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Defining SNAP by cross-sectional and longitudinal definitions of neurodegeneration

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ABSTRACT

Introduction: Suspected non-Alzheimer's pathophysiology (SNAP) is a biomarker driven designation that represents a heterogeneous group in terms of etiology and prognosis. SNAP has only been identified by cross-sectional neurodegeneration measures, whereas longitudinal measures might better reflect "active" neurodegeneration and might be more tightly linked to prognosis. We compare neurodegeneration defined by cross-sectional 'hippocampal volume' only (SNAP/L−) versus both cross-sectional and longitudinal 'hippocampal atrophy rate' (SNAP/L+) and investigate how these definitions impact prevalence and the clinical and biomarker profile of SNAP in Mild Cognitive Impairment (MCI).

Methods: 276 MCI patients from ADNI-GO/2 were designated amyloid "positive" (A+) or "negative" (A−) based on their florbetapir scan and neurodegeneration 'positive' or 'negative' based on cross-sectional hippocampal volume and longitudinal hippocampal atrophy rate.

Results: 74.1% of all SNAP participants defined by the cross-sectional definition of neurodegeneration also met the longitudinal definition of neurodegeneration, whereas 25.9% did not. SNAP/L+ displayed larger white matter hyperintensity volume, a higher conversion rate to dementia over 5 years and a steeper decline on cognitive tasks compared to SNAP/L− and the A- CN group. SNAP/L− had more abnormal values on neuroimaging markers and worse performance on cognitive tasks than the A- CN group, but did not show a difference in dementia conversion rate or longitudinal cognition.

Discussion: Using a longitudinal definition of neurodegeneration in addition to a cross-sectional one identifies SNAP participants with significant cognitive decline and a worse clinical prognosis for which cerebrovascular disease may be an important driver.

1. Introduction

Biomarkers of Alzheimer's disease (AD) have generally been divided into two classes: molecular (e.g. amyloid PET, cerebrospinal fluid (CSF) Aβ) and neurodegenerative (e.g. volumetric MRI and FDG PET). Neurodegeneration is by definition a dynamic process; however, most studies classify individuals on this dimension with cross-sectional measures. While a static measure captures past neurodegeneration, other factors may confound these measurements, for example, some individuals may have smaller hippocampal volumes for developmental or other reasons not related to neurodegeneration. A measure of declining volume over time, on the other hand, is likely a more specific indicator of a neurodegenerative process.

How we define neurodegeneration is gaining importance, as neurodegeneration is often used for classification in staging models. For example, the presence of atrophy or hypometabolism in the absence of cerebral amyloid defines the recently labeled category of suspected non-Alzheimer's pathophysiology (SNAP). A significant proportion of patients with Mild Cognitive Impairment (MCI) have received this classification based on cross-sectional measures of neurodegeneration

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(Caroli et al., 2015; Petersen et al., 2013; Prestia et al., 2013). However, the clinical implication of SNAP-MCI status remains unclear, as previous reports have shown widely varying results with regard to progression to dementia and cognitive decline. The reported progression vary from 0% to 56% in 2–3 years of follow-up (Caroli et al., 2015; Prestia et al., 2013; Wisse et al., 2015; Schreiber et al., 2017) and one study even reported a higher dementia progression rate in SNAP than in an amyloid and neurodegeneration positive, or prodromal AD (pAD), group (Petersen et al., 2013). Similar inconsistent findings are present for cognitive decline in these groups, with some studies showing almost similar cognitive decline in SNAP and pAD (Caroli et al., 2015), whereas others showed significantly less cognitive decline in SNAP as compared to pAD (Schreiber et al., 2017; Knopman et al., 2015; Chung et al., 2017). It is possible that these mixed results are partly attributable to heterogeneity in underlying 'active' neurodegeneration in SNAP, but also in pAD. While extant studies have investigated longitudinal change in neurodegeneration markers in SNAP ((Knopman et al., 2015), also note (Burnham et al., 2016; Gordon et al., 2016) in CN older adults), no prior study has utilized a longitudinal measure of neurodegeneration to *define* this group.

We therefore compare cross-sectional evidence of neurodegeneration using hippocampal volume only (L−) versus evidence of both cross-sectional and longitudinal neurodegeneration using hippocampal atrophy rate (L+) in the classification of MCI patients. As a conceptual study, we aim to examine the impact of these definitions on progression to dementia and cognitive decline. We hypothesize that the SNAP/L+ group will be enriched in individuals with a higher rate of progression to dementia and more cognitive decline than the SNAP/L− group. Additionally, we compare these groups on a number of biofluid and imaging markers aiming to gain understanding in the underlying pathology, e.g. the role of subthreshold amyloid or vascular pathology. We hypothesize that these groups have different biomarker profiles reflecting differences in the presence of more rapid neurodegeneration.

