD)	*p*-value	Cohen's d
Demographic Characteristics				
Age (years)	70.10 (3.24)	74.81 (4.32)	<.001***	-1.20
Education (years)	17.05 (2.22)	16.94 (2.35)	.864	.05
Male:Female (total)	3:18	13:18	.034*	.62
CVD risk				
FSRP Score	4.24 (.77)	10.74 (5.52)	<.001***	-1.51
Systolic blood pressure	118.52 (16.51)	136.2 (16.33)	<.001***	-1.08
Diastolic blood pressure	72.29 (13.25)	78.47 (9.18)	.073	-.56
Mood & Cognition				
m-GDS Score	3.24 (3.39)	2.16 (2.41)	.186	.38
Memory (z-scores)	.10 (.63)	-.07 (.91)	.468	.21
ECog Total	50.90 (9.23)	52.16 (11.28)	.674	-.12
Average CBF (ml/100g/min)				
Hippocampal	41.03 (9.36)	40.75 (10.11)	.919	.03
Parahippocampal	41.52 (10.36)	37.10 (8.80)	.104	.47
Entorhinal	40.33 (12.64)	38.51 (17.01)	.678	.12

Table 1.4. Regression models of ECog predicting memory and CBF stratified by CVD risk group.

Note: Stratified regression models were fully adjusted for age, sex education, and modified GDS scores. B (SE) denotes unstandardized coefficient and corresponding standard error. β denotes the standardized coefficient. Abbreviations: FSRP=Framingham Stroke Risk Profile; CBF=cerebral blood flow.
* $p < .05$, ** $p < .01$, *** $p < .001$.

					***95% Confidence Interval for* B**	
Outcome: Memory	**B (SE)**	**β**	***t***	***p***	**Lower Bound**	**Upper Bound**
Lower FSRP Score Group (n=21)	-.01 (.02)	-.09	-.25	.804	-.06	.04
Higher FSRP Score Group (n=31)	-.04 (.02)	-.50	-2.21	.037*	-.08	-.003
Outcome: Entorhinal CBF						
Lower FSRP Score Group (n=21)	-.18 (.42)	-.13	-.44	.669	-1.08	.71
Higher FSRP Score Group (n=31)	-.95 (.30)	-.63	-3.17	.004**	-1.57	-.33

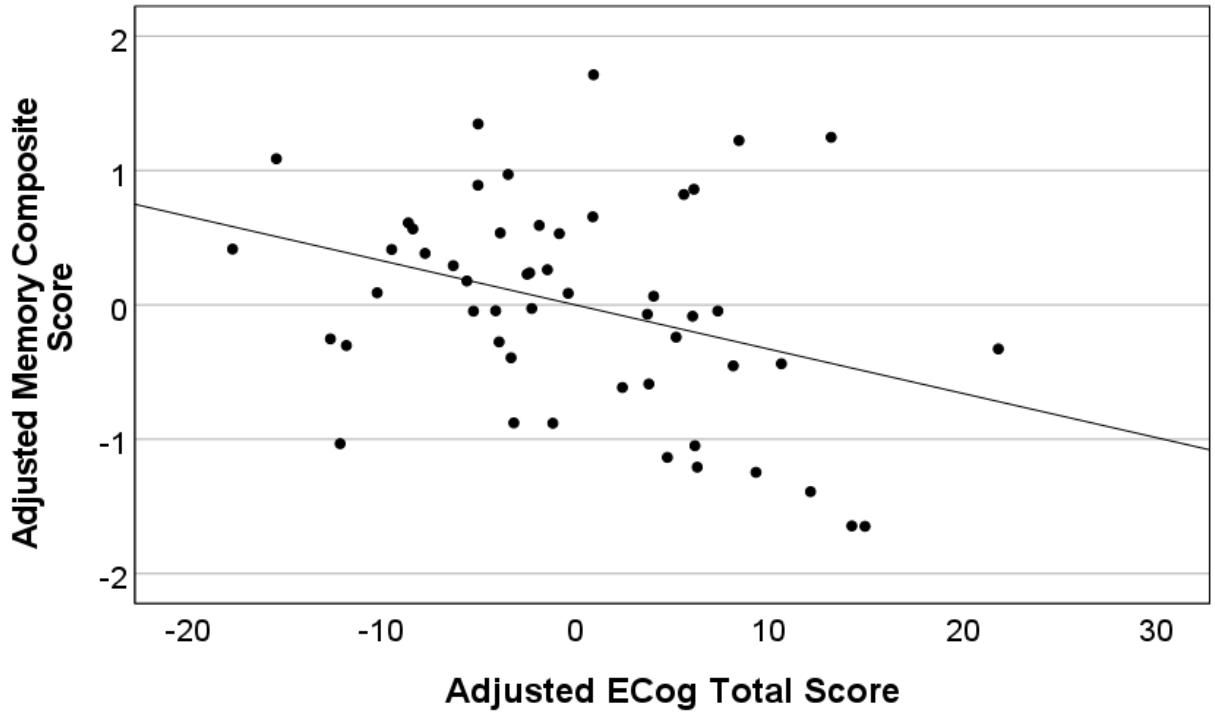

Figure 1.1. Higher ECog total scores predict lower memory performance in the total sample (n=52).

Abbreviations: ECog=Everyday Cognition Scale.
Note: Partial regression plot depicts residual values adjusted for age, years of education, sex, and modified GDS scores.

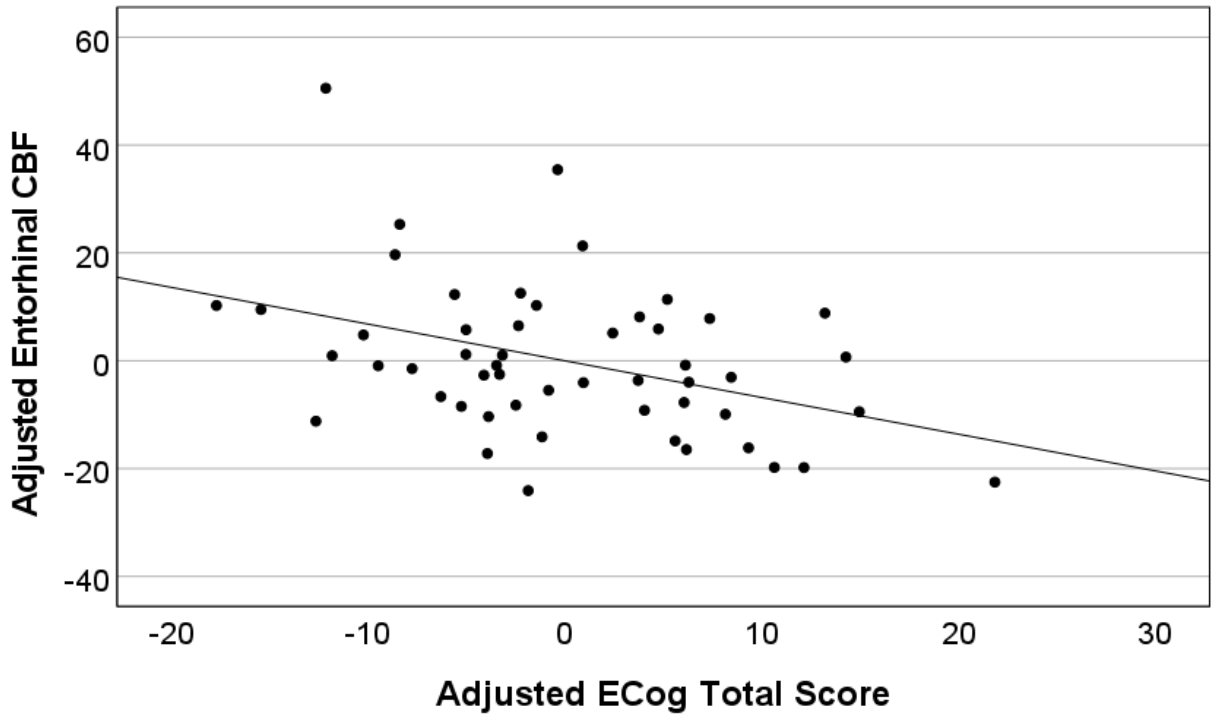

Figure 1.2. Higher ECog total scores predict lower entorhinal CBF in the total sample (n=52).

Abbreviations: ECog=Everyday Cognition Scale.
Note: Partial regression plot depicts residual values adjusted for age, years of education, sex, and modified GDS scores.

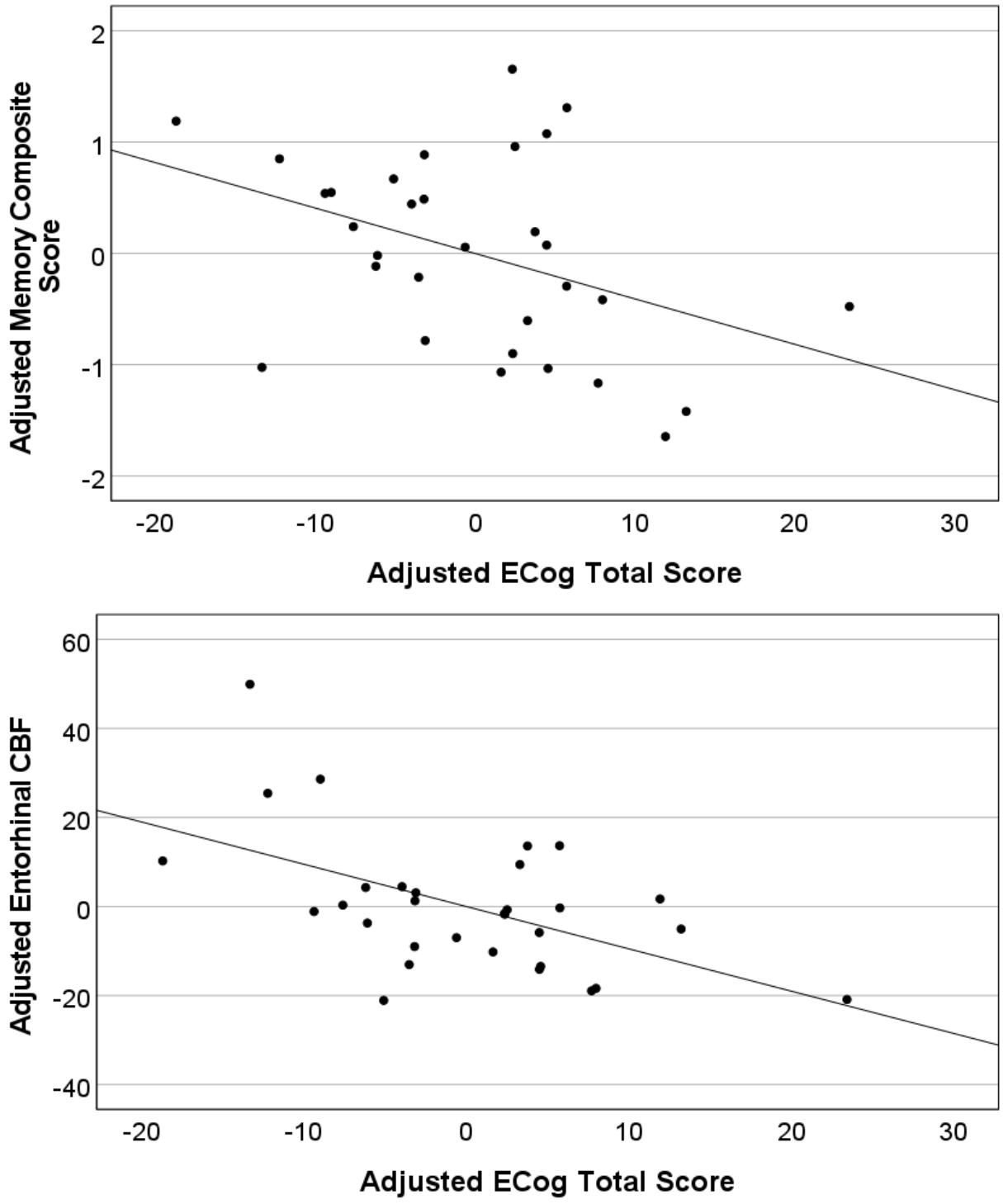

Figure 1.3. Higher ECog total scores predict lower memory and entorhinal CBF in the higher FSRP score group (n=31).

Note: Partial regression plots depict residual values adjusted for age, years of education, sex, and modified GDS scores.
Abbreviations: ECog=Everyday Cognition Scale.

Chapter 2 : STUDY 2

The content within this section, titled “Chapter 2: Study 2,” reflects material from a paper that has been published in the *Journal of Clinical and Experimental Neuropsychology*. The proper citation is as follows:

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Abstract

Although subjective cognitive decline (SCD) may be an early risk marker of Alzheimer's Disease (AD), research on SCD among Hispanics/Latinos/as/x (henceforth Latinos/as) living in the U.S. is lacking. We investigated if the cross-sectional relationship of self-reported SCD with objective cognition varies as a function of ethnic background (Latinos/as versus Non-Hispanic Whites [NHWs]). Secondary analyses conducted solely within the Latino/a group investigated if informant reported SCD is associated with objective cognition and whether self-reported SCD is related to markers of brain health in a sub-sample of Latinos/as with available MRI data. Eighty-three participants (≥60 years of age) without dementia (35 Latinos/as; 48 NHWs) completed the Mattis Dementia Rating Scale (MDRS) and the Subjective Cognitive Decline-Questionnaire (SCD-Q). Additionally, 22 Latino/a informants completed the informant-version of the SCD-Q. Hierarchical regression models investigated if ethnicity moderates the association of MDRS and SCD-Q scores after adjusting for demographics and depressive symptoms. Correlational analyses within the Latino/a group investigated self- and informant-reported associations of SCD-Q scores with objective cognition, and associations of self-reported SCD-Q scores with medial temporal lobe volume and thickness. Latinos/as had lower education and MDRS scores than NHWs. Higher SCD-Q scores were associated with lower MDRS scores only in Latinos/as. Within the Latino/a group, self, but not informant reported SCD was related to objective cognition. Medium to large effect sizes were found whereby higher self-reported SCD was associated with lower entorhinal cortex thickness and left hippocampal volume in Latinos/as. The association of SCD and concurrent objectively measured global cognition varied by ethnic background and was only significant in Latinos/as. Self-reported SCD may be an indicator of cognitive and brain health in Latinos/as without

dementia, prompting clinicians to monitor cognition. Future studies should explore if SCD predicts objective cognitive decline in diverse groups of Latinos/as living in the U.S.

