NeuroImage 105 (2015) 357–368

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The mediational effects of FDG hypometabolism on the association between cerebrospinal fluid biomarkers and neurocognitive function

N. Maritza Dowling [a,b,*], Sterling C. Johnson [b,c], Carey E. Gleason [b,c], William J. Jagust [d,e], for the Alzheimer's Disease Neuroimaging Initiative [1]

[a] Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA
[b] Alzheimer's Disease Research Center, University of Wisconsin, Madison, WI, USA
[c] Geriatric Research Education and Clinical Center, William S. Middleton Memorial Veterans Hospital, Madison, WI, USA
[d] Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA, USA
[e] Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA

ARTICLE INFO

Article history:
Accepted 20 October 2014
Available online 29 October 2014

Keywords:
CSF biomarkers
Beta amyloid
FDG-PET
Tau
Alzheimer's disease
Longitudinal mediation
Parallel process latent growth
Structural equation modeling

ABSTRACT

Positive cerebrospinal fluid (CSF) biomarkers of tau and amyloid beta42 suggest possible active underlying Alzheimer's disease (AD) including neurometabolic dysfunction and neurodegeneration leading to eventual cognitive decline. But the temporal relationship between CSF, imaging markers of neural function, and cognition has not been described. Using a statistical mediation model, we examined relationships between cerebrospinal fluid (CSF) analytes (hyperphosphorylated tau (p-Tau$_{181p}$), β-amyloid peptides 1–42 (Aβ$_{1-42}$), total tau (t-Tau), and their ratios); change in cognitive function; and change in [18F]fluorodeoxyglucose (FDG) uptake using positron emission tomography (PET). We hypothesized that a) abnormal CSF protein values at baseline, result in cognitive declines by decreasing neuronal glucose metabolism across time, and b) the role of altered glucose metabolism in the assumed causal chain varies by brain region and the nature of CSF protein alteration.

Data from 412 individuals participating in Alzheimer's Disease Neuroimaging (ADNI) cohort studies were included in analyses. At baseline, individuals were cognitively normal (N = 82), or impaired: 241 with mild cognitive impairment, and 89 with Alzheimer's disease. A parallel-process latent growth curve model was used to test mediational effects of changes in regional FDG-PET uptake over time in relation to baseline CSF biomarkers and changes in cognition, measured with the 13-item Alzheimer Disease's Assessment Scale–cognitive subscale (ADAS–Cog).

Findings suggested a causal sequence of events; specifically, FDG hypometabolism acted as a mediator between antecedent CSF biomarker alterations and subsequent cognitive impairment. Higher baseline concentrations of t-Tau, and p-Tau$_{181p}$ were more predictive of decline in cerebral glucose metabolism than lower baseline concentrations of Aβ$_{1-42}$. FDG-PET changes appeared to mediate t-Tau or t-Tau/Aβ$_{1-42}$-associated cognitive change across all brain regions examined. Significant direct effects of alterations in Aβ$_{1-42}$ levels on hypometabolism were observed in a single brain region: middle/inferior temporal gyrus.

Results support a temporal framework model in which reduced CSF amyloid-related biomarkers occur earlier in the pathogenic pathway, ultimately leading to detrimental cognitive effects. Also consistent with this temporal framework model, baseline markers of neurofibrillary degeneration predicted changes in brain glucose metabolism in turn causing longitudinal cognitive changes, suggesting that tau-related burden precedes neurometabolic dysfunction. While intriguing, the hypothesized mediational relationships require further validation.

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Abbreviations: AD, Alzheimer's disease; ADAS–Cog, Alzheimer Disease's Assessment Scale–cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging; ApoE, Apolipoprotein E; Aβ, β-amyloid; Aβ$_{1-42}$, β-amyloid peptides 1 to 42; Bc, Bias-corrected; CFI, Comparative fit index; CI, Confidence interval; CN, Cognitively normal; CSF, Cerebrospinal fluid; FDG, [18F] fluorodeoxyglucose; LGC, Latent growth curve; MCI, Mild cognitive impairment; MMSE, Mini Mental State Examination; PET, Positron emission tomography; PPLGC, Parallel-process latent growth curve; p-Tau$_{181p}$, Hyperphosphorylated tau; RMSEA, Root mean square error of approximation; ROI, Region of interest; SMC, Significant memory concern; TLI, Tucker–Lewis Index; t-Tau, Total tau.

* Corresponding author at: Department of Biostatistics and Medical Informatics, University of Wisconsin, School of Medicine and Public Health, Madison, WI 53792, USA.
E-mail address: nmdowlin@biostat.wisc.edu (N.M. Dowling).

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

http://dx.doi.org/10.1016/j.neuroimage.2014.10.050
1053-8119/Published by Elsevier Inc.

