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Daily Functioning and Prefrontal Brain Morphology in Healthy and Depressed Community-Dwelling Elderly

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Abstract

Objective—Self-perceived emotional vitality, intact mood, physical activity and social engagement are recognized as important indicators for lowered rates of morbidity and increased longevity in late-life, but little is known about their underlying neural substrates. This study examined relationships between self-reported levels of general functioning and the combined volume of three integrated prefrontal structures associated with self-perception and emotion.

Design—Cross-sectional

Setting—UCLA Semel Institute for Neuroscience, Los Angeles, CA

Participants—Depressed (N=43) and comparison (N=41) elderly subjects.

Measurements—Magnetic resonance images of orbitofrontal, gyrus rectus and anterior cingulate gray and white matter volumes were corrected for intracranial volume and combined across structures to form white matter and gray matter scales. Subjects completed the RAND Short-Form 36 Questionnaire, a self-report evaluation of daily functioning. Subscales used for analysis were Physical Function, Energy, and General Health, which were not correlated with depression.

Results—White matter volumes were associated with self-perceptions of Energy for healthy as well as depressed individuals, and gray matter volume was associated with General Health. This latter association was strongest among patients with late-onset of depression, i.e., onset > age 50, although it appeared in all diagnostic groups.

Conclusions—Although mild to moderate atrophy is expected in late-life, prefrontal atrophy may represent changes to neuroanatomical substrates that qualitatively modulate self-perceptions of energy and general health for both depressed and non-depressed persons.

Keywords

limbic; prefrontal; health attitude; elderly; MRI; daily functioning; geriatric; atrophy; orbitofrontal; anterior cingulate; gyrus rectus

Increasing the percentage of people who age successfully and require minimal health services would foster independence, activity and productivity among today's elderly as well as reduce health care utilization. Successful aging is no longer defined as freedom from physical or cognitive decline but now includes psychosocial functioning, freedom from depression, moderate levels of physical activity and self-perceived wellness, which may include some or minimal disability or chronic illness. (See review by Depp & Jeste.¹) Individuals who meet these modified criteria would be expected to have lower medical utilization rates than those who do not meet criteria.²

Another aspect of successful aging is a positive perception of one's general health. The reliability of self-perceptions of health and functioning for estimating future morbidity and mortality was demonstrated over 20 years ago in the Manitoba Longitudinal Study. Self-ratings of health by elderly Canadians predicted seven-year survival better than medical records or self-reported medical conditions.³ In 1997, a review of 27 longitudinal studies demonstrated that respondents' self-ratings of global health independently predicted mortality.⁴ The follow-up occurred between 2 and 28 years after baseline and included other known mortality risks, such as number of chronic conditions, functional disability, medications, hospitalizations, and cardiovascular symptoms. Most of the medical information was self-reported, although a few studies included physician examinations and ratings. In studies that used medical evaluations, self-reported global assessment remained an independent predictor of morbidity after controlling for physician assessment. The predictive value of self-perceived wellness is equally important among institutionalized people.⁵

Among those 75 and older, about 30 percent suffer depressive symptoms, and the rates are higher in rural areas than urban areas.^{6,7} Depressive symptoms work against successful aging by reducing daily functioning more than chronic pain,⁸ decreasing performance on basic activities of daily living^{9,10} and on independent activities of living (e.g., shopping, meal-preparation, yard-work, paying bills),¹¹ and reducing the likelihood of recovering independent functioning after stroke.¹² Depression is a risk factor for deterioration in multiple serious medical conditions (e.g., cancer, Parkinson's disease, cerebrovascular disease, diabetes, and Alzheimer's disease¹³⁻¹⁵) and death within 3 to 10 years.^{16,17}