Introduction

The worldwide older adult population is expected to more than double to 98 million by the year 2060 (Colby & Ortman, 2015; Mather et al., 2015), with concomitant increases in the number of people living with Alzheimer's disease (AD) (Barnes & Yaffe, 2011; Desa, 2010; Langa, 2018). Hispanics/Latinos/as/x, hereafter referred to as Latinos/as, are expected to comprise over 28% of the U.S. population (Colby & Ortman, 2015; U.S. Census Bureau, 2018a) and are projected to remain the largest immigrant group, with 3.5 million living with AD by the year 2060 (Wu et al., 2016). As such, identifying early risk markers of AD can help with assessment and intervention efforts, and identify individuals who may need further diagnostic workup or follow-up. Unfortunately, the study of early risk markers of AD in Latinos/as has lagged in the U.S. (Babulal et al., 2019), despite numerous studies suggesting that they are at higher risk of developing mild cognitive impairment (MCI) and AD compared to non-Hispanic Whites (NHWs) (Black et al., 1999; Manly et al., 2008; Mayeda et al., 2016). Therefore, there is a need to fill this gap to improve diagnostic accuracy and early intervention (Rose, 2005) in this growing segment of the U.S. population.

Subjective cognitive decline (SCD), which refers to a person's (or their informant's) perception of decline in cognitive functioning (Rabin et al., 2017), has emerged as a potential early risk marker of AD (Jessen, 2014; Molinuevo et al., 2017; Verfaillie et al., 2019). Compared to those without self-reported SCD, individuals with normal cognition who report SCD have

higher rates of cognitive impairment (Reisberg et al., 2010), more rapid rates of decline (Reisberg et al., 2010), higher risk of developing MCI (Gómez-Ramírez et al., 2020), and exhibit brain changes consistent with preclinical AD (Amariglio et al., 2012; Jessen, 2014), such as entorhinal cortex thinning (Holbrook et al., 2020; Jessen et al., 2006; Meiberth et al., 2015; Rabin et al., 2017) and reduced hippocampal volume (Holbrook et al., 2020; Perrotin et al., 2015; Rabin et al., 2017; Saykin et al., 2006; van der Flier & Scheltens, 2009). Approximately 11.2% of Latinos/as in the U.S. report SCD, a prevalence rate that is comparable to NHWs (10.8%) (Taylor et al., 2018).

There is limited and conflicting research on the relationship between SCD and cognition in Latinos/as. Our research group (Zlatar, Muniz, Espinoza, et al., 2018) previously found that symptoms of depression, rather than self-reports of SCD, were associated with objective cognition in a clinic-based sample of older Latinos/as living near the U.S.-Mexico border. Similar results were found in studies conducted in Spain (Alegret et al., 2015) and Brazil (Minett et al., 2008). However, these studies did not use validated SCD questionnaires (Zlatar, Muniz, Espinoza, et al., 2018), focused exclusively on SCD related to memory complaints (Alegret et al., 2015; Minett et al., 2008), or employed informal interviews to ascertain SCD (Minett et al., 2008). Conversely and consistent with previous findings in NHWs (Amariglio et al., 2012; Slot et al., 2019), studies conducted in Spain using a questionnaire developed specifically to measure SCD across various cognitive domains (i.e., the Subjective Cognitive Decline Questionnaire; SCD-Q) found associations between SCD and objective cognition (Sánchez-Benavides et al., 2018; Valech et al., 2015, 2018) as well as with risk markers of AD pathology (i.e., positive amyloid-beta status) (Sánchez-Benavides et al., 2020). Sánchez-Benavides and colleagues (2018) found that Spaniards who reported SCD performed significantly lower on episodic memory and

attention/processing speed compared to those who did not report SCD, even after accounting for patient demographics, genetic factors, and mood. In the U.S., older Mexican American adults with SCD performed lower on tasks of global cognition, language, and attention than those without SCD (Hall et al., 2018).

Although individuals' self-reported SCD is typically greater compared to that reported by their informants (Rabin et al., 2017; Valech et al., 2015), informant reports of cognitive decline better differentiate between cognitively normal and pre-AD groups in Spaniards (Valech et al., 2015, 2018). Moreover, informant reports are a stronger predictor of objective performance (Sánchez-Benavides et al., 2018), consistent with most research in NHWs (Rattanabannakit et al., 2016; Rueda et al., 2015; Slavin et al., 2010). This suggests that informant reports may be more useful than self-reports of SCD in providing information about early decline related to AD (Jessen et al., 2014; Valech et al., 2015). Nevertheless, findings from Spaniard populations cannot be generalized to Latinos/as living in the U.S., as cultural factors such as behavioral norms, values, language, traditions, and beliefs (Alarcón, 2009) may differ and impact SCD reporting (Rabin et al., 2017).

In summary, research is needed to better understand the relationship of culturally informed self- and informant- SCD reports with objective cognition in Latinos/as living in the U.S. This study used the Subjective Cognitive Decline Questionnaire (SCD-Q), originally developed in Spain (Rami et al., 2014), to measure SCD. We chose the SCD-Q since it was developed specifically to assess SCD in participants and their informants in Spanish, with an equivalent English version, and is in line with recommendations set forth by the SCD workgroup (Molinuevo et al., 2017). We evaluated if the relationship of self-reported SCD and global cognition varies as a function of ethnicity (Latinos/as compared to NHWs living in the U.S.) and

whether self- or informant- SCD reports are more strongly associated with objective cognition within the Latino/a group. We also explored whether those who self-reported higher SCD (indicating greater cognitive complaints) had smaller medial temporal lobe volume/thickness in a subsample of Latinos/as with available brain MRI scans. Since we employed an SCD questionnaire validated in Spanish, we hypothesized that the association of self-reported SCD and global cognition would be moderated by ethnicity, and would be attenuated after adjusting for depression and demographic characteristics known to influence SCD and cognition (Alegret et al., 2015; Minett et al., 2008; Zlatar, Muniz, Espinoza, et al., 2018). Furthermore, consistent with previous research, we expected that informant-reports would be more strongly associated with objective cognition in Latinos/as compared to self-reports (Jessen et al., 2014; Valech et al., 2015). Lastly, we expected that higher self-reported SCD would be related to lower brain volume and thickness in the medial temporal lobe in a subsample of Latinos/as with available brain MRI data (Peters, 2006; Rabin et al., 2017; Sánchez-Benavides et al., 2020).

Methods

Participants

Participants were 83 community-dwelling research volunteers with a wide range of cognitive performances who were selected from existing parent studies at the University of California, San Diego's (UCSD) Wellness Initiative for Senior Enrichment (WISE) Lab (NHWs) and the Shiley-Marcos Alzheimer's Disease Research Center (ADRC) (Latinos/as). Individuals from both studies who had available Subjective Cognitive Decline Questionnaire (SCD-Q) and Mattis Dementia Rating Scale (MDRS) data were selected. Only individuals aged 60 and older,

without major neurological (e.g., dementia, Parkinson's disease) or psychiatric disorders (e.g., schizophrenia, bipolar disorder), major vascular events (e.g., stroke), diabetes, self-reported alcohol or drug abuse, actively treated cancers, recent or remote history of severe TBI, or history of chemotherapy in the past 6 months were included in the analytic sample. Additionally, participants from the WISE Lab parent study were excluded if they had poorly controlled medical problems (e.g., renal failure), a history of head injury with loss of consciousness in the past 6 months, and a fall within the past year resulting in hospitalization. The final analytic sample for this study consisted of 48 NHWs (M_{age} = 71.81 years, SD_{age} = 4.27, $range_{years}$ = 65-80) and 35 Latinos/as (M_{age} = 73.97 years, SD_{age} = 7.06, $range_{years}$ = 61-91). To generalize our findings to a more representative sample and replicate previous studies (e.g., Alegret et al., 2015; Minett et al., 2008; Valech et al., 2015; Zlatar, Muniz, Espinoza, et al., 2018), we included participants with a wide range of cognitive performances, including mostly cognitively normal individuals and some with MCI (NHW=5 & Latino/a=8). Those with frank dementia were excluded from analyses.

Both the WISE Lab and ADRC longitudinal parent studies performed comprehensive neuropsychological testing to determine cognitive status. The WISE lab parent study screened out dementia cases based on total scores below 32 on the modified version of the Telephone Interview for Cognitive Status (Knopman et al., 2010). Upon formal testing, all individuals enrolled in the WISE Lab study had T-scores greater than 40 on the MDRS, suggesting that no participants had dementia, while MCI was defined as performance greater than one standard deviation below normative expectations on at least two measures within a cognitive domain (Jak et al., 2009). The ADRC defined the clinical diagnoses of dementia and MCI based on extensive neuropsychological testing using the National Institute of Neurological and Communicative

Disorders and Stroke (NINCDS) – Alzheimer's Disease and Related Disorders Association (ADRDA) criteria or the National Institute on Aging – Alzheimer's Association Criteria. These criteria require concern regarding cognitive change, impairment in one or more cognitive domains, preservation of independence in functional abilities and no dementia to diagnose MCI, and cognitive impairment in at least 2 cognitive domains which interfere with the ability to function for a diagnosis of dementia (Albert et al., 2011; McKhann et al., 2011). All data was reviewed by senior ADRC neurologists and the diagnosis was determined by a multidisciplinary team, which accounted for cultural considerations of clinical-neuropathological correlations (Soria et al., 2018).

Latino/a participants were mostly of Mexican descent (84.4% Mexican/Chicano, 3.1% Puerto Rican, 3.1% Central American, 9.4% Other) and were tested in their language of preference (37.1% in Spanish, 62.9% in English). Given that the Latino/a and NHW participants were recruited from different ongoing studies, only the Latino/a group had study partners (n=22) who completed the informant version of the SCD-Q. Informant's demographic data (e.g., age, education, gender, relationship to participant) was not included in this study because it was not collected contemporaneously to SCD-Q administration, which is not uncommon in the literature (e.g, refer to Edmonds et al., 2014; Rueda et al., 2015; Sánchez-Benavides et al., 2018 for articles that include informant reports without related demographics). Additionally, a small subset of participants in the Latino/a group (n=12) underwent neuroimaging approximately 4 and a half years prior to collection of SCD reports and cognitive testing (M_{years} = 4.60, SD_{years} = 1.46, $range_{years}$ = 1.00-6.34). The Institutional Review Board/Human Research Protections Program at the University of California, San Diego approved this study and all participants provided written informed consent.

Measures

Participants completed a series of standard neuropsychological tests and questionnaires during their respective study visits in a quiet room. Trained study personnel administered all cognitive tests and were available to answer any questions. The language of test administration was determined by the participant's stated preference and comfort level. For those whose preferred language was Spanish, trained bilingual and bicultural staff administered all cognitive tests and questionnaires in Spanish. Study partners completed the informant version of the SCD-Q when available.

Subjective Cognitive Decline (SCD): Subjective cognitive decline was measured with the Subjective Cognitive Decline Questionnaire (SCD-Q) (Rami et al., 2014): The SCD-Q is a 24-item self- and informant- report measure of perceived cognitive decline over the past two years, covering domains of memory, language, and executive functioning (Rami et al., 2014; Valech et al., 2018). The forms are available in English and Spanish. Both the self-report "MyCog" and informant-report "TheirCog" forms were used in this study. NHWs completed the MyCog form, whereas Latino/a participants and their informants (when available) completed the MyCog and TheirCog forms, respectively. Items are endorsed for the perceived difficulty in areas such as learning new material, remembering past events, and recalling recent events compared to the last 2 years. Higher scores (range 0-24) are indicative of greater SCD. The SCD-Q was validated in Spain for use in populations with varying degrees of cognitive functioning, ranging from normal cognition to dementia. The SCD-Q demonstrates adequate reliability (Cronbach's alpha of 0.90 and 0.93 for MyCog and TheirCog, respectively), internal validity, and sensitivity/specificity (MyCog 83% / 87%; TheirCog 85% / 80%) for discriminating between individuals with and without objective cognitive deficits (Rami et al., 2014). For this study, a professional translator

modified the wording of some of the Spanish version items to maximize understanding by individuals of Mexican background.

We selected the SCD-Q because it follows recommendations from the SCD-Initiative Working Group (Molinuevo et al., 2017), that SCD measures used in research should a) be validated and developed with a similar target population (i.e., Spanish-speakers), b) incorporate informant in conjunction with self-reports, and c) determine SCD in relation to a shorter time frame to yield more reliable results (Jessen et al., 2014; Rabin et al., 2015). The SCD-Q differs from other SCD measures developed in the U.S., such as the Everyday Cognition Scale (ECog) (Farias et al., 2008), in that it is much briefer (i.e., 24 versus 39 items) and assesses a shorter time frame of perceived decline (2 versus 10 years). Research suggests that assessing a shorter time frame may yield more reliable results (Molinuevo et al., 2017) and have higher predictive value for future dementia (Jessen et al., 2014). Although the SCD-Q was not validated with U.S. residing Latinos/as, we believe it is the best tool currently available to assess SCD in Spanish.

Global Cognition: Cognitive function was assessed with the Mattis Dementia Rating Scale (MDRS) (Mattis, 1988), an assessment of global cognitive function derived from measurement of attention, initiation/preservation, construction, conceptualization, and memory (Mattis, 1988). Higher scores (range 0-144) are indicative of better global cognitive function. For those who opted to be tested in Spanish, the Spanish version of the MDRS (Arnold et al., 1998) was administered.

Mood: Depression was assessed with the Geriatric Depression Scale (GDS) (Yesavage et al., 1982), a self-report questionnaire of depressive symptomatology experienced within the past week. Higher scores are indicative of worse depressive symptomatology. NHWs were administered the 30-item version (range 0-30) (Yesavage et al., 1982), whereas a majority of the

Latinos/as were administered the 15-item version (range 0-15) (Lesher & Berryhill, 1994). For those who opted to be tested in Spanish, the Spanish form of the GDS 15-item (Martínez de La Iglesia et al., 2002) was administered. Since participants completed different versions of the GDS, we standardized GDS scores by deriving the 15-item total score for the NHW group (i.e., GDS-15). A cut off score of 5 is indicative of depressive symptoms in elderly individuals (Bijl et al., 2006; Greenberg, 2012). Specifically, total scores of 5-8 suggest mild depression, 9-11 suggest moderate depression, and 12-15 suggest severe depression (Greenberg, 2012).

