Cognitive Resilience in Clinical and Preclinical Alzheimer's Disease: The Association of Amyloid and Tau Burden on Cognitive Performance

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Abstract

We explored the cross-sectional relationships between β-amyloid (Aβ) and inferior temporal tau deposition (IFT Tau) on cognitive performance and whether cognitive reserve (CR) modifies these associations. We studied 156 participants classified into groups of clinically normal (CN=133), mild cognitive impairment (MCI=17) and Alzheimer disease (AD=6) dementia. AMNART IQ served as a proxy of CR and cognitive performance was assessed using the MMSE. In separate linear regression models predicting MMSE, we examined the interactions of CR × global Aβ and CR × IFT tau across all participants and within the CN group alone. In the whole sample, the interaction between CR and IFT tau was significant (p<0.003), such that higher CR participants with elevated IFT tau had better MMSE scores compared with low CR participants with similar levels of IFT tau. The interaction between CR and Aβ status did not reach significance (p=0.093). In CN only, no cross-sectional interactions among CR, Aβ, and IFT tau were observed on MMSE. These findings imply that CR may be protective against early AD processes and enable some individuals to remain cognitively stable despite elevated tau and Aβ burden.

Keywords

Aging; Preclinical Alzheimer's disease; Amyloid PET imaging; Tau PET imaging; Resilience

Introduction

Advances in positron emission tomography (PET) using radiotracers that bind to β-amyloid (Aβ) has allowed for the *in vivo* detection of Alzheimer's disease (AD) pathology in otherwise clinically normal (CN) older adults (Klunk et al. 2004). Based on this evidence, we now understand that AD includes a long preclinical stage whereby CN exhibit biomarker abnormalities approximately 15 years prior to the onset of dementia (Bateman et al. 2012; Rowe et al. 2010; Sperling et al. 2011a). As the field moves toward the identification and treatment of individuals with preclinical AD (Sperling et al. 2011b), the factors that influence the relationships among cognition and pathologic burden have important implications. One important factor is the concept of "cognitive reserve" (CR), which attempts to explain how some individuals are able to maintain normal cognitive performance despite pathological disease burden (Katzman 1993; Stern 2012), thus delaying or reducing the risk of developing symptomatic AD (Bennett et al. 2003; Stern 2009). Several factors that might convey CR include intelligence (IQ), education, engagement in complex occupations, physical exercise and cognitively stimulating activities (Bennett et al. 2003; Rentz et al. 2007; Scarmeas et al. 2009; Scarmeas et al. 2003; Stern 2009; Stern et al. 1992; Stern et al. 1995; R. Wilson et al. 2003; R. S. Wilson et al. 2003; Wilson et al. 2007). Studies using PET and Pittsburgh Compound B (PiB PET) have found that amyloid burden has a weak but persistent effect on cognition and that CR modifies that effect (Kemppainen et al. 2008; Rentz et al. 2010; Roe et al. 2008). With the recent availability of an F^{18}-T807 radiotracer (aka F^{18}-AV-1451) (Chien et al. 2013), we can now image *in vivo* tau pathology. The availability of these *in vivo* biomarkers gives us the unique opportunity to explore the impact of both β-amyloid and tau pathology on cognition.

In this study, we explored the relationships of Aβ and tau burden on cognition and whether CR modifies these associations throughout the spectrum of AD, by examining these markers within a cross-sectional sample of clinically normal elderly (CN) and patients with mild cognitive impairment (MCI) and Alzheimer disease (AD) dementia. We also examined these relationships within the CN group alone.

Materials and Methods

Human Subjects

Our sample consisted of 133 CN individuals participating in the Harvard Aging Brain Study and 23 participants diagnosed with either MCI (n=17) or mild AD dementia (n=6) who underwent both C^{11}-Amyloid PET Imaging using Pittsburgh Compound B (PiB PET) and Tau PET imaging using F^{18}-T807 (T807 PET). They also underwent neuropsychological assessment within 1 year of PET imaging. The study was conducted at the Massachusetts General Hospital (MGH) using protocols and informed consent procedures approved by the Partners Human Research Committee. Informed consent was obtained from all individual participants included in the study.

