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Regional glucose metabolism and instrumental activities of daily living across the Alzheimer's disease spectrum

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**REGIONAL GLUCOSE METABOLISM AND INSTRUMENTAL ACTIVITIES
OF DAILY LIVING ACROSS THE ALZHEIMER'S DISEASE SPECTRUM**

by

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ABSTRACT

Background: Impairment in instrumental activities of daily living (IADL) begins as individuals with amnesic mild cognitive impairment (MCI) transition to Alzheimer's disease (AD) dementia. IADL impairment in AD dementia has been associated with inferior parietal, inferior temporal, and superior occipital hypometabolism using 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET).

Objective: The objective of this study was to investigate the relationship between regional cerebral FDG metabolism and IADL cross-sectionally and longitudinally in clinically normal (CN) elderly, MCI, and mild AD dementia subjects.

Methods: Four hundred and two subjects (104 CN, 203 MCI, 95 AD dementia) participating in the Alzheimer's Disease Neuroimaging Initiative at academic centers across North America underwent clinical assessments every 6 to 12 months for up to 3 years and FDG-PET at their baseline visits. The subjective informant-based Functional Activities Questionnaire (FAQ) was used to assess IADL. Data reduction analyses were first conducted to reduce 35 FDG regions to 6 regions that significantly associated with

total FAQ score after adjusting for multiple tests. These 6 FDG regions were then entered into a general linear model with backward elimination ($p < 0.05$) assessing their cross-sectional relation to baseline FAQ and a mixed random and fixed coefficient linear longitudinal regression model assessing their relation to FAQ over time. Analyses included the following covariates: diagnosis, demographics, Apolipoprotein E4 (ApoE4) carrier status, memory and executive function, and behavioral factors.

Results: The cross-sectional analysis showed that middle frontal ($p = 0.003$) and orbitofrontal hypometabolism ($p = 0.009$) were significantly associated with greater IADL impairment. Additionally, the interaction of diagnosis with posterior cingulate ($p < 0.0001$) and with parahippocampal hypometabolism ($p = 0.0008$) showed a steeper decline in IADL performance as FDG metabolism decreased for the AD dementia group relative to the MCI group, and the MCI group relative to the CN group. The longitudinal analysis showed that baseline middle frontal ($p = 0.0005$) and posterior cingulate hypometabolism ($p = 0.004$) were significantly associated with greater rate of increase in IADL impairment over time.

Conclusions: These results suggest that frontal and medial parietal synaptic dysfunction relates to functional decline at baseline and over time across the AD spectrum independent of demographics, APOE4 carrier status, memory and executive function performance, and behavioral factors.

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ABBREVIATIONS

AC-PC	anterior commissure – posterior commissure
AD	Alzheimer’s disease
ADRDA	Alzheimer’s Disease and Related Disorders Association Work Group
ADL	activities of daily living
ADNI	Alzheimer’s Disease Neuroimaging Initiative
AMNART IQ	American National Adult Reading Test intelligence quotient
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APOE4	Apolipoprotein E4 allele
β	partial unstandardized regression coefficient estimate
CI	confidence interval
CN	clinically normal elderly
CDR	Clinical Dementia Rating
FAQ	Functional Activities Questionnaire
FDG	[¹⁸ F]-2-fluoro-2-deoxy-D-glucose (fluorodeoxyglucose)
GLM	general linear model
IADL	instrumental activities of daily living
IRB	Institutional Review Board
LM-IIa	Logical Memory story
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination

NINCDS	National Institute of Neurologic and Communicative Disorders and Stroke
NPI-Q	Neuropsychiatric Inventory brief questionnaire form
PET	positron emission tomography
RAVLT	Rey Auditory Verbal Learning Test
ROI	regions of interest
SUV	standardized uptake value
VIQ	verbal intelligence quotient
WMS-R	Wechsler Memory Scale-Revised

GLOSSARY

AC-PC line - A reference line used in brain imaging that extends from the superior surface of the anterior commissure to the center of the posterior commissure of the brain (<http://airto.ccn.ucla.edu/BMCweb/HowTo/AC-PC.html>; Tailarach, 1988).

ANCOVA - The analysis of covariance is used to analyze data with a continuous numeric dependent variable and one or more categorical or discrete predictor variables with the optional inclusion of some continuous numeric 'covariates' whose linear or nonlinear relations to the dependent variable are statistically discrete from other predictor variable effects (Locascio and Atri, 2011).

Bonferroni correction - A simpler, slightly more conservative approximation of the Sidak correction for multiple comparisons, in which obtained p values are multiplied by n. Conversely, the significance cutoff can be equivalently divided by n. (Kleinbaum, 2008; Myers, 1979; Locascio et al., 1997).

Homoscedasticity - This assumption also called homogeneity of variance states that the variance of any dependent variable Y has the same finite value for any independent variable of X (Kleinbaum et al., 2008).

Multicollinearity - The assumption occurs when one independent variable is a linear function of other independent variables in a statistical regression model (Monti, 2011).

Sidak correction - A p value adjustment for multiple comparisons that assumes independence of n significance tests each with a type I error rate of α , and a greater probability of yielding significant results under a global null hypothesis if all the tests are perfectly positively correlated (Šidák, 1967; Locascio et al., 1997).

INTRODUCTION

The rapid growth of the aging population in the United States has fueled the rising prevalence of Alzheimer's disease (AD) dementia now endemic to this demographic. Currently, AD dementia is estimated to affect nearly 1 out of 10 individuals over the age of 65. The multi-staged disease is believed to transition from clinically normal (CN) with evidence of underlying AD pathology, representing preclinical AD, to mild cognitive impairment (MCI), followed by an ultimate decline towards dementia (Sperling et al., 2011).

As AD progresses, patients experience worsening symptoms, including episodic memory impairment, other cognitive deficits, mood and behavioral changes, and impaired daily functioning (Marshall et al., 2011; Vidoni et al., 2010). These symptoms greatly compromise an individual's quality of life, but perhaps none more than impaired daily functioning. Daily functioning is measured by performance of activities of daily living (ADL), impairment in which is integral for the diagnosis of AD dementia. These patients experience an early loss of independence, which increases the burden of responsibilities on patient caregivers. ADL are categorized as either basic or instrumental with the former including eating, grooming, bathing, dressing and toileting, while the latter is comprised of more complex tasks such as managing one's own schedule, performing household chores like cleaning and preparing meals, handling finances, driving or using public transportation and shopping (Marshall et al., 2012).

Impaired ADL also play a significant role in understanding disease progression. While impairment in basic ADL is found in the moderate-to-severe stage of AD

dementia, decline in instrumental ADL (IADL) has been found to accompany the earlier transition from the MCI stage to AD dementia (Tabert et al, 2002; Luck et al., 2011; Marshall et al., 2011). This feature of IADL impairment is of particular importance given disappointing results from recent AD clinical trials, which indicated the need for earlier intervention in order to slow disease progression and improve treatment outcomes (Sperling, et al., 2011).

Clinicians use functional assessment scales to detect the changes in IADL impairment that occur throughout the course of AD. These scales are administered with either caregivers (informant-based) or patients (self-reported), and are typically subjective or performance-based. The Functional Assessment Questionnaire (FAQ) (Pfeffer et al., 1982) is a ten-item subjective, informant-based scale primarily used to detect IADL impairment in MCI and mild dementia (Marshall et al., 2012). Recently, two large multicenter studies established that the FAQ clearly distinguishes between the three stages of AD progression; CN, MCI and AD dementia (Marshall et al., 2011; Morris, 2012).

IADL impairment has also been associated with changes in brain metabolism as measured by positron emission tomography (PET). Using radio-labeled glucose, ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG) as a metabolic detection agent, Landau et al. demonstrated an association between FDG hypometabolism in a composite of brain regions typically implicated in AD (temporal, lateral parietal and posterior cingulate cortices), and greater IADL impairment in a longitudinal study in MCI and mild AD dementia subjects (Landau et al., 2011). Cross-sectional analyses have also been

conducted to localize IADL impairment to specific brain regions. One such study revealed an association between IADL impairment and decreased regional glucose metabolism in the inferior parietal, superior occipital, and inferior temporal cortices in AD dementia (Salmon et al., 2005).

Loss of independence in AD dementia patients due to disease progression is a significant challenge faced by both patients and their caregivers and is attributable to impaired IADL and later basic ADL performance. Measurement of IADL impairment with the FAQ scale and the associated synaptic dysfunction seen on FDG-PET, have demonstrated the utility of IADL in tracking disease progression, a critical step for improving treatment outcomes in AD clinical trials.

