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Differential FDDNP PET patterns in non-demented middle-aged and older adults

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Abstract

Objective—We explored whether positron emission tomography (PET) with 2-(1-{6-[(2-[F-18] fluoroethyl)(methyl) amino]-2-naphthyl} ethylidene)malononitrile (FDDNP), a molecule that binds to plaques and tangles in vitro, might identify homogeneous subgroups of persons in middle-aged and older persons with mild cognitive impairment (MCI) or normal cognition.

Participants—Fifty-six subjects (MCI, N = 29; normal cognition, N = 27).

Measurements—FDDNP-PET scans were performed. Logan parametric images were produced using cerebellum as a reference region, and relative distribution volumes were obtained for regions of interest (ROIs) known to accumulate plaques and tangles in Alzheimer's disease (AD). Cluster analysis was used to identify subgroups of subjects according to FDDNP signal distribution. Once the FDDNP clusters were identified, we then characterized the clusters also with respect to diagnosis and cognitive test performances and conducted analyses on cluster differences on these variables.

Results—We identified three FDDNP clusters: high signal in lateral temporal and posterior cingulate ROIs (high temporal-posterior cingulate HT/PC); low signal in all ROIs (low global cluster, LG); high frontal and parietal signal with intermediate temporal and posterior cingulate signal (HF/PA). Most MCI subjects belonged to the HT/PC and HF/PA clusters, while most cognitively normal subjects were in the LG cluster. On cognitive tests, the HT/PC and HF/PA clusters performed significantly worse than LG; but did not significantly differ from each other.

Conclusions—This approach may be useful in identifying potential high risk imaging cluster patterns. Longitudinal follow-up would be performed to determine the association of these subgroups with diagnostic and functional outcome.

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DISCLOSURES

The University of California, Los Angeles, owns the U.S. patent (6,274,119) entitled "Methods for Labeling β -Amyloid Plaques and Neurofibrillary Tangles," which has been licensed Siemens. Drs. Small, Huang, Cole, Satyamurthy, and Barrio are among the inventors. Dr. Small reports having served as a consultant and received lecture fees from Abbott, AstraZeneca, Eisai, Forest, Memory Fitness Institute, Novartis, Ortho-McNeil, Pfizer, and Siemens. Dr. Lavretsky reports having received lecture fees from Eisai, Janssen, and Pfizer and received a research grant from Forrest. Dr. Ercoli reports having received lecture fees from the Memory Fitness Institute, and has also received funds to attend the Larry L. Hillblom Foundation annual meeting to present these and other results. Dr. Barrio reports having served as a consultant and received lecture fees from Nihon Medi-Physics Co, Bristol-Meyer Squibb, PETNet Pharmaceuticals, and Siemens.

Keywords

mild cognitive impairment; positron emission tomography; amyloid neuritic plaques; neurofibrillary tangles

OBJECTIVE

Early detection of Alzheimer's disease (AD) is important for identifying candidates for therapeutic interventions that can delay the onset and/or slow the progression of AD. One approach to early detection is to identify individuals with mild cognitive impairment (MCI), a transitional stage between normal aging and AD^{1,2}. The number, type and cut-offs used on cognitive tests to identify impairment may influence the accuracy of detecting MCI³. Overall, About 15% of persons with MCI develop dementia annually, yet, MCI is heterogeneous disorder with varied outcomes, and the ability to predict dementia is imperfect^{1,2}.

Neuropathologic studies indicate that two abnormal proteins, beta-amyloid (in senile plaques) and tau (neurofibrillary tangles), accumulate in a predictable spatial pattern in aging and AD.^{4,5} These changes may begin before age 30 and increase in prevalence gradually with age. High brain cortical concentrations of amyloid senile plaques and neurofibrillary tangles are necessary for a diagnosis of definite AD at autopsy. Autopsy studies indicate that the level of AD pathology in MCI is intermediate to that of cognitively normal persons and those with dementia.^{6,7} Amnesic MCI patients are more similar to healthy controls than to AD patients with respect to the cortical density of amyloid plaques, but are more advanced than controls with respect to NFTs.⁶ Despite such autopsy findings, an antemortem MCI diagnosis with progression to clinical AD does not always predict primary neuropathological AD.⁸ Overall, discrepancies between a clinical diagnosis of MCI and clinical and neuropathological outcomes raise concerns about selecting homogeneous groups of individuals with high AD risk for clinical trials and new anti-dementia interventions.⁸