Neuroimaging Data: Structural Magnetic Resonance Imaging (MRI) consisted of a high resolution T1-weighted image acquired at UCSD (TE: 2.8 ms/3.8 ms; TR: 6.5 ms/8.5 ms; TI: 600 ms/500 ms; flip angle: 8°/10° matrix: 256 × 256; voxel size: 0.9375 mm × 0.9375 mm × 1.2000 mm; values separated by '/' are for 3.0 T data/1.5 T data). The FreeSurfer (version 6.0; http://surfer.nmr.mgh.harvard.edu/) pipeline (Fischl, 2012; Fischl et al., 2002, 2004) was used to derive automated brain volume and cortical thickness values for regions typically implicated in AD (i.e., hippocampal, parahippocampal, and entorhinal regions) to explore their associations with SCD-Q scores. MRI scans were collected on average 4.60 years (min years= 1.00, max years= 6.34) prior to the SCD-Q completion, hence our preliminary analyses explore if current SCD reports may be indicative of long-standing brain changes typically seen in AD.

Statistical Analyses

All analyses were conducted using IBM SPSS Version 26.0 (IBM, 2019). Data were screened for normality by inspecting skewness and kurtosis limits (Field, 2009), and no significant outliers were detected for the MDRS, SCD-Q, and brain variables. Independent samples *t*-tests and chi-square tests were conducted to determine mean group differences in

demographic characteristics, mood, and SCD-Q and cognitive scores among NHWs and Latinos/as.

Bivariate Pearson correlations were conducted to investigate demographic characteristics that may significantly influence MDRS scores ($p<.05$) to be entered as covariates in all models. (Maxwell et al., 2017; Tabachnick & Fidell, 2013). Since GDS scores are known to influence the association of SCD reporting and cognition (Buckley et al., 2016; Molinuevo et al., 2017; Zlatar et al., 2014; Zlatar, Muniz, Espinoza, et al., 2018), the GDS-15 was entered as an a-priori covariate in fully adjusted models regardless of statistical significance.

Effects of ethnicity in the association of self-reported SCD and global cognition

A hierarchical linear regression model was employed to investigate if the association of MDRS and SCD-Q scores is moderated by ethnicity. Regression blocks were defined as follows (all variables were centered): Block 1 = significant covariates (i.e., age, education); Block 2 = GDS-15; Block 3 = SCD-Q and ethnicity; Block 4 = SCD-Q x ethnicity. Follow-up linear regression models stratified by ethnic group were conducted to determine the strength and direction of associations between SCD and cognition for each group separately. All analyses investigating the association of SCD with cognition are reported as non-adjusted (no covariates), demographically adjusted (including significant covariates), and fully adjusted (including significant covariates and GDS-15 scores) models. Since the SCD-Q was developed in Spain and was not validated with NHWs living in the U.S., we also collected the Everyday Cognition Scale [ECog] (Farias et al., 2008), a widely used self-report measure of perceived decline in cognitively mediated daily activities. We used the ECog to validate our SCD-Q results within the NHW group. The ECog was not collected in the Latino/a sample.

Exploratory Analyses

Self- versus Informant-Reported SCD in Latinos/as

Only Latinos/as with identified informants were included in this sub-sample. 22 Latino/a participants and their informants completed the SCD-Q. Independent samples *t*-tests assessed for differences between self (i.e., MyCog) and informant (i.e., TheirCog) SCD-Q total scores. Subsequently, bivariate Pearson correlations explored the relationship between self and informant SCD-Q total scores with MDRS total scores.

Self-reported SCD and medial temporal lobe thickness and volume in Latinos/as

Only Latinos/as with available neuroimaging data were included in the sample (n=12). Age was entered as an a-priori covariate due to its known effects on brain structure (J. H. Cole et al., 2019). Partial correlations evaluated whether self-reported SCD-Q total scores were associated with right and left hippocampal volume, right and left entorhinal thickness, and right and left parahippocampal thickness, adjusting for age. Since brain volume is influenced by total brain size (Kijonka et al., 2020; Voevodskaya et al., 2014), associations of self-reported SCD-Q with right and left hippocampal volume were additionally adjusted for intracranial volume. Due to the small sample included in this exploratory analysis, interpretation was based on effect size, which conveys information about the practical significance/importance of results (Lakens, 2013; Tabachnick & Fidell, 2013). We interpreted medium ($r \geq .30$) and large ($r \geq .50$) effect sizes as clinically meaningful.

Sensitivity Analyses

Groups filtered based on lowest education level and MDRS scores: To ensure our analyses were not heavily influenced by ethnic group differences in cognitive performance and education level, we ran the fully adjusted models, stratified by ethnic group, excluding individuals with <12 years

of education and those with MDRS scores < 132 from both groups (Green et al., 1995), which included 48 NHWs and 27 Latinos/as.

Running all models excluding participants with MCI

To ensure our analyses were not heavily influenced by cognitive status, all the analyses described above (i.e., effects of ethnicity in the association of self-reported SCD and global cognition and exploratory analyses) were conducted including only participants diagnosed with normal cognition based on neuropsychological assessment and expert consensus as described in the methods section. This excluded 8 Latinos/as and 5 NHWs with an MCI diagnosis.

Results

Ethnic groups did not differ significantly on age, GDS-15 total scores, or SCD-Q total scores. NHWs had significantly more years of education and higher MDRS total scores and were more likely to be women compared to Latinos/as (Table 2.1). Bivariate Pearson correlations indicated that age (for Latinos/as only) and years of education (for NHWs and Latinos/as) were significantly correlated with MDRS total scores. As such, our demographically adjusted models corrected for age and education, while fully adjusted models additionally corrected for GDS-15 scores.

Effects of ethnicity in the association of self-reported SCD and global cognition *(NHW n=48; Latinos/as n=35)*

Fully adjusted hierarchical linear regression models (i.e., age, education, and GDS-15 scores) revealed a significant interaction between ethnic group and SCD-Q total scores on MDRS total scores. Follow-up regression analyses stratified by ethnicity showed that higher

SCD-Q total scores were significantly correlated with lower MDRS total scores only in Latinos/as (Table 2.2 and Figure 2.1). The association of SCD-Q and MDRS total scores within Latinos/as remained significant after full covariate adjustment, increasing the magnitude of the association by ~30% (from non-adjusted to fully-adjusted model) rather than attenuating it. The results of the ECog corroborated those of the SCD-Q. Specifically, ECog total scores were not significantly correlated with MDRS scores in the NHW group after full covariate adjustment (b= -.008, SE= .028, β= -.042, *t*= -.269, *p*= .789).

Exploratory Analyses

Self- versus Informant-Reported SCD in Latinos/as (n=22)

Independent samples *t*-test revealed no significant differences between self-reports ("MyCog") and informant-reports ("TheirCog") of SCD, although there was a trend for self-reported (mean= 7.68, SD= 4.90) SCD scores to be higher than informant-reports (mean= 4.68, SD= 5.30, *p*= .058, Cohen's d= .58). Bivariate Pearson correlations revealed that higher SCD-Q total scores were significantly correlated with lower MDRS scores for self-reports (*r*= -.672, *p*= .001), but not for informant-reports (*r*= -.044, *p*= .850) (Figure 2.2).

Self-reported SCD and medial temporal lobe thickness and volume in Latinos/as (n=12)

We found large and medium effect sizes when exploring the association of self-reported SCD-Q total scores with left (*r*= -.547, *p*= .082) and right entorhinal cortex thickness (*r*= -.442, *p*= .173), respectively. There was a medium effect size for the association of SCD-Q with left hippocampal volume (*r*= -.393, *p*= .261). Effect sizes in the parahippocampi and the right hippocampus were small (*r's* ≤.30). Refer to Figure 2.3 for a visual depiction of the relationship between the SCD-Q, left and right entorhinal cortex thickness, and left hippocampal volume in Latinos/as.

Sensitivity Analyses

Groups filtered based on lowest education level and MDRS scores (NHW n=48; Latinos/as n=27): After applying these filters (sample reduced from 83 to 75 participants, with 3 missing GDS-15 and 4 missing SCD-Q), ethnic groups did not differ significantly on age, GDS-15 total scores, SCD-Q total scores, MDRS total scores, or sex distribution. However, there was a trend for higher education in NHWs compared to Latinos/as (p= .051). The interaction between ethnicity and SCD-Q total scores approached significance in the fully adjusted model (b= -.312, SE= .158, β= -.288, t= -1.976, p= .052). An interrogation of the interaction analyses revealed that higher SCD-Q scores were significantly associated with lower MDRS scores in Latinos/as, but not in NHWs (Table 2.3), corroborating results from the full analytic sample. This indicates that the significant association of SCD-Q and MDRS scores in this small sample is not heavily influenced by group differences in education and global cognition.

Running all models excluding participants with MCI (NHW n=43; Latinos/as n=27):

In those with normal cognition only (sample reduced from 83 to 70 participants after removing MCI, with 1 participant missing SCD-Q and 1 missing GDS-15 data), the fully adjusted hierarchical linear regression model revealed a significant interaction between ethnic group and SCD-Q total scores on MDRS total scores (b= -.429, SE= .158, β= -.921, t= -2.710, p= .009). Consistent with findings of the full analytic sample, higher SCD-Q total scores were significantly associated with lower MDRS scores in Latinos/as scores (b= -.604, SE= .164, β= -.836, t= -3.68, p= .001) but not in NHWs scores (b= -.122, SE= .101, β= .20, t= 1.21, p= .235). In the Latino/a group only (sample reduced from 22 to 18 participants after removing MCI), independent samples t-tests revealed no significant differences between self-reports (“MyCog”) and informant-reports (“TheirCog") of SCD (t= 1.77, p= .085, Cohen’s d= .59), although self-

reported (mean= 6.94, SD= 5.00) SCD scores were still higher than informant-reports (mean= 4.11, SD= 4.57). Bivariate Pearson correlations revealed that higher SCD-Q total scores were significantly correlated with lower MDRS scores for self-reports (r= -.625, p= .006), but not for informant-reports (r= -.293, p= .238). Regarding the association of SCD-Q self-reports with medial temporal lobe volume and thickness (sample reduced from 12 to 10 participants after removing MCI), there were large effect sizes for left (r= -.578, p= .103) and right (r= -.564, p= .114) entorhinal cortex thickness, and a medium effect size for left hippocampal volume (r= -.397, p= .330). Overall, this indicates that the results obtained from the full analytic sample were not influenced by the few individuals diagnosed with MCI.

Discussion

This study evaluated if there are ethnic differences (Latino/a versus NHW) in the association of SCD reporting and global cognition. We found that ethnicity moderated the association of SCD and global cognition such that SCD reporting was associated with worse global cognition only within Latinos/as and not in NHWs. The pattern of results did not change when we excluded individuals with lower global cognitive performance (MDRS scores < 132), lower educational levels (< 12 years), and MCI diagnosis. These preliminary findings suggest that among community samples of Latino/a older adults of mostly Mexican descent, higher SCD reporting may be indicative of lower global cognitive status (Jessen, 2014; Mendonça et al., 2016), consistent with recently published findings in a large and diverse community-based sample of U.S. residing Latinos/as (Zlatar et al., 2022) and with studies conducted in Spain (Sánchez-Benavides et al., 2018; Valech et al., 2015, 2018). This is conflicting with our prior

work in a clinical sample of Latinos/as in the U.S., which found that SCD reflected depression symptoms rather than objective cognition (Zlatar, Muniz, Espinoza, et al., 2018). One potential explanation for the discrepant results is that, compared to our previous study (2018), our current participants, on average, reported lower levels of depressive symptoms (GDS-15 item raw score of 1.32 vs. 4.00 points) even though neither study excluded participants based on depression scores. Moreover, our current sample is community-based, rather than clinic-based, and therefore participants may not have been worried enough about their SCD to seek medical attention. Most importantly, the use of a validated SCD scale that was developed specifically to measure SCD in Spanish may have been better able to predict cognition than our prior 5-item scale (Zlatar, Muniz, Espinoza, et al., 2018).

Although we did not find an association of SCD with global cognition in NHWs, this is not surprising since the SCD-Q was developed in Spain and was not validated for use in NHWs living in the U.S., which may be considered a limitation of the current study. That said, we also collected the Everyday Cognition Scale (ECog) (Farias et al., 2008) on the NHW group and were able to replicate our findings (there was no association between ECog total scores and cognition in the NHW group after adjusting for covariates), indicating that the lack of association between SCD and cognition in the NHW sample is reliable. Moreover, previous cross-sectional studies by our research group and others using English-based measures of SCD with NHWs show similar findings suggesting that depression, rather than SCD, is related to cognition in some samples (Markova et al., 2017; Yates et al., 2015; Zlatar et al., 2014; Zlatar, Muniz, Galasko, et al., 2018). Given our small sample size, we cannot rule out the possibility that we did not have enough power to detect an association in NHWs. However, our Latino/a group was smaller than the NHW group and we detected strong effects. Unfortunately, there is no gold standard

questionnaire to measure SCD, and utilizing a single, standardized questionnaire across samples and cultures may not be a practical or feasible solution (Molinuevo et al., 2017). It will be important for future studies to select SCD measures that have adequate psychometric properties, have been validated with different samples, measure several cognitive domains, and that follow the SCD-Initiative Working Group (Molinuevo et al., 2017) recommendations for how to operationalize SCD.

In contrast to our hypothesis, informant-based SCD reports were not significantly associated with participants' global cognition within the Latino/a group, suggesting that self-reported SCD may be more sensitive to objective concurrent cognition than informant-reported SCD in Latino/a older adults without dementia. Due to the small sample size, these results are interpreted with caution and are presented to generate new hypotheses. Nonetheless, consistent with findings in NHWs, there was a trend for self-reports of SCD to be higher than informant-reports (Slavin et al., 2010), which is thought to reflect an overestimation of SCD by individuals who are aging normally (Edmonds et al., 2014). Given the exploratory nature of this analysis, larger studies should confirm these preliminary findings to determine the value of self- versus informant- SCD reports and explore their utility in predicting cognitive performance in Latinos/as.

In the Latino/a culture, respect for older persons and their experiences is highly valued (Beyene et al., 2002). Furthermore, family responsibilities and perceived societal roles may influence the perception of cognitive issues within this population (Cuevas & Zuñiga, 2020). More specifically, Latino/a culture highlights the importance of family loyalty and support. These values and experiences, in addition to potential discrimination within the healthcare system (Cuevas & Zuñiga, 2020), may have resulted in informants underreporting SCD to

protect their family members. Moreover, informant's education levels, acculturation, health literacy about cognitive decline, personal exposure to dementia, and comorbidity with other physical or mental conditions could have influenced SCD reports (G. J. Lee et al., 2020; Morrell et al., 2019). For instance, some Latino/a individuals may believe that cognitive decline is expected with aging given lower health literacy about dementia (Laditka et al., 2011). It will be important to incorporate sociocultural measures (e.g., acculturation, language proficiency, bilingualism, access to healthcare, knowledge about and exposure to Alzheimer's disease, perceived social support) in future research of SCD and cognition in Latinos/as to better understand their influence on SCD reporting.