The objective of this study was to investigate the relationship between cerebral glucose metabolism in FDG-PET regions of interest (ROIs) and IADL as measured by FAQ both cross-sectionally and longitudinally across the AD continuum (CN, MCI, and mild AD dementia), while controlling for subject demographics, diagnosis, behavioral changes, and cognitive performance.

METHODS

Subjects

This study analyzed data acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI) (Weiner et al., 2012). ADNI is a multi-center, observational trial that follows CN, amnesic MCI, and mild AD dementia subjects recruited from the United States and Canada. Subjects undergo longitudinal clinical and neuropsychological assessments, multi-modal neuroimaging, and biomarker assays. ADNI aims to establish a large dataset further characterizing the stages of disease progression and to determine reliable biomarkers and standardized brain imaging techniques for use in treatment outcomes of AD clinical trials. ADNI has been made possible by the collaborative efforts of co-investigators from numerous academic institutions and private corporations across North America (Weiner et al., 2012).

Four hundred and two subjects underwent clinical assessments every 6 to 12 months up to 3 years including baseline FDG PET in the ADNI study (diagnoses at baseline: 104 CN, 203 amnesic MCI, 95 AD dementia) and were selected as previously described (Marshall et al., 2011). At screening, subjects were ages 55-91 (inclusive), were medically stable and in generally good health, did not have significant neurological conditions, and had a study partner able to provide collateral information about the subject's daily functioning, cognition, and behavior. Subjects did not have significant cerebrovascular disease and had a Modified Hachinski Ischemic Score (Rosen et al., 1980) ≤ 4 . Subjects did not have active psychiatric disorders and had a Geriatric Depression Scale, short form (Sheikh et al., 1986) ≤ 5 .

Subjects were assigned to diagnostic groups (CN, amnesic MCI, mild AD dementia) as determined by site investigators at screening and baseline visits. Briefly, CN subjects had a global Clinical Dementia Rating (CDR) (Morris, 1993) score of 0, a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score of 25-30 (inclusive), intact IADL, and demonstrated an absence of significant memory impairment by performance within 1.5 standard deviations of education adjusted cut-off scores on the delayed recall portion of one Logical Memory story (LM-IIa) of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987). Amnesic MCI subjects had a CDR global score of 0.5 and memory box score ≥ 0.5 , MMSE score of 24-30 (inclusive), a self-reported or informant-based memory complaint, objective memory loss on the WMS-R LM-IIa, essentially preserved IADL (based on qualitative determination of clinical judgment by the site investigator), and were not demented. Mild AD dementia subjects had a CDR global score of 0.5 or 1.0, MMSE score of 20-26 (inclusive), and met the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association Work Group (NINCDS/ADRDA) criteria for probable AD (McKhann et al., 1984).

The study was approved by the Institutional Review Board (IRB) of each participating site. Written informed consent was obtained from all subjects and study partners prior to initiation of any study procedures in accordance with local IRB guidelines.

Clinical Assessments

Clinical assessments were performed as previously described (Marshall et al., 2011). IADL were assessed with the FAQ, which consists of 10 items where higher scores indicate greater impairment; the score range for each item is 0-3. The sum of the scores of the 10 items, a total FAQ score, was used in the current analyses (range 0-30). There is no established cut-off score for impairment on the FAQ. However, one study reported that a score of ≥ 6 is suggestive of functional impairment (Nitrini et al., 2004).

Other assessments used in this study included: the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) total learning score, which measures episodic memory performance with lower scores indicating greater impairment (range 0-75); the Wechsler Adult Intelligence Scale-Revised Digit Symbol (Wechsler, 1981), which measures processing speed, working memory, and visual scanning with lower scores indicating greater impairment (range 0-110); the Neuropsychiatric Inventory brief questionnaire form (NPI-Q) (Kaufer, 2000) apathy and depression items, which measure apathy and depression with higher scores indicating greater mood disturbance (range 0-3); the American National Adult Reading Test (AMNART) intelligence quotient (IQ) (Nelson, 1978), which estimates premorbid verbal IQ (VIQ) and can serve as a proxy of cognitive reserve with higher scores indicate higher premorbid intelligence (range 74-132).

Apolipoprotein E4 (APOE4) carrier status (homozygous carrier, heterozygous carrier, or non-carrier) was reported for subjects, while duration of AD symptoms (in years) was reported only for those subjects with a diagnosis of mild AD dementia at

screening. Duration of AD symptoms was noted as zero for CN and MCI subjects (Marshall, 2011).

FDG PET Data

FDG PET images were acquired for subjects using multiple scanners in locations throughout the United States. Images were acquired within 30-60 minutes of injection of the FDG imaging agent and were scanned using either static or dynamic methods. Dynamic scans involved the acquisition of six frames that were averaged to yield a single representative image, while static scans, single-frame images were averaged and standardized to an imaging grid about the anterior commissure - posterior commissure (AC-PC) line. All acquired images were scaled using a subject-specific intensity normalization mask to control for differences in scan intensity attributed by the use of multiple scanners. The images were filtered for uniform resolution before smoothing and final processing (Landau et al., 2011). Full details of FDG PET data acquisition ADNI protocol are available to the public on the UCLA Laboratory of Neuroimaging website (http://www.loni.ucla.edu/ADNI/Data?ADNI_Data.shtml).

FDG ROI Generation & Selection

Cortical FDG metabolism was expressed as the standardized uptake value (SUV) and normalized to an aggregate of cerebellar grey, pons, and primary cortex for each ROI. These regions were sampled using the Harvard-Oxford probabilistic atlas (<http://neuro.debian.net/pkgs/fsl-harvard-oxford-atlases.html>; Frazier et al., 2005;

Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007). Thirty-five bilateral cortical ROIs were used in the preliminary analyses, which were reduced to six ROIs that significantly associated with total FAQ score. These six ROIs were used in the main cross-sectional and longitudinal analyses and are depicted in Figure 2.

Statistical Analyses

All analyses performed in this study were run using SAS Version 9.3 and JMP Version Pro 10 statistical and graphical software. Associations between diagnostic groups and subject demographics and characteristics were evaluated using analysis of variance (ANOVA) with the Tukey post hoc test for continuous variables and the Pearson chi-square test for categorical variables.

Preliminary Multiple Test Protection and Data Reduction Screening Tests

Using a preliminary multivariate approach, separate analyses of covariance (ANCOVA) were run for each of the thirty-five respective FDG ROIs in determining p values and as a data reduction method. The main effect of diagnosis at baseline with a covariate of the given FDG ROI was included in the model with the total baseline FAQ score serving as the dependent variable. Only the MCI and AD groups were included because of the floor effect for the CN population (Marshall et al., 2011). The thirty-five resulting p values for each respective FDG ROI were then adjusted for using the stepdown Sidak correction method (Šidák, 1967; Finner, 1993). This method assumes the tests are independent despite the inter-correlations of the FDG ROIs and adjusts p values for the number of significance tests while treating each result as a separate

univariate test in which the given FDG ROI was not adjusted for relations with other FDG ROIs. It provides a conservative protection that subsequent multiple tests are not chance effects.

To further reduce the data, a general linear model (GLM) regressing the baseline FAQ score on baseline diagnosis (excluding the CN population) including all thirty-five FDG ROIs as covariates was run with backward elimination using a 0.05 alpha cutoff for inclusion of terms. This method is the converse of the previously employed Sidak correction as it adjusts each FAQ versus FDG ROI relation for its relations to all other FDG ROIs included in the model. However, it does not adjust p values for multiple test chance effects (Šidák 1967 and Myers 1979). The FDG ROIs significantly associated with total baseline FAQ were used in the main cross-sectional and longitudinal mixed effects models.

Cross Sectional Analyses

The six FDG ROI surviving the backward elimination approach above were then entered as simultaneous covariates in another backward elimination GLM (with a cutoff of 0.05) regressing baseline FAQ on these covariate as well as diagnosis (including CN), and the interaction of each of these FDG ROIs with diagnosis. Additional factors and covariates serving as initial predictors included sex, the interaction of sex and diagnosis, baseline age (linear and quadratic terms), duration of AD dementia symptoms (set to mean zero with slight random error for MCI and CN), RAVLT total learning, Digit Symbol, the NPI-Q apathy and depression items, the number of APOE4 alleles, and VIQ.

Significance test results (p values) were complemented with effect size estimates such as partial regression coefficient estimates (β) with confidence intervals (CI), covariate adjusted means and estimates of percent variance accounted for in the dependent variable uniquely by individual predictors, as well as by the model as a whole (R^2). Residuals from the final model were checked for conformance to assumptions of normality and homoscedasticity.