The orbitofrontal cortex is associated with both depression and self-perception. Functional magnetic resonance imaging has shown that the medial orbitofrontal region is activated in tasks requiring direct appraisal of self-beliefs,¹⁸ reflection about one's own personality,¹⁹ and adoption of a first-person perspective.²⁰ Anterior and posterior cingulate were noted in some studies as additional areas of activation with self-focused tasks.²¹⁻²³ The orbitofrontal is also associated with emotional processing via bidirectional connections with the amygdaloid complex. The densest connections are to the posterior medial orbitofrontal,²⁴ which forms part of a "limbic lobe" that also connects with memory-related anterior temporal structures.^{25,26} The anterior orbitofrontal, on the other hand, is part of another neural circuit that has rich cortico-cortical connections with multisensory areas in the ventrolateral prefrontal cortex.²⁷ Depressed elderly patients have reduced cortical thickness in the orbitofrontal, anterior cingulate and gyrus rectus regions compared to a comparison group, and the difference is greatest among late-onset patients.^{28,29} The confluence of emotional, sensory and self-reflective processing in this prefrontal region make it an area of interest for understanding self-perceptions of well-being and feelings of vitality during the aging process for healthy and depressed elderly people.

This study investigated the relationship between volumes of the combined orbitofrontal, anterior cingulate and gyrus rectus regions – referred to here as the prefrontal region – and subjective feelings of general health and daily functioning. Although the anterior cingulate is

not normally considered a structural part of the orbitofrontal cortex, it has robust connections with the orbitofrontal cortex particularly via the gyrus rectus. The gyrus rectus can be conceptualized as an extension of the cingulate tissue into the orbitofrontal³⁰ because it shares cytoarchitecture with the anterior cingulate. We hypothesized that self-reported indices of daily functioning would be associated with white and gray matter volumes of the prefrontal region for healthy subjects as well as depressed subjects, although depression diagnosis was expected to add additional explanation to self-perceived functioning. We were also interested in examining whether the age of onset of depressive symptoms, i.e., early- *versus* late-onset, modulated the self-perceived functional status.

Methods

Subjects

Elderly community-dwelling residents (43 depressed and 41 comparison) were recruited for a larger NIMH-funded study of late-life depression. Exclusionary criterion for dementia was based on Mini-Mental State Examination (MMSE)³¹ score ≥ 24 and assessment by a geriatric psychiatrist. Other exclusionary criteria were determined by self-report: chronic neurological or endocrine disease; head trauma or lifetime loss of consciousness of any duration; unstable medical illness requiring recent hospitalization; contraindications for neuroimaging; transient ischemic attack, stroke or myocardial infarction; history or evidence of psychotic symptoms; concurrent psychiatric disorder or Axis I disorder other than depression; recent change in medication.

Patients were diagnosed per DSM-IV criteria for major depression. All patients were free of antidepressants, antipsychotics and anxiolytic agents for a minimum of two weeks before the study, but none were removed from medication for this study. Patients remained on standard treatment regimens for stable comorbid medical disorders. After a complete description of the study to the subjects, written and informed consent was obtained. The study was approved by the Institutional Review Board of UCLA Medical Center.

Procedures

Volunteers were screened by research assistants who administered the MMSE, Structured Clinical Interview for Diagnosis of Axis I Disorders (SCID), Hamilton Rating Scale for Depression (HAM-D)³² and RAND 36-Item Health Survey (SF-36).³³ Subjects met with a licensed geriatric psychiatrist for clinical review of Axis I disorders and completed a Cerebrovascular Risk Factor Assessment (CVRF)³⁴ and Cumulative Illness Rating Scale (CIRS),³⁵ a commonly used measure for geriatric patients that quantifies comorbid medical burden on seven major organ systems. Volunteers completed an EKG and standard battery of laboratory tests (complete and differential blood counts; hemocrit, electrolyte and markers of hepatic, renal and thyroid markers). Depressed patients scored ≥ 15 on the 17-item HAM-D ($M = 17.65 \pm 2.93$, range 15 to 29). Patients were classified as early- (< 50 years of age at onset) ($N=25$) or late-onset (≥ 50 years of age at onset) ($N=18$) per self-report.

MRI Methods

The MRI methods were first reported by Ballmaier and colleagues and are briefly reviewed here.²⁸ Subjects were imaged with a 1.5-T Signa MRI scanner (GE Medical Systems, Milwaukee) that used a coronal T₁-weighted three dimensional (3D) spoiled gradient/recall acquisition (SPGR) in the steady state with the following parameters: repetition time (TR)=20 msec; echo time (TE)=6 msec; flip angle=45°; 1.4-mm slice thickness without gaps; field of view (FOV)=22 cm; number of excitations (NEX)=1.5; matrix size=256x256 mm; in-plane resolution=0.859375x0.859375.

