

## Suspected non-AD pathology in mild cognitive impairment

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### ABSTRACT

We aim to better characterize mild cognitive impairment (MCI) patients with suspected non-Alzheimer's disease (AD) pathology (SNAP) based on their longitudinal outcome, cognition, biofluid, and neuroimaging profile. MCI participants ( $n = 361$ ) from ADNI-GO/2 were designated "amyloid positive" with abnormal amyloid-beta 42 levels (AMY+) and "neurodegeneration positive" (NEU+) with abnormal hippocampal volume or hypometabolism using fluorodeoxyglucose–positron emission tomography. SNAP was compared with the other MCI groups and with AMY– controls. AMY–NEU+/SNAP, 16.6%, were older than the NEU– groups but not AMY– controls. They had a lower conversion rate to AD after 24 months than AMY+NEU+ MCI participants. SNAP-MCI participants had similar amyloid-beta 42 levels, florbetapir and tau levels, but larger white matter hyperintensity volumes than AMY– controls and AMY–NEU– MCI participants. SNAP participants performed worse on all memory domains and on other cognitive domains, than AMY–NEU– participants but less so than AMY+NEU+ participants. Subthreshold levels of cerebral amyloidosis are unlikely to play a role in SNAP-MCI, but pathologies involving the hippocampus and cerebrovascular disease may underlie the neurodegeneration and cognitive impairment in this group.

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### 1. Introduction

Biomarker evidence indicates that the pathological process of Alzheimer's disease (AD) begins at least a decade before the onset of clinical symptoms (Jack et al., 2013a). An influential model of the "Preclinical Stage" of AD posits that cerebral amyloid deposition develops first (stage 1), followed by neurodegeneration (stage 2), and then subtle cognitive symptoms (stage 3) (Sperling et al., 2011). Several groups have applied biomarkers of cerebral amyloidosis (e.g., amyloid positron emission tomography (PET), cerebrospinal

fluid [CSF] amyloid-beta [ $A\beta$ ]) and AD-like neurodegeneration (e.g., FDG-PET, hippocampal volume) to cohorts of cognitively normal adults to classify them into these stages of preclinical AD (Jack et al., 2012; Mormino et al., 2014; Vos et al., 2013; Wirth et al., 2013). Surprisingly, a substantial minority of these individuals (~20%) display evidence of neurodegeneration in the absence of cerebral amyloid and have been given the moniker of SNAP, or "suspected non-AD pathology" (Jack et al., 2012), reflecting the notion that pathologies outside of AD underlie their neurodegenerative change.

Compelled by these studies in cognitively normal adults, a few groups have similarly classified mild cognitive impairment (MCI) patients based on the presence or absence of both cerebral amyloid and neurodegenerative biomarkers. As observed in cognitively normal adults, a significant proportion (~15%–30%) of MCI patients display evidence of AD-like neurodegeneration without evidence of amyloid deposition and could be best classified as "SNAP-MCI" (Caroli et al., 2015; Petersen et al., 2013; Prestia et al., 2013). Interestingly, these studies have reported high rates of progression to dementia in SNAP-MCI patients that is similar to those displaying evidence of both cerebral amyloid and

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neurodegeneration. However, it remains unclear what underlying pathology, or pathologies, leads to cognitive impairment and/or neurodegeneration in these patients.

One possibility is that, although this group is thought to reflect “non-AD” pathology, they may actually have some degree of cerebral amyloid but at a subthreshold level relative to commonly used cutoffs for amyloid PET and CSF A $\beta$ , which is sufficient to accelerate neurodegeneration. Another hypothesis is that SNAP-MCI may be the clinical manifestation of the recent pathologically defined condition of “primary age-related tauopathy” (PART) (Crary et al., 2014; Jack, 2014). These individuals display evidence of tangle pathology after Braak distribution (Braak and Braak, 1991) in the medial temporal lobe in the absence of cerebral amyloid and may have associated mild cognitive deficits. This would be consistent with the fact that SNAP is usually defined, in part, on the basis of hippocampal atrophy. Other etiologies of hippocampal-specific pathologies, such as hippocampal sclerosis and argyrophilic grain disease, may also explain neurodegeneration in the absence of amyloid deposition in MCI patients (Duara et al., 2013; Jack et al., 2013b; Prestia et al., 2013), as well as in other neurodegenerative conditions, such as Lewy body disease or frontotemporal lobar degeneration associated with either tau- or TDP-43-based pathology. Finally, cerebrovascular disease (CVD) may also produce both hippocampal and cortical atrophy, which could also account for SNAP presentations (Knopman et al., 2013; Wirth et al., 2013). Although support for some of these aforementioned hypotheses has been suggested in “neurodegeneration only” cognitively normal participants (Jack et al., 2013b; Mormino et al., 2014; Wirth et al., 2013), it has not been investigated in MCI patients.

Pathologic studies will be necessary to truly determine the etiology of individuals with SNAP; however, insight can be gained by a more thorough assessment of their clinical presentation, including cognitive profile, which has not been extensively studied, and additional biomarker and imaging characteristics. The present study will expand on prior work focused on SNAP-MCI both in depth, by more extensively examining phenotypic, imaging, and molecular biomarker features, and in breadth, by studying a larger cohort. In particular, we look to (1) replicate prior work on the prevalence and longitudinal outcome of SNAP-MCI, (2) assess the potential role of subthreshold amyloid, tau and CVD in this population, and (3) determine the nature of the cognitive impairment in this population relative to those with evidence of amyloid (MCI likely because of AD), as well as those MCI patients without evidence of amyloid or neurodegeneration.

## 2. Material and methods

### 2.1. Research participants

Data from the ADNI-GO and ADNI-2 cohorts were used ([www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a \$60-million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco.

ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and research participants have been recruited from >50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults but ADNI has been followed by ADNI-GO and ADNI-2. To date these 3 protocols have recruited >1500 adults, ages 55–90 years, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Research participants originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see [www.adni-info.org](http://www.adni-info.org).

For the present study, data from all MCI participants enrolled before January 10, 2012 with available biomarkers of cerebral amyloidosis (CSF A $\beta$ ) and neurodegeneration (FDG-PET and hippocampal volume) ( $n = 361$ ) from the ADNI-GO and ADNI-2 cohorts were used. The MCI participants with biomarkers of cerebral amyloidosis and neurodegeneration did not differ on age, sex, and education from those without available biomarkers ( $n = 108$ ). In addition, we used all data from amyloid-negative cognitively normal adults [CSF A $\beta$ 42  $\geq 192$  pg/mL (Shaw et al., 2009)] ( $n = 87$ ) and amyloid positive participants with AD dementia [CSF A $\beta$ 42 < 192 pg/mL (Shaw et al., 2009)] ( $n = 113$ ) from ADNI-GO or ADNI-2 to establish cutoff points for the markers of neurodegeneration, and we used data from the amyloid-negative cognitively normal adults as a comparison group for the SNAP-MCI participants to analyze the potential role of subthreshold amyloid, tau, and white matter hyperintensities (WMHs) in SNAP.

### 2.2. Standard protocol approvals, registrations, and patient consents

The study was approved after ethical review of each site’s local review board, and all research participants provided informed written consent.

