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Vascular Risk and FDDNP-PET Influence Cognitive Performance

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Abstract

The relationship of cerebrovascular risk and Alzheimer's disease (AD) pathology to cognition in pre-dementia has been extensively investigated and is well-established. Cerebrovascular risk can be measured using a Framingham Stroke Risk Profile (FSRP) score, while positron emission tomography (PET) scans with 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) measure AD neuropathology (i.e., amyloid- β plaques and tau tangles). Here we report results of 75 healthy non-demented subjects (mean age, 63 years) who underwent neuropsychological testing, physical assessments, and FDDNP-PET scans. Controlling for AD family history, education, and APOE4 status in a general linear model, higher FSRP risk and global FDDNP-PET binding were each associated with poorer cognitive functioning. The interaction of FSRP and global FDDNP-PET binding was not significant in the model, indicating that stroke risk and plaque and tangle burden each contributed to worse cognitive performance. Within our healthy volunteers, age, blood pressure, and antihypertensive medication use were vascular risks that contributed significantly to the above findings. These findings suggest that even mild cerebrovascular risk may influence the extent of cognitive dysfunction in pre-dementia, along with amyloid- β and tau burden.

Keywords

Aging; Alzheimer's disease; amyloid- μ plaques; FDDNP; Framingham stroke risk profile; mild cognitive impairment; older adults; positron emission tomography; tau tangles

INTRODUCTION

Age is the greatest single risk factor for memory decline. Nearly half of adults age 65 and older report trouble with memory [1], while an estimated 10 to 20% meet diagnostic criteria for mild cognitive impairment (MCI) [2, 3], a risk-state for developing Alzheimer's disease (AD). Recent demographic data indicate a general aging of the U.S. population, and the number of individuals diagnosed with AD is expected to rise from 5.4 million in 2012 to over 10 million within the next several decades [4]. Prior studies have found that, in a majority of cases, vascular disease contributes to the severity of age-related memory loss and dementia [5, 6]. Autopsy studies have directly shown that cerebral infarctions contribute to the probability of developing dementia, along with the risk conferred by AD pathology [7].

In living subjects, several strategies can be used to measure the impact of vascular health on cognition. Surrogate markers of vascular risk, such as diabetes, smoking status, systolic blood pressure, and midlife total cholesterol level have demonstrated a modest relationship to cognition and/or elevated risk of developing dementia [8–13]. Structural magnetic resonance imaging (MRI) studies measuring white matter hyperintensities and lacunar strokes have likewise found associations between vascular disease burden and cognitive function [14, 15], and midlife vascular risk exposure appears to accelerate brain aging and cognitive decline [16]. A prior functional MRI study found that blood pressure and body mass index, but not total cholesterol, correlate with level of brain activity in older adults [17].

The Framingham Stroke Risk Profile (FSRP) is a validated index of overall cerebrovascular disease (CVD) that includes several risk factors (e.g., age, systolic blood pressure, diabetes, smoking status) as predictors of 10-year stroke risk [18, 19]. FSRP has previously been shown to correlate with cognitive performance [20, 21] and predict future cognitive decline [22, 23].

Recently developed positron emission tomography (PET) ligands allow *in vivo* measurement of AD pathology in the brain. The amyloid- β (A β) PET ligand Pittsburgh compound B (PIB) [24] has been shown at times to correlate with aspects of memory function [25–28] and predict cognitive decline [29], while other studies show elevated PIB signals in cognitively normal older adults [30]. By contrast, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl} ethylidene)malononitrile (FDDNP) [31] provides a measure of both A β plaques and tau neurofibrillary tangle binding levels. FDDNP-PET has previously been shown to correlate with cognitive function in older adults [32, 33] and to predict cognitive decline [34].

Two recent studies have examined the relationship between vascular disease and PIB-PET. A PIB study in cognitively normal older adults used MRI to define the presence or absence of CVD by measuring white matter hyperintensity burden and/or presence of infarctions. The investigators found that CVD but not PIB-PET binding was correlated with lower scores on tests of executive function [35]. A second study combining PIB-PET with Framingham Coronary Risk Profile (FCRP), a proxy for vascular risk similar to FSRP, found that, when several coronary risk factors were examined together, higher coronary risk was associated with higher cerebral A β levels [36].