The use of biomarkers offers the potential for more effective and earlier diagnosis of AD⁹. In neuroimaging, recent developments of PET molecular imaging probes for imaging amyloid¹⁰ or amyloid and tau¹¹ show promise for detecting homogeneous groups of persons at risk for AD according to underlying neuropathology. Our group developed a small molecule, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP), for use as an *in vivo* chemical marker of cerebral aggregates of amyloid and tau proteins.¹¹ Both FDDNP and its parent molecule, DDNP, are fluorescent and provide clear *in vitro* visualizations of plaques and tangles in Alzheimer's brain specimens examined under a confocal fluorescence microscope.¹² We recently reported¹³ that FDDNP-PET scanning differentiated patients with MCI from AD patients and cognitively normal older adults. Global (temporal, parietal, posterior cingulate, and frontal region of interest averages) FDDNP-PET signal was highest in AD, intermediate in MCI and lowest in normal control subjects. A brain autopsy of an MCI patient who converted to AD showed high plaque and tangle concentrations in regions that showed high FDDNP binding.¹³

In the current study we explored additional methods to identify with FDDNP subjects with high AD risk. We included cognitively normal and amnesic MCI subjects. We included cognitively normal subjects because, although asymptomatic, some may nevertheless have underlying increasing accumulations of amyloid and tau suggestive of increased AD risk. We hypothesized that if subjects vary according to underlying burden and patterns of plaque and tangle distribution, FDDNP-PET would be able to identify homogeneous subject subgroups, and that these FDDNP subgroups would differ according to cognitive, demographic and AD genetic risk attributes.

If subgroups are identified according to patterns of FDDNP-PET accumulations, then this may be useful for generating hypotheses about dementia risk, and for identifying subjects for longitudinal monitoring.

METHODS

Subjects were drawn from a larger, longitudinal AD study¹³ Data for six more MCI subjects that became available since that publication are included in the current study. Baseline cognitive assessments and PET with FDDNP were performed in 116 persons selected from a pool of 745 (age range 45 to 84 years) volunteers, recruited through advertisements of a study of mild memory impairment, media coverage of the study, and referrals by physicians and families.

From the original volunteer pool, 40 persons taking medications that might affect cognition, such as sedatives, or nonsteroidal anti-inflammatory drugs, which bind to amyloid plaques and thus can affect FDDNP binding values, were excluded.¹⁴ Persons were excluded for other reasons, including four because of head movement during scanning (two with MCI, and two potential controls). We excluded the AD subjects from the larger study, because the current study focused only on nondemented persons. We excluded 5 subjects with non-amnesic MCI. The final sample included 56 subjects. Investigators were unaware of the clinical data when excluding potential subjects on the basis of PET scan quality, and were unaware of the scans when excluding potential subjects on the basis of clinical data.

Of the 56 subjects, 10 with MCI were receiving cognitive enhancing drugs (a cholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist) at a steady dose for at least 3 months before entering the study. All subjects underwent screening laboratory testing, psychiatric and neurologic evaluation, and structural imaging scanning to rule out other causes of cognitive impairment (e.g., stroke or tumor). Most subjects (N = 52) underwent magnetic resonance imaging (MRI); 4 subjects who could not tolerate MRI (because of claustrophobia or metal in the body) underwent computed tomography (CT) scanning. We administered the Mini-Mental State Examination,¹⁵ and assessed mood with the Hamilton Rating Scale for Depression¹⁶ and a clinical interview. We administered a battery of neuropsychological tests¹⁷ to assess five cognitive domains: memory (Wechsler Memory Scale Third Edition Logical Memory and Verbal Paired Associations II, Buschke-Fuld Selective Reminding Test, Rey-Osterrieth Complex Figure delayed recall); language (Boston Naming, Letter Fluency, Animal Naming tests); attention and speed of information processing (Trail Making Test-A, Stroop Color Naming [Kaplan version], and Wechsler Adult Intelligence Scale-Third Edition [WAIS-III] Digit Symbol); executive functioning (Trail Making Test-B, Stroop interference, Wisconsin Card Sorting Test-Perseverative Errors); and, visuospatial functioning (WAIS-III Block Design, Rey-Osterrieth Complex Figure copy, Benton Visual Retention Test). Raw scores for cognitive tests in each domain were converted to Z scores and then averaged to form an average Z score for each domain.¹⁸ Domain Z scores were the dependent variables for comparing clusters on cognitive tests.