### 2.3. Biofluid and imaging biomarkers

All biofluid and imaging biomarker data were from publicly available, processed data on the ADNI Web site. Apolipoprotein E (APOE)- $\epsilon$ 4 carrier status was obtained via standard methods (Saykin et al., 2010). Positive APOE- $\epsilon$ 4 status was defined as having at least 1 APOE- $\epsilon$ 4 allele. CSF levels of A $\beta$ 42, total-tau (tau), and phospho-tau (p-tau) were measured as previously described (Shaw et al., 2009). Three-dimensional magnetization-prepared rapid gradient echo 3 tesla images were acquired in all research participants. Hippocampal volume and intracranial volume (ICV) were computed using a multiatlas consensus-based label fusion scheme (Davatzikos et al., 2014), see [http://adni.bitbucket.org/upenn\\_roi\\_mars.html](http://adni.bitbucket.org/upenn_roi_mars.html). WMH volume was obtained using an automated detection method using T1-, T2-, and proton density weighted images, as previously described (Carmichael et al., 2010; Schwarz et al., 2009). WMH volumes were corrected for ICV and log-transformed for better approximation of normality. FDG-PET images for glucose metabolism and florbetapir F 18 PET images were obtained using standard methods, also described in Landau et al., (2012). A composite, standardized uptake value ratio (SUVR) for the florbetapir images was calculated by taking the mean SUVR of a set of regions typically associated with increased uptake in AD, using gray matter of the cerebellum as reference region (Landau et al., 2012). In addition, the regions of interest (ROIs) were investigated separately. For the FDG-PET images, SUVR in a “meta-ROI” associated with hypometabolism in AD was calculated as the mean of 5 regions with pons and vermis as reference (Landau et al., 2012). Voxelwise thickness analyses were performed as described

previously (Das et al., 2015a). In short, gray matter, white matter, and CSF probability maps were generated using the Atropos tool (Avants et al., 2011), and gray matter thickness was calculated using the DiReCT algorithm (Das et al., 2009). To obtain voxelwise thickness values for each subject in a common image space, a population template was obtained (Tustison et al., 2014) using the ANTs tool (Avants et al., 2008). Isotropic spatial smoothing with a Gaussian kernel with a width of 3 mm was performed.

FDG-PET, hippocampal volumes, and log-transformed WMHs were converted into z-scores based on the means and standard deviations of the amyloid-negative controls of ADNI-2.

#### 2.4. Clinical and neuropsychological assessment

The Geriatric Depression Scale (Sheikh and Yesavage, 1986) was administered during screening and the sum of the boxes of the Clinical Dementia Rating (CDR) scale was obtained (Morris, 1993). Diagnosis after 12 and 24 months was also analyzed for those participants for whom it was available (diagnosis after 12 months:  $n = 338$ ; 24 months:  $n = 272$ ). The distinction of early and late MCI was based on the Logical Memory delayed recall score, as previously described (Aisen et al., 2010). In addition, information on height, weight, blood pressure, history of smoking, hypertension and cardiovascular disease was obtained during screening.

All participants underwent a comprehensive psychometric test battery, as previously described (Gross et al., 2012). For this article, we examined the Mini-Mental Status Examination (MMSE) (Folstein et al., 1975), American National Adult Reading Test (ANART) (Nelson and O'Connell, 1978), Auditory Verbal Learning Test (AVLT) (Rey, 1964), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-COG) (Rosen et al., 1984), Trail Making Test A and B (Reitan, 1958), category fluency (animals) (Butters et al., 1987), and the Boston Naming Test (Kaplan et al., 1983). All test scores, except the MMSE and the ANART, were transformed into z-scores based on the means and standard deviations of amyloid-negative controls. Trail Making Test A and B were log-transformed before they were transformed into z-scores and inverted so that lower values represent a worse performance. Composite scores were calculated for the different memory domains: immediate memory was based on the first trial of the AVLT and the ADAS-COG word recall task, delayed recall was based on the 30-minute delayed recall of the AVLT and delayed recall task of the ADAS-COG word recall task, and recognition memory was based on the delayed recognition memory of the AVLT and word recognition task of the ADAS-COG. The ANART was converted into an estimate for verbal IQ using the following equation: verbal IQ =  $118.2 - 0.89$  (ANART error score) +  $0.64$  (years of education) (Grober and Sliwinski, 1991).

#### 2.5. Classification based on markers of cerebral amyloidosis and neurodegeneration

CSF A $\beta$ 42 concentration was selected as a marker for cerebral amyloidosis. MCI participants were designated "amyloid positive" (AMY+) if A $\beta$ 42 levels were  $< 192$  pg/mL, a cutoff point which was established in an autopsy study, and ADNI data (Shaw et al., 2009). Neurodegeneration was assessed with an FDG-PET meta-ROI associated with AD-related hypometabolism and with mean hippocampal volume, corrected for ICV. Cutoff points for both measures were derived to optimize sensitivity and specificity in discrimination of AMY- controls and AMY+ participants with AD dementia from ADNI-GO or ADNI-2. MCI participants were considered "neurodegeneration positive" with an SUVR value for the FDG-PET meta-ROI  $\leq 1.19$  and/or a value for hippocampal volume  $\leq 3.68$  mL. MCI participants were divided into 4 groups: AMY-NEU-, AMY+NEU-, AMY+NEU+, and AMY-NEU+ (SNAP).

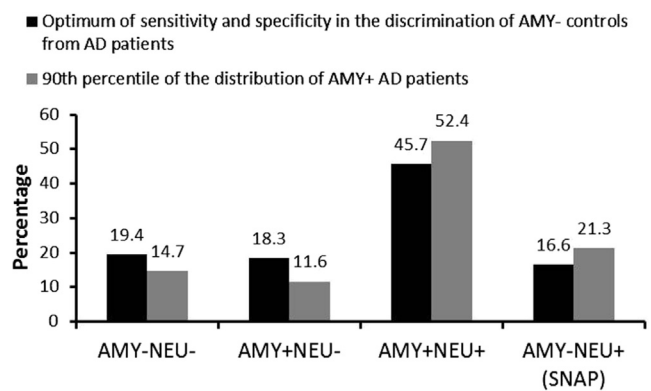


Fig. 1. Frequency of positive biomarkers in mild cognitive impairment patients using 2 different cutoffs for the neurodegeneration biomarkers. Abbreviations: AD, Alzheimer's disease; AMY, amyloid; NEU, neurodegeneration; SNAP, suspected non-Alzheimer's disease pathology.

We chose to derive the cutoff points from the optimum of sensitivity and specificity in discrimination of AMY- controls and AMY+ participants with AD dementia. By selecting AMY- controls, we exclude preclinical AD in this group (Sperling et al., 2011), and by selecting AMY+ participants with AD dementia, we are increasing the probability of selecting participants with dementia truly due to AD. In addition, this method generates more stringent cutoff points thereby increasing the probability that "positive neurodegeneration" in the SNAP group represents meaningful neurodegeneration and decreases the noise in this group.

Additionally, to compare with other work, we also used cutoff points for the neurodegeneration markers by determining the 90th percentile of the distribution of amyloid positive participants with AD dementia as done by others in similar analyses (Jack et al., 2012; Petersen et al., 2013). The cutoff points were slightly more liberal than by the previous method, with 1.23 for FDG-PET ratio and 3.85 mL for hippocampal volume.

