

UC San Diego

UC San Diego Electronic Theses and Dissertations

Title

The Cognitive Effects of Alzheimer's Disease in Hispanic Older Adults

Permalink

<https://escholarship.org/uc/item/7dt2x9ks>

Author

Weissberger, Gali Helena

Publication Date

2015

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

The Cognitive Effects of Alzheimer's Disease in Hispanic Older Adults

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

in

Clinical Psychology

by

Gali Helena Weissberger

Committee in charge:

University of California, San Diego

Professor Tamar H. Gollan, Chair
Professor Mark W. Bondi, Co-Chair
Professor David P. Salmon
Professor Christina E. Wierenga

San Diego State University

Professor Paul E. Gilbert
Professor May Yeh

2015

Copyright.

Gali Helena Weissberger, 2015

All rights reserved.

The Dissertation of Gali Helena Weissberger is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Co-Chair

Chair

University of California, San Diego

San Diego State University

2015

DEDICATION

I dedicate this dissertation to my parents, Joel and Rachel Weissberger, who left their homes and their families in Israel to provide a better life for my brother and I.

TABLE OF CONTENTS

Signature Page.....	iii
Dedication.....	iv
Table of Contents.....	v
List of Figures.....	vi
List of Tables.....	vii
Acknowledgments.....	viii
Vita.....	x
Abstract of the Dissertation.....	xi
Chapter 1: Introduction.....	1
Chapter 2: Partially Overlapping Mechanisms of Language and Task Control in Young and Older Bilinguals.....	7
Chapter 3: Which Neuropsychological Tests Predict Progression to Alzheimer’s Disease in Hispanics?.....	56
Chapter 4: Neuropsychological and Neuropathological Profiles in Hispanic Older Adults with Autopsy-Confirmed Alzheimer’s Disease.....	103
Chapter 5: Longitudinal Semantic Fluency Performance in Hispanic Older Adults in the Early Stages of AD.....	151
Chapter 6: Disucssion.....	192

LIST OF FIGURES

Figure 2.1: Computer screen display for the color-shape task (top-panel) and language-switching task (bottom panel). Top left and bottom left panels indicate the size of each feature.....	53
Figure 2.2: Mean RTs (ms) and proportion of error for single, stay, and switch trials in the cross-task comparison (collapsed across dominance within each task)...	54
Figure 2.3: Distribution of reaction times (ms) for naming numbers in the language task for older bilinguals who could not complete the color-shape task and matched controls.....	54
Figure 2.4: Mean RTs (ms) for single, stay, and switch trials for 12 bilinguals tested in a first testing session on the color-shape task with button-press responses, and the language-task with voice responses, and repeated testing on both tasks in a second testing session as well as a voice-response version of the color-shape task...	55
Figure 3.1: Cross-over interaction for semantic fluency total score and subcategories.....	102
Figure 4.1: Cognitive deficit scores of Hispanic and Non-Hispanic patients with Alzheimer's Disease across domains.....	150
Figure 5.1: Mean number of words generated (total across animals, fruits, and vegetables) by Hispanic and non-Hispanic decliners and normal controls on category fluency at the four annual evaluations (Years 1-4).....	188
Figure 5.2: The mean decline in the likelihood of generating weak items (i.e., items that were produced in Year 1 but not Year 2) relative to strong items (items produced in both Years 1 and 2) in Years 3 and 4 on the category fluency task for Hispanic and non-Hispanic decliner and control participants.....	189
Figure 5.3: The mean standard scores of the decline in the likelihood of generating weak items relative to strong items in Years 3 and 4 on the category fluency task for Hispanic and non-Hispanic decliners based on respective cultural control group.....	190
Figure 5.4: Comparison of category and letter fluency in young and older monolinguals and bilinguals; means were compiled from Rosselli et al. (2000) and Gollan et al. (2002).....	191

LIST OF TABLES

Table 2.1: Participant characteristics for young and older bilinguals who were able to complete both linguistic and non-linguistic switching tasks.....	49
Table 2.2: Mean and standard deviation by participant group and condition for the language task.....	50
Table 2.3: Mean and standard deviation by participant group and condition for the color-shape task.....	51
Table 2.4: Participant characteristics for older adults who could not complete the color-shape task and matched controls.....	52
Table 3.1: Participant demographics for non-Hispanic normal controls and decliners and Hispanic normal controls and decliners.....	99
Table 3.2: Means and standard deviations for participants on all neuropsychological measures.....	100
Table 4.1: Demographic Information and Measures of Cognitive and Functional Ability for Hispanic and Non-Hispanic NC Participants and Patients with AD.....	143
Table 4.2: Cardiovascular Health Measures for Hispanic and Non-Hispanic Participants at Year 1.....	144
Table 4.3: Brain Weight, Braak Stage, and Number of Plaques, Neuritic Plaques, and Neurofibrillary Tangles in Several Cortical Regions and the Hippocampus for Hispanics and Non-Hispanics with Autopsy-Confirmed AD.....	145
Table 4.4: Frequency of Vascular Neuropathology in Hispanics and Non-Hispanics with Autopsy-Confirmed Alzheimer's Disease.	146
Table 4.5: Scores achieved by Hispanic and Non-Hispanic patients with Alzheimer's Disease on neuropsychological tests in four cognitive domains. Scores are z-transformed based on respective normal control groups.	147
Table 4.6: Mean raw scores (and SDs) achieved by Hispanic and Non-Hispanic patients and normal control participants on all neuropsychological measures.....	148
Table 5.1: Participant demographics for non-Hispanic controls and decliners and Hispanic controls and decliners.....	186
Table 5.2: Language history for a subset of Hispanic controls and decliners.....	187

ACKNOWLEDGMENTS

I am thankful for this opportunity to acknowledge a group of individuals who have shaped who I am today, as a person, a student, and a developing researcher. First, I would like to acknowledge several pre-graduate mentors who have taught me invaluable skills necessary for graduate school. Thank you to Mr. Chamberlin, my 9th and 10th grade English teacher, for sharing his love of writing with all of his students, teaching me how to write a thesis, and teaching me to persevere even when writer's block afflicts. I would also like to acknowledge Dr. John Polich. His unwavering dedication to his students was always felt and his high expectations for me fueled my desire to pursue higher education. It is safe to say that without his unconditional guidance, I would not be where I am today.

I would like to acknowledge Professors Tamar H. Gollan and Mark W. Bondi for their support as my graduate advisers. Their guidance and commitment to my training has proved to be invaluable. They have taught me to think critically about research questions, write scientifically, and pursue innovative and important research projects. I still feel that I have a world of knowledge to learn from both of them, and thank them in advance for responding to future research-related emails.

I also extend my gratitude to Professor David P. Salmon for his guidance and for providing me with the opportunity to pursue research goals through the Alzheimer's Disease Research Center. I thank my other committee members, Drs. Paul Gilbert, Christina Wierenga, and May Yeh, for reading this long document and for their encouragement and expertise.

In addition, I thank all of the individuals who have helped with data collection and coding, especially Mayra Murillo, Reina Mizrahi, and Mario Attie.

Lastly, I would like to acknowledge my JDP friends and my lab mates, who have made San Diego my home away from home.

Chapter 2, in full, is a reprint of the material as it appears in: Weissberger, Gali H., Wierenga, Christina E., Bondi, Mark W., & Gollan, Tamar H. “Partially Overlapping Mechanisms of Language and Task Control in Young and Older Bilinguals”, *Psychology and Aging*, vol. 27, 2012. The dissertation author was the primary investigator and author of this material.

Chapter 3, in full, is a reprint of the material as it appears in: Weissberger, Gali H., Salmon, David P., Bondi, Mark W., & Gollan, Tamar H. “Which Neuropsychological Tests Predict Progression to Alzheimer’s Disease in Hispanics?”, *Neuropsychology*, vol. 27, 2013. The dissertation author was the primary investigator and author of this material.

Chapter 4, in part is currently being prepared for submission for publication of the material: Weissberger, Gali H., Gollan, Tamar H., Bondi, Mark W., Nation, Daniel A., Hansen, Lawrence A., Galasko, D., & Salmon, David P. “Neuropsychological and Neuropathological Profiles of Hispanic Older Adults with Autopsy-Confirmed Alzheimer’s Disease”. The dissertation author was the primary investigator and author of this material.

VITA

2008	Bachelor of Arts, University of California, San Diego
2011	Master of Science, San Diego State University
2015	Doctor of Philosophy, University of California, San Diego and San Diego State University

PUBLICATIONS

Weissberger, G. H., Gollan, T. H., Bondi, M. W., Clark, L. R., & Wierenga, C. E. (2015). Language and task switching in the bilingual brain: Bilinguals are staying, not switching, experts. *Neuropsychologia*, 66, 193-203.

Bangen, K. J., Nation, D. A., Delano-Wood, L., Weissberger, G. H., Hansen, L. A., Galasko, D. R., Salmon, D. P., & Bondi, M. W. (2014). Aggregate effects of vascular risk factors on cerebrovascular changes in autopsy-confirmed Alzheimer's disease. *Alzheimer's and Dementia*, 11, 394-403.

Weissberger, G. H., Salmon, D. P., Bondi, M. W., Gollan, T. H. (2013). Which neuropsychological tests predict progression to Alzheimer's disease in Hispanics? *Neuropsychology*, 27, 343-355.

Weissberger, G. H., Gollan, T. H., Wierenga, C. E., & Bondi, M. W. (2012). Partially overlapping mechanisms of language and task control in young and older bilinguals. *Psychology and Aging*, 27, 959-974.

Gollan, T. H., Weissberger, G. H., Runnqvist, E., Montoya, R. I., & Cera, C. M. (2012). Self- ratings of spoken language dominance: A Multi-Lingual Naming Test (MINT) and preliminary norms for young and aging Spanish-English bilinguals. *Bilingualism: Language and Cognition*, 15, 594-615.

Clark, L. R., Schiehser, D. M., Weissberger, G. H., Salmon, D. P., Delis, D. C., & Bondi, M. W. (2011). Specific measures of executive function predict cognitive decline in older adults. *Journal of the International Neuropsychological Society*, 18, 118-127.

ABSTRACT OF DISSERTATION

The Cognitive Effects of Alzheimer's Disease
in
Hispanic Older Adults

by

Gali Helena Weissberger

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2015
San Diego State University, 2015

Professor Tamar H. Gollan, Chair
Professor Mark W. Bondi, Co-Chair

Rationale. Differences in prevalence, age of onset, and mortality rates have been found between Hispanic and non-Hispanic older adults with Alzheimer's disease (AD). Examination of factors such as bilingualism and cultural differences in diagnostic measures is needed to improve understanding of how they may affect the diagnosis and progression of AD in Hispanic older adults. The proposed set of studies aims to elucidate the mechanisms underlying cognitive changes in Hispanics with AD.

Design. In Study 1, young and older Spanish-English bilinguals were tested on language-switching and non-linguistic color-shape-switching paradigms to identify age-

related changes in language control. Study 2 investigated which neuropsychological tests are predictive of progression to AD in Hispanics to better understand preclinical markers of AD in this cohort. Study 3 compared the neuropathological and neuropsychological profiles of Hispanic and non-Hispanic patients with autopsy-confirmed AD. A follow-up study (Study 4) examined four consecutive years of semantic fluency performance in a subset of decliners from Study 2 to investigate the consistency of semantic exemplar loss over time in both cultural groups.

Results. Study 1 revealed subtle parallels between executive control and language control, but also some differences suggesting that language control remains relatively sheltered from aging-related decline in executive control. In Study 2, many assessment measures revealed significant disadvantages in Hispanic controls, but nevertheless predicted AD in Hispanic decliners. Conversely, some tests were not sensitive to AD in Hispanic decliners. Unexpectedly, semantic fluency revealed a cross-over interaction: Hispanic controls generated fewer correct responses than non-Hispanics, whereas Hispanic decliners outperformed non-Hispanics. In Study 3, this semantic fluency pattern emerged across many neuropsychological measures. Hispanics with AD were also found to have less AD pathology but greater neurovascular pathology than non-Hispanics. In Study 4, Hispanic decliners outperformed non-Hispanics across four years of category fluency, but groups did not differ in consistency of semantic exemplar loss.

Conclusions. Findings highlight the importance of a comprehensive approach to understanding the cognitive effects of AD in Hispanics. Together, the studies provide preliminary evidence that factors such as bilingualism, vascular risk, and sociological

issues may complicate interpretation of neuropsychological profiles and diagnosis of AD in Hispanics.

CHAPTER 1: GENERAL INTRODUCTION

Alzheimer's disease (AD) is one of the leading causes of death in the United States and AD is currently estimated to afflict 5.4 million Americans. Furthermore, the prevalence of AD is expected to increase to 11 to 16 million by the year 2050. Health care costs related to AD in the year 2012 alone are expected to be \$200 billion (Alzheimer's Association Report, 2012). Along with the growing prevalence rate of AD in older adults is a growing minority population in the United States (Census, 2010). Specifically, the population of Hispanic older adults is projected to be 11 times greater by the year 2050 (cf. Manly & Mayeux, 2004) and according to the 2007 American Community Survey, English-Spanish bilinguals represent more than half of bilinguals in the United States (Shin & Kominski, 2010). In addition, studies report an increased rate of AD in Hispanic older adults relative to non-Hispanic older adults (Alzheimer's Association Report, 2012; Demirovic et al., 2003; Gurland et al., 1999; Manly & Mayeux, 2004; Tang et al., 2001) and there is growing evidence that many Hispanic older adults are under- or misdiagnosed with AD (e.g., Fitten, Ortiz, & Potón, 2001).

To date, research of AD with Hispanic older adults has focused on differences in prevalence rates, age of diagnosis, and mortality rates relative to non-Hispanic older adults. Specifically, studies report an increased rate of AD in Hispanic older adults (e.g., Alzheimer's Association Report, 2012) and several studies report an earlier age of onset of AD in Hispanic older adults compared with non-Hispanics after adjusting for education (Clark et al., 2005; Gurland et al., 1999; Harwood et al., 2004; 2010; Livney et al., 2011; also see Ringman and Flores, 2005). In contrast, several studies have found no difference in the age of onset of AD in Hispanics and non-Hispanics (Duara et al., 1996;

Kwon, Khaleeq, Chan, Pavlik, and Doody, 2010). Complicating these findings is the fact that while Hispanic culture has been associated with earlier age of onset of AD, bilingualism has been associated with a delayed age of onset (Bialystok, Craik, & Freedman, 2007; Craik, Bialystok, & Freedman, 2010). More recent work reveals bilingualism and education level to be interacting predictors of age of onset in Hispanics, with increasing degrees of bilingualism delaying diagnosis of AD in Hispanics with low-education but not in those with high-education (Gollan, Salmon, Montoya, & Galasko, 2011).

Despite evidence of higher prevalence rates and earlier age of onset of AD in Hispanic older adults, some studies report longer survival rates in Hispanics with AD compared to non-Hispanics (Cosentino, Scarmeas, Albert, and Stern, 2006; Helzner, Scarmeas, Cosentino, Tang, Schupf & Stern, 2008; Mehta et al., 2008; Waring, Doody, Pavlik, Massman, and Chan, 2005). One study reported a 72% higher mortality rate in white non-Hispanics relative to Hispanics (Steenland, MacNeil, Vega, & Levey, 2009). As is the case with age of onset, bilingualism may also play a role in influencing differences in mortality rates. Specifically, research suggests that bilingualism may actually serve as a form of “cognitive reserve” and studies have found increased white matter integrity in bilinguals and decreased cognitive impairment in the context of greater atrophy in bilinguals relative to monolingual older adults with AD (e.g., Luk, Bialystok, Craik, and Grady, 2011; Schweizer, Ware, Fischer, Craik, & Bialystok, 2011).

Despite these findings, few studies have investigated mediating factors (e.g., bilingualism, test bias) that may impact prevalence, age of onset, and mortality rates in Hispanic older adults. Ringman and Flores (2005) suggest that idiosyncrasies within the

Hispanic population may influence the age of onset of AD in Hispanic older adults.

Whether the above-mentioned findings are due to biological factors or factors unrelated to pathological processes of AD, understanding the nature of such findings will both improve our understanding of AD within the Hispanic population as well as our understanding of AD more generally.

The goal of the proposed set of studies is to elucidate the cognitive effects of AD and improve diagnosis of AD in Hispanic older adults by considering factors that may influence diagnosis and progression of AD in Hispanic older adults. The first study takes an experimental approach in order to investigate the impact of bilingualism on aging. The second study attempts to identify neuropsychological assessments that are culturally biased and make predictions regarding which tests will be able to detect preclinical AD in Hispanic older adults. The third study investigates the neuropsychological and neuropathological profiles of Hispanic older adults who have autopsy-confirmed Alzheimer's disease. Finally, follow-up studies were conducted to expand upon findings of the three studies in an attempt to elucidate the process of semantic degradation in bilingual Hispanic older adults with AD. Together the studies aim to identify factors that may influence progression of AD in Hispanic older adults.

References

- Alzheimer's Association (2012). Alzheimer's association report: 2012 Alzheimer's disease facts and figures. *Alzheimer's and Dementia*, 8, 131-168.
- Bialystok, E., Craik, F. I. M., & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia*, 45, 459-464.
- Clark, C. M., DeCarli, C., Mungas, D., Chui, H. I., Higdon, R., Nuñez, J., . . . van Belle, G. (2005). Earlier onset of Alzheimer disease symptoms in Latino individuals compared with Anglo individuals. *Archives of Neurology*, 62, 774-778.
- Consentino, S., Scarmeas, N., Albert, S. M., & Stern, Y. (2006). Verbal fluency predicts mortality in Alzheimer's disease. *Cognitive and Behavioral Neurology*, 19, 123-129.
- Craik, F. I. M., Bialystok, E., & Freedman, M. (2010). Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve. *Neurology*, 75, 1726-1729.
- Demirovic, J., Prineas, R., Loewenstein, D., Bean, J., Duara, R., Sevush, S., & Szapocznik, J. (2003). Prevalence of dementia in three ethnic groups: The south Florida program on aging and health. *Annals of Epidemiology*, 13, 472-478.
- Duara, R., Barker, W. W., Lopez-Alberola, R., Loewenstein, D. A., Grau, L. B., Gilchrist, D., . . . St. George-Hyslop, P. H. (1996). Alzheimer's disease: Interaction of apolipoprotein E genotype, family history of dementia, gender, education, ethnicity, and age of onset. *Neurology*, 46, 1575-1579.
- Fitten, Ortiz, & Pontón (2001). Frequency of Alzheimer's disease and other dementias in a community outreach sample of Hispanics. *Journal of the American Geriatrics Society*, 49, 1301-1308.
- Gollan, T. H., Salmon, D.P., Montoya, R.I., & Galasko, D.R. (2011). Degree of Bilingualism Predicts Age of Diagnosis of Alzheimer's Disease in Low-Education but not in Highly-Educated Hispanics, *Neuropsychologia*, 49, 3826-3830.
- Gurland, B. J., Wilder, D. E., Lantigua, R., Stern, Y., Chen, J., Killeffer, E. H., & Mayeux, R. (1999). Rates of dementia in three ethnoracial groups. *International Journal of Geriatric Psychiatry*, 14, 481-493.
- Harwood, D. G., Barker, W. W., Ownby, R. L., St. George-Hyslop, P., Mullan, M., & Duara, R. (2004). Apolipoprotein E polymorphism and age of onset for Alzheimer's disease in a bi-ethnic sample. *International Psychogeriatrics*, 16, 317-326.

- Harwood, D. G., Kalechstein, A., Barker, W. W., Strauman, S., St. George-Hyslop, P., Iglesias, C.,..., Duara, R. (2010). The effect of alcohol and tobacco consumption and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 25, 511-518.
- Helzner, E. P., Scarmeas, N., Cosentino, S., Tang, M. X., Schupf, N., & Stern, Y. (2008). Survival in Alzheimer's disease: A multiethnic, population-based study of incident cases. *Neurology*, 71, 1489-1495.
- Kwon, O. D., Khaleeq, A., Chan, W., Pavlik, V. N., & Doody, R. S. (2010). Apolipoprotein E polymorphism and age at onset of Alzheimer's disease in a quadriethnic sample. *Dementia and Geriatric Cognitive Disorders*, 30, 486-491.
- Livney, M. G., Clark, C. M., Karlawish, J. H., Cartmell, S., Negrón, M., Nuñez-Lopez, J.,...Arnold, S. E. (2011). Ethnoracial differences in the clinical characteristics of Alzheimer's disease at initial presentation at an urban Alzheimer's disease center. *American Journal of Geriatric Psychiatry*, 19, 430-439.
- Luk, G., Bialystok, E., Craik, F. I. M., & Grady, C. L. (2011). Lifelong bilingualism maintains white matter integrity in older adults. *The Journal of Neuroscience*, 31, 16808-16813.
- Manly J. J., Mayeux R. Ethnic differences in dementia and Alzheimer's disease. In: Anderson N, Bulatao R, Cohen B, eds. *Critical Perspectives on Racial and Ethnic Differentials in Health in Late Life*. Washington, DC: National Academies Press; 2004. p. 95-141.
- Mehta, K. M., Yaffe, K., Pérez-Stable, E. J., Stewart, A., Barnes, D., Kurland, B. F., & Miller, B. L. (2008). Race/ethnic differences in AD survival in US Alzheimer's disease centers. *Neurology*, 70, 1163-1170.
- Ringman, J. M., & Flores, D. L. (2005). Effects of Alzheimer's onset in Latino persons: Ethnic differences vs. selection bias. *Archives of Neurology*, 62, 1786-1787.
- Schweizer, T. A., Ware, J., Fischer, C. E., Craik, F. I. M., & Bialystok, E. (2011). Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease. *Cortex*, 48, 991-996.
- Shin, H. B., & Kominski, R. A. (2010). Language use in the United States: 2007. *American Community Survey Reports, ACS-12*, U.S. Census Bureau, Washington, D.C.
- Steenland, MacNeil, Vega, & Levey (2009). Recent trends in Alzheimer's disease mortality in the United States, 1999-2004. *Alzheimer's Disease and Associated Disorders*, 23, 165-170.

Tang, M. -X., Cross, P., Andrews, H., Jacobs, D. M., Small, S., Bell, K.,..., Mayeux, R. (2001). Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*, 56, 49-56.

US Census Bureau. Available at: [http:// www.census.gov](http://www.census.gov). Accessed 2010.

Waring, S. C., Doody, R. S., Pavlik, V. N., Massman, P. J., & Chan, W. (2005). Survival among patients with dementia from a large multi-ethnic population. *Alzheimer's Disease and Associated Disorders*, 19, 178-183.

CHAPTER 2: PARTIALLY OVER-LAPPING MECHANISMS OF LANGUAGE AND TASK CONTROL IN YOUNG AND OLDER BILINGUALS

Gali H. Weissberger¹, Christina E. Wierenga^{3,2}, Mark W. Bondi^{2,3} & Tamar H. Gollan²

¹ San Diego State University and University of California, San Diego Joint Doctoral
Program

in Clinical Psychology

² Department of Psychiatry, University of California San Diego

³ VA San Diego Healthcare System

Author's Note: This research was supported by NIH (NIDCD 011492, NICHD 050287 and 051030, and NIA P50, AG05131). We would like to thank Dan Kleinman for his help in programming the computer tasks.

Address for correspondence:

Tamar H. Gollan
Department of Psychiatry
University of California, San Diego
9500 Gilman Drive, 0948
La Jolla, CA 92093-0948
e-mail: tgollan@ucsd.edu

Abstract

The current study tested the hypothesis that bilinguals rely on domain-general mechanisms of executive control to achieve language control by asking if linguistic and non-linguistic switching tasks exhibit similar patterns of aging-related decline. Thirty young and thirty aging bilinguals completed a cued language-switching task, and a cued color-shape switching task. Both tasks demonstrated significant aging effects, but age-related slowing, and the aging-related increase in errors, were significantly larger on the color-shape than on the language task. In the language-task, aging increased language-switching costs in both response times (RTs) and errors, and language-mixing costs only in RTs. In contrast, the color-shape task exhibited an aging-related increase in costs only in mixing errors. Additionally, a subset of the older bilinguals could not do the color-shape task, but were able to do the language task, and exhibited significantly larger language-switching costs than matched controls. These differences, and some subtle similarities, in aging effects observed across tasks imply that mechanisms of non-linguistic task and language control are only partly shared, and demonstrate relatively preserved language control in aging. More broadly, these data suggest that age-deficits in switching and mixing costs may depend on task expertise - with mixing deficits emerging for less practiced tasks, and switching deficits for highly practiced, possibly “expert” tasks (i.e., language).

Introduction

A remarkable feature of bilingualism is the ability to fluently switch between languages when conversing in natural contexts. From an observer’s perspective bilinguals do this without difficulty. Exactly how bilinguals manage to select the right language at

the right time, while avoiding interference from the non-target language, has been a much-debated topic in the current literature on bilingualism. However, there is an emerging consensus that bilingual language control is achieved at least in part by reliance on domain-general mechanisms of executive control (Abutalebi & Green, 2007; Gollan & Ferreira, 2009; for review, Bialystok, Craik, Green, & Gollan, 2009; Hernandez, 2009). The goal of the present study was to test this hypothesis by comparing age-related changes in linguistic and non-linguistic switching. A secondary goal was to reveal mechanisms fundamental to bilingual language control, and to better characterize age-related changes therein.

Aging bilinguals offer an opportunity to test the role of domain-general control in bilingual language control because the ability to shift between tasks has been shown to decline with increased age (for review see Mayr & Liebscher, 2001). Although bilingualism may protect against some aspects of age-related decline in executive control ability, comparisons of young to older bilinguals reveal substantial age-related decline in non-linguistic executive control even for bilinguals (e.g., in the Simon task; Bialystok et al., 2004)). Thus, unless bilinguals are equipped with specialized mechanisms for language control that are sheltered from age-related decline in domain-general executive control, bilinguals should exhibit parallel age-related changes in linguistic and non-linguistic switching.

Gollan, Sandoval, & Salmon (2011) examined the association between linguistic and non-linguistic control in aging bilinguals with a flanker task and verbal fluency tests. Against the hypothesis of shared control mechanisms for linguistic and non-linguistic tasks, the rate of cross-language intrusion errors was very low (1% on average, and only

3% at most), even in aging bilinguals with deficits in executive control. More specifically, aging bilinguals who made over 50% errors on incongruent trials of the flanker task (and one who could not do the task at all), exhibited little to no difficulty achieving language control. This relative preservation of language control in the face of obvious difficulty with executive control implies the presence of powerful domain-specific mechanisms of language control that are largely independent of general executive control mechanisms. However, this same study also provided evidence that supports the notion of at least partially overlapping control mechanisms for language and non-linguistic control; that is, (a) cross-language intrusion errors increased with aging, and (b) older bilinguals exhibited a highly robust correlation between errors on the flanker task and cross-language intrusion errors in the verbal fluency task.

Other support for the notion that domain-general control mechanisms are used to achieve bilingual language control comes from a growing literature documenting bilingual advantages on non-linguistic tasks of executive function. For example, bilinguals were faster to resolve response conflict in the Simon Task (Bialystok, Craik, Klein, & Viswanathan, 2004), and in the Attentional Network Task (Costa, Hernández, Costa-Faidella, & Sebastián-Gallés, 2009; Costa, Hernández, Sebastián-Gallés, 2008), and exhibited smaller Stroop interference effects (e.g., Bialystok, Craik, & Luk, 2008), when compared with matched monolinguals. Another recent study provided evidence of an explicit connection between language switching and non-linguistic task switching. Prior and Gollan (2011) tested participants on a language-switching task in which they switched between naming numbers 1-9 in their first language (L1) and second language (L2), and a non-linguistic task in which they switched between making color and shape

judgments (a task that previously revealed more efficient switching in bilinguals than in monolinguals; Prior and MacWhinney, 2010). In addition to monolinguals, two types of bilinguals were tested: Spanish-English bilinguals who reported switching languages often in daily life, and Mandarin-English bilinguals who reported switching languages significantly less often than the Spanish-English group. The bilingual advantage for task-switching was replicated only in the Spanish-English group, and Spanish-English bilinguals also exhibited smaller language-switching costs than Mandarin-English bilinguals. Both results illustrate an explicit connection between bilingual language use and general switching ability (hence the title of the paper “Good Language Switchers are Good Task Switchers”), and imply that the ability to flexibly shift mental sets is enhanced by a bilingual’s lifelong experience in switching between languages.

Another way to investigate the hypothesis that executive control abilities underlie language control is through direct comparisons of aging effects across non-linguistic and linguistic switching paradigms. An important distinction for understanding previously reported aging effects on task shifting is between switching and mixing costs. In single-task blocks participants perform just one task. In mixed-task blocks participants are cued to switch between tasks on some proportion of trials. Within these paradigms there are three types of trials, including switch trials in mixed-task blocks, non-switch trials in mixed task blocks (stay trials), and responses in single task blocks. Contrasting the three types of trials, two types of costs can be considered. *Switching* costs reflect the increase in RTs (response times) on switch versus non-switch trials within the mixed-task block. *Mixing* costs reflect a different increase in RTs that can be seen when comparing non-switch trials in the mixed-task block to responses in a single-task block (which are

necessarily non-switch trials because in single-task blocks individuals perform just one task). The costs associated with mixing have been proposed to reflect global sustained control mechanisms that are needed on non-switch trials in a mixed block to maintain two competing task goals available for response, monitor task cues, and keep track of which task must be completed (Braver, Reynolds, & Donaldson, 2003; Koch, Prinz, & Allport, 2005; Rubin & Meiran, 2005). In contrast, switching costs have been described as reflecting transient control mechanisms that are needed to select the correct task on any given trial (Braver et al., 2003; Mayr & Kliegl, 2000, 2003).

Recent reviews of aging effects on task shifting reveal robust deficits in mixing but relatively intact task-switching abilities in older age (Kray & Lindenberger, 2000; Mayr & Liebscher, 2001; Reimers & Maylor, 2005; Verhaeghen & Cerella, 2002; for meta-analysis see Wasylyshyn, Verhaeghen, & Sliwinski, 2011). Such findings suggest that age-deficits may be circumscribed to the maintenance of two task sets, possibly reflecting working memory deficits, and implying preserved processes of selective attention associated with local switching costs (Wasylyshyn et al., 2011). However, some individual studies have also identified age-deficits in task switching. For example, Meiran, Gotler, and Perlman (2001) found an age-related increase in both mixing and switching costs in a cued-switching task requiring monolinguals to switch between indicating if a stimulus was in the left/right or up/down position of a grid. In addition, Kray, Li, and Lindenberger (2002) found a greater age-related deficit in switching than mixing under conditions of greater task uncertainty (using 4 tasks instead of just 2). A different study by the same investigators found the opposite pattern (a larger age-deficit in mixing than in switching) in a paradigm using predictable task sequences (instead of

task cues; Kray & Lindenberger, 2000). Kray et al. (2002) suggested that task-cues reduce task uncertainty and reduce age-related differences associated with mixing costs. Thus, the presence or absence of aging deficits, and the nature of the deficit, can vary substantially with small changes in methodology that influence which underlying cognitive processes are involved.

In contrast to the breadth of literature on aging effects in task switching and mixing, relatively little is known about aging effects on language switching. Hernandez and Kohnert (1999) compared a group of older Spanish-English bilinguals to college-aged bilinguals in a picture-naming task with cued language switching. Older bilinguals made more errors and were slower to respond particularly in the mixed-language blocks. Particularly robust in this study was an age-related increase in failures to switch when cued to do so. In contrast, there were little to no differences between young and older bilinguals in RTs and errors in the blocked conditions in which pictures were named in one or the other language (though there was a trend in the direction of age-related slowing; $p < .06$). One limitation of this study is that the mixing and switching costs were not differentiated (stay and switch trials were not considered separately in analyses of responses in the mixed-language blocks).

One additional study investigated aging effects on language switching. Gollan and Ferreira (2009) distinguished between switching and mixing costs in a voluntary language switching paradigm with young and older Spanish-English bilinguals. In this study, bilinguals were given the option to switch between languages or not on each trial using “whichever language comes to mind” in the mixed blocks. With these task demands there was no age-related increase in the magnitude of voluntary language

mixing costs, but there was a small but significant age-related increase in voluntary switching costs. The age-related increase in voluntary language switching but not mixing costs again differs from the more typical result in the monolingual task-switching literature (which, as reviewed above, more often exhibits age-related increases in mixing rather than switching costs). This raises the question of whether age-related deficits might be found for cued language-mixing, or if something specific to language makes switching more vulnerable than mixing in older age whether cued or voluntary.

In the current study we compared aging effects on cued non-linguistic and linguistic mixing and switching. Similarities in age deficits across tasks would support the notion of domain-general control mechanisms that subserve language control. Conversely, dissociations in aging effects across tasks would imply limitations on the extent to which language control relies on a general executive system, and might reveal unique mechanisms underlying bilingual language control. For this purpose we examined aging effects on a non-linguistic switching task that previously revealed a bilingual switching advantage (Prior & MacWhinney, 2010), and an explicit relationship with language switching (Prior & Gollan, 2011).

To date, no study has contrasted aging effects on cued language switching with mixing. Based on results reported for aging effects on voluntary language switching (Gollan & Ferreira, 2009), and high error rates on switch trials for aging bilinguals in a study of cued-language switching (Hernandez & Kohnert, 1999), we predicted a significant age-related increase in cued language switching costs. With respect to mixing costs, Gollan and Ferreira (2009) observed no aging deficit in voluntary language mixing and concluded that age-related mixing deficits reflect processing mechanisms associated

with cue-driven language selection (for related discussion see Mayr & Liebscher, 2001).

If so, an age-related increase in cued-language mixing costs should be observed. An alternative possibility is that aging bilinguals may be less vulnerable to mixing deficits in general, or more specifically that aging does not affect language mixing, in which case no mixing deficit would be observed even in a cued paradigm.

For the color-shape task, aging bilinguals might show robust switching deficits, as aging bilinguals exhibited in language-switching. This would suggest that switching rather than mixing is vulnerable in aging for bilinguals, and would support the notion of shared mechanisms of non-linguistic and linguistic control. Alternatively, aging bilinguals might show more robust mixing deficits in the non-linguistic task, as has previously been reported in the aging literature on task switching in monolinguals. This would suggest that age-related switching deficits are specific to bilingual language control, and would imply some degree of independence for mechanisms of non-linguistic and linguistic control.

Method

Participants

Thirty young bilinguals (22 women) were recruited from the University of California, San Diego (UCSD) and participated in the study for course credit. Thirty older bilinguals (21 women) were recruited from a cohort of healthy control participants at the UCSD Alzheimer's Disease Research Center (ADRC) and from the San Diego community. Eighteen older bilinguals were diagnosed as cognitively intact by two senior staff neurologists using criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and

Related Disorders Association (ADRDA; McKhann, et al., 1984) and based on medical, neurological, and neuropsychological evaluations and a number of laboratory tests (to rule out dementia). Twelve additional aging bilinguals were recruited from the San Diego area and were classified as cognitively intact based on high levels of reported independent functioning in daily life and Dementia Rating Scale scores (DRS; Mattis, 1988).

Bilinguals' responses in each language in the language-switching task were assigned as dominant or non-dominant based on their ability to name pictures in English and in Spanish on the Multilingual Naming Test (MINT; Gollan, Weissberger, Runnqvist, Montoya, & Cera, in press). The MINT includes 68 black and white line drawings that are presented in order of estimated increasing difficulty. Bilinguals who named more pictures correctly in Spanish than in English on the MINT were classified as Spanish-dominant (7 older adults and 7 young adults), and those who named more pictures correctly in English than in Spanish were classified as English-dominant (15 older adults and 23 young adults; these numbers of older bilinguals sum to the 22 older bilinguals included in the primary analyses below). No bilingual had identical naming scores in English and Spanish.

Matching. Participant characteristics and statistics for the difference between young and older bilinguals are presented in Table 2.1. Young and older bilinguals were matched for education level, and bilingual language proficiency as measured by the MINT in both Spanish and English. In addition, young and older bilinguals did not differ in the extent of language dominance (dominance was determined by subtracting Spanish from English MINT index scores).

Materials and Procedure

Participants signed consent forms and completed a Language History Questionnaire at the start of the testing session. Older bilinguals not recruited through the ADRC were tested on the Dementia Rating Scale (DRS; Mattis 1988) and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) in their self-reported dominant language. For ADRC participants, test scores were obtained from their most recent annual testing at the ADRC.

Participants were tested with the MINT in both English and Spanish, with language of testing in counterbalanced order (first or second) between participants. After administration of the MINT, the color-shape and language switching paradigms were administered in counterbalanced order. The language and color-shape tasks were the same as those used by Prior and Gollan (2011) with two modifications. First, we reduced the number of trials to 20 trials per block (after reanalysis of those data which revealed substantial power even with the reduced number of trials). Second, the button mappings for the color-shape task appeared directly on the computer screen (instead of as an overlay on the button box). An example of the display in the two tasks is shown in Figure 2.1. Following Rubin and Meiran (2005) we used a sandwich design such that participants completed 2 single-task blocks, 4 mixed-task blocks, followed by 2 more single-task blocks for each trial type in each task (e.g., color-shape and language). Within each task the order of English versus Spanish, and color versus shape, was counterbalanced for the single-task blocks. In the color-shape task, participants were cued to judge color with a rainbow patch, and shape with a series of black shapes, and were instructed to respond with a different button press for each color (red, green) and shape

(triangle, circle). In the language task, participants named numbers in English or Spanish based on a cue (American flag for English, and Mexican flag for Spanish). Each trial was preceded by a fixation point that lasted for 500 ms. The fixation point was replaced by a cue that appeared on the screen throughout the remainder of the trial, after which the stimuli appeared alongside the cue. After a delay of 750 ms, another fixation point appeared for 1750 ms, after which it was replaced by the stimulus. The cue and stimuli (and in the color-shape task also the button mappings legend) remained on the screen until the subject responded or 2000 ms passed. At the end of each 20-trial block, a fixation point appeared on the screen for a prolonged period (5 seconds). Preceding each run, the subject was presented with brief instructions prompting them to “Press any button to begin”.

Participants first completed practice trials with feedback (12 single, and 16 mixed responses in each task). After pilot testing, an “easy practice” block was created to accommodate older bilinguals who could not complete the practice trials accurately. The easy version did not impose a response deadline (i.e., did not shift the target stimulus until the participant responded) and also provided feedback. Participants who were unable to complete the regular practice trials with 80% accuracy were tested on the easy practice trials and then retested on the regular practice block again. Participants who could not complete the regular practice trials with 80% accuracy or better after three attempts were excluded from analysis (see below).

In the language switching task, all young and older bilinguals completed practice trials accurately and proceeded immediately to the experimental task (and there was no need to create an easy version of practice trials for the language task). In the color-shape

task, all young bilinguals completed one run through regular practice trials; task-switching proved to be more difficult for older adults who averaged 1.25 (range 1-3 runs) on regular practice trials and 0.5 (range 0-2 runs) on the easy version.

Results

Eight (5 women) of the 30 older adult bilinguals were excluded from analyses. Five (16.7%) of these were excluded because they were unable to do the color-shape task despite repeated attempts at the practice trials. Of interest, all five of these bilinguals were able to complete the language switching task and the language-switching data for these five participants are reported in a separate analysis below. Another older bilingual was unable to complete the color-shape task due to arthritis and associated difficulty with button presses, and two more were excluded from analysis because of low education level (6 and 9 years) and resulting lack of education-matched young bilingual controls at UCSD. All young bilinguals were able to complete both tasks.

Response times (RTs) for incorrect responses were excluded from analyses. Outlier RTs were trimmed for individual participants by calculating a mean RT across all trials and excluding any response deviating by more than 3 SDs of the mean. This procedure eliminated 1.9% of the language task data for both older and young bilinguals. In addition, 2.1% of the color-shape task data were eliminated for young bilinguals and 1.5% of the color-shape task data were eliminated for older bilinguals.

For both language and color-shape tasks we report separate analyses of mixing costs which contrast non-switch (stay) trials within mixed-task blocks with non-switch (single) trials in single-task blocks, and switching costs which contrast stay (non-switch) with switch trials in mixed-task blocks. Direct comparisons of the two tasks (again

separated by switching and mixing effects) are reported after analyses separated by task.

To determine whether older bilinguals have a harder time with language mixing and switching, we conducted 2 x 2 ANOVAs with age as a between subject variable (young, older), and trial type (single versus stay for the mixing analyses, and stay versus switch for the switching analyses) as within subject variables. Initially we also conducted 2 x 2 x 2 ANOVAs adding language dominance (dominant, non-dominant) as another repeated measures factor. However, with one exception¹, none of the two- or three-way interactions with language-dominance were significant; therefore, for ease of exposition we excluded the dominance factor in reporting our results, although Table 2.2 shows the results separated by language-dominance.

Language Mixing

RTs. Older bilinguals responded more slowly than young bilinguals, ($F(1,50)=11.14$, $MSE=19,895$, $\eta_p^2=.18$, $p<.01$), and participants responded more quickly in the single-task blocks than on stay trials in the mixed block, ($F(1,50)=70.19$, $MSE=2,318$, $\eta_p^2=.58$, $p<.01$). Of interest, older bilinguals exhibited significantly larger cued language mixing costs than younger bilinguals, although this interaction between age group and mixing costs was not especially robust, and just reached significance, ($F(1,50)=3.89$, $MSE=2,318$, $\eta_p^2=.07$, $p=.05$).

Errors. Error rates in the single task block and on stay trials in the mixed language blocks were very low in both young and older bilinguals. Older bilinguals did not make more errors than young bilinguals ($F<1$), participants made fewer errors in the single-language blocks than on stay trials in the mixed block, ($F(1,50)=7.46$, $MSE=.0002$, $\eta_p^2=.13$, $p=.01$), and unlike the RTs analysis, there was no indication of a mixing cost

increase for older relative to younger bilinguals, ($F(1,50)=2.16$, $MSE=.0002$, $\eta_p^2=.04$, $p=.15$).

Language Switching.

RTs. Older bilinguals responded more slowly than young bilinguals, ($F(1,50)=11.87$, $MSE=34,121$, $\eta_p^2=.19$, $p<.01$), and participants responded more slowly on switch than on stay trials, ($F(1,50)=113.31$, $MSE=975$, $\eta_p^2=.69$, $p<.01$). Of interest, older bilinguals exhibited significantly larger cued language switching costs than young bilinguals, a significant interaction between age-group and trial type, ($F(1,50)=5.12$, $MSE=975$, $\eta_p^2=.09$, $p=.03$).

Errors. Error analyses parallel the RT findings. Older bilinguals made more errors than young bilinguals, ($F(1,50)=6.83$, $MSE=.004$, $\eta_p^2=.12$, $p=.01$), and participants made more errors on switch than on stay trials, ($F(1,50)=36.414$, $p<.001$, $MSE=.003$, $\eta_p^2=.42$). The age-related increase in error rates was especially striking on switch trials; a significant interaction between age and switch costs, ($F(1,50)=6.18$, $MSE=.003$, $\eta_p^2=.11$, $p=.02$).

Language-task Adjustment for Baseline Speed. A question of interest, given that older bilinguals named numbers more slowly than young bilinguals, was whether the age-related increase in costs would be significant after adjusting for age-related slowing. For this analysis we calculated proportional mixing and switching costs by dividing mix costs by single-block trial RTs and switch costs by stay trial RTs respectively, and then submitted the means to a 2 x 2 ANOVA with age as a between subject variable (young, older), and cost type (percent mix cost, percent switch cost) as within subject variables. This analysis revealed a significant main effect of age; thus the age-related increase in

costs (collapsed across switching and mixing) survived an adjustment for baseline speed ($F(1,50)=4.23$, $MSE=.007$, $\eta_p^2=.08$, $p=.045$).