Lastly, on a small sub-sample (n=12) of Latinos/as with available brain MRI data, we found that higher self-reported SCD-Q scores were linked to lower thickness in the left and right entorhinal cortex and lower left hippocampal volume an average of 4.6 years prior to SCD-Q data collection. Although not statistically significant, these medium to large effect sizes suggest that the self-report version of the SCD-Q may be sensitive to neural signatures of AD (Holbrook et al., 2020; Meiberth et al., 2015; Meiberth et al., 2020) and possibly identify those who are at risk (Jessen, 2014; Sánchez-Benavides et al., 2020). This is consistent with previous literature implicating reduced entorhinal cortex thickness (Holbrook et al., 2020) and hippocampal volume loss (Holbrook et al., 2020; van der Flier & Scheltens, 2009) as biomarkers for early detection of AD. Additionally, progressive decrease in entorhinal and hippocampal volumes has been associated with the trajectory from normal cognition to MCI and dementia in Latinos/as living in the U.S. (Burke et al., 2018). Given our small sample size, these preliminary findings are interpreted with caution but can help propel new studies investigating the utility of SCD to not

only predict cognition but biomarkers of AD to improve early identification and clinical outcomes in Latinos/as.

An important limitation of this study is the small sample size, particularly for informant reports and brain MRI data. Furthermore, MRI data was collected on average 4.6 years prior to the SCD-Q completion rather than contemporaneously. Thus, the exploratory analysis of associations between SCD-Q scores and medial temporal lobe thickness and volume within Latinos/as reflects long-standing brain changes typically seen in AD that may be associated with later SCD reporting. Larger studies with the simultaneous collection of neuroimaging and neuropsychological data are needed to confirm our findings. A second limitation is that a majority of the Latino/a participants were of Mexican descent. As such, results may not generalize to other Latino/a subgroups living in the U.S. A third limitation is that this study was cross-sectional in nature. Thus, future research on the ability of SCD to predict cognitive decline and progression to MCI and AD with diverse Latino/a samples is also warranted. Furthermore, we modified some of the SCD-Q items to ease readability by individuals of Mexican background. Future research should validate the SCD-Q with larger populations of Latinos/as living in the U.S. Given the need to investigate culturally relevant variables that may modify the association of SCD and cognition in Latinos/as to address disparities, acculturation factors (e.g., where education was obtained, quality of education, time spent in the U.S., fluency in English, socioeconomic status, health literacy) should also be considered in future studies to better characterize the association of SCD and cognition.

In conclusion, our study fills an important gap in the literature by indicating that the SCD-Q may reflect current global cognition in a community sample of Latinos/as without dementia. This is especially important for the Latino/a population who are more likely to

experience socioeconomic stressors (Gallagher-Thompson et al., 2006; Morales et al., 2002) and barriers to healthcare (Azar et al., 2017) making it difficult to receive proper diagnosis and treatment. The SCD-Q could be used as a tool to identify individuals who may be experiencing cognitive difficulties for referral to comprehensive neuropsychological testing and continued monitoring.

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Table 2.1. Demographic characteristics by ethnic group (n=83).

All values listed are means (standard deviations) unless otherwise noted. P-values were derived from independent samples *t*-tests and χ^2 tests.
Abbreviations: GDS-15=Geriatric Depression Scale-15; MDRS=Mattis Dementia Rating Scale; SCD-Q=Subjective Cognitive Decline Questionnaire.
* $p < .05$, ** $p < .01$, *** $p < .001$.

	Non-Hispanic Whites (n = 48)	**Latinos/as (n = 35)**	***t or*** χ^2	***p*-value**	**Cohen's d**
Demographic Characteristics					
Age (years)	71.81 (4.27)	73.97 (7.06)	-1.73	.087	.39
Education (years)	16.71 (2.23)	14.94 (2.96)	3.10	.003**	.69
Men:Women (total)	12:36	16:19	3.89	.049*	---
Mood & Cognition					
GDS-15 Total Score	1.13 (1.44)	1.32 (1.59)	-.57	.572	.13
MDRS Total Score	139.54 (2.89)	136.97 (4.10)	3.33	.001**	.75
SCD-Q Total Score	5.21 (4.63)	7.32 (4.65)	-1.97	.053	.46

Table 2.2. Effects of ethnicity in the association of SCD-Q with MDRS total scores and follow-up analyses stratified by ethnicity.

Note: [a] = Model 1: Non-adjusted Model (no covariates); [b] = Model 2: Demographically Adjusted Model (includes age and education); [c] = Model 3: Fully Adjusted Model (includes age, education, and GDS-15 scores).

For the full analytic sample analysis, NHWs served as the reference group to test the interaction of ethnicity in the association of SCD and cognition. B (SE) denotes unstandardized b-coefficient and corresponding standard error. β denotes the standardized coefficient. All variables included in the full analytic sample analysis (i.e., interaction analysis) were centered.

Abbreviations: MDRS=Mattis Dementia Rating Scale; SCD-Q=Subjective Cognitive Decline Questionnaire; NHWs=Non-Hispanic Whites

* $p < .05$, ** $p < .01$, *** $p < .001$.

	MDRS Scores			
Full Analytic Sample (n=83)	B (SE)	β	*t*	*p*
Ethnic Group x SCD-Q Total[a]	-.65 (.15)	-1.30	-4.33	<.001***
Ethnic Group x SCD-Q Total[b]	-.52 (.16)	-1.05	-3.33	.001**
Ethnic Group x SCD-Q Total[c]	-.55 (.16)	-1.09	-3.46	<.001***

Stratified by Ethnicity

	MDRS Scores			
NHWs (n=48)	B (SE)	β	*t*	*p*
SDQ-Total[a]	.10 (.09)	.15	1.03	.308
SCD-Q Total[b]	.11 (.09)	.17	1.25	.220
SCD-Q Total[c]	.11 (.10)	.18	1.14	.260
Latinos/as (n=35)	B (SE)	β	t	p
SDQ-Total[a]	-.56 (.12)	-.66	-4.61	<.001***
SCD-Q Total[b]	-.52 (.15)	-.62	-3.40	.002**
SCD-Q Total[c]	-.70 (.17)	-.83	-4.18	<.001***

Table 2.3. Sensitivity Analyses: Association of SCD-Q scores with MDRS scores filtering groups based on lowest education level and MDRS scores <132.

Note: Coefficients and statistics listed portray fully adjusted (age, education, and GDS-15 scores) regression analyses for each ethnic group separately after filtering out individuals based on lowest education level and scores <132 on the MDRS.
Abbreviations: MDRS=Mattis Dementia Rating Scale; SCD-Q=Subjective Cognitive Decline Questionnaire
* $p < .05$, ** $p < .01$, *** $p < .001$.

	MDRS Scores			
	B (SE)	β	*t*	*p*
Non-Hispanic Whites (n = 48)				
SCD-Q Total	.11 (.10)	.18	1.14	.260
Latinos/as (n = 27)				
SCD-Q Total	-.45 (.14)	-.82	-3.21	.005**

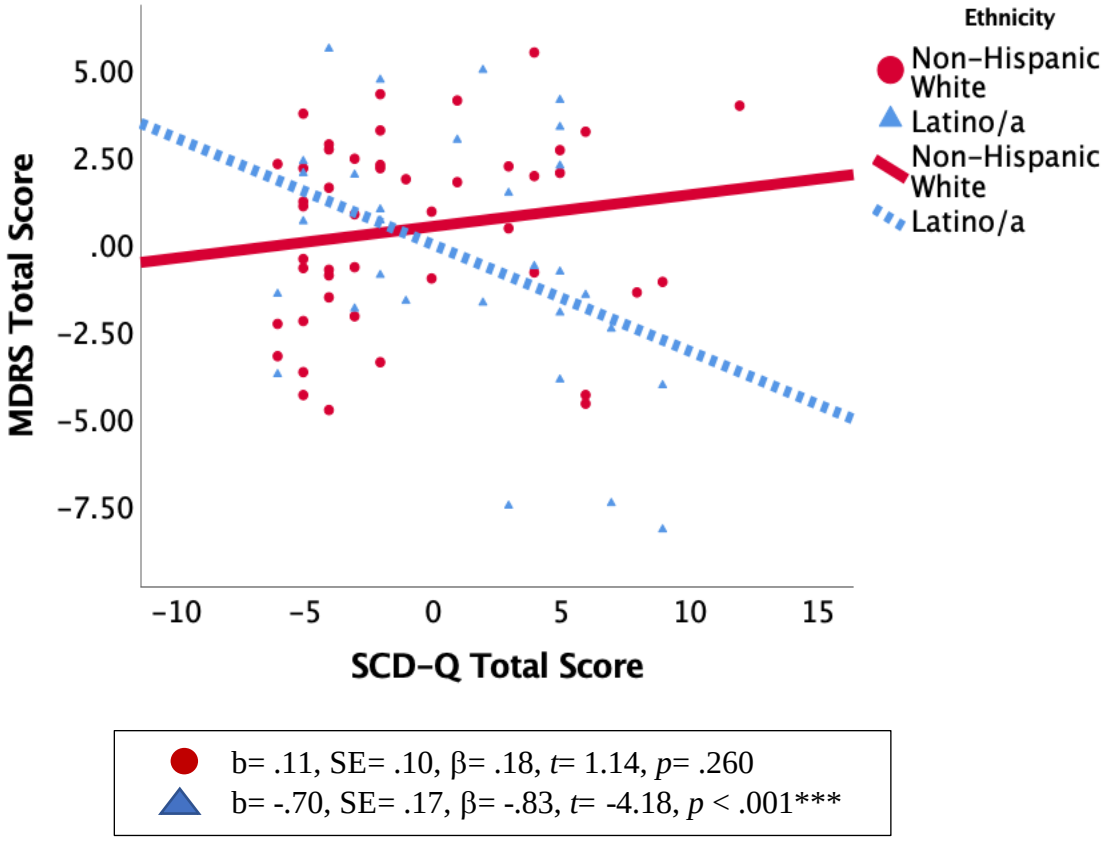

Figure 2.1. Ethnic differences in the association of SCD-Q and MDRS total scores.

Abbreviations: MDRS=Mattis Dementia Rating Scale; SCD-Q=Subjective Cognitive Decline Questionnaire
Note: MDRS total scores reflect unstandardized residual values, adjusted for age, education, and GDS-15 scores. SCD-Q total scores reflect centered values.
* $p < .05$, ** $p < .01$, *** $p < .001$.

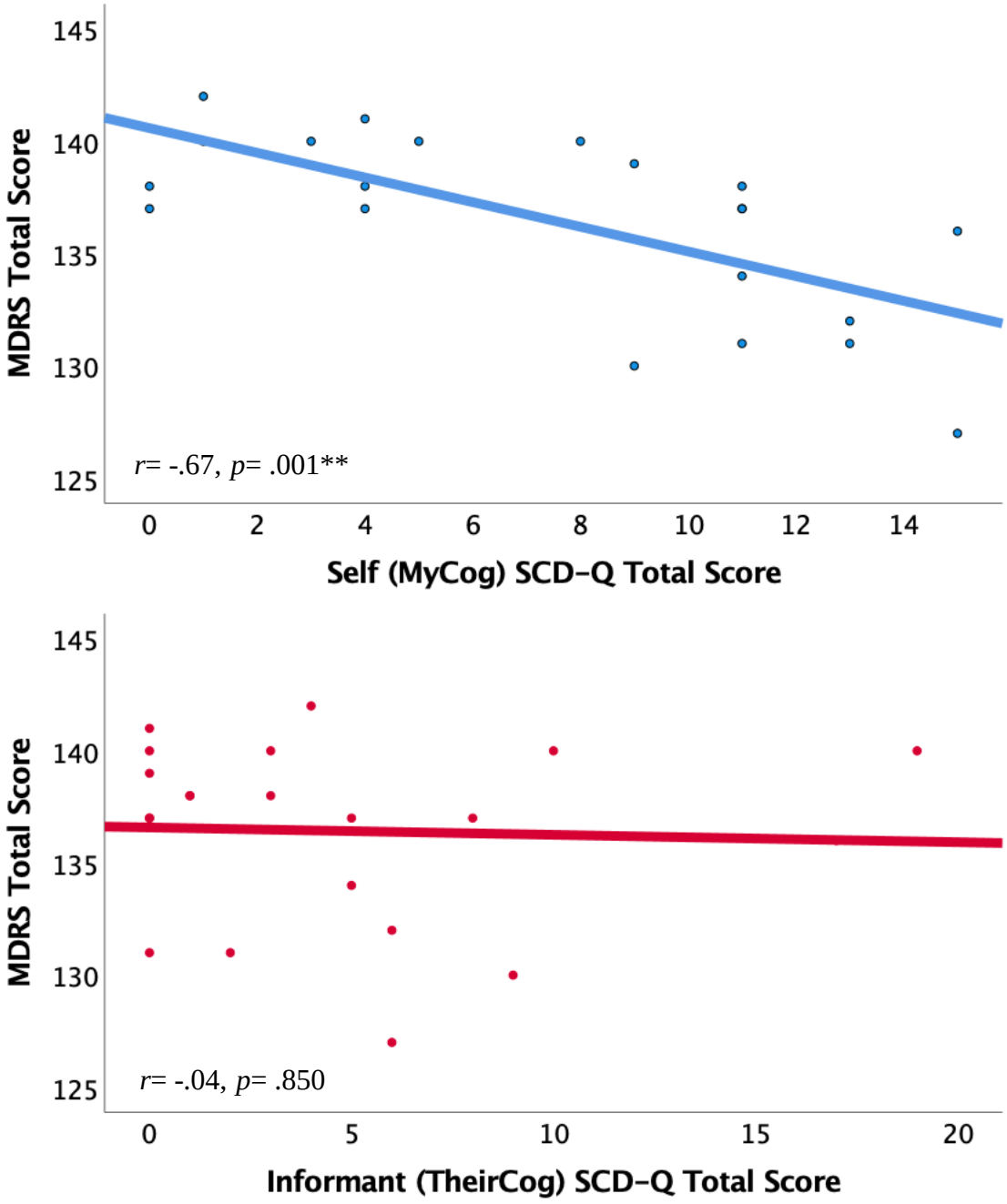

Figure 2.2. Relationship between self and informant SCD-Q scores and MDRS performance within the Latino/a group (n=22).

