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Left lateralized cerebral glucose metabolism declines in amyloid-β positive persons with mild cognitive impairment

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ABSTRACT

Background: Previous publications indicate that Alzheimer's Disease (AD) related cortical atrophy may develop in asymmetric patterns, with accentuation of the left hemisphere. Since fluorodeoxyglucose positron emission tomography (FDG PET) measurements of the regional cerebral metabolic rate of glucose (rCMRgl) provide a sensitive and specific marker of neurodegenerative disease progression, we sought to investigate the longitudinal pattern of rCMRgl in amyloid-positive persons with mild cognitive impairment (MCI) and dementia, hypothesizing asymmetric declines of cerebral glucose metabolism.

Methods: Using florbetapir PET and cerebrospinal fluid (CSF) measures to define amyloid-β (Aβ) positivity, 40 Aβ negative (Aβ-) cognitively unimpaired controls (CU; 76 ± 5y), 76 Aβ positive (Aβ+) persons with MCI (76 ± 7y) and 51 Aβ + persons with probable AD dementia (75 ± 7y) from the AD Neuroimaging Initiative (ADNI) were included in this study with baseline and 2-year follow-up FDG PET scans. The degree of lateralization of longitudinal rCMRgl declines in subjects with Aβ + MCI and AD in comparison with Aβ- CU were statistically quantified via bootstrapped lateralization indices [(LI); range − 1 (right) to 1 (left)].

Results: Compared to Aβ- CU, Aβ + MCI patients showed marked left hemispheric lateralization (LI: 0.78). In contrast, modest right hemispheric lateralization (LI: −0.33) of rCMRgl declines was found in Aβ + persons with probable AD dementia. Additional comparisons of Aβ + groups (i.e. MCI and probable AD dementia) consequently indicated right hemispheric lateralization (LI: −0.79) of stronger rCMRgl declines in dementia stages of AD. For all comparisons, voxel-based analyses confirmed significant (pFWE < 0.05) declines of rCMRgl within AD-typical brain regions. Analyses of cognitive data yielded predominant decline of memory functions in both MCI and dementia stages of AD.

Conclusions: These data indicate that in early stages, AD may be characterized by a more lateralized pattern of left hemispheric rCMRgl declines. However, metabolic differences between hemispheres appear to diminish with further progression of the disease.

1. Introduction

Alzheimer's disease (AD) is the most common cause of cognitive impairment in older persons. In recent years, AD has been conceptualized as a progressive sequence of pathophysiological changes that include the extracellular accumulation of amyloid-β (Aβ), tau-mediated neuronal dysfunction/death and brain atrophy that correspond roughly to cognitively unimpaired, mild cognitive impairment

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(MCI) and dementia stages (Jack et al. 2011, 2018).

Brain imaging measurements have been used to detect and track Aβ, tau, and neurodegenerative features of AD in the preclinical (cognitively unimpaired), MCI and dementia stages. The best established examples include PET measurements of fibrillar Aβ deposition, PET measurements of paired helical filament (PHF) tau deposition, MRI measurements of hippocampal and whole brain atrophy, and fluorodeoxyglucose PET measurements of regional cerebral metabolic rate for glucose (rCMRgl) decline in brain regions preferentially affected by AD (Herholz and Ebmeier 2011; Reiman and Jagust 2012; Saint-Aubert et al. 2017). In the most recent conceptualization (Jack et al. 2018), biomarker evidence of amyloid-β (Aβ) pathology reflects "AD pathophysiological change", biomarker evidence of both amyloid-β and tau pathology reflects "AD", and individuals can also be characterized in terms of the evidence of neurodegenerative disease changes that may include rCMRgl declines and brain atrophy (i.e., "AT(N)" research criteria for AD; Jack et al. 2018)).

AD and related disorders are associated with distinctive MRI and FDG PET patterns of neurodegeneration. Some neurodegenerative diseases appear to begin with or are characterized by asymmetric patterns of neurodegeneration (e.g., Parkinson's Disease (PD) and Primary Progressive Aphasia (PPA), (Claassen et al. 2016; Gorno-Tempini et al. 2004). While AD has been characterized by bilateral neurodegenerative disease changes in medial temporal and heteromodal sensory association areas, several neuroimaging studies have suggested a pronunciation of the left hemisphere with respect to amyloid deposition (Raji et al. 2008) gray matter atrophy (Janke et al. 2001; Shi et al. 2009; Thompson et al. 1998, 2001), cerebral perfusion and metabolism (Friedland et al. 1985; Loewenstein et al. 1989; Volkow et al. 2002) in persons with AD. Whereas many of these findings (particularly from studies of brain metabolism) have been cross-sectional, we sought to investigate the possibility that amyloid-β positive (Aβ+) persons might demonstrate asymmetric left lateralized longitudinal patterns of neurodegeneration, especially during the earlier clinical stages of AD. To address this possibility we compared longitudinal patterns of rCMRgl declines in Aβ + probable AD dementia, MCI and an amyloid-β negative (Aβ-) cognitively unimpaired control group from the AD Neuroimaging Initiative (ADNI).