Language-task Comparison of Age Effects on Switching and Mixing.

The analyses to this point revealed age-related increases in both language switching and mixing costs. Unlike previous studies of aging effects on non-linguistic task switching (in which age deficits in mixing were more robust than age deficits in switching), in the above results, the effect size for the age-deficit in language switching ($\eta_p^2=.09$) was larger than for language mixing ($\eta_p^2=.07$), and switching but not mixing also revealed an age related increase in the errors analysis. To directly compare age deficits in language switching and mixing, we calculated switch and mix costs for each participant and submitted these values to 2 x 2 ANOVAs with age (young, old) as a non-repeated factor, and cost type (switch, mix) as a repeated factor. In the analysis of RTs, there was no indication that aging differentially affected switch and mix costs (the interaction between age and cost type did not approach significance, $F<1$). However, the analysis of errors, produced a trend towards stronger aging effects on language-switching than on language-mixing, ($F(1,50)= 3.29$, $MSE=.002$, $\eta_p^2=.06$, $p=.08$).

Summary of Language-task Results: Aging bilinguals exhibited significantly larger switching and mixing costs in RTs, and the age-related switch cost deficit was also highly robust in error rates. The age-related increase in costs survived an adjustment for baseline speed differences across age groups, and aging deficits in language control were not stronger for mixing than for switching. These results distinguish aging effects on language control from previously observed aging effects on non-linguistic task control in which aging seemed to affect mixing more than switching (e.g., Wasylyshyn et al., 2011).

Instead, if anything, age deficits on language control exhibited some trends in the opposite direction (more robust switching than mixing deficits, as previously reported for voluntary language switching in Gollan & Ferreira, 2009). The analyses in the next section will be informative as to whether mechanisms specific to language control or to bilingualism in general are critical in producing this difference.

To determine whether aging bilinguals have more difficulty with non-linguistic task control, we conducted a 2 x 2 ANOVA with age as a between subject variable (young, older), and trial type (single versus stay for the mixing analyses, and stay versus switch for the switching analyses) as a within subject variables. Initially we also conducted 2 x 2 x 2 ANOVAs adding decision type (color, shape) as another repeated measures factor. However, with one exception², none of the two- or three-way interactions with decision type were significant; therefore, for ease of exposition we excluded decision type as a factor in reporting our results, although Table 2.3 shows the results separated by decision type.

Color-Shape Mixing

RTs. Older bilinguals responded more slowly than young bilinguals, ($F(1,50)=51.89$, $MSE=30,649$, $\eta_p^2=.51$, $p<.01$), and participants responded more quickly in the single-task blocks than on stay trials in the mixed block, ($F(1,50)=35.87$, $MSE=3,561$, $\eta_p^2=.42$, $p<.01$). Unlike the language-mixing results which exhibited a significant age-related increase in mixing costs, in the color-shape task, there was no age-related increase in mixing costs, ($F(1,50)=1.04$, $MSE=3,561$, $\eta_p^2=.02$, $p=.31$).

Errors. Although the RTs did not exhibit an age-related increase in mixing costs, a robust age-related mixing deficit appeared in the error rates. Older bilinguals made

more errors than young adult bilinguals, ($F(1,50)=9.26$, $MSE=.005$, $\eta_p^2=.16$, $p<.01$), and participants made more errors on stay trials in the mixed block than in the single task blocks, ($F(1,50)=34.89$, $MSE=.001$, $\eta_p^2=.41$, $p<.01$). In addition, there was a significant interaction between trial type and age group, such that older bilinguals made significantly more errors than young bilinguals, particularly on stay trials in the mixed block, ($F(1,50)=8.76$, $MSE=.001$, $\eta_p^2=.15$, $p=.01$).

Color-Shape Switching

RTs. Older bilinguals responded more slowly than young bilinguals, ($F(1,50)=39.63$, $MSE=47,952$, $\eta_p^2=.44$, $p<.01$), and participants responded more slowly on switch than on stay trials, ($F(1,50)=48.48$, $MSE=1,813$, $\eta_p^2=.49$, $p<.01$). Unlike the language-switching results, there was no indication of an age-related increase in switch-costs; the interaction between age and trial type was not significant, ($F(1,50)=1.76$, $MSE=1,813$, $\eta_p^2=.03$, $p=.19$).

Errors. Error analyses parallel the RT findings. Older bilinguals made more errors than young bilinguals, ($F(1,50)=12.88$, $MSE=.01$, $\eta_p^2=.21$, $p<.01$), and participants made more errors on switch than on stay trials, ($F(1,50)=17.93$, $MSE=.002$, $\eta_p^2=.26$, $p<.01$), but the interaction between age and trial type was not significant, ($F(1,50)=2.03$, $MSE=.002$, $\eta_p^2=.04$, $p=.16$).

Summary of Color-Shape Task Results. The pattern of aging deficits in the color-shape task was quite different from that seen in the language task. Although older bilinguals responded more slowly than young bilinguals in both tasks, only the language task exhibited robust age-related increases in switching and mixing costs in RTs, and a robust age-related increase in switching costs in the error rates. Conversely, in the color-

shape task, there was no age-related increase in costs in RTs, and only mixing errors exhibited an age-related increase in costs. In addition, aging deficits seemed to be more pronounced for the color-shape task compared to the language control task suggesting a relative preservation of language compared to nonlinguistic tasks in aging. For example, in the color-shape task, age-related slowing was significant across all three trial types (single, stay, and switch), whereas in the language task, slowing was restricted mostly to switch trials. To test if the apparently greater aging effect on the color-shape than the language task was significant we compared the two tasks directly in two additional analyses.

Task Comparison: Color-Shape versus Language

To compare aging effects across tasks we conducted 2 x 2 x 2 ANOVAs, with task (language, color-shape) and trial type (single versus stay for the mixing analyses, and stay versus switch for the switching analyses) as within subject factors, and age (young, older) as a between subject factor. The contrast between tasks is illustrated in Figure 2.2.

The primary goal in these analyses was to answer two questions: (a) Is age-related slowing, and the age-related increase in errors, larger in one task than in the other (i.e., to look for interactions between age and task), and (b) is the age-related increase in switching and mixing costs significantly larger in one task than in the other (i.e., three-way interactions between age, task, & trial-type). To emphasize the main points, in this section we forgo the convention of reporting main effects, then 2-way interactions (which were largely redundant with results already reported above), and then 3-way interactions, and instead focus specifically on interactions between age and task.

Cross-task Mixing Effects

RTs. Of interest, age-related slowing was substantially greater in the color-shape task than in the language task, a highly robust crossover interaction between age group and task, ($F(1,50)=28.19$, $MSE=11,074$, $\eta_p^2=.36$, $p<.01$). More specifically, aging caused a complete *task dominance reversal* such that older bilinguals named numbers more quickly than they made color-shape judgments ($p=.01$), whereas young bilinguals exhibited the opposite pattern (i.e., made color-shape judgments more quickly than they named numbers; $p<.01$). Turning to mixing costs, the three-way interaction between age, task-type, and mixing cost (trial type) was not significant ($F<1$). Thus although the language task exhibited an age-related increase in mixing costs in the analyses above, and the color-shape task did not, this difference between tasks did not approach statistical significance.

Errors. As for RTs, the age-effect on error rate was larger in the color-shape than in the language task, ($F(1,50)=7.48$, $MSE=.002$, $\eta_p^2=.13$, $p=.01$), although in this case it was not a cross-over interaction (both young and older bilinguals made more errors on color than on shape decisions). Of interest, the age-related deficit in mixing errors on the color-shape task, was significantly larger than aging effects on mixing errors in the language task (which, as reported above, did not exhibit an age-deficit in mixing errors), a significant three-way interaction between age, task-type, and mixing cost, ($F(1,50)=4.05$, $MSE=.001$, $\eta_p^2=.08$, $p=.050$).

Cross-task Switching Effects

RTs. As just reported for the cross-task mixing costs comparison, there was again a significant task-dominance reversal in the analysis of switching costs; age-related

slowing was significantly larger for the color-shape task than it was in the language task, ($F(1,50)=28.19$, $MSE=11,074$, $\eta_p^2=.36$, $p<.01$). The three-way interaction did not approach significance ($F<1$).

Errors. As for RTs, the age-effect on error rates was larger in the color-shape than in the language task, ($F(1,50)=4.61$, $MSE=.004$, $\eta_p^2=.08$, $p=.04$). Whereas young adults showed relatively equal error rates between tasks, older adults produced more errors in the color-shape task than in the language switching task. The 3-way interaction was not significant ($F<1$).

Summary of Task-Comparison: First, in both the mixing and the switching comparisons, and in both RTs and errors analyses, the color-shape task exhibited significantly larger aging effects than the language task. In the analysis of RTs, this was expressed in the form of a full task-dominance reversal across the aging contrast (i.e., with older bilinguals responding more quickly in the language task than in color-shape, and young bilinguals responding more quickly in color-shape than in the language task). Second, comparing aging effects on switching and mixing costs across tasks, these were significantly larger in the color-shape than in language task only in the analysis of task-mixing effects on error rates.

Association Between Tasks Via Inability to Do the Color-shape Task in Some Older Bilinguals

The results reported thus far reveal many differences between the color-shape and language tasks. Above we reported that five aging bilinguals were unable to accurately complete the color-shape task despite multiple attempts at practice trials. However, these same five aging bilinguals were all able to complete the language task. This dissociation

seems to confirm the hypothesis of separate control mechanisms for linguistic and non-linguistic switching. In this final analysis, we probed for possible parallels in aging effects across tasks by considering if the five bilinguals who were unable to complete the color-shape task exhibited any evidence of a control deficit in their performance on the language task. To this end, we matched these five older bilinguals to ten older bilinguals who were able to complete both tasks on age, education, and English and Spanish naming scores. To achieve this matching we included two older bilinguals who were excluded from the original analysis because of low education levels. Participant characteristics for bilinguals included in these comparisons are shown in Table 2.4.

On the hypothesis of partially shared control mechanisms for language and nonlinguistic tasks, we predicted that the older bilinguals who could not complete the color-shape task, would exhibit relatively impaired language control, when compared to age- and education matched older bilinguals who were able to complete both tasks. The data for these analyses are shown in Figure 2.3 (because of the small number of participants in these analyses, we plotted the distribution of data points for each group in each condition; statistical comparisons are to be interpreted with caution).

In the analysis of language mixing effects, there were no significant main effects or interactions ($p \geq .16$). Aging bilinguals who could not do the color-shape task did not respond more slowly on single and stay trials, and did not exhibit larger mixing costs, relative to matched controls. However, in the analysis of language switching costs, there was a marginally significant main effect of group such that older bilinguals who could not do the color-shape task responded more slowly than matched controls in the mixed-language block, ($F(1,13)=3.35$, $MSE=106,876$, $\eta_p^2=.20$, $p=.09$). Of greatest interest,

older bilinguals who could not do the color-shape task exhibited significantly larger language-switching costs than matched bilinguals who were able to do both tasks, a significant trial type by group interaction, ($F(1,13)=10.38$, $MSE=2,812$, $\eta_p^2=.44$, $p=.01$). Importantly, the larger language switch costs for bilinguals who could not do the color-shape task were not the result of a speed-accuracy tradeoff; there was no age by condition interaction in the error analyses of language-mixing ($p=.46$) and language-switching ($p=.90$).

The appearance of larger language-switching costs in aging bilinguals who could not do the color-shape task reveals an explicit connection between linguistic and non-linguistic control, and implies shared mechanisms underlying these processes.

General Discussion

The present study was designed to investigate the hypothesis of a domain-general control mechanism for language selection and non-linguistic task shifting by directly comparing aging effects on the two. Previous studies appeared to reveal a dissociation between aging effects across tasks with aging affecting mixing more than switching in studies of monolinguals performing non-linguistic tasks (e.g., Mayr & Liebscher, 2001; for review see Wasylyshyn et al., 2011), and aging affecting language switching but not mixing in a voluntary language-switching paradigm (Gollan & Ferreira, 2009). However, left unanswered was the question of whether aging affects cued language mixing or not. The current data largely confirm the apparent dissociation between linguistic and non-linguistic control; revealing an age-related increase in both language-mixing and language-switching costs, and confirming that these aging effects were in some ways more robust for switching than for mixing. In contrast, in non-linguistic task control, the

same aging bilinguals exhibited a significant mixing deficit (in error rates) and no switching deficit, a result more typical of the aging literature on task-switching.

Summarizing the key findings, several differences, and some more limited similarities were found in the comparison of aging effects on linguistic and non-linguistic tasks:

1. *Language Task (see Table 2.2): Aging related increase in mixing and switching costs in RTs, switching more affected than mixing in errors:* Older bilinguals showed significantly larger mixing and switching costs than young bilinguals, and this increase in costs survived an adjustment for older bilinguals' overall slower baseline response speed. Aging affected switching and mixing to the same extent in the analysis of RTs, but only the switching deficit was also robust in errors (i.e., older bilinguals failed to switch languages when cued to do so much more often than young bilinguals).
2. *Color-Shape Task (see Table 2.3): Aging-related increase in mixing cost errors only.* In contrast with the language task, in the color-shape task there was no age-related increase in switching and mixing costs in RTs. Instead, older bilinguals responded much more slowly than young bilinguals on all trial types, and exhibited significantly larger mixing costs than young bilinguals in the error analyses.
3. *Larger aging-related slowing, larger aging-related increase in errors, larger aging-related increase in mixing cost errors, in color-shape than in language task:* Although older bilinguals responded more slowly, and made more errors, than young bilinguals in both tasks, both of these main effects of aging were significantly larger in the color-shape than in the language task. In the analysis of

RTs this was expressed as a significant task-dominance reversal across the aging contrast; whereas the color-shape task was easier than the language-task for young bilinguals, the language task was easier than the color-shape task for older bilinguals (see Figure 2.2)³. The aging-related increase in mixing costs in errors was significantly larger in the color-shape task, than in the language task (which exhibited an aging-related increase in mixing costs only in RTs).

4. *Inability to do the color-shape task associated with larger language-switching costs*: Five older bilinguals who were unable to do the color-shape task were all able to do the language switching task, but also exhibited significantly larger language switching costs than matched older bilinguals who were able to do both tasks.

Theoretical Implications of Differences in Aging Effects Across Tasks

This summary of key findings reveals more differences than similarities in the aging effects observed across tasks. Furthermore, these differences were found even though the cross-task comparison was within-subjects; that is, although the same young and older bilinguals completed both tasks, very different aging effects were found in each. Perhaps the most striking difference was that aging effects overall were greater on the color-shape than on the language task. This result was particularly apparent in the RTs which exhibited task-dominance reversal across age groups (see Figure 2.2). This result, along with the finding that older bilinguals who could not do the color-shape task had no problem doing the language switching task, suggests domain-specific control mechanisms, and relatively spared language control in older age.

An important consideration, when interpreting the finding of greater aging effects

on the color-shape than on the language task (here referring to main effects of slowing and increase in errors), is that it is not likely that this result was a simple function of task-difficulty. In fact, it could be argued that the color-shape task was the “objectively easier” task if young bilinguals provide the means for judging task difficulty given that young bilinguals responded more quickly in the color-shape task than in the language-task (see Figure 2.2). A priori it might have seemed that the language task should be objectively more difficult for all participants. Specifically, while the color-shape task had only two possible response options in the single task and four possible responses in mixed-task blocks, the language task had 9 possible responses in single task blocks and 18 possible responses (1-9 in English or 1-9 in Spanish) in mixed task blocks. Thus, it could be argued that the larger response set makes the language task objectively more difficult than the color-shape task.

A further difference across tasks was that although both tasks exhibited aging related increases in costs, these varied across tasks in a manner that largely confirms a contrast that seemed apparent when reviewing the existing literatures on linguistic and non-linguistic switching. In particular, in the language task, aging was associated with a highly robust increase in cued switching costs (in both errors and RTs), whereas mixing was more affected in the color-shape task. The vulnerability of switching rather than mixing in aging bilingual language control was further confirmed in an analysis that showed greater language switching (but not mixing) costs in five older bilinguals who were unable to do the color-shape task. Taken together these findings point to a dissociation in control mechanisms across domains with a vulnerability in language *switching* to the effects of aging, and a vulnerability in non-linguistic task *mixing* to the

effects of aging (recent research on young bilinguals reveals similar dissociations between task and language control; Calabria, Hernández, Branzi, & Costa, 2012).

A further difference between tasks that deserves some comment is that only language switching exhibited significant age-related increases in switching and mixing costs in response times. Importantly, the absence of an age-related increase in costs in RTs in the color-shape task should not be taken as evidence of spared nonlinguistic task control in aging bilinguals. First, the error data revealed a significant age-related increase in mixing costs (ruling out the notion of fully intact non-linguistic control). In addition, there may be tradeoffs between aging effects on overall speed versus on costs; mixing and switching costs have been reduced in experimental settings by varying the timing of the cue display which allows for increased preparation time (e.g., Meiran, 1996; Rogers & Monsell, 1995). In the color-shape task older bilinguals may have slowed their rate of response execution to a point that was closer to the ceiling of possible costs associated with switching and mixing. The presence of slowing across all trial types in the color-shape task could reflect the joint consequences of increased difficulty with the tasks, reduced resources available for control processing in the context of a more difficult task, and decline in control processes.

In recent studies, slowed responses without an increase in switching costs have sometimes been interpreted as a relative advantage in task control. For example, one study reported that Spanish-English bilinguals with lower SES (measured by parents' education level), responded more slowly overall than monolinguals but exhibited equivalent switch costs relative to monolinguals (Prior & Gollan, 2011). Similarly, in another study kindergarten aged Spanish-English bilinguals performed equally well as

their monolingual peers, and after controlling for verbal scores, and parent education/income level, the bilinguals performed significantly better on tasks that require managing conflicting attentional demands such as the Attentional Network Task (Carlson & Meltzoff, 2008). In both studies, it was suggested that bilingualism offsets the effects of SES. Importantly, in the current study if we adjust for baseline response speed in the color-shape task older bilinguals exhibited 9% ($SD = .2\%$) switch costs, and 10% ($SD = .3\%$) mixing costs, and young bilinguals exhibited 8% ($SD = 2\%$) switch costs, and 11% ($SD = 2\%$) mixing costs, yielding non-significant aging effects on proportionally adjusted switching and mixing costs, $p = .53$ and $p = .54$ respectively. Thus, the lack of an age-related increase in switch and mix costs despite slower RTs in the color-shape task should certainly not be interpreted as an age-related advantage over young bilinguals in task control.

Although we observed differences between aging effects on the two tasks, the extent to which such differences challenge the hypothesis of shared-control-mechanisms for linguistic and non-linguistic task control is inherently limited in some ways. Differences between tasks could arise for a variety of reasons that have little to do with control mechanisms, and instead reflect other processes that are necessarily different across the two tasks. One noteworthy difference was the requirement to respond with button presses in the color-shape but not the language task. In previous studies age-related slowing is always observed, but robust age-deficits in costs were found only with overlapping mappings (e.g., Mayr, 2001). In the current study button-mappings did not overlap in the color-shape task (i.e., each of the four possible responses was associated with one of four different buttons on the response box), but in the language-task

responses for both languages are produced by the same (overlapping) mouth. This could have introduced some apparent differences between tasks. Importantly, there was no requirement to memorize the button mappings (which were displayed at the bottom of the screen on every trial; see Figure 2.1). Additionally, the sandwich design allowed participants substantial practice with the button mappings for each task prior to the mixed-task block. Below we consider the possible effects of button-responses in the color-shape but not the language task in greater detail.

Vulnerability of Language Switching in Aging: Language as an Expert Task

The current data add to an emerging body of evidence documenting reduced language control in aging bilinguals, and pinpointing language switching as being particularly vulnerable to aging effects. The age related decline in language switching was expressed both as an increase in switch costs in RTs, and also as a failure to switch languages when cued to do so (for similar findings see Hernandez & Kohnert, 1999). The current study added a finding of significant age-related increase in language-mixing costs (in RTs but not in errors), and this result contrasts with previous findings of intact language mixing for aging bilinguals in a voluntary switching paradigm (Gollan & Ferreira, 2009), and establish an association between language mixing deficits and being forced to select a language in response to a cue. As noted above, the presence of a robust switching deficit in aging language control seems to be different from aging effects observed in previous studies of task switching in monolinguals in which mixing deficits were often more robust than switching deficits in older age (for most recent review see Wasylyshyn et al., 2011). Importantly, some studies of aging monolinguals also revealed robust age-related increases in cued task-switching costs (e.g., Kray et al., 2002). Further

investigation of the conditions which change the expression of age-related deficits in executive control (which sometimes appear as increased switch costs and other times as increased mixing costs) with changes in the experimental tasks are likely to reveal the mechanisms underlying both task and language control.

These considerations reveal the importance of interpreting costs, and measures of executive control, in the context of overall performance. Caution should be used when interpreting results with adjustments for baseline response speed, and presentation of results exclusively in the form of difference scores (costs) should be avoided as this practice can obscure important differences. Though the difference in the magnitude of age-related slowing across tasks is not expected on the assumption of shared mechanisms of control for linguistic and non-linguistic task-switching, strictly speaking we cannot rule out the possibility that the requirement of button responses (e.g., rather than spoken responses), or some specific difficulty with shape judgments in aging, caused the larger aging effects.

To investigate if requirement to respond with button responses in the color-shape task but not in the language task may have spuriously caused differences between aging effects across the two tasks, we re-tested twelve of the older bilinguals (approximately 9 months after their initial participation; range: 2 to 17 months) on a voice version of the color-shape task. In the voice version, participants were instructed to simply say the color or shape names (in whichever language they preferred). In the same testing session, participants also repeated the original tasks (i.e., the language task, and color-shape with button press responses using the same button mappings as on the first testing session). The two color-shape versions were counterbalanced and either administered before or

after the language task.

The data from this follow-up study are shown in Figure 2.4. Most notably, in the mixed task block, response times on the second administration of the color-shape button-press task (single $M = 752$; stay $M = 788$; switch $M = 857$), were significantly slower than responses in the voice version of the color-shape task, (single $M = 698$; stay $M = 731$; switch $M = 789$; $p \leq .03$), but switching and mix costs were not different across the two versions of the task (both $F_s < 1$). Thus, overall speed, and the requirement to respond with button presses, do *not* appear to determine the size of switch and mixing costs. Also of interest, in both tasks, mixing costs, but not switching costs, were significantly smaller on the second testing session than on the first testing session. For the 12 older bilinguals who were tested a second time, language-mixing costs were 87 ms in the first testing session (single $M = 691$; stay $M = 788$; switch $M = 841$), and only 39 ms in the second testing session (single $M = 669$; stay $M = 708$; switch $M = 776$), a significant interaction between testing session and mixing-cost size, ($F(1,11) = 7.09$, $\eta_p^2 = .39$, $p = .02$). Similarly, in the color-shape task (button press version), mixing-costs were 84 ms in the first testing session (single $M = 752$; stay $M = 836$; switch $M = 906$), and only 39 ms in the second testing session (see previous paragraph for means), a marginally significant interaction between testing session and mixing-cost size, ($F(1,11) = 3.66$, $\eta_p^2 = .249$, $p = .08$). In contrast, switch costs did not change in size across testing sessions (both $F_s < 1$; 63 ms and 68 ms respectively for first and second testing sessions in the language task, and 70 ms and 69 ms respectively for first and second testing sessions in the color-shape task). These data seem to imply that mixing costs decrease with increasing experience with a task. This in turn might explain why age-related deficits in language control tend to

appear in switching (a highly practiced task), whereas age-related deficits in non-linguistic (and relatively less practiced) tasks tend to appear in mixing. These data increase confidence in our conclusion that aging differentially affects language and task control, and that the differences we observed in aging effects across the two tasks were not an artifact of methodological differences in how we implemented the two tasks.

The differences we observed between tasks imply that there is not complete overlap between mechanisms of task and language control. A question of interest is whether or not anything else in the aging effects we observed can pinpoint the nature of sharing between non-linguistic and linguistic control mechanisms.

Theoretical Implications of Similarities Between Aging Effects Across Tasks

Despite the striking differences in aging effects across tasks, we also observed some similarities between tasks that provide some clues as to the nature of shared control mechanisms that decline in concert as bilinguals age. One obvious place to look for similarities between language and task switching, would be to look for evidence of reduced inhibitory control in aging bilinguals in both tasks. Inhibition has been proposed to play an important role in efficient task (Anderson, Reinholz, Kuhl, & Mayr, 2011; Mayr, Diedrichsen, Ivry, & Keele, 2006; see also Mayr & Keele, 2000) and language control (Green, 1998; Meuter & Allport, 1999; Phillip & Koch, 2009; but see Finkbeiner, Almeida, Janssen, & Caramazza, 2006), both of which may be achieved in part by inhibiting dominant responses as a means for allowing non-dominant responses to be selected when cued. According to the Inhibitory Deficit Hypothesis (IDH; Hasher & Zacks, 1988), aging results in a reduction in inhibitory control mechanisms across all cognitive systems. Numerous studies have supported this hypothesis across domains such

as language comprehension, episodic memory, and speech production (e.g., Connelly, Hasher, & Zacks, 1991; Hartmen & Hasher, 1991; May, Zacks, Hasher, & Multhaup, 1999; but see e.g., Burke, 1997; Graham & Burke, 2011; Mayr, 2001). If inhibitory control is impaired in older age then older bilinguals would be less able to use inhibition for both task and language selection. In bilinguals, inhibition might be useful in tasks that require language mixing, to equalize the relative accessibility of the two languages that need to be produced (Gollan & Ferreira, 2009). Early studies of language switching revealed significant switch-cost asymmetries (with larger switch costs for the dominant language; Meuter & Allport, 1999), and this was taken as evidence for role of inhibition in bilingual language production (Green, 1998; Kroll, Bobb, Misra, & Guo, 2008). Importantly, the young and older adult bilinguals in the current study were matched for bilingual language proficiency (using scores on a picture naming test), and thus were equally balanced in their knowledge of English and Spanish (see Table 2.1). Moreover, the possible relevance of inhibition for the present tasks does not seem as important (but see footnotes 1-2) given that language dominance and task dominance effects were not particularly strong in the current paradigms (e.g., bilinguals named numbers equally quickly in their two languages, and only older, but not younger, bilinguals were slower to make shape than color judgments).

One result in the present study simultaneously provides evidence for shared mechanisms of control for linguistic and non-linguistic switching (i.e., domain-general control), but also demonstrates the relative preservation of language control in aging (i.e., domain-specific control). This was the finding that older bilinguals who could not do the color-shape task both (a) exhibited larger language switching costs than matched aging

bilinguals who were able to do the color-shape task, and (b) were still able to do the language switching task (see Figure 2.3; these findings are to be interpreted with caution given the small number of participants who were included in this comparison). The finding of a significant switching deficit for these participants demonstrates an explicit link between ability to perform the color-shape task and the magnitude of switch costs in the language task and points to a basic connection between linguistic and non-linguistic switching. At the same time, the fact that these bilinguals were able to do the language switching task with no more practice than young bilinguals, but could not perform the color-shape task despite multiple opportunities at slower paced practice trials reveals some fundamental differences between aging effects on the two tasks and suggests relatively sheltered and preserved language abilities in older age.

Conclusions

Direct comparisons of aging effects on linguistic and non-linguistic switching and mixing reveal some striking differences between tasks, and relative preservation of bilingual language processing in aging. Although the differences far outnumbered the similarities in aging effects observed across tasks, it is important to consider that many possible factors could produce differences between tasks, and that it is difficult to pinpoint the differences specifically to control processes. Moreover, despite the many differences between tasks, some subtle but interesting parallels were also found, and these support the hypothesis that language selection is at least partially dependent on a general control system. Having found many differences but also some similarities in aging effects across the two tasks, the most likely conclusion to be drawn is that language control mechanisms overlap only partially with non-linguistic control mechanisms.

Similar conclusions were recently drawn in a study of aging effects on cross-language intrusion errors and correlations with a non-linguistic flanker task (Gollan et al., in press). However, to what extent the differences observed in the current study reflect specifics of the tasks that are necessarily different across domains, versus differences in underlying control mechanisms remains to be further explored.

A more general possible implication of the current data is that the nature of control processes may change, or domain-specificity in control mechanisms may develop, with task expertise (whether linguistic or non-linguistic). On this view, language control may be distinct from non-linguistic control precisely because language is a highly practiced (possibly “expert” system), rather than reflecting functionally independent specialized mechanisms of language control per se. Further investigation would be needed to explore the notion of language as an expert task, however, given that people use language constantly throughout every day of their lives, language might reasonably fit some proposed requirements for achieving expert ability on a task (e.g., Ericsson & Lehmann, 1996). By exploring the possibility of at least some domain-specificity in language control, research on bilingualism will contribute to longer standing debates concerning the extent to which cognitive control is domain-general versus domain-specific across other tasks as well (e.g., for reviews see Egner, 2008; Monsell & Driver, 2000).

Chapter 2, in full, is a reprint of the material as it appears in: Weissberger, Gali H., Wierenga, Christina E., Bondi, Mark W., & Gollan, Tamar H. “Partially Overlapping Mechanisms of Language and Task Control in Young and Older Bilinguals”, *Psychology and Aging*, vol. 27, 2012. The dissertation author was the primary investigator and author

of this material.

References

- Abutalebi, J., & Green, D. (2007). Bilingual language production: The neurocognition of language representation and control. *Journal of Neurolinguistics*, 20, 242-275.
- Anderson, M. C., Reinholz, J., Kuhl, B., & Mayr, U. (2011). Intentional suppression of unwanted memories grows more difficult as we age. *Psychology and Aging*, 26, 397-405.
- Bialystok, E., Craik, F.I.M., Klein, R., Viswanathan, M. (2004). Bilingualism, Aging, and Cognitive Control: Evidence from the Simon Task. *Psychology and Aging*, 19, 290-303.
- Bialystok, E., Craik, F.I.M., Green, D.W., & Gollan, T.H. (2009). Bilingual minds. *Psychological Science in the Public Interest*, 10, 89-129.
- Bialystok, E., Craik, F.I.M., & Luk, G. (2008). Cognitive control and lexical access in younger and older bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 34, 859-873.
- Calabria, M., Hernández, M., Branzi, F.M., & Costa, A. (2012). Qualitative differences between bilingual language control and executive control: Evidence from task-switching. *Frontiers in Psychology*, 2, 1-10.
- Connelly, S. L., Hasher, L., & Zacks, R. T. (1991). Age and reading: The impact of distraction. *Psychology and Aging*, 6, 533-541.
- Egner, T. (2008). Multiple conflict-driven control mechanisms in the human brain. *Trends in Cognitive Sciences*, 12, 374-380.
- Ericsson, K. A., & Lehmann, A. C. (1996). Expert and exceptional performance: Evidence of maximal adaptation to task constraints. *Annual Review of Psychology*, 47, 273-305.
- Gollan, T.H., Sandoval, T., & Salmon, D.P. (2011). Cross-language intrusion errors in aging bilinguals reveal the link between executive control and language selection. *Psychological Science*, 22, 1155-1164.
- Gollan, T.H., Weissberger, G., Runnqvist, E., Montoya, R.I., & Cera, C.M. (in press) Self-ratings of spoken language dominance: A multi-lingual naming test (MINT) and preliminary norms for young and aging Spanish-English bilinguals. *Bilingualism: Language and Cognition*
- Graham, E. R., & Burke, D. M. (in press). Aging increases inattentional blindness to the gorilla in our midst. *Psychology and Aging*

- Green, D. W. (1998). Mental control of the bilingual lexico-semantic system. *Bilingualism language and cognition*, 1, 67.
- Hartmen, M., & Hasher, L. (1991). Aging and suppression: Memory for previously relevant information. *Psychology and Aging*, 6, 587-594.
- Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. *The Psychology of Learning and Motivation*, 22, 193-225.
- Hernandez, A. E. (2009). Language switching in the bilingual brain: What's next? *Brain and Language*, 109, 133-140.
- Hernandez, A. E., Kohnert, K. J. (1999). Aging and language switching in bilinguals. *Aging, Neuropsychology, and Cognition*, 6, 69-83.
- Koch, I., Prinz, W., & Allport, A. (2005). Involuntary retrieval in alphabet-arithmetic tasks: Task- mixing and task-switching costs. *Psychological Research*, 69, 252-261.
- Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging*, 15, 126-147.
- Kray, J., Li, K. Z. H., & Lindenberger, U. (2002). Age-related changes in task-switching components: The role of task uncertainty. *Brain and Cognition*, 49, 363-381.
- Kroll J. F., Bobb S.C., Misra M., & Guo T. (2008). Language selection in bilingual speech: Evidence for inhibitory processes. *Acta Psychologica*, 128, 416-430.
- Mattis, S. (1988). Dementia Rating Scale: Professional Manual. Odessa, Fla: Psychological Assessment Resources Inc.
- Mayr, U. (2001). Age differences in the selection of mental sets: The role of inhibition, stimulus ambiguity, and response-set overlap. *Psychology and Aging*, 16, 96-109.
- Mayr, U., Diedrichsen, J., Ivry, R., & Keele, S. W. (2006). Dissociating task-set selection from task-set inhibition in the prefrontal cortex. *Journal of Cognitive Neuroscience*, 18, 14-21.
- Mayr, U., & Kliegl, R. (2000). Task-set switching and long-term memory retrieval. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 26, 1124-1140.
- Mayr, U., & Kliegl, R. (2003). Differential effects of cue changes and task changes on task-set selection costs. *Journal of Experimental Psychology: Learning, Memory,*

and Cognition, 29, 362-372.

- Mayr, U., & Liebscher, T. (2001). Is there an age deficit in the selection of mental sets? *European Journal of Cognitive Psychology*, 13, 47-69.
- May, C. P., Zacks, R. T., Hasher, L., & Multhaup, K. S. (1999). Inhibition in the processing of garden-path sequences. *Psychology and Aging*, 14, 304-313.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*, 7, 939-944.
- Meiran, N. (1996). Reconfiguration of processing mode prior to task performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 22, 1423-1442.
- Meiran, N., Gotler, A., & Perlman, A. (2001). Old age is associated with a pattern of relatively intact and relatively impaired task-set switching abilities. *Journal of Gerontology: Psychological Sciences*, 56B, P88-P102.
- Meuter, R. F. I., & Allport, A. (1999). Bilingual language switching in naming: Asymmetrical costs of language selection. *Journal of Memory and Language*, 40, 25-40.
- Monsell, S. and Driver, J. (2000). Banishing the control homunculus. In *Attention and Performance XVIII: Control of Cognitive Processes* (Monsell, S. and Driver, J., eds), pp. 3-32, MIT Press.
- Phillip, A. M., & Koch, I. (2009). Inhibition in language switching: What is inhibited when switching between languages in naming tasks? *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 35, 1187-1195.
- Prior, A. & Gollan, T.H. (2011). Good language-switchers are good task-switchers: Evidence from Spanish-English and Mandarin-English bilinguals. *The Journal of the International Neuropsychological Society*, 17, 682-691.
- Prior, A., & MacWhinney, B. (2010). A bilingual advantage in task switching. *Bilingualism: Language and Cognition*, 13, 253-262.
- Reimers, S., & Maylor, E. A. (2005). Task switching across the life span: Effects of age on general and specific switch costs. *Developmental Psychology*, 41, 661-671.
- Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General*, 124, 207-231.

- Rubin, O., & Meiran, N. (2005). On the origins of the task mixing cost in the cuing task-switching paradigm. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 31, 1477-1491.
- Verhaeghen, & Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neuroscience and Behavioral Reviews*, 26, 849-857.
- Wasylyshyn, C., Verhaeghen, P., & Sliwinski, M. (2011). Aging and task switching. A meta-analysis. *Psychology and Aging*, 26, 15-20.

Footnotes

¹ In mixed-language block (switch cost analyses), young bilinguals responded more slowly in their dominant language than in their non-dominant language, whereas older bilinguals always responded more quickly in the dominant than in the non-dominant language (see Table 2.2). This interaction between age and language-dominance in the mixed-language block was significant ($F(1,50)=3.95$, $MSE=1,727$, $\eta_p^2=.073$, $p=.05$). Reversed language dominance in young bilinguals in mixed language blocks may reflect inhibition of the dominant language (Gollan & Ferreira, 2009), and thus this interaction between dominance and age could be taken as evidence of an inhibitory control deficit in older bilinguals (e.g., Hasher & Zacks, 1988). Also consistent with this interpretation, the age-related mixing deficit (mix cost analyses) was restricted to non-dominant language responses; ($F(1,50)=6.97$, $p<.01$, $MSE=2,160$, $\eta_p^2=.122$), and was not significant in the dominant language ($p=.26$). This was because young ($F(1,29)=3.72$, $MSE=3,928$, $\eta_p^2=.11$, $p=.06$), but not older bilinguals ($p=.94$), tended to exhibit greater switch costs in the dominant than the non-dominant language (a switch-cost asymmetry). These data imply that young but not older bilinguals may inhibit the dominant language as a means for mixing languages more efficiently.

²In the analysis of mixing costs, older bilinguals were slower to make shape than color judgments ($F(1,21)=6.91$, $MSE=3,824$, $\eta_p^2=.25$, $p=.02$), whereas young bilinguals made shape and color judgments equally quickly ($p=.19$); a marginally significant interaction between decision type and age, ($F(1,50)=3.60$, $MSE=2,360$, $\eta_p^2=.10$, $p=.06$). Greater difficulty with shape than with color decisions is sometimes also found in

children (see Chevalier, Blaye, Dufau, & Lucenet, 2010; Ellefson, Shapiro, & Chater, 2006). The aging-related preference for color over shape could suggest a form of regressed functioning associated with older age.

In the mixed-task block (switch cost analysis), young bilinguals exhibited significantly larger switch costs in making color than shape decisions ($F(1,29)=8.56$, $MSE=1,051$, $\eta_p^2=.23$, $p=.01$), whereas older bilinguals exhibited similarly sized switch-costs for color as for shape decisions ($p=.39$). This finding might seem parallel to the above reported finding (see footnote 1) in which only young bilinguals showed a tendency towards a language mixing-cost asymmetry; however, it is not clear how to interpret the asymmetry of switch costs in young bilinguals with the color-shape task given that they did not exhibit any task dominance effects (i.e., young bilinguals responded equally quickly in making color versus shape decisions).

³Note that in Prior & Gollan, (2011) button mappings were displayed on the button box instead of on the computer screen, and in those conditions young bilinguals recruited from the same population responded more slowly in the color-shape than in the language task. Thus, this small change in method seems to have had a profound effect on overall RTs for the color-shape task (speeding responses for young bilinguals).

Table 2.1: Participant characteristics for young and older bilinguals who were able to complete both linguistic and non-linguistic switching tasks.

	<u>Young Bilinguals</u> (n = 30)		<u>Older Bilinguals</u> (n = 22)	
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Age	20.7	2.2	75.6***	8.7
% Female	73.3%	N/A	73.0%	N/A
Education	14.1	1.1	14.0	2.2
Age 1 st Exposure to English	4.0	3.3	6.6**	5.8
Age 1 st Exposure to Spanish	0.4	1.3	2.0	8.0
%Currently Using Spanish	24.2	17.4	28.7	26.4
%Grow Up Using Spanish	45.8	19.3	58.0*	32.9
How often speak to bilinguals currently ¹	2.7	1.3	2.7	1.1
How often speak to bilinguals growing up ¹	3.0	1.5	2.4	1.3
Dementia Rating Scale	N/A	N/A	136.8	4.2
Mini Mental Status Exam	N/A	N/A	28.3	1.7
MINT English percent correct	88.9	6.8	88.7	11.8
MINT Spanish percent correct	73.9	12.2	76.9	12.6
Self Ratings ² :				
English Speak	6.5	0.7	5.9**	1.2
English Listen	6.7	0.6	6.1**	1.3
English Write	6.5	0.8	5.8**	1.4
English Read	6.8	0.6	6.1***	1.0
Spanish Speak	6.2	0.9	5.8	1.2
Spanish Listen	6.0	1.0	5.4*	1.7
Spanish Write	5.3	1.2	5.0	1.8
Spanish Read	6.6	0.6	6.0**	1.1

*marginally significant t-test comparing older adults to young adults ($p < .10$)

**significant t-test comparing older adults to young adults ($p < .05$)

***significant t-test comparing older adults to young adults ($p < .01$)

¹ The following 7-point scale was used: 1 (rarely or never), 2 (less than one hour/day), 3 (about one hour/day), 4 (about 2 hours/day), 5 (about 3-4 hours/day), 6 (about 5 hours/day), 7 (6 or more hours/day).

²Self-ratings were based on a 7-point scale: 1 (almost none), 2 (very poor), 3 (fair), 4 (functional), 5 (good), 6 (very good), 7 (like native speaker).

Table 2.2: Mean and standard deviation by participant group and condition for the language task.

		<u>Language Task RTs</u>							
<u>participant</u>		<u>single</u>		<u>stay</u>		<u>switch</u>		<u><i>mix</i></u>	<u><i>switch</i></u>
<u>group</u>	<u>language</u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>cost</i></u>	<u><i>cost</i></u>
older	dominant	685	86	784	150	874	172	99	90
bilinguals	nondominant	710	118	808	152	879	176	98	71
	<i>difference</i>	25		24		5			
young	dominant	616	58	688	116	740	115	72	52
bilinguals	nondominant	630	76	679	104	731	114	49	52
	<i>difference</i>	14		-9		-9			

		<u>Language Task Percent Errors</u>							
		<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>		
older	dominant	1.5	0.1	2.0	0.1	9.0	0.1	0.5	7.1
bilinguals	nondominant	0.6	0.0	2.8	0.0	9.5	0.1	2.2	6.7
	<i>difference</i>	-0.9		0.8		0.5			
young	dominant	0.6	0.0	1.0	0.0	3.7	0.1	0.4	2.7
bilinguals	nondominant	0.9	0.0	1.4	0.0	4.3	0.1	0.4	3.0
	<i>difference</i>	0.3		0.3		0.6			

Table 2.3: Mean and standard deviation by participant group and condition for the color-shape task.

		<u>Non-linguistic Task RTs</u>							
<u>participant</u>		<u>single</u>		<u>stay</u>		<u>switch</u>		<u><i>mix</i></u>	<u><i>switch</i></u>
<u>group</u>	<u>language</u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>cost</i></u>	<u><i>cost</i></u>
older	color	781	118	854	181	937	173	74	82
bilinguals	shape	806	124	898	212	955	204	92	57
	<i>difference</i>	26		44		18			
young	color	556	90	605	123	670	146	50	65
bilinguals	shape	555	93	624	133	654	149	69	30
	<i>difference</i>	-1		19		-16			
		<u>Non-linguistic Task Percent Errors</u>							
		<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>		
older	color	3.4	0.1	6.4	0.1	12.7	0.1	3.0	6.4
bilinguals	shape	3.4	0.1	11.5	0.1	13.9	0.1	8.1	2.4
	<i>difference</i>	0.0		5.1		1.1			
young	color	1.1	0.0	2.8	0.0	5.8	0.1	1.8	3.0
bilinguals	shape	0.8	0.0	2.6	0.1	4.1	0.0	1.9	1.5
	<i>difference</i>	-0.3		-0.2		-1.7			

Table 2.4: Participant characteristics for older adults who could not complete the color-shape task and matched controls.

