

Cognitive Reserve and Longitudinal Changes in Brain and Cognition in Semantic variant Primary Progressive Aphasia



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Introduction

- Cognitive reserve (CR) theory suggests that specific lifetime exposures (education, social activities) can maintain cognitive performance despite disease burden^{2,8}
- This theory is well-studied in Alzheimer's disease (AD) but less in frontotemporal dementia (FTD), including primary progressive aphasia (PPA)
- Separate variants of PPA have not been examined, nor using language measures for cognitive performance, nor using longitudinal designs
- Research questions:
 - How do education and occupation relate to brain volume and cognitive performance in a longitudinally followed cohort of individuals with svPPA?
 - How do education and occupation moderate the relationship between brain volume and cognition in a longitudinally followed cohort of individuals with svPPA?

Methodology

- 58 participants diagnosed with svPPA from the University of California San Francisco (UCSF) Memory and Aging Center (MAC); 31 included in longitudinal analysis (Table 1)
- Education, occupation, total brain volume, and cognitive performance were collected
- Education recorded as number of years of formal schooling equivalent to highest degree obtained
- Occupation recorded on a 5-point scale similar to previous studies^{1,4}

Table 1. Demographic Information		
	Baseline Analyses	Longitudinal Analyses
Number of Participants	58	31
Sex/Gender (M:F)	27:31	13:18
Race/Ethnicity	White=57, Filipino=1	White=31
Handedness	R=50, L=8	R=26, L=5
Age at Initial MRI	64.86 (7.16)	64.71 (7.09)
Days Between Scans	-	443.7 (81.26)
Education (Years)	16.28 (2.32)	16.16 (2.35)
Occupation Levels	0=0, 1=1, 2=18, 3=30, 4=9	0=0, 1=0, 2=8, 3=18, 4=5
MMSE	23.19 (6.41)	Baseline: 24.84 (5.31) Follow-up: 21.29 (6.52)
CDR-Box	3.41 (2.15)	Baseline: 3.07 (1.77) Follow-up: 4.52 (2.60)
Letter Fluency	7.61 (4.40)	Baseline: 8.39 (4.36) Follow-up: 7.48 (3.80)
Category Fluency	7.19 (4.02)	Baseline: 7.39 (4.25) Follow-up: 5.07 (3.94)
15-item BNT	3.98 (3.10)	Baseline: 4.29 (2.91) Follow-up: 2.55 (1.88)
CVLT trial correct	15.33 (6.78)	Baseline: 17.61 (5.58) Follow-up: 12.03 (8.05)
Modified Trials time (seconds)	51.67 (34.49)	Baseline: 55.07 (39.44) Follow-up: 42.91 (38.49)

Note: M = Male, F = Female, R = Right-handed, L = Left-handed, A = Ambidextrous, MMSE = Mini-Mental State Examination, CDR = Clinical Dementia Rating, CVLT = California Verbal Learning Test, BNT = Boston Naming Test, Occupation Levels: 0 = no occupation, 1 = unskilled labor, 2 = skilled labor, 3 = mid-level management, 4 = senior management

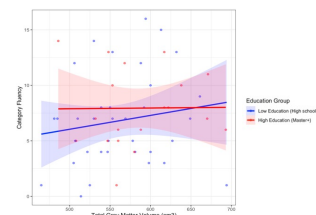
Methodology (continued)

- Verbal memory was based on trials 1-4 on the California Verbal Learning Test (CVLT)
- Executive functioning was based on the Modified Trails task⁸; ratio of correct sequences to completion time
- Lexical retrieval was based on letter fluency (i.e., letter D) performance
- Semantic retrieval was based on performance on the 15-item Boston Naming Test (BNT) and category fluency (i.e., animals)
- Total brain volume (cm³) collected from T1-weighted structural MRI scans
- Multiple linear regressions were used to examine relationships between brain volume, education and occupation, and clinical performance
- Interaction analyses were used to investigate the moderating effect of education and occupation on cognitive performance and brain volume
- Multiple linear regression models were used to examine the relationship between education and occupation on follow-up brain volume, and change in cognitive performance

Baseline Results

- Main effect found between occupation and brain volume; participants in occupation level 3 showed higher brain volume than those in occupation level 2
- Higher brain volume associated with better performance across all cognitive tasks
- Interactions were found between education and brain volume on category fluency performance and BNT (e.g., category fluency in Figure 1)

Figure 1. Observed category fluency by gray matter volume and education levels



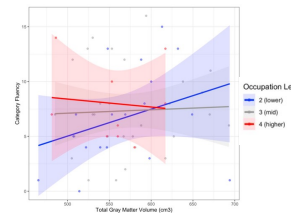
Note. The designated groups are for visualization purposes only—education was included as a continuous variable in the statistical models

- When brain volume was lower, participants with higher education demonstrated better performance on category fluency and BNT (i.e., in line with CR theory)

Baseline Results (continued)

- Interactions were found between occupation and brain volume on category fluency and BNT (e.g., category fluency in Figure 2)
- Similarly, when brain volume was lower, participants with higher occupation levels performed better on category fluency and BNT tasks than those with lower occupation levels

Figure 2. Observed category fluency by gray matter volume and occupation levels

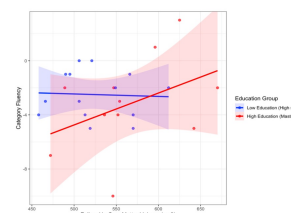


- No interactions were found between education/occupation and brain volume on letter fluency, CVLT, or Modified Trails

Longitudinal Results

- Like baseline, individuals in occupation level 3 showed higher brain volume than those in occupation level 2
- Interactions were found between education and follow-up brain volume on change in category fluency performance (Figure 3)
- Interactions were also found between occupation and follow-up brain volume on change in category fluency and BNT
- For these interactions, when follow-up brain volume was low, individuals with higher education or occupation showed faster semantic retrieval decline

Figure 3. Observed change in category fluency by follow up gray matter volume and education levels



Conclusion

- The results emphasize the importance of using specific speech and language measures when investigating CR in PPA
- As hypothesized and in line with CR theory, participants with higher CR maintain better performance in the context of structural pathological decline at baseline^{3,4,6}
- These findings underscore the specificity of semantic impairment in svPPA
- Longitudinally, an opposite pattern emerged: those with high CR demonstrate worse performance in semantic retrieval when follow-up brain volume was low, than those with low CR
- Individuals with higher CR may initially compensate for brain volume loss in cognitive performance, but subsequently show a steeper decline once reserve is possibly depleted⁷
- Interactions not found for CVLT, modified trails, or letter fluency, suggesting these may be less sensitive to performance differences in svPPA
- The current study provides new evidence on the role of education and occupation in the progression of language impairment in svPPA

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