We used most recent standard diagnostic criteria to diagnose MCI², which include (1) patient awareness of memory decline, preferably confirmed by another person; (2) greater-than-normal cognitive impairment on standardized tests; (3) normal daily activities performance, and (4) no dementia. We used guidelines^{2,19} to identify MCI subtypes, including memory impairment alone (amnesic MCI; MCI-A), and memory impairment plus additional cognitive domains impaired (MCI-A+). We included MCI subjects who scored ≥ 1 SD below age-corrected norms, as this impairment threshold yields high sensitivity for predicting dementia²⁰. To balance increased sensitivity with specificity we required impairment on at least two neuropsychological tests per cognitive domain. We documented subjective memory

complaints using the Memory Functioning Questionnaire²¹ and clinical interview. Of the 29 MCI subjects, 13 had MCI-A, 16 had MCI-A+. The MCI group included 2 African-American, 1 Latino and 26 Caucasian individuals. The control group included 1 African-American, 1 Latino and 24 Caucasian individuals.

Scanning Methods

As described elsewhere, FDDNP was prepared at very high specific activities (>37 GBq/mol).^{11,22,23} All scans were performed with the ECAT HR or EXACT HR+ tomograph (Siemens-CTI, Knoxville, TN) with subjects supine with the imaging plane parallel to the orbito-meatal line. A bolus of FDDNP (320 – 550 MBq) was injected via an in-dwelling venous catheter and consecutive dynamic PET scans were performed for 2 hours. Scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5 mm FWHM) with scatter and measured attenuation correction. The resulting images contained 47 contiguous slices with plane separation of 3.37 mm (ECAT HR) or 63 contiguous slices with plane separation of 2.42 mm (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 scanners (p-values ranging from .18 to 0.84).

To quantify FDDNP binding, we performed Logan graphical analysis with cerebellum as the reference region for time points between 30 and 125 minutes.^{22,24} 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 a region of interest (ROI) divided by that in the reference region. We generated DVR parametric images and analyzed them using regions of interest (ROIs) drawn manually on the co-registered MRI or CT scans, or on the FDDNP image obtained in first 5 min after injection (perfusion image), bilaterally on parietal, medial temporal (containing limbic regions, including hippocampus, parahippocampal, and entorhinal areas), lateral temporal, posterior cingulate, parietal and frontal regions, as previously described.²² Each regional DVR or binding value was expressed as an average of left and right regions. Cerebellar ROIs were drawn on PET images, which were generated by summing frames covering the first 5 minutes of the scan (perfusion image, frames 1 to 7). This image shows the perfusion pattern and has sufficient anatomical information to identify the cerebellum and cerebellar grey matter. Rules for ROI drawing were based on the atlas of Talairach and Tournoux,²⁵ which we used as a visual guide for identifying the important gyral and sulcal landmarks needed in delineating the ROI. Anatomical brain MRI scans were obtained using either a 1.5 Tesla or 3 Tesla magnet (General Electric-Signa, Milwaukee, WI) 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 (TR = 6000 [3T] and 2000 [1.5T]; TE = 17/85 [3T] and 30/90 [1.5T]). The ROI determinations were performed by individuals blind to clinical assessments.