	<u>Older Bilinguals</u> <u>Who Couldn't Do</u> <u>Color-Shape Task</u> (n = 5)		<u>Matched¹ Controls</u> (n = 10)	
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Age	80.8	6.4	78.2	6.7
% Female	80.0	N/A	70.0	N/A
Education	10.6	1.9	12.4	3.6
Age 1 st Exposure to English	6.5	4.7	12.2	7.1
Age 1 st Exposure to Spanish	0	0	0	0
%Currently Using Spanish	53.0	19.9	52.0	32.5
%Use of Spanish in childhood	76.0	25.1	83.4	20.7
How often speak to bilinguals currently ¹	3	1.4	2.6	1.0
How often speak to bilinguals in childhood ¹	3.5	0.7	2.3	1.5
DRS	134.5	2.6	136.5	4.0
MMSE	27.6	2.6	28.6	1.7
MINT English percent correct	81.5	8.5	86.5	7.4
MINT Spanish percent correct	80.6	6.0	87.5	7.7
Self Ratings ² :				
English Speak	5.4	1.1	5.2	1.2
English Listen	5.2	0.4	5.3	1.7
English Write	4.2	1.9	4.9	2.0
English Read	5.8	0.8	5.7	1.2
Spanish Speak	6.1	1.0	6.5	0.8
Spanish Listen	5.6	2.1	6.4	1.1
Spanish Write	5.6	2.1	6.2	0.9
Spanish Read	6.2	0.8	6.5	1.0

¹ No significant differences were found between the older adults who could not complete the color-shape task and their matched controls on any of the variables listed (all $ps \geq .10$). They differed marginally on Spanish naming scores ($p = .10$), in which matched controls did slightly better on the Spanish portion of the MINT. They also differed marginally on age of first exposure to Spanish ($p = .13$), in which the matched controls learned Spanish slightly later in life.

²The following 7-point scale was used: 1 (rarely or never), 2 (less than one hour/day), 3 (about one hour/day), 4 (about 2 hours/day), 5 (about 3-4 hours/day), 6 (about 5 hours/day), 7 (6 or more hours/day).

³Self-ratings were based on a 7-point scale: 1 (almost none), 2 (very poor), 3 (fair), 4 (functional), 5 (good), 6 (very good), 7 (like native speaker).

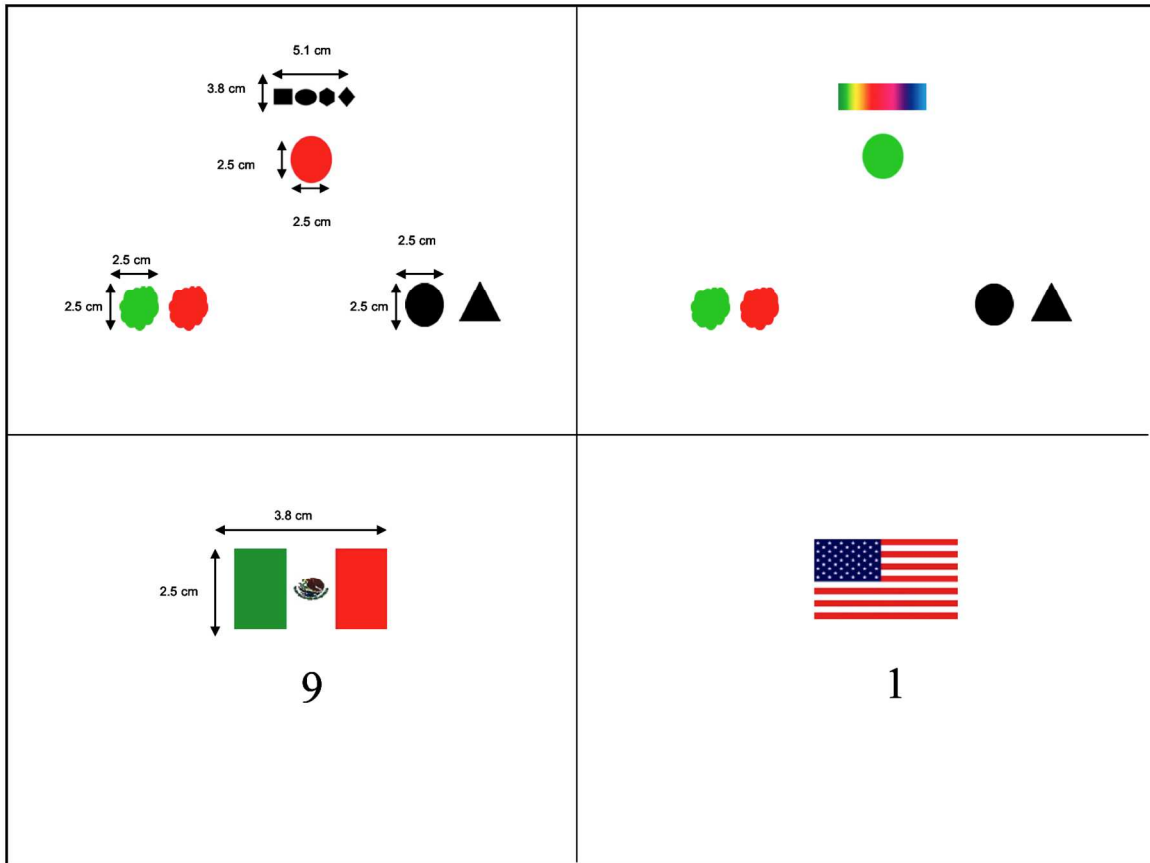


Figure 2.1: Computer screen display for the color-shape task (top-panel) and language-switching task (bottom panel). Top left and bottom left panels indicate the size of each feature.

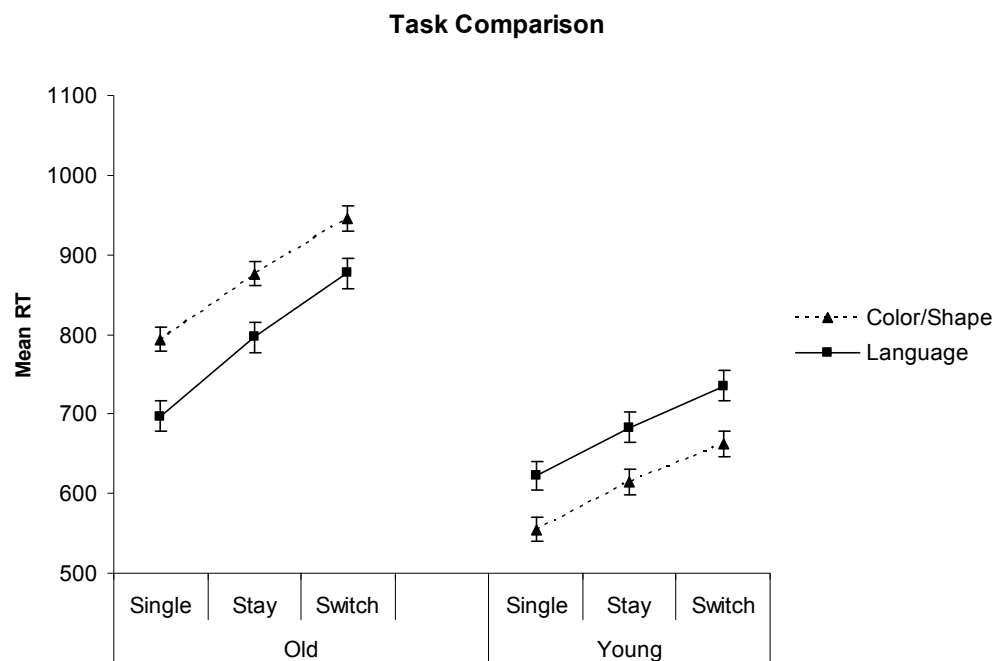


Figure 2.2: Mean RTs (ms) and proportion of error for single, stay, and switch trials in the cross-task comparison (collapsed across dominance within each task).

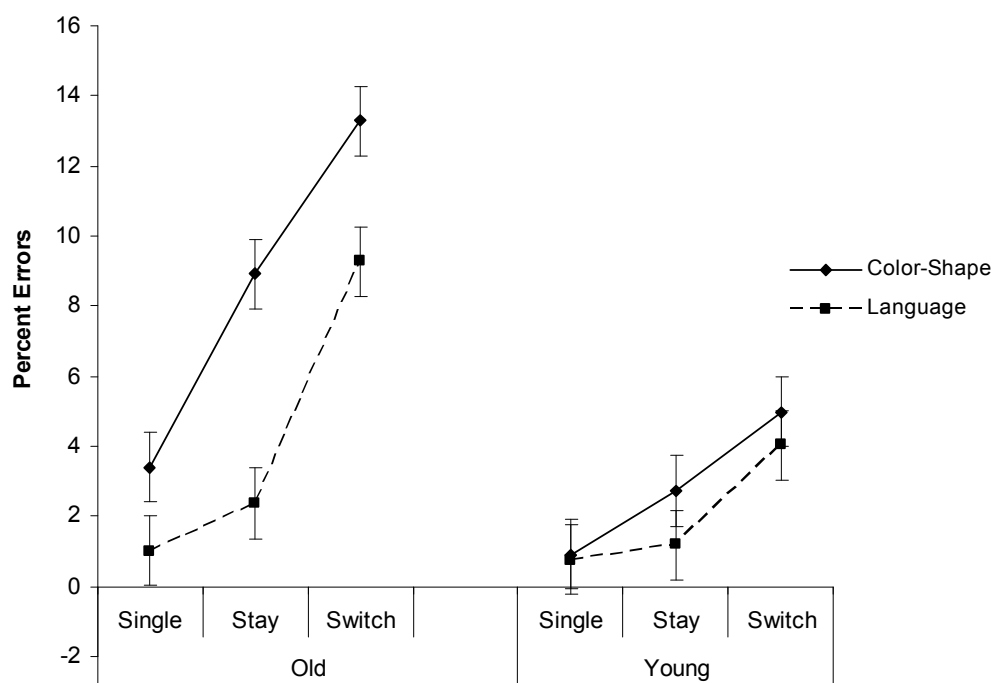


Figure 2.3: Distribution of reaction times (ms) for naming numbers in the language task for older bilinguals who could not complete the color-shape task and matched controls.

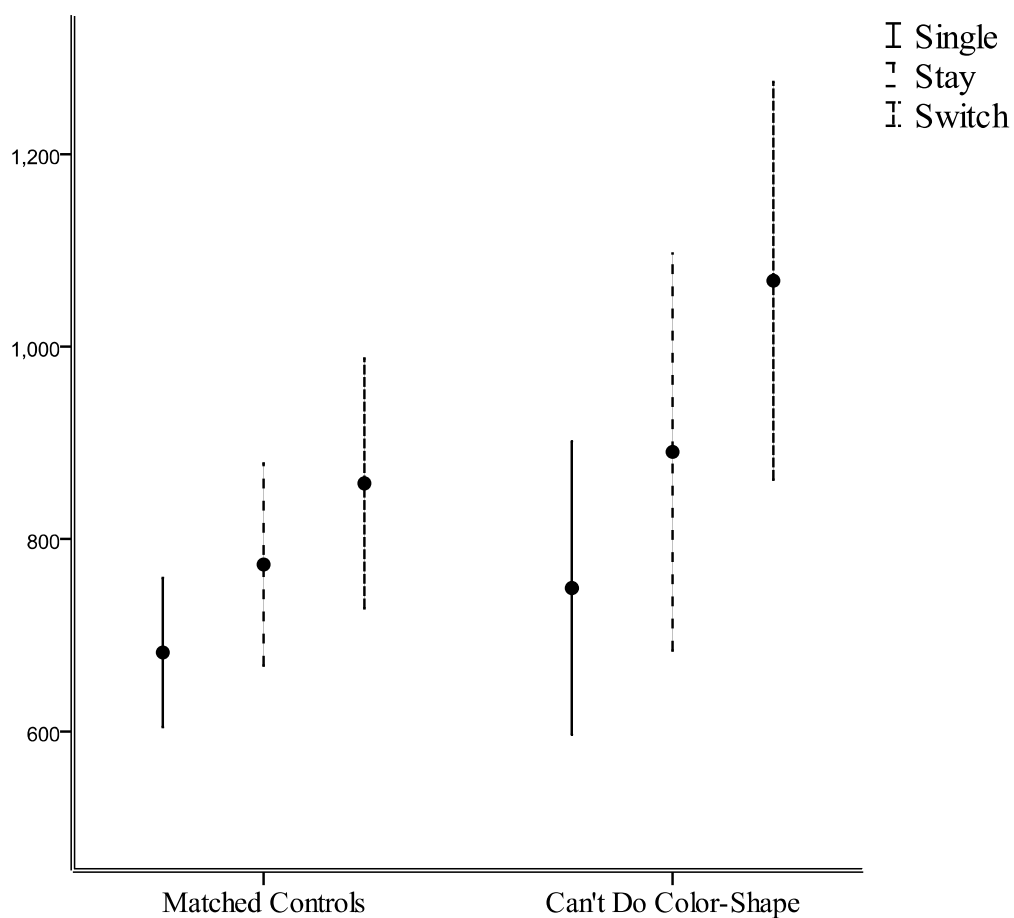


Figure 2.4: Mean RTs (ms) for single, stay, and switch trials for 12 bilinguals tested in a first testing session on the color-shape task with button-press responses, and the language-task with voice responses, and repeated testing on both tasks in a second testing session as well as a voice-response version of the color-shape task.

CHAPTER 3: WHICH NEUROPSYCHOLOGICAL TESTS PREDICT PROGRESSION
TO ALZHEIMER'S DISEASE IN HISPANICS?

Gali H. Weissberger^{1,2}, David P. Salmon², Mark W. Bondi^{3,2} & Tamar H. Gollan²

¹ San Diego State University

²University of California, San Diego

³VA San Diego Healthcare System

Address for correspondence:

Tamar H. Gollan
Department of Psychiatry
University of California, San Diego
9500 Gilman Drive, 0948
La Jolla, CA 92093-0948
e-mail: tgollan@ucsd.edu

Abstract

To investigate which neuropsychological tests might predict eventual progression to AD in both Hispanic and non-Hispanic individuals. Although our approach was exploratory in nature, we predicted that tests that underestimate cognitive ability in healthy aging Hispanics (due to cultural bias, translation of tests, bilingualism, etc.) might not be sensitive to future cognitive decline in this cultural group.

We compared first-year test data of 22 older adults (11 Hispanic) who were initially diagnosed as cognitively normal but eventually developed AD (decliners), to 60 age- and education-matched controls (27 Hispanic) who remained cognitively normal (controls). To identify tests that may be culturally biased in our sample, we first compared Hispanic to non-Hispanic controls on all tests. We then asked which tests were sensitive to future decline in each cultural group.

When compared with age-, education-, and gender-matched non-Hispanic normal controls, aging Hispanic controls obtained lower scores on tests of language, executive function, and some measures of global cognitive ability. In line with our predictions, some tests identified non-Hispanic, but not Hispanic, decliners (Vocabulary and semantic fluency). Contrary to our predictions, and despite lower scores for Hispanics, a number of tests on which Hispanics obtained lower scores than non-Hispanics nevertheless predicted eventual progression to AD in both cultural groups (e.g., BNT and Trails A and B).

Cross-cultural variation in test sensitivity to future decline may reflect greater resistance of medium difficulty items to cognitive decline, and bilingual advantages that initially protect Hispanics against some aspects of cognitive decline commonly observed in preclinical AD in non-Hispanics. These findings highlight a need for further consideration of cross-cultural differences in neuropsychological test performance, and development of culturally un-biased measures.

Introduction

Neuropsychological testing provides important information that aids in the diagnosis of dementia associated with probable Alzheimer's disease (AD). The clinical utility of neuropsychological testing has grown as normative data have been developed to gauge cognitive impairment at an early stage of the disease. There is also consensus that neural changes of AD begin prior to the observation of significant clinical symptoms (i.e., "preclinical AD"; see Sperling et al. 2011), suggesting that subtle cognitive changes occur prior to the point at which a clinical diagnosis of probable AD can be made with any certainty. Thus, the field has shifted to identifying preclinical neuropsychological markers of AD in an attempt to provide earlier diagnosis and treatment options for individuals who will eventually develop AD (for review see Twamley, Ropacki, & Bondi, 2006). This shift in neuropsychological research in recent years has shown that episodic and semantic memory are particularly vulnerable to early change in preclinical AD (Bäckman, Small, & Fratiglioni, 2001; Bondi et al., 1994, 1999; Lange et al., 2002; Linn et al., 1995; Mickes et al., 2007; Woodard et al. 2010). Subtle deficits on tests of executive functioning have also been found in elderly individuals who later develop AD

(Chen et al., 2000; 2001; Clark et al., 2012; Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Rapp & Reischies, 2007), but may not be as prominent as those in episodic and semantic memory (Mickes et al., 2007).

An important omission from research on cognitive changes in preclinical AD is the consideration of cultural differences that may exist in normative data or in the impact of disease on cognition in minority populations compared to the dominant population that is usually studied. Given that there is a growing minority population in the United States (US Census, 2010) it is increasingly important to determine to what extent existing normative data can be used with minority populations for the purpose of early diagnosis of AD. A number of studies have shown that individuals of other cultures underperform on certain neuropsychological tests, and steps have been taken to reduce or eliminate such biases (e.g., Ardila, Rosselli, and Puente, 1994; Judd et al., 2009; Pedraza and Mungas, 2008; Siedlecki, Manly, Brickman, Schupf, Tang, & Stern 2010). For example, Siedlecki and colleagues (2010) used structural equation modeling to determine whether a set of neuropsychological tests exhibited measurement invariance across English and Spanish speakers and found that English speakers obtained higher scores on all tests in the battery. Because of this scalar invariance, they cautioned against comparing means across English and Spanish-speaking samples. However, given the metric invariance they observed, they also concluded that the same constructs are likely being measured across both language groups – a conclusion which could suggest that despite measurement bias, the measures will be sensitive to impairment across groups. A review by Pontón and Ardila (1999) suggested that education, ethnicity, language spoken, acculturation, and age are important and complex variables that cannot be ignored as they can impact test

performance in Hispanics.

Along these lines, Hispanic minorities in the US are often Spanish-English bilinguals and this can also influence neuropsychological test performance. Bilingualism is associated with advantages on some cognitive tests and disadvantages on others (for review see Bialystok, Craik, Green, & Gollan, 2009), either of which can make it more difficult to interpret an individual's pattern of performance with reference to monolingual normative data. Bilinguals may exhibit cognitive advantages compared to matched monolinguals on several measures of executive function. For example, young adult bilinguals exhibited smaller Stroop interference effects (e.g., Bialystok, Craik, & Luk, 2008) and were faster to resolve response conflict than monolinguals on the Simon Task (Bialystok, Craik, Klein, & Viswanathan, 2004) and the Attentional Network Task (e.g., Costa, Hernández, Costa-Faidella, & Sebastián-Gallés, 2009; Costa, Hernández, Sebastián-Gallés, 2008). Bilingual advantages may also increase with age. For example, Bialystok et al. (2004) found that the bilingual advantage on the Simon Task was larger in older than in younger adults. This suggests that executive control may decline more slowly in aging bilinguals than in aging monolinguals. Consistent with this possibility, Kavé, Eyal, Shorek, and Cohen-Mansfield (2008) found better maintenance of cognitive status in aging with increasing number of languages spoken.

Bilingual advantages on executive tasks have also been found in young children and even in 7-12 month old babies (Kovács, 2009; Kovács, & Mehler, 2009; also see Bialystok, 1999; Bialystok, 2010; Bialystok & Martin, 2004; Bialystok & Shapero, 2005; Carlson & Meltzoff, 2008; Martin-Rhee & Bialystok, 2008). For example, Bialystok (2010) found that bilingual six year olds were faster in completing both Trailmaking Test

Parts A and B than matched monolinguals. These bilingual advantages in executive control may have developed to allow bilinguals to manage competition between their two languages when conversing. Though the precise underlying mechanisms and cause of bilingual advantages are currently being debated, there is an emerging consensus that some form of executive control is necessary for successful language control in bilinguals (Abutalebi & Green, 2007; Bialystok, et al., 2009; Gollan & Ferreira, 2009; Hernandez, 2009).

Contrary to the effects reviewed above, bilingualism has been shown to produce disadvantages on language tasks (for review, see Kroll & Gollan, in press). Bilinguals have more difficulty naming pictures than monolinguals, resulting in more tip-of-the-tongue states (Gollan and Silverberg, 2001), slower naming times, and higher error rates, even when naming pictures in their dominant language (Gollan, Montoya, Fennema-Notestine, and Morris, 2005; Ivanova & Costa, 2008). Bilinguals also produce lower scores on standardized measures of picture naming, such as the Boston Naming Test (BNT). Roberts, Garcia, Desrochers, and Hernandez (2002) administered the BNT to monolingual and French-English and Spanish-English bilingual adults and found significantly lower scores for bilinguals compared to age and education matched monolinguals. The BNT is commonly used in the neuropsychological assessment of dementia and has shown declines during the preclinical period of AD (e.g. Howieson et al., 1997; Jacobs et al., 1995; Mickes et al., 2007). It is not clear, however, if this test would be diagnostically useful in bilinguals given that cognitively healthy bilinguals perform less well on this test than matched monolinguals.

Verbal fluency is another commonly used neuropsychological measure that is

susceptible to a bilingual disadvantage. Cognitively healthy young adult bilinguals produce fewer correct responses than monolinguals on verbal fluency tests (Gollan, Montoya, & Werner, 2002; Portocarrero, Burright, & Donovanick, 2007). Even more problematic for the detection of early AD is that this bilingual disadvantage resembles the effect of AD on fluency. Studies have shown that semantic fluency is more adversely affected by AD than phonemic fluency (e.g., Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Henry, Crawford & Phillips, 2004). Similarly, the bilingual disadvantage is greater for semantic fluency than phonemic fluency in both young (Gollan et al., 2002) and older adults (Rosselli et al., 2000). Given these results, it is not clear if bilingualism will attenuate the pattern of fluency deficits associated with AD in monolinguals or if a further discrepancy between semantic and phonemic fluency should be expected for bilinguals when they begin to develop AD. It is interesting to note, however, that a study by Salvatierra, Rosselli, Acevedo, and Duara (2007) showed that cognitively healthy bilinguals produced more responses in semantic than in phonemic fluency tasks (but see Gollan et al., 2002), while bilinguals with AD produced equal (though lower than normal) numbers of responses in both tasks. These results suggest that a greater decline in semantic fluency than phonemic fluency remains evident in bilinguals with AD. It remains to be determined, however, whether or not verbal fluency (particularly semantic fluency) is as effective in detecting preclinical AD in bilinguals as it is in monolinguals (e.g. Clark et al., 2009; Albert, Moss, Tanzi, & Jones, 2001; for reviews see Twamley et al., 2006, and Henry et al., 2004).

A further complication for predicting future onset of AD in Hispanic elderly is that differences have been reported for age of onset and rate of progression of AD in

Hispanics compared to non-Hispanics. Several studies report an earlier age of onset of AD in Hispanic older adults compared with non-Hispanics after adjusting for education (Clark et al., 2005; Livney et al., 2011; also see Ringman and Flores, 2005). In contrast, several studies have found no difference in the age of onset of AD in Hispanics and non-Hispanics (Duara et al., 1996; Kwon, Khaleeq, Chan, Pavlik, and Doody, 2010). More recent work reveals bilingualism and education level to be interacting predictors of age of onset in Hispanics, with increasing degrees of bilingualism delaying diagnosis of AD in Hispanics with low-education but not in those with high-education (Gollan, Salmon, Montoya, & Galasko, 2011).

Some studies report longer survival rates in Hispanics with AD compared to non-Hispanics (Cosentino, Scarmeas, Albert, and Stern, 2006; Helzner, Scarmeas, Cosentino, Tang, Schupf & Stern, 2008; Mehta et al., 2008; Waring, Doody, Pavlik, Massman, and Chan, 2005). Whether this is due to differences in age of diagnosis or biological factors is still unclear. Mehta and colleagues (2008) suggest that future studies can address such concerns by examining longitudinal data that can indicate a person's degree of cognitive decline independent of population normative data that may not be applicable to groups who are limited by language barriers and education level (see also Mulgrew, Morgenstern, Shetterly, Baxter, Barón, & Hamman, 1999). An open question given these many differences between cultural groups is whether the same tests are sensitive to preclinical AD across groups. It seems possible that the answer to this question would be "yes", provided that culturally and linguistically matched normative samples are used as has sometimes been done in the past (e.g. Lucas et al., 2005; Pontón et al., 1996). On the other hand, it is likely that culture-specific normative data could not circumvent all of the

problems associated with the use of tests that were designed for a different cultural group (see Gasquoine, 1999; Manly & Echemendia, 2007; Pontón & Ardila, 1999). For example, Peña (2007; see also Artiola y Fortuny et al., 2005) warns that translated tests focus on linguistic equivalence but do not consider functional, cultural, and metric equivalence, which are of equal importance and, if not considered, may threaten the validity of even carefully and accurately translated measures (see also Judd et al., 2009, and standards recommended by the International Test Commission, 2002).

Given these questions, we took an exploratory approach to investigating differences between Hispanic and non-Hispanic elderly adults on a battery of commonly used neuropsychological tests. Our overarching goal was to determine which tests might be useful as preclinical markers of AD regardless of cultural group. Existing research on cognitive measures that are useful for predicting future decline in individuals with preclinical AD has focused almost exclusively on non-Hispanic Caucasians (e.g., Mickes et al., 2007; for review see Twamley et al., 2006). We began by comparing baseline neuropsychological test performance of non-Hispanic and Hispanic participants who remained cognitively healthy in subsequent years (i.e., ‘robust’ normal controls) in a longitudinal study at the UCSD Alzheimer’s Disease Research Center (ADRC) to determine which cognitive tests might be affected by culture or bilingualism. We then examined which tests were sensitive to eventual progression to AD in patients who were initially diagnosed as normal but subsequently declined. Finally, we asked if some tests that were sensitive to eventual progression to AD in one cultural group were sensitive in the other cultural group, and considered the possible theoretical implications of such differences.

Methods

Participants

Participant characteristics are summarized in Table 3.1. All procedures at the ADRC (Alzheimer's Disease Research Center) received institutional ethics approval from the UCSD Human Research Protection Program, and all participants provided written informed consent. To identify Hispanics and non-Hispanics who began participation at the ADRC (Alzheimer's Disease Research Center) prior to developing a diagnosis of probable AD, we screened longitudinal data from 126 Hispanic and 370 non-Hispanic participants who entered the ADRC study as normal control participants (1990-present). Participants with a history of alcoholism, drug abuse, severe psychiatric disturbances, severe head injury, and learning disabilities are excluded from participation in the ADRC study. Upon their first evaluation (i.e., Year 1 or baseline), participants were judged to be cognitively normal by two senior staff neurologists based on medical, neurological and neuropsychological evaluations, and a number of laboratory tests used to rule out possible causes of dementia (see Galasko et al., 1994 for more details). Of these participants, 11 initially-normal Hispanics were eventually diagnosed with probable AD during annual ADRC re-evaluations, an average of 5.0 years later (see Table 3.1)¹. Probable AD was diagnosed using criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann, et al., 1984). Diagnosing neurologists were not aware of specific test scores, but were provided with a general statement regarding the evaluation results (e.g., "a deficit in two or more areas of cognition"). These "decliner" participants were then matched for age, education, and

years prior to diagnosis, to 11 non-Hispanic participants who were also normal initially and were later diagnosed with probable AD an average of 5.2 years later. These 11 non-Hispanic decliners were randomly selected from a larger group of non-Hispanic decliners who were carefully matched to Hispanics on age, education, and years prior to diagnosis. The respective non-Hispanic and Hispanic decliners were then matched for age and education to 33 non-Hispanic and 27 Hispanic normal controls who remained cognitively healthy for the duration of their participation in the ADRC study, and for at least two consecutive years, but many remained in the study as controls for additional years (an average of 9.2 years for Hispanics, and 6.7 years for non-Hispanics).

Demographic Characteristics. Multiple independent sample t-tests were conducted to ensure that matching conditions were met (see Table 3.1). Hispanics who remained cognitively healthy, henceforth “normal controls,” did not differ from non-Hispanic normal controls on age, gender, and education (all p 's $\geq .26$). Further analyses comparing non-Hispanic controls to non-Hispanic decliners revealed that controls did not differ from decliners on age, gender, or education (all p 's $\geq .60$). A comparison of Hispanic controls to Hispanic decliners also yielded no significant effects on all demographic variables (all p 's $\geq .66$) except for gender, in which all decliners were female ($\chi^2(1, n = 38) = 5.12; p = .02$; Fisher's exact test $p = .03$). We address this possible limitation below. Non-Hispanic decliners did not differ from Hispanic decliners in age or education (all p 's $\geq .57$), but did differ on gender ($\chi^2(1, n = 22) = 3.67; p = .06$; Fisher's exact test $p = .15$). Although non-Hispanics can potentially represent a heterogeneous group, all non-Hispanics included in our sample were Caucasian, with the exception of one decliner who was African American.

Language Proficiency. A majority of Hispanic participants at the ADRC are bilingual with varying degrees of proficiency in each of their two languages. Of Hispanic decliners, 5 were born in the USA, 4 in Mexico, 1 in Argentina, and 1 was born in Poland but immigrated to Mexico at age 5. Of matched Hispanic controls, 19 were born in the USA, 6 in Mexico, 1 in Colombia, and 1 in Chile. All Hispanics at the ADRC are tested in their self-reported dominant language during annual neuropsychological evaluations. Similar proportions of decliners (64%) and non-decliners (59%) preferred to be tested in English (and the rest preferred to be tested in Spanish). Qualitatively, there appeared to be a relationship between country of origin (e.g., United States, Mexico, or other Spanish speaking country) and language in which the participants preferred to be tested. Of all participants tested (combining decliners and controls), 71% preferred to be tested in the dominant language of their country of origin. Detailed information (see Table 3.1) on language background was available for 8 of the 11 Hispanic decliners, and for a subset of the Hispanics who remained cognitively healthy (15 of 27 controls). For these individuals, those born in a Spanish speaking country were exposed to English on average at age 20.14; this is in contrast to participants born in the United States ($M=3.14$). We excluded Hispanics who reported a third proficient language and the level of bilingualism in the non-Hispanic cohort is negligible.

Vascular Risk Factors. Hispanics have been shown to have greater risk of stroke compared to non-Hispanics (e.g. Sacco et al., 1998; Sacco, Hauser, & Mohr, 1991). Thus, it was important for the purposes of our study to consider this potential confound given that strokes and vascular dementia affect test performance differently than AD (e.g. Looi & Sachdev, 1999). To address this potential confound we compared baseline Hachinski

ischemia scores, a measure of stroke risk, across the Hispanic and non-Hispanic decliner groups. Although we did not have year 1 scores for three decliners (two non-Hispanics and one Hispanic), these individuals obtained scores of 0 in subsequent years of testing (years 2, 4, and 9). We found no difference in stroke risk between the two decliner groups ($p=.29$). We also assessed for diabetes given its greater risk in Hispanics (e.g., Harris, 1991) and the relationship between diabetes and dementia (e.g., Ott et al., 1999). Only four individuals had a diabetes diagnosis (2 non-Hispanic decliners; 2 Hispanic normal controls), making diabetes an unlikely confound in our study.

Activities of Daily Living. Everyday functioning was assessed with the Pfeffer Outpatient Disabilities Scale (PODS; Pfeffer, Kurosaki, Harrah, & Chance, & Filos, 1982). Non-Hispanic decliners did not differ from Hispanic decliners on year 1 PODS scores, nor did decliners differ from controls in either cultural group (all $ps \geq .25$). The Clinical Dementia Rating (CDR; Hughes, Berg, Danzinger, Coben, & Martin, 1982; Morris, et al., 1991) was adopted by the ADRC relatively recently, and thus only 6 of 21 decliners with CDR scores had year 1 CDR scores available. All but one of these 6 decliners endorsed none of the questions (i.e., obtained global CDR scores of 0) and one received a score of 0.5, which reflects mild forgetfulness but intact functioning and self-care (Hughes et al., 1982). We obtained the earliest CDR available for the remaining 15 decliners, although all of these participants had been in the ADRC for at least two years (average of 4.9 years) before they received a CDR score. Despite this delay, average global CDR for both groups was only slightly above 0 (0.36 for Hispanics and 0.35 for non-Hispanics) and did not differ for Hispanic and non-Hispanic decliners ($p=.93$).

Measures

Neuropsychological tests are administered to participants annually by trained psychometrists at the UCSD ADRC. Psychometrists for the Hispanic cohort were bilingual and bicultural, with most having Mexican-American heritage, and some from Central-American countries and Puerto Rico. All psychometrists at the ADRC have had BA or MA level education at universities in the United States. Here we report data from the first year of ADRC participation (i.e. year 1) from all tests that were available for all (or most) participants. When necessary, translation of test materials was performed by bilingual psychologists and physicians in consultation with one of the ADRC psychometrists who is a certified translator. Back translation was performed for any tests with materials shown to the participant during testing.

The measures are described below. In previous studies, measures most sensitive to future decline included episodic memory assessed with verbal memory tests such as Word List Learning (Chen et al., 2000) and the California Verbal Learning Test (Bondi et al., 1994). Unfortunately, Hispanics who ‘prefer-English’ and those who ‘prefer-Spanish’ were tested with different verbal memory tests, and therefore we could not include these measures in our analyses. We were, however, able to include a measure of non-verbal episodic memory.

Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975): a brief, standardized 30-point scale that assesses orientation to time and place, attention and concentration, recall, language, and visual construction.

Dementia Rating Scale (DRS; Mattis, 1988): a standardized 144-point mental status test with subscales for Attention (37 points), Initiation and Perseveration (39 points), Construction (6 points), Conceptualization (37 points), and Memory (25 points).

Vocabulary Subtest, Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981): Participants are asked to define 35 words of increasing difficulty. The test is discontinued after three consecutive incorrect responses. Definitions are scored on a 0 to 2 point scale for a total possible score of 70 points.

Digit Symbol Substitution Test, Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981): Participants are presented with a key which associates nine unfamiliar symbols with the numbers 1 through 9. They are then asked to use the key to draw the appropriate symbols below a random series of their associated numbers as quickly as possible for 90 seconds. The number of correctly completed symbols is the score of interest.

Visual Reproduction Test (Wechsler Memory Scale, Russell, 1975 adaptation): Three figures of increasing complexity are presented to participants for 10 seconds each. Immediately after each presentation, participants are asked to draw the figure from memory. After 30 minutes of unrelated testing, participants are again asked to draw the three figures from memory. Immediately after this delayed recall attempt, participants are asked to copy the figures to assess their perceptual and constructional abilities. Three scores are obtained: the sum of scores for all three figures (21 possible points) in the immediate recall, delayed recall, and copy conditions.

Trail Making Test A and B (TMT A and TMT B; from the Halstead Reitan Neuropsychological Test Battery; see Reitan, 1958; cf. Mickes et al., 2007): In Part A (TMT A), participants draw a line to connect the numbers 1-25 in consecutive order as quickly as possible within a 150 second time-limit. In Part B (TMT B), participants draw a line to connect 25 numbers and letters in alternating, consecutive order as quickly as possible within a 300 second time-limit. Time-to-complete each task is scored.

Boston Naming Test – 30 item version (BNT; Kaplan, Goodglass, & Weintraub, 1983): This abbreviated version of the BNT requires the participant to name 30 objects depicted in outline drawings. The drawings are graded in difficulty with the easiest drawings presented first. If the participant encounters difficulty in naming an object, a stimulus (i.e., semantic) or phonemic cue is provided. Correct responses produced spontaneously and after semantic cues are summed to provide the score of interest for a maximum score of 30.

Verbal Fluency Test (Thurstone & Thurstone, 1941): In the phonemic Fluency task, participants are asked to verbally generate as many different words as possible in one minute that begin with the letter “F”, then “A” and then “S”². In the Semantic Fluency task, they are asked to verbally generate as many exemplars as possible in one minute from the category “animals”, then “fruits”, and then “vegetables”. Scores are based on number of unique words produced, excluding repetitions and variants (e.g., horse, horses).

Modified Wisconsin Card Sorting Test (Nelson, 1976): Participants must sort 48 cards into three distinct categories (twice for each category) based on various perceptual features of the cards. The sorting rule in effect changes throughout the test and must be determined by the participant through examiner-provided feedback regarding accuracy of the sort. The number of categories achieved out of six possible categories, and the number of perseverative and non-perseverative errors produced, are scored.

Results and Discussion

The means and standard deviations of neuropsychological test scores of the four groups at year 1 are shown in Table 3.2. Because previous studies have shown that

bilingualism and differences in culture can affect performance on neuropsychological tests in cognitively healthy individuals, we first compared non-Hispanic and Hispanic normal controls to examine these effects. These initial comparisons are necessary because baseline group differences could impact the sensitivity of cognitive tests to distinguish between controls and those who go on to develop probable AD. We then examined which cognitive tests in year 1 distinguished decliners from controls in the Hispanic and non-Hispanic groups. After this initial comparison, we then present the remaining results in the following order: 1) tests that did not distinguish between decliners and controls in either group, 2) tests that distinguished between decliners and controls in both groups, 3) tests that distinguished between decliners and controls in Hispanics but not non-Hispanics, and 4) tests that distinguished between decliners and controls in non-Hispanics but not Hispanics. Sample sizes for each analysis differed based on the availability of specific tests for each subject.

Non-Hispanic v. Hispanic Normal Control Group Comparisons

Based on previous studies, we anticipated that Hispanics would obtain lower score lowers on the MMSE (Bohnstedt, Fox, & Kohatsu, 1994; Mulgrew et al., 1999, but see Hohl et al., 1999), some subscales of the DRS (e.g., Lyness, Hernandez, Chui, & Teng, 2006; Hohl et al., 1999), and because of their bilingualism, on language measures including semantic fluency (Bialystok, Craik, & Luk, 2008; Rosselli et al., 2000), possibly phonemic fluency (e.g., Bialystok, Craik, & Luk, 2008; Gollan, et al., 2002), and the BNT (Gollan, Fenema-Notestine, Montoya, & Jernigan, 2007; Kohnert, Hernandez, & Bates, 1998; Roberts, Garcia, Desrochers, & Hernandez, 2002; Gollan, Weissberger, Runnqvist, Montoya, & Cera, 2012). We also expected WAIS-R Vocabulary and Digit

Symbol Substitution subtest scores to be lower in Hispanics based on reported lower full scale IQ scores for college-aged Mexican Americans than for matched non-Hispanic Caucasians (Verney, Granholm, Marshall, Malcarne, and Saccuzzo, 2005).

Our predictions for tests of executive function were less clear. Although the Trail-Making Test sometimes reveals bilingual advantages (e.g. Bialystok, 2010), some have argued that the test is culturally biased because of the required familiarity with English letters. In one study, a version of the test that was meant to be culture neutral (i.e., the Color Trails Test; Maj et al., 1993) nevertheless revealed differences between cultural groups (i.e., lower scores for older cognitively normal Hispanics than for non-Hispanics; La Rue, Romero, Ortiz, Lang, & Lindeman, 2010). Another test of executive functioning, the WCST, may be culturally fair in cognitively normal Hispanic adults (Rey, Feldman, Rivas-Vasquez, Levin, & Benton, 1999; Proctor & Zhang, 2008), but one study reported that increased mainstream acculturation in Mexican American adults improved performance on this test (Coffey, Marmol, Schock, and Adams, 2005). Given these discrepant findings, either culture- or bilingual-related advantages or disadvantages seemed possible for our participants.

We conducted a series of one-way ANOVAs to compare the Hispanic ($n=27$) and non-Hispanic ($n=33$) normal control groups on the various cognitive tests. Confirming our predictions, Hispanics obtained lower scores relative to non-Hispanic normal controls on all language tests. As previously reported for bilinguals versus monolinguals (e.g., Roberts, Garcia, Desrochers, & Hernandez, 2002), Hispanics (many of whom were bilingual) scored significantly lower than non-Hispanics (who were almost exclusively monolingual) on the BNT, ($F(1,58)=8.05$, $MSE=5.27$, $p=.006$, $\eta_p^2=.12$). In addition,

Hispanics scored significantly lower on the Vocabulary subtest of the WAIS-R, ($F(1,51)=19.09$, $MSE=108.82$, $p<.001$, $\eta_p^2=.27$). Hispanic controls also produced fewer correct responses than non-Hispanics on the letter fluency task (combining scores on letters “F,” “A,” and “S”), although – replicating prior studies which revealed weaker (Gollan et al., 2002) or no disadvantage for bilinguals on letter relative to semantic fluency (Rosselli et al., 2000) – this difference was not significant overall³, ($F(1,58)=2.85$, $MSE=156.70$, $p=.10$, $\eta_p^2=.05$). Hispanics did produce significantly more intrusion errors than non-Hispanics on the letter fluency test ($F(1,58)=4.01$, $MSE=.75$, $p=.05$, $\eta_p^2=.07$). A similar general pattern of results emerged for semantic fluency. Hispanic controls also tended to produce fewer correct responses than non-Hispanics on the semantic fluency task (combining scores on “animals,” “fruits,” and “vegetables”), a marginally significant difference overall ($F(1,58)=3.82$, $MSE=103.42$, $p=.06$, $\eta_p^2=.06$). Looking at *animals* (likely the most commonly administered semantic category), the Hispanic disadvantage was significant (see also Gollan et al., 2002; Rosselli et al., 2000; $F(1,58)=4.35$, $MSE=21.26$, $p=.04$, $\eta_p^2=.07$, *vegetables* also produced a significant difference, $p=.04$, but *fruits* did not, $p=.47$). Hispanic and non-Hispanic controls did not differ on the number of intrusion errors produced on the semantic fluency categories ($F<1$).

Consistent with the results of Verney et al. (2005), Hispanic controls obtained lower scores than non-Hispanic controls on the WAIS-R Digit Symbol Substitution ($F(1,56)=13.07$, $MSE=234.48$, $p=.001$, $\eta_p^2=.19$). We found no difference in the MMSE scores of Hispanic and non-Hispanic controls ($p=.23$; see also Hohl et al., 1999), but Hispanic controls obtained lower total DRS scores than non-Hispanics ($F(1,55)=7.91$,

$MSE=21.86$, $p=.007$, $\eta_p^2=.13$). In particular, they had significantly lower scores on the *Attention* ($F(1,55)=5.04$, $MSE=1.47$, $p=.029$, $\eta_p^2=.08$), *Conceptualization* ($F(1,55)=7.37$, $MSE=6.80$, $p=.009$, $\eta_p^2=.12$), and *Memory* ($F(1,55)=6.98$, $MSE=1.36$, $p=.01$, $\eta_p^2=.11$) subtests. These results are consistent with a study by Lyness and colleagues (2006) that showed lower scores in cognitively normal Hispanics compared to non-Hispanics on these same DRS subtests. Even though a large component of the DRS *Initiation and Perseveration* subtest involves supermarket fluency, there was no difference between Hispanic and non-Hispanic controls on this subtest, perhaps because scoring procedures impose a hard ceiling on the number of items credited.

On tests of visuospatial function and executive function respectively, Hispanic controls were significantly slower than non-Hispanics on TMT-A ($F(1,58)=6.19$, $MSE=172.92$, $p=.02$, $\eta_p^2=.10$) and TMT-B ($F(1,57)=6.77$, $MSE=1049.33$, $p=.012$, $\eta_p^2=.11$). This is consistent with the results of La Rue et al. (2010) using the Color Trails Test, but not with the advantage found in bilingual children (e.g. Bialystok, 2010). The Hispanic and non-Hispanic controls did not differ in the number of categories sorted on the modified WCST, but Hispanic controls made marginally more perseverative errors than did non-Hispanics ($F(1,50)=3.80$, $MSE=84.18$, $p=.06$, $\eta_p^2=.07$).