Longitudinal Analyses

A mixed effect longitudinal analysis analogous to the cross sectional analysis above was run with FAQ as the dependent variable and including the same covariates as described for the cross-sectional model, a random intercept and linear effect of years in the study, as well as a baseline FAQ covariate and its interaction with time, the interaction of diagnosis with time, and the separate interactions of the six significant FDG ROIs with time. Random intercepts and slope terms for time were initially allowed to be correlated, and then all fixed and random covariance terms were subjected to backward elimination at a cutoff of 0.05. Residuals from the full mixed fixed and random term model were also checked for conformance to assumptions of normality and homoscedasticity.

RESULTS

Table 1 provides baseline demographic and clinical data for all subjects and for each of the three diagnostic groups (CN, MCI, mild AD dementia). There were significant differences between diagnostic groups for all variables in expected directions except for age and sex, which was similar across all groups. Table 2 summarizes the longitudinal data for FAQ scores collected over the three-year study duration; this is further illustrated by diagnostic group in Figure 1.

Preliminary Multiple Test Protection and Data Reduction Screening Tests

The thirty-five univariate ANCOVAs illustrated the expected negative relations of baseline FAQ with each of the thirty-five FDG ROI (higher FAQ score indicating greater IADL impairment was associated with decreased metabolism), of which twenty-seven were statistically significant at $p < 0.05$ with twenty-five of these remaining significant after applying the Sidak correction. This demonstrated widespread, real within diagnostic group negative relations of individual FDG ROI to total baseline FAQ univariately, and any reported significant relations are therefore not likely chance effects related to multiple testing.

The backward elimination GLM of the total baseline FAQ regressed on all thirty-five FDG ROI simultaneously with initial predictors, along with baseline diagnosis, reduced down to six FDG ROI that significantly associated with total FAQ score and demonstrated an additive significant diagnosis effect (AD FAQ mean > MCI mean). The FDG ROI surviving backward elimination were the posterior cingulate gyrus,

orbitofrontal cortex, frontal pole, lingual gyrus, middle frontal gyrus, and parahippocampal gyrus. All regions showed expected negative relations with total baseline FAQ partialled from the relations to other FDG-ROI except for the frontal pole and lingual gyrus, whose counterintuitive positive partialled relations may have been due to multicollinearity. The two regions, especially frontal pole, demonstrated moderate to high positive correlations with the other FDG ROI in the model. Moreover, the unadjusted univariate relation of these two regions to FAQ was negative (frontal pole: $r=-0.27$, $p<0.0001$; lingual gyrus: $r=-0.10$, $p=0.08$). This suggests that the true relation of these two regions with FAQ is negative similarly to the other regions and that the multicollinearity within the multivariate model led to the counterintuitive positive relation. Table 3 summarizes the results for the six FDG ROI surviving the backward elimination GLM analysis. The model as a whole accounted for 60 percent of the variance of FAQ. Figure 2 illustrates the location of these ROI in the brain.

Table 1. Baseline demographic and characteristics of subjects.

Group	All subjects	CN	MCI	AD dementia
N	402	104	203	95
Age (years)	75.4±6.7	75.9±4.8	75.0±7.2	75.7±7.4
Sex (% male)	63.9	62.0	67.5	59.0
Education (years)	15.5±3.1‡	15.9±3.1	15.8±2.9	14.6±3.3
AMNART VIQ	117.5±11.5‡	120.7±11.29	117.2 ±11.0	114.4±11.9
Duration of AD symptoms (years)	-	0	0	3.7±2.4
APOE4 (% non-carrier/ heterozygous carrier/ homozygous carrier)	51.0/38.3/ 10.7*	75.0/23.1/ 1.9	46.8/40.4/ 12.8	33.7/50.5/ 15.8
MMSE	26.8±2.6*	29.0±1.1	27.2±1.7	23.5±2.1
RAVLT Total Learning	32.2±11.1*	42.2±9.8	31.4±9.1	22.9±6.9
Digit Symbol	36.5±13.0*	44.5±10.4	37.4±10.9	26.0±12.4
NPI-Q Apathy (% present)	0.3±0.6 (18.2)*	0.02±0.1 (1.9)	0.2±0.6 (15.3)	0.6±0.8 (42.1)
NPI-Q Depression (% present)	0.2±0.5 (18.7)*	0.1±0.3 (6.7)	0.2±0.5 (17.2)	0.4±0.7 (34.7)
FAQ	5.0±6.6*	0.2±0.8	3.4±3.9	13.6±6.7

AD (Alzheimer's disease), AMNART VIQ (American National Adult Reading Test verbal intelligence quotient), APOE4 (Apolipoprotein E4), CN (clinically normal elderly), FAQ (Functional Activities Questionnaire), MCI (mild cognitive impairment), MMSE (Mini-Mental State Examination), NPI-Q (Neuropsychiatric Inventory brief questionnaire form), RAVLT (Rey Auditory Verbal Learning Test).

All values (except n, sex, APOE4) represent mean ± standard deviation.

*p<0.0001 for CN vs. MCI, CN vs. AD and MCI vs. AD.

‡ p<0.01 for CN vs. MCI, CN vs. AD and MCI vs. AD.

‡‡p<0.05 for CN vs. MCI, CN vs. AD and MCI vs. AD.

‡‡‡p<0.001 for CN vs. AD and MCI vs. AD.

‡‡‡‡p<0.01 for CN vs. MCI and MCI vs. AD.

Table 2. Longitudinal Age and FAQ data.

	Baseline	Month 6	Year 1	Month 18	Year 2	Year 3
N_{Age}	402	388	360	170	316	217
Age	75.4±6.7	75.9±6.7	76.5±6.7	76.6±7.0	77.6±6.5	78.6±6.4
N_{FAQ}	402	386	360	169	318	209
FAQ	5.0±6.6	5.8±7.5	6.4±7.9	5.7±5.9	8.2±9.3	6.9±8.3

N = number of subjects in sample

Age and FAQ values represent mean ± standard deviation.

Figure 1. Predicted longitudinal FAQ scores from fixed effects models by diagnosis: Fixed effects include demographics and baseline clinical variables

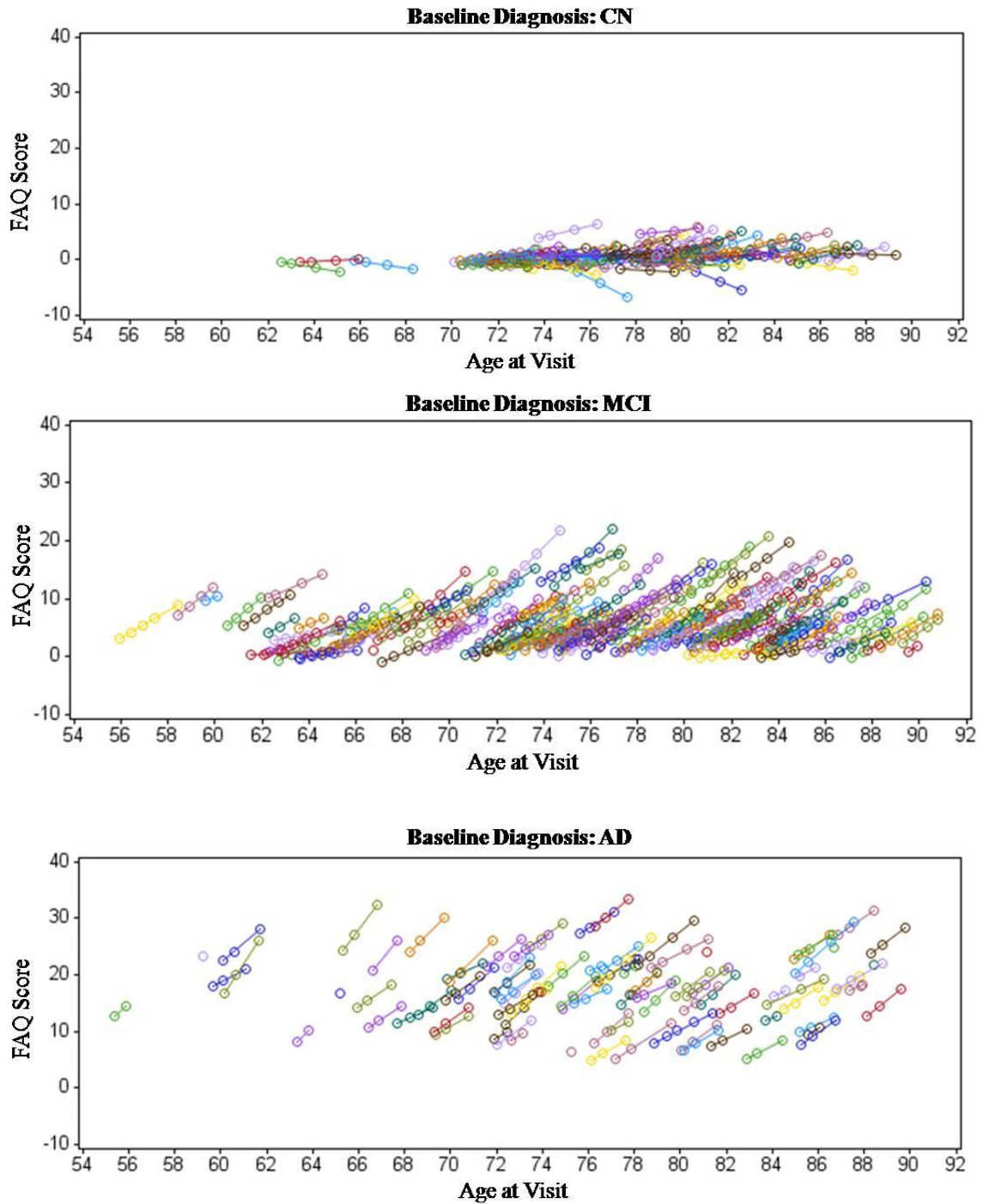


Table 3. FDG ROIs surviving data reduction analysis using backward elimination GLM.