Data Analysis

Prior to statistical analyses, all data were inspected for outliers, skewness, kurtosis and homogeneity of variance to ensure appropriateness for parametric statistical tests. A disjoint cluster analysis was performed on the basis of Euclidean distances computed from the five regional FDDNP binding signals. This clustering method, also known as k-means clustering, yields clusters with minimal variability within and maximal variability between clusters. The FDDNP binding signals (DVRs) were first standardized to a mean of 0 and standard deviation of 1 before performing cluster analysis. The selection of the number *k* of clusters was done as follows: (1) since it is already known that FDDNP binding signals differentiate between MCI and cognitively normal subjects¹³ and the primary goal of this study is to explore subtypes within MCI and cognitively normal subjects, three or four clusters were hypothesized. Cluster analyses were conducted for both of these values of *k*. Then, cluster membership was taken as

the group variable in a k group discriminant analysis. The test statistic for the equality of means of the FDDNP binding signals was then compared for the two values of k to determine the value of k to be selected. Based on both the cubic clustering criterion and the test statistics from the discriminant analyses, three clusters were identified as the optimal number. The three clusters were then compared on FDDNP signals and cognitive domain Z scores using two separate MANCOVAs. Univariate ANCOVAs were then conducted to determine which regions or cognitive domains were significantly different between clusters and post-hoc tests were conducted to determine which of the clusters differed from each other. We estimated effect sizes for all pair-wise comparisons of clusters using Cohen's d .

RESULTS

Subjects' demographic variables are presented in Table 1. The cluster analysis identified three distinct clusters. By visual inspection (Figure 1), one cluster had low FDDNP signal in all regions (Low Global, LG). Two other clusters showed relatively higher regional FDDNP signals. One of these showed high FDDNP signal in lateral temporal and posterior cingulate regions (HT/PC), and the other showed high FDDNP signal in frontal and parietal regions (HF/PA). Both HF/PA and HT/PC had elevated FDDNP signal in the medial temporal region. As expected, a MANCOVA, controlling for age and education, comparing FDDNP signal in the clusters in the five ROI was significant, $F(10, 94) = 14.55$ ($p < .0001$). We present effect sizes (ES) obtained from post-hoc pair-wise comparisons among the three clusters as summary descriptors of regional FDDNP signal pattern differences (Table 2). The ES show the magnitude of the regional differences in FDDNP signals that characterize the three clusters. Figure 2 shows group FDDNP DVR parametric images for each of the clusters. An Alzheimer's disease group FDDNP DVR parametric image generated from images of ten AD patients is shown for comparison. Subjects in clusters did not significantly differ in age, education, gender, APOE-4 status, or AD family history.

We examined the clusters according to clinical diagnosis (Table 3). HT/PC was comprised of 88% MCI and 12 % cognitively normal subjects. By contrast, LG was comprised of 21% MCI and 79% cognitively normal subjects. The HF/PA cluster included 71% MCI and 29% cognitively normal subjects. The distribution of MCI and cognitively normal subjects in the three clusters was significantly different $\chi^2(2) = 16.8$, $p < .001$.

The clusters differed in cognitive performances (Figure 3) according to a MANCOVA, controlling for age and education [$F(10, 84) = 2.75$, $p = .005$]. ANCOVAs showed that the clusters were significantly different on all five cognitive domains: Memory [$F(2, 46) = 8.07$; $p = .001$], Executive [$F(2, 46) = 5.25$, $p = .009$], Language [$F(2, 46) = 6.46$, $p = .003$], Visuospatial [$F(2, 46) = 3.31$, $p = .05$], and Psychomotor speed [$F(2, 46) = 4.55$, $p = .02$].

Post-hoc pair-wise comparisons for Memory, Executive, Language, Visuospatial and Psychomotor speed domains, controlling for age and education, were conducted. The HT/PC cluster performed significantly worse than the LG cluster in the Memory (ES = 1.38) and Visuospatial (ES = 1.07) domains. The HF/PA cluster performed significantly worse than the LG cluster in Memory (ES = .96), Executive (ES = 1.08), Language (ES = .92), Visuospatial (ES = 1.58) and Psychomotor speed (ES = .89). The HT/PC and HF/PA clusters did not differ significantly on any domain.