To our knowledge, no previous study has examined cognitive function in relation to *in vivo* A β and tau levels and degree of vascular risk in pre-dementia states. To address this knowledge gap, we determined whether *in vivo* plaque and tangle accumulation, as measured by FDDNP-PET binding levels, and cerebrovascular risk, as estimated by FSRP

scores, were associated with cognitive performance in healthy non-demented volunteers. We hypothesized that, controlling for previously reported AD risk factors such as presence of the apolipoprotein E4 (APOE4) allele, dementia family history, and lower educational achievement, increased regional cerebral FDDNP-PET binding and cerebrovascular risk would be associated with poorer cognitive performance.

MATERIALS AND METHODS

Subjects

A total of 75 non-demented subjects who had complete neuropsychological testing, physical assessments to allow calculation of FSRP scores, and FDDNP-PET scans were drawn from a larger, longitudinal study of predictors of cognitive decline [32, 37, 38]. Briefly, volunteers from the community were recruited through advertisements of a study of mild memory impairment, media coverage of the study, and referrals by physicians and families. Members of the research staff screened potential volunteers via telephone interviews. Subjects received neurological and psychiatric evaluations, 3-dimensional MRI or computed tomography (CT), and routine screening laboratory tests to rule out other causes of cognitive impairment (e.g., tumor or stroke) or potential cognitive confounding factors (e.g., severe sensory deficits or medication interactions). CT scans instead of MRI were performed on four subjects because they could not tolerate MRI (e.g., owing to claustrophobia, metal in body). Subjects with evidence of strokes on the MRI or CT scan were also excluded from the study. All subjects were proficient in the English language and underwent comprehensive clinical and cognitive assessment to characterize cognitive status at the time of baseline assessment. All clinical assessments were performed blinded to the results of FDDNP-PET scans. Written informed consent was obtained in accordance with the University of California, Los Angeles Human Subjects Protection Committee procedures. Cumulative radiation dosimetry for all scans was below the mandated maximum annual dose and in compliance with state and federal regulations.

A total of 754 volunteers were assessed for eligibility, of which 575 were excluded for various reasons (illness [$n = 262$], loss of interest [$n = 212$], cognitively-altering medications [$n = 40$], MRI intolerance [$n = 37$], and other reasons, e.g., non-English speaking, too young [$n = 24$]). Of the 179 eligible volunteers, five refused to participate, and the remaining 174 consented. Of consented subjects, 26 dropped out because of fatigue or loss of interest. A total of 148 subjects completed neuropsychological testing, after which 23 dropped out because of fatigue or loss of interest. The remaining 125 subjects completed FDDNP-PET scans, but 9 were excluded because of head motion during scanning and an additional 16 were excluded because of other diagnoses (e.g., frontotemporal dementia, traumatic head injury, brain tumor). From the remaining 100 subjects, 25 additional subjects were excluded for diagnosis of AD because the current study focused only on non-demented persons, leaving a total of 75 non-demented subjects for the current analysis (38 with MCI and 37 with normal cognition).

Neuropsychological testing

In addition to a Mini-Mental State Examination (MMSE) [39], a neuropsychological test battery was administered to quantify cognitive performance and to confirm the diagnostic category of each study subject (normal aging, MCI, or dementia). We used the following diagnostic criteria for MCI: (1) patient awareness of a memory problem, preferably confirmed by another person who knows the patient; (2) memory impairment detected with standardized assessment tests; and (3) ability to perform normal daily activities [40]. To increase specificity for detecting impairment, we included subjects who scored -1 standard deviation below the mean on at least two tests [41] and the diagnosis was corroborated by

clinical judgment [42]. Subjects were categorized as normal if they had neither objective deficits on neuropsychological test measures after correction for age and education nor functional deficits in daily functioning and did not meet criteria for MCI. The Hamilton Rating Scales for both Depression and Anxiety were administered to assess mood and anxiety, respectively. For the current analysis, subjects meeting criteria for dementia, depression, or anxiety disorders were excluded.