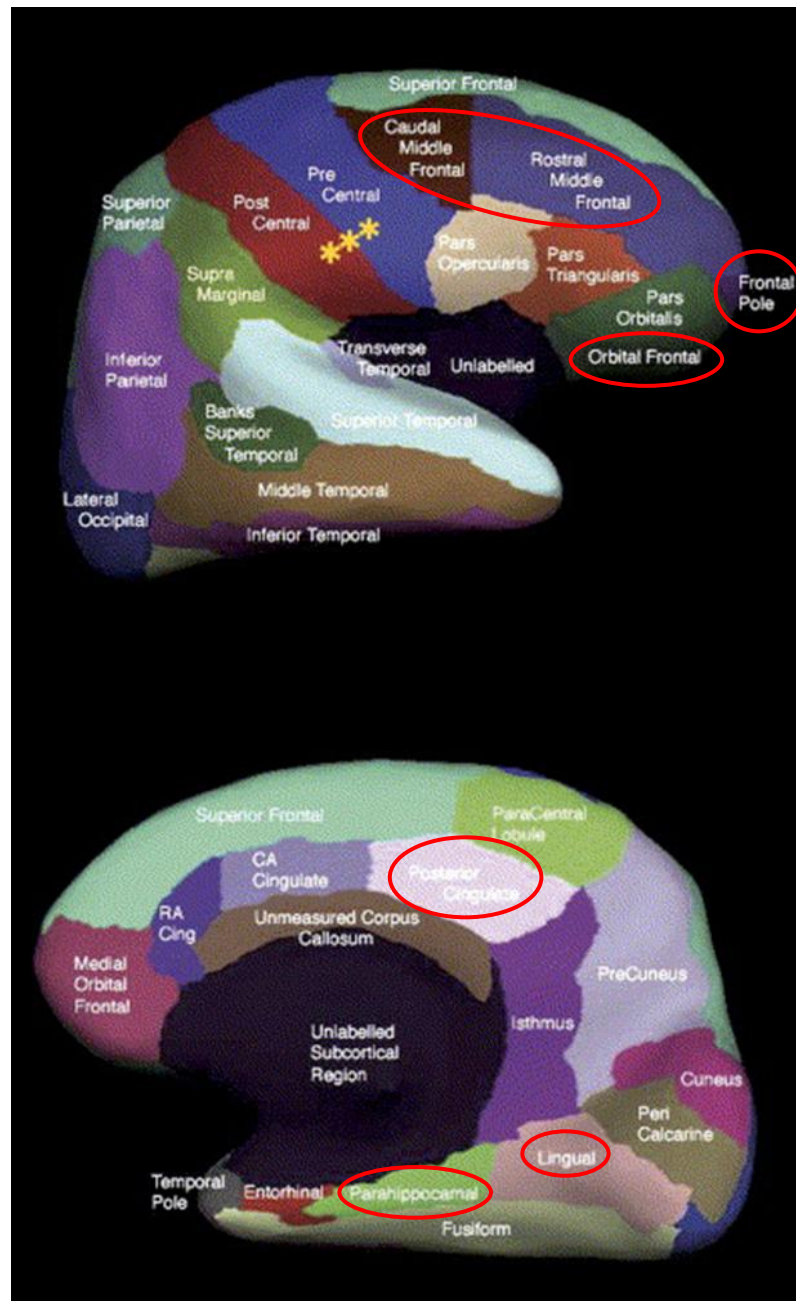
Model: $R^2 = 0.60$, $p < 0.0001$						
Predictor		β	95% CI for β	P	% Variance Accounted for	
					Total	Partial
Baseline Diagnosis	AD	7.63	6.4, 8.9	<0.0001	20.4	33.2
	MCI	0				
Posterior cingulate gyrus		-14.14	-21.1, -7.1	<0.0001	2.1	4.7
Orbitofrontal gyrus		-22.88	-37.5, -8.3	0.002	1.2	2.8
Frontal pole		32.88	16.4, 49.4	0.0001	2.0	4.6
Lingual gyrus		8.22	1.1, 15.4	0.02	0.6	1.4
Middle frontal gyrus		-23.19	-34.5, -11.9	<0.0001	2.1	4.9
Parahippocampal gyrus		-17.95	-28.2, -7.8	0.0006	1.5	3.6

AD (Alzheimer’s disease), β (partial unstandardized regression coefficient estimate), CI (confidence interval), MCI (mild cognitive impairment)

“%Variance Total” represents percent of total variance of FAQ uniquely associated with the indicated predictor (unbiased population estimate).

“%Variance Partial” represents percent of variance of FAQ with portion associated with other predictors pre-removed, which is uniquely associated with the indicated predictor (unbiased population estimate).

Figure 2. Localization of six FDG ROIs associated with total FAQ in one brain hemisphere. (Top) lateral view of the hemisphere, (bottom) medial view of the hemisphere with significant FDG ROIs from data reduction analyses encircled in red. The yellow asterisks on the inflated surface indicate the cortex around the perimeter of the central sulcus that has been ‘inflated’ and is now visible. Figure adapted from Desikan et al., 2006.



Cross Sectional Analyses

Table 4 summarizes the results of the cross-sectional analysis. The six FDG ROI discovered to have significant, within diagnosis group, relations to FAQ in the preliminary screening analysis reported above were included in the cross sectional analysis as described in the Methods section. Following the second tier backward elimination, significant interactions were found for diagnosis with posterior cingulate ($p < 0.0001$) and parahippocampal ($p = 0.0008$) FDG hypometabolism. The diagnostic interactions with the posterior cingulate and parahippocampal regions showed a steeper decline in IADL performance as FDG metabolism decreased for the AD dementia group relative to the MCI group, and the MCI group relative to the CN group (see Figure 3A and 3B).

Main effects were found for orbitofrontal ($p = 0.009$, Figure 3C) and middle frontal ($p = 0.003$, Figure 3D) FDG hypometabolism in the expected negative direction with FAQ scores increasing as FDG metabolism decreased. Interestingly, while the univariate unadjusted relationship for frontal pole FDG hypometabolism paralleled the negative direction found with the other FDG ROI main effects, this region demonstrated multicollinearity when adjusted to eliminate other covariates, excluding diagnosis. That is, frontal pole FDG hypometabolism showed a positive partialled relation to baseline FAQ, likely due to its high positive correlations with some of the other FDG ROIs in the model, see Figures 3E and 3F (Figure 3E demonstrates the unadjusted FDG values with the negative relation and Figure 3F demonstrates the adjusted FDG values with the positive relation).

Additionally, significant relations were found for the covariates digit symbol and NPI-Q apathy item in expected directions (negative and positive, respectively). The model as a whole accounted for 71 percent of the variance of FAQ and residuals conformed reasonably to assumptions (Table 4).

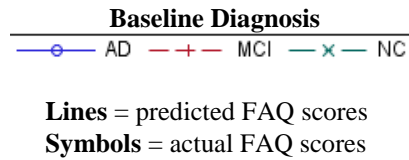
Table 4. Cross-sectional GLM of the association between baseline FAQ and regional FDG metabolism and covariates, displaying predictors retained in the final model after backward elimination.