CONCLUSION

The cluster analysis identified three significantly different patterns of FDDNP signal—a low global (LG) cluster with lower FDDNP signal in all ROIs; a cluster that had high signal in frontal and parietal regions (HF/PA); a HT/PC cluster, showing highest FDDNP signal in the

lateral temporal and posterior cingulate regions, with similar medial temporal and relatively lower frontal and parietal signal compared to HF/PA.

To interpret these different signal patterns we examined the clusters according to diagnosis, demographics, APOE genetic risk, and cognition. The HT/PC was comprised almost entirely of clinically defined MCI patients (88%) with one cognitively normal subject, LG was mostly comprised (79%) of cognitively normal subjects. The HF/PA cluster was the most diagnostically diverse, with 71% MCI and 29% cognitively normal subjects.

Neuropathological studies indicate a greater degree of amyloid and tau pathology in MCI compared to cognitively normal older persons^{6,7, 26}, which is consistent with the current findings of more MCI patients in the two clusters with relatively higher FDDNP signal. Others have found variable binding patterns in MCI and healthy controls using Pittsburgh Compound B ([11C]PIB)²⁷, which has been reported to have in vivo specificity for A-beta plaques, but is not known to label neurofibrillary tangle pathology. In that study, visual inspection of DVR images indicated that 5 of 9 MCI subjects showed greatest PIB binding in posterior cingulate/precuneus, frontal cortex, and caudate regions, followed by lateral temporal and parietal cortex ("AD-like" pathology), and the remainder showed no cortical or subcortical gray matter binding, similar to that of many cognitively normal persons. Of 27 cognitively normal subjects, 4 showed orbitofrontal, variable cingulate/precuneus and temporal binding, while 2 had either occipital or several focal areas of cortical binding. In comparing this study with ours, it can be observed that in vivo binding patterns of PIB and FDDNP were not identical. Most notable, is the higher signal using FDDNP in NFT rich areas in the MCI subjects such as the medial temporal region, and this discrepancy would be expected given that FDDNP is a marker of aggregates of tau and amyloid.

Most MCI patients were in the HT/PC and HF/PA clusters, but subjects with amnesic MCI or amnesic MCI plus other domains impaired were not differentially represented in those clusters. It should be recognized, however, that subtypes of MCI have not been consistently distinguished earlier from each other using other imaging methods..²⁸ MRI measures of cerebral volumes²⁹ in medial temporal and association cortex and cortical thickness³⁰ in the precuneus have distinguished amnesic MCI from multiple domain MCI.

FDDNP signal clusters in our subject population differed on neuropsychological testing. The LG group, which included mostly cognitively intact individuals, had the best cognitive performances. Relative to LG, the other two clusters showed memory and visuospatial deficits; but HF/PA cluster had the most extensive cognitive deficits, while the HT/PC cluster had more variability in performances across the domains. The HT/PC and HF/PA clusters did not differ from each other. Having more extensive cognitive deficits, such as impairment in memory plus other domains, has been associated with more rapid progression to dementia than having memory impairment alone³¹. Longitudinal follow-up will be important in determining not only diagnostic outcomes, but also whether the more extensive cognitive deficits in HF/PA has implications for rate of progression.

Eight cognitively normal persons were members of the higher binding clusters—seven were in HF/PA and one was in HT/PC. It would be expected that some normal subjects would have higher FDDNP signal because of the probability that they may eventually develop AD. Autopsy determinations have identified asymptomatic individuals with AD neuropathology.^{5,26,32,33, 34}

To understand the significance of higher FDDNP signal in the eight cognitively normal subjects, we examined their demographics, APOE genotype, and cognition. The subjects were similar in age, APOE-4 genotype, dementia family history, and education to the entire sample of cognitively normal subjects in the current study. Two subjects had no memory impairment;

the remaining six performed more than 1 sd below the mean on the selective reminding test, but on no other memory tests. The significance of impairment on Selective Reminding is unclear; although it was earlier reported that this test is a significant predictor of dementia.³⁵ Impairment on *only* one memory test was not sufficient for an MCI diagnosis in this study, but this highlights the complexities of defining impairment for MCI.