Abbreviations: MDRS=Mattis Dementia Rating Scale; SCD-Q=Subjective Cognitive Decline Questionnaire
* $p < .05$, ** $p < .01$, *** $p < .001$.

*Figure 2.3A.**

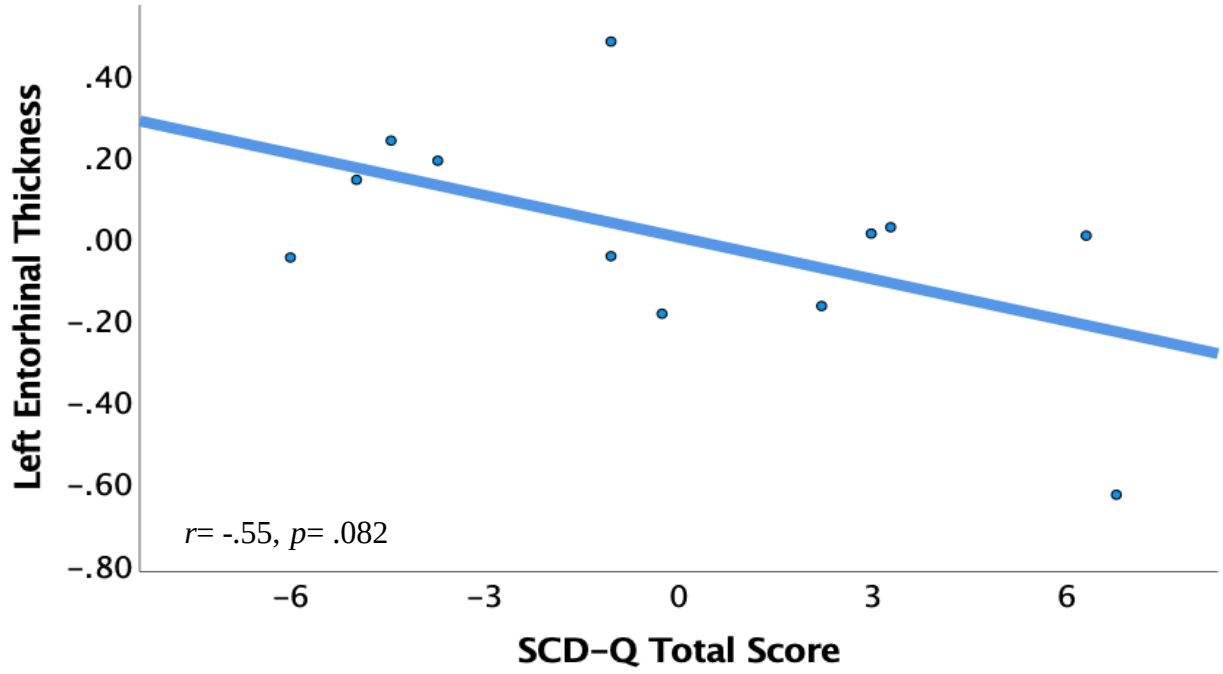

Figure 2.3. Preliminary associations of SCD-Q, entorhinal cortex thickness, and left hippocampal volume in Latinos/as (n=12).

Abbreviations: SCD-Q=Subjective Cognitive Decline Questionnaire
* Scatterplot reflects unstandardized residuals adjusted for age. Residuals were calculated between age and SCD-Q total scores, then age and entorhinal thickness. SCD-Q total residuals were plotted against entorhinal thickness residuals.
** Scatterplot reflects unstandardized residuals adjusted for age and intracranial volume. Residuals were calculated between age, intracranial volume, and SCD-Q total scores, then age, intracranial volume, and entorhinal thickness. SCD-Q total residuals were plotted against left hippocampal volume residuals.
* $p < .05$, ** $p < .01$, *** $p < .001$.

*Figure 2.3B.**

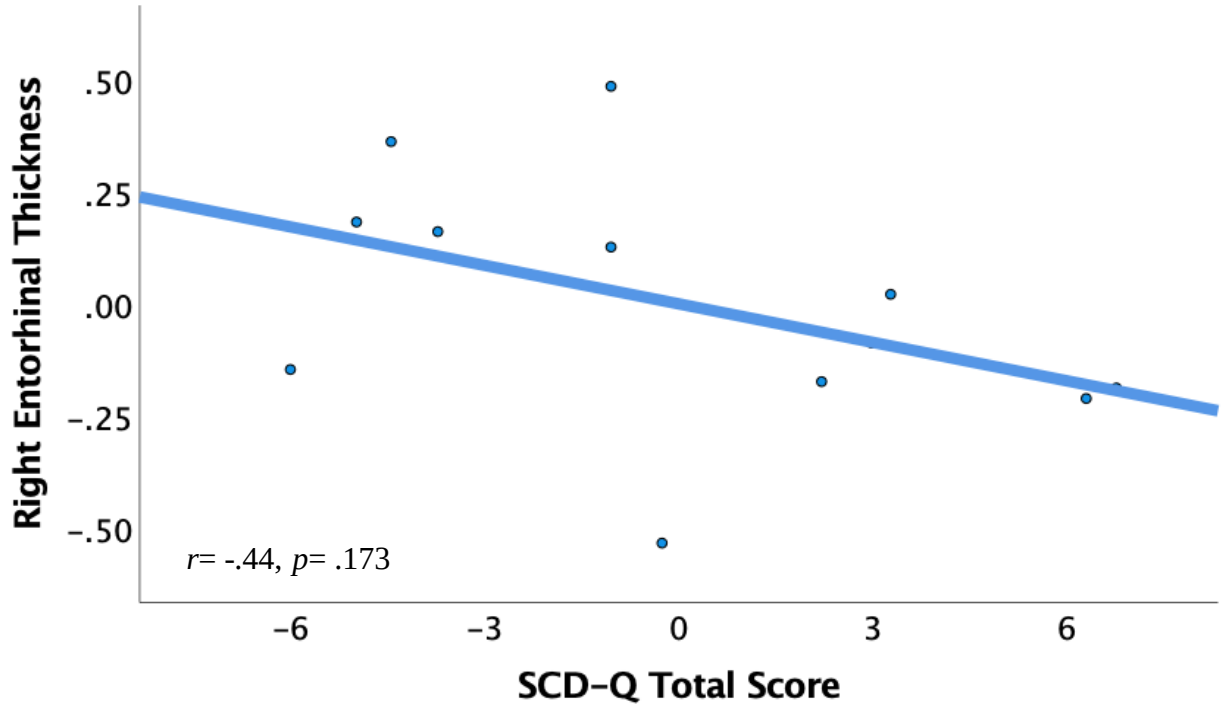

*Figure 2.3C.***

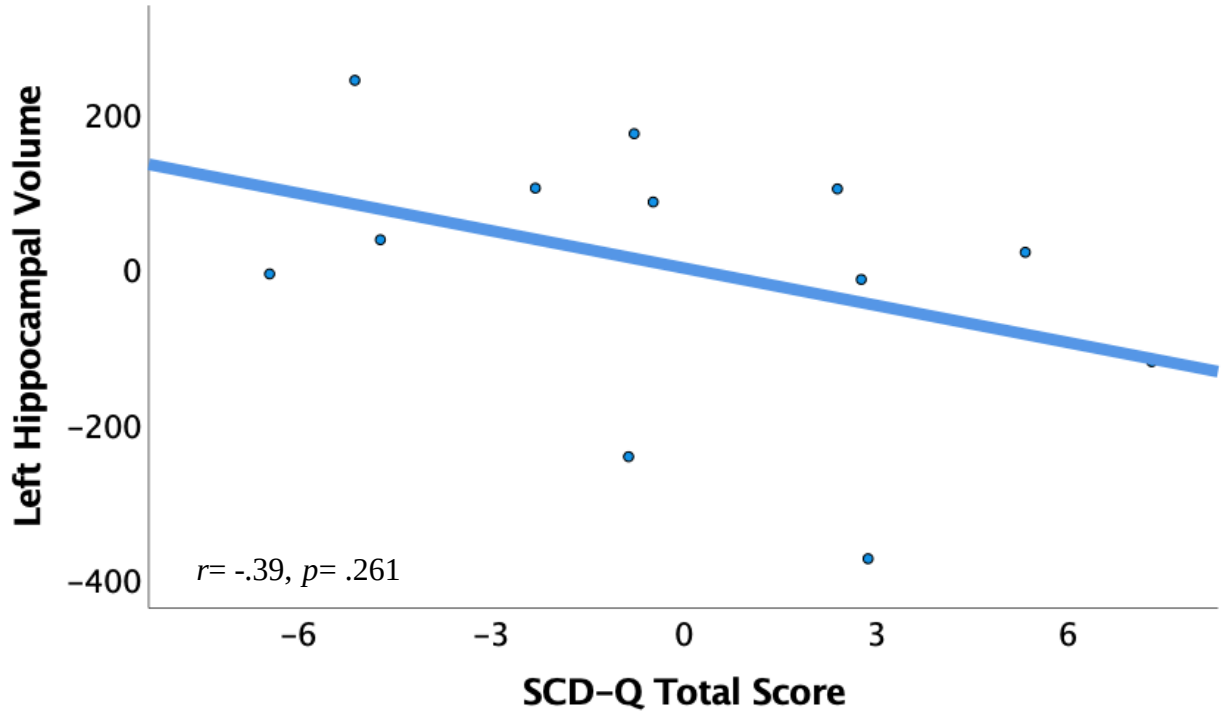

Figure 2.3. Preliminary associations of SCD-Q, Continued

Chapter 3 : STUDY 3

The content within this section, titled “Chapter 3: Study 3,” reflects material from a paper that has been published in the *Journal of the International Neuropsychological Society* journal. The proper citation is as follows:

Nakhla, M. Z., Holiday, K. A., Filoteo, J. V., Zlatar, Z. Z., Malcarne, V., Lessig, S., Litvan, I., & Schiehser, D. M. (2021). Informant-reported cognitive decline is associated with objective cognitive performance in Parkinson’s disease. *Journal of the International Neuropsychological Society, 27*(5), 439-449. doi:10.1017/S1355617720001137

Abstract

The utility of informant-based measures of cognitive decline to accurately describe objective cognitive performance in Parkinson's disease (PD) without dementia is uncertain. Due to the clinical relevance of this information, the purpose of this study was to examine the relationship between informant-based reports of patient cognitive decline via the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) and objective cognition in non-demented PD controlling for cognitive status (i.e., mild cognitive impairment; PD-MCI and normal cognition; PD-NC). One-hundred and thirty-nine non-demented PD participants (PD-MCI n = 38; PD-NC n = 101) were administered measures of language, executive function, attention, learning, delayed recall, visuospatial function, mood, and motor function. Each participant identified an informant to complete the IQCODE and a mood questionnaire. Greater levels of informant-based responses of patient cognitive decline on the IQCODE were significantly associated with worse objective performance on measures of global cognition, attention, learning, delayed recall, and executive function in the overall sample, above and beyond covariates and cognitive status. However, the IQCODE was not significantly associated with language or visuospatial function. Results indicate that informant responses, as measured by the IQCODE, may provide adequate information on a wide range of cognitive abilities in non-demented PD, including those with MCI and normal cognition. Findings have important clinical implications for the utility of the IQCODE in the identification of PD patients in need of further evaluation, monitoring, and treatment.

Introduction

Parkinson's disease (PD) is the second-most common neurodegenerative disorder in the United States (Kowal et al., 2013) and is characterized by both motor and non-motor symptoms, including cognitive deficits. There is considerable heterogeneity in the expression of cognitive deficits among PD patients (Kehagia et al., 2010), but deficits in learning and memory, attention/working memory, and executive function are common (Kehagia et al., 2010, 2013). These cognitive deficits have been recognized even in early stages of PD (Muslimović et al., 2007; Olchik et al., 2016; Stefanova et al., 2015) and warrant a diagnosis of mild cognitive impairment (MCI) in approximately 27% of patients (Litvan et al., 2012). PD-MCI is often a precursor to dementia in PD (Hoogland et al., 2019; Leroi et al., 2012; Saredakis et al., 2019), rendering the early detection of PD-MCI and accompanying cognitive deficits critical for the purposes of monitoring and treatment (Barone et al., 2011).

Subjective cognitive complaints – either by patient, informant, or clinician – are often the first indication that a patient may have bonafide cognitive deficits (Erro et al., 2014; Jessen, 2014). However, there is substantial debate regarding the utility of subjective complaints in clinical practice as the concordance of subjective complaints and objective deficits is not well established and likely confounded by several factors (Copeland et al., 2016; Naismith et al., 2011), such as the relationship of the reporter to the patient, sample characteristics (e.g., cognitive status, mood symptoms), potential over- or under-estimation of symptoms, and assessment tools utilized (Rabin et al., 2015). Evaluating the relationship of subjective and objective cognition in PD within the context of these potential confounds is important in order to establish the utility and validity of subjective cognitive assessment.

Subjective cognitive *decline*, defined as the perceived experience of change and deterioration of cognitive performance (Studart Neto & Nitrini, 2016), is a risk marker of dementia (Jessen & Rodriguez Francisca, 2018) and future objectively-established cognitive decline in non-demented PD (Erro et al., 2014; Jessen & Rodriguez Francisca, 2018). Furthermore, subjective reports of cognitive decline, in addition to objectively measured deficits, are required for a diagnosis of PD-MCI (Litvan et al., 2012). Despite the critical importance of subjective reports of decline, self-reports can be problematic due to PD patients' possible lack of insight into their deficits, especially within the context of cognitive impairment (Lehrner et al., 2015; Seltzer et al., 2001). Inaccurate self-reports have been cited as a rationale for the exclusion of subjective cognitive complaints from prior PD-MCI criteria (Copeland et al., 2016). Reliable informants may provide valuable information about a patient's cognitive decline (Goldman et al., 2018), especially when the patient exhibits frontal behaviors (Zgaljardic et al., 2003) or even lacks awareness or minimizes symptoms (Papay et al., 2011). As objective cognitive impairments increase, PD patients' insight into their deficits may decrease (Lehrner et al., 2015), which may render informant-based measures even more important as the disease progresses. Thus, informant-based subjective measures of cognitive decline have been recommended due to potential sensitivity to subtle changes in patients' symptoms (Naismith et al., 2011).