Subjects were deemed CN at baseline if they met the following criteria: 1) a global Clinical Dementia Rating (CDR) (Morris 1993) score of 0, 2) scores above age and education-adjusted cutoffs on the 30-Minute Delayed Recall of the Logical Memory Story (II) (ADNI

based cut-offs; http://www.adni-info.org/), and 3) normal performance on the Mini Mental State Exam (MMSE) (Folstein et al. 1975) using published age and education corrected adjustments (Mungas et al. 1996). Review of medical history and physical and neurological examinations confirmed their status as clinically normal. None of the subjects had a history of alcoholism, drug abuse, head trauma, or current serious medical/psychiatric illness.

MCI and AD patients were recruited from physicians in the Memory Disorders Clinic at MGH. Diagnosis was determined based on a comprehensive neurological exam. Subjects were selected for this analysis if they had a CDR score between 0.5 and 1.0, MMSE >19, underwent PiB-PET and T807 PET imaging within 6 months of each other and neuropsychological testing within 1 year of PET scans.

Neuropsychological Testing

While CN participants underwent yearly neuropsychological testing with a large array of measures, only a limited number of neuropsychological tests were available for MCI/AD subjects. Here we examine performance on the MMSE in order to maximize the sample size. Estimated verbal IQ from the American National Reading Test (AMNART IQ) (Ryan and Paolo 1992) served as a proxy for CR. Given that T807 PET was introduced mid-study, the MMSE that was closest to T807 PET was examined (all of the MMSE scores were within one year of the T807 scan).

PET Imaging

F^{18} T807 and C^{11} Pittsburgh Compound B were prepared at MGH using published methods (Gomperts et al. 2008; Johnson et al. 2016). All PET data are acquired using a Siemens/CTI ECAT HR+ scanner (3D mode; 63 image planes; 15.2cm axial field of view; 5.6mm transaxial resolution and 2.4mm slice interval). PiB PET is acquired with an 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12×15 seconds, 57×60 seconds). T807 PET is acquired from 80–100 minutes after a 9.0 to 11.0 mCi bolus injection in 4 × 5-minute frames. PET data are reconstructed and attenuation-corrected. To evaluate the anatomy of cortical T807 binding, each individual PET data set is co-registered to the subject's MPRAGE data using SPM8. The cortical ribbon and subcortical ROIs defined by MR (described below) are transformed into the PET native space. T807 signal from bilateral inferior temporal ROI was extracted and normalized by cerebellar grey. The inferior temporal region (IFT Tau) was used in all analyses based on autopsy data that suggests that when tau deposition spreads beyond the entorhinal cortex it is more proximal to cognitive impairment in AD (Braak et al. 2006; Johnson et al. 2016; Nelson et al. 2012). PiB PET data are expressed as a DVR with cerebellar grey as reference tissue; regional time-activity curves are used to compute regional DVRs for each ROI using the Logan graphical method. PiB retention is assessed using a large cortical ROI aggregate that includes frontal, lateral temporal and retrosplenial cortices.

MR Imaging

MRI was completed at the MGH Martinos Center on a Siemens TIM Trio 3T System with a 12-channel head coil. Structural T1-weighted volumetric magnetization-prepared, rapid acquisition gradient echo scans (TR/TE/TI=6400/2.8/900ms, flip angle=8°, 1×1×1.2mm

resolution) were processed with FreeSurfer v5.1 to define regions of interest in each participant's native space (Desikan et al. 2006; Fischl et al. 2002).

Statistical Methods

Statistical analyses were completed using R v3 (http://CRAN.R-project.org/doc/). Demographic characteristics were examined using t-tests for continuous variables and χ^2 tests for dichotomous variables. Two sets of analyses were completed. First, we examined cross-sectional relationships in the whole sample, controlling for diagnosis (CN versus MCI/ AD). Second, analyses were repeated within the CN group alone.

Multiple linear regression analyses were used in the entire sample to predict MMSE performance in relation to PET biomarkers and the interaction between each biomarker and CR (Aβ × CR and IFT Tau × CR). All models included age, level of education, AMNART VIQ and clinical status (CN versus MCI/AD). Model 1 included PiB-PET(Aβ) alone as a predictor. Model 2 included inferior temporal tau aggregation alone (IFT tau) as a predictor. Model 3 included both Aβ and IFT tau as independent predictors. Model 4 included the interaction of CR and Aβ. Model 5 included the interaction of CR and IFT tau. Comparable analyses were completed in the CN only group (Models 6 through 9).