Five MCI patients were in the LG cluster. These patients had less extensive cognitive deficits, as four were MCI-A and one was MCI-A+. No other variables set these MCI subjects apart from the rest.

As these data are part of an ongoing larger longitudinal study, follow-up cognitive data were available for 14 subjects (6 MCI and 8 cognitively normal) averaging 3.5 (range 1.5 to 7) years. Half of the MCI and cognitively normal subjects remained stable, and the remainder declined cognitively. Of the four cognitively normal subjects who declined, one developed a visuoconstruction deficit, and three developed MCI. Of the three MCI subjects who declined, two converted to dementia, and one developed more extensive deficits. Among the declining subjects, one was from HT/PC (the subject with worsening MCI), three were from LG (all cognitively normal), and three were from HF/PA (two MCI converted to dementia, and a cognitively normal developed MCI-A+ over two years).

These findings may be useful for generating new hypotheses about the utility of these imaging clusters for predicting further cognitive decline and diagnostic outcomes, particularly as our group collects additional longitudinal data on these subjects. The HT/PC cluster, comprised almost entirely of MCI patients, had higher binding in temporal (particularly lateral temporal) and posterior cingulate regions with memory and visuospatial deficits. The high frontal-parietal signal with relatively lower signal in temporal and PC regions of the HF/PA cluster is not consistent with the pattern of FDDNP accumulation in AD patients,¹³ or in subjects with frontotemporal dementia,³⁶ where we have observed elevated frontal and temporal FDDNP signals. The HF/PA cluster had the most extensive deficits. Overall, these results may have implications for using regional FDDNP signal patterns over global signal burden in further characterizing MCI, given the heterogeneous manifestations of this disorder. However, at this time, it is not clear whether these clusters represent different etiologies, variants, severities or different stages of disease (or some combination) related to underlying amyloid or tau pathologies. Longitudinal follow-up of these subjects will be important in further clarifying the significance of these clusters.

In conclusion, these results suggest that FDDNP can identify homogeneous groups of nondemented subjects with distinct signal patterns. Most MCI patients belonged to the two clusters with higher regional signal while most cognitively normal subjects had uniformly low FDDNP regional signal. Future longitudinal studies will help clarify whether any of these clusters predict an increase risk for AD. The major limitations of this study are the small number of subjects, and the limited follow-up data currently available. Increasing the number of recruits, adding a non-amnesic MCI group, and additional longitudinal follow-ups are underway to establish the prognostic implications of FDDNP.

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Figure 1. Graph of FDDNP signal in regions of interest in the three clusters

DVR = relative distribution volume. The standardized DVR values are DVR values that were standardized to have a mean of 0 with a standard deviation of 1. High standardized DVR values indicate higher FDDNP signal and low standardized DVR values indicate relatively lower FDDNP signal. HT/PC = High lateral temporal/posterior cingulate FDDNP signal cluster, LG = Low global FDDNP signal cluster, HF/PA = FDDNP signal is relatively higher in frontal and parietal regions, and intermediate in the rest. MT = Medial temporal region: HT/PC = HF/PA > LG; LT = Lateral temporal region: HT/PC > HF/PA > LG; PC = Posterior cingulate region, HT/PC > HF/PA > LG. PA = Parietal region, HF/PA > HT/PC > LG. FR = Frontal region, HF/PA > HT/PC > LG.

Figure 2.

Group FDDNP DVR parametric images are shown for each of the clusters at the level of parietal lobe (upper row) and at the level of medial temporal lobe (lower row). An Alzheimer's disease group FDDNP DVR parametric image generated from images of ten AD patients, is shown for comparison. Warmer colors represent higher DVR values. LG = Low global FDDNP Signal Pattern; HT/PC = High lateral temporal and posterior cingulate FDDNP signal pattern; HF/PA = High frontal/parietal signal and intermediate temporal and posterior cingulate. Note: Pons signal is frequently elevated in MCI and AD patients with FDDNP, as is also observed with other amyloid binding agents (e.g., [C-11]PIB; Lopresti et al., 2005)