Taken together, our results revealed consistently lower scores for Hispanic normal controls relative to age-, education-, and gender-matched non-Hispanic controls on tests of language, executive function, and global cognitive ability. This discrepancy in performance is evident even though the controls in the present study were longitudinally followed for a number of years to ensure that individuals with preclinical or prodromal AD (or other neurodegenerative conditions) were not included in the Hispanic or non-

Hispanic group. Whether the discrepancy in performance between groups is related to culture (such as test bias), bilingualism, or other demographic differences (e.g., SES), or a combination of these factors remains unclear. Having found several significant baseline group differences in performance, we next turned to consider possible impact on the utility of cognitive tests for distinguishing between Hispanics with preclinical or prodromal AD (i.e., decliners) from those who remained cognitively normal.

Sensitivity of Measures to Eventual Progression to AD

Based on previous literature, we predicted that tests of global functioning (e.g. MMSE, DRS) and the WCST would be insensitive to future decline (e.g., Bondi, Monsch, Galasko, Butters, Salmon, & Delis, 1994; for review Twamley et al., 2006). The utility of phonemic fluency and visual memory for detecting preclinical AD is mixed (see review by Twamley et al., 2006), so we made no specific predictions regarding those tests. Although previous studies have shown that certain tests of episodic memory, semantic memory, and attention are sensitive to preclinical AD in non-Hispanics (for review, see Twamley et al., 2006), we were hesitant to predict that such tests would be sensitive in Hispanics given the significant differences we observed between Hispanic and non-Hispanic controls (see Table 3.2). Tests on which Hispanic controls obtained lower scores may have underestimated performance in this group, or could be culturally biased, and for this reason may be less sensitive to small changes in cognitive status.

Tests not sensitive to progression to AD in either group. As predicted, the MMSE (p 's $\geq .34$), DRS *Conceptualization* (p 's $\geq .47$) and *Initiation and Perseveration* (p 's $\geq .18$) subscales, and the number of categories sorted (p 's $\geq .13$) and perseverative errors (p 's $\geq .53$) on the WCST were not significantly different between decliners and controls

in either cultural group. Tests of visual memory were also insensitive to future decline for both groups: VR immediate recall (p 's $\geq .60$), VR delayed recall (p 's $> .28$) and VR copy (p 's $\geq .76$). This finding is consistent with a number of previous studies. Twamley et al. (2006) reported that only 28% of studies reviewed found that tests of visual memory were sensitive to future decline. Total score on the phonemic fluency task (p 's $\geq .48$), and all the letters "F", "A", and "S" (all p 's $\geq .19$), were insensitive to eventual progression to AD for both Hispanics and non-Hispanics. The numbers of intrusions and perseveration errors on the phonemic fluency task (all p 's $\geq .21$) were also insensitive to future decline in both groups. Similarly, the number of intrusion errors produced in semantic fluency were not sensitive to future decline in either group (all p 's $\geq .31$), even though semantic fluency scores were not sensitive to decline in Hispanics as they were for non-Hispanics (see below).

Tests sensitive to progression to AD in both groups. Given the paucity of research in this area, we made limited predictions. Despite the robust bilingual disadvantages in picture-naming reported in the literature (reviewed above), and the significantly lower scores for Hispanic relative to non-Hispanic controls on the BNT (in the current study), the BNT was sensitive to progression to AD in both Hispanics ($F(1,36)=8.19$, $MSE=8.81$, $p=.007$, $\eta_p^2=.19$) and non-Hispanics ($F(1,41)=6.27$, $MSE=5.54$, $p=.02$, $\eta_p^2=.13$). Similarly, times to complete TMT-A and TMT-B were sensitive to eventual progression to AD in both Hispanics ($F(1,36)=4.99$, $MSE=497.56$, $p=.03$, $\eta_p^2=.12$ and $F(1,35)=8.74$, $MSE=2456.10$, $p=.006$, $\eta_p^2=.20$ for TMT-A and TMT-B, respectively) and non-Hispanics ($F(1,42)=7.42$, $MSE=239.27$, $p=.009$, $\eta_p^2=.15$ and $F(1,42)=10.53$, $MSE=1775.56$, $p=.002$, $\eta_p^2=.20$ for TMT-A and TMT-B, respectively), even though

cognitively healthy Hispanics required significantly more time to complete the TMT-A and TMT-B tests than cognitively healthy non-Hispanics.

Tests sensitive to progression to AD in Hispanics but not non-Hispanics.

Cognitive measures that were sensitive to eventual progression to AD exclusively in Hispanics were limited to error scores with the possible exception of the Digit Symbol Substitution subtest of the WAIS-R which was marginally sensitive to future decline in Hispanics⁴ ($F(1,36)=3.64$, $MSE=90.15$, $p=.06$, $\eta_p^2=.09$) compared to non-Hispanics in which it was sensitive to future decline ($p=.84$). Hispanic decliners made significantly more errors on TMT-A ($F(1,36)=5.88$, $MSE=.37$, $p=.02$, $\eta_p^2=.14$), TMT-B ($F(1,35)=4.29$, $MSE=5.38$, $p=.05$, $\eta_p^2=.11$), and non-perseverative errors on the WCST ($F(1,34)=9.96$, $MSE=36.47$, $p=.003$, $\eta_p^2=.23$), than did Hispanic normal controls ($ps \geq .50$).

Tests sensitive to progression to AD in non-Hispanics but not Hispanics.

Contrary to our prediction that tests of global cognition would not be sensitive to decline, non-Hispanic normal controls scored significantly higher on the DRS *construction* subtest ($F(1,39)=4.79$, $MSE=.52$, $p=.04$, $\eta_p^2=.11$) and marginally higher on the DRS *memory* subtest ($F(1,39)=2.95$, $MSE=1.2$, $p=.09$, $\eta_p^2=.07$), than non-Hispanic decliners. This was not found in the Hispanic group ($ps \geq .25$).

Consistent with our prediction that verbal tests might be less sensitive to eventual progression to AD in Hispanic than in non-Hispanic participants, the WAIS-R Vocabulary subtest was not sensitive to future decline in the Hispanic group ($p=.40$) but was sensitive to decline in the non-Hispanic group ($F(1,32)=4.21$, $MSE=57.32$, $p=.05$, $\eta_p^2=.12$; for similar findings see Powell et al, 2006). Semantic fluency score was not

sensitive to future decline in Hispanics ($p=.19$) but was sensitive to decline in non-Hispanics ($F(1,42)=15.04$, $MSE=104.75$, $p<.001$, $\eta_p^2=.26$). Although none of the differences between Hispanic normal controls and Hispanic decliners approached significance across all three semantic fluency categories (i.e., *animals*, *vegetables*, and *fruits*; all $ps\geq.20$), non-Hispanic controls scored significantly higher than non-Hispanic decliners on all three semantic fluency categories (all $p's\leq.02$)

Of interest, Hispanic decliners produced significantly higher semantic fluency scores overall (collapsing all three fluency categories) than non-Hispanic decliners ($p=.02$). This result stands out in contrast to the otherwise consistently lower scores that cognitively healthy Hispanics had in semantic fluency (e.g., as reported above and in previous studies; e.g., Gollan et al., 2002; Portocarrero et al., 2007; Rosselli et al., 2000), and in many other measures in the current study (see above). To further explore this apparent reversal of the disadvantage with pending onset of AD, we conducted a series of 2 (normal controls vs. decliners) x 2 (Hispanic vs. non-Hispanic) ANOVAs with total semantic fluency scores, and with each of the individual subcategories (animals, fruits, and vegetables), as dependent variables. These analyses confirmed the presence of a significant crossover interaction effect: in those who remained cognitively normal, Hispanics produced fewer correct semantic fluency responses than non-Hispanics, whereas in those who later developed AD, Hispanics produced more correct responses than non-Hispanics (see Figure 3.1). This interaction was significant for total semantic fluency scores ($F(1,78)=4.60$, $MSE=399.19$, $p=.04$, $\eta_p^2=.06$), and for *animals* ($F(1,78)=4.38$, $MSE=84.41$, $p=.04$, $\eta_p^2=.05$) and *vegetables* ($F(1,78)=6.63$, $MSE=80.97$, $p=.01$, $\eta_p^2=.08$) categories, but not for the *fruits* category ($p=.60$). These results suggest

that semantic fluency scores remain stable in Hispanics for a longer period of time prior to clinical presentation of AD.

General Discussion

The goal of this study was to determine which neuropsychological tests are sensitive to preclinical AD and future cognitive decline in elderly Hispanic adults. Our prediction was that tests sensitive to future decline in monolingual non-Hispanics might not be sensitive to future decline in Hispanics because of cultural and linguistic differences that could affect test performance. Possible effects of these factors in our participants were initially assessed by comparing cognitively healthy Hispanics to non-Hispanics and these comparisons revealed a number of significant differences in test performance between cultural groups. Despite these differences, the results only partially confirmed our predictions, with some notable exceptions that have clinical implications in terms of the diagnostic utility of neuropsychological tests for identifying cognitive changes cross-culturally. In addition, the results may shed light on the nature of cognitive changes in preclinical Alzheimer's disease.

Looking first at participants who remained cognitively healthy for years after initial testing (i.e., 'robust' normal controls), Hispanics obtained significantly lower scores relative to age- and education-matched non-Hispanics on a number of verbal measures including the BNT, the Vocabulary subtest from the WAIS-R, and with trends in this direction for semantic and letter fluency (and significant differences for *animals*, *vegetables*, and "F" words). Hispanic controls also obtained lower scores than non-Hispanic controls on a number of non-verbal (or at least less verbally dependent) measures including the WAIS-R Digit Symbol Substitution test, and several subscales of

the DRS (*Attention, Conceptualization, and Memory*). These lower scores in Hispanic participants on these tests is consistent with previous reports and could be related to bilingualism, cultural bias, unidentified differences in socioeconomic status (SES) between the Hispanics and non-Hispanics, differences in the quality of education between the groups, or some combination of these or other factors.

A number of measures were not sensitive to future cognitive decline in Hispanics or non-Hispanics. These included brief measures of mental status (MMSE, several DRS subscales), some measures of executive function (categories sorted on the WCST, phonemic fluency), and a non-verbal measure of episodic memory (Visual Reproduction Test). The lack of sensitivity to preclinical AD for these measures (at least in the non-Hispanic group) is generally consistent with previous reports (see review in Twamley et al., 2006). It was somewhat surprising, that our only measure of delayed recall, the Visual Reproduction Test, lacked sensitivity to preclinical AD. Previous studies showed that tests of delayed recall predict future cognitive decline, but these studies have typically used sensitive tests of verbal episodic memory (Twamley et al., 2006). Additional power may be needed to detect relatively subtle changes in visual memory if they occur in preclinical AD.

A primary goal of the present study was to identify if cognitive tests that are sensitive to preclinical AD in non-Hispanics would also be sensitive in Hispanics. Contrary to our prediction, a number of tests seemed to predict future cognitive decline in both cultural groups. A few measures emerged as uniquely sensitive for detecting preclinical AD in Hispanic but not in non-Hispanic participants (e.g., the production of errors in TMT A, B, and the WCST). It is not clear why these measures should be

uniquely sensitive in one cultural group more than the other, but if replicated in future work this might provide useful information for early diagnosis of AD in Hispanics. In addition, a number of other measures revealed sensitivity to future decline in Hispanics even though Hispanics were disadvantaged, with medium to large effect sizes, on these measures. For example, the BNT, a picture naming task known to exhibit robust bilingual disadvantages (e.g., Roberts et al. 2002), and which exhibited a large disadvantage for Hispanics in the current study ($\eta_p^2=.12$), was nevertheless sensitive to future cognitive decline in this group. Similarly, the TMT-A and TMT-B were both sensitive to future decline in both cultural groups despite lower scores for Hispanic than non-Hispanic normal controls (and medium effect sizes; $\eta_p^2 \geq .10$). It is not clear why certain cognitive tests are sensitive to future decline in both groups despite robust cultural group effects on performance – but it could suggest that despite cultural bias, similar constructs are measured cross-culturally by these tests (see Siedlecki et al., 2010). Although it may be tempting to use these measures to predict cognitive decline in Hispanic older adults, we caution against this approach as it may lead to inappropriate conclusions in other respects. As suggested by Mehta and colleagues (2008), one solution (if available) is to examine longitudinal data that can indicate a person's degree of cognitive decline independent of population normative data. However this is only a temporary solution to a larger issue in neuropsychology. The reported findings speak to the importance of considering how demographic differences (e.g., SES), culture, bilingualism, and early AD might interact to affect test performance with the ultimate goal of producing accurate assessments for individuals of all cultural, demographic, and linguistic backgrounds.

More in line with our prediction, two verbal tests were sensitive to future decline

in non-Hispanics but not in Hispanics. Specifically, non-Hispanic decliners had lower vocabulary and semantic fluency scores relative to matched controls, whereas Hispanic decliners and their matched controls performed similarly. Based on a closer examination of the mean scores for these two tests, we speculate that they may be insensitive to future decline in Hispanics for different reasons. Looking at the Vocabulary test, the non-Hispanic controls' score stands out as being higher than the scores of all other groups (which are all about the same). For Hispanics on this test, the effects of education level, and degree of language exposure (due to bilingualism), may override any effects of an underlying disease process. Indeed vocabulary test scores may be more resistant to decline than other tests (e.g. see Martin & Fedio, 1983; though this cannot explain why this test was sensitive to decline in non-Hispanics). The sensitivity of picture naming across both cultural groups suggests that picture naming may be more strongly affected by Alzheimer's disease than vocabulary knowledge (e.g., see Huff, Corkin, & Growdon, 1986). A different pattern of results was observed for the semantic fluency test. Hispanic decliners had significantly higher semantic fluency scores than non-Hispanic decliners – a pattern not seen on any other test we examined. As shown in Figure 3.1, this interaction between cultural group (Hispanic, non-Hispanic) and cognitive status (decliner, control) was consistent across two (animals and vegetables) of the three semantic categories tested. Although speculative, this pattern could suggest that Hispanics with preclinical AD may be protected from the vulnerability in semantic fluency that characterizes preclinical AD in non-Hispanics. It is not clear why this was not observed for the fruits category, a category that also exhibited the numerically smallest difference of all three categories tested between decliners and controls in the

non-Hispanic group. Note that patterns of performance on individual fluency categories (and sensitivity to disease effects) can vary within category type; e.g., semantic categories usually (but not in all cases) generate more correct responses than most letter categories (Acevedo et al., 2000; Azuma et al., 1997; Bayles, Salmon, Tomoeda, Jacobs, Caffrey, Kaszniak, & Troster, 1989). It is possible that our findings reflect inherent differences between the individual categories, but given the small number of decliners tested it also seems possible that the results would change with increased power.

A possible explanation for the protective effect for Hispanics with preclinical AD may be related to effects of bilingualism on semantic fluency, and life-long competition between languages. Cognitively healthy Spanish-English bilinguals exhibit a semantic fluency disadvantage relative to matched monolinguals (Gollan et al., 2002; Portocarrero et al., 2007; Rosselli et al., 2000) that seems to be caused by competition for selection between languages (Sandoval, Gollan Ferreira, & Salmon, 2010). As exemplars from both languages become active, bilinguals are effectively placed in a dual-task scenario in which they have to simultaneously generate semantic category members, verify that exemplars belong to the target language, and inhibit production of non-target language category members. Similar competition effects present during normal language production may lead bilinguals to develop processing mechanisms that subsequently make them better able to produce exemplars from semantic memory despite changes to the integrity of semantic memory representations (e.g., Salmon & Bondi, 2009). This explanation is tentative but suggests avenues for future research that may ultimately lead to a better understanding of semantic fluency deficits in bilingualism and in AD.

A number of limitations in the current study call for some caution in interpretation

of the findings and suggest a need for further investigation. The longitudinal design of the ADRC study requires that test versions not be changed over time, and as a result several of the measures used in the current study have since been updated, and the results would need to be verified with updated versions (e.g., we used the WAIS-R not the WAIS-IV). Another limitation is that we did not have a detailed measure of verbal episodic memory, a cognitive domain that previous work has been shown to be particularly sensitive to preclinical AD (e.g., Bondi et al. 1999; Mickes et al., 2007). It will be important in future work to determine if there are cultural or bilingual effects that limit the effectiveness of verbal episodic memory tests in predicting future cognitive decline in elderly Hispanics. A third limitation is that there were more women than men decliners (particularly in the Hispanic group; see Table 3.1; but note that key results, e.g., the interaction between cultural group and cognitive status in semantic fluency, did not change when analyzed without men). Perhaps the most notable limitation is that we had a very small number of decliners (11 in each cultural group). This was because of our strict requirement that decliners be diagnosed as *normal controls* (e.g., we excluded MCI) in their first year of testing. Nevertheless, our results confirm the presence of bilingual disadvantages, suggest sensitivity in some but not all measures for detecting future decline across cultural groups, and highlight the potential advantages of considering cross-cultural differences in neuropsychological test performance when evaluating cognition in the elderly.

In sum, the results we reported reveal significant differences between cultural groups in sensitivity of tests to future cognitive decline, and contrary to our predictions, some sensitivity of a number of existing test measures to progression to AD in Spanish and English speaking Hispanics. These data may help to improve early diagnosis of AD

in Hispanics, but in future work it will be important to create tests that can optimally detect cognitive impairment across multiple cultural groups (e.g., see Ivanova, Salmon, & Gollan, 2012). In addition, the results we reported suggest some between group variability in the pattern of deficits that emerge at earliest stages of the disease (e.g., the presence or absence of semantic fluency deficits). If replicated (in future studies with a larger numbers of participants), these could reflect some cognitive advantages associated with cultural differences perhaps related to the need to manage two-languages in a single cognitive system. In this respect, the current study illustrates how cross-cultural comparisons can shed light on the cognitive mechanisms underlying neuropsychological test performance, and the effects of AD on these tests.

Chapter 3, in full, is a reprint of the material as it appears in: Weissberger, Gali H., Salmon, David P., Bondi, Mark W., & Gollan, Tamar H. "Which Neuropsychological Tests Predict Progression to Alzheimer's Disease in Hispanics?", *Neuropsychology*, vol. 27, 2013. The dissertation author was the primary investigator and author of this material.

References

- Abutalebi, J., & Green, D. (2007). Bilingual language production: The neurocognition of language representation and control. *Journal of Neurolinguistics*, 20, 242-275.
- Acevedo, A., Loewenstein, D. A., Barker, W. W., Harwood, D. G., Luis, C., Bravo, M.,... Duara, R. (2000). Category fluency test: Normative data for English- and Spanish-speaking elderly. *Journal of International Neuropsychological Conference*, 6, 760-769.
- Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of International Neuropsychological Society*, 7, 631-639.
- Ardila, A., Rosseli, M., & Puente, A. E., (1994). *Neuropsychological evaluation of the Spanish speaker*. New York: Plenum Press.
- Artiola i Fortuny, L., Heaton, R. K., & Hermosillo, D. (1998). Neuropsychological comparisons of Spanish-speaking participants from the U.S. – Mexico border region versus Spain. *Journal of the International Neuropsychological Society*, 4, 363-379.
- Artiola i Fortuny L, Garolera M, Hermosillo Romo D, Feldman E, Fernandez Barillas H, Keefe R, et al. (2005) Research with Spanish-speaking populations in the United States: Lost in translation a commentary and a plea. *Journal of Clinical and Experimental Neuropsychology*, 27, 555–564.
- Azuma, T., Bayles, K. A., Cruz, R. F., Tomoeda, C. K., Wood, J. A., McGeagh, A., & Montgomery, E. B. (1997). Comparing the difficulty of letter, semantic, and name fluency tasks for normal elderly and patients with Parkinson's disease. *Neuropsychology*, 11, 488-497.
- Bayles, K. A., Salmon, D. P., Tomoeda, C. K., Jacobs, D., Caffrey, J. T., Kaszniak, A. W., & Troster, A. I. (1989). Semantic and letter category naming in Alzheimer's patients: A predictable difference. *Developmental Neuropsychology*, 5, 335-347.
- Bäckman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain*, 124, 96-102.
- Bialystok, E. (1999). Cognitive complexity and attentional control in the bilingual mind. *Child Development*, 70, 636-644.
- Bialystok, E. (2010). Global–Local and Trail-Making Tasks by monolingual and bilingual children: Beyond inhibition. *Developmental Psychology*, 46, 93-105
- Bialystok, E., Craik, F.I.M., Green, D.W., & Gollan, T.H. (2009). Bilingual minds.

- Bialystok, E., Craik, F. I. M., Klein, R., & Viswanathan, M. (2004). Bilingualism, aging, and cognitive control: Evidence from the Simon Task. *Psychology and Aging*, 19, 290-303.
- Bialystok, E., Craik, F. I. M., & Luk, G. (2008). Cognitive control and lexical access in younger and older bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 34, 859-873.
- Bialystok, E., & Martin, M. M., (2004). Attention and inhibition in bilingual children: Evidence from the dimensional change card sort task. *Developmental Science*, 7, 325-339.
- Bialystok, E., & Shapero, D. (2005). Ambiguous benefits: The effect of bilingualism on reversing ambiguous figures. *Developmental Science*, 8, 595-604.
- Bohnstedt, M., Fox, P. J., & Kohatsu, N. D. (1994). Correlates of Mini-Mental-Status-Examination scores among elderly demented patients: The influence of race-ethnicity. *Journal of Clinical Epidemiology*, 47, 1381-1387.
- Bondi, M.W., Salmon, D.P., Galasko, D., Thomas, R.G., Thal, L.J. (1999). Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychology and Aging*, 14, 295-303
- Bondi, M. W., Monsch, A. U., Galasko, D., Butters, N., Salmon, D. P., & Delis, D. C. (1994). Preclinical cognitive markers of dementia of the Alzheimer type. *Neuropsychology*, 8, 374-384.
- Butters, N., Granholm, E., Salmon, D. P., Grant, I., & Wolfe, J. (1987). Episodic and semantic memory: A comparison of amnesic and demented patients. *Journal of Clinical and Experimental Neuropsychology*, 9, 479-497.
- Carlson, S.M., & Meltzoff, A.N. (2008). Bilingual experience and executive functioning in young children. *Developmental Science*, 11, 282-298.
- Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2000). Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology*, 55, 1847-1853.
- Chen, P., Ratcliff, G., Belle, S. H., Cauley, J.A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer's disease. *Archives of General Psychiatry*, 58, 853-858.
- Clark, C. M., DeCarli, C., Mungas, D., Chui, H. I., Higdon, R., Nuñez, J., . . . van Belle,

- G. (2005). Earlier onset of Alzheimer disease symptoms in Latino individuals compared with Anglo individuals. *Archives of Neurology*, 62, 774-778.
- Clark, L. J., Gatz, M., Zheng, L., Chen, Y-L, McCleary, C., & Mack, W. J. (2009). Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer disease. *American Journal of Alzheimer's Disease and Other Dementias*, 24, 461-468.
- Clark, L. R., Schiehser, D. M., Weissberger, G. H., Salmon, D. P., Delis, D. C., & Bondi, M. W. (2012). Specific measures of executive function predict cognitive decline in older adults. *Journal of the International Neuropsychological Society*, 18, 118-27.
- Coffey, D. M., Marmol, L., Schock, L., & Adams, W. (2005). The influence of acculturation on the Wisconsin Card Sorting Test by Mexican Americans. *Archives of Clinical Neuropsychology*, 20, 795-803.
- Consentino, S., Scarmeas, N., Albert, S. M., & Stern, Y. (2006). Verbal fluency predicts mortality in Alzheimer's disease. *Cognitive and Behavioral Neurology*, 19, 123-129.
- Costa, A., Hernández, M., Costa-Faidella, J., & Sebastián-Gallés, N. (2009). On the bilingual advantage in conflict processing: Now you see it, now you don't. *Cognition*, 113, 135-149.
- Costa, A., Hernández, M., & Sebastián-Gallés, N. (2008). Bilingualism aids conflict resolution: Evidence from the ANT task. *Cognition*, 106, 59-86.
- Dickerson, B. C., Sperling, R. A., Hyman, B. T., Albert, M. S., & Blacker, D. (2007). Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. *Archives of General Psychiatry*, 64, 1443-1450.
- Duara, R., Barker, W. W., Lopez-Alberola, R., Loewenstein, D. A., Grau, L. B., Gilchrist, D., ... St. George-Hyslop, P. H. (1996). Alzheimer's disease: Interaction of apolipoprotein E genotype, family history of dementia, gender, education, ethnicity, and age of onset. *Neurology*, 46, 1575-1579.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189-198.
- Galasko, D., Hansen, L., Katzman, R., Widerholt, W., Masliah, E., Terry, R., ..., Thal, L. J. (1994). Clinical-Neuropathological correlations in Alzheimer's disease and related dementias. *Archives of Neurology*, 51, 1994.

- Gasquoine, P. G. (1999). Variables moderating cultural and ethnic differences in neuropsychological assessment: The case of Hispanic Americans. *The Clinical Neuropsychologist*, 13, 376-383.
- Gollan, T. H., Fenema-Notestine, C., Montoya, R. I., & Jernigan, T. L. (2007). The bilingual effect on Boston Naming Test performance. *Journal of the International Neuropsychological Society*, 13, 197-208.
- Gollan, T. H., & Ferreira, V. S. (2009). Should I stay or should I switch? A cost-benefit analysis of voluntary language switching in young and aging bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 35, 640-665.
- Gollan, T. H., Montoya, R. I., Fennema-Notestine, C., & Morris, S. K. (2005). Bilingualism affects picture naming but not picture classification. *Memory and Cognition*, 33, 1220-1234.
- Gollan, T. H., Montoya, R. I., & Werner, G. A. (2002). Semantic and letter fluency in Spanish-English bilinguals. *Neuropsychology*, 16, 562-576.
- Gollan, T. H., Salmon, D.P., Montoya, R.I., & Galasko, D.R. (2011). Degree of Bilingualism Predicts Age of Diagnosis of Alzheimer's Disease in Low-Education but not in Highly-Educated Hispanics, *Neuropsychologia*, 49, 3826-3830.
- Gollan, T. H., & Silverberg, N. B. (2001). Tip-of-the-tongue states in Hebrew-English bilinguals. *Bilingualism: Language and Cognition*, 4, 63-83.
- Gollan, T.H., Weissberger, G., Runnqvist, E., Montoya, R.I., & Cera, C.M. (2011) Self-ratings of spoken language dominance: A multi-lingual naming test (MINT) and preliminary norms for young and aging Spanish-English bilinguals. *Bilingualism: Language and Cognition*, 15, 594-615.
- Harris, M. I. (1991). Epidemiological correlates of NIDDM in Hispanics, Whites, and Blacks in the U.S. population. *Diabetes Care*, 14, 639-648.
- Helzner, E. P., Scarmeas, N., Cosentino, S., Tang, M. X., Schupf, N., & Stern, Y. (2008). Survival in Alzheimer's disease: A multiethnic, population-based study of incident cases. *Neurology*, 71, 1489-1495.
- Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: A meta-analysis. *Neuropsychologia*, 42(9), 1212-1222.
- Hernandez, A. E. (2009). Language switching in the bilingual brain: What's next? *Brain and Language*, 109, 133-140.

- Hohl, U., Grundman, M., Salmon, D. P., Thomas, R. G., & Thal, L. J. (1999). Mini-Mental State Examination and Mattis Dementia Rating Scale performance differs in Hispanics and non-Hispanic Alzheimer's disease patients. *Journal of the International Neuropsychological Society*, 5, 301-307.
- Howieson, D. B., Dame, A., Camicioli, R., Sexton, G., Payami, H., & Kaye, J. (1997). Cognitive markers preceding Alzheimer's dementia in healthy oldest old. *Neurology*, 45, 584-589.
- Huff, F. J., Corkin, S., & Growdon, J. H. (1986). Semantic impairment and anomia in Alzheimer's disease. *Brain and Language*, 28, 235-249.
- Hughes, C.P., Berg, L., Danzinger, W.L., Coben, L.A., & Martin, R.L. (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry*, 140, 566-572.
- International Test Commission. (2002). *International Test Commission test adaptation guidelines*, from www.intestcom.org
- Ivanova, I., & Costa, A. (2008). Does bilingualism hamper lexical access in speech production? *Acta Psychologica*, 127, 277-288.
- Ivanova, I., Salmon, D.P., & Gollan, T.H. (2012). The Multilingual Naming Test in Alzheimer's Disease: Clues to the Origin of Naming Impairments *The Journal of the International Neuropsychological Society*
- Jacobs, D. M., Sano, M., Dooneief, G., Marder, K., Bell, K. L., & Stern, Y. (1995). Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology*, 45, 957-962.
- Judd, T., Capetillo, D., Carrión-Baralt, Mármol, L. M., San Miguel-Montes, L., Navarrete, M. G.,...Silver, C. H. (2009). Professional considerations for improving the neuropsychological evaluation of Hispanics: A National Academy of Neuropsychology education paper. *Archives of Clinical Neuropsychology*, 24, 127-135.
- Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia: Lea & Febiger.
- Kavé, G., Eyal, N., Shorek, A., & Cohen-Mansfield, J. (2008). Multilingualism and cognitive state in the oldest old. *Psychology and Aging*, 23, 70-78.
- Kohnert, K. J., Hernandez, A. E., & Bates, E. (1998). Bilingual performance on the Boston Naming Test: Preliminary norms in Spanish and English. *Brain and*

Language, 65, 422-440.

- Kovács, A. (2009). Early bilingualism enhances mechanisms of false-belief reasoning. *Developmental Science*, 12, 48-54.
- Kovács, A.M., & Mehler, J. (2009). Cognitive gains in 7-month-old bilingual infants. *Proceedings of the National Academy of Sciences, USA*, 106, 6556–6560.
- Kroll, J. F., & Gollan, T. H. (in press). Speech planning in two languages: What bilinguals tell us about language production. In V. Ferreira, M. Goldrick, & M. Miozzo (Eds.). *The Oxford handbook of language production*. Oxford: Oxford University Press.
- Kwon, O. D., Khaleeq, A., Chan, W., Pavlik, V. N., & Doody, R. S. (2010). Apolipoprotein E polymorphism and age at onset of Alzheimer's disease in a quadriethnic sample. *Dementia and Geriatric Cognitive Disorders*, 30, 486-491.
- La Rue, A., Romero, L. J., Ortiz, I. E., Lang, H. C., & Lindeman, R. D. (2010). Neuropsychological performance of Hispanic and non-Hispanic older adults: An epidemiologic survey. *The Clinical Neuropsychologist*, 13, 474-486.
- Lange, K. L., Bondi, M. W., Salmon, D. P., Galasko, D., Delis, D. C., Thomas, R. G., & Thal, L. J. (2002). Decline in verbal memory during preclinical Alzheimer's disease: Examination of the effect of APOE genotype. *Journal of International Neuropsychological Society*, 8, 943-955.
- Linn, R. T., Wolf, P., Bachman, D. L., Knoefel, J. E., Cobb, J. L., Belanger, A. J.,... D'Agostino, R. B. (1995). The 'preclinical phase' of probable Alzheimer's disease: A 13-year prospective study of the Framingham cohort. *Archives of Neurology*, 52, 485-490.
- Livney, M. G., Clark, C. M., Karlawish, J. H., Cartmell, S., Negrón, M., Nuñez-Lopez, J.,... Arnold, S. E. (2011). Ethnoracial differences in the clinical characteristics of Alzheimer's disease at initial presentation at an urban Alzheimer's disease center. *American Journal of Geriatric Psychiatry*, 19, 430-439.
- Looi, J. C. L., & Sachdev, P. S. (1999). Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology*, 53, 670-678.
- Lucas, J. A., Ivnik, R. J., Willis, F. B., Ferman, T. J., Smith, G. E., Parfitt, F. C.,... Graff-Radford, N. R. (2005). Mayo's older African American normative studies: Normative data for commonly used clinical neuropsychological measures. *The Clinical Neuropsychologist*, 19, 162-183.
- Lyness, S. A., Hernandez, I., Chui, H. C., & Teng, E. L. (2006). Performance of Spanish

- speakers on the Mattis dementia rating scale (MDRS). *Archives of Clinical Neuropsychology*, 21, 827-836.
- Maj, M., D'Elia, L., Satz, P., Janssen, R., Zaudig, M., Uchiyama, C.,...Galderisi, S. (1993). Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: A WHO study. *Archives of Clinical Neuropsychology*, 8, 123-135.
- Manly, J. J., & Echemendia, R. J. (2007). Race-specific norms: Using the model of hypertension to understand issues of race, culture, and education in neuropsychology. *Archives of Clinical Neuropsychology*, 22, 319-325.
- Martin, A., & Fedio, P. (1983). Word production and comprehension in Alzheimer's disease: The breakdown of semantic knowledge. *Brain and Language*, 19, 124-141.
- Martin-Rhee, M.M., & Bialystok, E. (2008). The development of two types of inhibitory control in monolingual and bilingual children. *Bilingualism: Language and Cognition*, 11, 81-93.
- Mattis, S. (1988). Dementia Rating Scale: Professional Manual. Odessa, Florida: Psychological Assessment Resources
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E.M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group. *Neurology*, 34, 939-944.
- Mehta, K. M., Yaffe, K., Pérez-Stable, E. J., Stewart, A., Barnes, D., Kurland, B. F., & Miller, B. L. (2008). Race/ethnic differences in AD survival in US Alzheimer's disease centers. *Neurology*, 70, 1163-1170.
- Mickes, L., Wixted, J. T., Fenema-Notestine, C., Galasko, D., Bondi, M. W., Thal, L. J., & Salmon, D. P. (2007). Progressive impairment on neuropsychological tasks in a longitudinal study of preclinical Alzheimer's disease. *Neuropsychology*, 21, 696-705.
- Morris, J.C., McKeel, D.W., Storandt, M., Rubin, E.H., Price, J.L., Grant, E.A., Ball, M.J., & Berg, L. (1991). Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathologic distinction from normal aging. *Neurology*, 41, 469-478.
- Mulgrew, C. L., Morgenstern, N., Shetterly, S. M., Baxter, J., Barón, A. E., & Hamman, R. F. (1999). Cognitive functioning and impairment among rural elderly Hispanics and non-Hispanic Whites as assessed by the Mini-Mental State Examination. *Journal of Gerontology*, 54, 223-230.

- Nelson, H.E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex*, 12, 313-324.
- Ott, A., Stolk, R. P., van Harskamp, F., Pols, H. A. P., Hofman, A., & Breteler, M. M. B. (1999). Diabetes mellitus and the risk of dementia: The Rotterdam study. *Neurology*, 53, 1937-1942.
- Pedraza, O., & Mungas, D. (2008). Measurement in cross-cultural neuropsychology. *Neuropsychological Review*, 18, 184-193.
- Peña, E. D. (2007). Lost in translation: Methodological considerations in cross-cultural research. *Child Development*, 78, 1255-1264.
- Peña-Casanova, J., Quiñones-Úbeda, S., Gramunt-Fombuena, N., Quintana-Aparicio, M., Aguilar, M., Badenes, D..., Blesa, R. (2009). Spanish multicenter normative studies (NEURONORMA Project): Norms for verbal fluency tests. *Archives of Clinical Neuropsychology*, 24, 395-411.
- Pfeffer, R., Kurosaki, T.T., Harrah, C.H., Chance, J.M., & Filos S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology*, 37, 323-329.
- Pontón, M. O., & Ardila, A. (1999). The future of neuropsychology with Hispanic populations in the United States. *Archives of Clinical Neuropsychology*, 14, 565-580.
- Pontón, M. O., Satz, P., Herrera, L., Ortiz, F., Urrutia, C. P., Young, R.,...Namerow, N. (1996). Normative data stratified by age and education for the Neuropsychological Screening Battery for Hispanics (NeSBHIS): Initial report. *Journal of the International Neuropsychological Society*, 2, 96-104.
- Portocarrero, J. S., Burright, R. G. & Donovanick, P. J. (2007). Vocabulary and verbal fluency of bilingual and monolingual college students. *Archives of Clinical Neuropsychology*, 22, 415-422.
- Powell, M.R., Smith, G.E., Knopman, D.S., Parisi, J.E., Boeve, B.F., Petersen, R.C., Ivnik, R.J. (2006). Cognitive measures predict pathologic Alzheimer disease. *Archives of Neurology* 63, 865-868.
- Proctor, A., & Zhang, J. (2008). Performance of three racial/ethnic groups on two tests of executive function: Clinical implications for traumatic brain injury (TBI). *Neurorehabilitation*, 23, 529-536.
- Rapp, M. A., & Reischies, F. M. (2005). Attention and executive control predict

- Alzheimer's disease in late life: Results from the Berlin aging study (BASE). *American Journal of Geriatric Psychiatry*, 13, 134-141.
- Ringman, J. M., & Flores, D. L. (2005). Effects of Alzheimer's onset in Latino persons: Ethnic differences vs. selection bias. *Archives of Neurology*, 62, 1786-1787.
- Reitan, R. M. (1958). Validity of the Trail Making Test to organic brain damage. *Perceptual Motor Skills*, 8, 271-276.
- Rey, G. J., Feldman, E., Rivas-Vasquez, R., Levin, B. E., & Benton, A. (1999). Neuropsychological test development and normative data on Hispanics. *Archives of Clinical Neuropsychology*, 14, 593-601.
- Roberts, P. M., Garcia, L. J., Desrochers, A., Hernandez, D. (2002). English performance of proficient bilingual adults on the Boston Naming Test. *Apahsiology*, 16, 635-645.
- Rosselli, M., Ardila, A., Araujo, K., Weekes, V. A., Caracciolo, V., Padilla, M., & Ostrosky-Solís, F. (2000). Verbal fluency and repetition skills in healthy older Spanish-English bilinguals. *Applied Neuropsychology*, 7, 17-24.
- Russell, E. W. (1975). A multiple scoring method for the assessment of complex memory functions. *Journal of Consulting and Clinical Psychology*, 43, 800-809.
- Sacco, R. L., Boden-Albala, B., Gan, R., Chen, X., Kargman, D. E., Shea, S., Paik, M. C., & Hauser, W. A. (1998). Stroke incidence among white, black, and Hispanic residents of an urban community: The northern Manhattan stroke study. *American Journal of Epidemiology*, 147, 259-268.
- Sacco, R. L., Hauser, W. A., & Mohr, J. P. (1991). Hospitalized stroke in blacks and Hispanics in northern Manhattan. *Stroke*, 22, 1491-1496.
- Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annual Review of Psychology*, 60, 257-282.
- Salvatierra, J., Rosselli, M., Acevedo, A., & Duara, R. (2007). Verbal fluency in bilingual Spanish/English alzheimer's disease patients. *American Journal of Alzheimer's Disease and Other Dementias*, 22(3), 190-201.
- Sandoval, T.C., Gollan, T.H., Ferreira, V.S., & Salmon, D.P. (2010). What causes the bilingual disadvantage in verbal fluency: The dual-task analogy. *Bilingualism: Language and Cognition*, 13, 231-252.
- Siedlecki, K.L., Manly, J.J., Brickman, A.M., Schupf, N., Tang, M.X., Stern, Y. (2010). Do neuropsychological tests have the same meaning in Spanish speakers as they

do in English speakers? *Neuropsychology*, 24, 402-411.

- Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R. Jr., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V., Phelps, C.H. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dementia*, 7, 280-92.
- Thurstone, L. L., & Thurstone, T. G. (1941). Factorial studies of intelligence. *Psychometric Monographs*, 2, 94.
- Twamley, E. W., Ropacki, S. A., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society*, 12, 707-735.
- US Census Bureau. Available at: <http://www.census.gov>. Accessed 2010.
- Verney, S. P., Granholm, E., Marshall, S. P., Malcarne, V. L., and Saccuzzo, D. P. (2005). Culture-fair cognitive ability assessment: Information processing and psychophysiological approaches. *Assessment*, 12, 303-319.
- Waring, S. C., Doody, R. S., Pavlik, V. N., Massman, P. J., & Chan, W. (2005). Survival among patients with dementia from a large multi-ethnic population. *Alzheimer's Disease and Associated Disorders*, 19, 178-183.
- Wechsler, D. (1981). Wechsler Adult Intelligence Scale Revised Manual. San Antonio, CA: The Psychological Corporation.
- Woodard, J.L., Seidenberg, M., Nielson, K.A., Smith, J.C., Antuono, P., Durgerian, S., Guidotti, L., Zhang, Q., Butts, A., Hantke, N., Lancaster, M., Rao, S.M. (2010). Prediction of cognitive decline in healthy older adults using fMRI. *Journal of Alzheimers Disease*, 21, 871-85.

Footnotes

1. These inclusion criteria were relaxed for two Hispanic decliners. One was diagnosed with Mild Neurocognitive Disorder in year 1 of testing, but was then re-classified as a normal control for six subsequent years, before receiving a diagnosis of probable AD. Analyzing the data with and without this participant did not change the findings reported below. The second was diagnosed as a normal control in year 1 of testing and with possible AD at year 2 (only 2 years of testing were available). McKhann et al. (1984) criteria for possible AD state the presence of a dementia syndrome in which there are variations in onset, presentation, or clinical course, or in which there is a second systemic or neurologic disorder that is insufficient to produce dementia. Analyzing the data without this participant slightly changed one finding which is reported below in a footnote.

2. Because the ADRC longitudinal study was initiated in 1990, Spanish-speakers were also tested with “F” “A” and “S” despite later indications in the literature that the “P”, “M”, and “R” may be preferred when testing in Spanish (see Artiola y Fortuny, Heaton, & Hermosillo, 1998; Peña et al., 2009).

3. Only letter “F” produced a significant difference between Hispanic and non-Hispanic normal controls, ($F(1,58)=4.25$, $MSE=18.34$, $p=.04$, $\eta_p^2=.07$), letters “S” & “A” did not, ($ps \geq .11$). In addition, although Spanish speakers may be better assessed with letters P, M, and R (Artiola et al., 1998; Peña-Casanova et al., 2009), we did not observe significant differences in the present study in total letter fluency scores between Hispanics tested in English versus Spanish on the letters F, A, and S, for normal controls ($p = .46$) or decliners ($p = .13$).

4. Difference between Hispanic normal controls and decliners on Digit Symbol changed from marginally significant to significant when excluding the participant with a diagnosis of possible AD ($F(1,35)=4.29$, $MSE=90.62$, $p=.05$, $\eta_p^2=.11$).

Table 3.1: Participant demographics for non-Hispanic normal controls and decliners and Hispanic normal controls and decliners.

	Hispanic Normal Controls (n = 27)		Hispanic Decliners (n = 11)		non-Hispanic Normal Controls (n = 33)		non-Hispanic Decliners (n = 11)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age	72.1	4.0	71.7	5.1	73.5	5.4	73.0	8.2
% Female	52%	-	91%	-	55%	N/A	55%	N/A
Education	12.3	3.2	12.8	3.7	11.9	0.9	12.1	1.8
Years prior to diagnosis	-	-	5.0	3.6	-	-	5.2	2.8
Percent tested in English	41%	-	36%	-	-	-	-	-
Age 1 st Exposure to English	9.1 ²	10.1	8.0 ³	11.2	-	-	-	-
Age 1 st Exposure to Spanish	0.0 ²	0.0	0.0 ⁴	0.0	-	-	-	-
%Currently Using Spanish	39.9% ²	39.8%	44.8% ⁴	43.9%	-	-	-	-
Self Ratings ¹ :								
Spoken English	5.6 ²	1.9	5.8 ⁴	1.5	-	-	-	-
Spoken Spanish	5.7 ²	1.3	5.8 ⁴	1.6	-	-	-	-
Writing English	5.2 ²	2.0	5.7 ⁴	1.8	-	-	-	-
Writing Spanish	4.6 ²	2.1	5.6 ⁴	2.2	-	-	-	-
Reading English	5.5 ²	1.8	5.9 ⁴	1.3	-	-	-	-
Reading Spanish	4.7 ²	1.9	5.5 ⁴	2.3	-	-	-	-

¹Self-ratings were based on a 7-point scale: 1 (almost none), 2 (very poor), 3 (fair), 4 (functional), 5 (good), 6 (very good), 7 (like native speaker).