Introduction

A number of studies have investigated the efficacy of specific potential biomarkers of Alzheimer's disease (AD) pathology in the cerebrospinal fluid (CSF) and regional cerebral glucose metabolic rate, measured by positron emission tomography (PET) imaging with [18F]fluorodeoxyglucose uptake (FDG-PET), to predict outcomes, discriminate between disease stages, and assess prognosis (Choo et al., 2013; Herholz, 2003; Landau et al., 2010). The most frequently studied CSF analytes in AD for prognostic accuracy include markers for neurofibrillary degeneration (i.e., total tau [t-Tau] and hyperphosphorylated tau at threonine 181 [p-Tau_{181p}] proteins) and β-amyloid (Aβ) plaque pathology (Aβ peptides 1 to 42 [$A\beta_{1-42}$]). Compared to individual markers, ratios combining CSF measures have been shown to be stronger predictors of cognitive decline in different populations. For example, elevated ratios of p-$Tau_{181p}/A\beta_{1-42}$ and/or t-$Tau/A\beta_{1-42}$ predict cognitive impairment within a few years of onset in non-demented older adults (Craig-Schapiro et al., 2010; Fagan et al., 2007; Li et al., 2007; Roe et al., 2013), conversion from mild cognitive impairment (MCI) to AD (Hansson et al., 2006), and faster progression of functional and cognitive deficits in individuals with incipient dementia of the Alzheimer type (Snider et al., 2009). Similarly, in group studies FDG-PET has been consistently shown to be sensitive in detecting neurometabolic dysfunction even at the preclinical asymptomatic stage of AD, which strongly suggests its suitability as a marker to study the effect of disease pathology on brain metabolic function (de Leon et al., 2001; Drzezga et al., 2011; Jagust et al., 2006; Mosconi et al., 2013, 2010, 2009; Reiman et al., 2001). Furthermore, FDG-PET studies with cohorts of cognitively intact middle-age and young Apolipoprotein E (*ApoE*) ε4 carriers have also revealed MCI- and AD-like patterns of metabolic lesions in the same brain regions typically affected in clinical AD (Mosconi et al., 2008; Reiman et al., 2001, 1996). FDG PET and tau-related CSF analytes are both indicators of neural injury, but the temporal effects of these markers on each other and on cognitive decline have not been studied in a multimodal framework allowing for *formal tests* of mediational hypotheses.

Over the past decade, many studies have focused on defining the associations between symptom severity, alterations in CSF constituents or Aβ deposition, and concomitant or co-occurring decreased FDG uptake in several brain regions including parietal, temporal, and posterior cingulate gyrus. These associations have been largely studied in cognitively normal individuals (Petrie et al., 2009), those with MCI and AD compared with normal controls (Arlt et al., 2009; Fellgiebel et al., 2007, 2004; Hunt et al., 2006), or asymptomatic middle-age adults at increased risk for AD (Mosconi et al., 2013, 2008). Despite the consistent longitudinal research evidence on key AD-related biological changes, only a few studies have investigated longitudinal dynamic changes in multiple biomarkers associated with AD pathology (see, for example, de Leon et al., 2006; Lo et al., 2011; Sluimer et al., 2010; Zhang and Shen, 2011, 2012). One of these studies (Lo et al., 2011) used separate models, instead of a single multiple-group growth model (Muthén and Curran, 1997), to examine the relative associations between rates of change in $A\beta_{1-42}$ levels, FDG uptake, hippocampal volume, and rates of change in cognitive function in individuals enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The authors concluded that the pattern of changes across diagnostic groups (cognitively normal, CN; MCI; and AD) obtained in separate analyses provided evidence in support of a *sequential association* of events in which Aβ amyloid deposition preceded hypometabolism or hippocampal atrophy. However, to the best of our knowledge, no studies have applied longitudinal mediation models to explicate possible causal relationships between multiple biomarkers and their effect on cognitive outcomes in a heterogeneous sporadic disease population. The application of these modeling approaches is important in exploring and testing hypotheses on the role of biological markers in the chain of events that ultimately cause axonal dysfunction and neuronal degeneration. Although the mechanisms underlying these effects are still unknown, model-based hypothesis testing may elucidate causal relationships as possible explanations of these effects.

The present study applied a parallel-process latent growth curve (PPLGC) model (Cheong et al., 2003; MacKinnon et al., 2004) to test whether the relationship between several analytes in CSF, including p-Tau_{181p}, $A\beta_{1-42}$, t-Tau, and their ratios, and changes in cognitive function was mediated by changes in glucose metabolism in subjects diagnosed at baseline as CN, MCI, or AD. We hypothesized that a) abnormal CSF protein values at baseline increase the rate of decline in cognitive function by decreasing glucose metabolism across time, and b) the role of the mediator in the assumed causal chain varies across brain regions and the form of CSF protein level affected at baseline.

Materials and methods

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (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 to 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 co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, 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. Subjects 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. The study obtained written informed consent from all participants and was conducted with prior institutional review board approval at each participating center.

The population for this study included all participants with FDG-PET measures (up to the 24-month visit) and neuropsychological data (up to the 36-month follow-up visit) for at least two time points and available baseline CSF data. FDG measures that "failed" local quality control standards, had missing quality assessments, or obtained a "partial" assessment were excluded from the analysis. The study comprised 85.5% of the total sample in ADNI who underwent lumbar puncture at baseline. As shown in Table 1, the final analytical sample included 412 older adults with available data on variables of interest (1363 person–time observations) diagnosed at study entry as NC ($N = 82$), MCI ($N = 241$), and AD ($N = 89$). The participants were mostly male (57.5%), ranged in age from 48 to 89 years ($M = 72.28$, SD = 7.32), reported an average of 16.33 years of education (SD = 2.62; range, 8–20 years), and roughly 54% were carriers of at least one ApoE-ε4 allele. Table 1 also reports global cognition at baseline measured by the Mini Mental State Examination (MMSE; Folstein et al., 1975). As a way of evaluating the selectivity of the studied sample, we compared its demographic characteristics with those of the full ADNI participant