2. Materials and methods

2.1. Participants

We used data from ADNI-GO/2 (see Supplementary material) from 276 MCI participants with florbetapir and MRI scans at baseline and within 7–18 months after.

To establish cut-off points for neurodegenerative measures, we used data from amyloid positive (A+) participants (see Group definitions) with AD dementia for whom a baseline and follow-up (7–18 months after baseline) MRI scan were available ($n = 66$). Additionally, amyloid negative (A−) cognitively normal older adults with MRI scans at these points ($n = 76$) were used as a reference for the analyses in the different SNAP- and pAD-defined groups.

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

2.2. Imaging and biofluid markers

For hippocampal volume, baseline 3T T1-MRI scans were used. Hippocampal volume was measured using a previously published multi-atlas segmentation method (Wang et al., 2011). Hippocampal atrophy rates were computed with an unbiased deformation-based morphometry technique (described in (Yushkevich et al., 2010)) that measures change in hippocampal volume between baseline and follow-up MRI. See details in Supplementary material. Hippocampal volume at baseline was corrected for intracranial volume (ICV), obtained as described below. The difference in hippocampal volume between the two time points was expressed as percentage volume loss per year. An average over the two hemispheres was used for both measures.

ICV, white matter hyperintensity (WMH) volume, standardized uptake value ratio (SUVR) for the florbetapir and FDG-PET images, SPARE-AD (Spatial pattern of Abnormality for Recognition of Early AD) – an index derived from imaging data to quantify brain atrophy patterns typical of AD (Davatzikos et al., 2009), APOE-ε4 carrier status and CSF levels of Aβ42 came from publicly available processed data on the ADNI website. See Supplementary material for details.

2.3. Clinical and neuropsychological assessment

The Clinical Dementia Rating sum of boxes score (Morris, 1993) was obtained for all subjects during screening and diagnosis up to 5 years after baseline was analyzed. All participants underwent the Mini Mental Status Examination (MMSE) (Folstein et al., 1975) and tests of specific cognitive domains at baseline. A composite score was calculated for delayed recall, based on the 5- and 30-min trial of the Auditory Verbal Learning Test (Rey, 1964) and the Delayed Recall Task of the Alzheimer's Disease Assessment Scale-Cognitive (Rosen et al., 1984). Given the potential role of vascular disease in SNAP and its potential impact on executive functioning, we also examined the Trail Making Test B (TMT-B), which was log-transformed before conversion to z-score and inverted so that lower values represent worse performance. *Z*-scores were calculated using the means and standard deviations of the A- CN group at baseline. We also analyzed change over time using data from the 1, 2, 3 and 4 year visits.

2.4. Group definitions

Amyloid status was defined by a florbetapir SUVR value of 1.11 (Landau et al., 2012). Neurodegeneration status was defined by two different measures: baseline hippocampal volume (corrected for ICV) and annual hippocampal atrophy rate. As done previously (Petersen et al., 2013; Jack Jr et al., 2012; Knopman et al., 2013), the cut-off point for the cross-sectional measure was obtained by taking the 90th percentile of the A+ participants with AD dementia. The 90th percentile for the longitudinal measure provided a cut-off point of −0.22, which is not reflective of active neurodegeneration. We therefore chose a stricter cut-off point at the 80th percentile. A cut-off point of 2044 mL for ICV-corrected hippocampal volume and −0.80%/year for hippocampal atrophy rate was established with this approach.

2.5. Statistical analyses

Cross-sectional cognitive and biomarker profile for the differentially defined SNAP groups was analyzed using analyses of variance for normally distributed data, Mann-Whitney *U* tests for non-normally distributed data and Pearson χ^2 tests for categorical data. In a second analysis, we corrected for age, gender and education for the cognitive tests in cases where there was a significant group difference. Moreover, we performed linear mixed-effects models (Laird and Ware, 1982) with group, time and a group*time interaction term to assess a group difference in cognitive decline over time. The fixed effects in the mixed-effects model included the above three terms and covariates (the specific cognitive task at baseline, age, gender and education). Subject-specific random intercept and slope for time were included in the mixed-effects model to account for correlations among repeated measures of the cognitive outcomes.

3. Results

3.1. Cross-sectional characterization of the SNAP groups

3.1.1. SNAP/L− vs SNAP/L+

Fifty-five MCI patients were considered SNAP with 25.9% receiving this designation based on only the cross-sectional measure (SNAP/L−) and 74.1% also meeting the longitudinal definition of neurodegeneration (SNAP/L+) (Table 1). SNAP/L− had a larger percentage of males, more years of education both at a trend level, and, interestingly, a