² n=15 due to missing language history questionnaire data

³ n=6 due to missing language history questionnaire data

⁴ n=8 due to missing language history questionnaire data

□

Table 3.2: Means and standard deviations for participants on all neuropsychological measures.

Test Name	Hispanics			Non-Hispanics			Significant Differences	
	Normal Control	Decliner		Normal Control	Decliner		NC vs. decliner	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	NC vs. non-Hisp	Non-Hisp vs. Hispanic
MMSE	29.3	(0.9)	28.9	(1.6)	29.0	(1.2)		
Dementia Rating Scale:								
Total Score	134.8	(5.1)	131.6	(7.6)	138.3	(4.2)	**	
Attention	35.4	(1.3)	34.2	(1.7)	36.2	(1.1)	*	*
Construction	5.3	(0.8)	5.1	(0.7)	5.5	(0.7)		*
Initiation and Perseveration	35.3	(2.3)	34.1	(3.1)	35.6	(3.0)		
Conceptualization	34.9	(3.2)	35.6	(3.0)	36.8	(2.0)	**	
Memory	23.5	(1.4)	22.6	(3.2)	24.3	(1.0)	**	†
Visual Reproduction								
Copy	16.7	(2.4)	17.0	(2.1)	17.1	(2.2)		
Immediate	11.3	(3.9)	10.6	(4.0)	12.2	(3.9)		
Delay	8.2	(3.4)	6.9	(2.8)	8.3	(4.8)		
WAIS-R Digit Symbol	37.3	(8.8)	30.8	(11.0)	51.9	(19.2)	**	†
WAIS-R Vocabulary	43.6	(13.2)	39.1	(17.5)	56.2	(6.3)	**	*
Trail Making Test A								
Time to Complete	47.2	(13.7)	65.0	(36.1)	38.7	(12.7)	*	**
Errors of Commission	0.1	(0.3)	0.6	(1.0)	0.2	(0.7)		*
Trail Making Test B								
Time to Complete	113.8	(36.9)	166.0	(72.1)	91.7	(28.4)	**	**
Errors of Commission	0.5	(0.7)	0.6	(0.9)	0.6	(0.7)		
Boston Naming Test	26.0	(2.5)	23.0	(3.8)	27.7	(2.1)	**	*

Table 3.2: Means and standard deviations for participants on all neuropsychological measures.

Test Name	Hispanics				Non-Hispanics				Significant Differences	
	Normal Control		Decliner		Normal Control		Decliner		NC Hisp vs. non-Hisp	NC vs. decliner
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Phonemic Fluency:										
Total Correct	34.9	(12.3)	32.6	(12.7)	40.3	(12.7)	37.4	(8.9)	†	
Letter F	11.4	(4.1)	12.3	(4.9)	13.7	(4.4)	11.8	(2.6)	*	
Letter A	10.4	(5.0)	9.6	(5.3)	11.3	(4.4)	11.9	(3.2)		
Letter S	13.0	(5.2)	10.7	(4.0)	15.3	(5.4)	13.6	(5.4)	†	
Intrusions	0.8	(1.0)	1.0	(1.5)	0.4	(0.7)	0.6	(0.8)	*	
Perseveration	1.4	(1.2)	2.2	(2.7)	1.3	(1.3)	1.47	(1.6)		
Semantic Fluency:										
Total Correct	43.5	(8.7)	39.6	(6.2)	48.6	(11.2)	34.8	(6.2)	†	**
Animals	17.8	(4.1)	16.0	(3.1)	20.3	(5.0)	13.6	(3.7)	*	**
Vegetables	12.3	(4.0)	12.7	(2.5)	14.4	(3.8)	9.6	(2.0)	*	**
Fruits	15.0	(3.2)	13.6	(3.0)	15.7	(4.3)	12.3	(2.9)		*
Intrusions	0.4	(1.4)	0.9	(1.3)	0.2	(0.7)	0.2	(0.6)		†
Perseveration	1.2	(1.3)	1.7	(1.9)	1.5	(2.1)	0.4	(0.9)		
Wisconsin Card										
Sorting Test										
Total Categories	4.8	(1.7)	3.8	(1.8)	5.2	(1.3)	4.6	(2.0)		
Non-Perseverative Errors	6.3	(4.8)	13.4	(8.6)	7.7	(4.5)	9.4	(9.7)		**
Perseverative Errors	7.0	(12.5)	6.4	(7.4)	2.0	(3.4)	3.1	(6.6)	†	

†Marginally significant trend towards a difference, $p \leq .10$ * Significant difference of $p \leq .05$; ** Significant difference of $p \leq .01$

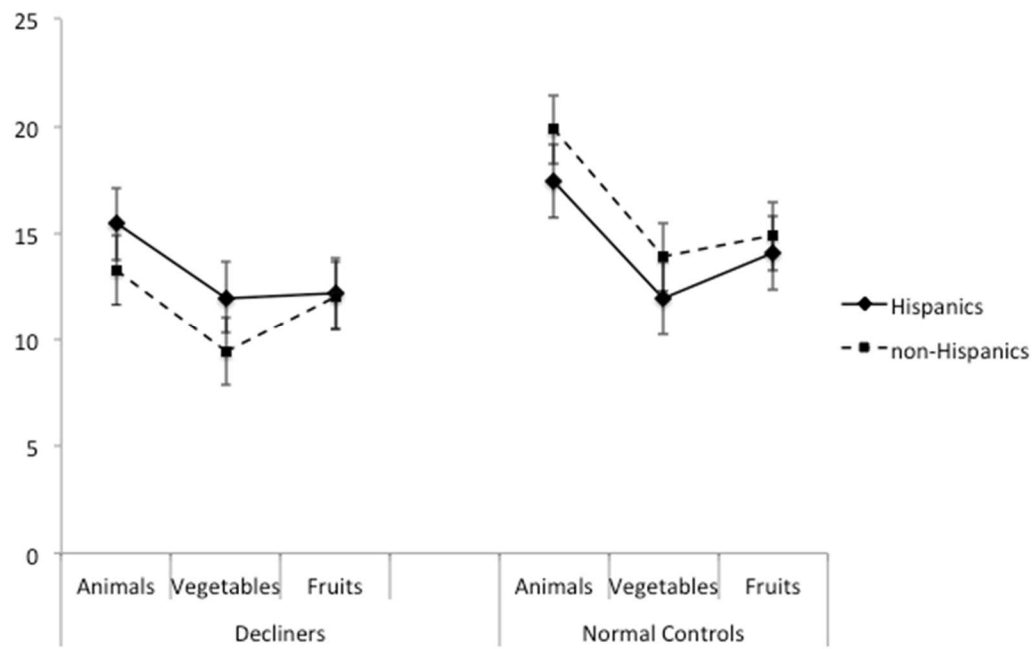


Figure 3.1: Cross-over interaction for semantic fluency total score and subcategories.

CHAPTER 4: NEUROPSYCHOLOGICAL AND NEUROPATHOLOGICAL
PROFILES OF HISPANIC OLDER ADULTS WITH AUTOPSY-CONFIRMED
ALZHEIMER'S DISEASE

Gali H. Weissberger¹, Tamar H. Gollan^{2,3}, Mark W. Bondi^{2,7}, Daniel A. Nation⁸,
Lawrence A. Hansen^{4,5}, Douglas Galasko^{4,6} & David P. Salmon⁴

¹ Joint Doctoral Program in Clinical Psychology, San Diego State University/University
of California, San Diego, 6363 Alvarado Ct. #103, San Diego, 92120-4913

Departments of ²Psychiatry, ³Psychology, ⁴Neurosciences, and ⁵Neuropathology,
University of California, San Diego, 9500 Gilman Dr., MC: 0603, La Jolla, CA 92093-
0603

⁶Neurology and ⁷Psychiatry Services, VA San Diego Healthcare System, 3350 La Jolla
Village Dr., San Diego, 92161

⁸Department of Psychology, University of Southern California, 3620 South McClintock
Ave. Los Angeles, 90089

Address for correspondence:

Gali Weissberger
VA San Diego Healthcare System
3350 La Jolla Village Dr., MC 116B
San Diego, CA 92161
Email: gweissbe@gmail.com

Abstract

Differing patterns of neuropsychological deficits exhibited by Hispanics and non-Hispanics with Alzheimer's disease (AD) could arise from 1) cultural/language biases in tests that lead to inaccurate clinical diagnosis, or 2) a higher prevalence of concomitant non-AD brain pathology in Hispanics. Twenty-nine Hispanics who participated in the University of California, San Diego (UCSD) Alzheimer's Disease Research Center (ADRC) died and came to autopsy. We compared the cognitive and neuropathological profiles of a subset of Hispanics with autopsy-confirmed AD ($n = 10$) who scored ≥ 100 on the Dementia Rating Scale at baseline testing to non-Hispanics ($n = 25$) with autopsy-confirmed AD who were matched on age, education, DRS, and test-death interval. Patients were also compared to age- and education-matched healthy-aging controls (10 Hispanic; 25 non-Hispanic) on baseline neuropsychological testing. Across many neuropsychological measures, an overall pattern arose in which non-Hispanic AD patients performed worse than Hispanic AD patients, while non-Hispanic controls performed better than Hispanic controls. Hispanic AD patients had lower Braak stages and less plaque/tangle pathology than non-Hispanics, but more small parenchymal arteriolar disease. Findings suggest that cognitive deficit profiles in AD patients are less salient and less severe in Hispanics than non-Hispanics. Nonetheless, we found 86% sensitivity in clinically diagnosing AD and 75% specificity in diagnosing non-AD cases.

Introduction

Alzheimer's disease (AD) currently affects approximately 5.2 million Americans and is one of the leading cause of death in the United States. The prevalence of AD is expected to increase to 11-16 million Americans by the year 2050 (Alzheimer's Association Report, 2012). The growing prevalence of AD in the United States is occurring in conjunction with a growing Hispanic population (US Census, 2010). Therefore, the increase in prevalence of AD will be particularly severe in the Hispanic community. As the presence of AD increases in Hispanics, consideration must be given to how cultural factors might influence the clinical manifestation of the disease within this minority population. It is important to ensure that current clinical and neuropsychological procedures used to detect AD, developed in largely non-Hispanic Caucasian populations, are effective in accurately detecting the disease in elderly Hispanic individuals. A crucial component of this effort is to verify the clinical diagnosis of AD with neuropathological evidence of the disease at autopsy, and then to retrospectively determine how the neuropsychological presentation of the disease might differ in Hispanics and non-Hispanics.

There are several factors that could influence the neuropsychological presentation of AD in Hispanic older adults. First, the Hispanic population in the United States has a higher than average rate of neurovascular risk factors such as cardiovascular disease, diabetes, and stroke (e.g., Daviglus et al., 2012; Ennis, Rios-Vargas, Albert, 2010; McBean, Li, Gilbertson, & Collins, 2004; Roger et al., 2012; Winkleby, Kraemer, Ahn, & Varady, 1998). Consistent with these findings, there is neuroimaging evidence of more white matter hyperintensities in Hispanics than non-Hispanics (Brickman et al.,

2008). Increased neurovascular risk is related to accelerated cognitive decline and greater rates of dementia in the elderly (Cheng, Huang, Deng, & Wang, 2012; Haan et al., 2003; for reviews, see Allen, Frier, & Strachan, 2004; Feldstein, 2012; Gorelick et al., 2011; Qiu, 2011). The contribution of neurovascular risk to the likelihood of dementia appears to be independent of AD pathology (e.g., Lo & Jagust, 2012; Schneider, Wilson, Bienias, Evans, & Bennett, 2004). Lo and Jagust (2012), for example, found that white matter hyperintensities and severity of cardiovascular risk did not predict rate of change in AD biomarkers in normal elderly, but did predict cognitive decline, particularly in executive functioning. These results suggest that neurovascular disease and AD are separate pathological processes that can independently or synergistically contribute to neuropsychological deficits. Because neurovascular disease and AD lead to distinct (but overlapping) patterns of cognitive deficits (Reed et al., 2007), over-representation of neurovascular disease in elderly Hispanic individuals might modify the typical pattern of cognitive deficits associated with AD and make it more difficult to clinically diagnose AD in this cohort than in a non-Hispanic cohort.

A second factor that might impact the clinical presentation of AD in elderly Hispanic individuals is the high rate of bilingualism in this cohort in the United States. Bilingualism is associated with advantages and disadvantages on neuropsychological tests that are often used in the assessment of dementia (for review, see Bialystok, Craik, Green, & Gollan, 2009). Bilinguals perform better than monolinguals on tests of executive function (e.g., Stroop Test, see Bialystok, Craik, & Luk, 2008; Trail Making Test, see Bialystok, 2010; Zahodne, Schofield, Farrell, Stern, & Manly, 2013), but worse on linguistic tasks that assess confrontation naming ability (Roberts, Garcia, Desrochers,

& Hernandez, 2002; Weissberger, Salmon, Bondi, & Gollan, 2013), vocabulary knowledge (e.g., WAIS-R Vocabulary, Weissberger et al., 2013) or verbal fluency (Gollan, Montoya, & Werner, 2002; Portocarrero, Burright, & Donovan, 2007). These advantages and disadvantages could affect the ability to neuropsychologically identify AD in elderly Hispanics in two ways. First, tests that are sensitive to AD pathology might be more sensitive or less sensitive in bilinguals than in monolinguals (depending on whether there is a bilingual advantage or disadvantage) because bilingualism strengthens or weakens the neural basis of the tested ability (e.g., see Weissberger et al., 2013). For example, extensive use of executive function to monitor and control the use of two languages could enhance its neural substrate and make it less vulnerable to the adverse effects of AD pathology. Second, cognitive deficits associated with AD in bilinguals occur against the background of normal cognitive advantages and disadvantages so comparison to normative data from monolingual cohorts (that don't have these advantages and disadvantages) might lead to underestimation or overestimation of their deficit.

To address these possibilities, we compared neuropsychological deficit profiles in Hispanic and non-Hispanic older adults with autopsy-confirmed AD.

Neuropsychological test data were taken from the initial evaluation each patient received as part of a longitudinal study carried out at the UCSD Alzheimer's Disease Research Center (ADRC). Deficit profiles were determined relative to the test performance of separate age- and education-matched normal control groups that were culturally appropriate for each patient group. We also compared the prevalence of neurovascular risk factors and concomitant neurovascular pathology at autopsy in the Hispanic and non-

Hispanic patient groups. We predicted that Hispanic and non-Hispanic older adults with AD would exhibit different patterns of cognitive impairment, relative to their respective healthy control group. Specifically, we hypothesized that more vascular pathology and elevated cardiovascular disease risk would be evident in Hispanics than non-Hispanics, and that this over-representation of neurovascular changes would lead to greater deficits in executive function and visuospatial/psychomotor skills in Hispanics with AD relative to non-Hispanics with AD, even if memory deficits were at the same level in the two groups. We also hypothesized that bilingualism in the Hispanic participants would impact performance on tests of language abilities so that Hispanic patients would be less likely than monolingual non-Hispanic patients to display significant language deficits relative to their culturally-appropriate control groups. These differences across cognitive domains were expected to reduce the saliency of the pattern used to differentiate AD from normal aging or other dementia-producing neurodegenerative diseases. Previous studies with non-Hispanic cohorts have shown that patients with AD typically exhibit a pattern of deficits on neuropsychological testing that is characterized by episodic memory, semantic knowledge (e.g., language) and executive function deficits that are greater than those of visuospatial abilities, attention and psychomotor skills (for reviews, see Salmon & Bondi, 1999; 2009). Alteration of this pattern by cardiovascular risk or bilingualism could increase the difficulty in accurately diagnosing mild AD early in its course.

Methods

Participants

Twenty-nine Hispanic patients with dementia died and came to autopsy during their participation in the longitudinal study of the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). Twenty-one of these 29 received a neuropathological diagnosis of AD. Ten of the autopsy-confirmed AD patients scored above 100 on the Dementia Rating Scale (DRS) at their first ADRC evaluation and were selected for detailed study of neuropsychological test performance with comparison to 10 Hispanic cognitively normal control (NC) participants who did not differ with regards to age and education. Both Hispanic groups (patients and controls) were also compared to 25 monolingual non-Hispanic (24 Caucasian, 1 African-American) patients with autopsy-confirmed AD who were selected from the ADRC cohort to match the Hispanics on age, education and DRS scores. We also selected a group of 25 non-Hispanic NC patients who were matched in age and education to the non-Hispanic AD group. Hispanic and non-Hispanic NC participants remained normal for all years of participation in the ADRC (Hispanic: mean = 7.3 years, $SD = 3.9$; non-Hispanic: mean = 6.2 years; $SD = 5.3$; $p=.55$).

Participant characteristics at the time of the initial ADRC evaluation are summarized in Table 4.1. There were no significant differences among the four groups in age ($F(1,66)<1$, $MSE=31.87$, $p=.79$), education ($F(1,66)<1$, $MSE=10.29$, $p=.68$) or gender distribution (Hispanic vs. non-Hispanic $\chi^2<1$, $p=.49$; AD vs. normal controls $\chi^2<1$, $p=.50$). Patients performed worse than NC participants on the DRS in both the Hispanic ($F(1,18)=26.55$, $MSE=33.54$, $p<.001$) and non-Hispanic cohorts ($F(1,47)=212.28$, $MSE=44.67$, $p<.001$). Similarly, the Hispanic and non-Hispanic patient groups did not differ on total DRS score ($p=.30$); however, the Hispanic normal controls had

significantly lower total DRS scores than the non-Hispanic normal controls ($F(1,32)=9.57$, $MSE=26.84$, $p=.004$). Patients were rated worse than NC participants on the Pfeffer Outpatient Disabilities Scale, a measure of activities of daily living (PODS; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) in both the Hispanic ($p<.001$) and non-Hispanic cohorts ($p<.001$), but the Hispanic and non-Hispanic patient groups did not differ ($p=.76$), nor did the Hispanic and non-Hispanic NC groups ($p=.55$). The Hispanic and non-Hispanic AD groups did not differ significantly in the interval between initial evaluation and death ($p=.20$).

Clinical and Neuropsychological Procedures

All participants completed yearly neurologic, neuropsychiatric, and neuropsychological evaluations for the duration of their participation in the UCSD ADRC. The details of these evaluation procedures have been reported previously (Galasko et al., 1994). The neurologic evaluation included a review of history with the informant or patient, calculation of the Hachinski ischemic score (Hachinski et al., 1975; Rosen, Terry, Fuld, Katzman, & Peck, 1980), clinical mental status testing, and a physical neurological examination that included the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1980) or its equivalent (in patients assessed before the UPDRS was formalized). The neuropsychiatric evaluation consisted of interviews of the patient and informant by nurse practitioners using the Diagnostic Interview Schedules (DIS) for psychosis, depression, and substance dependence, and the Neuropsychiatric Inventory (for patients seen after 2000). The results of the interviews were reviewed by a psychiatrist to establish the presence of psychiatric symptoms and any psychiatric diagnosis. Activities of daily living were assessed with the PODS.

A battery of neuropsychological tests was administered by a trained psychometrist. Detailed descriptions of the tests have been previously published (Salmon & Butters, 1992). The battery included measures from the following cognitive domains:

Memory. Memory subscale of the Dementia Rating Scale (Mattis, 1976), Wechsler Memory Scale (WMS) Visual Reproduction Test immediate and delayed recall (Russell, 1975 adaptation) and a Verbal Memory Test. The Verbal Memory Test was a z-transformed score (based on the scores of the NC group) for total number of words recalled across the learning trials on one of three word list learning tests, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) List Learning Test (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988), the Buschke Selective Reminding Test (Buschke, 1973), or the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987). The three word list learning tests were used at different times throughout the existence of the UCSD ADRC.

Language. Boston Naming Test-30 item version (BNT; Kaplan, Goodglass, & Weintraub, 1983), Letter Fluency Test (FAS; Thurstone & Thurstone, 1941), Category Fluency Test ("animals", "fruits", and "vegetables"), and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary Subtest (Wechsler, 1981).

Executive Function and Attention. Modified Wisconsin Card Sorting Test (Nelson, 1976), WAIS-R Digit Symbol Substitution Test (Wechsler, 1981), Trail Making Test Parts A and B (TMT B; Reitan, 1958), and the Clock Setting Test (Goodglass & Kaplan, 1972).

Visuospatial Abilities. Wechsler Intelligence Scale for Children-Revised (WISC-R) Block Design Test, Clock Drawing Test, Copy a Cube Test (Goodglass & Kaplan, 1972), and Visual Reproduction Test Copy.

Translation of test materials was performed by bilingual psychologists and physicians in consultation with a certified translator. Back translation was performed for all materials that were shown or read to the participant during testing. Psychometrists who tested Hispanic participants were bilingual and bicultural, and had Mexican-American, Central American, or Puerto Rican heritage. Testing was conducted individually in a quiet well-lit room. Although we did not have detailed language history on the majority of Hispanic participants, in previous work we have shown that the majority of participants in the Hispanic cohort are bilingual to at least some degree (ranging from relatively unbalanced to highly proficient and balanced bilinguals; e.g., see Gollan et al., 2011). Language of testing was determined based on the participant's self-reported dominant language. There was no significant difference in the percentages of Hispanic AD patients (40%) and Hispanic NC participants (60%) tested in Spanish ($X^2 < 1, p = .33$).

The results of the clinical evaluation were independently reviewed by two senior neurologists with expertise in dementia to establish a dementia diagnosis and presumed etiology. The diagnosing neurologists were provided with a general statement regarding the results of the neuropsychological evaluation (e.g., “a deficit in two or more areas of cognition”), but were not made aware of specific test scores. Standard, published diagnostic criteria were applied for the following conditions: Dementia (DSM-IV; American Psychiatric Association, 1994), probable or possible Alzheimer's disease

(McKhann et al., 1984; 2011), mild cognitive impairment (Albert et al., 2011; Petersen et al., 19xx), probable or possible DLB (McKeith et al., 2005), PDD (Emre et al., 2007), behavioral variant FTD (Rascovsky et al., 2011), Primary Progressive Aphasia (Gorno-Tempini et al., 2011), and Vascular Dementia (Roman et al., 1993). In the few cases where the neurologists' diagnoses differed, a final clinical diagnosis was made jointly following consensus conference.

Neuropathologic Procedures

Autopsy was performed within 12 hours of death using a protocol described by Terry, Peck, DeTeresa, Schechter and Horoupian (1981). Briefly, the left hemibrain was fixed by immersion in 10% formalin for 5–7 days. Paraffin-embedded blocks from midfrontal, rostral superior temporal and inferior parietal neocortex, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon, and pons were cut at 7- μ m thickness for hematoxylineosin (H & E) and thioflavin-S counts. Total plaques, neuritic plaques, and neurofibrillary tangle (NFT) counts, and the presence or absence of Lewy bodies in the locus coeruleus, substantia nigra, nucleus basalis and neocortex, were determined by the same examiner (LAH) using the same criteria. A modified Braak stage was obtained for each case using methods described by Hansen and Terry (1997). Briefly, the modified Braak stage for AD pathology involves counting the number of NFT in at least five neuron clusters in layer two of the entorhinal cortex and then averaging the results. Cases with modified Braak Stage I to IV have fewer than 18 tangles, on average, in layer two of the entorhinal cortex and sparse neocortical tangles. Modified Braak Stage V cases have moderate numbers of tangles in at least two neocortical sections. In modified Braak Stage VI, all neocortical areas assessed have at

least moderate numbers of tangles. Lewy bodies were absent in cases of “pure” AD. NIA-Reagan Institute criteria for the neuropathological diagnosis of Alzheimer’s disease, which is based on the number of plaques and tangles in the neocortex, limbic, and paralimbic regions (Hyman & Trojanowski, 1997; NIA-Reagan Work Group, 1997) were also applied. Patients were classified as having a “high likelihood of dementia being due to AD”, “intermediate likelihood of dementia being due to AD”, or “low likelihood of dementia due to AD”.

Cases of Dementia with Lewy Bodies (DLB) met consensus criteria for the pathologic diagnosis of DLB based on H & E staining and antiubiquitin immunostaining and anti- α -synuclein immunostaining. Cases were only construed as DLB if dementia was the presenting clinical symptom and Lewy bodies were found in the locus coeruleus, substantia nigra, and/or nucleus basalis of Meynert, as well as in the neocortex. Since all cases categorized as DLB had at least some Lewy bodies in multiple brainstem nuclei and the superior temporal gyrus neocortex, all Lewy body cases in the study qualified for either limbic (transitional) or diffuse neocortical categories proposed in consensus guidelines for the pathologic diagnosis of DLB (McKeith et al., 2005). Cases were not classified as DLB if Lewy bodies were only found in the amygdala. All DLB cases had some degree of concomitant AD pathology. If Lewy body pathology alone was diffusely distributed in the neocortex, the case was considered Diffuse Lewy Body Disease (DLBD).

All autopsied brains were examined for Cerebral Amyloid Angiopathy (CAA) and Cerebrovascular Disease (CVD; i.e., hemorrhage, large artery infarction, lacunes, cortical microinfarcts, arteriosclerosis, and atherosclerosis in the Circle of Willis). The severity of

CAA was semi-quantitatively measured as mild, moderate, or severe on thioflavin-S stained preparations of the midfrontal cortex, superior temporal gyrus, inferior parietal cortex, and posterior hippocampus using a method described previously (Olichney et al., 1996). Capillary CAA was not calculated. CVD, arteriosclerosis, and atherosclerosis were also semi-quantitatively measured as mild, moderate, or severe. Other forms of vascular neuropathology (lacunar infarction, large artery infarction, hemorrhage, cortical microinfarcts) were also noted (as cited in Nation et al., 2012).

Informed Consent

The research protocol was reviewed and approved by the human subjects review board at UCSD. Written informed consent to participate in the study was obtained prior to testing from all participants or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

Results

Accuracy of Clinical Diagnosis

Of the 29 Hispanics who were autopsied at the ADRC, 21 had Alzheimer's disease or Alzheimer's disease pathology (e.g., Dementia with Lewy Bodies; see Appendix A). Of those 21, 18 were given a clinical diagnosis of Alzheimer's disease on their Year 1 testing. Of the three who were not given a clinical diagnosis of AD, two were given a mixed AD/vascular clinical diagnosis and one was given a pseudodementia/depression diagnosis on Year 1. Thus, sensitivity for the clinical diagnosis of AD was 86% (18/21). Eight of the 29 Hispanic participants who were autopsied did not have Alzheimer's disease pathology on autopsy. Of those eight, only 2

were clinically diagnosed with probable AD on Year 1 testing. Based on these figures, specificity in identifying non-AD cases was 75% (6/8).

Cardiovascular Disease Risk Factors in Hispanic vs. Non-Hispanic Patients with AD

For the subset of matched Hispanic and non-Hispanic patients with AD and their respective normal control counterparts, information related to cardiovascular disease risk was collected on first year of testing at the ADRC. Table 4.2 indicates blood pressure, glucose, cholesterol, triglyceride, and body mass index (BMI) levels for Hispanics and non-Hispanics. Presence or absence of hypertension, diabetes, cardiovascular disease, atrial fibrillation, congestive heart failure, angina, and intermittent claudication, as well as history of stroke and transient ischemic attacks, are also displayed in Table 4.2.

Notably, Hispanic and non-Hispanic normal controls did not differ on most variables with the exception of significantly higher BMI ($F(1,31)=7.88$, $MSE=21.65$, $p=.009$) and greater rates of hypertension in the Hispanic group ($p=.043$). In the AD groups, non-Hispanics had significantly higher systolic blood pressure ($F(1,29)=12.8$, $MSE=232.53$, $p=.001$), higher pulse pressure (systolic – diastolic; $F(1,29)=11.7$, $MSE=137.44$, $p=.002$), and higher cholesterol ($F(1,29)=7.21$, $MSE=1212.43$, $p=.013$). However, the Hispanics with AD had higher rates of diabetes ($X^2=10.64$, $p=.001$), angina ($X^2=4.77$, $p=.03$) and congestive heart failure ($X^2=4.69$, $p=.03$).

Neuropathological Findings in Hispanic vs. non-Hispanic Patients with AD

The subset of matched Hispanic and non-Hispanic patients with AD did not differ significantly in total brain weight ($p=.93$; see Table 4.3). Braak stage was significantly lower in Hispanics than in non-Hispanics ($F(1,29)=7.26$, $MSE=.93$, $p=.012$, $\eta_p^2=.20$). There were no differences between Hispanics and non-Hispanics in total plaques in any

brain region examined (all $ps \geq .14$). However, Hispanics had significantly fewer neuritic plaques than non-Hispanics in the midfrontal cortex ($F(1,31)=9.40$, $MSE=196.34$, $p=.004$, $\eta_p^2=.23$), the superior temporal cortex ($F(1,29)=6.34$, $MSE=135.22$, $p=.018$, $\eta_p^2=.18$), the inferior parietal cortex ($F(1,30)=11.31$, $MSE=162.33$, $p=.002$, $\eta_p^2=.27$), and the hippocampus ($F(1,28)=9.28$, $MSE=23.92$, $p=.005$, $\eta_p^2=.25$). Hispanics also had significantly fewer neurofibrillary tangles than non-Hispanics in the superior temporal cortex ($F(1,31)=4.63$, $MSE=27.51$, $p=.039$, $\eta_p^2=.13$) and inferior parietal cortex ($F(1,31)=5.70$, $MSE=8.78$, $p=.023$, $\eta_p^2=.16$). The groups did not differ in number of tangles in the midfrontal cortex ($p=.13$) or hippocampus ($p=.19$).

NIA-Reagan Institute criteria classified 4 of the 9 Hispanics who had available data as having a “high likelihood” of AD, 4 of the 9 Hispanics as having “intermediate likelihood”, and 1 of the 9 as having “low likelihood”¹. In the non-Hispanic group, 20 of the 22 with this data collected were classified as having “high likelihood” of AD, and 2 of the 22 were classified as having “intermediate likelihood”. This yielded a statistically significant difference in the frequencies of these categories ($X^2=8.35$; $p=.02$).

The prevalence of various aspects of concomitant vascular neuropathology in the Hispanic and non-Hispanic patients with AD is shown in Table 4.4. Hispanics had a significantly higher prevalence of small parenchymal arteriolar disease than non-Hispanics ($\chi^2(1, n=28)=9.31$; $p=.025$). The groups did not differ with respect to prevalence of overall vascular pathology, large infarcts, microinfarcts, lacunar infarcts, hemorrhages, subcortical arteriosclerosis, cortical necrosis, medial temporal lobe sclerosis, hippocampal sclerosis, or atherosclerosis (all $ps \geq .16$).

Cognitive Profile Analysis

The test scores of the two AD groups were z-transformed relative to their respective NC group and submitted to a profile analysis using multivariate analysis of variance (MANOVA). The z-scores, displayed in Table 4.5, were modified, as needed, so that negative scores reflected poorer performance. The tests were grouped into the following cognitive domains based largely on the results of a previous factor analytic studies using UCSD ADRC samples (Bondi et al., 2002; Paxton et al., 2007): 1)

Executive Functioning: modified Wisconsin Card Sorting Test (WCST) categories achieved and perseverative errors, WAIS-R Digit Symbol Substitution Test; and Trail-Making Test Part B; 2) Visuoconstructive and Psychomotor Skills: WISC-R Block Design test, Trail-Making Test Part A, and copy condition of the Visual Reproduction Test; 3) Language: Boston Naming Test, Letter and Category fluency tests, WAIS-R Vocabulary Test; and 4) Memory: DRS Memory subscale, Immediate and delay conditions of the Visual Reproduction Test, and Derived Verbal Memory Test.

The four neuropsychological domain composites, representing a within-subject factor, were submitted along with the between-subject factor of ethnicity to a mixed-model MANOVA. Results of the MANOVA revealed a significant main effect of ethnicity ($F(1,33)=17.08$, $MSE=2.16$, $p<.01$, $\eta_p^2=.34$) and a main effect of domain ($Multivariate F(3,31) = 18.89$; $p < .01$, $\eta_p^2=.65$), but no interaction of ethnicity by domain ($Multivariate F(3,31) < 1$; $p = .92$). As shown in Figure 4.1, pairwise comparisons (with Bonferroni-corrected significant level: $.05/4 = .013$) revealed that non-Hispanics obtained significantly worse z-scores than Hispanics on tests of language ($t(33)=2.69$, $p=.01$, $\eta_p^2=.18$), memory ($t(33)=3.33$, $p<.01$, $\eta_p^2=.25$), and executive functioning ($t(33)=3.29$, $p=.002$, $\eta_p^2=.25$). Differences on visuoconstructive and psychomotor skills only

approached significance ($t(33) = 2.14$; $p = .04$). Furthermore, both groups showed the greatest impairment in the memory domain, as evidenced by multiple paired sample t -tests: Memory vs. Language (Hispanics: $t(9)=5.60$, $p<.01$; non-Hispanics: $t(24)=5.17$, $p<.01$); Memory vs. Visuoconstructive and Psychomotor Skills (Hispanics: $t(9)=5.77$, $p<.01$; non-Hispanics: $t(24)=5.50$, $p<.01$); Memory vs. Executive Functioning (Hispanics: $t(9)=6.56$, $p<.01$; non-Hispanics: $t(24)=5.72$, $p<.01$). The other domains did not significantly differ from each other in either cultural groups (all $ps \geq .35$).

Comparisons of Raw Scores on Individual Cognitive Tests.

Because the cognitive profile analyses used normalized scores (i.e., z -scores) it is impossible to know if the observed differences between Hispanic and non-Hispanic patients are due to differences in patient performance, NC performance, or both. Therefore, we compared raw test scores across Hispanic and non-Hispanic patients and controls. As shown in Table 4.6, the Hispanic NC group produced lower mean raw scores than the non-Hispanic NC group on many of the neuropsychological measures. Conversely, non-Hispanic AD patients produced lower mean raw scores than Hispanic AD patients on many of the neuropsychological measures. To explore these differences, we conducted a series of 2x2 ANOVAs (Hispanic vs. non-Hispanic, AD vs. controls) with each measure as a dependent variable. A general pattern emerged (see Figure 4.1) in which Hispanic NC performed equally well or more poorly than non-Hispanic NC on all measures, whereas this pattern reversed for patients such that Hispanics with AD performed equally well or better than non-Hispanics with AD on all measures. Specific results of these analyses are presented below by cognitive domain.

Memory. Hispanics with AD performed significantly better than non-Hispanics with AD on the immediate recall portion of the Visual Reproduction test ($F(1,63)=7.48$, $MSE=10.12$, $p<.01$, $\eta_p^2=.11$); however, Hispanic and non-Hispanic NC did not differ. This yielded a significant 2-way (group by ethnicity) interaction effect ($F(1,63)=7.48$, $MSE=10.12$, $p<.01$, $\eta_p^2=.11$). A significant group by ethnicity interaction effect was also obtained for the derived verbal memory measure ($F(1,66)=7.55$, $MSE=.61$, $p=.008$, $\eta_p^2=.10$). Hispanics with AD had significantly higher scores than non-Hispanics with AD on this measure ($F(1,33)=33.56$, $MSE=.272$, $p<.001$, $\eta_p^2=.50$) whereas the two NC groups did not differ. The same pattern was obtained for the CERAD Word List Learning task (total recalled across trials 1-3) when analyses were limited to the subset of patients and controls that completed that test. Hispanics with AD recalled significantly more words than non-Hispanics with AD, NC groups did not differ ($F(1,31)=6.05$, $MSE=12.22$, $p=.02$, $\eta_p^2=.16$). Group by ethnicity interactions were not observed for the delay portion of the Visual Reproduction test ($p = .74$) or the DRS Memory subscale ($p = .44$).

Language. A marginally significant group by ethnicity interaction effect was observed for the Category Fluency test ($F(1,66)=3.75$, $MSE=80.92$, $p=.06$, $\eta_p^2=.05$). Hispanics with AD produced more words than non-Hispanics with AD, but the two NC groups did not differ. When each semantic category (i.e., Animals, Fruits, and Vegetables) was examined separately, the interaction was significant for Vegetable fluency, ($F(1,66)=5.19$, $MSE=12.26$, $p=.03$, $\eta_p^2=.07$) but not for Animal or Fruit fluency (both $ps \geq .12$). Simple effects analysis of Vegetable fluency revealed a marginally significant ($p = .07$) difference between the two AD groups. A marginally significant

group by ethnicity interaction effect was also observed for total number of errors (i.e., perseverations and intrusions) produced during the Category fluency test ($F(1,66)=3.36$, $MSE=12.26$, $p=.07$, $\eta_p^2=.05$). Patients with AD made more errors than NCs in the non-Hispanic group ($F(1,48)=5.11$, $MSE=5.97$, $p=.03$, $\eta_p^2=.01$), but not in the Hispanic group ($p=.38$). A similar pattern emerged for letter fluency in which non-Hispanics with AD performed significantly worse than their control group ($F(1,48)=15.04$, $MSE=172.34$, $p<.001$, $\eta_p^2=.24$), but Hispanics with AD did not differ from Hispanic controls ($p=.16$). However, this interaction was not significant for total number of words produced across all three letters (sum of “F”, “A”, and “S”) or for number of words produced for each individual letter (all $ps \geq .28$). A significant group by ethnicity interaction effect was observed for the WAIS-R Vocabulary test ($F(1,63)=12.42$, $MSE=114.46$, $p=.001$, $\eta_p^2=.17$), but in this case Hispanic NCs performed significantly worse than non-Hispanic NCs, whereas Hispanic and non-Hispanic patients with AD did not differ. No group by ethnicity interaction effect was observed for total correct responses on the Boston Naming Test ($p = .20$).

Executive Function. A group by Ethnicity interaction effect was evident on the Trail-Making Test part B ($F(1,61)=3.9$, $MSE=3710.2$, $p=.05$, $\eta_p^2=.06$). Hispanic NCs took longer to complete the test than non-Hispanic NCs, whereas Hispanics with AD performed slightly better than non-Hispanics with AD (however these simple effects were not statistically significant; $ps \geq .16$). In addition, Hispanics with AD made significantly fewer errors of omission on this test ($p=.003$) than did non-Hispanics with AD, while the NC groups did not differ. This interaction effect was significant ($F(1,61)=9.8$, $MSE=18.4$, $p=.003$, $\eta_p^2=.14$). A similar pattern was evident on the Digit

Symbol Substitution Test: Hispanics with AD performed significantly better than non-Hispanics with AD ($F(1,32)=4.08$, $MSE=141.6$, $p=.05$, $\eta_p^2=.11$), whereas Hispanic NC performed worse than non-Hispanic NC ($F(1,33)=6.34$, $MSE=89.22$, $p=.02$, $\eta_p^2=.16$). This resulted in a significant cross-over group by ethnicity interaction effect ($F(1,65)=9.94$, $MSE=115.01$, $p=.002$, $\eta_p^2=.13$). No significant group by ethnicity interaction effects were observed for total categories sorted on the WCST or WCST perseverative or non-perseverative errors (all $p \geq .28$).

Visuoconstructive and Psychomotor Skills. On the WISC-R Block Design test, there was a marginally significant group by ethnicity interaction effect ($F(1,66)=3.10$, $MSE=118.55$, $p=.08$, $\eta_p^2=.05$); examining the means shows that Hispanics with AD obtained higher scores than non-Hispanics with AD and Hispanic controls obtained lower scores than non-Hispanic controls. However, simple effects analysis revealed that these differences in performance between Hispanics and non-Hispanics within patient and control groups were not significantly different (both $ps \geq .16$). A marginally significant group by ethnicity interaction was also found on the clock setting test ($F(1,63)=2.86$, $MSE=39.91$, $p=.10$, $\eta_p^2=.04$). On this measure, Hispanics with AD performed significantly better than non-Hispanics with AD ($p=.04$), but the Hispanic and non-Hispanic NC did not differ. No significant group by ethnicity interaction effects were observed for the Clock Drawing Test (command or copy conditions), the Copy a Cube test, or Trail-Making Test part A (all $ps \geq .15$).

Discussion

Neuropsychological deficits in Hispanic older adults with autopsy-confirmed AD were less severe than those of non-Hispanic older adults with AD even though the groups

were matched on age, education, global dementia severity (as measured by the Mattis DRS), the interval between testing and death, and degree of functional impairment. This was true for many of the individual tests within each cognitive domain when the severity of impairment was expressed as a standardized score (i.e., z-score) relative to the performance of the appropriate normal control group, and when the patient groups were compared within cognitive domains using a multivariate approach. Multivariate analyses of composite z-scores showed that Hispanics with AD were significantly less impaired than non-Hispanics with AD across memory, language, and executive functioning domains. Differences in visuoconstructive/psychomotor skills trended in the same direction, but were not significant. It could be argued that the reduced severity of cognitive deficits in the Hispanics with AD is due to the performance of the control reference group used to create their z-scores. Hispanic controls had lower mean scores and greater variance than non-Hispanic controls on most cognitive tests. However, this explanation is challenged by significant interactions between disease status and ethnicity that were observed. Univariate analyses revealed several cross-over interactions on tests of memory, language, executive function, and visuoconstructive /psychomotor skills in which Hispanic controls performed worse than non-Hispanic controls, whereas Hispanics with AD performed better than non-Hispanics with AD.

These interaction effects also suggest that the profile of cognitive deficits characteristic of AD in non-Hispanics may be less salient in Hispanics with AD. Although multivariate analyses showed little overall difference between the patient groups with regard to the pattern of impairment across domain scores, examination of individual tests within each domain showed a number of differences that may have

clinical relevance. For example, Hispanics with AD were less impaired than non-Hispanics with AD, relative to their respective controls, on the immediate recall condition of the Visual Reproduction test, the derived Verbal Memory Score (a measure of learning across trials), Trail-Making Test Part B, Category Fluency, the Vocabulary subtest, and the Digit Symbol Substitution test. On several of these measures (e.g., Digit Symbol Substitution test, Visual Reproduction test), there was no significant difference in the scores achieved by Hispanic patients and controls, whereas non-Hispanic patients scored significantly worse than their controls. Each of these measures has been shown to be particularly sensitive to early cognitive decline associated with AD in non-Hispanics and to contribute to effective clinical diagnosis (Salmon et al., 2002). Thus, their reduced salience in the Hispanic cohort may adversely impact the ability to neuropsychologically detect AD and to distinguish it from other neurodegenerative disorders, particularly early in the course of disease.

A factor that could contribute to differences in the saliency of neuropsychological profiles in Hispanic and non-Hispanic patients with AD is the higher level of vascular neuropathology (i.e., small parenchymal arteriolar disease) in the context of lower AD pathology (e.g., lower mean Braak stage and less plaque/tangle pathology) in the Hispanic group. Hispanic older adults with AD also had a higher prevalence of vascular risk factors such as diabetes, congestive heart failure, and angina compared to non-Hispanics with AD at the initial evaluation. Although the relationship between vascular risk and AD pathology is an area of debate, there is growing evidence that vascular risk does not directly increase AD pathology, but rather has an additive effect on cognitive impairment and dementia severity (Bangen et al., in press; Chui et al., 2012). A recent

study, for example, showed that the presence of cerebrovascular disease in patients with autopsy-confirmed AD was associated with a lower Braak stage for a given level of dementia severity (Bangen et al., in press). A similar study showed a correlation between the extent of small vessel lesions and CDR score in patients with AD (Thal et al., 2003). The present results are consistent with these findings. Hispanics with AD had a greater extent of arteriosclerosis and more vascular risk factors, but a lower level of AD pathology, than non-Hispanics with AD, even though the groups had equivalent levels of dementia at a similar time point prior to death.