Results

Demographic Characteristics

Demographic characteristics of the CN and MCI/AD sample are displayed in Table 1. The CN group was older and comprised of more females compared with the MCI/AD group. The CN group was less likely to be Aβ+ and had lower levels of IFT tau. The CN group exhibited higher MMSE scores and less clinical progression on the CDR in comparison with the MCI/AD group. There were no differences between groups in education level or AMNART IQ scores. Although all CN were CDR 0 at baseline, nine CN participants were CDR 0.5 at the neuropsychological testing session closest to the time of T807 scanning. However, none of these individuals met ADNI criteria for Mild Cognitive Impairment and were therefore included in analyses as CN in order to maximize sample size. We did not observe a relationship between CR and amyloid (r=0.034, p=0.673) or between CR and IFT tau (r=−0.065, p=0.422). When examining the CN group alone, we again did not find a relationship between CR and amyloid (r=0.142, p=0.102) or CR and IFT tau (r=0.037, p=0.671).

Cross-Sectional Results of Multiple Linear Regression Analyses Predicting MMSE in the Whole Sample (CN + MCI/AD)

As expected, performance on the MMSE was related to clinical status in all models (see Table 2). Aβ deposition (Model 1) and IFT tau (Model 2) were significant contributors to MMSE score, wherein lower performance was related to higher biomarker values. When both Aβ and IFT tau were included together in the model, only IFT tau was a predictor of MMSE performance (Model 3). Furthermore, there was an interaction between CR and IFT tau such that higher IFT tau showed a greater association with lower MMSE score among low CR participants than high CR participants (Model 5). Figure 1 provides a visual

representation of this model showing the relationship between slope in MMSE and biomarker abnormality in tertiles of low (VIQ<118), medium, (119<VIQ<125), and high (VIQ>126–132) AMNART scores. This same interaction with CR did not reach statistical significance for Aβ, though was at trend level (Model 4, see Figure 2).

Cross-Sectional Results of Multiple Linear Regression Analysis Predicting MMSE in CN Only Sample

As shown in Model 6 (see Table 3), less Aβ aggregation was associated with better MMSE. Similarly, in Model 7, less IFT tau was associated with better MMSE. Model 8 shows that there is no interaction between Aβ and CR on MMSE performance. Similarly, Model 9 shows no interaction between IFT tau deposition and CR on MMSE performance.

Discussion

We report that higher Aβ and IFT tau are associated with lower cognitive performance across the AD trajectory suggesting that these biomarkers are not benign but have a deleterious effect on cognitive performance even in cognitively normal older adults. Across the whole sample, the interaction between CR and Aβ in predicting MMSE did not reach statistical significance ($p=0.093$) whereas the interaction between CR and tau was significant ($p<0.003$). The reduced strength of the interaction between Aβ and CR with cognition compared to tau may be related to the more proximal association of tau to cognitive impairment (Delacourte et al. 2002; Nelson et al. 2012), indicating that tau takes precedent over Aβ deposition along the AD trajectory. Among CN individuals, we found a relation between AD biomarkers and MMSE performance at baseline, but no modifying effect of CR on MMSE in relation to either AD biomarker. Overall, these findings offer support that CR may afford a protective effect on cognition throughout the AD spectrum.

Understanding the relation of CR to cognitive performance in the context of preclinical AD has important implications for early diagnosis and enrollment into AD prevention trials. At baseline, we did not find an association between CR, Aβ and tau burden when analyses were restricted to CN adults. These findings are consistent with our previous report where CR failed to modify cognitive performance in CN with a canonical composite of less challenging tasks but did emerge with the inclusion of more challenging tests of memory (Rentz et al. 2010). It is not surprising that our use of the MMSE, a simple screening measure of global cognition, failed to detect a protective effect of CR at baseline in CN adults, given that most CN score at ceiling. Future work will examine whether CR modifies the association between AD markers of pathology and cognition among the CN sample using more challenging tests as well as longitudinal cognitive decline. Nevertheless, this initial study examining the full spectrum of AD provide compelling evidence that the protection inferred by CR may act through mechanisms that mask the detrimental effect of tau aggregation.