Model: $R^2=0.71$, $p<0.0001$						
Predictor		β	95% CI for β	p	% Variance Accounted for	
					Total	Partial
Baseline Diagnosis	AD	60.4	44.92, 75.89	<0.0001	5.2	14.7
	MCI	19.1	5.09, 33.03			
	CN	0				
Posterior Cingulate x Diagnosis	AD	-28.62	-41.18, -16.07	<0.0001	1.5	4.6
	MCI	-8.64	-19.05, 1.77			
	CN	0				
Parahippocampus x Diagnosis	AD	-31.91	-49.77, -14.04	0.0008	0.9	3.0
	MCI	-10.32	-27.19, 6.54			
	CN	0				
Orbitofrontal		-13.86	-24.28, -3.43	0.009	0.4	1.4
Frontal pole		16.34	4.38, 28.29	0.008	0.5	1.5
Middle frontal		-12.81	-21.32, -4.30	0.003	0.6	1.9
Digit Symbol		-0.04	-0.08, -0.01	0.02	0.3	1.1
NPI-Q apathy		1.68	1.02, 2.33	<0.0001	1.8	5.7

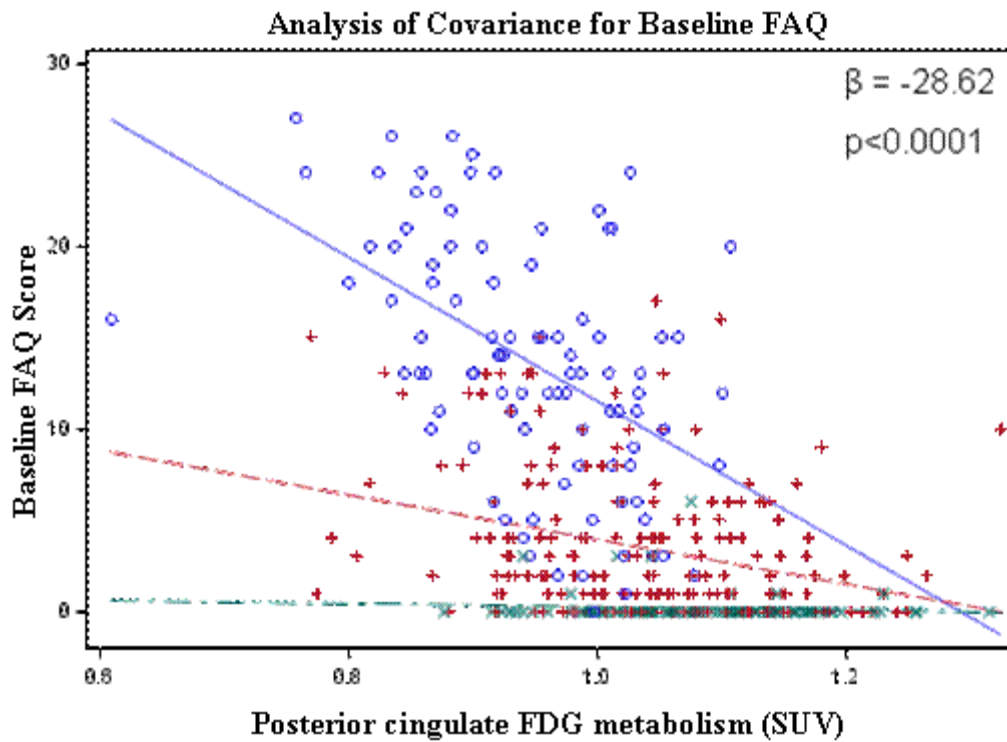
AD (Alzheimer’s disease), β (partial unstandardized regression coefficient estimate), CI (confidence interval), CN (clinically normal elderly), MCI (mild cognitive impairment), NPI-Q (Neuropsychiatric Inventory brief questionnaire form), ‘x’ indicates an interaction,

“%Variance Total” represents percent of total variance of FAQ uniquely associated with the indicated predictor (unbiased population estimate), “%Variance Partial” represents percent of variance of FAQ with portion associated with other predictors pre-removed, which is uniquely associated with the indicated predictor (unbiased population estimate).

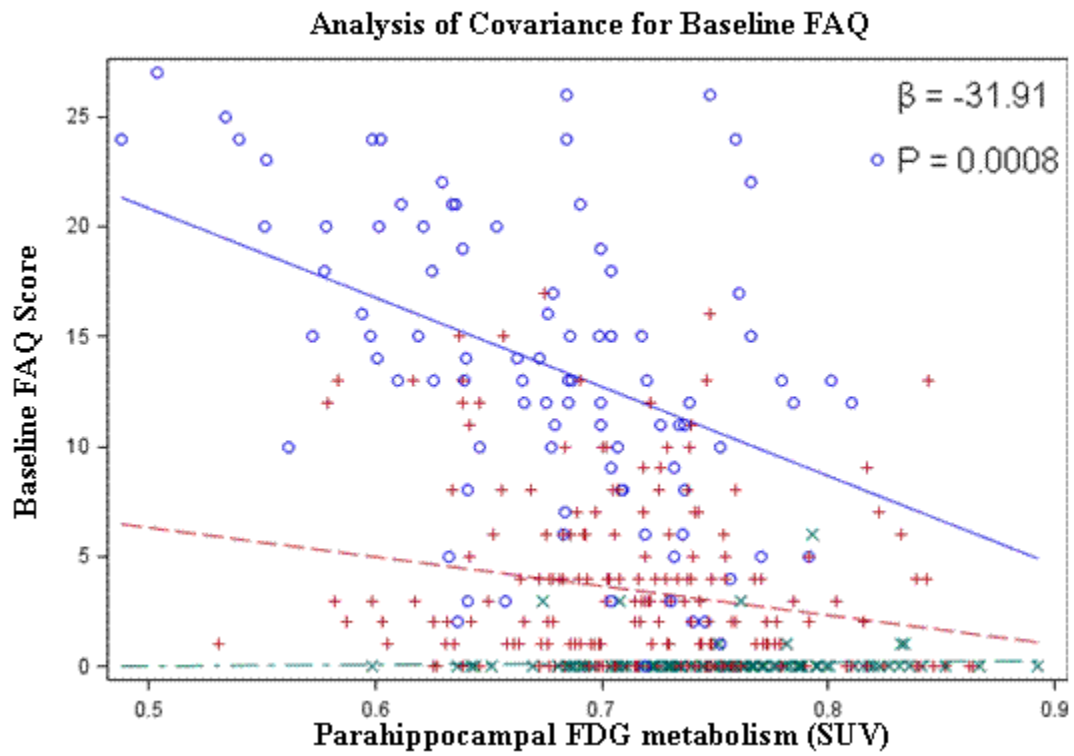
Figure 3. Cross-sectional graphs for predictor FDG ROI and baseline FAQ. Predictors including the indicated FDG ROI, diagnosis and the interaction of the indicated FDG ROI with diagnosis, if applicable. The coefficient estimates were similar to those in the full model.