Although greater vascular pathology and vascular risk in Hispanics with AD may explain differences in the pattern of cognitive deficits across domains, it does not explain the overall reduced severity of deficits in this group compared to non-Hispanics. One factor that may explain the less severe deficits in the Hispanic group is that non-Hispanic older adults with AD had higher systolic blood pressure and significantly higher pulse pressure than Hispanics with AD. Pulse pressure, a measure of arterial stiffness, is associated with cognitive impairment in domains affected in early AD (Dahle, Jacobs, & Raz, 2009; Nation et al., 2010; Waldstein et al. 2008); an association that remains after controlling for other vascular risk factors (Nation et al., 2010). The mechanisms underlying this relationship are not completely understood, but it has been hypothesized that pulse pressure places increased pulsatile strain on cerebral microvessels and leads to elevated risk of microvascular disease (Mitchell, 2008).

Another explanation for the reduced severity of cognitive deficits in Hispanics with AD despite greater vascular risk is the possibility that Hispanic patients were at an earlier stage of AD than non-Hispanics, as implied by the lower levels of AD pathology.

One way that this may have occurred is through our strategy of matching non-Hispanics to Hispanics on functional status and days between baseline testing and death to ensure that groups were at a similar stage of the AD process. If greater vascular risk in the Hispanic participants with AD negatively impacted their functional status for reasons other than AD pathology, then the same degree of functional performance would be associated with different levels of cognitive performance in the two groups.

One reason that functional deficits could be more prominent in Hispanics with AD than non-Hispanics with AD is the existence of potential barriers to healthcare access in the Hispanic population. Research suggests that obstacles to healthcare access for older Hispanics include lower overall socioeconomic status, language barriers, lack of familiarity with the healthcare system, and cultural differences in personal beliefs related to health (e.g., Ginzberg, 1991; Gordon, 1995; Haan & Weldon, 1996; Ortiz & Fitten, 2000). It has been shown that illness perceptions, beliefs about the utility of medicine, language proficiency, and economic status all influence the use of healthcare services by older Hispanic patients with dementia, and that these characteristics can ultimately delay treatment of dementia in this cohort (Ortiz & Fitten, 2000). This could lead to greater functional impairment in Hispanics despite lower levels of cognitive impairment as non-Hispanics. Thus, our attempt to match non-Hispanics with AD to Hispanics with AD on functional status and test-death interval may have led us to select non-Hispanics at a later stage of the AD process.

Given the possibility that the Hispanic patients were at an earlier stage of AD than non-Hispanic patients due to matching conditions, we investigated whether Hispanic and non-Hispanic patients who were matched on level of AD pathology would still exhibit

the same pattern of findings on baseline neuropsychological testing. To this end, we conducted a post-hoc analysis with a subset of participants who were matched on level of AD pathology (e.g., Braak stage and number of plaques and tangles across the four brain regions). We compared the raw test scores of the Hispanics ($n=8$) and non-Hispanics ($n=15$) matched on pathology to see whether differences between groups remained. As was the case for the entire sample, the subset of Hispanics with AD outperformed the non-Hispanics with AD on the immediate trial of Visual Reproduction ($p=.02$), Category Fluency ($p=.002$), and Digit Symbol Substitution ($p=.005$). Differences between the patient groups were diminished for Part B of the Trail Making Test ($p=.16$), WAIS-R Vocabulary ($p=.53$), and Block Design ($p=.17$). Thus, even when matched on level of AD pathology Hispanics exhibited less severe cognitive deficits than non-Hispanics. These results suggest that there are protective factors that contribute to the reduced severity and diminished saliency of cognitive deficits in Hispanics with AD in certain domains of testing.

One potential protective factor is bilingualism. Participants in the Hispanic cohort at the UCSD ADRC are mostly bilingual to at least some degree (see Gollan et al., 2011)². Recent research suggests that bilingualism confers a degree of cognitive reserve that may delay the cognitive manifestations of AD (Bialystok, Craik, & Freedman, 2007; Chertkow et al., 2010; Craik, Bialystok, & Freedman, 2010; Schweizer, Ware, Fischer, Craik, & Bialystok, 2011). Bialystok et al. (2007), for example, reported a delay of over four years in the age of onset of AD symptoms in bilinguals relative to monolinguals. Schweizer and colleagues (2011) matched bilinguals and monolinguals on level of cognitive performance, age and education, and found greater brain atrophy in bilinguals

than in monolinguals in the radial width of the temporal horn and the temporal horn ratio, areas commonly used to distinguish AD patients from healthy controls. These results suggest that cognitive reserve related to bilingualism allows more AD pathology to be tolerated before dementia symptoms become apparent. Although the mechanism by which bilingualism contributes to cognitive reserve remains unclear, studies suggest that bilinguals develop advantages on tests of executive function and attentional control, and this may lead to stronger performance in these areas of cognition during normal and abnormal aging (for review, see Bialystok et al., 2009). Supportive of this possibility, Hispanics with AD performed an average of 1.28 standard deviations better than non-Hispanics with AD on tests of executive functioning. This difference on executive function testing is larger than the difference between Hispanic and non-Hispanic patients on memory testing (mean z-score difference of -1.06).

The diminished severity of deficits in the Hispanics with AD was not limited to tests of executive functioning and attentional control, and it is possible that other factors related to bilingualism (e.g., knowledge of two lexicons) may have strengthened cognitive abilities in the Hispanic group. In line with this, the difference in mean z-scores between Hispanics and non-Hispanics was also larger for language functioning (mean z-score difference of -1.21) than for memory (as reported above, mean z-score difference of -1.06). Although bilinguals are often disadvantaged in language tasks when not cognitively impaired (e.g., Gollan et al., 2002), this result suggests that language skills may be relatively better preserved in bilinguals with AD. For example, we found an interaction in semantic fluency in which non-Hispanic normal controls outperformed Hispanic normal controls, with the reverse being true in the AD groups. A recent study

by Weissberger et al. (2013) found a similar pattern on animal and vegetable fluency subtests of category fluency in which Hispanic older adults who later develop AD outperformed non-Hispanics who later develop AD. The authors suggest that Hispanics with preclinical AD may be protected from the vulnerability in semantic fluency that characterizes clinical AD. Increased resilience of linguistic function may be due to lifelong need to control and manage competition for selection between two languages (Sandoval, Gollan, Ferreira, & Salmon, 2010) which may lead bilinguals to develop processing mechanisms that make them better able to produce exemplars from semantic memory despite changes to the integrity of the semantic system (Weissberger et al., 2013). This protective effect related to bilingualism may account for the present semantic fluency findings, and for greater preservation of language than memory in Hispanic older adults with AD.

Even though the saliency of cognitive deficits was diminished in Hispanics with AD, the accuracy of the diagnosis of AD dementia at their initial ADRC evaluation was quite good. Sensitivity of 86% was attained in assigning a diagnosis of AD or one of its variants (DLB) to individuals who had AD pathology either solely or in combination with other pathologic conditions. This level of sensitivity is comparable to the approximately 90% level that is reported for largely non-Hispanic Caucasian populations in our centers (Galasko et al., 1994) and across a large number of clinical pathological studies that use the NINCDS-ADRDA criteria (81% sensitivity rate reported; McKhann et al., 2011). It should be noted, however, that a number of the Hispanic patients were beyond a mild stage of dementia. Better normative data from non-demented elderly Hispanic cohorts would improve the ability to effectively detect subtle cognitive impairment in those in the

earliest stages of AD and would improve diagnostic accuracy. Specificity of the clinical diagnosis of AD in elderly Hispanics with dementia was 75%. This level of specificity is in line with clinical pathological studies that use the NINCDS-ADRDA criteria (70% specificity rate reported; McKhann et al., 2011). Lower specificity relative to sensitivity may be related to a reduced ability to see differential patterns of cognitive deficits across disorders that have different underlying pathology. If the pattern of cognitive deficits typically seen in AD is obscured by factors such as an increased vascular contribution or the modifying effects of bilingualism, it becomes harder to differentiate the disease from other dementing disorders such as vascular dementia, frontotemporal dementia, or dementia associated primarily with subcortical pathology (e.g., progressive supranuclear palsy). This may be particularly true if the memory deficit that most strongly characterizes AD is less apparent in Hispanic patients with AD than in non-Hispanic patients. Further characterization of the pattern of neuropsychological deficits associated with AD in elderly Hispanic patients should improve the ability to differentiate AD from other dementia-producing neurodegenerative disorders in this population.

The present study has several limitations. First, we had a limited sample size of Hispanics who had autopsy-confirmed AD and who met our inclusionary criteria. Thus, replicating our findings in future studies with a larger sample of autopsy-confirmed Hispanics with AD and with other subpopulations of Hispanics would broaden the implications of our findings. Second, we did not have a consistent verbal memory measure for all participants. Given that episodic memory is a domain affected early and to a greater extent than other domains in the AD process, a uniform verbal memory measure would be the ideal. We attempted to overcome this limitation by z-transforming

one of three memory measures for each participant to derive a *verbal memory score*. A third limitation was the lack of comprehensive language history for the Hispanic participants in our study. Although bilingualism may play a role in the findings reported, this explanation is speculative given the absence of detailed information regarding degree of bilingualism in Hispanics with autopsy-confirmed AD. Future studies should expand on these findings with a larger sample of bilingual participants.

Despite these limitations, the present study has several notable strengths. This is the first study to our knowledge that provides autopsy-confirmation of AD in prospectively evaluated Hispanic elderly. Although we had a small sample of autopsied cases, our data confirm 86% sensitivity and 75% specificity in clinical diagnosis of the 29 autopsied Hispanics and provides confidence in the utility of neuropsychological testing for clinical diagnosis of probable AD in Hispanic older adults. This study also points to potential factors that may impact neuropsychological and neuropathological outcomes in Hispanic older adults such as increased vascular risk, bilingualism, and sociological factors. Although the impact of these factors are not fully understood, it is clear that an interaction of one or more of these factors with AD pathogenesis may impact the progression of AD in Hispanic older adults. Future studies assessing the influence of each of these factors will help inform prevention and treatment for Hispanics who are at risk for AD.

Chapter 4, in part is currently being prepared for submission for publication of the material: Weissberger, Gali H., Gollan, Tamar H., Bondi, Mark W., Nation, Daniel A., Hansen, Lawrence A., Galasko, D., & Salmon, David P. "Neuropsychological and Neuropathological Profiles of Hispanic Older Adults with Autopsy-Confirmed

Alzheimer's Disease". The dissertation author was the primary investigator and author of this material.

References

- Alzheimer's Association (2012). Alzheimer's association report: 2012 Alzheimer's disease facts and figures. *Alzheimer's and Dementia*, 8, 131-168.
- Almeida, O. P., & Flicker, L. (2001). The mind of a failing heart: a systematic review of the association between congestive heart failure and cognitive functioning. *Internal Medicine Journal*, 31, 290-295.
- Artiola i Fortuny, L., Garolera, M., Hermosillo Romo, D., Feldman, E., Fernandez Barillas, H., Keefe, R., . . . Verger Maestre, K. (2005). Research with Spanish-speaking populations in the United States: Lost in translation a commentary and a plea. *Journal of Clinical and Experimental Neuropsychology*, 27, 555-564.
- Allen, K. V., Frier, B. M., & Strachan, M. W. J. (2004). The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations. *European Journal of Pharmacology*, 490, 169-175.
- Bangen, K. J., Nation, D. A., Delano-Wood, L., Weissberger, G. H., Hansen, L. A., Galasko, D. R., Salmon, D. P., & Bondi, M. W. (in press). Aggregate but not individual vascular risk factors predict cerebrovascular disease in autopsy confirmed Alzheimer's disease. *Journal of Alzheimer's Disease*.
- Bialystok, E. (2010). Global-Local and Trail-Making Tasks by monolingual and bilingual children: Beyond inhibition. *Developmental Psychology*, 46, 93-105
- Bialystok, E., Craik, F. I. M., & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia*, 45, 459-464.
- Bialystok, E., Craik, F. I. M., Green, D. W., & Gollan, T.H. (2009). Bilingual minds. *Psychological Science in the Public Interest*, 10, 89-129
- Bialystok, E., Craik, F. I. M., & Luk, G. (2008). Cognitive control and lexical access in younger and older bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 34, 859-873.
- Bowen, J. D., Malter, A. D., Sheppard, L., Kukull, W. A., McCormick, W. C., Teri, L., & Larson, E. B. (1996). Predictors of mortality in patients diagnosed with probable Alzheimer's disease. *Neurology*, 47, 433-439.
- Brickman, A. M., Schupf, N., Manly, J. J., Luchsinger, J. A., Andrews, H., Tang, M. X., . . . Brown, T. R. (2008). Brain morphology in elderly African Americans, Caribbean Hispanics, and Caucasians from Northern Manhattan. *Archives of Neurology*, 65, 1053-1061.

- Buschke, H. (1973). Selective reminding for analysis of memory and learning. *Journal of Verbal Learning and Verbal Behavior*, 12, 543-550.
- Cheng, G., Huang, C., Deng, H., & Wang, H. (2012). Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Internal Medicine Journal*, 42, 481-491.
- Chertkow, H., Whitehead, V., Phillips, N., Wolfson, C., Atherton, J., & Bergman, H. (2010). Multilingualism (but not always bilingualism) delays the onset of Alzheimer's disease: Evidence from a bilingual community. *Alzheimer's Disease and Associated Disorders*, 24, 118-125.
- Chui, H. C., Zheng, L., Reed, B. R., Vinters, H. V., & Mack, W. J. (2012). Vascular risk factors and Alzheimer's disease: Are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. *Alzheimer's Research and Therapy*, 4, 1-13.
- Clark, C. M., DeCarli, C., Mungas, D., Chui, H. I., Higdon, R., Nuñez, J., . . . van Belle, G. (2005). Earlier onset of Alzheimer disease symptoms in Latino individuals compared with Anglo individuals. *Archives of Neurology*, 62, 774-778.
- Consentino, S., Scarmeas, N., Albert, S. M., & Stern, Y. (2006). Verbal fluency predicts mortality in Alzheimer's disease. *Cognitive and Behavioral Neurology*, 19, 123-129.
- Craik, F. I. M., Bialystok, E., & Freedman, M. (2010). Delaying the onset of Alzheimer's disease: Bilingualism as a form of cognitive reserve. *Neurology*, 75, 1726-1729.
- Critchley, M. (1953, reprinted 1966). *The Parietal Lobes*. Hafner, New York.
- Dahle, C. L., Jacobs, B. S., & Raz, N. (2009). Aging, vascular risk, and cognition : Blood glucose, pulse pressure, and cognitive performance in healthy adults. *Psychology and Aging*, 24, 154-162.
- Daviglus, M. L., Talavera, G. A., Avilés-Santa, M. L., Allison, M., Cai, J., Criqui, M. H., . . . Stamler, J. (2012). Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *Journal of the American Medical Association*, 308, 1775-1784.
- Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *The California Verbal Learning Test*. New York: Psychological Corporation.
- Ennis, S., Rios-Vargas, M., & Albert, N. (2010). 2010 Census Briefs: The Hispanic population. <http://www.census.gov/prod/cen2010/briefs/c2010br-04.pdf>.

- Fahn S, Elton RL, UPDRS program members. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. *Recent Developments in Parkinson's Disease*, vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p153–163, 293–304
- Feldstein, C. A. (2012). Association between chronic blood pressure changes and development of Alzheimer's disease. *Journal of Alzheimer's Disease*, 32, 753-763.
- Fitten, L. J., Ortiz, F., & Pontón, M. (2001). Frequency of Alzheimer's disease and other dementias in a community outreach sample of Hispanics. *Journal of the American Geriatrics Society*, 49, 1301-1308.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.
- Galasko, D., Hansen, L. A., Katzman, R., Wiederholt, W., Masliah, E., Terry, R.,...,Thal, L. (1994). Clinical-neuropathological correlates in Alzheimer's disease and relate dementias. *Archives of Neurology*, 51, 888-895.
- Ginzberg, E. (1991). Access to healthcare for Hispanics. *Journal of the American Medical Association*, 265, 238-241.
- Gollan, T. H., Montoya, R. I., & Werner, G. A. (2002). Semantic and letter fluency in Spanish-English bilinguals. *Neuropsychology*, 16, 562-576.
- Gollan, T. H., Salmon, D.P., Montoya, R.I., & Galasko, D.R. (2011). Degree of Bilingualism Predicts Age of Diagnosis of Alzheimer's Disease in Low-Education but not in Highly-Educated Hispanics, *Neuropsychologia*, 49, 3826-3830.
- Goodglass, H., & Kaplan, E. (1972). *The assessment of aphasia and related disorders*. Lea & Febiger: Philadelphia, PA.
- Gordan, A. K. (1995). Deterrents to access and service for blacks and Hispanics: the Medicare Hospice Benefit, healthcare utilization, and cultural barriers. *Hospice Journal*, 10, 65-83.
- Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C.,...,Seshadri, S. (2011). Vascular contributions to cognitive impairment and dementia. *Stroke*, 42, 2672-2713.
- Gurland, B. J., Wilder, D. E., Lantigua, R., Stern, Y., Chen, J., Killeffer, E. H., &

- Mayeux, R. (1999). Rates of dementia in three ethnoracial groups. *International Journal of Geriatric Psychiatry*, 14, 481-493.
- Haan, M. N., Mungas, D. M., Gonzalez, H. M., Ortiz, T. A., Acharya, A., & Jagust, W. J. (2003). Prevalence of dementia in older Latinos: The influence of type 2 Diabetes Mellitus, stroke, and genetic factors. *Journal of the American Geriatrics Society*, 51, 169-177.
- Haan, M. N., & Weldon, M. (1996). The influence of diabetes, hypertension, and stroke on ethnic differences in physical and cognitive functioning in an ethnically diverse older population. *Annals of Epidemiology*, 6, 392-398.
- Hachinski, V.C., Iliff, L. D., Zilhka, E., DuBoulay, G. J., McAllister, V. L., Marshall, J., Russell, R. W. R., & Symon, L. (1975). Cerebral blood flow in dementia. *Archives of Neurology*, 32, 632-637.
- Hansen, L.A., Terry, R.D. (1997). Position paper on diagnostic criteria for Alzheimer disease. *Neurobiology of Aging*, 18, S71-S73.
- Harwood, D. G., Barker, W. W., Loewenstein, D. A., Ownby, R. L., St. George-Hyslop, P., Mullan, M., & Duara, R. (1999). A cross-ethnic analysis of risk factors for AD in white Hispanics and white non-Hispanics. *Neurology*, 52, 551-556.
- Helzner, E. P., Scarmeas, N., Cosentino, S., Tang, M. X., Schupf, N., & Stern, Y. (2008). Survival in Alzheimer's disease: A multiethnic, population-based study of incident cases. *Neurology*, 71, 1489-1495.
- Hughes, C. P., Berg, L., Danzinger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry*, 140, 566-572.
- Hyman, B. T., & Trojanowski, J. Q. (1997). Consensus recommendations for the postmortem diagnosis of Alzheimer's disease from the National Institute of Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*, 56, 1095-1097.
- Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia, PA: Lea & Febiger.
- Kwon, O. D., Khaleeq, A., Chan, W., Pavlik, V. N., & Doody, R. S. (2010). Apolipoprotein E polymorphism and age at onset of Alzheimer's disease in a quadriethnic sample. *Dementia and Geriatric Cognitive Disorders*, 30, 486-491.
- La Rue, A., Romero, L. J., Ortiz, I. E., Liang, H. C., & Lindeman, R. D. (1999).

- Neuropsychological performance of Hispanic and non-Hispanic older adults: An epidemiologic survey. *The Clinical Neuropsychologist*, 13, 474-486.
- Livney, M. G., Clark, C. M., Karlawish, J. H., Cartmell, S., Negrón, M., Nuñez-Lopez, J.,...Arnold, S. E. (2011). Ethnoracial differences in the clinical characteristics of Alzheimer's disease at initial presentation at an urban Alzheimer's disease center. *American Journal of Geriatric Psychiatry*, 19, 430-439.
- Duara et al., 1996
- Lo, R. Y., & Jagust, W. J. (2012). Vascular burden and Alzheimer's disease pathologic progression. *Neurology*, 79, 1349 – 1355.
- Luchsinger, J. A., Reitz, C., Patel, B., Tang, M-X., Manly, J. J., & Mayeux, R. (2007). Relation of Diabetes to Mild Cognitive Impairment. *Archives of Neurology*, 64, 570-575.
- Luchsinger, J. A., Tang, M-X., Stern, Y., Shea, S., & Mayeux, R. (2001). Diabetes Mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *American Journal of Epidemiology*, 154, 635-641.
- Lyness, S. A., Hernandez, I., Chui, H. C., Teng, E. L. (2006). Performance of Spanish speakers on the Mattis dementia rating scale (MDRS). *Archives of Clinical Neuropsychology*, 21, 827-836.
- Mattis, S. (1988). *Dementia Rating Scale: Professional manual*. Odessa, FL: Psychological Assessment Resources.
- McBean, A. M., Li, S., Gilbertson, D. T., & Collins, A. J. (2004). Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: Whites, Blacks, Hispanics, and Asians. *Diabetes Care*, 27, 2317 – 2324.
- McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., et al. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*, 65, 1863–1872.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group. *Neurology*, 34, 939–944.
- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H.,...,Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 263-269.
- Mickes, L., Wixted, J. T., Fenema-Notestine, C., Galasko, D., Bondi, M. W., Thal, L. J.,

- & Salmon, D. P. (2007). Progressive impairment on neuropsychological tasks in a longitudinal study of preclinical Alzheimer's disease. *Neuropsychology*, *21*, 696–705.
- Mitchell, G. F. (2008). Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *Journal of Applied Physiology*, *105*, 1652-1660.
- Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., ... Mellits, E. D., & Clark, C. (1989). The consortium to establish a registry for Alzheimer's disease (CERAD): 1. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*, *39*, 1159-1165.
- Morris, J. C., McKeel, D. W., Storandt, M., Rubin, E. H., Price, J. L., Grant, E. A., . . . Berg, L. (1991). Very mild Alzheimer's disease: Informant-based clinical, psychometric, and pathologic distinction from normal aging. *Neurology*, *41*, 469–478.
- Morris, J. C., Mohs, R. C., Rogers, H., Fillenbaum, G., Heyman, A. (1988). Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacology Bulletin*, *24*, 641-652.
- Nation, D. A., Delano-Wood, L., Bangen, K. J., Wierenga, C. E., Jak, A. J., Hansen, L. A., . . . Bondi, M. W. (2012). Antemortem pulse pressure elevation predicts cerebrovascular disease in autopsy-confirmed Alzheimer's disease. *Journal of Alzheimer's Disease*, *30*, 595-603.
- Nation, D. A., Wierenga, C. E., Delano-Wood, L., Jak, A. J., Delis, D. C., Salmon, D. P., & Bondi, M. W. (2010). Elevated pulse pressure is associated with age-related decline in language ability. *Journal of the International Neuropsychological Society*, *16*, 933-938.
- Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*, *12*, 313–324.
- The NIA-Reagan Working Group. (1997). Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. *Neurobiology of Aging*, *18*, S1-S27.
- Olichney, J. M., Hansen, L. A., Galasko, D., Saitoh, T., Hofstetter, C. R., Katzman, R., Thal, L. J. (1996). The apolipoprotein E ϵ 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. *Neurology* *47*, 190-196.

- Ortiz, F., & Fitten, L. J. (2000). Barriers to healthcare access for cognitively impaired older Hispanics. *Alzheimer's Disease and Associated Disorders*, 14, 141-150.
- Paxton, J. L., Peavy, G. M., Jenkins, C., Rice, V. A., Heindel, W. C., & Salmon, D. P. (2007). Deterioration of visual-perceptual organization ability in Alzheimer's disease. *Cortex*, 43, 967-975.
- Peña-Casanova, J., Quiñones-Úbeda, S., Gramunt-Fombuena, N., Quintana-Aparicio, M., Aguilar, M., Badenes, D., . . . Blesa, R. (2009). Spanish multicenter normative studies (NEURONORMA Project): Norms for verbal fluency tests. *Archives of Clinical Neuropsychology*, 24, 395-411.
- Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology*, 37, 323-329.
- Portocarrero, J. S., Burright, R. G. & Donovan, P. J. (2007). Vocabulary and verbal fluency of bilingual and monolingual college students. *Archives of Clinical Neuropsychology*, 22, 415-422.
- Qiu, C. (2011). Epidemiological findings of vascular risk factors in Alzheimer's disease: Implications for therapeutic and preventive intervention. *Expert Review of Neurotherapeutics*, 11, 1593-1607.
- Reed, B. R., Mungas, D. M., Kramer, J. H., Ellis, W., Vinters, H. V., Zarow, C., Jagust, W. J., & Chui, H. C. (2007). Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain*, 130, 731-739.
- Reitan, R. M. (1958). Validity of the Trail Making Test to organic brain damage. *Perceptual and Motor Skills*, 8, 271-276.
- Reijmer, Y. D., van den Berg, E., Ruis, C., Kappelle, L. J., Biessels, G. J. (2010). Cognitive dysfunction in patients with type 2 diabetes. *Diabetes/Metabolism Research and Reviews*, 26, 507-519.
- Roberts, P. M., Garcia, L. J., Desrochers, A., Hernandez, D. (2002). English performance of proficient bilingual adults on the Boston Naming Test. *Apahsiology*, 16, 635-645.
- Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2012). Heart disease and stroke statistics – 2012 update: A report from the American Heart Association. *Circulation*, 125, e2-e220.
- Rosen, W. G., Terry, R. D., Fuld, P. A., Katzman, R., & Peck, A. (1980). Pathological

- verification of ischemic score in differentiation of dementias. *Annals of Neurology*, 7, 486-488.
- Russell, E. W. (1975). A multiple scoring method for the assessment of complex memory functions. *Journal of Consulting and Clinical Psychology*, 43, 800-809.
- Salmon, D. P., & Bondi, M. W. (1999). Neuropsychology of Alzheimer's disease. In R.D. Terry, R. Katzman, K.L. Bick, & S.S. Sisodia (Eds), *Alzheimer's disease* (2nd ed., pp. 39-56). Philadelphia: Lippincott Williams & Wilkins.
- Salmon, D.P., Thomas, R.G., Booth, A., Hofstetter, C.R., Thal, L.J. & Katzman, R. (2002). Alzheimer's disease can be accurately diagnosed in very mildly impaired individuals. *Neurology*, 59, 1022-1028.
- Schneider, J. A., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology*, 62, 1148-1155.
- Terry, R.D., Peck, A., DeTeresa, R., Schechter, R., Horoupian, D.S. (1981). Some morphometric aspects of the brain in senile dementia of the Alzheimer type. *Annals of Neurology*, 10, 184-192.
- Thal, D. R., Ghebremedhin, E., Orantes, M., & Wiestler, O. D. (2003). Vascular pathology in Alzheimer's disease: Correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. *Journal of Neuropathology and Experimental Neurology*, 62, 1287-1301.
- Thurstone, L. L., & Thurstone, T. G. (1941). Factorial studies of intelligence. *Psychometric Monographs*, 2, 94.
- U.S. Census Bureau (2010). 2010 Census Data. Retrieved from <http://www.census.gov/2010census/data/>
- Verney, S. P., Granholm, E., Marshall, S. P., Malcarne, V. L., & Saccuzzo, D. P. (2005). Culture-fair cognitive ability assessment: Information processing and psychophysiological approaches. *Assessment*, 12, 303-319.
- Waldstein, S. R., Carrington Rice, S., Thayer, J. F., Najjar, S. S., Scuteri, A., & Zonderman, A. B. (2008). Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore longitudinal study of aging. *Hypertension*, 51, 99-104.
- Waring, S. C., Doody, R. S., Pavlik, V. N., Massman, P. J., & Chan, W. (2005). Survival among patients with dementia from a large multi-ethnic population. *Alzheimer's Disease and Associated Disorders*, 19, 178-183.

- Wechsler, D. (1981). *Wechsler Adult Intelligence Scale Revised manual*. San Antonio, CA: Psychological Corporation.
- Weissberger, G. H., Salmon, D. P., Bondi, M. W., & Gollan, T. H. (2013). Which neuropsychological tests predict progression to Alzheimer's disease in Hispanics? *Neuropsychology*, 27, 343-355.
- Winkleby, M. A., Kraemer, H. C., Ahn, D. K., & Varady, A. N. (1998). Findings for Women from the third national health and nutrition examination survey, 1988-1994. *Journal of the American Medical Association*, 280, 356 – 362.
- Zahodne, L .B., Schofield, P. W., Farrell, M. T., Stern, Y., & Manly, J. J. (2013). Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. *Neuropsychology*, 28, 238-246.

Footnotes

1. Given the NIA-Reagan “low likelihood” rating for one Hispanic with AD, we conducted the same analyses reported in the paper without this subject. Doing so did not change most of the findings reported, with the exception of Trail Making Test part B; with the participant included, Hispanics were significantly faster than non-Hispanics, as reported ($p = .02$). However, without this participant, this effect became marginally significant ($p = .06$).
2. While six Hispanic decliners were tested in English, only four Hispanic normal controls were tested in English. To investigate whether findings were driven by one of the two language groups, we ran 2 (Hispanic vs. non-Hispanic) x2 (patients vs. normal controls) ANOVAs for each of the neuropsychological measures and for each language group. Although the significance of findings was reduced (likely due to reduced power), examining the means revealed trends in similar directions for each language group across all measures, reflecting our findings for the larger sample. There was one exception to this; the significantly higher category fluency score in the Hispanic AD group compared to the non-Hispanic AD group seemed to be driven by Hispanics who preferred to be tested in English. Specifically, English-speaking Hispanics with AD generated more words overall ($m = 30.3$) compared to Spanish-speaking Hispanics with AD ($m = 22.75$) and non-Hispanics with AD ($m = 22.76$). Furthermore, the lower scores for Hispanic normal controls appeared to be driven by the Spanish-speaking Hispanic normal controls ($m = 44.2$) and not by the English-speaking Hispanic normal controls ($m = 46.8$), who obtained similar scores with the non-Hispanic normal controls ($m = 46.6$).

Table 4.1: Demographic Information and Measures of Cognitive and Functional Ability for Hispanic and Non-Hispanic Normal Control Participants and Patients with Alzheimer's Disease.

	<u>Hispanic</u>				<u>Non-Hispanic</u>			
	<u>Probable AD</u>		<u>Normal Controls</u>		<u>Probable AD</u>		<u>Normal Controls</u>	
	(n=10)		(n=10)		(n=25)		(n=25)	
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Age at Year 1	80.5	(4.0)	78.2	(3.3)	78.2	(6.3)	76.8	(6.1)
Education	9.9	(5.7)	9.8	(4.4)	10.5	(1.8)	11.1	(2.4)
% Female	70	-	70	-	64	-	70	-
Days Between Year 1 and Death	2689.8	(524.3)	-	-	2185.6	(1165.8)	-	-
Dementia Rating Scale	115.4	(7.4)	130.8	(5.8)	112.7	(6.5)	136.8	(4.9)
Clinical Dementia Rating: Global	1.3	(0.5)	0	(0)	1.1	(0.4)	0	(0)
Pfeffer Outpatient Disability Scale	12.1	(5.0)	0.2	(0.6)	12.6	(4.0)	0.3	(0.6)

Table 4.3: Brain Weight, Braak Stage, and Number of Plaques, Neuritic Plaques, and Neurofibrillary Tangles (per high powered field) in Several Cortical Regions and the Hippocampus for Hispanics and Non-Hispanics with Autopsy-Confirmed Alzheimer's Disease.

	<i>n</i> ¹	<u>Hispanic</u>		<u>Non-Hispanic</u>		<i>p-value</i>		
		<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>		<i>SD</i>	
<u>Cortical Region</u>	Brain Weight	8	1069.25	(58.1)	25	1063.64	(177.3)	0.931
	Braak Stage	9	4.33	(1.5)	22	5.36	(0.7)	0.012
	Total Plaques	9	36.22	(15.8)	25	44.20	(13.0)	0.143
	Neuritic Plaques	9	15.33	(12.3)	24	32.13	(14.6)	0.004
	Tangles	9	1.22	(2.2)	25	3.20	(3.5)	0.125
Superior Temporal	Total Plaques	8	32.63	(14.2)	25	39.40	(13.2)	0.224
	Neuritic Plaques	8	12.38	(8.4)	23	24.39	(12.5)	0.018
	Tangles	8	2.38	(2.1)	25	6.96	(5.9)	0.039
Inferior Parietal	Total Plaques	9	37.11	(12.3)	24	42.58	(13.0)	0.284
	Neuritic Plaques	9	15.11	(9.6)	23	31.96	(13.7)	0.002
	Tangles	9	1.44	(2.1)	24	4.21	(3.2)	0.023
Hippocampus	Total Plaques	9	13.11	(6.4)	24	15.96	(8.1)	0.352
	Neuritic Plaques	9	7.78	(4.3)	21	13.71	(5.1)	0.005
	Tangles	9	14.00	(7.8)	24	21.33	(15.6)	0.191

¹For one Hispanic participant, AD pathology data were not available.

Table 4.4: Frequency of Vascular Neuropathology in Hispanics and Non-Hispanics with Autopsy-Confirmed Alzheimer’s Disease.

	Hispanic (n=10)		Non-Hispanic (n=25)		
	<u>Yes</u>	<u>No</u>	<u>Yes</u>	<u>Mild</u>	<u>Severe</u>
Vascular Pathology	9	1	24	5	6
Large Infarcts	0	10	5 ⁺	3	1
Microinfarcts	0	10	2	10	3
Lacunar Infarcts	1	9	4	6	3
Hemorrhages	0	10	1	10	3
Subcortical Arteriosclerosis	0	9	0	10	3
Cortical Necrosis	0	10	0	10	3
Medial Temporal Lobe Sclerosis	2	8	1	10	3
Atherosclerosis (circle of Willis)	2	3	4	5	6
Small Parenchymal Arteriolar Disease*	2	4	17	3	1
Amyloid Angiopathy	2	3	6	10	3

*Significant difference of $p<.05$ in frequency between Hispanics and non-Hispanics. ⁺ $n=3$ infarcts occurred at time of death; $n=2$ missing data.

Table 4.5: Scores achieved by Hispanic and Non-Hispanic patients with Alzheimer's Disease on neuropsychological tests in four cognitive domains. Scores are z-transformed based on respective normal control groups.

	<u>Test Name</u>	<u>Hispanics (n = 10)</u>		<u>Non-Hispanics (n = 25)</u>		<u>p-value</u>
		<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	
<i>Memory</i>	Verbal Memory Composite	-1.49	(0.38)	-2.62	(0.57)	<.001
	Visual Reproduction Immediate	-0.60	(0.77)	-1.77	(0.58)	<.001
	Visual Reproduction Delay	-1.58	(0.40)	-1.42	(0.22)	.140
<i>Executive Function</i>	Trail Making Test (Part B: sec)	-1.54	(1.61)	-2.87	(1.32)	.021
	WCST Categories	-0.96	(0.77)	-1.53	(0.96)	.131
	WCST Perseverative Errors	-0.27	(1.0)	-0.92	(1.51)	.209
	Digit Symbol Substitution	-0.38	(0.56)	-2.48	(1.48)	<.001
<i>Language</i>	Boston Naming Test (30 Item)	-1.55	(2.13)	-2.82	(2.22)	.130
	Letter Fluency (FAS Total)	-0.59	(0.79)	-0.96	(0.73)	.194
	Category Fluency (AFV Total)	-1.83	(0.78)	-2.20	(0.51)	.110
<i>Visuoconstructive/Psychomotor Skills</i>	Vocabulary	0.84	(1.16)	-2.15	(3.49)	.017
	Block Design	-1.05	(0.73)	-2.03	(0.93)	.005
	Trail Making Test (Part A: sec)	-1.25	(1.85)	-2.64	(2.58)	.133
	Visual Reproduction Copy	-0.40	(0.72)	-0.94	(1.24)	.214

Table 4.6: Mean raw scores (and standard deviations) achieved by Hispanic and Non-Hispanic patients and normal control participants on all neuropsychological measures.

Test Name	Probable AD				Normal Controls				<u>p- values</u>	<u>2x2 Interactions</u>
	<u>Hispanic (n=10)</u>		<u>Non-Hispanic (n=25)</u>		<u>Hispanic (n=10)</u>		<u>Non-Hispanic (n=25)</u>			
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>		
<i>Memory</i>										
Verbal Memory Composite	-1.49	-0.38	-2.62	-0.57	0	-0.9	0.0001	-1	1	p=.008
Visual Reproduction Immediate	7.1	-2.8	4.5	-2.2	9.3	-3.7	11.3	-3.9	0.17	p=.008
Visual Reproduction Delay	0.7	-1.6	0.6	-1.1	6.8	-3.9	7.3	-4.7	0.77	p=.740
CERAD T1-3*	12.7	-3	9.3	-3.3	19.4	-4.3	21.9	-3.4	0.24	p=.020
DRS Memory	13.8	-3.7	13.4	-3.5	23.6	-1.4	24.3	-1.3	0.2	p=.444
<i>Executive Functioning</i>										
WCST Categories	2.9	-1.4	2.2	-1.6	4.6	-1.8	4.7	-1.6	0.9	p=.377
WCST Non-Pers Errors	14.7	-7.2	13	-6.5	6.4	-4.8	8.3	-5.8	0.36	p=.280
WCST Pers Errors	10.4	-12	12.3	-12.8	14.7	-7.2	4	-8.5	0.38	p=.404
Digit Symbol Substitution	28.7	-5.9	19.3	-13.3	32.7	-10.6	41.6	-9	0.02	p=.002
Clock Setting	8.9	-4.2	5.5	-4.2	9.9	-2.6	9.9	-3.4	0.99	p=.096
TMT B Seconds	218.2	-77.6	256.9	-68.1	135.5	-48.2	108.4	-51.8	0.16	p=.053
TMT B Commission Errors	1.1	-1.7	1.9	-1.6	0.7	-0.8	0.7	-0.8	0.95	p=.268
TMT B Omission Errors	0.2	-0.4	7.6	-7.5	0	0	0	0	-	p=.003
<i>Language</i>										
BNT Spontaneous Correct	17.4	-7.5	16.4	-6.6	22.9	-3.9	26.1	-3.5	0.02	p=.159
BNT Correct with Stim Cues	19	-7	18	-6.9	24.1	-3.3	26.7	-3.1	0.03	p=.203
FAS Total	23.4	-10.8	23.5	-10.9	31.5	-13.7	37.9	-15	0.25	p=.360

**n*=7 for non-Hispanic normal controls; *n*=10 for non-Hispanics with AD; *n*=8 for Hispanics with AD.

Table 4.6: Mean raw scores (and standard deviations) achieved by Hispanic and Non-Hispanic patients and normal control participants on all neuropsychological measures. continued.

Test Name	Probable AD				Normal Controls				p-values	2x2 Interactions
	Hispanic (n=10)		Non-Hispanic (n=25)		Hispanic (n=10)		Non-Hispanic (n=25)			
	M	SD	M	SD	M	SD	M	SD		
Language cont.										
FAS Total Errors	2.8	-2.9	4	-3.2	2.3	-2.3	2.2	-1.4	0.83	p=300
Categories Total	27.3	-7.1	22.8	-6	43.8	-9	48.5	-11.7	0.27	p=057
Category Total Errors	1.8	-1.1	4.3	-5.6	2.8	-3.3	1.6	-1.7	0.18	p=071
WAIS-R Vocabulary	42.7	-9.9	39.1	-13.2	35.5	-8.5	52.4	-8.8	p<.001	p=001
Visuoconstructive/Psychomotor/Attention										
Block Design	23.6	-9	18.2	-10.5	36.5	-12.3	41.2	-11.3	0.29	p=083
Clock Command	2.3	-0.8	1.8	-0.8	2.6	-0.5	2.6	-0.6	0.99	p=154
Clock Copy	2.8	-0.4	2.4	-0.7	2.9	-0.3	2.8	-0.4	0.49	p=332
Visual Reproduction Copy	14.2	-2.9	14.1	-2.8	15.8	-4	16.2	-2.2	0.7	p=750
Copy a Cube	10.8	-2.9	9.1	-3.3	11.3	-1.8	11.2	-2	0.92	p=263
TMT A Seconds	86.5	-40.8	86	-40.5	58.9	-22	44.5	-15.7	0.04	p=402
TMT A Commission Errors	0.2	-0.6	0.2	-0.5	0	0	0.2	-0.8	0.45	p=613
TMT A Omission Errors	1.9	-4.2	1.6	-3.5	0	0	0	0	-	p=797

* $u_c=7$ for non-Hispanic normal controls; $n=10$ for non-Hispanics with AD; $n=8$ for Hispanics with AD.

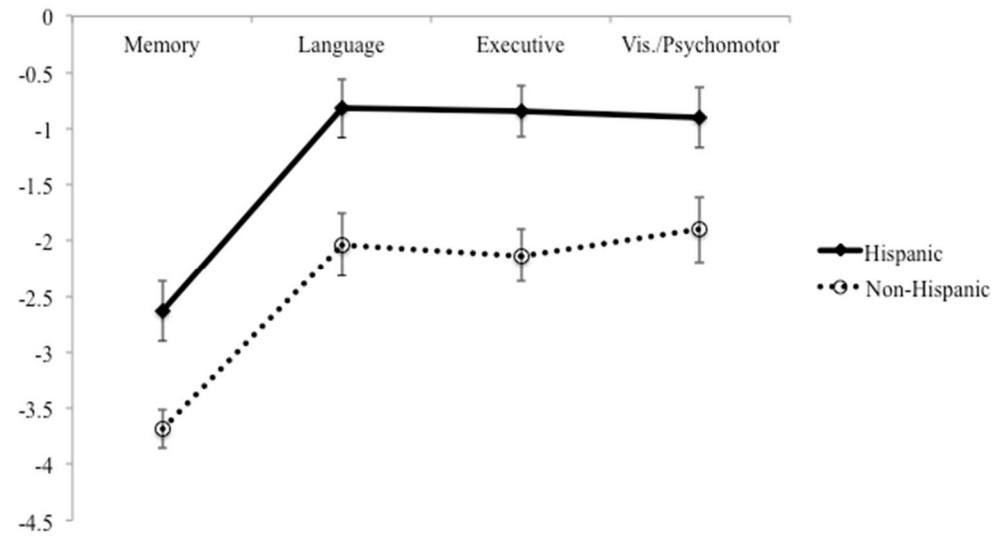


Figure 4.1: Cognitive deficit scores of Hispanic and Non-Hispanic patients with Alzheimer's Disease across domains.

CHAPTER 5: LONGITUDINAL SEMANTIC FLUENCY PERFORMANCE IN HISPANIC OLDER ADULTS IN THE EARLY STAGES OF AD

Abstract

The ability to generate words during category fluency was assessed longitudinally across four consecutive annual testing sessions in Hispanic and non-Hispanic individuals who are in the preclinical stages of Alzheimer's disease (AD). Based on a previous report of a semantic fluency advantage in Hispanic older adults who are normal but eventually develop AD ("decliners"; Weissberger, Salmon, Bondi, & Gollan, 2013), we asked if these advantages would hold longitudinally and whether there would be qualitative differences in the consistency with which semantic exemplars are lost over time. We selected Hispanic bilingual ($n = 9$ decliners; $n = 10$ controls) and matched non-Hispanic monolingual ($n = 11$ decliners; $n = 11$ controls) participants from Weissberger et al. (2013) and compared their category fluency performance over time. If Hispanics show less consistency of loss of semantic exemplars over time relative to non-Hispanics, this would support the notion that a stronger semantic system underlies the Hispanic advantage. Hispanic decliners outperformed their non-Hispanic counterparts across all four years of category fluency assessed. However, although means were in the predicted direction, Hispanic and non-Hispanic decliners did not differ with respect to their consistency of loss in semantic exemplars, and both groups demonstrated significantly greater consistency of decline than controls. We discuss two retrieval-based alternative accounts of the Hispanic fluency advantage including (a) translation-equivalent retrieval cues and (b) executive control benefits.