A recent neuropathology study by Bennett et al. (2012) found that both Aβ and IFT tau were related to cognition in persons without cognitive impairment. However, a recent meta-analysis of PiB PET imaging and cognition found the effect of Aβ on cognition in CN appears small (Hedden et al. 2013). In contrast, IFT tau, in our sample, had a much stronger

relation to cognition than Aβ, consistent with the hypothetical model that Aβ deposition may occur at an earlier stage than inferior temporal tau (Hardy, 2009; Jack et al. 2013) and with other studies that suggest neocortical tau may be more proximal to AD-related cognitive impairment or decline (Braak et al. 2006; Johnson et al. 2016; Nelson et al. 2012). Furthermore, degree of tangle pathology has been related to the severity and duration of AD dementia and not Aβ burden alone (Arriagada et al. 1992a; Arriagada et al. 1992b; Price and Morris 1999). The fact that we observed a stronger interaction between tau and CR in predicting MMSE across the clinical spectrum than between Aβ and CR is also consistent with tau being more closely linked with cognition. This tau, CR interaction further suggests that CR may exert a protective effect on cognition even after tau pathology has started to spread from the medial temporal lobe to the neocortex. Given that higher CR has been hypothesized to be associated with a faster progression of cognitive symptoms after disease onset (Stern 2009), it will be important for future work to understand if this acceleration is related to a corresponding biomarker signature.

Tangle pathology imaged by T807 is specific for paired helical filament tangles in AD (Marquie et al. 2015) and not to other tangle pathology seen in frontotemporal and other atypical AD dementias (Wolk et al. 2012) or chronic traumatic encephalopathy (McKee et al. 2009). Our understanding of IFT tau in CN requires further exploration, as we understand the role tau plays in aging and other neurodegenerative diseases (Delacourte et al. 2002). Even the concept of cognitive reserve can be applied to many different types of pathologies and is not solely related to AD (Bieliauskas et al. 2007; Sumowski et al. 2009).

There are several limitations to this study. In order to maximize sample size across the whole sample of CN, MCI and AD, we used the MMSE as our measure of cognition. While this was optimal across all diagnostic groups, examination of more challenging or specific tests of cognition will be preferable when exploring the relations of cognition, CR and AD biomarkers in CN populations. Furthermore, we chose to use AMNART as our proxy of CR to be consistent with our previous report (Rentz et al. 2010) but recognize that there are other factors that also contribute to CR including level of education, occupational status and even amount of cognitive activities performed during life. In the future, it will be important to explore whether a composite of reserve factors would be preferable to exploring the multiple dimensions of CR on cognition and whether there are differential modifying effects of CR on Aβ and tau-related performance in a group of individuals with subjective cognitive decline. While our sample tended to be well educated with high IQ, despite this skewed distribution, we were still able to identify these interactions. Unlike a recent article that described a modifying effect of cognitive activity/reserve on amyloid burden in ApoE-4 carriers (Wirth et al. 2014), we were unable to examine this relationship as APOE genotyping was not available for our entire sample. In future work, we will attempt to tease out the relationship between E4 status and CR on both Aβ and IFT tau accumulation. Finally, we plan on exploring the longitudinal effects of CR on cognition, particularly as we collect more longitudinal data.

In summary, we found that AD biomarkers of Aβ and IFT tau deposition have a negative association on cognitive performance but CR modifies that relationship. Higher IFT Tau had a stronger and more direct association with poorer cognition than Aβ burden. Our analyses

provide further evidence of the protective effect of CR in the course of Alzheimer's disease, and suggest that CR may exert its beneficial effect by reducing the detrimental cognitive consequences of tau aggregation. Understanding the factors that mediate the relationships among cognition and pathologic burden have important implications for early diagnosis and identifying individuals for AD prevention trials.