Image Analysis

Images were initially masked to remove nonbrain tissue and cerebellum. Brain volumes were corrected for signal intensity inhomogeneities, aligned, and placed into stereotaxic coordinates without scaling to correct for head position. Fully automated tissue segmentation was then applied to the brain volumes, where voxels were classified as gray or white matter or cerebrospinal fluid. A high-resolution shape representation of the cortex was extracted for each subject with automated software.³⁶ These surface/shape extractions were used to aid in delineation of the prefrontal region. See Figure 1. Total intracranial volume was calculated on the intracranial space within – but not including – the meninges down to the last horizontal slice showing the first cerebellar tissue, which occurred at approximately the first spinal disc.

Anatomical Boundaries

Details of the written anatomical protocols can be found on the World Wide Web at <http://www.loni.ucla.edu/NCRR/protocols.aspx>. All anatomical delineations were reconciled using each individual's three-dimensional surface model and three planes to corroborate sulcal and subregion identity. Delineations were also verified by using two neuroanatomical atlases. Intraclass correlation coefficients for reliability of gray matter, white matter, and CSF volumes, as well as total volumes in all subregions ranged between 0.84 and 0.92 (n=10).

Functional Tests

Function was assessed with the SF-36 developed by RAND Corporation,³³ a self-report health survey with 36 questions yielding a profile of functional health and well-being across eight subscales. Three subscales were of interest: Physical Functioning, Energy, and General Health. The Physical Function scale asks about self-perceived limitations for participating in vigorous activities such as running or participating in strenuous sports, or moderate activities such as pushing a vacuum cleaner, bowling, playing golf or climbing several flights of stairs. The Energy subscale queries how often in the past 4 weeks “Did you feel full of pep/energy/ or feel worn out/ tired.” The General Health subscale assesses how true or false counterbalanced statements are for the participant: “I seem to get sick a little easier than other people - I am as healthy as anybody I know, I expect my health to get worse - my health is excellent” and a general personal rating of health at the time of the assessment. The Emotional Well-Being subscale queries feelings of mood and anxiety and has shown good sensitivity and specificity for the identification of depression in a community-dwelling sample of elderly and was expected to overlap with HAM-D scores. Two other scales, Social Functioning and Bodily Pain, would be examined for independence from HAM-D.

Statistical Analyses

Sample demographic characteristics were examined with ANOVAs and χ^2 tests. For variables with significant ANOVA results, follow-up t-tests contrasted each patient group to the comparison group. Anatomical and functioning indices were tested with ANCOVAs using age and sex as covariates, and follow-up t-tests again contrasted patient groups to the comparison group. Three subscales had significant intercorrelations with the HAM-D scale for depressed patients and were dropped from further analysis (Emotional Well-Being ($r = -.31$, $df=43$, $p = .04$), Social Functioning $r = -.40$, $df=43$, $p < .01$), and Bodily Pain ($r = -.36$, $df=43$, $p = .02$)). Remaining subscales (Physical Function, Energy, Physical Health) were expected to show bimodal distribution given the different levels of functioning in the comparison and depressed groups. Examination of the scatterplots showed appropriate distribution for bimodal analysis. We constructed dichotomous (high and low) functioning variables based on cutoff points at which 95% of the comparison group functioned above and 5% functioned below the selected point for each subscale. The resulting cutoff points

were 65 for Physical Functioning, 41 for Energy levels, and 65 for General Health on 0–100 point scales.

White and gray matter volumes were transformed into ratios based on intracranial volume. This transformation adjusts for head size and is a rough marker of the degree of atrophy based on the reduction in brain tissue compared to original cranial volume. Gray and white matter ratios of the three structures were averaged to form two aggregated scales. Three hierarchical logistic regression analyses predicting function were computed in which age, education and diagnosis were entered on the first step along with contrast terms for late-onset depression to the comparison group and to early-onset depression. Second, the number of reported systems on the CIRS evaluation was entered to determine the explanatory power of physician rated medical comorbidity. Gray and white matter volume ratios were entered third to determine if volumes explained any additional variance after the demographic and medical variables. Last, interaction terms for time of onset (early *versus* late) by white and gray matter volumes were entered to determine if there were morphometrically significant differences across onset groups.