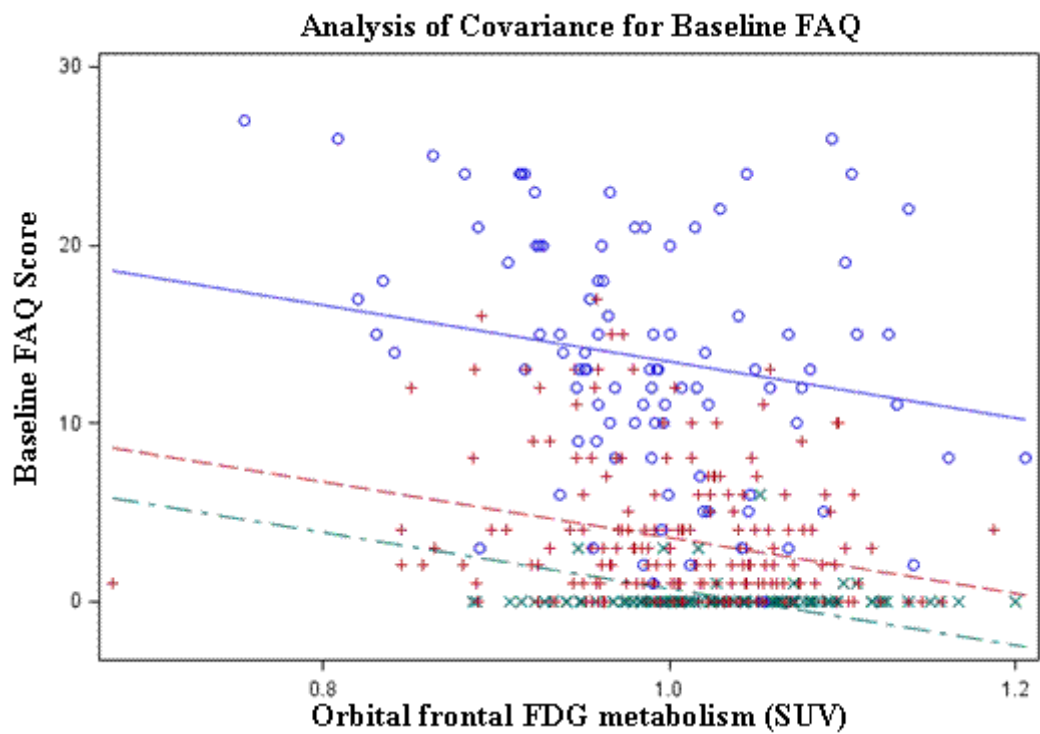
3A



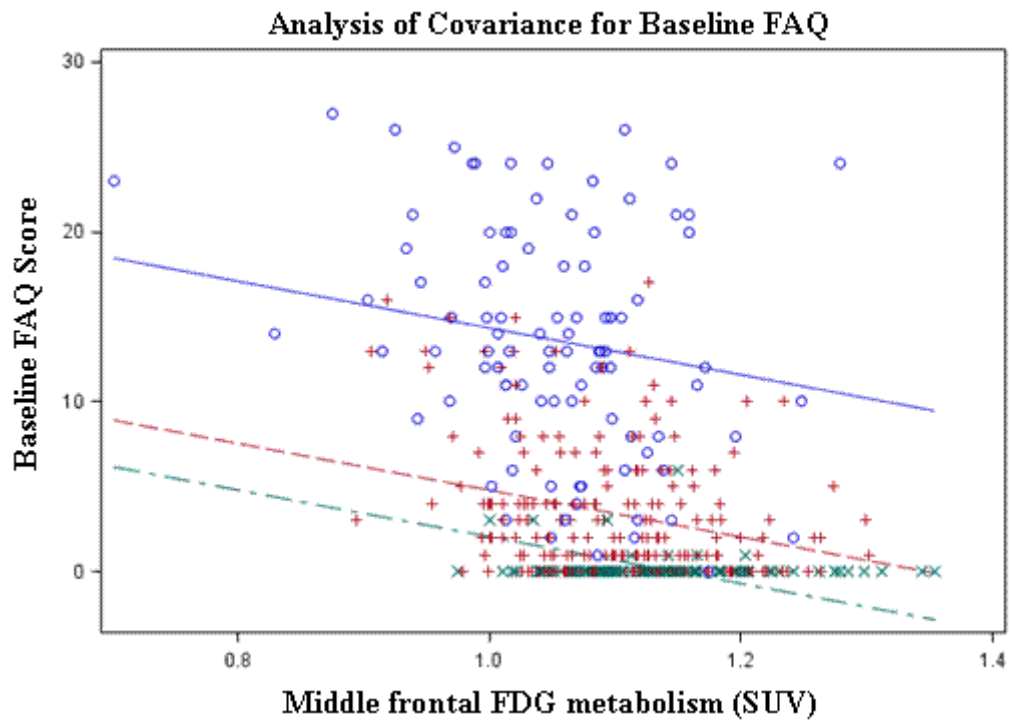
3B



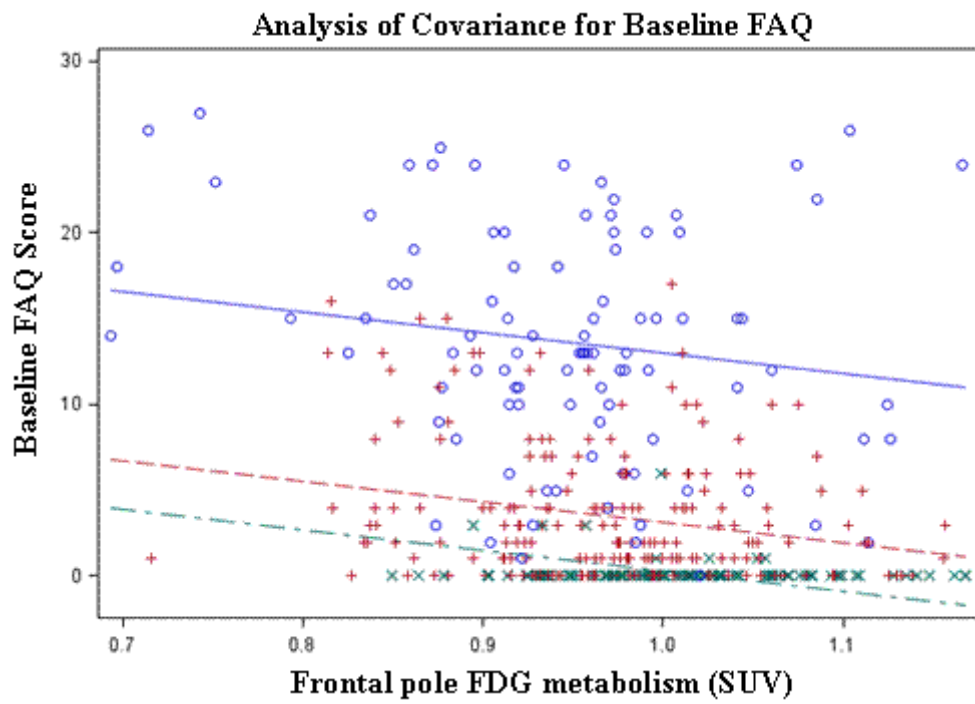
3C



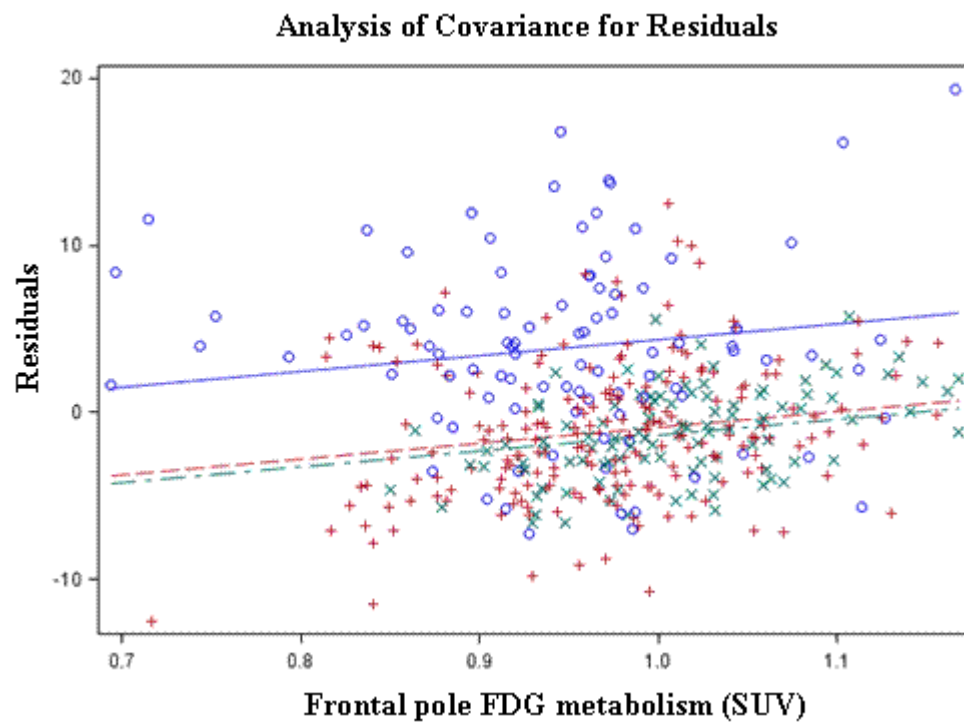
3D



3E



3F



Longitudinal Analyses

Table 5 summarizes the results of the mixed effects longitudinal analysis. The mixed effects backward elimination model resulted in a significant interaction for both posterior cingulate ($p=0.004$) and middle frontal ($p=0.0005$) FDG hypometabolism with time whereby individuals with lower baseline FAQ scores demonstrated worsening IADL impairment with increasing FAQ scores over time. The faster trajectory of deterioration in FAQ scores for these FDG-ROI is depicted for each population across the AD spectrum in Figure 4. The circles indicate when posterior cingulate gyrus FDG metabolism is one standard deviation below its mean SUV, while the squares indicate when it is one standard deviation above its mean SUV. The solid blue lines are where middle frontal gyrus FDG metabolism is one standard deviation below its mean SUV and the dashed red lines indicate when it is one standard deviation above its mean SUV. All other covariates were set at their grand means or illustrative values and included sex set to female, the number of APOE4 alleles set to 1, NPI-Q apathy score set to 1, baseline FAQ score set to 5, and RAVLT total learning score set to 32. Low FDG metabolism in the posterior cingulate and middle frontal regions varied with the highest FAQ scores as represented by the uppermost line (solid blue line with circles).