The neuropsychological test battery was administered to assess global cognition and five specific cognitive domains: (1) Memory, including the Wechsler Memory Scale Third Edition (WMS-III) logical memory (delayed score), Buschke selective reminding (total score), and Rey-Osterrieth complex figure recall (3-minute delayed recall score); (2) Language, including the Boston naming test and letter (F.A.S.) and category (Animal naming test) fluency; (3) Attention and information-processing speed, including Trail making task A, Stroop color naming (Kaplan version), and Wechsler Adult Intelligence Scale Third Edition (WAIS-III) digit symbol; (4) Executive functioning, including Trail making task B, and Stroop Interference (Kaplan version); and (5) Visuospatial ability, including WAIS-III block design, and Rey-Osterrieth complex figure copy. The raw test scores were converted to Z scores by standardizing them to a mean of 0 and a standard deviation of 1. A domain Z score was obtained by averaging those Z scores belonging to the cognitive tests in that domain. The domain Z scores were used to examine associations with FSRP scores and FDDNP-PET brain regional binding levels.

Framingham stroke risk profile (FSRP)

The FSRP is a previously validated index of CVD originating from the Framingham Heart Study [18, 19]. FSRP estimates the risk of stroke within 10 years for individuals free of stroke at baseline. The FSRP takes into account the following component risk factors: gender, age, systolic blood pressure, use of antihypertensive medications, diabetes, smoking status, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. During study intake for each subject, gender and age were recorded and right arm blood pressure was measured once by a registered nurse with the subject seated. Medical history was obtained to determine use of antihypertensive medications, cigarette smoking status (categorized as current smoker or not), presence or absence of diabetes (defined as prior diagnosis of diabetes or use of diabetes medications), cardiovascular disease (defined as history of coronary artery disease, myocardial infarction, angina pectoris, congestive heart failure, intermittent claudication, or peripheral vascular disease), and atrial fibrillation. Electrocardiograms were obtained to evaluate for arrhythmias and presence or absence of left ventricular hypertrophy. Each risk factor was assigned the appropriate point value, based on the FSRP scale, and the sum of the point values for each individual was translated into a 10-year stroke risk probability score expressed as a percentage [19].

Neuroimaging

Global plaque and tangle load from an FDDNP-PET scan was the single pathology score used for each subject. Global plaque and tangle load was calculated by averaging the load from five brain regions of interest (ROIs) known to accumulate pathology in AD (medial temporal, lateral temporal, posterior cingulate, parietal, frontal cortices). Pathology load in each cerebral regional was expressed as an average of left and right regions, and global load values were calculated as averages of the values for all these regions.

FDDNP was prepared at very high specific activities (>37 GBq/mol) [43]. All scans were performed with the ECAT HR or EXACT HR+ tomograph (Siemens-CTI, Knoxville, TN) with subjects supine and the imaging plane parallel to the orbitomeatal line. A bolus of FDDNP (320–550 MBq) was injected via an indwelling venous catheter, and consecutive

dynamic PET scans were performed for 2 hours. Scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5mm FWHM) with scatter and measured attenuation correction. The resulting images contained 47 contiguous slices with plane separation of 3.37mm (ECAT HR) or 63 contiguous slices with plane separation of 2.42mm (EXACT HR+). Nonparametric Wilcoxon two-sample tests within MCI and cognitively normal groups separately found no significant differences in regional FDDNP signals between the two PET scanners (p values ranging from 0.18 to 0.84).

FDDNP-PET binding levels were quantified as previously described [37]. Briefly, we performed Logan graphical analysis with cerebellum as the reference region for time points between 30 and 125 minutes [44]. The slope of the linear portion of the Logan plot is the relative distribution volume (DVR), which is equal to the distribution volume of the tracer in an ROI divided by that in the reference region. We generated DVR parametric images and analyzed them using grey matter ROIs drawn manually on the FDDNP-PET image obtained in the first 5 minutes after injection (the perfusion image). This image shows the perfusion pattern and has sufficient anatomical information to identify the cerebellum and cerebellar gray matter. ROIs were drawn bilaterally on the medial temporal (containing limbic regions, including hippocampus, parahippocampal, and entorhinal areas), lateral temporal, posterior cingulate, parietal, frontal, and cerebellar regions, as previously described [45]. Each cerebral regional DVR or binding value was expressed as an average of left and right regions, and global DVR values were calculated as averages of the values for all these regions. Rules for ROI drawing were based on the atlas of Talairach and Tournoux [46], which we used as a visual guide for identifying the important gyral and sulcal landmarks needed in delineating the ROI. The ROI determinations were performed by one individual blind to clinical assessments; previous inter-rater reliability studies have confirmed high consistency and reliability using this method [47].