2. Subjects and methods

2.1. Subjects

Participant data for this study were drawn from the ADNI dataset, an ongoing longitudinal study (currently ADNI-3) devoted to the establishment of biological and neuroimaging biomarkers of MCI and Alzheimer's disease. Detailed information on participant recruitment, inclusion- and exclusion criteria are provided on the ADNI website (www.adni-info.org/index.php). In order to maximise the sensitivity of our analyses we only included amyloid-β negative (Aβ-) cognitively unimpaired control subjects (CU) based on CSF measures (threshold > 192) or florbetapir PET (threshold < 1.18) with cerebellum reference region, thereby optimally avoiding the inclusion of subjects with preclinical and asymptomatic stages of AD. Similarly only amyloid-β positive (Aβ+) MCI and AD patients were included, thus avoiding misclassification of patients and maximising the probability of AD pathology being the underlying cause of cognitive impairment. In total, we selected a sample of $n = 167$ subjects, based on availability of longitudinal FDG PET scans and information on amyloid pathology, resulting in a sample of 51 Aβ + subjects with AD dementia, 76 Aβ + subjects with MCI, and 40 Aβ- CU. In the following, we will refer to MCI-AD and dementia-AD for MCI and dementia subjects with evidence of AD pathology.

2.2. Clinical evaluation

For each subject, cognitive function was evaluated at each visit (for details please see www.adni-info.org). Measures of cognitive function included - next to others - the Auditory Verbal Learning Test [AVLT; (Rey 1964)] Total and Long-Term Memory (LTM) scores, CDR sum of boxes (CDR-SOB; (Morris 1993)), MMSE (Folstein et al. 1975), Category Fluency (animals) (Rosen 1980) and the modified AD Assessment Scale-Cognitive Subscale (i.e. ADAS-Cog 11/13; Mohs et al. 1997; Rosen et al. 1984). Delta values were calculated for each test and participant. In addition subdomains and individual subitems of the ADAS-cog 13 were analyzed with the goal to further evaluate baseline impairment and subsequent decline of specific cognitive domains. Subitems of the ADAS-cog 13 comprise the following cognitive subdomains: Memory and new learning (i.e. Word Recall, Orientation, Word Recognition, Delayed Word Recall, Recall Instructions), language (i.e. Commands, Naming, Spoken Language, Word Finding, Comprehension), praxis (i.e. Construction, Ideational Praxis) and processing speed (i.e. Number Cancellation) with higher scores indicating worse performance. For the item "Number Cancellation" data points were missing for $N = 5$ subjects ($N = 4$ dementia-AD; $N = 1$ CU). Since individual subitems of the ADAS-cog 13 differ with respect to the maximum possible value, results were illustrated as percentage of the maximum possible scores. Non-imaging data were analyzed using ANOVA or Chi Square whenever applicable. For post-hoc between group comparisons Duncan's multiple range test was applied. Results are reported at alpha 0.05 uncorrected.

2.3. Imaging procedures

Longitudinal imaging data from different participating sites were subjected to a standardized protocol (http://www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml) of measured-attenuation correction and specific reconstruction algorithms in order to account for site specific differences. These preprocessing steps were performed by the ADNI PET Coordinating Center at the University of Michigan made available for download at the LONI ADNI website. After download of PET images additional pre-processing steps were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm), including deformation into a standard space of the Talairach atlas and spatial smoothing with a 3-dimensional Gaussian filter with 8 mm full width at half maximum. Next, subtraction images of the FDG scans scaled by the global counts were calculated (i.e. baseline/global_at_baseline – followup/global_at_followup) for characterization and comparisons of 24-month rCMRgl declines.

To test the hypothesis of lateralized longitudinal declines of rCMRgl declines we used SPM8 (www.fil.ion.ucl.ac.uk) and the LI-toolbox (Wilke and Lidzba 2007). First, SPM8 was used for voxel-based analyses of rCMRgl declines by applying either two-sample *t*-test for group comparisons or one sample *t*-tests for within group analyses to the above mentioned subtraction images. In addition, post-hoc regression analyses were performed to investigate associations of cognitive decline [(i.e. ADAS-cog 13 and Category Fluency (animals)] with rCMRgl declines in dementia-AD and MCI-AD subjects. Then, SPM derived T-maps were analyzed with the LI-toolbox by calculating an overall weighted bootstrapped lateralization index (LI) for the unthresholded maps. This approach combines the commonly used lateralization eq. (LI = (left-right)/(left + right)) with adaptive thresholding and automated bootstrapping algorithms to minimize the impact of outliers. For our analyses we furthermore used an inclusive standard gray matter mask and an additional exclusive mask (i.e. midline +/− 5 mm) as provided by the LI-toolbox, in order to reduce noise related artifacts. For the calculated LI weighted means (LIwm), negative values indicate right hemispheric lateralization and positive values indicate left hemispheric lateralization. Based on the LIwm, lateralization was classified as either absent (LIwm −0.25 to 0.25), weak (LIwm −0.25 to −0.50 and 0.25 to 0.50) or strong (LIwm < −0.50 and > 0.50) (e.g. De Winter et al. 2015). Importantly, this approach largely avoids the introduction of