RESULTS

There were no significant differences in between depressed patients and comparison subjects on handedness, ethnicity, education, or CVRF (Table 1). Patient subgroups did not differ on severity of depression per the HAM-D. There were differences across the three groups on age, MMSE, sex, and CIRS, gray matter volume and functioning on the three SF-36 subscales. Early-onset patients were younger than the comparison group, and late-onset patients scored lower on the MMSE and reported more categories of symptoms on the CIRS. Both early- and late-onset patients differed from the comparison group on gray matter volumes and level of functioning on the RAND Short Form scales.

When the two patient subgroups were contrasted for differences using follow-on t-tests, the only differences appeared in age [$t(df\ 1,41) = -5.55, p = .02$] and gray matter [$t(df\ 1,41) = -.01, p < .01$].

Age and CIRS were used as covariates in the logistic regression analyses, as was education, which was decided a priori to contribute to functional status based on current literature.^{37–39} Correlations indicated that education was correlated with Energy for the comparison group ($r = -.351, df = 41, p = .03$) and with General Health for depressed patients ($r = -.32, df = 43, p < .05$). MMSE did not correlate with any scale.

Bivariate Logistic Regression Models

In the first analysis, Physical Function was predicted well by age and diagnosis. See Table 2. Self-perceived Physical Function scores among late-onset depressed were significantly lower than comparison individuals ($\chi^2[df\ 1] = 4.1, p = .04$) but not early-onset depressed patients ($\chi^2[df\ 1] = 2.1, p = .15$). The addition of CIRS categories did not add significantly to the explanatory power of the model ($\chi^2[df\ 1] = 2.84, p = .09$). Adding gray and white matter volumes and their interactions did not improve the model ($\chi^2[df\ 2] = .25, p = .88$, and $\chi^2[df\ 4] = 6.14, p = .19$, respectively). In the final analysis, variance was spread over all predictors and nothing emerged as independently significant.

The second bivariate regression for reported levels of Energy showed a good fit of the model to the data when age, education and diagnosis were entered (Table 3) although only diagnosis was an independent predictor. One interaction emerged in which late-onset depressed patients had lower scores than comparison individuals ($\chi^2[df\ 1] = 19.00, p < .01$) but not early-onset depressed patients ($\chi^2[df\ 1] = 2.94, p = .09$). In the second step when

CIRS entered the equation, neither age, education nor CIRS was independently associated with Energy levels. In the 3rd step the addition of brain volumes significantly increased the explanatory power of the model (χ^2 [df 2] = 7.90, $p=.02$) although only white matter volume was significantly associated with Energy scores (χ^2 [df 1] = 5.26, $p=.02$). There were no significant interactions. In the final equation, the combination of variables did an excellent job of explaining the variance in Energy levels, (χ^2 [df 4,11] = 73.31, $p<.01$), but only white matter volume independently predicted reported Energy level ($p=.01$).

As with the first analyses, the initial independent variables of age, education and diagnosis produced a significant fit for perceptions of General Health (Table 4). Both diagnosis (χ^2 [df 2] = 18.47, $p<.01$) and education (χ^2 [df 1] = 6.13, $p=.01$) were independently related to General Health. There was also an interaction in which late-onset depressed patients had lower scores than the comparison group (χ^2 [df 1] = 14.62, $p<.01$) but not early-onset depressed patients (χ^2 [df 1] = 2.52, $p<.11$). The addition of white and gray matter volumes did not improve the explanatory power (χ^2 [df 2] = 4.64, $p=.10$), but the addition of interaction terms clarified the model. In the final step, white matter ratios trended toward significance (χ^2 [df 1] = 3.21, $p=.07$) and gray matter ratios were significant (χ^2 [df 1] = 4.22, $p=.04$) indicating an effect across diagnostic groups of brain volumes on perceptions of well-being. Follow-up analysis showed the association between prefrontal gray matter and General Health is stronger among late-onset depressed patients ($t= 3.77$, $p<.01$) than comparison group ($t= -1.46$, $p=.16$) or early-onset depressed patients ($t= -1.39$, $p=.19$).