Among the subjects who underwent MRI, anatomical brain MRI scans were obtained using either a 1.5 T or 3 T magnet (General Electric-Signa, Milwaukee) scanner. Fifty-four transverse planes were collected throughout the brain, superior to the cerebellum, using a double-echo, fast-spin echo series with a 24-cm field of view and 256×256 matrix with 3 mm/0 gap (repetition time = 6000 [3 T] and 2000 [1.5 T]; echo time = 17/85 [3 T] and 30/90 [1.5 T]).

Statistical analysis

Data were screened for outliers and normality assumptions. Subjects were classified as lower cerebrovascular risk if their FSRP scores were 10% or less and as higher risk otherwise (11% or more risk). This stratification strategy was used because of the general good health of our study sample, making it impossible to stratify the current sample into multiple 10% point increments of 10-year stroke risk using FSRP (a method previously shown to significantly predict cognitive function) [20, 21]. A general linear model was used to determine the predictors of cognitive performance. The 5 cognitive domain Z scores were used as the dependent variables; FSRP risk group and global FDDNP-PET binding levels were used as predictors and APOE4 status, family history of AD, and years of education were used as covariates. We also investigated the significance of the interaction term of FSRP group and global FDDNP-PET binding levels, as well as, with each of the covariates separately. *Post hoc t*-tests were used to examine which cognitive domains were affected by these risk factors. In order to determine which of the variables included in the FSRP score were significantly influencing cognition, we also estimated an additional model where we included age, systolic blood pressure and medication for hypertension as predictors.

Similar models were estimated for each of the five ROIs (medial temporal, lateral temporal, frontal, posterior cingulate, and parietal) to ascertain whether plaque and tangle binding in

specific regions contributed to cognitive performance. All tests were 2-tailed, and a significance level of $p = 0.05$ was used for all inferences.

RESULTS

Clinical characteristics and FSRP factors

Clinical characteristics and FSRP factors of the overall sample, higher risk and lower risk groups were compared for significant differences and are shown in Table 1. The higher risk and lower risk groups differed significantly in years of education ($p = 0.04$), AD family history ($p = 0.02$), and MMSE scores ($p = 0.01$). For the FSRP factors, the groups differed significantly in age ($p < 0.0001$); systolic blood pressure ($p < 0.0001$); and use of antihypertensive medications ($p < 0.0001$).

Predictors of cognitive function

Controlling for family history of AD, education, and APOE4 status, higher global FDDNP-PET binding and higher FSRP risk (an index which includes gender, age, systolic blood pressure, use of antihypertensive medications, diabetes, smoking status, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy) were associated with poorer cognitive functioning (Table 2). None of the interaction terms were significant in the model, indicating that stroke risk and FDDNP-PET binding each contributed to worse cognitive performance. The FSRP risk groups differed significantly in their overall cognitive performance (-0.77 (95% confidence interval: $-1.16, -0.38$)). The lower risk group had greater scores in all of the cognitive domains compared to the higher risk group (Fig. 1, Supplementary Data Table 1; available online: <http://www.j-alz.com/issues/34/vol35-1.html#supplementarydata02>): language (0.16 ($-0.08, 0.39$) versus -0.46 ($-0.87, -0.04$)); attention and information-processing speed (0.16 ($-0.09, 0.40$) versus -0.47 ($-0.89, -0.04$)); memory (0.21 ($-0.03, 0.45$) versus -0.62 ($-1.04, -0.21$)); visual-spatial functioning (0.22 ($-0.03, 0.47$) versus -0.64 ($-1.07, -0.22$)); and executive functioning (0.25 ($0.02, 0.48$) versus -0.74 ($-1.13, -0.34$)). Including age, blood pressure, and use of medication for hypertension in the model, we find that age is significantly associated with cognitive function (Table 3).