#### 2.6. Statistical analyses

Group comparisons for outcomes and demographics were performed using an analysis of variance (ANOVA) with Fisher's least significant difference post hoc tests for normally distributed data and using Mann-Whitney U tests for non-normally distributed data.  $\chi^2$  tests were used to compare groups on dichotomous data.

To test whether the SNAP group had subthreshold levels of cerebral amyloidosis, this group was compared on CSF A $\beta$ 42 and florbetapir PET with the AMY-NEU- MCI participants and with amyloid-negative controls. To examine the potential relationship of neurofibrillary tangle (NFT) pathology and CVD to the neurodegeneration in the SNAP group, we compared their levels of CSF tau and WMHs with the AMY-NEU- MCI participants and amyloid-negative controls, groups in which the salient difference with the SNAP participants is the absence of neurodegeneration. Lower z-scores represent more abnormal values.

We also aimed to characterize the SNAP group on other biomarkers and on cognitive measures. To determine the role of neurodegeneration in the absence of amyloid, we compared the SNAP group to the AMY-NEU- MCI participants. Alternatively, to determine the modulatory role of amyloid in the context of neurodegeneration on cognition and other biomarkers, we also compared the SNAP group to the AMY+NEU+ group. For the voxelwise thickness analyses, a general linear model was performed for each voxel in the template images space with cortical thickness per voxel as dependent variable, diagnostic group as independent

**Table 1**  
Demographics and longitudinal outcome of the SNAP group, compared with the other MCI groups and the AMY– controls

	AMY–NEU–	AMY+NEU–	AMY+NEU+	AMY–NEU+ (SNAP)	AMY– controls
Number (%)	70 (19.4)	66 (18.3)	165 (45.7)	60 (16.6)	87
Age	67.2 (6.6) <sup>a,b,c</sup>	70.9 (8.0) <sup>d,e,*</sup>	73.8 (6.5)	73.3 (7.7)	72.6 (6.0)
Sex (% men)	33 (47.1)	38 (57.6)	95 (57.6)	31 (51.7)	54.0
Education (y)	16.3 (2.3)	16.2 (2.8)	16.2 (2.6)	16.1 (2.9)	16.8 (2.6)
GDS	1.66 (1.65)	1.94 (1.70)	1.51 (1.18)	1.41 (1.44)	0.97 (1.40)
APOE-ε4 (%)	16 (23.2) <sup>a,b</sup>	39 (59.1) <sup>e</sup>	112 (67.9) <sup>f</sup>	10 (16.7)	16 (18.6)
CDR sum	1.2 (0.7) <sup>b</sup>	1.3 (0.8) <sup>d</sup>	1.8 (1.0) <sup>f</sup>	1.3 (0.7)	0.0 (0.1)
Early MCI (%)	52 (74.3) <sup>b</sup>	47 (71.2) <sup>d</sup>	43.0 <sup>f</sup>	70.0	N/A
Late MCI (%)	18 (25.7) <sup>b</sup>	19 (28.8) <sup>d</sup>	57.3 <sup>f</sup>	30.0	N/A
After 12 mo					
CN (%)	6 (9.4) <sup>b,c</sup>	2 (3.3)	4 (2.5)	0 (0)	81 (95.3)
MCI (%)	56 (87.5) <sup>b,c,*</sup>	57 (95.0) <sup>d</sup>	122 (77.2) <sup>f</sup>	54 (96.4)	4 (4.7)
Dementia (%)	2 (3.1) <sup>b</sup>	1 (1.7) <sup>d</sup>	32 (20.3) <sup>f</sup>	2 (3.6)	0 (0)
After 24 mo					
N (%)	6 (10.5) <sup>b</sup>	3 (6.5)	4 (3.2)	1 (2.3)	69 (93.2)
MCI (%)	50 (87.7) <sup>b</sup>	41 (89.1) <sup>d</sup>	68 (54.4) <sup>f</sup>	42 (95.5)	3 (4.1)
Dementia (%)	1 (1.8) <sup>b</sup>	2 (4.3) <sup>d</sup>	53 (42.4) <sup>f</sup>	1 (2.3) <sup>g</sup>	2 (2.7)

Means and standard deviations are displayed. Number is displayed for all categorical variables, with percentages within parentheses.

Analyses of variance are performed for the normally distributed data, Mann-Whitney U tests for non-normally distributed data and Pearson  $\chi^2$  tests for dichotomous data. Key: AD, Alzheimer's disease; AMY, amyloid; APOE, apolipoprotein E; CDR, Clinical Dementia Rating; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; NEU, neurodegeneration; CN, Cognitively Normal; SNAP, suspected non-AD pathology.

<sup>a</sup> Significant difference between AMY–NEU– and AMY+NEU–.

<sup>b</sup> Significant difference between AMY–NEU– and AMY+NEU+.

<sup>c</sup> Significant difference between AMY–NEU– and AMY–NEU+.

<sup>d</sup> Significant difference between AMY+NEU– and AMY+NEU+.

<sup>e</sup> Significant difference between AMY+NEU– and AMY–NEU+.

<sup>f</sup> Significant difference between AMY+NEU+ and AMY–NEU+.

<sup>g</sup> Conversion rates at 24 months can be lower than at 12 months because of loss to follow-up.

\* Trend

variable, and age and education as covariates. The threshold-free cluster enhancement method (Smith and Nichols, 2009) in the FSL toolkit (Smith et al., 2004) was used to define clusters of significant effect, which were subsequently corrected with a family-wise error rate correction based on permutation-based clustering (Nichols and Holmes, 2002). For the voxelwise analyses, a threshold of  $p < 0.01$  was chosen.

### 3. Results

#### 3.1. Description of the 4 groups

Of the MCI participants, 19.4% fell in the AMY–NEU– group, 18.3% in the AMY+NEU– groups, 45.7% in the AMY+NEU+ group, and 16.6% in the AMY–NEU+, or SNAP, group (Fig. 1). The SNAP