Post-hoc Analyses

To clarify whether the associations between brain volumes and daily activity were unique to the limbic-associated structures in the prefrontal region or whether they extended to other regions of the frontal brain, associations between lateral prefrontal cortex and functioning were examined. The Bonferroni level of significance was set at $\alpha=.015$. Gray and white matter volumes of the inferior, middle and superior frontal gyri were averaged and submitted to the same bivariate analyses used previously for predicting functional scales. (See Figure 2). Age and diagnosis alone were good fits for data from the three subscales (χ^2 [df 4] = 14.1, $p<.01$ for Physical Function; χ^2 [df 4] = 55.9, $p<.01$ for Energy; and χ^2 [df 4] = 40.8, $p<.01$ for General Health). CIRS symptomatology, gray matter, white matter and all interactions were nonsignificant.

DISCUSSION

The first hypothesis was partially supported. Smaller volumes of white matter were associated with lower self-perceived Energy for depressed and non-depressed subjects. Smaller gray matter volumes were associated with lower self-perceived General Health for both diagnostic groups, and smaller white matter volumes trended toward significance for General Health. The association between gray matter volumes and General Health was particularly prominent for late-onset depressed patients, as anticipated. Contrary to expectations, Physical Function did not correlate with brain volumes although it trended toward a correlation with medical status.

Loss of energy is a common symptom of clinically-relevant depression⁴⁰ and/or developing frailty.^{41,42} However, in this study, reduced volumes were related to decreased energy and/or increased fatigue for depressed and non-depressed participants. In the final regression equation, age, education, depression diagnosis, depression onset age and co-morbidity were all non-significant while white matter volume remained a significant predictor of self-perceived Energy. For otherwise healthy individuals, this finding suggests that early brain atrophic changes that are perceptible to the individual but are not yet linked to a clinical syndrome.

Self-reported perceptions of General Health showed multiple independent predictors, which is consistent with a multi-dimensional evaluation of general function. Education, depression diagnosis and gray matter volume, plus a trend from white matter volume, predicted perceived health. Of interest is the absence of age and concurrent morbidity as predictors of general health. This is consistent with Depp and Jeste's (2006)¹⁰ review of successful aging studies in which elderly people considered absence of disability more significant to their lives than the presence of medical problems. In a series of focus group discussions, a majority felt a positive attitude, feeling of stability and security, health and wellness, and a source of engagement or continuing stimulation were more important than physical health.⁴³ The group members expressed a view concurrent with a recent American Geriatrics Society/ National Institute on Aging Conference on Frailty in Older Adults that defined frailty in medical terms as a spectrum of resilience that varies from highly independent to most frail.⁴⁴ The concept is intrinsically independent from physiological disease, although they often develop concurrently,⁴⁵ i.e., one can be highly robust yet have some physical disability or chronic condition.

If patients mention changes in their daily routines, they are likely to report them in vague terms, or not report them at all because they perceive them as normal for their age group or as appropriate for an accumulation of minor conditions. However, the process of aging affects the immune system by increasing circulating pro-inflammatory cytokines, so when aging is combined with additional environmental stress, it takes a greater toll on an elderly adult than a young adult.^{46,47} Elderly people also find it more difficult to return to homeostasis. Even viral infections can result in elevated pro-inflammatory cytokine mRNA expression in the central nervous system similar to more serious physical or psychological stressors.^{48,49}

A pronounced increase in circulating pro-inflammatory cytokines (interleukin 1, interleukin 6, tumor necrosis factor α) is associated with a nonspecific sickness syndrome that manifests with loss of appetite, withdrawal from normal social activities, anorexia, fatigue, increased pain, sleep disturbances and/or confusion.⁵⁰ Current results suggest that some mechanism, possibly early pro-inflammatory cytokines, is associated with even minor volumetric changes and is perceived by elders as a decline in general health. Researchers have found preliminary evidence establishing a link between prolonged immune activation and the onset of depression⁵¹ and/or frailty.⁵² Elderly often deal with several major stressors that involve negative emotions such as care-giving, bereavement, relocating and loss of familiar neighborhoods, major medical events or problems with grown children that could precipitate slight increases in circulating pro-inflammatory cytokines. There are also indications that prenatal or early life stress may increase the likelihood of maladaptive immune responses to stress in late life.⁵³