Introduction

Numerous studies have shown that in addition to a loss in the ability to retain and learn new information (episodic memory), semantic memory is also vulnerable to effects of the Alzheimer's disease (AD) process (Tulving, 1983; for review see Verma & Howard, 2012). This is evidenced by studies reporting naming and fluency deficits in individuals with Mild Cognitive Impairment (MCI) and Alzheimer's disease (Henry et al., 2004; Hodges & Patterson, 1995; Hodges, Patterson, Graham, & Dawson, 1996; Joubert et al., 2009; Salmon, Heindel, & Lange, 1999; Taler & Phillips, 2008). Furthermore, recent studies attempting to identify early changes that occur prior to the clinical diagnosis of MCI or probable AD have shown that, in addition to episodic memory, semantic memory is particularly vulnerable to early changes in preclinical AD (Bäckman, Small, & Fratiglioni, 2001; Bondi et al., 1994; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Lange et al., 2002; Linn et al., 1995; Mickes et al., 2007; Woodard et al., 2010).

A recent study by Weissberger, Salmon, Bondi, & Gollan (2013) investigated whether measures that have been shown to detect preclinical AD in non-Hispanics would do the same in Hispanic older adults. The authors compared Hispanic and non-Hispanic controls and decliners (participants who are normal but eventually develop AD) on semantic fluency, among other neuropsychological measures, to investigate the ability of such measures to detect future progression to AD in Hispanic older adults. Like many studies that report a disadvantage on semantic fluency for bilinguals compared to monolinguals (Gollan, Montoya, & Werner, 2002; Portocarrero, Burright, & Donnovick 2007; Rosselli et al., 2000), Weissberger et al. found that the Hispanic

(bilingual) controls generated fewer words during semantic (animals, vegetables, and fruits) fluency than non-Hispanic (monolingual) controls. In contrast, they found that Hispanic decliners performed better on semantic fluency compared to non-Hispanic decliners and did not significantly differ from Hispanic controls, rendering the test unhelpful for detecting future decline in Hispanics.

The present study aims to further elaborate on findings reported by Weissberger et al. (2013) by examining longitudinal semantic fluency performance in a subset of the Hispanic and non-Hispanic controls and decliners evaluated by Weissberger and colleagues. The first aim is to evaluate whether the Hispanic advantage on semantic fluency in the decliner group is maintained over time, or whether the advantage is reduced over a four-year time period. The second aim is to elaborate on the nature of the advantage in semantic fluency. To achieve these two goals, we looked at both quantitative (e.g., total words produced longitudinally) and qualitative (word loss over time) features of semantic fluency using methodology introduced by Salmon, Heindel, and Lange (1999). Salmon et al. aimed to validate the idea that deficits in semantic fluency in AD patients are due to deterioration of the semantic system and not due to retrieval deficits that prevent a semantic exemplar from being produced. They postulated that if semantic memory deteriorates throughout the course of AD, patients would be more consistent than controls in their failure to generate previously produced exemplars in subsequent years after the year that the exemplar initially dropped out. This is because, if semantic knowledge of an exemplar is lost in one year, it will not be reproduced in subsequent years. If a retrieval deficit is the cause of reduced semantic fluency performance in AD patients, then consistency of loss will be similar to that of controls

because whether an exemplar is retrieved in a subsequent year is random and based on the retrieval conditions, which can change from year to year. Findings were consistent with a deficit above and beyond what can be explained by a retrieval deficit. Specifically, AD patients were more consistent than normal controls in failing to produce a previously generated semantic category exemplar (Salmon et al., 1999).

We propose two possibilities for the advantage in semantic fluency. The first possibility is that the advantage in semantic fluency is due to a *stronger semantic system* due to knowledge of two languages and two cultures (or both). The second possibility is that bilingualism results in a benefit at the *retrieval level*, with two different possible underlying mechanisms. Weissberger et al. (2013) suggested that bilingual advantages in *executive control* may facilitate retrieval of semantic concepts, particularly when faced with the challenge of a degrading semantic system in Alzheimer's disease. An additional retrieval-based account could be that bilingualism facilitates retrieval of semantic concepts via *translation equivalent cues* (i.e., the presence of two lexical routes to each semantic concept).

If bilinguals have stronger semantic systems due to their experience with two languages (and perhaps two cultures), we would expect there to be less consistency of word loss relative to non-Hispanic monolinguals. Conversely, if the benefit in semantic fluency is at a retrieval level due to either enhanced executive control or translation facilitation, then bilinguals who eventually develop AD should exhibit semantic degradation at the same rate as monolinguals, but they will be better equipped to retrieve exemplars that are still intact from within their semantic memory store. In other words, they will exhibit the same degree of consistent loss as non-Hispanic monolinguals

because their semantic system is presumably deteriorating at a similar rate. We will consider each of these hypotheses separately.

1. Possibility of a stronger semantic system. One possibility that may account for preserved semantic fluency performance in bilingual older adults at risk for AD is the idea that the semantic system in bilinguals is relatively strengthened as a result of bilingualism. Specifically, some research suggests that language shapes the way we think about the world and that bilinguals may respond differently to tasks depending on the language they are using (e.g., Boroditsky, 2001; Cook, Bassetti, Kasai, Sasaki, & Takahashi, 2006; Keysar, Hayakawa, & Gyu An, 2012; Richard & Toffoli, 2009; also see Whorfian Hypothesis, cf. Hunt & Agnoli, 1991). A study by Botha (1968) found significant differences in scores on a test of values when comparing bilingual responses in one language versus the other language (also see Richard & Toffoli, 2009). In addition, Boroditsky (2001) investigated whether language influences the way people think about time. Specifically, English has metaphors that refer to time as moving horizontally (e.g., “move the meeting *forward*”, “push the deadline *back*”). In contrast, Mandarin has both front/back metaphors of time, and vertical references (e.g., “up” and “down”) of time (see Boroditsky, 2001). In a study of Mandarin-English bilinguals, Boroditsky found that bilinguals who learned English later in life showed a greater bias to think about time vertically than Mandarin-English bilinguals who learned English early in life. This research implies that in addition to managing two lexicons, bilinguals may have two ways of thinking about the world at a semantic level of representation due to experience with speaking two languages (see also Keysar et al., 2012).

In line with this, van Hell and De Groot (1998) argued that certain types of

translation equivalents overlap in conceptual representation to a greater extent across languages (e.g., concrete versus abstract words). Specifically, the authors asked participants to retrieve associates for words that were in either the same language as the word or in their other language. They found that the associates retrieved for concrete (vs. abstract) words, cognates (vs. non-cognates), and nouns (vs. verbs) in one language were more likely to be translations of the associates retrieved for these types of words in the other language. This work suggests that while the conceptual representations of certain word-types (nouns, cognates, and concrete words) may overlap a great deal with associates in either the same language or the other language (e.g., concrete words such as “skirt” and its within-language associate “dress” or between-language associate “vestido” in Spanish), other word-types overlap less in conceptual features both with their within- and between-language associations (e.g., abstract words such as “revenge”; Van Hell & De Groot, 1998). In essence, such work implies that not all words overlap conceptually between a bilingual’s two languages and certain words may be conceptually distinct from their closest translation. Furthermore, conceptual representations are often influenced by culture and may evolve over time with experience. For example, a bilingual’s view of Thanksgiving may be very different than a monolingual’s view of the holiday because of cross-cultural differences in how the holiday is celebrated (e.g., De Groot, 2000). De Groot (2000) discusses that the content of conceptual memory often varies between individuals, the experiences they have, and the languages they speak. Thus, it is possible that bilingualism lends to a richer conceptual network and a stronger semantic system.

2a. Translation Equivalents Aid Retrieval. An alternative account is that having two lexicons assists bilinguals in retrieving lexical representations from semantic

memory. Bilinguals have translation equivalent words for most concepts, and thus bilinguals might have two routes to each semantic concept via translation equivalents (e.g., *apple* and *manzana*; note that here full or near full conceptual overlap is assumed for translation equivalent terms). Research on bilingual language processing has revealed automatic connections between translation equivalents in the form of priming effects in lexical decision tasks (e.g., Chen & Ng, 1989), even when bilinguals are unaware that two languages are being presented (using masking) and between languages with very distinct writing systems (e.g., in Hebrew-English bilinguals; Gollan, Forster, & Frost, 1997). Furthermore, translation priming is stronger than semantic priming within languages (e.g., *watch* priming *clock*; see Chen & Ng, 1989). A study by Grainger & French-Mestre (1998) tested the effects of translation equivalent priming for both a lexical decision task (e.g., deciding whether a word is a real word) and semantic categorization task (e.g., deciding whether a word belongs to a specific category). The authors found a stronger priming effect for the semantic categorization task than the lexical decision task when using translation equivalents. These data support the notion that translation equivalents are linked by an amodal semantic system (e.g., see Chen & Ng, 1989).

Although speculative, it is possible that bilinguals with AD maintain semantic fluency integrity longer than monolinguals as a result of having two lexicons from which to retrieve or access concepts. In normal development and aging, bilingual disadvantages related to managing two languages override any benefits. However, in the context of AD, when monolinguals begin to lose their semantic memory integrity, bilinguals may be able to compensate due to the benefit of having two lexicons, and as a result, two routes to

reaching a semantic concept. For example, when attempting to retrieve a fruit, the word *apple* or *manzana* may trigger production. In contrast, monolinguals only have one lexical representation for the semantic exemplar “apple”. Thus instead of a relative preservation of semantic memory in bilingual older adults as a result of lifelong experiences with processing semantic information, it is possible that having two lexicons simply assists in the retrieval of exemplars.

2a. Enhanced Executive Control Aids Retrieval. In line with Weissberger et al. (2013), another possibility for the advantage in semantic fluency in Hispanic decliners relates to the role of executive control in retrieval during category fluency generation. Researchers of bilingualism agree that bilinguals cannot “turn one language off” to effectively function like monolinguals, and so are faced with constant dual-language activation. Specific to fluency, Gollan et al. (2002) suggest that healthy bilinguals may have more difficulty with semantic fluency compared to monolinguals because of dual-language activation. In other words, a task requiring explicit processing in one language will activate information about the words in both languages (e.g., Marian & Spivey, 2003; van Heuven, Dijkstra, & Grainger, 1998; Sandoval, Gollan, Ferreira, and Salmon, 2008; for reviews see Kroll, 1993; Kroll & De Groot 1997), and this direct competition between languages will slow the retrieval of the lexical item while the non-target language must be inhibited (e.g., Hermans, Bongaerts, De Bot, & Schreuder, 1998). For example, during animal fluency, producing *dog* will activate the translation *perro*, which appropriately fits the category but must be suppressed. Weissberger et al. suggest that, because of this lifelong competition between languages, bilinguals develop enhanced executive control mechanisms that subsequently make them better able to retrieve

exemplars from semantic memory despite changes to the integrity of semantic memory representations in the face of disease (e.g., Salmon & Bondi, 2009). A study by Tippett, Gendall, Farah, and Thompson-Schill (2004) showed that participants with AD have difficulty retrieving one response from a number of possible responses during letter fluency. Interestingly, they showed that the AD effect on fluency was greater on a relatively easier task (fluency for the letter F) than a more difficult task (fluency for words that begin with FL). They suggest that because there are more F words than FL words, there is more response competition in generating F words, and thus a greater retrieval deficit for the easier task. Considering that bilinguals are constantly in a scenario in which they have to inhibit production of the non-target language to retrieve exemplars from the target language, it is possible that in the face of AD, they are better equipped to deal with this type of competition during fluency.

Method

Participants. Participant characteristics are summarized in Table 5.1. All procedures at the ADRC received institutional ethics approval from the UCSD Human Research Program, and all participants provided written informed consent. We selected a subset of Hispanics ($n=19$) and a subset of non-Hispanics ($n=22$) whose neuropsychological test data were reported by Weissberger et al. (2013) and who had at least four consecutive years of category fluency data. Weissberger et al. identified 11 Hispanics and 11 non-Hispanics classified as “decliners” and 27 Hispanic and 33 non-Hispanic controls by screening data from 126 Hispanic and 370 non-Hispanic participants who entered the ADRC study as normal control participants (1990 to the present). The selected “decliners” began participation at the ADRC as normal controls

and eventually developed a diagnosis of probable AD. History of alcoholism, drug abuse, severe head injury, severe psychiatric disturbances, and learning disabilities are exclusionary criteria for participation in the ADRC study. All participants were judged to be cognitively normal upon their first evaluation (i.e., Year 1 testing) by two senior staff neurologists based on medical, neurological, and neuropsychological evaluations, and a number of laboratory tests used to rule out possible causes of dementia (see Galasko et al., 1994, for more details). Of the “decliner” participants selected for inclusion in Weissberger et al., 9 of the 11 Hispanics and 11 of the 11 non-Hispanics had four years or greater of category fluency data and thus were included in the present study. These participants were diagnosed with probable AD on average 7.7 years after their initial (baseline) evaluation at the ADRC using criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA; McKhann et al., 1984).

Diagnosing neurologists were not aware of specific test scores but were provided with a general statement regarding the evaluation results (e.g., “a deficit in two or more areas of cognition”). Longitudinal category fluency data were selected based on the year of probable AD diagnosis (Year 4) of each participant and backdated three years for a total of four years of data¹. We also selected a subset of the non-Hispanic ($n=11$) and Hispanic controls ($n=10$) included in Weissberger et al.’s study who had greater than four years of category fluency data and who were matched to the decliners on age and education. To select the four years of category fluency test data in controls, we matched the Year 1 test date of the decliners to the Year 1 test date in the controls in order to control for practice effects that may arise in both groups. All controls remained

cognitively healthy throughout the duration of their ADRC participation, and for at least one consecutive year after the Year 4 date used (an average of 2.1 years for Hispanics and 3.3 years for non-Hispanics).

Demographic characteristics. Multiple independent sample *t*-tests were conducted to ensure that matching conditions were met (see Table 5.1). All four participant groups were matched on age and education (all $ps \geq .50$) and decliners were matched on total Dementia Rating Scale (DRS) and Mini Mental Status Examination (MMSE) scores on first year of verbal fluency (Year 1; $p = .30$ for DRS; $p = .70$ for MMSE). None of the four groups differed with regards to gender breakdown (all $ps \geq .11$), although there was a greater proportion of females in the Hispanic decliner group (80%) and in the non-Hispanic control group (82%) relative to Hispanic controls and non-Hispanic decliners who were relatively balanced in proportion of females to males (50% female and 55% female respectively). As was the case in Weissberger et al. (2013), non-Hispanic normal controls obtained higher scores on the DRS relative to Hispanic normal controls (see Table 5.1; $t(18) = 3.26$; $p = .004$).

Language proficiency. A majority of Hispanic participants tested at the ADRC are bilinguals with varying degrees of proficiency in English and Spanish. A subset of Hispanic decliners ($n = 8$) and a subset of Hispanic normal controls ($n = 8$) filled out extensive language history questionnaires. Extensive language background for these participants is reported in Table 5.2. Of the decliners, 5 were born in the United States, two were born in Mexico, and one was born in Argentina. Of the Hispanic normal controls, five were born in the United States, two were born in Mexico, and one was born in Colombia.

All Hispanics tested at the ADRC are tested in their self-reported dominant language during the annual neuropsychological evaluations, and thus language of testing can vary from year to year. More than half of the Hispanic decliners preferred to be tested in Spanish (56% or 5 out of 9) for the majority of the four test years, while only 2 of the 10 normal controls preferred to be tested in Spanish (20%), a trend that fell just short of approaching significance ($\chi^2[1, n = 19] = 2.57, p = .11$; Fisher's exact test, $p = .17$). Notably, 2 of the 5 decliners who preferred testing in Spanish, asked to be tested in English in the first year of verbal fluency testing, but were then tested in Spanish for the three subsequent years of testing. Given these differences, some of the effects reported below could be related to this confound in language of testing and we consider this possibility in the discussion section. Qualitatively, there appeared to be a relationship between country of birth and testing preference. Of the 6 Hispanics born in countries outside of the United States, a majority ($n = 4$) preferred to be tested in Spanish for the majority of years (one participant was tested in English during Year 1). Most participants learned both languages at an early age; only two of the 16 Hispanic participants with language history data reported learning English as adults (ages 28 and 30). The remaining participants reported learning English before the age of 8 ($M=6.9$ for normal controls; $M=6.9$ for decliners). We excluded Hispanics who reported a third proficient language. Additionally, the level of bilingualism in the non-Hispanic cohort is negligible.

Vascular risk factors. Hispanics have been shown to have greater risk of stroke, diabetes, and other vascular risk factors compared to non-Hispanics (e.g., Harris, 1991; Sacco et al., 1998; Sacco, Hauser, & Mohr, 1991), which can affect verbal fluency test performance differently than AD (e.g., Looi & Sachdev, 1999; Ott et al., 1999). Thus to

reduce the potential confound of including patients with vascular dementia or high vascular risk, we compared Hispanic and non-Hispanic normal controls and decliners on their Year 1 Rosen-modified Hachinski ischemia scale scores (Hachinski et al., 1975; Rosen et al., 1980). Due to missing data, we were unable to obtain Year 1 scores for 13 participants. To overcome this large subset of participants with missing stroke-risk data, we collected Rosen-modified Hachinski ischemia scale scores from the next closest year, which was on average 2 years ($SD = 1$) from the Year 1 test date. We found no difference in stroke risk between the two normal control groups ($p=.31$) and decliners groups ($p=.43$). With regards to diabetes, only two participants had diabetes, both of whom belonged to the non-Hispanic decliner group. This was not a statistically significant chi-square difference ($\chi^2[1, n = 20] = 2.57, p = .18$; Fisher's exact test, $p = .48$), thus making diabetes an unlikely confound.

Activities of Daily Living. Every day functioning was assessed with the Pfeffer Outpatient Disabilities Scale (PODS; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) and global dementia ratings were obtained through the Clinical Dementia Rating scale (CDR; Hughes, Berg, Danzinger, Coben, & Martin, 1982; Morris et al., 1991), both of which are reported in Table 5.1. As was the case with the Rosen-modified Hachinski ischemia scale, a substantial number of participants were missing PODS ($n=10$ missing) and CDR ($n=26$ missing) scores on their Year 1 testing. Thus, as was done with stroke-risk, we collected scores from the next closest year. As this could potentially impact the extent of impairment in the decliner group (e.g., if a much earlier year is selected), we elected to take a conservative approach and select a later year unless it was unavailable. For the PODS, this was only possible for 2 of the 10 participants who both had PODS

scores available for Year 2; for the eight remaining participants, PODS scores were gathered on average 2 years prior to Year 1 ($SD = .64$). Nevertheless, decliners did not differ from controls in either cultural group (all $ps \geq .27$), and Hispanic normal controls did not differ from non-Hispanic normal controls ($p = .17$). However, potentially due to the fact that more Hispanic decliners were missing PODS ($n = 2$ missing) compared to non-Hispanic decliners (none missing) and thus PODS scores from earlier test years were obtained for these two participants, Hispanic decliners had significantly lower PODS scores than non-Hispanic decliners ($F(1,18)=6.34$, $MSE=1.09$, $p=.02$, $\eta_p^2=.26$).

The Clinical Dementia Rating was adopted by the ADRC relatively recently, and thus we were able to gather later years of CDR data ($M = 3.3$ years later; $SD = 2.0$) for all but four of the 26 participants missing CDR scores on Year 1; of the four, one participant's CDR score was obtained for the year prior to Year 1 testing and three participants did not have CDR scores at any time point in their participation in the ADRC study. As would be expected, Hispanic and non-Hispanic controls all obtained CDR scores of 0, and thus did not differ from each other. Also as expected, non-Hispanic decliners had higher CDR scores than non-Hispanic normal controls ($F(1,17)=16.0$, $MSE=0.9$, $p=.001$, $\eta_p^2=.47$) and Hispanic decliners had higher CDR scores than the Hispanic normal controls ($F(1,16)=18.18$, $MSE=1.22$, $p=.001$, $\eta_p^2=.53$). Importantly, Hispanic decliners and non-Hispanic decliners also did not differ in CDR scores ($p=.35$).

Measures. As part of their annual ADRC neuropsychological evaluations, participants performed a category fluency task. The category fluency task allotted 60 seconds per category and asked participants to generate as many “animals”, “fruits”, and “vegetables” as possible. Participants were instructed to not generate the same word with

a different suffix (e.g., horse, horses). In the present study, the words produced across all three categories were summed to produce a total category score. Words were excluded from the total score if they were repetitions or variants of previous words, or if they did not belong to the particular category tested.

All participants were tested with the category fluency test over four consecutive years, with approximately 1 year separating each test². Thus the interval between the first test date investigated (Year 1) and the fourth and final evaluation (Year 4) spanned 3 years for most participants. Trained psychometrists tested participants annually in a quiet room. All psychometrists at the ADRC have had BA- or MA-level education at universities in the United States. During each annual evaluation, bilingual participants were asked which language they preferred to be tested in. All non-Hispanics preferred to be tested in English. For participants who preferred testing in Spanish, bilingual psychometrists fluent in both English and Spanish administered testing.

Results

The mean number of words generated by Hispanic and non-Hispanic decliners and controls on category fluency is displayed in Figure 5.1. We conducted a three-way repeated-measures ANOVA to investigate longitudinal differences in category fluency within each cultural group. A Group (decliners vs. controls) by Ethnicity (Hispanic vs. non-Hispanic) by Years (1-4) repeated measures ANOVA revealed a main effect of Group in which controls generated more words than decliners, ($F(1,37)=33.52$, $MSE=215.37$, $p<.001$, $\eta_p^2=.48$), and of Year, in that the total words generated steadily declined across the 3-year time span ($F(3,111)=11.28$, $MSE=21.75$, $p<.001$, $\eta_p^2=.23$) but

no main effect of Ethnicity ($p = .57$). The Group x Year interaction was also significant, reflecting the fact that the decline in mean words generated overtime was driven by decliners ($F(3,111)=4.89$, $MSE=21.75$, $p=.003$, $\eta_p^2=.12$). As can be seen in Figure 5.1, Hispanic decliners obtained higher scores than non-Hispanic decliners across all four time points, while controls showed the opposite pattern, yielding an Ethnicity X Group interaction ($F(1,37)=9.76$, $MSE=215.37$, $p=.003$, $\eta_p^2=.21$). The Year X Ethnicity or Group X Year X Ethnicity interactions were not significant (both $ps \geq .34$).

To further investigate the Group X Ethnicity interaction, we conducted two follow-up repeated measures ANOVAs of Ethnicity (Hispanic vs. non-Hispanic) X Year (1-4) separately for normal controls and decliners. Doing so with the normal control participants revealed a main effect of ethnicity in which non-Hispanic controls generated significantly more words than Hispanic controls ($F(1,19)=5.11$, $MSE=295.58$, $p=.04$, $\eta_p^2=.21$). There was no main effect of Year ($p = .57$) or interaction of Ethnicity X Year ($p = .18$) suggesting that control groups did not significantly decline in total words generated on category fluency and that the difference between Hispanic and non-Hispanic controls was maintained across all four years. The Ethnicity X Year ANOVA for the decliner group also revealed a main effect of Ethnicity ($F(1,18)=5.23$, $MSE=130.69$, $p=.04$, $\eta_p^2=.23$), however, investigating the means revealed the opposite pattern than the control groups: Hispanic decliners obtained higher category fluency scores than non-Hispanic decliners across all four years. Unlike the controls, the main effect of Year was significant ($F(3,54)=17.39$, $MSE=18.77$, $p<.001$, $\eta_p^2=.49$), indicating that both groups steadily declined in total fluency output across all four years. However,

the Ethnicity X Year interaction was not significant ($p = .82$), suggesting that the rate of decline did not differ by ethnicity.

Given the Group X Ethnicity interaction and the report of better category fluency performance in Hispanic decliners relative to non-Hispanics in initial evaluation at the ADRC despite poorer performance in normal controls (e.g., Weissberger et al., 2013), we wondered whether this pattern would hold for each of the four time points selected for this longitudinal study. We submitted mean total category fluency scores to four separate Ethnicity X Group ANOVAs, one for each time point. Doing so revealed significant main effects of group for all four time points (Year 1, $F(1,37)=14.22$, $MSE=58.38$, $p=.001$, $\eta_p^2=.28$; Year 2, $F(1,37)=23.48$, $MSE=71.35$, $p<.001$, $\eta_p^2=.39$; Year 3, $F(1,37)=33.80$, $MSE=66.67$, $p<.001$, $\eta_p^2=.53$; and Year 4, $F(1,37)=33.01$, $MSE=84.22$, $p<.001$, $\eta_p^2=.47$), but no main effects of ethnicity for all four years (all $ps \geq .26$). However, as was the case in Weissberger et al. (2013), we found a Group X Ethnicity interaction across all four time points (Year 1, $F(1,37)=8.70$, $MSE=58.38$, $p=.005$, $\eta_p^2=.19$; Year 2, $F(1,37)=12.24$, $MSE=71.35$, $p=.001$, $\eta_p^2=.25$; Year 3, $F(1,37)=5.72$, $MSE=66.67$, $p=.02$, $\eta_p^2=.13$; and Year 4, $F(1,37)=4.79$, $MSE=84.22$, $p=.04$, $\eta_p^2=.12$). As can be seen in Figure 5.1, non-Hispanic normal controls generated more words on category fluency than Hispanic normal controls across all four years; however, in the decliner group, the reverse was true in that Hispanic decliners generated more words than non-Hispanic decliners across all four years.

Qualitative Analyses. To better understand the nature of differences between Hispanic and non-Hispanic decliners on category fluency, we conducted qualitative analyses similar to those described in Salmon et al. (1999). Salmon et al. found patients

with AD to exhibit greater consistency of loss of semantic exemplars over time relative to controls, particularly for category fluency. If Hispanic older adults in the beginning stages of Alzheimer's disease have a stronger semantic system due to bilingualism or biculturalism, we predicted that the difference in mean consistent loss between normal controls and Hispanic decliners will be smaller than the difference between non-Hispanic normal controls and decliners. On the flip side, if bilinguals are benefited at the retrieval level due to benefits related to executive functioning or translation facilitation, then semantic exemplars will be lost at the same rate as the non-Hispanic decliners and mean consistent loss over time will not differ between cultural groups.

To investigate these predictions, we first examined percentage of consistently lost items. The percentage of consistently lost and inconsistently lost items was calculated as follows. If a word was generated in either Year 1 or Year 2 and was not generated in the subsequent year (i.e., Year 2 or Year 3, respectively) then the opportunity for a consistently lost or inconsistently lost item was available. If that item was never generated again (in either Year 3 or Year 4), a consistent loss was counted. If that item was re-generated in either Year 3 or Year 4, it was counted as an inconsistent loss. The percentage of consistently lost items was calculated by dividing the total number of consistently lost items by the total number of opportunities for either a consistent or inconsistent loss using the following formula: Total Consistent Loss/Total Opportunities for Consistent Loss.

An Ethnicity X Group between-subjects ANOVA revealed no main effects of group or ethnicity, and no interaction (all $ps \geq .29$), suggesting that groups did not differ in the percentage of items that were consistently lost across the 3-year time-span.

However, because the number of consistently lost items could be influenced by total output in later years, and groups differed significantly in terms of mean output for all years, an additional variable was calculated to control for total output. As is also described in Salmon et al. (1999), words that were generated in Year 1 and produced again in Year 2 were categorized as having a *strong* representation, and words that were generated in Year 1 but not in Year 2 were categorized as having a *weak* representation. The number of weak words and the number of strong words reproduced in either Year 3 or Year 4 was then calculated. The ratio of initial weak to strong words determined by Year 1 and Year 2 was compared to the ratio of reproduced weak to reproduced strong words in either Year 3 or Year 4 using the following formula: $(\text{Initial Weak})/(\text{Initial Strong}) - (\text{Kept Weak})/(\text{Kept Strong})^3$. If retrieval was random in Years 3 and 4 and not dependent on whether it was consistently generated (i.e., *strong*) or inconsistently generated (i.e., *weak*) in Years 1 and 2, the two ratios should be similar because the generation of weak and strong items should maintain the original probability or likelihood (even if the total number of generated items go down over time). However, if weak items are more likely than strong items to be lost over time and never regenerated, the size of the ratio for Years 3 to 4 should decrease relative to the original ratio. The greater decline in this likelihood ratio, the more consistent an individual was in not generating presumably lost items (i.e., items that were generated in Year 1 but not in Year 2) in Years 3 and 4 (as described in Salmon et al., 1999). Thus, if Hispanic decliners maintain semantic exemplars longer than non-Hispanics due to a stronger semantic system, we expected the difference in *mean decline in the likelihood of generating weak items* between controls and decliners to be greater for non-Hispanics than Hispanics. On

the flip side, if Hispanics are helped by enhanced retrieval mechanisms (either because of enhanced executive control or translation facilitation) then the *mean decline in the likelihood of generating weak items* will be similar for Hispanic and non-Hispanic decliners.

The mean decline in the likelihood of generating weak items relative to strong items in Years 3 and 4 on the category fluency task for Hispanic and non-Hispanic controls and decliners is presented in Figure 5.2. A between-subjects ANOVA of Group (decliner vs. control) X Ethnicity (Hispanic vs. non-Hispanic) revealed a significant main effect of Group ($F(1,37)=4.88$, $MSE=.29$, $p=.03$, $\eta_p^2=.12$) in which decliners showed greater decline than controls, but no main effect of Ethnicity ($p=.79$) and no interaction of Group X Ethnicity ($p=.60$). These findings replicate those reported by Salmon et al. (1999) in which participants in the early stages of AD had greater mean decline than normal controls.

Discussion

The goal of the present study was to shed light on the preclinical stages of AD in Hispanic older adults with regards to semantic memory. The results demonstrate that Hispanic older adults in the early stages of AD generate a greater number of words across four years of category fluency than non-Hispanic older adults in the early stages of AD, despite being matched on age, education, and global dementia ratings. This is in contrast to a semantic fluency disadvantage in Hispanic controls relative to non-Hispanics. Despite advantages in fluency in Hispanic decliners, both Hispanic and non-Hispanic decliners' performances declined at the same rate across the four years of evaluation.

Given these findings, we wondered whether the nature of semantic fluency advantages related to protective factors of bilingualism. We predicted that if bilinguals had a stronger semantic system, then the consistency of loss of semantic exemplars would be lower than that of monolingual non-Hispanics. On the flip side, if bilinguals were benefited at the retrieval level, either due to enhanced executive functioning or translation facilitation, consistency of loss in Hispanic decliners would not differ to that of non-Hispanic decliners. We conducted two analyses to investigate these predictions. The analysis of consistency of loss yielded no main effects or interactions, likely because of the influence that total output can have on this variable. Thus, we conducted a second analysis investigating the mean decline in the likelihood of generating weak items relative to strong items and found that both decliner groups had greater mean decline relative to controls, but did not differ from each other. The finding that Hispanic and non-Hispanic decliners exhibited a similar degree of consistent loss longitudinally suggests that both groups exhibited reduced integrity of the semantic system at a similar stage of the AD process. Based on our predictions outlined above, these findings support the notion that bilingualism benefits semantic fluency performance of Hispanic decliners at the retrieval level rather than the semantic level.

There are two possible routes with which bilingualism can benefit retrieval of semantic exemplars and lend to better performances in semantic fluency despite degradation of the semantic system. One of the possibilities is the notion of translation facilitation. Studies investigating bilingual language representation find evidence for an amodal semantic system (e.g., see Chen & Ng, 1989) linking two translation equivalents. This implies that activation of either of a bilingual's two languages will assist in retrieval

of a semantic concept. During the AD process when semantic memory begins to deteriorate, bilinguals may be better equipped for retrieving concepts that still remain in their semantic memory stores than monolinguals who only have one route (or word) to retrieving the concept. Although this possibility is plausible, further research is needed to verify that this is indeed the case. One factor that does not lend well to this notion is that bilingual controls have been shown to have lower performances on semantic fluency than monolinguals (Gollan et al., 2002; Portocarrero, Burright, & Donnovick, 2007; Rosselli et al., 2000). If translation facilitation assists bilinguals in the early stages of AD, it is unclear why it would not also do so in young and older healthy bilinguals. One possibility along these lines is that other factors of bilingualism impact performance independently of translation facilitation. It has been well cited that disadvantages on linguistic tasks such as semantic fluency arise due to dual-language activation which slows the retrieval of the lexical item while the non-target language is inhibited (e.g., Hermans et al., 1998). Thus, when the semantic system begins to degrade, it is possible that benefits of translation facilitation override costs of competition between languages. Future studies that can separate these two processes and directly test the idea of translation facilitation may shed light on whether translation facilitation is indeed contributing to enhanced semantic fluency performance in Hispanic older adults who eventually develop AD.

A second possibility that explains both the disadvantages observed in bilingual controls and advantages observed in bilingual decliners, relates to enhanced executive control. The notion that lifelong practice with managing two languages enhances the executive control system in bilinguals has been supported by numerous studies that report executive control advantages in bilinguals relative to monolinguals (for review see

Bialystok, Craik, Green, & Gollan, 2009). It is thought that such advantages arise due to a bilingual's life long practice switching between languages and inhibiting the non-target language whenever necessary. Such mechanisms of control contribute to enhanced executive control but also to poorer performance on linguistic tasks (for review, see Kroll & Gollan, 2014). However, such mechanisms may enhance retrieval of semantic exemplars in the face of semantic degradation. As suggested by Weissberger et al. (2013), both monolinguals and bilinguals are faced with competition between possible responses in the fluency task (e.g., whether to say *cat* or *dog* during animal fluency) and resolving this competition between upcoming and previously uttered responses (which need to be suppressed to avoid perseverations) can slow production. Levelt, Roelofs, & Meyer (1999) argue that language production is a competitive process, showing that picture naming in monolinguals was slowed when semantically related words were presented simultaneously with the to-be-named pictures, relative to semantically unrelated words. For example, when showing monolinguals a picture of a cat with the word *dog* written next to it, the picture was named more slowly relative to an unrelated distracter (e.g., *rag*). Thus, although semantic fluency may create interference in both monolinguals and bilinguals, and although bilinguals may be disadvantaged when cognitively normal because of dual-language activation, when monolinguals' ability to manage competition for selection is impaired by AD (Tippett et al., 2004), this may allow bilinguals' more efficient processes for managing competition in language tasks to be observed. This executive-control effect on retrieval may account for reduced effects of preclinical AD in the semantic fluency scores of Hispanic older adults.

Although non-significant differences between Hispanic and non-Hispanic decliners on mean decline points away from the *stronger semantic system* possibility, examining the means of this variable (Figure 5.2) reveals that mean decline is slightly higher for Hispanic controls ($M = .58, SD = .37$) than non-Hispanic controls ($M = .53, SD = .21$), but that the reverse is true for decliners; Hispanic decliners had less mean decline ($M = .86, SD = .75$) than non-Hispanic decliners ($M = .99, SD = .68$). As a follow-up investigation of this pattern, we z-transformed the mean decline scores in the decliner groups based on their respective cultural control group. The result of this z-transformation is presented in Figure 5.3. A one-way ANOVA comparing the z-transformed scores of Hispanic decliners ($M = -.77, SD = 2.03$) to those of non-Hispanic decliners ($M = -2.22, SD = 3.26$) was not statistically significant ($p = .26$), but revealed that non-Hispanic decliners were on average greater than 2 standard deviations below their respective control group, while Hispanic decliners were less than 1 standard deviation below their respective control group. Notably, partial eta squared is .07, indicating a medium effect size. These findings suggest that, perhaps with more power, a difference between Hispanic decliners and non-Hispanic decliners may arise. If this were to be the case, it would provide strong evidence for a strengthened semantic system in Hispanic bilingual older adults.

As this was an exploratory study and we are unable to distinguish between the two retrieval possibilities or rule out the *stronger semantic system* possibility, future studies that are designed to distinguish between the two (i.e., enhanced executive control, translation facilitation) and have more power should be conducted. One avenue of clarification would be through examination of phonemic fluency in Hispanic and non-

Hispanic older adults with preclinical AD. We were unable to investigate phonemic fluency performance due to the imbalance in language of testing between Hispanic decliners and controls, which would have introduced an important confound (see limitations below; Pena et al., 2009). However, a study that compares phonemic fluency to semantic fluency performance could dissociate between the three possibilities outlined above. Specifically, if a stronger semantic system in Hispanic bilinguals is the basis for the semantic fluency advantage, we would not expect phonemic fluency to be equally benefited. On a similar note, if translation facilitation assists with performance on semantic fluency, we would also not expect phonemic fluency to benefit. This is because although translation equivalents share the same semantic representation and can thus cue people to relevant responses within the same semantic category (e.g., Chen & Ng, 1989; Gollan et al., 2002), translation equivalents rarely begin with the same letter. However, a study with older bilinguals by Rosselli et al. (2000) may suggest that phonemic fluency also benefits from bilingualism in older adults. Specifically, Rosselli et al. (2000) found lower scores on semantic fluency in normally aging bilinguals compared to normally aging monolinguals. Interestingly, comparing Rosselli et al. to Gollan et al.'s (2002) findings with young bilinguals and monolinguals on fluency tasks has some interesting implications. Specifically, Gollan et al. tested bilinguals and monolinguals on 10 letter fluency categories and 12 semantic fluency categories. Although Rosselli et al. only used letters "F", "A", and "S", and semantic categories "animals" and "fruits", comparing across studies on just these conditions reveals that, in contrast to the younger adults tested in Gollan et al.'s (2002) study, older bilinguals scored equally well on phonemic fluency relative to older monolinguals and the difference between monolinguals and bilinguals on

semantic categories was reduced (although note that this is not the case for Letter F, in which both studies did not find significant differences across language group; see Figure 5.4 for a depiction of verbal fluency means across both studies). A glance at Figure 5.4 (e.g., comparing Rosselli et al. and Gollan et al. means) reveals that there may be attenuated age differences for bilinguals relative to monolinguals on semantic fluency and on some letters of phonemic fluency as well. Although a statistical comparison of the two studies cannot be conducted, if the findings hold, they would suggest that bilingualism may also benefit letter fluency – and this would support the *executive control* account (also see, Luo, Luk, & Bialystok, 2010 for an advantage in phonemic fluency in young bilinguals who are matched to monolinguals on vocabulary level). However, if the findings do not hold, and phonemic fluency does not exhibit attenuated age differences for bilinguals, this would provide support for either translation facilitation or a stronger semantic system.

The present study is not without limitations, which call for some caution in interpretation of the findings and suggest a need for further investigation. For one, our Hispanic controls and decliners were unbalanced in terms of their preferred language of testing. While eight of the ten normal controls preferred to be tested in English, more than half of the Hispanic decliners preferred to be tested in Spanish (56% or 5 out of 9). This imbalance could potentially impact verbal fluency performance for factors unrelated to the AD process. For example, the literature suggests that letters “F” “A” and “S” are not ideal for use with Spanish speakers because they are not matched in level of difficulty between bilinguals and monolinguals (see Artiola i Fortuny, Heaton, & Hermosillo, 1998; Peña et al., 2009) and because of this, we were unable to examine phonemic

fluency performance. However, cross-cultural research of category fluency suggest that it is relatively impervious to language and cultural differences (e.g., Acevedo et al., 2000; Ardila & Moreno, 2001), and thus the confound of language of testing is unlikely to impact our category fluency findings. A second limitation is our small sample size of decliners and controls. Due to matching conditions, we had to exclude a number of controls included in Weissberger et al. (2013). Nevertheless, we still showed the same interaction observed in baseline testing by Weissberger et al.⁴ for the four years of category fluency under investigation, suggesting that we had enough power to detect such differences. However, we did not find differences between Hispanic decliners and non-Hispanic decliners on the qualitative measure of category fluency decline and this could have been due to lack of power to detect differences. Future studies with larger samples may elaborate upon these differences or lack thereof.

This study is the first of its kind to investigate category fluency longitudinally in a group of Hispanic older adults who are in the preclinical stages of AD. Findings shed light on the process of semantic degradation in Hispanic older adults and confirm gradual decline of category fluency in this cultural group, as has been reported in non-Hispanics in the early stages of AD (e.g., Salmon et al., 1999). Furthermore, the findings highlight the possibility that protective factors of bilingualism, more likely due to benefits at the retrieval level, enhance semantic fluency performance in Hispanic bilinguals who eventually develop AD. These data do not only help to better understand the normal and abnormal bilingual aging process as it relates to integrity of the semantic system, but also contribute to the current understanding of cognitive processes that underlie bilingual language control.

References

- Acevedo, A., Loewenstein, D. A., Barker, W. W., Harwood, D. G., Luis, C., Bravo, M.,...Duara, R. (2000). Category fluency test: Normative data for English- and Spanish-speaking elderly. *Journal of the International Neuropsychological Society*, 6, 760-769.
- Ardila, A., & Moreno, S. (2011). Neuropsychological test performance in Aruaco Indians: An exploratory study. *Journal of the International Neuropsychological Society*, 7, 510-515.
- Artiola i Fortuny, L., Heaton, R. K., & Hermosillo, D. (1998). Neuropsychological comparisons of Spanish-speaking participants from the U.S.– Mexico border region versus Spain. *Journal of the International Neuropsychological Society*, 4, 363–379.
- Bäckman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain*, 124, 96-102.
- Benton, A. L. (1968). Differential behavioral effects in frontal lobe disease. *Neuropsychologia*, 6, 53-60.
- Bialystok, E., Craik, F.I.M., Green, D.W., & Gollan, T.H. (2009). Bilingual minds. *Psychological Science in the Public Interest*, 10, 89-129.
- Bondi, M. W., Monsch, A. U., Galasko, D., Butters, N., Salmon, D. P., & Delis, D. C. (1994). Preclinical cognitive markers of dementia of the Alzheimer type. *Neuropsychology*, 8, 374-384.
- Bondi, M.W., Salmon, D.P., Galasko, D., Thomas, R.G., Thal, L.J. (1999). Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. *Psychology and Aging*, 14, 295–303.
- Borkowski, J. G., Benton, A. L., & Spreen, O. (1967). Word fluency and brain damage. *Neuropsychologia*, 5, 135-140.
- Boroditsky, L. (2001). Does language shape thought?: Mandarin and English speakers' conceptions of time. *Cognitive Psychology*, 43, 1-22.
- Botha, E. (1968). Verbally expressed values of bilinguals. *The Journal of Social Psychology*, 75, 159-164.
- Chen, P., Ratcliff, G., Belle, S. H., Cauley, J.A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer's disease. *Archives of General Psychiatry*, 58, 853-858.