Although informant-based measures of patients' cognitive decline could provide insight into everyday difficulties that PD patients may experience, the concordance between these reports and objective testing has been debated (Erro et al., 2014). On one hand, Koerts et al. (2012) found that informant-based measures of cognition and objective cognition were not related in PD. However, this study only evaluated subjective and objective cognition with executive function tests (specifically, dysexecutive behavioral changes); thus, limited

conclusions can be drawn for other cognitive domains. Other studies have found that informant-based measures are associated with patients' objective cognitive performance. For example, Naismith et al. (2011) found that informant reports of cognitive decline in memory/orientation were significantly correlated with lower objective performance on tests of psychomotor speed, learning/memory, language, and executive functioning within patients with PD-MCI. Likewise, Cooper et al. (2017) found that higher scores on the Everyday Cognition Scale, an informant-based measure of patients' decline in cognitively-mediated daily activities over the past 10 years, were significantly correlated with poorer overall cognition in PD patients (combined sample of 12 PD-normal control, 24 probable PD-MCI, and 13 probable PD-dementia), even after controlling for disease duration and demographic factors (i.e., age and education; Cooper, Benge, Lantrip, & Soileau, 2017). However, both studies did not control for mood symptoms or other demographic factors (i.e., gender). As mood and gender have been shown to impact self-reported cognitive decline (Jiménez-Huete et al., 2017), it is important to account for these variables when assessing the relationship between informant-based measures and objective cognitive decline.

Importantly, none of the aforementioned studies (i.e., Cooper et al., 2017; Koerts et al., 2012; Naismith et al., 2011) examined relationships between informant-based measures of cognitive decline controlling for cognitive status. Understanding this relationship while accounting for a range of cognitive diagnoses is important given that cognitive deficits can diminish insight and subsequently impact the quality of self-reports (Lehrner et al., 2015), particularly in those with MCI or dementia (Vogel et al., 2004). Thus, providers may rely on informant – particularly family member/close friend – reports of patient functioning and decline as a primary source of information (Potter et al., 2009). However, informant reports may be influenced by the informant's perceived caregiver burden or own psychological symptoms (e.g.,

depression, anxiety; Kudlicka, Clare, & Hindle, 2011; Morrell et al., 2019), which calls into question the accuracy of their reports. Moreover, other factors, such as patient mood and disease severity, may also impact informant reports of cognition (Morrell et al., 2019). Therefore, evaluating the concordance of informant-based measures and objective cognitive functioning controlling for relevant factors is essential for the clinical care of PD patients.

There is currently no gold standard to assess for subjective cognitive decline in PD (Goldman et al., 2018; Kjeldsen & Damholdt, 2019). However, one of the most commonly utilized comprehensive measures of informant-based subjective cognitive decline in non-PD associated MCI and dementia is the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE; Ding et al., 2018; Jorm, 2004), which assesses change (i.e., improved, worsened, no change) on a wide range of cognitive abilities over a 10-year period. In non-PD samples without dementia (i.e., geriatric samples, elderly community samples), the IQCODE has been found to be significantly associated with worse cognitive performance in episodic memory/learning, language, attention/working memory, and executive functioning (Jorm et al., 1996; Jorm, 2004; Jorm, Christensen, Korten, Jacomb, & Henderson, 2000), and global cognition as indicated by a brief screening measure (i.e., Mini-Mental Status Exam; Jorm et al., 2000; Jorm, Scott, & Jacomb, 1989). The studies that do exist in PD have only examined the IQCODE as an indicator of subjective cognitive impairment for classifying PD-MCI versus PD-normal cognition (e.g., Pedersen, Larsen, Tysnes, & Alves, 2017; Pirogovsky-Turk et al., 2014). Thus, research examining whether the IQCODE is associated with a range of objective cognitive abilities in non-demented PD would be beneficial to both clinical research and practice.

In summary, the relationship between informant-based measures of decline and objective cognitive performance in PD is unclear. This is imperative research, as subjective cognitive

decline is a risk marker for future, objective cognitive decline and dementia (Amariglio et al., 2012; Fernandez-Blazquez, Ávila-Villanueva, Maestú, & Medina, 2016), and is an integral part of PD-MCI diagnosis (Litvan et al., 2012). Ascertaining these relationships in those with and without PD-MCI will increase knowledge about the utility of informant reports and improve the clinical identification of individuals who may require further evaluation and monitoring. Therefore, the purpose of this study was to evaluate the relationship between an informant measure of cognitive decline (IQCODE) and objective cognitive performance on a broad range of cognitive tests in non-demented PD patients. Based on previous studies of the IQCODE in non-PD samples (Jorm, 2004) as well as studies indicating the accuracy of informant reports in non-demented PD (Cooper et al., 2017; Naismith et al., 2011), it was hypothesized that above and beyond mood, demographic, and disease characteristics, greater levels of informant-reported patient cognitive decline (IQCODE) would be significantly associated with poorer performances in overall cognition, learning, delayed recall, attention, executive function, and language, above and beyond cognitive status.

Method

Participants and Procedures

Participants were 139 non-demented PD patients (38 PD-MCI; 101 PD with normal cognition [PD-NC]) and their caregivers/care partners derived from a parent study of cognition in PD conducted at the Veteran Administration San Diego Healthcare System. PD diagnosis was based on the United Kingdom Parkinson's Disease Society Bank Criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992) and determined by a board-certified neurologist specializing in movement

disorders. The Department of Veteran Affairs Institutional Review Board approved the study and all participants provided written consent. Exclusionary criteria included significant medical conditions (e.g., other neurological conditions, secondary causes of PD), prescribed medication with significant anticholinergic properties, or dementia based on the Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria (American Psychiatric Association, 2000) detailed in Emre at al. (2007). As part of the overarching study, individuals were also excluded if they had a score of < 124 on the Mattis Dementia Rating Scale[1] (MDRS; Llebaria et al., 2008). Lastly, participants were excluded if they did not demonstrate adequate performance validity on neuropsychological testing, as indicated by Forced Choice scores ≤ 14 on the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The original sample contained 142 PD patients, but 3 were excluded due to response bias. All patients were tested on their normal medication dosages (levodopa equivalent dosages; LED).

Informants were spouses (81.6%), adult children (5.4%), siblings (4.1%), parents (1.4%), and/or friends (7.5%). Age, education, and gender variables were collected from both PD patients and corresponding informants. On average, informants knew PD participants for approximately 38.41 (SD = 15.62) years.

PD participants were classified into PD-MCI and PD-NC groups. PD-MCI was diagnosed based on the International Parkinson and Movement Disorder Society (MDS) task force criteria (Litvan et al., 2012), which requires deficits in one or more cognitive domains (i.e., visuospatial function, language, executive function, attention/working memory, and memory). Specific PD-MCI criteria were modeled after those of Pirogovsky-Turk et al. (2014)[2]: ≤ 1.33 SD on the

[1] A slightly modified version of the Mattis Dementia Rating Scale (Mattis, 1988) was administered.
[2] All WMS-III subtests were normed on age and education (Wechsler, 1997). All D-KEFS subtests were normed on age (Delis et al., 2001). All CVLT-II subtests were normed on age and gender (Delis et al., 2000). WCST was

Judgment Line of Orientation Test (Benton et al., 1983) and ≤ 6 scaled score on the Wechsler Memory Scale (WMS)-III Visual Reproduction Scale – Copy Total (Wechsler, 1997) for visuospatial function; ≤ 1.33 SD on the MDRS – Similarities (Mattis, 1988) and ≤ 6 on the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency – Category Fluency Total Correct (Delis, Kaplan, & Kramer, 2001) for language; ≤ 37 standard score on the Wisconsin Card Sorting Test (WCST) – Perseverative Responses (Kongs, 2000) and ≤ 6 scaled score on the D-KEFS Color-Word Interference Test (CWIT) –Inhibition Condition (Delis, Kaplan, & Kramer, 2001) for executive functioning (Delis, Kaplan, & Kramer, 2001); ≤ 1.33 SD on the Adaptive Digit Ordering Test (Werheid et al., 2002) and ≤ 6 scaled score on the D-KEFS CWIT – Color Naming Condition (Delis, Kaplan, & Kramer, 2001) for attention; ≤ 1.33 SD on the CVLT-II Long Delay Free Recall (Delis, Kramer, Kaplan, & Ober, 2000) and ≤ 6 scaled score on the WMS-III Logical Memory II Recall Total (Wechsler, 1997) for memory. Standardized scores were derived from published manual and local normative data. Furthermore, intact independent functional abilities/activities of daily living as determined by informant responses on the medication management and handling finances items from the Lawton's Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) were required (Litvan et al., 2012).

For the purpose of this study, subjective cognitive decline was determined by the following: T-score ≥ 65 on the Self-Rating Frontal Systems Behavior Scale (FrSBe) – Executive Dysfunction (after illness) subscale (Grace & Molloy, 2001), self-endorsement of item #10 "Do you feel you have more problems with memory than most?" on the self-report Geriatric Depression Scale (GDS), or self-endorsement of any of the following three screening questions: "Have you noticed changes with remembering things?"; Have you noticed changes with

normed on age and education (Heaton & Staff, 1993). The Judgment Line of Orientation Test and Adaptive Digit Ordering Test were normed on gender (Schiehser et al., unpublished) using local data derived from healthy controls.

remembering people/names?"; "Have you noticed changes with getting around familiar places?". If patients did not meet both of the aforementioned criteria (i.e., cognitive dysfunction *AND* subjective cognitive complaints), then they were classified as PD-NC [3].

Subjective Measures

Informants completed the IQCODE (Jorm & Jacomb, 1989; Jorm, Scott, & Jacomb, 1989), which contains 26 items related to the informant's perception of a patient's cognitive decline (i.e., *changes* compared to 10 years ago) in learning, delayed recall, language, attention, and executive functioning that is demonstrated via difficulties in everyday tasks (e.g., items that assess recognition of familiar people, remembering recent events, recalling conversations, adjusting to routine changes, learning new material). For every statement, informants are required to choose a response on a scale from 1 ("much better") to 5 ("much worse"). Scores are then summed, ranging from 26 (lowest) to 130 (highest). Higher scores reflect higher informant-rated subjective cognitive decline over a ten-year period.

Both PD participants and their informants completed the GDS (Yesavage et al., 1982), which is a 30-item, self-report measure of depressive symptoms experienced within the past week. PD participants and informants completed the GDS to reflect their own symptoms. Higher scores reflect increased depressive symptomatology.

For the purposes of diagnosis, PD patients completed the FrSBe Executive Dysfunction subscale - Self-Rating Form (Grace & Molloy, 2001) as a measure of subjective cognitive decline. Higher scores reflect more problematic behaviors in the areas of problem solving, mental flexibility, organization, and planning.

Objective Cognitive Measures

[3] Exclusion of endorsement of subjective cognitive decline from the PD-MCI criteria did not change the classification of participants in this study.

PD participants completed a battery of cognitive tests. Scores from these cognitive tests were standardized into z-scores from raw means and standard deviations of the overall PD sample. Z-scores were then combined by averaging the cognitive test scores to create the following composites: [1] *Language:* D-KEFS Verbal Fluency – Category Fluency Total Correct (Delis, Kaplan, & Kramer, 2001), MDRS – Similarities (Mattis, 1988); [2] *Executive Function:* WCST – Perseverative Responses (Kongs, 2000), D-KEFS CWIT – Inhibition/Switching Condition (Delis et al., 2001), D-KEFS CWIT – Inhibition Condition (Delis et al., 2001); [3] *Attention/Working Memory:* Adaptive Digit Ordering Test – Total, (Werheid et al., 2002), California Verbal Learning Test (CVLT) II – Trial 1 (Delis et al., 2000), D-KEFS CWIT – Color Naming Condition (Delis et al., 2001); [4] *Learning:* CVLT-II – Trials 1 – 5 Total Score (Delis et al., 2000), WMS-III Logical Memory I – Recall Total Score (Wechsler, 1997), WMS-III Visual Reproduction I – Recall Total Score (Wechsler, 1997); [5] *Delayed Recall*: CVLT-II Long Delay Free Recall (Delis et al., 2000), WMS-III Logical Memory II – Recall Total Score (Wechsler, 1997), WMS-III Visual Reproduction II – Recall Total Score (Wechsler, 1997); and [6] *Visuospatial Function:* Judgment of Line Orientation Test – Total (Benton et al., 1983) and WMS-III Visual Reproduction – Copy Total (Wechsler, 1997). A Global Cognition composite was also calculated by taking an average of the six aforementioned composites. Reliabilities were assessed for all cognitive composites. Cronbach's alphas (α) ranged from .199 to .892 (Language $\alpha = .360$, Executive Function $\alpha = .604$, Attention $\alpha = .602$, Learning $\alpha = .700$, Delayed Recall $\alpha = .655$) and were within satisfactory limits (DeVellis, 2017; Taber, 2018), with the exception of Visuospatial Functioning ($\alpha = .199$). Cronbach's alpha for the Global Cognition composite was .892, and considered to be "very good" (DeVellis, 2017).

Motor Measures

Motor functioning was evaluated via the modified Hoehn and Yahr Scale (Goetz et al., 2004), with higher scores reflecting worse disease severity, and the bilateral score from the Finger Tapping Test (FTT; Reitan & Wolfson, 1993), with higher scores reflecting better motor function.

Statistical Analyses

IBM SPSS Version 26.0 was used for all statistical analyses (IBM, 2019). Data were screened for normality. Skewness and kurtosis of all cognitive composites fell within acceptable limits (+/- 3.29; Field, 2009), with the exception of the Visuospatial Function composite, in which there was one significant outlier. However, deletion of this outlier did not change the results and thus, this participant was left in the sample. One-way analyses of variance (ANOVAs) and chi-square analyses were conducted to determine group differences between the PD patients and informants. Pearson (for continuous variables) or point-biserial (for categorical variables) correlations were conducted between the cognitive composites and IQCODE with patient demographic (i.e., patient age, gender, and education) and disease variables (i.e., disease duration in years, LED, and motor function), as well as with patient's and informant's own GDS scores. To limit spurious results, p-values < .01 were considered significant.