Another possible explanation is cerebrovascular disease, which is associated with increased hyperintense lesions on magnetic resonance imaging.⁵⁴ Declines in daily functioning would not be tied directly to the presence of white matter hyperintensities, but rather indirectly through onset of depression and/or cognitive deficits.^{55,56} However, there were no differences across diagnostic groups in cardiovascular risk. Consequently, there is no obvious reason in terms of cerebrovascular disease why the late-onset depressed patients would perceive a stronger relationship between prefrontal brain volume and general health or energy levels than the other groups unless the late-onset group suffered significantly more hyperintensities without indication of this in their cardiovascular risk evaluation. If the diagnostic groups were equal in the amount of lesioned tissue, the amount of disruption caused by the hyperintense lesions would be the same for depressed patients and comparison individuals.⁵⁷ Cerebrovascular disease would also affect the brain globally. This study showed that the OFC-anterior cingulate-gyrus rectus, but not non-limbic regions

such as superior, middle and inferior frontal gyri, were associated with self-perceived energy and health, although both areas may be experiencing cerebrovascular changes.

Longitudinal research is needed that examines early stages of both sickness and frailty syndromes and accompanying biophysiologic and anatomic markers so that timely interventions can be suggested to patients before declines in functioning become clinically apparent.⁵⁸ Causality cannot be determined in this study, so the possibility must be considered that the brain differences reflect initial endowment in prefrontal volume. If brain volumes indicate hypodevelopment of prefrontal regions, they may potentiate exaggerated stress responses and decreased perceptions of health and well-being.

CONCLUSION

Linear associations exist between brain volumes and self-perceptions of energy and feelings of general health beyond that accounted for by depressive symptoms alone. White matter volumes were related to self-reported energy levels across all subjects, depressed and healthy. Both gray and white matter volumes contributed substantially to self-reports of overall general health for all subjects, although patients with late-onset depression have the strongest association. Consequently, the decreased functioning reported by depressed patients may be partially attributable to reduced volumes in prefrontal limbic-related structures rather than sequela to depressed mood. Relatively simple and straight-forward questions regarding patients' perceptions of their health and energy level may provide insight into the patient's overall functioning and open the discussion for more specific changes in elders' lives.

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Figure 1.

Frontal Areas Delimited as OFC, Anterior Cingulate and Gyrus Rectus.

OFC = orbitofrontal, AC = anterior cingulate, GR = gyrus rectus

Note. The ventral curve of the anterior cingulate (colored pink and blue-green) can be seen next to the gyrus rectus in the first and last drawings.

TABLE 1

Demographic and Clinical Data of Participants with and without Depression

	Comparison Subjects N=41	Early-Onset Depression N= 18	Late-Onset Depression N= 25	Value	df	Analyses p
Age	72.20 (± 7.27)	67.44 (± 5.87) *	73.00 (± 8.22)	F=3.48	2,81	.04
Mini Mental State Examination	29.51 (± 0.81)	28.88 (± 1.45)	28.60 (± 1.50) *	F=4.92	2,80	.01
Sex (Female/Male)	20/21	15/3	18/7	$\chi^2=7.63$	2	.02
Handedness (Right, %)	38 (93%)	16 (89%)	23 (92%)	$\chi^2= 2.44$	6	.88
Ethnicity (% White)	32 (78%)	16 (88%)	18 (72%)	$\chi^2=7.08$	8	.53
Education	15.49 (± 2.64)	15.00 (± 2.50)	14.56 (± 2.63)	F=1.34	2,81	.27
CIRS	2.83 (± 2.28)	4.33 (± 2.25)	5.00 (± 3.25) *	F=5.01	2,80	.01
Age of Onset	--	26.78 (± 12.93)	66.54 (± 10.77)	--	--	--
Hamilton Depression	--	17.78 (± 2.78)	18.12 (± 3.61)	t= -0.28	41	.78
CVRF	5.19 (± 4.78)	4.76 (± 2.99)	6.13 (± 4.47)	F=0.56	2,75	.58
Total Intracranial Volume (cc)	1311.71 (± 152.96)	1285.32 (± 146.93)	1294.07 (± 125.99)	F=0.34	2,81	.71
White Matter Volume (cc) / ICV	.00456 ($\pm .00060$)	.00448 ($\pm .00049$)	.00428 ($\pm .00093$)	F= 1.21	2,75	.30
Gray Matter volume (cc) / ICV	.01048 ($\pm .00102$)	.00936 ($\pm .00106$) **	.01005 ($\pm .00120$) **	F= 6.40	2,75	<.01
SF Physical Functioning	92.20 (± 11.94)	72.35 (± 14.30) **	67.60 (± 29.23) **	F= 14.53	2,80	<.01
SF Energy/Fatigue	76.10 (± 19.25)	22.10 (± 15.92) **	29.60 (± 18.25) **	F= 84.27	2,80	<.01
SF General Health	87.56 (± 9.75)	55.00 (± 19.70) **	60.45 (± 19.97) **	F= 37.05	2,80	<.01