- Chertkow, H., & Bub, D. (1990). Semantic memory loss in dementia of Alzheimer's type: What do various measures measure? *Brain*, 113, 397-417.
- Cook, V., Bassetti, B., Kasai, C., Sasaki, M., & Takahashi, J. A. (2006). Do bilinguals have different concepts? The case of shape and material in Japanese L2 users of English. *International Journal of Bilingualism*, 10, 137-152.
- De Groot, A. M. B. (2000). On the source and nature of semantic and conceptual knowledge. *Bilingualism: Language and Cognition*, 3, 7-9.
- Galasko, D., Hansen, L., Katzman, R., Widerholt, W., Masliah, E., Terry, R., . . . Thal, L. J. (1994). Clinical-neuropathological correlations in Alzheimer's disease and related dementias. *Archives of Neurology*, 51, 888-895.
- Gollan, T. H., Forster, K. I., & Frost, R. (1997). Translation priming with different scripts: Masked priming with cognates and noncognates in Hebrew-English bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 23, 1122-1139.
- Gollan, T. H., Montoya, R. I., & Werner, G. A. (2002). Semantic and letter fluency in Spanish-English bilinguals. *Neuropsychology*, 16, 562-576.
- Grainger, J. & Frenck-Mestre, C. 1998. Masked priming by translation equivalents in proficient bilinguals. *Language and Cognitive Processes*, 13, 601-623.
- Hachinski, V.C., Iliff, L. D., Zilhka, E., DuBoulay, G. J., McAllister, V. L., Marshall, J., Russell, R. W. R., & Symon, L. (1975). Cerebral blood flow in dementia. *Archives of Neurology*, 32, 632-637.
- Harris, M. I. (1991). Epidemiological correlates of NIDDM in Hispanics, Whites, and Blacks in the U.S. population. *Diabetes Care*, 14, 639 – 648.
- Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: A meta-analysis. *Neuropsychologia*, 42(9), 1212-1222.
- Hermans, D., Bongaerts, T., De Bot, K., & Schreuder, R. (1998). Producing words in a foreign language: Can speakers prevent interference from their first language? *Bilingualism: Language and Cognition*, 1, 213-229.
- Hodges, J. R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*, 33, 441-459.
- Hodges, J. R., Patterson, K., Graham, N., & Dawson, K. (1996). Naming and knowing in

- dementia of the Alzheimer's type. *Brain and Language*, 54, 302-325.
- Hughes, C. P., Berg, L., Danzinger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry*, 140, 566-572.
- Hunt, E., & Agnoli, F. (1991). The Whorfian hypothesis: A cognitive psychology perspective. *Psychological Review*, 98, 377-389.
- Joubert, S., Brambati, S. M., Ansado, J., Barbeau, E. J., Felician, O., Didic, M.,...Kergoat, M-J. (2010). The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia*, 48, 978-988.
- Keysar, B., Hayakawa, S. L., & Gyu An, S. (2012). The foreign-language effect: Thinking in a foreign tongue reduces decision bias. *Psychological Science*, 23, 661-668.
- Kroll, J. F. (1993). Accessing conceptual representation for words in a second language. In R. Schreuder & B. Weltens (Eds.), *The bilingual lexicon* (pp. 53-81). Amsterdam: John Benjamins.
- Kroll, J. F., & De Groot, A. M. B. (1997). Lexical and conceptual memory in the bilingual: Mapping form to meaning in two languages. In A. M. B. De Groot & J. F. Kroll (Eds.), *Tutorials in bilingualism: Psycholinguistic perspectives* (pp. 169-199). Mahwah, NJ: Erlbaum.
- Kroll, J. F., & Gollan, T. H. (2014). Speech planning in two languages: What bilinguals tell us about language production. In V. Ferreira, M. Goldrick, & M. Miozzo (Eds.), *The Oxford handbook of language production*. Oxford: Oxford University Press.
- Lange, K. L., Bondi, M. W., Salmon, D. P., Galasko, D., Delis, D. C., Thomas, R. G., & Thal, L. J. (2002). Decline in verbal memory during preclinical Alzheimer's disease: Examination of the effect of APOE genotype. *Journal of International Neuropsychological Society*, 8, 943-955.
- Linn, R. T., Wolf, P., Bachman, D. L., Knoefel, J. E., Cobb, J. L., Belanger, A. J.,... D'Agostino, R. B. (1995). The 'preclinical phase' of probable Alzheimer's disease: A 13-year prospective study of the Framingham cohort. *Archives of Neurology*, 52, 485-490.
- Looi, J. C. L., & Sachdev, P. S. (1999). Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology*, 53, 670-678.

- Luo, L., Luk, G., & Bialystok, E. (2010). Effect of language proficiency and executive control on verbal fluency performance in bilinguals. *Cognition*, *114*, 29-41.
- Marian, V., & Spivey, M. (2003). Bilingual and monolingual processing of competing lexical items. *Applied Psycholinguistics*, *24*, 173-193.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS ADRDA Work Group. *Neurology*, *34*, 939-944.
- Mickes, L., Wixted, J. T., Fenema-Notestine, C., Galasko, D., Bondi, M. W., Thal, L. J., & Salmon, D. P. (2007). Progressive impairment on neuropsychological tasks in a longitudinal study of preclinical Alzheimer's disease. *Neuropsychology*, *21*, 696-705.
- Morris, J. C., McKeel, D. W., Storandt, M., Rubin, E. H., Price, J. L., Grant, E. A., . . . Berg, L. (1991). Very mild Alzheimer's disease: Informant-based clinical, psychometric, and pathologic distinction from normal aging. *Neurology*, *41*, 469-478.
- Ott, A., Stolk, R. P., van Harskamp, F., Pols, H. A. P., Hofman, A., & Breteler, M. M. B. (1999). Diabetes mellitus and the risk of dementia: The Rotterdam study. *Neurology*, *53*, 1937-1942.
- Peña-Casanova, J., Quiñones-Úbeda, S., Gramunt-Fombuena, N., Quintana-Aparicio, M., Aguilar, M., Badenes, D., . . . Blesa, R. (2009). Spanish multicenter normative studies (NEURONORMA Project): Norms for verbal fluency tests. *Archives of Clinical Neuropsychology*, *24*, 395-411.
- Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology*, *37*, 323-329.
- Peña-Casanova, J., Quiñones-Úbeda, S., Gramunt-Fombuena, N., Quintana-Aparicio, M., Aguilar, M., Badenes, D., . . . Blesa, R. (2009). Spanish multicenter normative studies (NEURONORMA Project): Norms for verbal fluency tests. *Archives of Clinical Neuropsychology*, *24*, 395-411.
- Portocarrero, J. S., Burright, R. G. & Donovanick, P. J. (2007). Vocabulary and verbal fluency of bilingual and monolingual college students. *Archives of Clinical Neuropsychology*, *22*, 415-422.
- Richard, M-O., Toffoli, R. (2009). Language influence in responses to questionnaires by bilingual respondents: A test of the Whorfian hypothesis. *Journal of Business Research*, *62*, 987-994.

- Rosen, W. G., Terry, R. D., Fuld, P. A., Katzman, R., & Peck, A. (1980). Pathological verification of ischemia score in differentiation of dementias. *Annals of Neurology*, 7, 486-488.
- Rosselli, M., Ardila, A., Araujo, K., Weekes, V. A., Caracciolo, V., Padilla, M., & Ostrosky-Solís, F. (2000). Verbal fluency and repetition skills in healthy older Spanish-English bilinguals. *Applied Neuropsychology*, 7, 17-24.
- Sacco, R. L., Boden-Albala, B., Gan, R., Chen, X., Kargman, D. E., Shea, S., . . . Hauser, W. A. (1998). Stroke incidence among white, black, and Hispanic residents of an urban community: The northern Manhattan stroke study. *American Journal of Epidemiology*, 147, 259-268.
- Sacco, R. L., Hauser, W. A., & Mohr, J. P. (1991). Hospitalized stroke in blacks and Hispanics in northern Manhattan. *Stroke*, 22, 1491-1496.
- Salmon, D.P. and Bondi, M.W. (2009) Neuropsychological assessment of dementia. *Annual Review of Psychology*, 60, 257-282
- Salmon, D.P., Heindel, W. C., & Lange, K. L. (1999). Differential decline in word generation from phonemic and semantic categories during the course of Alzheimer's disease: Implications for the integrity of semantic memory. *Journal of the International Neuropsychological Society*, 5, 692-703.
- Sandoval, T.C., Gollan, T.H., Ferreira, V.S., & Salmon, D.P. (2010). What causes the bilingual disadvantage in verbal fluency: The dual-task analogy. *Bilingualism: Language and Cognition*, 13, 231-252.
- Taler, V., & Phillips, N. A. (2008). Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review. *Journal of Clinical and Experimental Neuropsychology*, 30, 501-556.
- Tippett, L. J., Gendall, A., Farah, M. J., & Thompson-Schill, S. L. (2004). Selection ability in Alzheimer's disease: Investigation of a component of semantic processing. *Neuropsychology*, 18, 163-173
- Tulving, E. (1983). *Elements of episodic memory*. New York: Oxford University Press.
- van Hell, J. G., & De Groot, A. M. B. (1998). Conceptual representation in bilingual memory: Effects of concreteness and cognate status in word association. *Bilingualism: Language and Cognition*, 1, 193-211.
- van Heuven, W. J. B., & Dijkstra, T. (1998). Orthographic neighborhood effects in bilingual word recognition. *Journal of Memory and Language*, 39, 458-483.

- Verma, M., & Howard, R. J. (in press). Semantic memory and language dysfunction in early Alzheimer's disease: A review. *International Journal of Geriatric Psychiatry*.
- Weissberger, G. H., Salmon, D. P., Bondi, M. W., & Gollan, T. H. (2013). Which neuropsychological tests predict progression to Alzheimer's disease in Hispanics? *Neuropsychology*, 27, 345-355.
- Woodard, J.L., Seidenberg, M., Nielson, K.A., Smith, J.C., Antuono, P., Durgerian, S. Guidotti, L., Zhang, Q., Butts, A., Hantke, N., Lancaster, M., Rao, S.M. (2010). Prediction of cognitive decline in healthy older adults using fMRI. *Journal of Alzheimers Disease*

Footnotes

1. Two non-Hispanic decliners did not have category fluency data in their first year of probable AD diagnosis; these participants had a diagnosis of MCI in Year 4.

Furthermore, one Hispanic decliner only had two years of data prior to a diagnosis of probable AD and thus this participant's diagnosis for Year 3 and Year 4 was probable AD. The remaining participants had a diagnosis of normal control, mild cognitive impairment (MCI), or possible AD in the three years prior to Year 4.
2. 6 participants had greater than 12 months but less than 24 months in between their consecutive test dates due to years in which participants missed an annual visit or the test was discontinued due to unforeseen circumstances (e.g., phone ringing). Four of these participants belonged to the Hispanic normal control group and 2 of these participants belonged to the non-Hispanic decliner group.
3. A concrete example of the mean decline in likelihood example is as follows: A (hypothetical) participant stated the following animals in year 1: dog, cat, bird, snake, fish, and the following animals in year 2: dog, snake, cat, giraffe, gorilla. Based on this, the number of strong words is 3 (dog, cat, and snake were stated in both Years 1 and 2) and the number of weak words is 2 (bird and fish were not re-stated in Year 2). The initial ratio is thus $2_{\text{weak}}/3_{\text{strong}}$ or .67. In Years 3 and 4 (these were combined for the analysis), the participant stated dog, cat, zebra, elephant, fish. Thus, 2 of the strong words from Years 1 and 2 (dog and cat) were stated, and only 1 of the weak words (fish) was stated. Thus, the ratio of "kept weak" to "kept strong" is $1_{\text{weak}}/2_{\text{strong}}$ or .50. The "mean decline" for this participant is .17 (.67 - .50).
4. We reanalyzed category fluency scores of initial evaluation (first year of testing, or

baseline, in the ADRC longitudinal study) to see if the findings of Weissberger et al. (2013) were replicated in our subset of participants. To this end, we conducted a 2 (Hispanic vs. non-Hispanic) X 2 (control vs. decliner) ANOVA examining total words generated on category fluency during initial evaluation. Unlike Weissberger et al., we did not find an interaction of Group X Ethnicity ($p = .28$). However, examination of the means shows that the data trend in the same direction as was reported by Weissberger et al. Specifically, while non-Hispanic controls ($M = 50.36$, $SD = 2.5$) outperformed Hispanic controls ($M = 47.1$, $SD = 2.6$), the reverse was true in the decliner groups: Hispanic decliners generated slightly more words ($M = 45.56$, $SD = 2.8$) than non-Hispanic decliners ($M = 43.09$, $SD = 2.5$). Given our smaller sample size, we do not interpret the lack of significance because of the substantial reduction in power (2 fewer Hispanic decliners; 19 fewer Hispanic controls; 22 fewer non-Hispanic controls)

Table 5.1: Participant demographics for non-Hispanic controls and decliners and Hispanic controls and decliners.

	<u>Hispanic</u>				<u>Non-Hispanic</u>			
	<u>Probable AD</u>		<u>Controls (n=10)</u>		<u>Probable AD</u>		<u>Controls (n=11)</u>	
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>
Age Year 1	77.1	(5.9)	78.7	(4.1)	77.3	(8.4)	78.2	(5.1)
Education	12.9	(3.4)	12.1	(3.6)	12.5	(2.2)	12.0	(1.1)
% Female	80.0	-	50.0	-	55.0	-	82.0	-
% Tested in English ¹	44	-	80	-	-	-	-	-
DRS ²	131.3	(5.9)	134.9	(2.6)	133.9	(4.8)	139.5	(3.6)
MMSE	28.2	(2.2)	29.9	(0.3)	28.5	(1.6)	29.2	(1.3)
CDR Global Score	0.6	(0.4)	0.0	-	0.4	(0.3)	0.0	-
PODS	0.0	-	0.0	-	1.2	(1.4)	0.5	(1.2)
% of current Spanish use	35.8	(39.9)	28.6	(38.4)	-	-	-	-
Year in Study ³	6.1	(3.7)	5.5	(3.2)	5.2	(3.1)	5.4	(2.8)

¹Percentages reflect percent tested in English for majority of years (i.e., 3 out of 4 years); two Hispanic decliners were tested in English during Year 1 and then Spanish for the three subsequent years; thus, they are not considered to have been “tested in English”.

²One non-Hispanic control did not have DRS during Year 1; for this participant, DRS score for Year 2 was used.

³This reflects the year of participation in the ADRC study that corresponds to Year 1

Table 5.2: Language history information for a subset of Hispanic controls and decliners.

	<u>Probable AD</u>		<u>Controls (n=8)</u>	
	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>
Age of first exposure to English	6.9	(10.7)	6.9	(9.2)
Age of first exposure to Spanish	0	(0)	0	(0)
Self-ratings ¹				
Spoken English	6.1	(1.5)	6.1	(1.5)
Spoken Spanish	5.3	(1.8)	5.4	(1.5)
Writing English	5.7	(1.8)	4.9	(2.1)
Writing Spanish	5.6	(2.2)	4.0	(2.4)
Reading English	5.9	(1.3)	5.1	(2.1)
Reading Spanish	5.5	(2.3)	4.0	(2.1)

¹Self-ratings were based on a 7-point scale: 1 (almost none), 2 (very poor), 3 (fair), 4 (functional), 5 (good), 6 (very good), 7 (like native speaker).

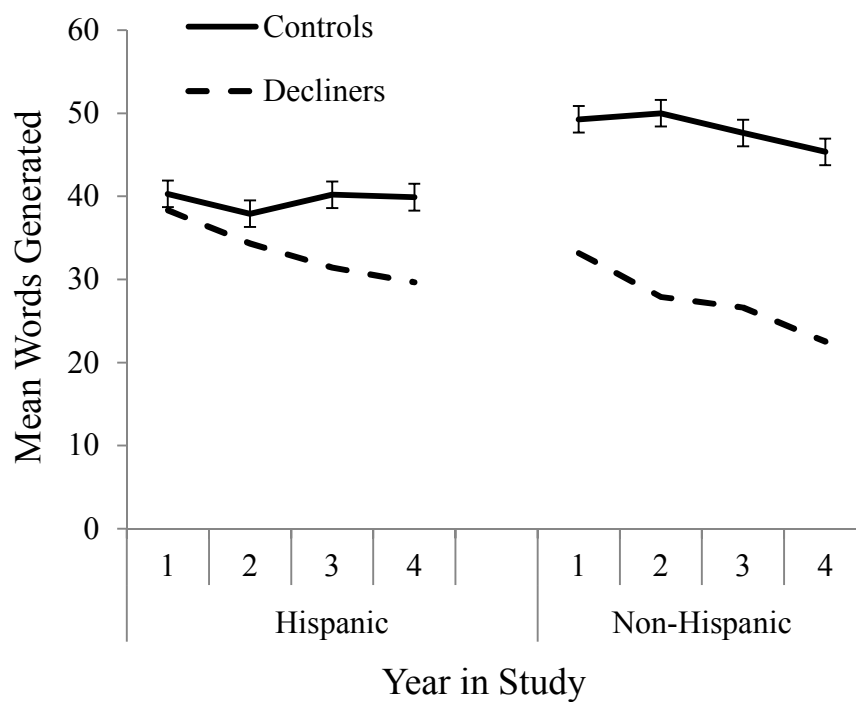


Figure 5.1: Mean number of words generated (total across animals, fruits, and vegetables) by Hispanic and non-Hispanic decliners and normal controls on category fluency at the four annual evaluations (Years 1-4).

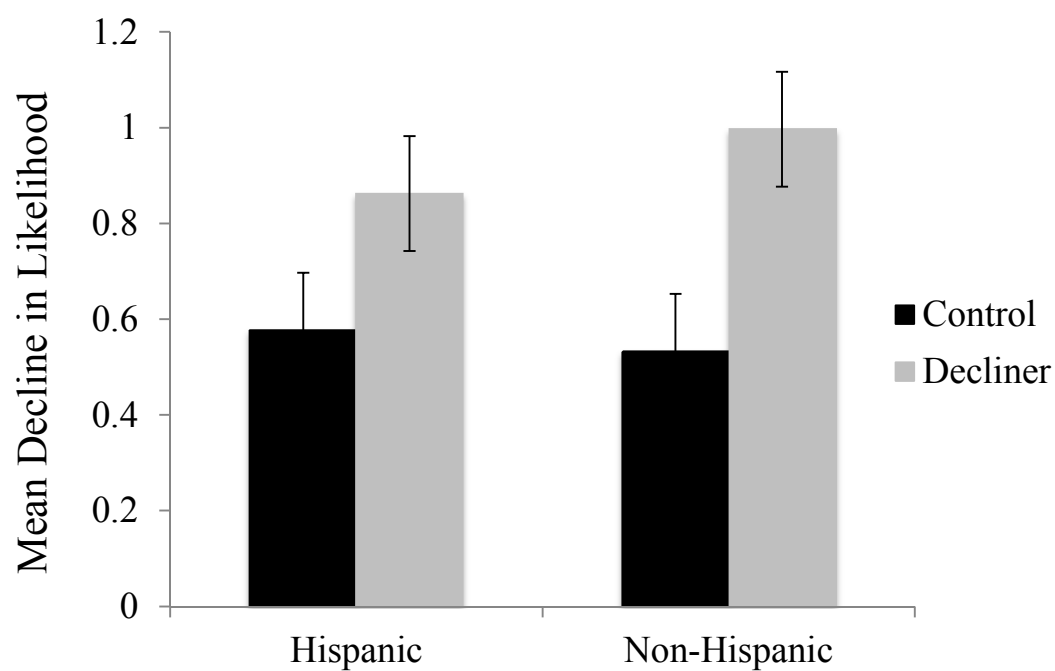


Figure 5.2: The mean decline in the likelihood of generating weak items (i.e., items that were produced in Year 1 but not Year 2) relative to strong items (items produced in both Years 1 and 2) in Years 3 and 4 on the category fluency task for Hispanic and non-Hispanic decliner and control participants.

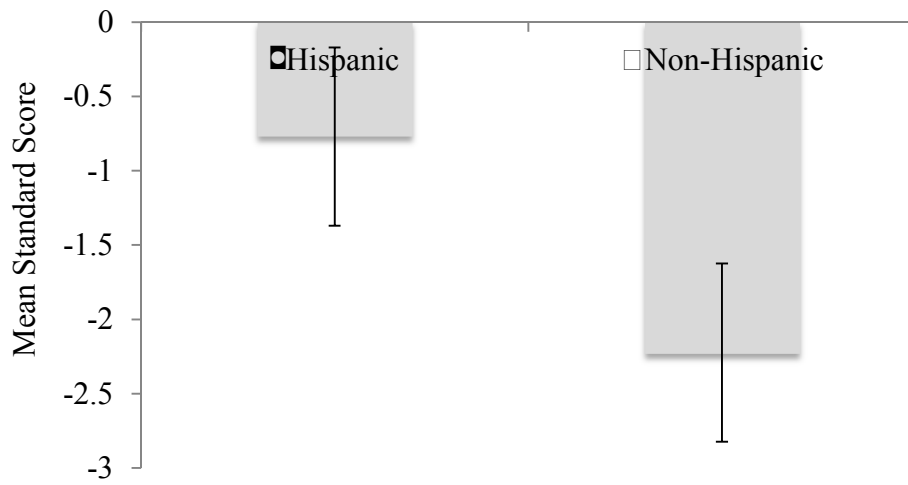


Figure 5.3: The mean standard scores of the decline in the likelihood of generating weak items relative to strong items in Years 3 and 4 on the category fluency task for Hispanic and non-Hispanic decliners based on their respective cultural control group.

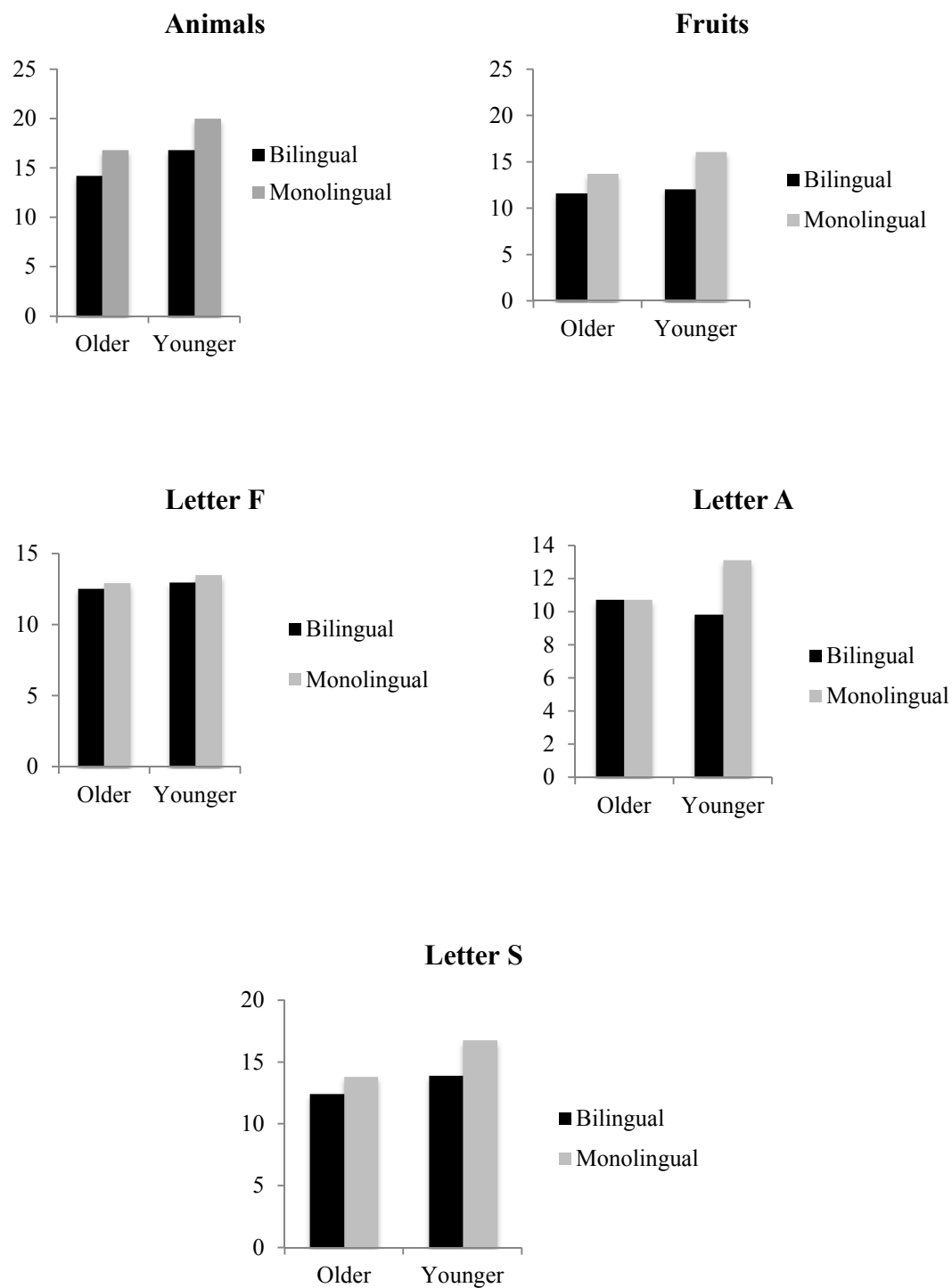


Figure 5.4: Comparison of category and letter fluency in young and older monolinguals and bilinguals; means were compiled from Rosselli et al. (2000) and Gollan et al. (2002).

CHAPTER 6: DISCUSSION

The series of studies aimed to elucidate the cognitive effects of Alzheimer's disease (AD) in Hispanic older adults. Differences in prevalence, age of onset, and mortality rates have been found between Hispanic and non-Hispanic older adults with AD (e.g., Clark et al., 2005, Mehta et al., 2008). However, despite the growing population of Hispanic older adults in the United States, little is known about the nature of these differences and the course and progression of AD in this cohort. For several reasons, accurately diagnosing Alzheimer's disease in Hispanic older adults may prove challenging. Together, the current studies provide preliminary evidence that factors such as bilingualism, vascular risk, cultural differences and associated socio-economic challenges (e.g., low education level) may complicate interpretation of neuropsychological profiles and the diagnosis of Alzheimer's disease in Hispanic older adults. The studies suggest that all of these factors must be considered in neuropsychological evaluations of Hispanic older adults for dementia.

Study 1, Chapter 2: Partially Overlapping Mechanisms of Language and Task Control in Young and Older Bilinguals

Study 1 tested the possibility that bilinguals rely on domain-general mechanisms of executive control to achieve language control in young and older adult English-Spanish bilinguals. This study demonstrated both shared and unique mechanisms of language and executive control by comparing a task-switching paradigm to a language-switching paradigm. Suggestive of shared control mechanisms, a subset of older bilinguals was unable to complete the task switching paradigm at better than chance

levels of performance, and these same bilinguals also exhibited greater switching costs during the language switching paradigm than matched controls. However, in support of unique control mechanisms, there was a crossover interaction between age and task such that aging effects appeared to be far greater for non-linguistic than for linguistic switching; whereas young bilinguals responded more slowly on language than on task switching, the reverse was true for older bilinguals. More broadly, the findings suggest that, unlike executive control, bilingual language control is an “expert” task that is relatively preserved in aging. Given evidence for a relationship between language control and executive control, and evidence that language control remains relatively preserved in aging, we questioned how such findings would translate to neuropsychological testing of bilinguals at risk for Alzheimer’s disease (AD).

Study 2, Chapter 3: Which Neuropsychological Tests Predict Progression to Alzheimer’s Disease in Hispanics?

Study 2 aimed to identify neuropsychological tests that would be sensitive to future progression to AD in Hispanic older adults. Given both advantages and disadvantages reported in the literature for Hispanics and bilinguals, we predicted that some tests that elicit a disadvantage in healthy Hispanic bilinguals would be insensitive to future AD in Hispanics relative to non-Hispanics. In line with this prediction, some tests that showed a disadvantage in Hispanic controls were insensitive to future AD in Hispanic decliners—interestingly in the language domain (e.g., vocabulary, semantic fluency). However, contrary to our prediction and despite lower scores for Hispanic controls, a number of tests nonetheless predicted progression to AD in Hispanic decliners

(e.g., Boston Naming Test, Trail Making Test A and B). One unexpected finding was a crossover interaction on semantic fluency in which Hispanic controls generated significantly fewer words than non-Hispanic controls, but Hispanic decliners generated significantly more words than non-Hispanic decliners. This finding suggests that factors specific to the Hispanic group, such as bilingualism, may contribute to enhanced performance on certain measures that are vulnerable to the early effects of AD. The next two studies investigate the possibility that factors associated with bilingualism, such as enhanced executive control or the possibility of a stronger semantic system, are protective in the face of early AD.

Study 3, Chapter 4: Neuropsychological and Neuropathological Profiles in Hispanic Older Adults with Autopsy-Confirmed Alzheimer's Disease

Given differences in the neuropsychological profiles of Hispanic decliners compared to non-Hispanic decliners, and the decreased sensitivity of some measures to identify future AD in Hispanics (Study 2), we asked whether these differences would negatively impact diagnosis of dementia in Hispanic older adults. To this end, Study 3 compared the neuropathological and neuropsychological profiles of Hispanic patients with autopsy-confirmed AD to non-Hispanics with autopsy-confirmed AD who are matched on age, education, Dementia Rating Scale during first year of testing, and test-death interval. A general pattern emerged across many of the neuropsychological measures (similar to that seen in Study 2 for semantic fluency) in which non-Hispanic patients performed worse than Hispanic patients, while non-Hispanic controls performed better than Hispanic controls. Overall, Study 3 demonstrates that the cognitive deficit

profiles in AD patients are less salient and less severe in Hispanics than non-Hispanics, potentially due to factors such as bilingualism, lower AD neuropathology,, and factors that may impact functional status and cognition but are unrelated to AD pathology (e.g., greater vascular risk and vascular neuropathology, barriers to healthcare access).

Nonetheless, despite differences in the pattern and severity of deficits, we found 86% sensitivity ($n = 18$ with a clinical diagnosis of AD out of 21 with AD pathology) in clinically diagnosing AD and 75% specificity ($n = 6$ given a non-AD clinical diagnosis out of 8 without AD pathology) in diagnosing non-AD cases.

Study 4, Chapter 5: Longitudinal Semantic Fluency Performance in Hispanic Older Adults in the Early Stages of AD

Study 4 was a follow-up exploratory study that aimed to elaborate upon the semantic fluency advantage seen in the Hispanic decliner group from Study 2 and the Hispanic AD patients in Study 3. Specifically, we asked if factors related to bilingualism bolster performance on semantic fluency in Hispanics when they have Alzheimer's dementia. We proposed two possibilities that may contribute to a bilingual benefit on fluency: 1) a benefit at the semantic level as a result of having two languages that lead to richer semantic representations; 2) a retrieval benefit due to enhanced executive control or translation-equivalent cues. Longitudinal data from a subset of bilingual decliners from Study 2 were examined to determine if the advantages would hold with disease progression and whether there would be qualitative differences in the consistency with which semantic exemplars are lost over time. If Hispanics showed less consistency of loss of semantic exemplars over time relative to non-Hispanics, this would have

supported the notion that a stronger semantic system underlies the Hispanic advantage. Conversely, if Hispanics and non-Hispanics did not differ in degree of consistent semantic loss, then an alternative explanation would be required (e.g., a retrieval-based benefit from knowing two languages). In line with Studies 2 and 3, Hispanic decliners outperformed non-Hispanics across all four years of category fluency. However, although means were nominally in the predicted direction, Hispanic and non-Hispanic decliners did not differ with respect to their consistency loss in semantic exemplars, and both groups demonstrated significantly greater consistency of decline than controls. The findings do not support the *stronger semantic system* hypothesis and, if replicated with larger samples, suggest that Hispanics outperform non-Hispanics as a result of a retrieval-based benefit of bilingualism. This preliminary study is a first step at elucidating factors of bilingualism that may contribute to differences in neuropsychological profiles in Hispanic older adults at risk for or who have AD.

Limitations

Limitations specific to each of the four studies are discussed within the four respective chapters. However, there are some general limitations that apply to all four studies. A first limitation that applies primarily to studies 2-4 relates to sample size. Due to a limited cohort of Hispanic older adults at the ADRC and our attempts to match Hispanic and non-Hispanic participants with regards to age and education (i.e., many Hispanic participants at the ADRC have very low education), we were limited to a smaller number of Hispanic participants than would have been ideal. This was especially relevant to Study 4, in which lack of differences on qualitative measures may be related

to lack of power. Nevertheless, large effect sizes were found for the majority of findings reported.

With the exception of Study 1, information regarding the degree of bilingualism is limited. The comprehensive language history questionnaire (used in Study 1) was not implemented at the Alzheimer's Disease Research Center (ADRC) until more recently. Thus, although the majority of participants in the Hispanic cohort are bilingual to at least some degree (ranging from relatively unbalanced to highly proficient and balanced bilinguals; e.g., see Gollan et al., 2011), we cannot completely rule out the possibility that some of the participants in studies 2-4 were not sufficiently bilingual.

A third related limitation is lack of information regarding important factors such as acculturation, socioeconomic status, occupation history, and quality of education, all of which are variables that can affect the psychometric characteristics of cognitive measures. For example, level of acculturation has been shown to relate to performance on a number of neuropsychological measures (e.g., Arnold, Montgomery, Castañeda, & Longoria, 1994; Pontón & Ardila, 1999). Level of education can also vary between cultural groups and the same number of years between two individuals may not be equated in terms of quality (see Pontón & Ardila, 1999). Thus, despite our matching procedures, there may be qualitative differences among these variables that are not captured through matching procedures. Lack of information related to these factors limits the generalizability of our studies to the larger Hispanic population and future studies that can capture such differences will help elucidate their influence on neuropsychological testing in Hispanic individuals from various backgrounds.

Implications and Future Directions

Patients with Alzheimer's disease typically exhibit a pattern of deficits on neuropsychological testing that is characterized by episodic memory, semantic knowledge (e.g., language) and executive function deficits that are greater than those of visuospatial abilities, attention and psychomotor skills (for reviews, see Salmon & Bondi, 1999; 2009). Given that clinical and neuropsychological procedures used to detect AD were developed in largely non-Hispanic Caucasian populations, evaluating how cultural factors influence the clinical manifestation of the disease in Hispanic older adults is of great importance. This series of studies suggests that the clinical and neuropathological manifestation of Alzheimer's disease in Hispanic older adults is affected by factors such as bilingualism, increased vascular risk, and sociological factors. Although the studies highlight the importance of considering these variables, they are not fully understood. However, it is clear that an interaction of one or more of these factors with AD pathogenesis impacts the progression of AD in Hispanic older adults. Future studies assessing the influence of each of these factors will help inform prevention and treatment for Hispanic older adults who have, or who are at risk for AD.

Bilingualism. As discussed in length, bilinguals sometimes outperform monolinguals on tests of executive function (e.g., Stroop Test, see Bialystok, Craik, & Luk, 2008; Trail Making Test, see Bialystok, 2010; Zahodne, Schofield, Farrell, Stern, & Manly, 2013), but are disadvantaged on linguistic tasks (Roberts, Garcia, Desrochers, & Hernandez, 2002; Gollan, Montoya, & Werner, 2002; Portocarrero, Burright, & Donovan, 2007). This series of studies suggests that such advantages and disadvantages can impact the clinical presentation of AD in Hispanic older adults. Specifically,

bilingualism may enhance cognitive reserve in Hispanic older adults, especially on tests measuring semantic fluency and executive functioning. Cognitive reserve due to bilingualism may have contributed to lack of sensitivity of some neuropsychological measures to detect future AD in Hispanics (Study 2); it may have also contributed to less salient and less severe cognitive deficits in Hispanics relative to non-Hispanics who have AD (Study 3). Given that the Hispanic population is heterogeneous and that degree of bilingualism may vary from patient to patient (e.g., degree of balance between languages), it is important to understand what mechanisms of bilingualism contribute to this reserve so clinicians can tailor testing and treatments to patients on an individual basis. Study 1 suggests that bilingualism contributes to preserved language control in aging and Study 4 is a first step towards understanding how knowledge of two languages may affect test performance (suggesting a retrieval rather than semantic based locus). Future studies with larger samples that are aimed at understanding the bilingual aging process will help elucidate the specific mechanisms that are at play.

Increased Vascular Risk. Like previous research reporting a higher rate of vascular risk in the Hispanic population (e.g., Daviglus et al., 2012; Ennis, Rios-Vargas, Albert, 2010; McBean, Li, Gilbertson, & Collins, 2004; Roger et al., 2012; Winkleby, Kraemer, Ahn, & Varady, 1998), Study 3 found greater vascular risk and vascular neuropathology in Hispanic older adults with AD. In addition to AD pathology, neurovascular pathology can independently or synergistically contribute to neuropsychological deficits and modify the typical pattern of cognitive deficits associated with AD (e.g., Lo & Jagust, 2012). For example, greater vascular pathology may contribute to retrieval-based impairments in memory and greater deficits in executive

functioning, which can ultimately impact the pattern and severity of deficits observed (e.g., Delis et al., 1991; Kramer, Reed, Mungas, Weiner, & Chui, 2002). Thus, greater vascular risk in Hispanics can make it more difficult to clinically diagnose AD and future studies with larger samples will be better equipped to dissociate the impact that various vascular risk factors have on the neuropsychological presentation of AD in Hispanic older adults.

Sociological Factors. The literature has demonstrated greater barriers to healthcare access in older Hispanics relative to the non-Hispanic population due to factors such as lower overall socioeconomic status, language barriers, lack of familiarity with the healthcare system, and cultural differences in personal beliefs related to health (e.g., Ginzberg, 1991; Gordon, 1995; Haan & Weldon, 1996; Ortiz & Fitten, 2000). Although the four studies do not have detailed information regarding these factors, it is clear that they could influence the manifestation and progression of AD in Hispanics. For example, in Study 3 we found that Hispanics with AD had lower levels of AD pathology despite being matched on functional status and test-death interval. One possibility for this finding is that barriers to healthcare access and more poorly treated vascular factors contribute to earlier death in Hispanics with AD for reasons unrelated to AD pathology. For this reason, future studies that investigate the contribution of healthcare access to functional status and prognosis are needed.

Concluding Comments

The present series of studies highlight the importance of taking a comprehensive approach to understanding the cognitive effects of AD in Hispanic older adults. As a group, Hispanics are often also bilingual, have increased vascular risk, and have greater

barriers to healthcare access, all of which can impact a neuropsychological profile.

However, Hispanics also make up a heterogeneous group and understanding individual differences (e.g., acculturation level, degree of bilingualism, quality of education) within the Hispanic population is also imperative (see Pontón & Ardila, 1999). It is not enough to consider just one of the many factors that impact the normal and abnormal aging process in this minority population. Rather, it is crucial to consider the multitude of cultural factors that can ultimately implicate the presentation and progression of AD in Hispanic older adults. Only then will clinicians be fully equipped with the tools necessary to confidently assess and treat a Hispanic older adult suspected of having Alzheimer's disease.

References

- Arnold, B. R., Montgomery, G. T., Castañeda, I., & Longoria, R. (1994). Acculturation and performance of Hispanics on selected Halstead-Reitan neuropsychological tests. *Assessment, 1*, 239-248.
- Bialystok, E. (2010). Global–Local and Trail-Making Tasks by monolingual and bilingual children: Beyond inhibition. *Developmental Psychology, 46*, 93-105
- Bialystok, E., Craik, F. I. M., & Luk, G. (2008). Cognitive control and lexical access in younger and older bilinguals. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 34*, 859-873.
- Clark, C. M., DeCarli, C., Mungas, D., Chui, H. I., Higdon, R., Nuñez, J., . . . van Belle, G. (2005). Earlier onset of Alzheimer disease symptoms in Latino individuals compared with Anglo individuals. *Archives of Neurology, 62*, 774-778.
- Daviglus, M. L., Talavera, G. A., Avilés-Santa, M. L., Allison, M., Cai, J., Criqui, M. H., . . . Stamler, J. (2012). Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *Journal of the American Medical Association, 308*, 1775-1784.
- Delis, D. C., Massman, P. J., Butters, N., & Salmon, D. P. (1991). Profiles of demented and amnesic patients on the California Verbal Learning Test: Implications for the assessment of memory disorders. *Psychological Assessment: A Journal of Consulting and Clinical Psychology, 3*, 19-26.
- Ennis, S., Rios-Vargas, M., & Albert, N. (2010). 2010 Census Briefs: The Hispanic population. <http://www.census.gov/prod/cen2010/briefs/c2010br-04.pdf>.
- Ginzberg, E. (1991). Access to healthcare for Hispanics. *Journal of the American Medical Association, 265*, 238-241.
- Gollan, T. H., Montoya, R. I., & Werner, G. A. (2002). Semantic and letter fluency in Spanish-English bilinguals. *Neuropsychology, 16*, 562-576.
- Gollan, T. H., Salmon, D.P., Montoya, R.I., & Galasko, D.R. (2011). Degree of Bilingualism Predicts Age of Diagnosis of Alzheimer's Disease in Low-Education but not in Highly-Educated Hispanics, *Neuropsychologia, 49*, 3826-3830.
- Gordan, A. K. (1995). Deterrents to access and service for blacks and Hispanics: the Medicare Hospice Benefit, healthcare utilization, and cultural barriers. *Hospice Journal, 10*, 65-83.

- Haan, M. N., & Weldon, M. (1996). The influence of diabetes, hypertension, and stroke on ethnic differences in physical and cognitive functioning in an ethnically diverse older population, *Annals of Epidemiology*, 6, 392–398.
- Kramer, J. H., Reed, B. R., Mungas, D., Weiner, M. W., & Chui, H. C. (2002). Executive dysfunction in subcortical ischaemic vascular disease. *Journal of Neurology, Neurosurgery, & Psychiatry*, 72, 217–220.
- Lo, R. Y., & Jagust, W. J. (2012). Vascular burden and Alzheimer's disease pathologic progression. *Neurology*, 79, 1349 – 1355.
- McBean, A. M., Li, S., Gilbertson, D. T., & Collins, A. J. (2004). Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: Whites, Blacks, Hispanics, and Asians. *Diabetes Care*, 27, 2317 – 2324.
- Mehta, K. M., Yaffe, K., Pérez-Stable, E. J., Stewart, A., Barnes, D., Kurland, B. F., & Miller, B. L. (2008). Race/ethnic differences in AD survival in US Alzheimer's disease centers. *Neurology*, 70, 1163–1170.
- Ortiz, F., & Fitten, L. J. (2000). Barriers to healthcare access for cognitively impaired older Hispanics. *Alzheimer's Disease and Associated Disorders*, 14, 141–150.
- Pontón, M. O., & Ardila, A. (1999). The future of neuropsychology with Hispanic populations in the United States. *Archives of Neuropsychology*, 14, 565–580.
- Portocarrero, J. S., Burright, R. G. & Donovanick, P. J. (2007). Vocabulary and verbal fluency of bilingual and monolingual college students. *Archives of Clinical Neuropsychology*, 22, 415–422.
- Roberts, P. M., Garcia, L. J., Desrochers, A., Hernandez, D. (2002). English performance of proficient bilingual adults on the Boston Naming Test. *Apahsiology*, 16, 635–645.
- Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B.,..., Turner, M. B. (2012). Heart disease and stroke statistics – 2012 update: A report from the American Heart Association. *Circulation*, 125, e2–e220.
- Salmon, D. P., & Bondi, M. W. (1999). Neuropsychology of Alzheimer's disease. In R.D. Terry, R. Katzman, K.L. Bick, & S.S. Sisodia (Eds), *Alzheimer's disease* (2nd ed., pp. 39–56). Philadelphia: Lippincott Williams & Wilkins.
- Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annual Review of Psychology*, 60, 257–282.
- Winkleby, M. A., Kraemer, H. C., Ahn, D. K., & Varady, A. N. (1998). Findings for

Women from the third national health and nutrition examination survey, 1988-1994. *Journal of the American Medical Association*, 280, 356 – 362.

Zahodne, L .B., Schofield, P. W., Farrell, M. T., Stern, Y., & Manly, J. J. (2013). Bilingualism does not alter cognitive decline or dementia risk among Spanish speaking immigrants. *Neuropsychology*, 28, 238-246.