All demographic variables (i.e., age, education, and gender), mood, and disease severity (.e., modified Hoehn & Yahr score) were included as covariates in the analyses with cognition based on both theoretical and actual statistical significance with the criterion (Jones et al., 2019; Maxwell et al., 2017; Siciliano et al., 2017). Seven hierarchical linear regressions were conducted with these covariates and cognitive status (i.e., PD-NC versus PD-MCI) entered in block 1, the IQCODE total score entered in block 2, and then each cognitive composite (i.e., Global Cognition, Language, Executive Function, Attention, Learning, Delayed Recall, and

Visuospatial Function) was entered as the criterion. Covariates were removed by backwards elimination if they were not significantly associated with the criterion (i.e., $p < .05$). P-values < .01 were considered significant for all analyses. Effect sizes were interpreted as the following: .10 for small, .30 for medium, and .50 and above as large (Cohen, 1988).

Results

Participants' characteristics for the overall PD (n = 139) and informant (n = 139) samples are displayed in Table 3.1. Fifty of the PD patients were veterans (36% of the entire sample). PD participants and informants were equivalent in terms of education, but the PD participants were significantly older and a had a greater proportion of men compared to the informants.

The total sample, patient age, education, and gender were significantly correlated with all cognitive domains, except age with Visuospatial Function, gender with Attention and Visuospatial Function, and education with Language, Attention, Learning, Delayed Recall, and Visuospatial Function. Hoehn and Yahr scores, FTT scores, and GDS scores (both patient and informant) were not significantly associated with any cognitive domains. Higher IQCODE scores were significantly associated with worse depressive symptoms for informants (i.e., higher GDS scores). The IQCODE was not associated with cognitive status ($r = .053$, $p = .536$). (Table 3.2).

Bivariate correlations revealed that higher IQCODE score totals were significantly associated with lower Global Cognition ($r = -.291$, $p = .001$), Executive Function ($r = -.235$, $p = .006$), Learning ($r = -.251$, $p = .003$), Delayed Recall ($r = -.247$, $p = .003$), and Attention ($r = -.310$ $p < .001$) composite scores. The IQCODE was not significantly associated with Language ($r = -.129$, $p = .131$) or Visuospatial Function ($r = -.093$, $p = .281$).

When controlling for significant covariates in addition to cognitive status (i.e., PD-NC versus PD-MCI), higher IQCODE total scores (i.e., greater levels of informant-rated patient subjective cognitive decline) were significantly associated with worse Global Cognition, Executive Function, Learning, Delayed Recall, and Attention. However, the IQCODE did not significantly predict Language or Visuospatial Function, and the size of these effects was small. For all regressions, tolerance levels and variance inflation factors were also within acceptable limits (tolerance > .10 and variance inflation factors < 10.0; Fields, 2009). (Table 3.3).

Discussion

The current study evaluated the relationship between informant-based measures of cognitive decline (as measured by the IQCODE) and cognitive functioning in non-demented patients with PD. The results supported our hypothesis that informant responses of cognitive decline were associated with PD patients' objective performance on measures of global cognition, learning, delayed recall, executive function, and attention, above and beyond patient and informant mood, patient demographic factors, and disease severity in the overall combined PD sample. Consistent with the IQCODE's purported broad measurement of cognitive abilities, our results indicate that informant-based responses of patient cognitive decline are sensitive to most areas of objective cognitive performance in a broad range of domains in non-demented PD patients. The current study also extended upon previous studies by demonstrating that these results held even when controlling for cognitive status (i.e., PD-MCI and PD-NC). Therefore, these results suggest that regardless of nondemented cognitive status (i.e., PD-MCI or normal cognition), informant responses on the IQCODE yield equally valuable clinical information

about objective performance. This information could be particularly useful in certain circumstances, such as with patients who may not be able to provide self-ratings or when comprehensive neuropsychological assessment is not feasible or readily available. These results also support the use of such reports to improve diagnostic accuracy and provide early intervention.

Given that subjective reporting of cognitive decline is a harbinger for future objectively-measured cognitive decline in PD (Hong et al., 2014), our results underscore the importance of querying PD patients' informants about the cognitive changes they observe in their partner. As informants typically assist PD patients with activities of daily living, provide emotional and social support, and offer advice on medical decisions (Goldman et al., 2018), our results support the likelihood that informants possess critical knowledge to help distinguish between normal aging in PD versus concerning cognitive changes. Thus, if an informant observes decrements in activities such as following a story (i.e., attention), remembering recent events (i.e., delayed recall), learning new material (i.e., learning), adjusting to changes in routine (i.e., executive function), this may provide insight into a PD patient's declining cognitive abilities.

Despite the association of the IQCODE with a broad range of patient cognitive abilities, informant-based measures were not significantly associated with objective language performance. Language is thought to involve access to mental lexicon ability, which involves the retrieval of grammatical representations and sound forms of words (Shao et al., 2014). Although the IQCODE may measure some aspects of language, informant-based responses on this measure do not appear to be sensitive to the objective semantic tasks that comprised the language composite in our current study. Future studies that utilize measures of comprehension may be more sensitive to phonemic and semantic domains and yield significant results. This contrasts

with prior IQCODE studies in geriatric populations (with varying health conditions and associated MCI) that have found these overall informant-based reports to be related to language and semantic processing (Jorm, 2004). Given that PD (e.g., PD-MCI) patients may have higher verbal comprehension than those with MCI due to other etiologies (Pistacchi et al., 2015), this may at least partially explain the lack of relationship with informant subjective measures.

Not unexpectedly, informant reports of cognitive decline also did not correlate with visuospatial functioning. The IQCODE does not purport to measure this ability, and thus, it may be limited in this regard. Considering that the IQCODE was developed for geriatric patients with memory problems, and that the majority of items appear to measure memory skills, the IQCODE itself may not be sensitive to language and visuospatial function in nondemented PD. These findings caution against reliance on the IQCODE for gauging these abilities, particularly in cases of diagnostic assessment in PD (e.g., PD-MCI criteria) when language is a concern. Alternatively, it is possible that neuropsychological assessments might detect subtle changes in cognition (i.e., language) that are not yet obvious to informants. As such, it may be that informants have difficulty characterizing cognition related to these areas. It may become easier to subjectively characterize these cognitive impairments as the disease progresses (i.e., PD-dementia). Therefore, the use of alternative measures for these domains is recommended to supplement the IQCODE in the assessment of cognitive decline in non-demented PD. Nevertheless, our overall findings support the general utility of the IQCODE in detecting a wide range of neurocognitive difficulties in PD, which could help identify those who may benefit from further evaluation and comprehensive assessment.

It is important to note that the IQCODE was not significantly associated with patient demographics and disease characteristics in the overall non-demented PD sample. These results

are consistent with previous literature, which has demonstrated either weak or non-significant relationships between the IQCODE and socioeconomic status, occupational status, and gender in samples of elderly individuals with varying health conditions (Jorm & Korten, 1988; Jorm, 2004) including dementia (Jorm, 2004; Jorm et al., 1989) and support adequate discriminant validity of the IQCODE. Depression scores, as measured by informant and patient GDS, were significantly correlated with the IQCODE. This is consistent with previous findings that higher IQCODE scores are related to higher informant depressive symptoms in older adults across a wide variety of health conditions (Jorm, 2004). While informant reporting can be impacted by their own mood as well as patients' mood (Jiménez-Huete et al., 2017; Jorm, 2004), our results clearly indicated that informant-based measures of cognitive decline related to objective cognitive performance above and beyond the influence of depressive symptoms. These findings support the overall accuracy of informant-based measures of cognitive decrements in their PD partners regardless of their partner's or their own mood symptoms.

Limitations of this study include a PD sample that was mostly male, of Caucasian/White descent, and highly educated, as well as informants that were mostly female of Caucasian/White descent, and similarly highly educated. Although the gender breakdown of the PD sample is consistent with the epidemiological studies of PD (Willis et al., 2010), these results may not generalize to non-demented female PD patients or those from more diverse cultural backgrounds. Likewise, our informants were mostly female spouses, which could limit the generalizability to male informants and informants who are not spouses. Furthermore, our informants had known their PD partners for much longer than 10 years, which could limit the generalizability of these results to informants with more limited interactions or knowledge regarding their partners. As such, future research on diverse samples with a broad range of educational, ethnic, and cultural

backgrounds is warranted. Also, this study only examined the relationship between the IQCODE and objective cognition in non-demented PD samples (i.e., those who were diagnosed with PD-MCI or PD-NC); thus, findings cannot be generalized to those with PD dementia. Future research examining the longitudinal relationship between the IQCODE and objective measures of cognition in non-demented PD is warranted. Lastly, future research should explore cut-off scores in order to increase the clinical application of the IQCODE in PD.

In summary, this is the first study to assess the relationship between the IQCODE and objective concurrent cognitive performance in non-demented PD. Findings provide evidence of concordance between informant-based measures of patient cognitive decline and objective patient performance on measures of overall cognition, executive function, learning, delayed recall, and attention in non-demented PD regardless of patient cognitive status (i.e., PD-MCI and PD-NC). These results provide support for the utility of the IQCODE in assessing concurrent cognitive functioning in non-demented PD on a wide array of cognitive domains. The IQCODE could also aid in the identification of patients who may need comprehensive objective cognitive testing, monitoring, and treatment.

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Table 3.1. Demographics and clinical characteristics for overall nondemented PD and informant samples.

Abbreviations: FTT=Finger Tapping Test; H&Y=Hoehn & Yahr Scale; LED=Levodopa Equivalent Dosage; GDS=Geriatric Depression Scale; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly
All values listed are means (standard deviations) unless otherwise indicated.
P-values were derived from one-way ANOVAs and X^2 tests. Bold font denotes $p < .01$.
*Levodopa equivalents were calculated using the Parkinson's Measurement online calculator (Turner, 2020) formula.
** Gender data is missing for 5 informants.
The cut-off score for impairment indicative of dementia on the IQCODE is a summed score of 87.9 (or an average score of 3.38; Jorm, 2004). 23 PD patients (16.6%) exceeded this cut-off score.

	PD Participants (n = 139)	**Informants (n = 139)**	***p*-value**	η_p^2
Demographic Characteristics				
Age (years)	67.56 (8.48)	63.36 (11.83)	< **.001**	.040
Education (years)	16.57 (2.41)	16.10 (2.37)	.102	.010
Males:Females (total)	98:41	37:97**	< **.001**	.184
Disease Characteristics				
PD-NC: PD-MCI (total)	101/38	---	---	
Disease Duration (years)	5.67 (5.14)	---	---	
FTT Bilateral Hand	40.02 (12.10)	---	---	
Modified H&Y stage Stage 0 Stage 1 Stage 1.5 Stage 2 Stage 2.5 Stage 3 Stage 4 Stage 5	 1.5% 22.1% 1.5% 53.7% 8.1% 11.0% 2.2% 0%	---	---	
LED (mg/day)*	741.16 (671.50)	---	---	
Mood & Cognition				
GDS Total	6.20 (5.00)	4.10 (4.35)	< **.001**	.048
IQCODE Total	---	82.25 (8.09)	---	

Table 3.2. Bivariate Pearson correlations between the cognitive outcomes, IQCODE, and clinical characteristics in overall PD patient (n = 139) sample.

Note: Bold font denotes significant association at $p < .01$.

		Patient Age	Patient Education	Patient Gender	Disease Duration	LED	FTT Bilateral	Hoehn & Yahr	Patient GDS	Informant GDS
Global Cognition										
	r	**-.41**	**.26**	**.23**	.02	.03	.15	-.22	-.05	.00
	p	**<.001**	**.003**	**.009**	.792	.755	.079	.014	.562	.989
Language										
	r	**-.33**	.21	**.27**	-.14	-.01	.11	-.13	.04	.14
	p	**<.001**	.011	**.001**	.105	.873	.198	.145	.645	.109
Executive Function										
	r	**-.38**	**.23**	**.22**	-.04	-.00	.09	-.19	-.14	.02
	p	**<.001**	**.007**	**.009**	.653	.976	.281	.028	.099	.807
Attention										
		-.33	.20	.15	-.02	-.00	.19	-.18	-.12	-.08
		<.001	.018	.087	.825	.972	.028	.035	.174	.378
Learning										
	r	**-.41**	.14	**.26**	.16	.07	.15	-.16	-.01	.01
	p	**<.001**	.096	**.002**	.065	.398	.094	.070	.948	.923
Delayed Recall										
		-.40	.14	**.27**	.14	.06	.12	-.16	.03	-.07
		<.001	.105	**<.001**	.106	.481	.183	.057	.744	.455
Visuospatial Function										
	r	.12	.19	-.19	.04	-.02	.13	-.14	-.02	-.02
	p	.166	.029	.026	.667	.860	.146	.106	.799	.826
IQCODE Total										
	r	.08	.07	-.05	-.03	.04	.02	-.01	.20	**.22**
	p	.325	.448	.547	.772	.637	.796	.906	.017	**.009**

Table 3.3. Models with IQCODE Predicting Objective Cognition.

Bold font denotes predictor variable $p < .01$. β = standardized beta; Patient GDS = Patient-reported Geriatric Depression Scale; Informant GDS = Informant Geriatric Depression Scale; IQCODE = Informant Questionnaire of Cognitive Decline in the Elderly.