Note. CIRS = Cumulative Illness Rating Scale, Geriatrics. CVRF = Cardiovascular Risk Factor adjusted for age. SF = Short Form. ICV = Intracranial Volume. Variables with significant ANOVA differences were followed with t-tests contrasting each patient group to the comparison group

* p<.05

** p<.01.

ANCOVA analyses for anatomical measures controlled for age and sex, and corrected for total intracranial volume by dividing the absolute volumes (cc) by intracranial volume (cc). RAND Short-Form functioning analyses used the continuous raw scores and controlled for age and sex.

TABLE 2

Logistic Regression Model of Clinical, Demographic and Anatomical Factors that Contribute to Patients' Perceptions of Physical Function.

Model Fit	Hierarchical Regression Models							
	1 st STEP OF MODEL		2 nd STEP OF MODEL		3 rd STEP OF MODEL		4 th STEP OF MODEL	
	B	p	B	p	B	p	B	p
VARIABLES								
Age	-.11	.03	-.07	.23	-.08	.22	-.08	.25
Education	-.07	.61	-.08	.57	-.09	.55	-.12	.46
Diagnostic Groups		.01		.06		.08		.78
Late-onset vs Comparison	1.84	.04	1.43	.13	1.42	.14	8.16	.53
Late-onset vs Early-onset	-1.19	.15	-1.09	.21	-1.34	.20	4.44	.62
CIRS categories			-.33	.11	-.33	.11	-.40	.09
White matter (cc) /ICV					183.29	.73	342.15	.62
Gray matter (cc) /ICV					-170.08	.67	80.21	.88
[†] White Matter Interactions								.31
[†] Gray Matter Interactions								.14

[†]Groups' differences were not reported for nonsignificant interactions.

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TABLE 4

Logistic Regression Model of Clinical, Demographic and Anatomical Factors that Contribute to Patients' Perceptions of General Health.

Model Fit	Hierarchical Regression Model											
	1 st STEP OF MODEL $\chi^2(df\ 4) = 40.82, p = .00$			2 nd STEP OF MODEL $\chi^2(df\ 5) = 40.84, p = .00$			3 rd STEP OF MODEL $\chi^2(df\ 7) = 45.48, p = .00$			4 th STEP OF MODEL $\chi^2(df\ 11) = 59.94, p = .00$		
VARIABLES	B	p		B	p		B	p		B	p	
Age	-.08	.13		-.07	.19		-.055	.39		-.10	.24	
Education	-.42	.01		-.42	.01		-.441	.02		-.74	.01	
Diagnostic Groups		<.01			<.01			<.01			.03	
Late-onset vs Comparison	3.87	<.01		3.85	<.01		3.84	<.01		54.32	<.01	
Late-onset vs Early-onset	-1.35	.11		-1.35	.11		-1.31	.20		30.79	.05	
CIRS categories				-.024	.91		-.048	.83		-.104	.69	
White matter (cc) /ICV							845.99	.11		1837.10	.07	
Gray matter (cc) /ICV							287.31	.39		2435.56	.04	
White Matter Interactions											.40	
Late-onset vs. Comparison										-2657.41	.18	
White matter: Late-onset vs Early-onset										-150.84	.93	

Model Fit	Hierarchical Regression Model					
	1 st STEP OF MODEL $\chi^2(df\ 4) = 40.82, p = .00$		2 nd STEP OF MODEL $\chi^2(df\ 4) = 40.82, p = .00$		3 rd STEP OF MODEL $\chi^2(df\ 4) = 40.82, p = .00$	
Gray Matter Interactions						
Late-onset vs Comparison						.05
Late-onset vs Early-onset						.02