Acknowledgments

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Figure 1.
Visual Representation of Model 5: Interaction Among MMSE Score, Inferior Temporal Tau, and Levels of Cognitive Reserve in Whole Sample (CN, MCI, AD)
Notes: purple= Low IQ (VIQ<118), turquoise=Middle IQ (119<VIQ<125), orange=High IQ (VIQ>126–132), unadjusted data shown.
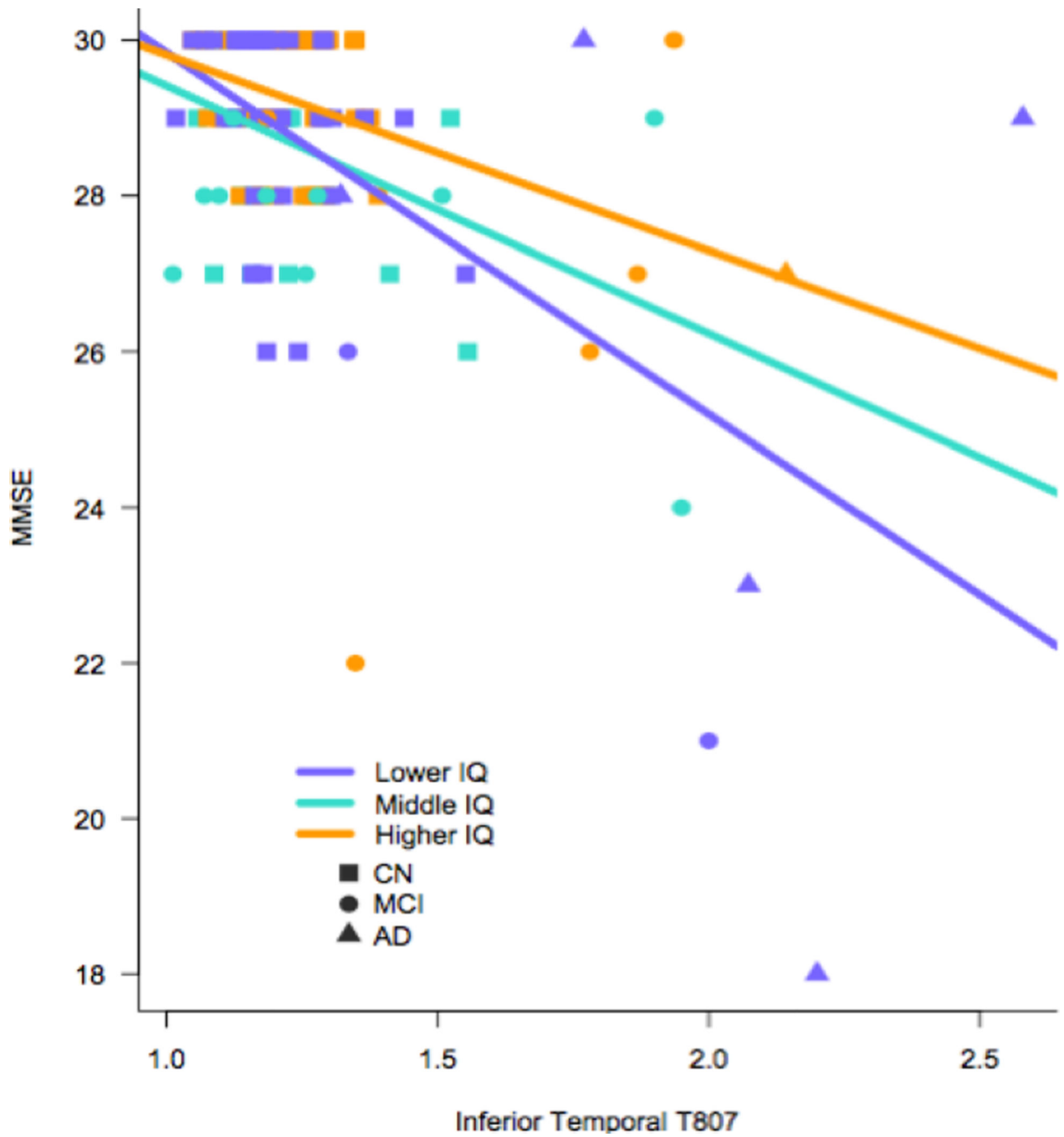
Figure 2.
Visual Representation of Model 4: Interaction Among MMSE Score, Global Amyloid
Burden, and Levels of Cognitive Reserve in Whole Sample (CN, MCI, AD)
Notes: purple= Low IQ (VIQ<118), turquoise=Middle IQ (119<VIQ<125), orange=High IQ
(VIQ>126–132), unadjusted data shown.
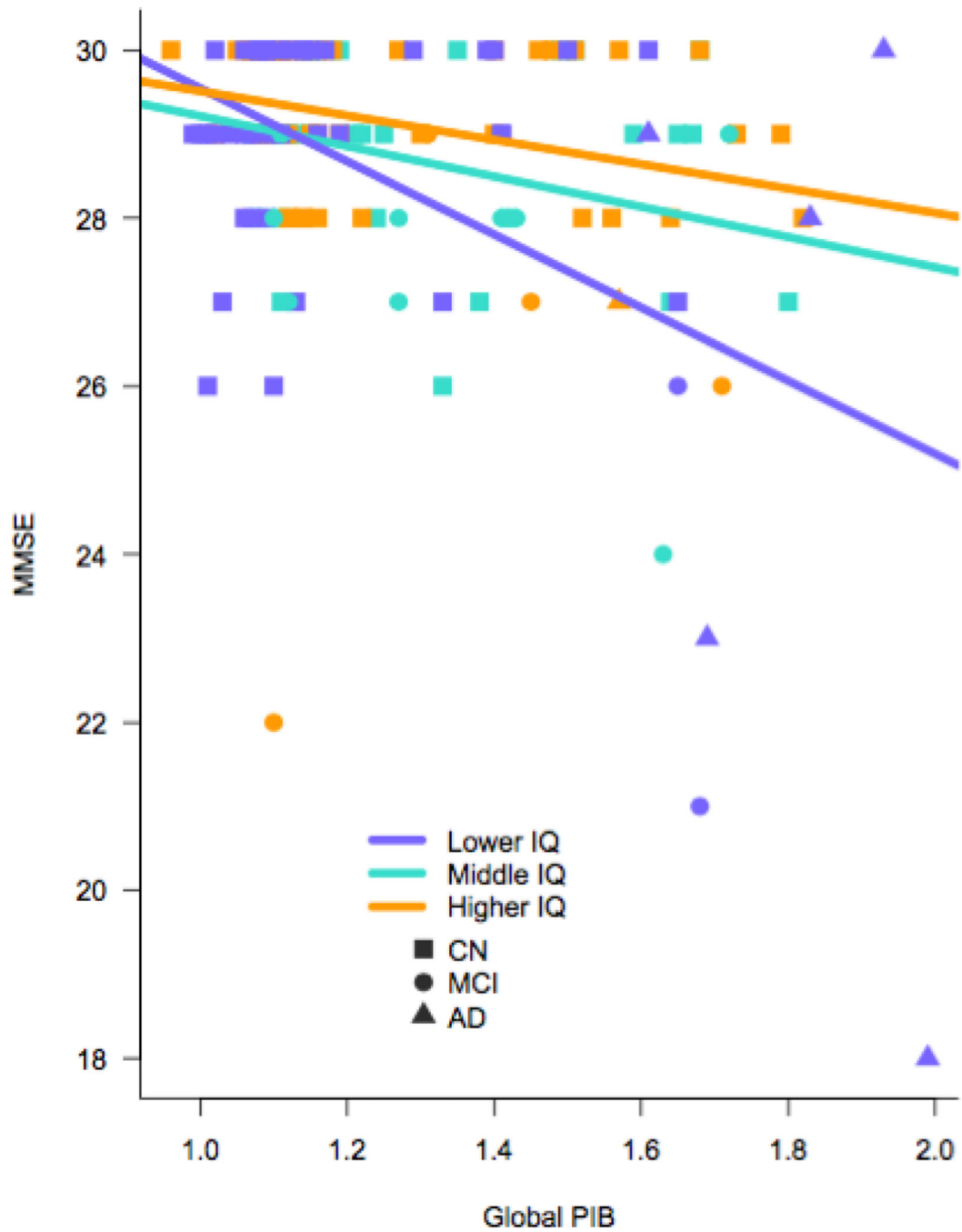
Table 1