A counter-intuitive finding was a significant partial interaction of the orbitofrontal FDG metabolism with time whereby higher values of FDG metabolism for the orbitofrontal cortex were significantly associated with faster deterioration (increasing FAQ scores). This finding was possibly suggestive of multicollinearity due to moderate

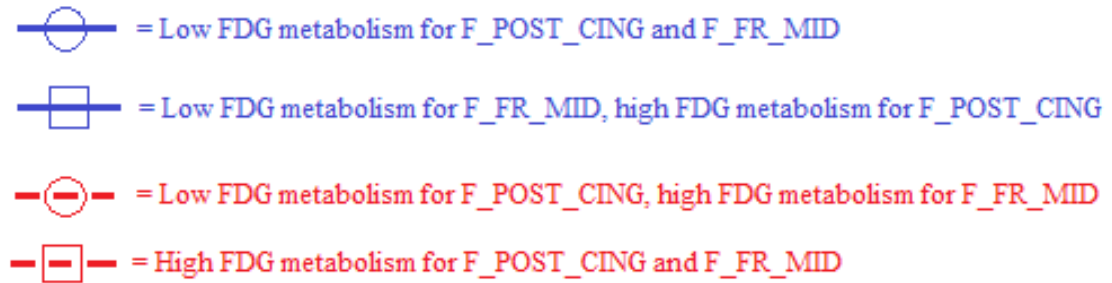
positive correlations of orbitofrontal cortex with the posterior cingulate gyrus and with the middle frontal gyrus.

Also seen were significant effects for FAQ in the expected direction for APOE4 (positive), RAVLT total learning (negative), NPI-Q Apathy (positive), baseline FAQ (positive), sex (female higher), and interactions of diagnosis with time such that the AD and MCI group deteriorated faster than did the CN group. The longitudinal interactions between diagnosis and time are explained by years of study participation; as time in study increases, a duration of time over which to observe disease progression follows. This trend is illustrated by the higher positive slopes seen in Figures 4B and 4C as compared to Figure 4A over the study's three years. The percent variance accounted for by the overall model fixed effects was 75% and when including random terms 95%. The residuals reasonably conformed to assumptions (Table 5).

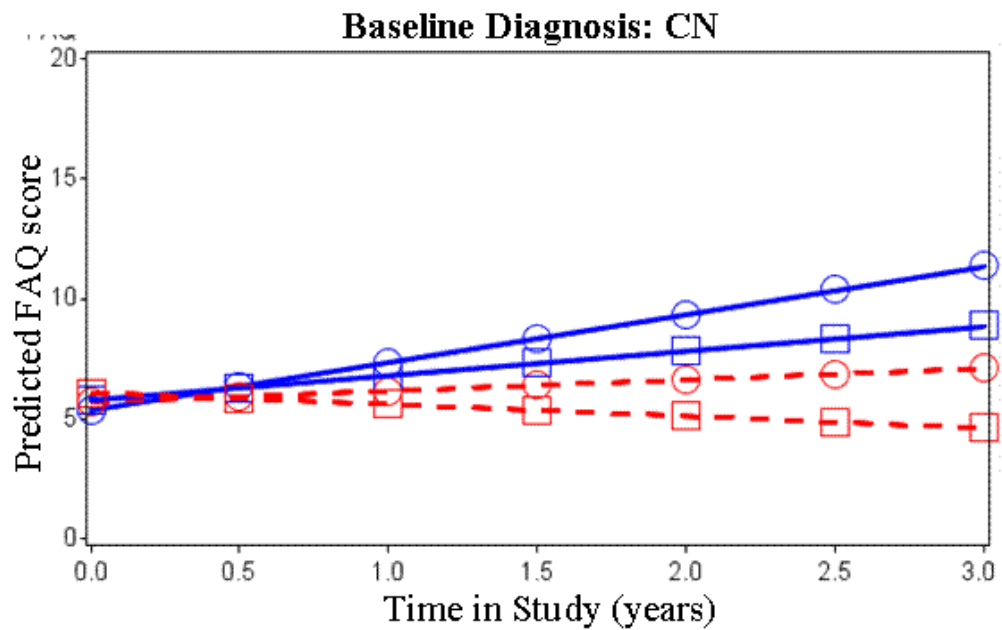
Table 5. Longitudinal mixed effects model of the association of FAQ over time to baseline regional FDG metabolism and covariates, displaying predictors retained in the final model after backward elimination.

Model: $R^2=0.75$ for fixed effects, $p<0.0001$; $R^2=0.95$ including random terms, $p<0.0001$				
Predictor		β	95% CI for β	P
Time in study (years)		5.58	0.95, 10.2	0.02
Baseline Diagnosis x time	AD	1.57	0.68, 2.47	0.05
	MCI	1.64	1.04, 2.25	
	CN	0		
RAVLT total learning		-0.05	-0.09, -0.02	0.01
APOE4		0.52	0.05, 1.00	0.03
NPI-Q apathy		0.60	0.01, 1.18	0.005
Posterior cingulate gyrus x time		-4.80	-8.10, -1.51	0.004
Orbitofrontal cortex x time		8.42	3.64, 13.20	0.001
Middle frontal gyrus x time		-7.67	-11.95, -3.39	0.001
Posterior cingulate gyrus		2.00	-3.00, 7.00	0.43
Orbitofrontal cortex		-5.72	-12.6, 1.15	0.10
Middle frontal gyrus		1.66	-4.55, 7.86	0.60
Baseline FAQ		0.79	0.71, 0.87	<0.0001
Sex	Female	0.67	0.02, 1.33	0.04
	Male	0		

Figure 4. Predicted FAQ scores from fixed effects longitudinal model across time for posterior cingulate and middle frontal regions by diagnostic groups: CN (A), MCI (B), AD dementia (C).