**Table 2**  
CSF, imaging markers, and cognitive performance in the SNAP group, compared with the other MCI groups

	AMY–NEU–	AMY+NEU–	AMY+NEU+	AMY–NEU+ (SNAP)
CSF Aβ42 pg/mL	233 (26) <sup>a,b</sup>	146 (25) <sup>d,e</sup>	137 (26) <sup>f</sup>	232 (28)
Florbetapir (SUVR)	1.02 (0.07) <sup>a,b</sup>	1.29 (0.21) <sup>d,e</sup>	1.34 (0.20) <sup>f</sup>	1.00 (0.06)
CSF tau pg/mL	54 (26) <sup>a,b</sup>	93 (48) <sup>d,e</sup>	112 (58) <sup>f</sup>	60 (28)
CSF p-tau pg/mL	28 (14) <sup>a,b</sup>	48 (29) <sup>e</sup>	51 (24) <sup>f</sup>	28 (15)
FDG-PET (z-score)	0.07 (0.87) <sup>b,c</sup>	0.11 (1.03) <sup>d,e</sup>	–1.28 (1.18) <sup>f</sup>	–0.52 (1.03)
HV (z-score)	0.74 (1.05) <sup>a,b,c</sup>	0.25 (0.76) <sup>d,e</sup>	–1.51 (1.00)	–1.27 (1.03)
WMH (z-score)	0.07 (0.93) <sup>a,b,c</sup>	–0.31 (1.25) <sup>c,d</sup>	–0.71 (1.06)	–0.46 (1.12)
ICV	1357 (126) <sup>b,c</sup>	1382 (126) <sup>d,*</sup>	1417 (145)	1419 (146)
VIQ	118.9 (7.2)	118.3 (9.0)	117.4 (8.7)	116.6 (8.9)
MMSE score	28.9 (1.1) <sup>b,c</sup>	28.6 (1.6) <sup>d</sup>	27.5 (1.8) <sup>f</sup>	28.1 (1.8)
Immediate memory (z-score)	–0.17 (0.75) <sup>a,b,c</sup>	–0.57 (0.67) <sup>d</sup>	–0.88 (0.61) <sup>f</sup>	–0.67 (0.65)
Delayed memory (z-score)	–0.24 (0.97) <sup>a,b,c</sup>	–0.72 (0.82) <sup>d</sup>	–1.53 (0.85) <sup>f</sup>	–0.96 (0.90)
Recognition memory (z-score)	–0.22 (0.81) <sup>a,b,c</sup>	–0.58 (1.06) <sup>d</sup>	–1.21 (0.93) <sup>f</sup>	–0.78 (1.01)
Trail A (z-score) <sup>h</sup>	–0.14 (1.06) <sup>b,c</sup>	–0.46 (1.21) <sup>d</sup>	–1.03 (1.20) <sup>f</sup>	–0.64 (1.05)
Trail B (z-score) <sup>h</sup>	–0.28 (0.92) <sup>a,b,c</sup>	–0.73 (1.14) <sup>d</sup>	–1.23 (1.23) <sup>f</sup>	–0.80 (1.04)
Verbal fluency (z-score)	–0.26 (0.91) <sup>a,b,c</sup>	–0.58 (1.00) <sup>d</sup>	–0.93 (0.90)	–0.75 (0.87)
BNT (z-score)	–0.36 (1.05) <sup>b</sup>	–0.54 (1.18)	–0.89 (1.51)	–0.60 (1.28)

Means and standard deviations are displayed. Analyses of variance are performed for the normally distributed data and Mann-Whitney U tests for non-normally distributed data.

Key: Aβ, amyloid-beta; AMY, amyloid; BNT, Boston Naming Test; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; HV, hippocampal volume; ICV, intracranial volume; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; NEU, neurodegeneration; SNAP, suspected non-AD pathology; SUVR, standardized uptake value ratio; VIQ, verbal Intelligent Quotient; WMH, white matter hyperintensity.

<sup>a</sup> Significant difference between AMY–NEU– and AMY+NEU–.

<sup>b</sup> Significant difference between AMY–NEU– and "amyloid AMY+NEU+."

<sup>c</sup> Significant difference between AMY–NEU– and AMY–NEU+.

<sup>d</sup> Significant difference between AMY+NEU– and AMY+NEU+.

<sup>e</sup> Significant difference between AMY+NEU– and AMY–NEU+.

<sup>f</sup> Significant difference between AMY+NEU+ and AMY–NEU+.

<sup>h</sup> Note that the z-scores of the Trail A and B are inverted, with lower scores reflecting worse performance on the test.

\* Trend



**Table 3**  
Description of the 3 SNAP groups

	HIPPO+	FDG+	HIPPO+FDG+
Number (%)	43 (71.7)	9 (15.0)	8 (13.3)
Age (y)	72.5 (7.5) <sup>b,*</sup>	73.2 (9.3)	77.5 (6.4)
APOE-ε4	16.3	22.2	12.5
CDR sum	1.1 (0.6)	1.3 (0.7)	1.8 (1.1)
Conversion after 12 mo			
CN (%)	0	0	0
MCI (%)	97.5	100	85.7
AD (%)	2.5	0	14.3
HV (z-score)	-1.53 (0.71) <sup>a</sup>	0.40 (0.45) <sup>c</sup>	-1.82 (1.15)
FDG-PET (z-score)	-0.05 (0.80) <sup>a,b</sup>	-1.73 (0.48)	-1.70 (0.32)
CSF Aβ pg/mL	234 (27) <sup>b,*</sup>	241 (40) <sup>c,*</sup>	214 (16)
Florbetapir (SUVR)	1.00 (0.06)	1.01 (0.08)	0.98 (0.06)
WMH (z-score)	-0.38 (1.12)	-0.73 (1.27)	-0.61 (1.08)
MMSE score	28.3 (1.5) <sup>b</sup>	29.1 (1.5) <sup>c</sup>	25.9 (1.6)
Immediate memory (z-score)	-0.62 (0.70)	-0.88 (0.41)	-0.69 (0.63)
Delayed memory (z-score)	-0.88 (0.91)	-1.10 (0.90)	-1.23 (0.94)
Recognition memory (z-score)	-0.76 (1.03)	-0.94 (0.93)	-0.72 (1.11)

Means and standard deviations are displayed. Analyses of variance are performed for the normally distributed data, Mann-Whitney U tests for non-normally distributed data and Pearson  $\chi^2$  tests for dichotomous data.

Key: Aβ, amyloid-beta; AD, Alzheimer's disease; APOE, apolipoprotein E; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; HV, hippocampal volume; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; CN, cognitively normal; SNAP, suspected non-Alzheimer's disease pathology; SUVR, standardized uptake value ratio; WMH, white matter hyperintensity.

<sup>a</sup> Significant difference between "HIPPO+" and "FDG+".

<sup>b</sup> Significant difference between "HIPPO+" and "HIPPO+FDG+".

<sup>c</sup> Significant difference between "FDG+" and "HIPPO+ FDG+".

\* Trend

group was older than the NEU- groups but was not different from the AMY+NEU+ group or AMY- controls (Table 1). The 4 MCI groups did not differ on sex and education; the SNAP group also did not differ on sex and education from the AMY- controls. The 4 MCI groups also did not differ on Geriatric Depression Scale. The AMY- groups had significantly lower prevalence of APOE-ε4 than the AMY+ groups. The SNAP group had a lower CDR sum of boxes score, a lower prevalence of late MCI, and a lower conversion rate to dementia after 12 and 24 months than the AMY+NEU+ group but was not different on these measures from either NEU- groups. However, the SNAP group (0%) and the AMY+NEU+ (2.5%) groups both have a lower rate of "reversion to normal" than the AMY-NEU- group (9.5%) at 12 months. Similar differences in reversion rate were also observed at 24 months although in this case only the difference between the AMY+NEU+ and AMY-NEU- group reached significance (AMY-NEU-: 10.5%; AMY+NEU+: 3.2%; SNAP: 2.3%).

When using the less stringent cutoff of the 90th percentile of the distribution of AMY+ participants with AD dementia, more MCI participants were counted toward the AMY+NEU+ and the SNAP group (Fig. 1). Repeating the analyses with these groups, in this and the following sections, did not notably change the results.