Reference:

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Figure 3. Cognitive domain performances in each of the FDDNP clusters

LG = Low Global FDDNP signal cluster; HT/PC = High lateral temporal/posterior cingulate FDDNP signal cluster; HF/PA = High frontal/parietal FDDNP signal cluster. Domains: Memory: HF/PA ($t(46) = 3.81, p = .0004$) and HT/PC ($t(46) = 2.39, p = .02$) and Signal clusters were significantly worse than the LG cluster, but did not differ from each other. Executive: HF/PA ($t(46) = 3.23, p = .002$) cluster was significantly worse than the LG cluster, HT/PC did not differ significantly from LG or HF/PA. Visuospatial: HF/PA cluster ($t(46) = 2.16, p = .04$) and HT/PC cluster ($t(46) = 2.00, p = .05$); were significantly worse than LG cluster, but did not differ from each other; Language: HF/PA ($t(46) = 3.51, p = .001$) cluster was significantly worse than the LG cluster; HT/PC was marginally worse than LG ($t(46) = 1.84, p = .07$), and did not differ from HF/PA. Psychomotor: HF/PA ($t(46) = -2.84, p = .007$) cluster was significantly worse than the LG cluster; and marginally worse than HT/PC ($t(46) = 1.77, p = .08$); HT/PC did not differ significantly from LG.

Table 1

Subject demographic variables

Characteristic	Diagnostic Groups		
	MCI (N = 29))	Control (N = 27)	All Subjects (N = 56)
Age — yr	68.6 ± 11.7	68.0 ± 11.6	68.3 ± 11.6
Education — yr [*]	16.1 ± 3.9	17.8 ± 2.7	17.0 ± 2.9
Female sex — no. (%)	16 (55)	9 (33)	25 (45)
AD family history—no (%)	12 (41)	14 (52)	26 (46)
APOE-4 carrier — no. (%) [†]	10 (38)	14 (52)	24 (45)
Mini Mental State Exam [§]	27.6 ± 1.7	29.1 ± 1.3	28.3 ± 1.7
HRSD-21 [‡]	1.9 ± 2.3	2.4 ± 2.4	2.2 ± 2.4

MCI = Mild Cognitive Impairment; AD = Alzheimer's disease; APOE-4 = Apolipoprotein Epsilon-4; HRSD = Hamilton Rating Scale for Depression 21-item version

^{*}t(54) = 2.2, p < 0.03;

[†]APOE-4 missing for 3 MCI subjects;

[§]t(54) = 3.9, p < 0.0002;

[‡]HRSD-21 missing for 1 MCI subject

Table 2

Effect Size Estimates for Pair-wise Comparisons of FDDNP Clusters.

Region of Interest	Effect Size Estimates		
	LG vs HT/PC	LG vs HF/PA	HT/PC vs HF/PA
MT	1.45	1.62	0.13
LT	3.05	1.56	1.07
PC	2.60	0.76	1.78
FR	1.15	2.41	1.28
PA	0.81	2.16	0.82

Effect sizes are differences between cluster means for regions of interest divided by the pooled standard deviation. LG = Low Global cluster, HT/PC = High lateral temporal/posterior cingulate, HF/PA = High frontal/parietal cluster. MT = Medial Temporal; LT = Lateral Temporal; PC = Posterior Cingulate, FR = Frontal, PA = Parietal.

Table 3

Cluster Membership of Subjects with Mild Cognitive Impairment and Controls According to FDDNP Signal in Regions of Interest

Diagnostic Group*	FDDNP Signal Clusters		
	No. of subjects per cluster		
	LG	HF/PA	HT/PC
Normal cognition	19	7	1
MCI	5	17	7
MCI-A	4	7	2
MCI-A+	1	10	5

LG = Low Global; HF/PA = High frontal/parietal signal with intermediate signal in temporal and posterior cingulate; HT/PC = High lateral temporal/posterior cingulate. MCI-A = amnesic mild cognitive impairment; MCI-A+ = MCI with memory plus additional cognitive domains impaired