Descriptive Characteristics

	CN	MCI/AD	Mean Difference	p
	Mean (SD) or count (n)	Mean (SD) or count (n)		
n	133	17/6		
Age	76.17 (6.23)	69.41 (9.97)	6.76	0.001
Sex (M/F)	59/74	19/4		0.001
Education (years)	15.91 (2.96)	16.29 (3.38)	0.38	0.597
Inferior Temporal T807	1.20 (0.09)	1.61 (0.44)	0.40	0.001
PiB	1.21 (0.21)	1.50 (0.26)	0.28	0.001
MMSE	29.18 (1.02)	26.61(3.06)	2.57	0.001
AMNART	121.59 (8.75)	121.22 (8.01)	0.37	0.850
Global CDR (1/0.5/0)	0.03 (0.13)	0.41 (0.05)	0.38	0.001

Notes.

Abbreviations: MMSE=Mini Mental Status Exam, CDR=Clinical Dementia Rating, MCI= Mild Cognitive Impairment, AD= Alzheimer's disease, AMNART- American National Adult Reading Test

Table 2

Cross-Sectional Results of Multiple Linear Regression Analysis Predicting MMSE in Whole Sample

	t	B(SE)	p	F	df	p	Adj. R²
Overall Model 1				21.66	5,148	0.000	0.40
Age	−0.81	−0.01 (0.02)	0.422				
Education	2.30	0.09 (0.04)	0.023				
VIQ	2.23	0.03 (0.01)	0.027				
Clinical Status	−7.05	−2.55 (0.36)	0.000				
PiB	−3.27	−1.70 (0.52)	0.001				
Overall Model 2				28.82	5,148	0.000	0.48
Age	−1.72	−0.03 (0.02)	0.088				
Education	2.02	0.08 (0.04)	0.045				
VIQ	2.24	0.03 (0.01)	0.027				
Clinical Status	−4.97	−1.85 (0.37)	0.000				
T807	−5.73	−3.47 (0.61)	0.000				
Overall Model 3				24.09	6,147	0.000	0.48
Age	−1.61	−0.03 (0.02)	0.109				
Education	2.04	0.08 (0.04)	0.044				
VIQ	2.29	0.03 (0.01)	0.024				
Clinical Status	−4.86	−1.82 (0.38)	0.000				
PiB	−0.84	−0.47 (0.56)	0.401				
T807	−4.62	−3.20 (0.69)	0.000				
Overall Model 4				18.76	6,147	0.000	0.41
Age	−0.71	−0.01(0.02)	0.477				
Education	2473	0.10 (0.04)	0.015				
VIQ	−1.18	−0.08 (0.07)	0.239				
Clinical Status	−6.81	−2.47 (0.36)	0.000				
PiB	−1.95	−12.55 (6.44)	0.053				
PiB×VIQ	1.69	0.09 (0.05)	0.093				
Overall Model 5				26.77	6,147	0.000	0.50
Age	−1.64	−0.03(0.02)	0.103				

	t	B(SE)	p	F	df	p	Adj. R²
Education	2.14	0.08 (0.04)	0.034				
VIQ	−2.43	−0.15 (0.06)	0.016				
Clinical Status	−5.21	−1.89 (0.36)	0.000				
T807	−3.58	−20.07 (5.61)	0.000				
T807×VIQ	2.97	0.14 (0.05)	0.003				

Table 3

Cross-Sectional Results of Multiple Linear Regression Analysis Predicting MMSE in Clinically Normal Older Adults Only

	t	B(SE)	p	F	df	p	Adj. R²
Overall Model 6				5.16	3,124	0.001	0.11
Age	−1.48	−0.02 (0.01)	0.141				
Education	1.26	0.04 (0.03)	0.209				
VIQ	2.74	0.03 (0.01)	0.007				
PiB	−2.21	−0.93 (0.42)	0.029				
Overall Model 7				6.66	3,124	0.000	0.15
Age	−0.76	−0.01(0.01)	0.451				
Education	1.74	0.06(0.03)	0.084				
VIQ	2.35	0.02(0.01)	0.020				
T807	−3.01	−2.88(0.96)	0.003				
Overall Model 8				4.34	4,124	0.001	0.11
Age	−1.50	−0.02 (0.01)	0.135				
Education	1.09	0.04 (0.03)	0.277				
VIQ	1.51	0.09 (0.06)	0.134				
PiB	0.85	4.93 (5.79)	0.396				
PiB×VIQ	−1.01	−0.05 (0.05)	0.312				
Overall Model 9				5.53	4.124	0.000	0.15
Age	−0.95	−0.01(0.01)	0.343				
Education	1.74	0.06 (0.03)	0.085				
VIQ	−0.09	−0.09 (0.16)	0.457				
T807	−2.64	−2.62 (0.99)	0.009				
T807×VIQ	0.97	0.09 (0.09)	0.335				