## 3.2. Potential role of subthreshold amyloid, tau, and WMHs in SNAP

### 3.2.1. Subthreshold presence of amyloid

We reasoned that if the SNAP category reflected individuals who had some degree of cerebral amyloid but did not reach the threshold defined by the CSF Aβ42 cutoff applied, they would tend to display CSF values closer to this cutoff than those AMY- MCI participants without neurodegeneration or amyloid-negative, cognitively normal adults. In fact, there was no hint of a lower CSF Aβ42 in SNAP (232 ± 28 pg/mL) relative to AMY-NEU- MCI participants (233 ± 26 pg/mL;  $p = 0.90$ ) (Table 2) nor a difference with cognitively normal adults (235 ± 26 pg/mL;  $p = 0.60$ ). Moreover, if the CSF Aβ42 results in the SNAP group reflected a subthreshold or false-negative based on CSF, we would expect to

see more evidence of amyloid signal using an alternative measure of cerebral amyloid, florbetapir PET. Again, SUVRs were, if anything, slightly lower in the SNAP group (1.00 ± 0.06) than the AMY-NEU- MCI participants (1.02 ± 0.07;  $p = 0.34$ ) and amyloid-negative controls (1.02 ± 0.07;  $p = 0.09$ ). To explore whether there may be a regional effect, we also compared florbetapir retention in the ROIs that make up the composite measure and, again, did not find evidence of increased uptake in the SNAP group. In fact, uptake trended to be higher in the amyloid-negative controls in the anterior and posterior cingulate ( $p = 0.07$ ) and the temporal lobe ( $p = 0.08$ ).

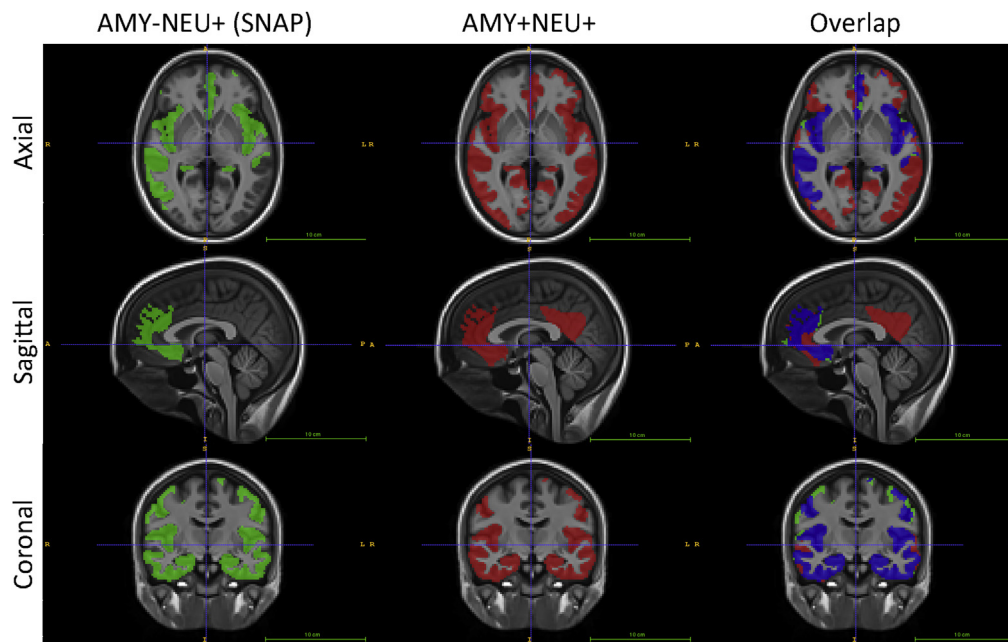
### 3.2.2. CSF tau levels

If PART underlies SNAP-MCI, we might expect to see elevated CSF levels of tau and p-tau relative to groups without neurodegeneration. However, the SNAP group did not differ from the AMY-NEU- MCI group on CSF tau (60 ± 28 vs. 54 ± 26 pg/mL, respectively  $p = 0.83$ ) or p-tau levels (28 ± 15 vs. 28 ± 14 pg/mL;  $p = 0.54$ ) (Table 2). The SNAP group also did not significantly differ from AMY- controls on tau (61 ± 25 pg/mL;  $p = 0.26$ ), but p-tau levels were actually slightly elevated in the AMY- controls compared with SNAP (31 ± 14 pg/mL;  $p = 0.02$ ).

### 3.2.3. White matter hyperintensities

We investigated the potential role of WMH, a proxy for CVD. The SNAP group had larger WMH volumes than the AMY-NEU- group (log-transformed WMHs: -2.57 ± 0.52 vs. -2.81 ± 0.43, see Table 2 for log-transformed z-scores;  $p = 0.01$ ) and the AMY- controls (log-transformed WMHs: -2.78 ± 0.46;  $p = 0.01$ ). The SNAP group was older than the AMY-NEU- MCI group, and age is known to be associated with WMHs. When repeating the analyses with age as a covariate, the difference in WMH volume was no longer significant ( $p = 0.39$ ). Nonetheless, this effect remained significant in the comparison of SNAP with AMY- controls ( $p = 0.01$ ).

In light of this association with WMH volume, we investigated whether the SNAP group also displayed higher rates of vascular risk factors. Indeed, there was some evidence to support this notion



**Fig. 2.** Cortical atrophy, compared with AMY<sup>−</sup> controls, in the SNAP group (green), the AMY+NEU<sup>+</sup> group (red), and both displayed in one image (green = cortical atrophy only in SNAP compared with AMY<sup>−</sup> controls, red = cortical atrophy only in AMY+NEU<sup>+</sup> mild MCI compared with AMY<sup>−</sup> controls, blue = cortical atrophy in both SNAP, and AMY+NEU<sup>+</sup> MCI compared with AMY<sup>−</sup> controls). Significant voxels thresholded at  $p < 0.01$  (FWE corrected), are displayed. Abbreviations: AMY, amyloid; NEU, neurodegeneration; SNAP, suspected non-Alzheimer's disease pathology. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(see [Supplementary Table 1](#)). The SNAP group differed significantly from the AMY<sup>−</sup>NEU<sup>−</sup> MCI group for history of hypertension (51.7 vs. 32.9%,  $p = 0.03$ ), cardiovascular disease (68.3 vs. 47.1%,  $p = 0.02$ ), and a trend level for history of smoking (38.3 vs. 24.3%,  $p = 0.08$ ) but not for mean arterial pressure (MAP) or body mass index. However, correcting for age, there was no longer a significant difference for history of hypertension ( $p = 0.26$ ) or smoking ( $p = 0.12$ ) and only trend level difference for cardiovascular disease ( $p = 0.10$ ). Alternatively, the comparison of the SNAP group with AMY<sup>−</sup> controls revealed that MAP was slightly elevated at a trend level in the SNAP group ( $99.7 \pm 8.3$  vs.  $93.3 \pm 8.1$  mm Hg;  $p = 0.054$ ; which remained after correcting for age:  $p = 0.055$ ) but no difference could be observed for the other risk factors. It is notable that the MAP difference between the SNAP group and both the AMY<sup>−</sup>NEU<sup>−</sup> MCI group and AMY<sup>−</sup> controls was quantitatively similar despite the difference in statistical significance.

#### 3.2.4. Other biomarkers

When comparing SNAP with AMY<sup>−</sup>NEU<sup>−</sup> MCI participants on other markers, we found, consistent with group definitions, that the SNAP group had smaller hippocampal volumes ( $p < 0.001$ ) and displayed greater hypometabolism measured by FDG-PET ( $p < 0.01$ ). Correcting for age did not notably change the results. In addition, SNAP had larger ICV ( $p = 0.01$ ). Correcting for age or sex did not notably change the results.