As expected, global FDDNP-PET binding levels predicted overall cognitive performance ($\beta = -5.31$ (95% CI: $-9.89, -0.56$)). *Post-hoc* tests indicated associations with language (-9.14 ($-15.58, -2.70$); Fig. 2A), attention and information-processing speed (-6.82 ($-13.26, -0.38$); Fig. 2B), and executive functioning (-6.54 ($-12.98, -0.28$); Fig. 2C) domain scores. The association with the memory domain score did not reach significance (-5.62 ($-12.06, 0.82$)) and visual-spatial functioning was not associated with global FDDNP-PET binding levels (0.27 ($-6.18, 6.71$)).

FDDNP-PET binding levels in the lateral temporal (-5.28 ($-10.29, -0.27$)), frontal (-6.57 ($-12.38, -0.76$)), and parietal lobes (-4.04 ($-7.11, -0.97$)) were associated with overall cognitive performance. Lateral temporal lobe FDDNP-PET binding correlated with performance on tasks measuring executive function (-5.44 ($-9.29, -1.59$)) and language (-6.67 ($-10.52, -2.82$)). Frontal FDDNP-PET binding correlated with performance on the language (-4.93 ($-8.98, -0.88$)) and memory (-5.61 ($-9.65, -1.55$)) domain scores. Parietal FDDNP-PET binding was related to the language domain scores (-4.69 ($-8.24, -1.14$)). As with the global FDDNP-PET binding levels, the interaction term of regional FDDNP-PET binding levels and FSRP risk groups was not significant. In the regressions using age, blood pressure, and use of medication for hypertension as predictors, age is consistently a significant predictor of cognitive function, while blood pressure and medication for hypertension are significant in some models (Table 3).

DISCUSSION

To our knowledge, this is the first study to examine cognitive function in relation to vascular risk and an *in vivo* marker of A β plaques and tau tangles. We found that degree of vascular risk, as measured by FSRP score, and FDDNP-PET binding levels each predicted cognitive performance in a sample of healthy non-demented middle-aged and older adults.

Our results, that greater FSRP risk related significantly to worse cognitive performance across the five domains studied, are in line with prior studies independently correlating FSRP with cognitive function [20–22, 48]. Within the Framingham Offspring Study, a similar inverse association between increments in 10-year risk of stroke and diverse domains of cognitive performance level was observed for over 2,000 subjects in tests of visual-spatial memory, attention, organization, scanning, and abstract reasoning [20]. FSRP was also used in the Framingham Offspring Study to demonstrate the association between stroke risk factors, smaller total brain volume, and poorer cognitive function among stroke- and dementia-free subjects [48]. In non-Framingham populations, Brady and colleagues found a more circumscribed impact of stroke risk on verbal fluency within a smaller sample [22], however, study of a larger non-Framingham population found FSRP relating to lowered performance across multiple cognitive domains [21]. Both structural and functional MRI studies have likewise found evidence for elevations in vascular risk leading to evidence of brain atrophy, dysfunction, and cognitive decline [16, 17].

The current observation that FDDNP-PET binding levels significantly correlate with cognitive performance in non-demented subjects confirms and extends prior findings from our group [32–34]. Using FDDNP-PET, we previously reported cognitive performance in a smaller sample of cognitively normal older adults ($n = 10$) and found significant correlation between cognitive performance and FDDNP-PET binding levels in frontal and parietal regions [33]. In the current larger sample of healthy non-demented subjects, which included both cognitively normal and MCI subjects, we confirmed the previously observed associations in frontal and parietal regions, and furthermore, found a significant association in the lateral temporal lobe relating FDDNP-PET binding levels to performance on tasks measuring executive function and language. This additional finding in lateral temporal lobe may relate to larger sample size and/or inclusion of MCI subjects within our analysis.

The current findings largely concur with prior studies using PIB-PET, which have found correlations between cognitive performance and A β deposition [25–28]. Episodic memory deficits have been shown to relate to PIB-PET measured A β deposition via a hippocampal-atrophy mediated mechanism [49], and a recent study examining regional PIB-PET binding found that temporal A β deposition provided independent contributions to episodic memory deficits in a mixed sample of non-demented older adults, which included subjects with both normal cognition and MCI [50]. Our FDDNP-PET study differs from PIB-PET studies in that FDDNP-PET binds to both A β plaques and tau tangles. This may explain both the partial overlap, and observed differences, between our study and prior PIB-PET reports.