	β	***t***	***p***	R^2	ΔR^2	ΔF
Global Cognition				.601	.045	**<.001**
Patient Age	-.36	-6.24	<.001			
Patient Education	.25	4.24	<.001			
Patient Gender	.15	2.49	.014			
Hoehn & Yahr	-.15	-2.63	.010			
Cognitive Status	-.47	-7.89	<.001			
IQCODE Total	-.21	-3.73	**<.001**			
Language				.413	.007	.204
Patient Age	-.32	-4.71	<.001			
Patient Education	.23	3.34	.001			
Patient Gender	.20	2.82	.005			
Cognitive Status	-.41	-5.86	<.001			
IQCODE Total	-.09	-1.28	.204			
Executive Function				.564	.024	**.009**
Patient Age	-.36	-6.02	<.001			
Patient Education	.21	3.45	.001			
Patient Gender	.13	2.10	.038			
Hoehn & Yahr	-.13	-2.20	.030			
Cognitive Status	-.51	-8.35	<.001			
IQCODE Total	-.16	-2.67	**.009**			
Learning				.431	.040	**.003**
Patient Age	-.38	-5.75	<.001			
Patient Education	.17	2.46	.015			
Patient Gender	.17	2.48	.015			
Cognitive Status	-.36	-5.29	<.001			
IQCODE Total	-.20	-3.06	**.003**			
Delayed Recall				.376	.041	**.004**
Patient Age	-.37	-5.36	<.001			
Patient Education	.18	2.53	.013			
Patient Gender	.21	2.85	.005			
Cognitive Status	-.27	-3.82	<.001			
IQCODE Total	-.20	-2.94	**.004**			

Table 3.3. Models with IQCODE Predicting Objective Cognition, Continued

	β	*t*	*p*	R^2	ΔR^2	ΔF
Attention				.483	.072	**<.001**
Patient Age	-.28	-4.45	<.001			
Patient Education	.18	2.84	.005			
Cognitive Status	-.50	-7.91	<.001			
IQCODE Total	-.27	-4.31	**<.001**			
Visuospatial Function				.077	.009	.271
Patient Gender	-.24	-2.74	.007			
Cognitive Status	-.18	-2.09	.039			
IQCODE Total	-.09	-1.10	.271			

INTEGRATED DISCUSSION

With the continued rise of the older adult population, accompanying chronic diseases, and elevated ADRD prevalence, it is crucial to identify potential early risk factors that can lead to cognitive decline since identifying those at risk early can aid with prevention and treatment efforts. Although there is a plethora of research establishing age as the most important factor increasing the risk of cognitive decline, recent research suggests that SCD may actually be considered a first clinical indication of MCI (Studart Neto & Nitrini, 2016) and dementia (Kielb et al., 2017; Lee et al., 2020). However, there are several factors that confound the association between SCD and objective cognitive performance, such as the type of subjective report administered (Rabin et al., 2015), type of respondent (e.g., self versus informant) (Molinuevo et al., 2017), disease stage (Rabin et al., 2017), mood (e.g., depression and anxiety), and demographic factors (e.g., age, education, sex, ethnicity) (Rabin et al., 2017). Moreover, research linking SCD with markers of brain health, which can help determine its utility as an early risk marker of dementia, remains scant. Therefore, the three studies that were proposed and completed in this dissertation have addressed gaps in the literature by demonstrating that self- and informant-based measures of SCD predict concurrent cognitive function across distinct older adult populations at increased risk for dementia.

Study 1 investigated the relationship between self-reported SCD and objective memory performance in a community-based sample of cognitively normal older adults (mostly NHWs) within the context of cardiovascular (CVD) risk (i.e., stroke risk status), as well as whether SCD is associated with cerebral blood flow in regions affected in early AD (i.e., medial temporal lobe). SCD was measured with the Everyday Cognition Scale (ECog), a widely used self-report measure of perceived decline in cognitively mediated daily activities that have been validated in

older adults with varying cognitive statuses including normal cognition, MCI, and dementia (Farias et al., 2008). This study provided evidence for the utility of self-reported SCD in its association with memory performance, consistent with other studies in older adult samples (Brailean et al., 2019; Corlier et al., 2020; Kielb et al., 2017; Rog et al., 2014). Additionally, results revealed that those with greater CVD risk may be driving this relationship. Furthermore, this study was novel in that it explored the relationship between SCD and CBF in the total sample, as well as stratified by CVD risk group (i.e., lower versus higher Framingham Stroke Risk Profile [FSRP] scores). Results revealed that higher SCD was associated with lower entorhinal CBF in the total sample and in the higher FSRP score group only. Entorhinal cortex dysfunction is affected in early AD (Khan et al., 2014; Zhou et al., 2016). Therefore, these findings demonstrate that SCD is not only sensitive to objective cognition, but also to CBF dysfunction in the entorhinal cortex, an important brain region implicated early in the trajectory of AD pathology. Overall, *Study 1* adds novel findings to the literature by providing support for the utility of SCD in predicting concurrent memory performance and entorhinal CBF in cognitively normal older adults. Additionally, *Study 1* suggests that this relationship may be more sensitive in individuals with higher vascular risk burden (as indicated by greater FSRP scores).

Based on *Study 1* findings showing the utility of SCD in predicting concurrent memory performance and entorhinal cortex CBF, *Study 2* explored whether the association of SCD with objective cognition differed in older adults with varying ethnic backgrounds (i.e., Latinos/as vs Non-Hispanic Whites [NHWs]) and cognitive statuses (i.e., normal cognition and MCI). Specifically, *Study 2* investigated whether the association of self-reported SCD with objective cognition (as measured by the Mattis Dementia Rating Scale: Mattis, 1988) was moderated by

ethnic background (Latinos/as compared to NHWs). Additionally, *Study 2* determined if self- and/or informant-reported SCD are correlated with objective global cognition in the Latino/a group. This study revealed that there was a significant interaction between SCD and ethnicity, such that higher self-reported SCD was associated with lower global cognition scores in the Latinos/as group, but not in the NHW group. Although *Study 1* showed a significant relationship between SCD and objective memory performance in a community-based sample that was largely comprised of NHW individuals, *Study 2* did not specifically assess memory performance, but rather focused on global cognition. Moreover, *Study 2* utilized a measure of SCD (i.e., Subjective Cognitive Decline Questionnaire: SCD-Q) that was specifically validated in Spain and for Spanish-speaking individuals (Rami et al., 2014). Therefore, a possible explanation for the lack of association in NHWs is that the SCD-Q was not validated for this population. However, neither *Study 1* nor *Study 2* could detect a significant relationship between the ECog and global cognition in NHWs, indicating that perhaps the ECog is not sensitive to global cognition, but rather to specific cognitive domains, such as memory, in NHWs. Furthermore, *Study 2* revealed that higher self-reported SCD may be more sensitive to global cognition than informant-reported SCD in the Latino/a group.

Study 2 included community-based samples of older adults with varying cognitive statuses (i.e., normal cognition and MCI) and ethnic backgrounds (i.e., Latinos/as and NHWs). Therefore, *Study 3* sought to assess the utility of informant-based SCD for older adults with Parkinson's disease (PD), a neurodegenerative disease that may increase the risk of dementia (Hindle et al., 2013; Hoogland et al., 2019; Litvan et al., 2012; Saredakis et al., 2019). Similar to healthy older adult populations without neurodegenerative diseases, the presence of SCD in PD has been found to be a risk factor for the later development of PD-dementia (Galtier et al., 2019).

Study 3 revealed that higher informant-reported SCD was associated with worse objective cognitive performance in global cognition, attention/working memory, and episodic memory learning in older adults with PD who were cognitively normal and MCI. SCD was measured with the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) (Jorm, 2004), a measure of informant-reported SCD that was validated in older adults across various community-based settings, which included individuals who were healthy and had varying medical conditions and cognitive statuses, including dementia (Jorm & Jacomb, 1989; Jorm & Korten, 1988; Jorm et al., 1989, 2000). These results highlight that informant reports of SCD may be useful in identifying PD patients who may be at risk for objective cognitive impairment and need more comprehensive neuropsychological assessment. Although self-reported SCD was not directly assessed, it is interesting to note that informant reports were significantly associated with objective cognition in *Study 3*, yet this was not the case in *Study 2*. As *Study 3* also consisted of mostly NHWs, these results bring attention to the notion that cultural factors may play a role in self versus informant reporting. Furthermore, it could be that informant reports are more useful for individuals with neurodegenerative diseases. Lastly, another reason for these differences could be the use of differing SCD questionnaires (i.e., *Study 2* uses the SCD-Q and *Study 3* uses the IQCODE).

Pros and Cons of the SCD Scales

This three-paper dissertation utilized three different measures of SCD. All three scales were validated for individuals with varying cognitive statuses including normal cognition, mild cognitive impairment, and dementia (Farias et al., 2008; Jorm & Jacomb, 1989; Rami et al., 2014). Furthermore, higher scores are indicative of higher SCD (or worse self-perceived cognitive decline) across these scales. The ECog and IQCODE are both on a Likert-type scale,

which is beneficial for quantifying the frequency or severity of SCD (Molinuevo et al., 2017; Rabin et al., 2015). In contrast, the SCD-Q is on a dichotomous scale ("yes" or "no" responses), although like the ECog and IQCODE, items can be summed to a total score. Therefore, this yields similar benefits for quantifying the frequency or severity of SCD. The ECog and IQCODE also inquire about cognitive decline over a 10-year period, which is a lengthy period of time that may be difficult for older adults to accurately recall (Molinuevo et al., 2017). On the other hand, the SCD-Q assesses decline over a 2-year period. Research suggests that shorter timeframes are preferred as they allow adults to focus on concrete recent events (Rabin et al., 2015) and may be more sensitive to preclinical AD (Molinuevo et al., 2017). The ECog and SCD-Q assess multiple cognitive domains including memory, language, and executive function, whereas the IQCODE is said to comprise one overall cognitive decline factor (Jorm, 2004). Limiting the measurement of SCD to focus on memory (or one cognitive domain) may be too restrictive (Molinuevo et al., 2017); therefore, the ECog and SCD-Q may be more advantageous in terms of assessing multiple, distinct cognitive domains. It is important to note that while our study found a significant relationship between the IQCODE and global cognition (supporting its assessment of overall or global cognition), the IQCODE was not associated with all cognitive domains assessed. Specifically, there was a relationship found between the IQCODE and attention, executive functioning, and memory, suggesting that the IQCODE may not capture all cognitive domains of interest. The ECog and SCD-Q have both self- and informant-versions, which is an added benefit as researchers and clinicians may use this to measure discrepancy scores and since the value of self and informant reports of SCD change over the course of disease. For example, self-reports may be more reliable earlier on in the disease course (pre MCI and early MCI), whereas informant reports may be more reliable later on in the disease course as individuals

develop anosognosia (Molinuevo et al., 2017). As such, both the ECog and SCD-Q have the advantage of including self and informant reports, whereas the IQCODE does not have a self-report version. This is a limitation as the availability of an informant is not always guaranteed (Harrison et al., 2016). As a final point, although all three scales were validated for individuals with varying cognitive statuses, the ECog and IQCODE were validated in predominantly White/Caucasian populations, whereas the SCD-Q was validated in a Hispanic/Latino population (i.e., Spaniards). It is important to note that the ECog and IQCODE have both been translated into several languages such as German and Chinese (Hsu et al., 2017; Jorm, 2004). Although there is no gold standard measure for SCD across different ethnic/racial groups, clinicians must account for measurement bias. Cultural bias refers to the systematic group differences that can be associated with ethnic group membership (Corral & Landrine, 2010); measurement scores can provide an interpretation that is relevant to one subgroup, but irrelevant for another (Cole & Moss, 1989). In the selection of a culturally appropriate measure, when feasible, clinicians should be mindful of what population the measure was validated in and measurement invariance. In the context of this study, it appears that the SCD-Q was more culturally appropriate for Hispanic/Latino individuals, whereas the ECog and IQCODE were more culturally appropriate for White/Caucasian individuals.

Limitations and Future Directions

One prevalent limitation of these studies is that participants were mostly Non-Hispanic White (particularly for studies 1 and 3), relatively healthy, well-educated, and did not report significant depression or anxiety symptoms. As such, these results may not be representative of individuals from diverse backgrounds and with more medical health and/or mood problems. Furthermore, given that these studies were cross-sectional, we were unable to determine whether

changes in cognition or changes in SCD occur first. There is some evidence to suggest that those with SCD progress to MCI and dementia at a faster rate compared to those without SCD (Thomas et al., 2018). Future studies should investigate the relationship between SCD and cognition longitudinally in individuals from demographically diverse backgrounds with normal cognition and MCI.

A specific limitation in *Study 1* was that we used a measure of stroke risk to denote cardiovascular burden, and our samples were relatively healthy. Therefore, our "lower" and "higher" Framingham Stroke Risk Profile groups were arbitrary (based on a median split) and not based on clinical cut off scores. Inclusion of larger and more diverse samples with greater cardiovascular risk, as well as additional measures of cardiovascular risk burden, will address this limitation. Nonetheless, *Study 1* was novel in that we investigated the relationship between SCD and CBF and accounted for markers of cardiovascular risk in a sample of Non-Hispanic Whites. It is important to note that Hispanics/Latinos have greater cardiovascular risk than Non-Hispanic Whites, including great matter white matter hyperintensity volume related to hemoglobin A1c (King et al., 2022), congestive heart failure (Balfour Jr et al., 2016), high blood pressure, obesity, diabetes mellitus, and ischemic stroke (Shaw et al., 2018). Given these risk differences, it will be important for future studies to explore the relationship between SCD, CBF, and markers of vascular burden in Hispanics/Latinos compared to NHWs. Relatedly, we did not have measures of acculturation to include in *Study 2*. Inclusion of acculturation measures is imperative because factors such as English as a second language, years of education in the U.S., number of years in the U.S., socioeconomic status, and other markers of health (e.g., diet, social engagement, sleep) may influence SCD reporting and cognition (Boone et al., 2007; Cuevas & Zuñiga, 2020). These acculturation factors may also explain or help us better understand why

self-reports were higher than informant-reports of SCD in Hispanics/Latinos in *Study 2*. *Study 3* added to the literature by exploring the utility of informant reports in PD while accounting for depression. However, one limitation is that this study did not account for apathy, which has been cited as a frequently reported neuropsychiatric symptom in PD (den Brok et al., 2015). Given that apathy has been identified as a correlate of cognitive dysfunction (Leentjens et al., 2008), future studies should better characterize the relationship between SCD and cognition in the context of varying levels of apathy.

Summary

Collectively, the findings from the three studies in this dissertation highlight the utility of self and informant SCD in identifying older adults who may be at risk for cognitive impairment and need more comprehensive neuropsychological assessment. As demonstrated across this three-paper dissertation, there are several factors that must be considered when assessing the relationship between SCD and concurrent objective cognitive performance, including the type of reporter (i.e., self or informant) (Jessen et al., 2014; Molinuevo et al., 2017), type of SCD assessment administered (e.g., decline over 2 years vs 10 years, present status vs decline) (Rabin et al., 2015), cognitive domains included (e.g., global cognition, memory, one vs multiple domains) (Rabin et al., 2015), patient cognitive status (e.g., cognitively normal, MCI) (Molinuevo et al., 2017), and mood symptoms (Molinuevo et al., 2017; Zlatar et al., 2014). However, a single approach for assessing SCD may not be feasible due to various factors, including cultural and linguistic differences (Molinuevo et al., 2017). Nonetheless, findings from the three studies in this dissertation project characterized the association of SCD and objective cognitive function in older adults with different cognitive statuses (i.e., cognitively normal, MCI), diseases that increase the risk for dementia (i.e., PD), and ethnic background (i.e.,

Hispanics/Latinos). These studies also integrated information from self and informant SCD reports, assessed various cognitive domains, and used different SCD instruments (i.e., ECog, SCD-Q, IQCODE). Taken altogether, the present findings highlight the clinical relevance of SCD and the need for continued research in this area.

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