Also consistent with its classification, the SNAP group had higher levels of CSF A $\beta$ 42 ( $p < 0.001$ ) and lower florbetapir uptake SUVR ( $p < 0.001$ ) relative to the AMY+NEU<sup>+</sup> group. However, the SNAP group did display a lesser degree of neurodegeneration; SNAP participants displayed less hypometabolism on FDG-PET ( $p < 0.001$ ) and had larger hippocampi than the AMY+NEU<sup>+</sup> group, though the latter did not reach significance ( $p = 0.11$ ). The SNAP group also displayed lower total tau ( $p < 0.001$ ) and p-tau levels ( $p < 0.001$ ) than the AMY+NEU<sup>+</sup> group but did not differ on WMHs ( $p = 0.13$ ) or ICV ( $p = 0.92$ ).

The discrepancy in neurodegeneration may, in part, drive differences in cognition (see the following section) and other markers between the 2 groups. To better account for this, we matched the groups on the degree of hippocampal atrophy; that is, every SNAP patient was matched with an AMY+NEU<sup>+</sup> patient with a comparable degree of hippocampal atrophy. It is notable that even when doing so, the AMY+NEU<sup>+</sup> group still displayed significantly more hypometabolism in the FDG-PET meta-ROI ( $p < 0.001$ ), suggesting more widespread cortical dysfunction than in SNAP. Results for all other measures were similar.

#### 3.3. Cognitive profile of SNAP

SNAP did not differ from the other groups on estimated verbal IQ but did have slightly higher MMSE scores than the AMY+NEU<sup>+</sup> group ( $p = 0.02$ ) ([Table 2](#)). While the SNAP group displayed greatest impairment, based on control-referenced z-scores, on delayed recall, nonmemory domains also were relatively impaired. In contrast, on most cognitive measures the AMY<sup>−</sup>NEU<sup>−</sup> group displayed z-scores that were just below the mean of the control group, most ~one-fourth of a standard deviation below control participants. Alternatively, AMY+NEU<sup>+</sup> participants displayed the most significant degree of impairment with the SNAP group intermediate. Indeed, the SNAP group performed significantly worse not only on all memory domains but also on the Trail Making Test and verbal fluency compared with the AMY<sup>−</sup>NEU<sup>−</sup> group. In turn, the AMY+NEU<sup>+</sup> performed worse than the SNAP group on most psychometric measures with the exception of verbal fluency and Boston Naming Test. Repeating the analyses when comparing the SNAP with the AMY<sup>−</sup>NEU<sup>−</sup> MCI group corrected for age, did not notably change the results, although the groups no longer differed on Trails A ( $p = 0.25$ ) and Trails B ( $p = 0.33$ ).

To determine whether the differences in cognition between the SNAP and AMY+NEU<sup>+</sup> groups were driven largely by differences in the degree of neurodegeneration, we examined cognitive

performance between the groups after matching for hippocampal volume. Nonetheless, this did not markedly change the results, although immediate memory no longer reached significance ( $p = 0.27$ ). Thus, the groups still differed significantly on MMSE ( $p = 0.04$ ), delayed recall ( $p = 0.00$ ), recognition memory ( $p = 0.02$ ), Trails A ( $p = 0.03$ ), and Trails B ( $p = 0.05$ ), suggesting that these differences were driven by more than just the degree of hippocampal involvement.

#### 3.4. Comparison of 3 SNAP groups

To further understand the nature of the SNAP category, we divided it into 3 subgroups based on whether the designation of neurodegeneration positive was achieved by hippocampal volume alone, FDG-PET alone, or both modalities (Table 3). Of all SNAP-MCI participants, 71.7% was positive by hippocampal volume (HIPPO+) alone, 15.0% by FDG-PET (FDG+) alone, and 13.3% were positive by both markers. Given the small number of the latter 2 groups, these analyses are exploratory in nature. The HIPPO+FDG+ group was more severely affected with a higher CDR sum of boxes score and lower MMSE than the other groups and more similar to the AMY+NEU+ group. Interestingly, there was a tendency for the SNAP participants with both abnormal FDG-PET and hippocampal volume to have lower CSF A $\beta$ 42 levels, perhaps consistent with the notion that this group's amyloid-negative status may reflect their falling in a subthreshold range based on standard cutoffs. However, this finding was not supported by a similar difference with florbetapir PET and, thus, is difficult to interpret. It is also worth noting that the largest subgroup with isolated hippocampal atrophy did not display any tendency toward evidence of hypometabolism in the FDG-PET meta-ROI ( $z$ -score =  $-0.05$ ), inconsistent with the notion that hypometabolism in these regions may simply reflect network level effects of hippocampal degeneration (Jack, 2014).

#### 3.5. Voxelwise cortical thickness analyses in the 4 MCI groups

The above data suggest greater hippocampal than cortical involvement overall in the SNAP group, at least as measured by magnetic resonance imaging volumetry and FDG-PET, respectively. Furthermore, the FDG data used a meta-ROI restricted to AD-specific posterior brain regions. To better determine the degree to which there is sparing of cortical structures in SNAP and to compare the overall pattern of involvement with the AMY+NEU+ group, we also performed an analysis of cortical thickness across the entire cortical mantle. We compared each of the MCI groups with the AMY– controls (see Fig. 2). The main findings from these analyses are (1) that, when compared to AMY– controls, neither the AMY–NEU– or AMY+NEU– groups showed significant cortical atrophy ( $p < 0.01$ , familywise error rate) confirming their “neurodegeneration negative” status, and (2) that, we found widespread atrophy in the NEU+ MCI groups, including broad temporal and frontal regions, such as the anterior medial temporal lobe; parahippocampal gyrus; fusiform gyrus; inferior, middle, superior temporal gyri; insula, anterior cingulate; and orbital, middle, and superior frontal regions (Fig. 2). In addition to these frontal and temporal regions, the AMY+NEU+ group, but not the SNAP group, also showed cortical thinning in posterior regions typically associated with atrophy in AD, such as the posterior cingulate gyrus, precuneus, and inferior parietal gyrus. Otherwise, there was considerable overlap. However, when directly comparing the SNAP with the AMY+NEU+ group no statistical differences were observed.

Because the 4 MCI groups differ in size, the power to detect statistical differences in the comparison with AMY– controls differs accordingly. We, therefore, also calculated the average difference in

absolute thickness between the MCI groups and the AMY– controls, a measure independent of group size and show that the results are similar to previously reported statistically thresholded findings (Supplementary Fig. 1).

## 4. Discussion

Consistent with the distribution seen in prior studies (Caroli et al., 2015; Petersen et al., 2013; Prestia et al., 2013), we found that 16.6% of MCI patients in the ADNI-GO or ADNI-2 cohort qualified as SNAP patients, 19.4% were negative on both amyloid and neurodegeneration biomarkers, 18.3% were positive on only the amyloid biomarker, and 45.7% displayed evidence of both cerebral amyloid and neurodegeneration, or had high likelihood of “prodromal AD”. The SNAP group was generally intermediate with regard to cognition and outcomes relative to the AMY–NEU– and AMY+NEU+ group. Although we did not find evidence that SNAP patients display subthreshold cerebral amyloid or CSF evidence of tau pathology, it does appear this category is associated with increased CVD. We will discuss these groups and relevant findings in turn in the following section.