Our FSRP and FDDNP-PET results indicate an impact of CVD risk factors on cognitive decline, which is largely consistent with previous studies of vascular disease and AD pathology. Autopsy studies have shown that vascular disease contributes in an additive fashion to the cognitive impairment caused by markers of AD pathology, such as A β plaques and tau neurofibrillary tangles [5–7]. Other prospective clinicopathologic evidence from the Honolulu-Asia Aging Study suggests that elevated cerebrovascular risk, as measured by increased midlife systolic blood pressure, is directly related to later observed brain atrophy, plaques, and tangles at autopsy [51]. Our findings suggest that the effects of elevated vascular risk and occult AD pathology in non-demented subjects become apparent early on

in vascular and neurodegenerative disease progression, even before the manifestation of vascular damage or diagnosis of dementia.

A study of PIB-PET used a different proxy for vascular risk, the FCRP, which focuses on cardiac rather than brain risk. The investigators found that higher coronary risk was associated with higher cerebral A β levels [36]. By contrast, when individual components of FCRP were compared against global PIB-PET binding (e.g., hypertension, hyperlipidemia, diabetes), no significant relationships were found. A study in cognitively normal older adults showed that CVD (measured by MRI) and PIB-PET binding appeared to be independent processes [35]. While the presence of CVD was associated with lower executive functioning but not episodic memory performance, PIB-PET binding did not relate to cognitive performance, and there was no interaction between CVD and PIB-PET binding. These results may differ from the current study in that our group specifically excluded subjects with evidence of significant CVD on MRI as part of study enrollment, and FDDNP-PET measures both A β and tau rather than just A β .

A limitation of the current study is that subjects with evidence of frank CVD (e.g., prior stroke) were excluded from the study. We selected a relatively healthy population to study, which dictated using a validated proxy of stroke risk (FSRP), rather than relying on direct MRI analysis of CVD. Given the small sample size and overall good health of our study sample, we stratified our sample into two groups, lower (<10%) versus higher (>10%) stroke risk. With a larger and more medically ill sample, we would have stratified subjects into 10% increments of stroke risk. In the current study of healthy volunteers, as expected, age was a consistently significant contributing vascular risk factor and systolic blood pressure and use of antihypertensive medications were also associated with cognitive function. This emphasizes the importance of monitoring blood pressure and appropriate use of antihypertensive medication in otherwise healthy older individuals.

FSRP includes age as a contributing variable to aggregate stroke risk. Stratification of our sample into lower versus higher stroke risk resulted in the two groups being significantly different in age, with higher stroke risk subjects forming a significantly older group. Given that multiple aspects of cognitive function decline with age, this age difference may have biased our results in favor of finding a difference in cognitive function between the two groups. By contrast, the lower risk stroke group had a significantly higher proportion of subjects with positive family history of AD, which may account for why this group still had a comparable proportion of MCI subjects despite being significantly younger. It is not surprising that the current lower and higher risk groups did not differ significantly on the MMSE. The MMSE has limited utility for identifying MCI, and is not as sensitive an indicator of mild impairment compared to other screening tools (e.g., the Montreal Cognitive Assessment) or a battery of neuropsychological tests [52].

Subjects in this study were non-demented and had intact global cognitive function regardless of MCI versus normal cognitive status, as evidenced by comparable MMSE scores in both lower and higher stroke risk groups. Cognitive deficits in these normal aging and MCI subjects by definition do not impair function and are determined by neuropsychological evaluation. A limitation of the current study is that inclusion of both subjects diagnosed as normal cognitively and those with MCI results in it being unclear the extent to which the high percentage of persons with MCI is driving the results. However, given the small sample size, it is not possible to perform the analyses with each group separately. Similarly, due to the small sample size in the higher FSRP risk group, the study may have been underpowered to detect interaction effects. Thus, we refrain from drawing such conclusions in this study. Future studies with more subjects are needed to replicate the current findings and extend our preliminary analysis of interaction effects. In addition, future larger studies may include