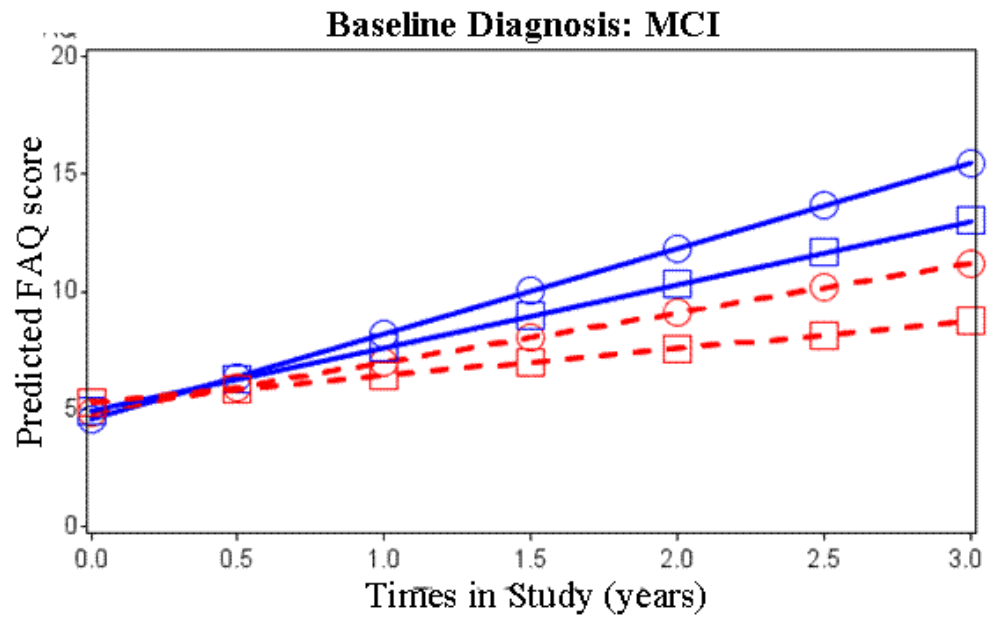


A



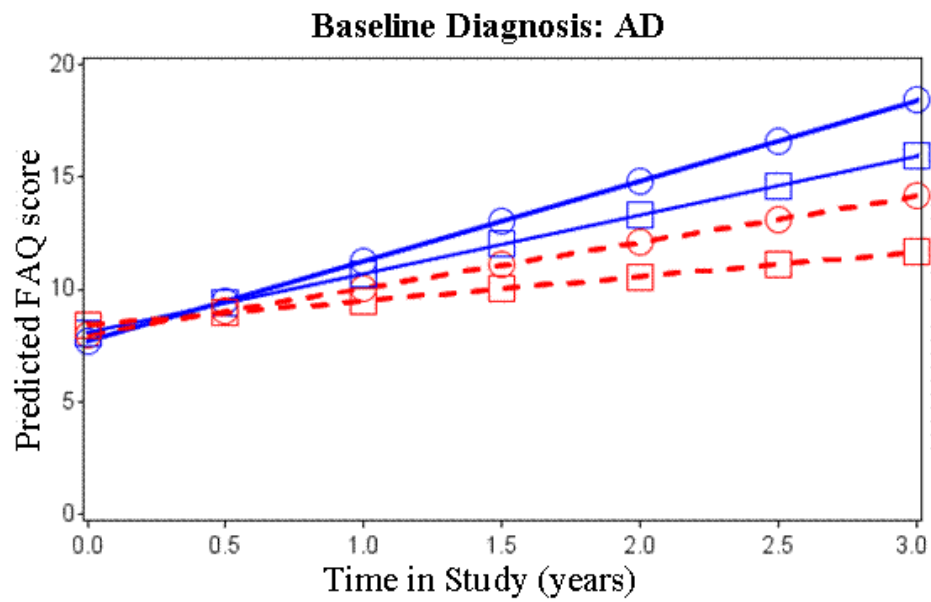
- = Low FDG metabolism for F_POST_CING and F_FR_MID
- = Low FDG metabolism for F_FR_MID, high FDG metabolism for F_POST_CING
- -○- - = Low FDG metabolism for F_POST_CING, high FDG metabolism for F_FR_MID
- -□- - = High FDG metabolism for F_POST_CING and F_FR_MID

B



- = Low FDG metabolism for F_POST_CING and F_FR_MID
- = Low FDG metabolism for F_FR_MID, high FDG metabolism for F_POST_CING
- -○- - = Low FDG metabolism for F_POST_CING, high FDG metabolism for F_FR_MID
- -□- - = High FDG metabolism for F_POST_CING and F_FR_MID

C



DISCUSSION

This data-driven analysis sought to characterize the relationship between regional FDG metabolism and IADL both cross-sectionally and longitudinally across the AD spectrum in CN, MCI, and mild AD dementia subjects. Our results suggest that frontal and medial parietal synaptic dysfunction relate to functional decline at baseline and over time across the AD spectrum independent of demographics, APOE4 carrier status, memory and executive function performance, and behavioral factors.

The cross-sectional results of our study suggest that orbitofrontal and middle frontal FDG hypometabolism significantly associates with greater IADL impairment, independent of diagnosis at baseline, while there were significant interactions for FDG posterior cingulate and parahippocampal hypometabolism with diagnosis illustrated by the steeper decline in IADL performance (increasing FAQ scores) as metabolism decreased for the AD dementia group relative to the MCI group, and the MCI group relative to the CN group. Salmon et al. demonstrated an association between IADL impairment and inferior temporal, inferior parietal, and superior occipital hypometabolism in patients with mild to moderate AD dementia in a cross-sectional study using FDG PET (Salmon et al., 2005). The cross-sectional results of the current study are in partial agreement with inferior temporal hypometabolism findings, as the parahippocampal gyrus is associated with the temporal cortex, see Figure 1.

The longitudinal analysis showed that baseline middle frontal and posterior cingulate FDG hypometabolism were significantly associated with a greater rate of increase in IADL impairment over time and across the AD spectrum. In their seminal

work using FDG-PET to assess the relationship of typical AD hypometabolic patterns with cognitive and functional impairments in the same database used here (ADNI), Landau et al. showed that *a priori* selected patterns of baseline FDG-ROI hypometabolism can be predictive of future increases in FAQ score indicative of IADL decline (Landau et al., 2011). Using a composite of FDG-ROI commonly accepted to be typical of AD dementia hypometabolism, they predicted longitudinal functional decline in MCI and mild AD dementia. Similarly, our results suggest a faster trajectory of decline in IADL performance over time across the AD spectrum. Individuals with lower baseline FAQ scores demonstrated worsening IADL impairment with increasing FAQ scores over time.

Additionally, there was regional overlap and differences between the FDG ROI determined to have significant associations with FAQ in both Landau et al. and our study. The *a priori* selected composite FDG-ROI employed by Landau et al. included the angular gyri of the lateral parietal lobe, the temporal gyri of the temporal lobe as well as the posterior cingulate gyrus, which demonstrated a significant interaction with FAQ over time in our analysis also. In our study, IADL deterioration was predicted by specific cortical regions that were determined through multivariate analyses to be significantly associated with FAQ. We showed a similar association with posterior cingulate and parahippocampus, which is part of the temporal gyri included in the composite employed by Landau et al. However, we also demonstrated associations with frontal regions (middle frontal and orbitofrontal), which were not included in the Landau composite since they are not generally considered to be highly typical of AD-related

hypometabolism. Therefore, our data-driven approach, allowed for a more in-depth localization of IADL impairment, reinforcing the cortical regional localization of progressive functional impairment in the AD spectrum.

The preliminary data reduction from thirty-five to six FDG ROI allowed the data to drive the localization of IADL impairment, and subsequently allowed for the most critical ROI to be identified. This approach highlights the advantages of the data driven method over the more commonly used standardized atlases or voxel-based methods for region identification. Specifically, patterns of hypometabolism discernible in atlas-derived subregions may be washed out when averaged across an entire atlas-derived ROI. Additionally, ROI identified using voxel-based methods have limited application to populations outside study samples because the precision of ROI locations and their variance are directly influenced by the subjects and data processing methods. However, FDG-ROI may not fully encompass significant regions of declining glucose metabolism, which are captured in voxel-based analyses (Landau et al., 2011). Together the use of data-derived FDG-ROI and a mixed effects longitudinal model allows the results to be more readily adaptable to patient populations.

The use of a mixed effects longitudinal model is favorable for extrapolating results beyond the study sample. By taking into account fixed and random effects within the model, implication of results from the model are not limited to fixed-subject sample. In order to understand the significance of each contributing predictor in our mixed effects longitudinal analysis, it was necessary to account for the fixed and random effects when designing the model. For example, the longitudinal analysis included years in study to

control for multiple time points for data collection from years in study, the baseline FAQ covariate and its interaction with time to control for changes in FAQ score over time, the interaction of baseline diagnosis with time to control for change in diagnosis over time, as well as the FDG metabolism patterns for each of the six FDG ROI and each of their interactions with time to control for changes in FDG metabolism over time.

This study features some limitations. The ADNI sample is not representative of the general population because the subjects are carefully selected to have limited general health issues, psychiatric conditions, and cerebrovascular disease. Moreover, the subjects were highly intelligent premorbidly and had a high proportion of APOE4 carriers. However, we adjusted for these elements in all analyses. Moreover, this sample resembles that of most AD spectrum clinical trials, making it easier to compare the results to clinical trial outcomes.

The IADL scale used in these analyses, the FAQ, has been shown to be a sensitive measure for differentiating between CN, MCI, and mild AD dementia, but nearly all CN subjects have a score of 0 at baseline, representing a major floor effect (Marshall et al., 2011 and Morris, 2012). Therefore, the cross-sectional results were driven by the MCI and AD dementia groups. However, the longitudinal results were significant across all diagnostic groups indicating that the FAQ is sensitive to the development of functional decline over time even in CN subjects.

One drawback to the data-driven regression models used in these analyses is the instances of multicollinearity in which counter-intuitive findings may falsely indicate the direction of an association (positive vs. negative). Instances of multicollinearity were

observed cross-sectionally for the main effect of frontal pole FDG hypometabolism with baseline FAQ and longitudinally with orbitofrontal FDG hypometabolism and FAQ decline in this study. In each case, the univariate unadjusted relationship was the reverse of the expected FDG ROI metabolism direction and may have been due to positive inter-correlations between FDG ROI. However, since significance tests run on the study results encompass numerous image pixels and mean SUV of the ROI and maximum pixel SUV are determined when generating FDG ROI, positive inter-correlations are expected and results are inherently conservative (Shankar et al., 2006; Locascio et al., 1997). In their study of time series analysis using functional magnetic resonance brain imaging, Locascio et al. determined possible sources of positive correlation as attributable to physiologically based associations, close spatial proximity of pixels, image smoothing, or image resolution that is finer than areas of (non-task-related) activation (Locascio et al., 1997).

In conclusion, posterior cingulate, parahippocampal, orbitofrontal and middle frontal FDG hypometabolism are associated with IADL impairment in mild AD dementia cross-sectionally, while baseline posterior cingulate and middle frontal FDG hypometabolism predict worsening IADL impairment over time across the AD spectrum. These results demonstrate the association between patterns of regional FDG hypometabolism and complex daily functioning decline in early AD, and subsequently reinforce the importance of measuring IADL impairment throughout the course of AD progression.

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