### 4.1. SNAP-MCI patients

The SNAP group presented as a distinct group of patients, who were relatively older than amyloid-negative MCI patients without neurodegeneration, had a low prevalence of APOE- $\epsilon$ 4 and a low conversion rate to dementia. They did display greater impairment on cognitive measures than the AMY–NEU– group but were less impaired and sustained less evidence of neurodegenerative change than the AMY+NEU+ group. The prevalence of 16.6% of this group falls in the lower end of the range of previous studies (Caroli et al., 2015; Petersen et al., 2013; Prestia et al., 2013), probably because our cutoff were more stringent than in most previous studies. Indeed, when using our less stringent cutoffs, a higher prevalence of 21.3% of SNAP was found.

The SNAP group in this cohort had a relatively low conversion rate to dementia of  $<5\%$  after 24 months. Previous studies on SNAP in MCI patients have reported higher conversion rates: from 20% after 15 months (Petersen et al., 2013) to 42% after 23 months (Prestia et al., 2013) to 56% after 6 years (Caroli et al., 2015). It is unclear why there is such a wide variation in conversion rates in the literature, but there are a number of differences in the nature of current cohort relative to these prior studies. One possible contribution is the different inclusion criteria used for MCI across the studies. Whereas in ADNI only MCI patients of the amnesic type were included, previous studies also included nonamnesic MCI patients (Caroli et al., 2015; Petersen et al., 2013; Prestia et al., 2013) who may have different pathophysiologic underpinnings, clinical phenotypes, and conversion rates. However, in the Petersen et al. cohort only the amnesic MCI SNAP patients were examined with regard to longitudinal outcome. The severity of cognitive impairment across these studies is also likely relevant, as the ADNI-GO or ADNI-2 cohort is generally more mild, particularly because of the inclusion of the “early MCI” category, than these other studies exploring SNAP. For example, the mean MMSE of the SNAP group in the present study was 28.1 versus 26.5 in the Caroli et al. study and a median MMSE of 25 in the Petersen et al. SNAP group. This difference in severity also may be reflected in the degree of neurodegeneration as only  $\sim 13\%$  of the SNAP cohort here displayed neurodegeneration for both FDG-PET and hippocampal volume while  $\sim 38\%$  did so in the Caroli et al. cohort. It is worth noting that the slow progression in this SNAP-MCI group is akin to prior studies of cognitively normal SNAP patients (Knopman et al., 2012; Vos et al., 2013). As the group here, which contained a high

proportion of early MCI patients, more closely approaches the boundary of normal age-associated cognition and MCI than prior SNAP-MCI studies, it is perhaps unsurprising that the current group would be more similar to reports in cognitively normal SNAP.

In addition, prior studies were associated with relatively smaller sample sizes, used different biomarker cutoffs and methodologies, as well as, in some cases, different modalities to define categories. For example, Petersen et al. defined hippocampal volume and FDG-PET cutoffs based on 90% sensitivity in an AD cohort. However, when we used a similar approach it did not have significant impact on the longitudinal data despite increasing the proportion of individuals in the SNAP category. Finally, the nature of the populations from which participants were recruited also differed considerably, from a population-based study of aging to referrals from memory clinics, which could further modulate outcomes. While differences across studies are almost certainly a consequence of the heterogeneity of methods used for defining the SNAP category, it does appear that a significant proportion of this group may have relatively slow progression.

It has been postulated that SNAP may reflect, in part, individuals with cerebral amyloid, but that they fall below the cutoffs applied for dichotomously determining amyloid status (Duara et al., 2013). In essence, they would be “false negatives” due to subthreshold measures of amyloid. If this were the case, one would expect that the SNAP group would display measures of amyloid that are closer to this threshold than amyloid-negative MCI patients without evidence of neurodegeneration or amyloid-negative controls. Indeed, in a prior study of SNAP in cognitively normal adults, SNAP patients had relatively higher, although below the threshold, Pittsburgh Compound B uptake than amyloid-negative controls without neurodegeneration (Mormino et al., 2014). Nonetheless, we found no evidence for this in this MCI cohort. Values of CSF A $\beta$ 42 were no different in the SNAP group and the AMY-NEU- MCI and the cognitively normal adults. Moreover, there was no hint of increased florbetapir uptake relative to either amyloid-negative group. This finding is perhaps most convincing, given that this imaging method was not used to dichotomize patients based on amyloid status.

Another hypothesis is that SNAP may be a clinical manifestation of the recently pathologically defined PART (Jack, 2014). Similar to PART (Crary et al., 2014), our SNAP patients are relatively older, have a low prevalence of APOE- $\epsilon$ 4 carriers, have a relatively low conversion rate, and predominantly have hippocampal atrophy (>70% of SNAP patients were defined as such based on hippocampal atrophy alone). PART patients have been described as spanning the range from cognitively normal to having mild impairments in cognition that would be consistent with the MCI group here although the overall cognitive profile of these patients remains to be well defined. While the link between PART and SNAP is compelling, we did not find evidence of elevated CSF tau or p-tau levels, which one might expect to be present if NFT pathology is the primary etiologic driver of the condition. Nonetheless, it is unclear how sensitive these CSF measures are to the earlier Braak stages associated with PART (mostly Braak I–III) and the expected slower rate of tangle progression compared to typical AD. Future studies using tau PET imaging (Ariza et al., 2015), which may more directly mark tau pathology, would likely clarify the role of PART in SNAP-MCI.

Another hypothesis that has been postulated is that CVD may play a role in this group. CVD has often been associated with cognitive decline (Au et al., 2006; Prins et al., 2005) and neurodegeneration, such as hippocampal atrophy (Chowdhury et al., 2011; den Heijer et al., 2005), and may therefore explain the cognitive impairments and neurodegeneration as seen in SNAP. Indeed, WMH volumes were higher in the SNAP-MCI patients than in amyloid-negative controls and AMY-NEU- MCI patients,

although the difference with the latter group disappeared after correcting for age perhaps reflecting a power issue. The importance of CVD is further supported by a recent study in cognitively normal participants in which WMHs were associated with abnormalities in biomarkers of AD-like neurodegeneration, including hippocampal volume and FDG-PET hypometabolism (Wirth et al., 2013). In addition, another study in cognitively normal adults showed that compared to adults without neurodegeneration and amyloid deposition, cognitively normal SNAP showed higher WMH volumes (Knopman et al., 2013). Although results for some of the vascular risk factors also displayed an association with the SNAP group, these findings were somewhat weak and inconsistent depending on whether comparison was with AMY-NEU- MCI participants or the AMY- controls. Future studies in larger sample sizes should clarify the role of vascular risk factors in the pathophysiology of SNAP.