populations with dementia or evidence of frank CVD on neuroimaging and direct comparison of MRI scans to FDDNP-PET binding levels. Nonetheless, the current findings reinforce the importance of managing stroke risk factors in preventing cognitive decline in individuals even before development of clinically significant dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Cognitive performance in higher and lower stroke risk subjects presented as mean Z values with SEM. The FSRP groups differed significantly in their overall cognitive performance (-0.77 (95% confidence interval: $-1.16, -0.38$)). The lower stroke risk group had significantly greater scores in all of the cognitive domains tested when compared to the higher stroke risk group: language (0.16 ($-0.08, 0.39$) versus -0.46 ($-0.87, -0.04$)); attention and information-processing speed (0.16 ($-0.09, 0.40$) versus -0.47 ($-0.89, -0.04$)); memory (0.21 ($-0.03, 0.45$) versus -0.62 ($-1.04, -0.21$)); visual-spatial functioning (0.22 ($-0.03, 0.47$) versus -0.64 ($-1.07, -0.22$)); and executive functioning (0.25 ($0.02, 0.48$) versus -0.74 ($-1.13, -0.34$)).

Fig. 2.

Global FDDNP-PET binding levels and cognitive performance. Global FDDNP-PET binding levels significantly predicted performance on cognitive tests assessing (A) language performance ($\beta = -9.14$ ($-15.58, -2.70$)), (B) attention and information-processing speed ($\beta = -6.82$ ($-13.26, -0.38$)), and (C) executive functioning ($\beta = -6.54$ ($-12.98, -0.28$)).

Table 1

Clinical characteristics and Framingham Stroke Risk Profile (FSRP) factors

Characteristics*	Overall (n= 75)	Higher risk (n= 19)	Lower risk (n= 56)
Caucasian	67 (89.3%)	18 (94.7%)	49 (87.5%)
Education [#]	16.7 ± 2.8 (12 to 22)	15.6 ± 2.8 (12 to 20)	17.1 ± 2.7 (12 to 22)
AD family history [#]	48 (64.4%)	8 (41.2%)	40 (71.4%)
Presence of APOE4 allele	38 (51.4%)	7 (38.9%)	31 (55.4%)
MMSE [#]	28.8 ± 1.5 (23 to 30)	28.1 ± 1.8 (25 to 30)	29.1 ± 1.4 (23 to 30)
Mild cognitive impairment	38 (50.7%)	10 (52.6%)	28 (50.0%)
HAM-A	4.2 ± 4.6 (0 to 17)	4.6 ± 4.7 (0 to 16)	4.1 ± 4.6 (0 to 17)
HAM-D	2.2 ± 3.0 (0 to 13)	3.1 ± 3.3 (0 to 9)	1.9 ± 2.9 (0 to 13)
FSRP factors			
Female	43 (57.3%)	10 (52.6%)	33 (58.9%)
Age [#]	63.1 ± 11.2 (40 to 85)	76.3 ± 6.0 (68 to 85)	58.7 ± 8.8 (40 to 76)
Systolic blood pressure [#]	127.6 ± 19.7 (85 to 177)	145.0 ± 18.6 (109 to 177)	121.7 ± 16.3 (85 to 157)
HYP RX [#]	18 (24.0%)	12 (63.2%)	6 (10.7%)
History of diabetes	1 (1.3%)	1 (5.3%)	0 (0%)
Smokes cigarettes	5 (6.7%)	2 (10.5%)	3 (5.4%)
History of CVD	0 (0%)	0 (0%)	0 (0%)
History of atrial fibrillation	1 (1.3%)	1 (5.3%)	0 (0%)
LVH on EKG	0 (0%)	0 (0%)	0 (0%)

* Figures indicate mean with standard deviation (and range) for continuous variables and frequency along with percentage (%) for categorical variables.