In addition to the previously mentioned potential etiologies of SNAP, a number of other conditions have been entertained, such as hippocampal sclerosis, argyrophilic grain disease, Lewy body disease, or frontotemporal lobar degeneration associated with either tau- or TDP-43-based pathology. It is almost certainly the case that, SNAP-MCI is not a homogeneous group, and several pathologies likely play a role in this group. It is worth noting that whatever the underlying pathology, at least in this sample, the condition is relatively indolent. There is some suggestion for subgroups within SNAP-MCI in this cohort when individuals are divided based on whether evidence of neurodegeneration was determined by either hippocampal volume and/or FDG-PET. Most patients fell into the “hippocampus only” group, which may be more affected by “hippocampus-specific” pathologies, such as PART or hippocampal sclerosis, whereas those with FDG-PET abnormalities may have more cortical involvement and other etiologies.

However, the cortical thickness results suggest that even those with absent FDG-PET abnormalities do display more widespread cortical involvement. This cortical atrophy overlaps considerably in temporal and frontal regions with the AMY+NEU+ group but less so in posterior regions, which are also the regions in which the meta-ROI for the FDG-PET biomarker was derived and may then explain the weaker association with this measure. This pattern of atrophy overlaps with areas of NFT pathology with significant anterior and inferior temporal and ventromedial and/or orbitofrontal cortical thinning but would imply at least Braak stage IV, which has been suggested to be more progressed than typically associated with PART (Crary et al., 2014). This pattern is also observed with TDP-43-based pathology (Vemuri et al., 2011) and grossly overlaps with the recently described anterior medial temporal lobe (MTL) network (Das et al., 2015b), which also appears to display evidence of neurodegeneration in prodromal AD, along with the posterior MTL network that largely recapitulates the default mode. Indeed, the AMY+NEU+ group displays cortical thinning in both of these networks. Finally, cardiovascular and cerebrovascular disease has also been associated with not only hippocampal atrophy but also cortical changes particularly in frontal and temporal regions (Beauchet et al., 2013; Tuladhar et al., 2015) consistent with the current distribution and may best unify these data.

Ultimately, autopsy studies of this population will be important for determining the various potential etiologies. It is worth noting that one of the few studies with autopsy data of patients with amnesic MCI consisted largely of individuals who would have potentially been amyloid-negative, as more than half had either no or sparse senile plaques (Petersen et al., 2006). These patients represented a mixture of those with hippocampal sclerosis, argyrophilic grain disease, and some that would likely be classified as PART based on NFT burden. One should be cautious in drawing too strong of a parallel between this autopsy study and the current analysis as the mean age of death was ~89 years in the former



study, more than a decade older than in ADNI, and there was no information about the presence of biomarker evidence for neurodegeneration.

#### 4.2. MCI patients negative for both biomarkers of amyloid deposition and neurodegeneration

The AMY–NEU– group is also an interesting subset of MCI patients. Despite qualifying for a designation of MCI and having a Logical Memory Delayed recall  $\sim 2$  standard deviations below the control group, this group was minimally impaired on other cognitive measures, including composite memory scores which were  $< \text{one-fourth}$  standard deviations below the control group. In addition, no sign of atrophy was found in the cortical thickness analyses. This suggests that a significant proportion of these patients may not have an underlying neurodegenerative process or cognitive deficit beyond normal aging but perhaps performed poorly just on one specific test. Indeed, the reversion rate of 10% in these patients indicates that at least a portion of this group may be misdiagnosed as “MCI”. This is further supported by an even higher reversion rate of 50% after 15 months in another recent article in MCI patients (Peterson et al., 2013). The difference in reversion rate may be in part due to methodological differences in establishing the follow-up diagnosis. Whereas investigators in the ADNI study are aware of the previous diagnosis, investigators in the Mayo study (Peterson et al., 2013) are blinded to previous clinical data, which may lead to more likelihood to alter judgment of clinical status and, as such, to higher reversion rates. It should be noted that amyloid-negative and neurodegeneration negative MCI patients displayed smaller ICVs than the SNAP and prodromal AD group. It is therefore possible that this group has less brain reserve which might render them more vulnerable to pathology or “normal” age-related brain changes.

#### 4.3. Amyloid-positive MCI patients

Fitting with the model of prodromal AD (Sperling et al., 2011), the AMY+NEU+ group had the worst outcomes with a conversion rate of 42.4% after 12 months, performed worst of all groups on cognitive tests, and displayed most abnormal biomarker levels. Interestingly, even when the prodromal AD group and the SNAP group were matched on hippocampal atrophy, the prodromal AD group performed worse on a number of cognitive tests, including memory measures, indicating that degree of hippocampal atrophy only explains part of this impairment in prodromal AD. It is possible that involvement of other aspects of the memory network, including posterior cingulate hypometabolism, may contribute to their impaired performance beyond MTL involvement. Indeed, more extensive cortical atrophy, especially in posterior regions, was found in this group compared with the SNAP group, although this difference did not reach statistical significance when the groups were directly compared.

Interestingly, despite their lack of obvious neurodegeneration, the AMY+NEU– group displayed cognitive impairments, including on memory measures, intermediate between the AMY–NEU– and the prodromal AD group. Although not statistically different, their performance was mildly poorer than the SNAP group as well. This finding suggests that amyloid deposition may independently modulate cognitive function from the downstream neurodegeneration revealed by hippocampal volume, cortical thickness, and FDG-PET. However, it is worth noting that this group did display evidence of elevated tau and p-tau relative to the amyloid-negative groups and only slightly less so than the AMY+NEU+ patients. As tau pathology may also be considered reflective of neurodegeneration, some of these individuals would be classified

as AMY+NEU+ if used as criteria. Thus, the presence of NFT pathology before obvious volumetric or metabolic change may still be sufficient to disrupt cognitive processes.

A strength of the present study is the large sample size. In addition, we used different methods to determine cutoff points for the neurodegenerative markers and provided a comprehensive characterization of the groups on a large number of biofluid, imaging, and cognitive measures. Another strength is the relatively long follow-up time. However, one previous study with much longer longitudinal data, 6 years of follow-up (Caroli et al., 2015), reported results, such as conversion rates, that were discordant from the present study. This suggests that a longer follow-up with multiple assessments may provide a more comprehensive picture of the conversion rates over time in the different MCI groups. Other limitations are that, we used only 1 marker for CVD, which was a global rather than regional measure, and that the psychometric measures emphasized the memory domain and were less comprehensive for other areas of cognition. In addition, according to our cutoff points for hippocampal volume and FDG-PET, our AMY– control group may have contained research participants with neurodegeneration, who would likely fall into the SNAP category as well and could obscure differences with the MCI SNAP group. However, repeating the analyses without these AMY– NEU+ controls did not notably change the results.

In conclusion, we provided further evidence for “SNAP” as a distinct group of MCI patients. We found evidence that sub-threshold levels of cerebral amyloidosis is unlikely to play a role, but the “hippocampus-specific” pathologies and CVD may underlie the neurodegeneration and cognitive impairments for many in this group. Moreover, MCI patients negative on both amyloid and neurodegeneration markers may reflect, in part, patients that have been “misdiagnosed” as MCI or patients with only very subtle cognitive impairment. Future studies should provide a more comprehensive analysis of different cognitive domains, longitudinal measurement of cortical, and hippocampal subfield change, which may suggest specific MTL pathologies based on the topography of atrophy. Certainly, a longer follow-up time and eventually autopsy data in SNAP patients will be needed to gain more insight in which pathologies drive this phenotype.

#### Disclosure statement

The authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neurobiolaging.2015.08.029>.

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