[#] Higher risk and lower risk group significantly different in education: $t(73) = 2.1, p = 0.04$; AD family history: $\chi^2(1) = 5.2, p = 0.02$; MMSE: $t(73) = 2.6, p = 0.01$; age: $t(73) = 8.1, p < 0.0001$; SBP: $t(73) = 5.2, p < 0.0001$; and HYP RX: $\chi^2(1) = 21.4, p < 0.0001$. AD, Alzheimer's disease; APOE4, apolipoprotein E4; CVD, myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication or congestive heart failure; Education, years of education; EKG, electrocardiogram; HAM-A, Hamilton Anxiety Inventory; HAM-D, Hamilton Depression Scale; HYP RX, under anti-hypertensive therapy; LVH, left ventricular hypertrophy; MMSE, Mini-Mental State Exam.

Table 2

Predictors of cognitive function

Model	Predictor	β (95%CI)
Global FDDNP binding*	FSRP risk group	-0.77 (-1.16, -0.38)
	FDDNP binding	-5.31 (-9.89, -0.56)
	FSRP*FDDNP	-8.62 (-22.72, 5.47)
Medial temporal FDDNP binding*	FSRP risk group	-0.82 (-1.20, -0.44)
	FDDNP binding	-2.30 (-5.77, 1.17)
	FSRP*FDDNP	-8.54 (-21.19, 4.96)
Lateral temporal FDDNP binding*	FSRP risk group	-0.72 (-1.16, -0.28)
	FDDNP binding	-5.28 (-10.29, -0.27)
	FSRP*FDDNP	-4.17 (-13.92, 5.59)
Frontal FDDNP binding*	FSRP risk group	-0.72 (-1.14, -0.30)
	FDDNP binding	-6.57 (-12.38, -0.76)
	FSRP*FDDNP	-8.60 (-19.94, 2.74)
Posterior cingulate FDDNP binding*	FSRP risk group	-0.88 (-1.36, -0.40)
	FDDNP binding	3.17 (-2.72, 9.06)
	FSRP*FDDNP	-9.96 (-25.58, 5.65)
Parietal FDDNP binding*	FSRP risk group	-0.82 (-1.24, -0.04)
	FDDNP binding	-4.04 (-7.11, -0.97)
	FSRP*FDDNP	-3.09 (-11.27, 5.08)

* For all models, education, E4 status, and family history of AD were included but since these were not significant, they were removed from the final estimation. As an example, for the model with global DDNP binding, the regression coefficients and the 95%CI were, for education: -0.007 (-0.07, 0.05); E4 status: -0.10 (-0.27, 0.24) and family history of AD: -0.02 (-0.38, 0.34).

Table 3

Age, blood pressure, hypertension medication, and FDDNP binding as predictors of cognitive function

Model	Predictor	β (95%CI)
Global FDDNP binding	Age	-0.02 (-0.03, -0.004)
	Blood pressure	-0.006 (-0.01, 0.002)
	Hypertension medication	0.37 (-0.04, 0.77)
	FDDNP binding	-4.85 (-9.38, -0.32)
Medial temporal FDDNP binding	Age	-0.02 (-0.03, -0.003)
	Blood pressure	-0.007 (-0.01, 0.001)
	Hypertension medication	0.38 (-0.03, 0.79)
	FDDNP binding	-2.78 (-5.90, 0.33)
Lateral temporal FDDNP binding	Age	-0.02 (-0.03, -0.01)
	Blood pressure	-0.006 (-0.01, 0.000)
	Hypertension medication	0.37 (0.01, 0.72)
	FDDNP binding	-2.86 (-5.08, -0.63)
Frontal FDDNP binding	Age	-0.02 (-0.03, -0.01)
	Blood pressure	-0.007 (-0.01, -0.001)
	Hypertension medication	0.39 (-0.01, 0.80)
	FDDNP binding	-3.35 (-5.63, -0.87)
Posterior cingulate FDDNP binding	Age	-0.02 (-0.03, -0.01)
	Blood pressure	-0.007 (-0.01, -0.001)
	Hypertension medication	0.44 (0.03, 0.86)
	FDDNP binding	-0.67 (-2.59, 1.25)
Parietal FDDNP binding	Age	-0.02 (-0.04, -0.004)
	Blood pressure	-0.006 (-0.01, 0.001)
	Hypertension medication	0.41 (-0.01, 0.82)
	FDDNP binding	-2.96 (-5.11, -0.83)