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High-dimensional morphometry

Mapping ventricular expansion onto cortical gray matter in older adults

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ABSTRACT

Dynamic changes in the brain's lateral ventricles on magnetic resonance imaging are powerful biomarkers of disease progression in mild cognitive impairment (MCI) and Alzheimer's disease (AD). Ventricular measures can represent accumulation of diffuse brain atrophy with very high effect sizes. Despite having no direct role in cognition, ventricular expansion co-occurs with volumetric loss in gray and white matter structures. To better understand relationships between ventricular and cortical changes over time, we related ventricular expansion to atrophy in cognitively relevant cortical gray matter surfaces, which are more challenging to segment. In ADNI participants, percent change in ventricular volumes at 1-year (N = 677) and 2-year (N = 536) intervals was significantly associated with baseline cortical thickness and volume in the full sample controlling for age, sex, and diagnosis, and in MCI separately. Ventricular expansion in MCI was associated with thinner gray matter in frontal, temporal, and parietal regions affected by AD. Ventricular expansion reflects cortical atrophy in early AD, offering a useful biomarker for clinical trials of interventions to slow AD progression.

1. Introduction

As brain tissue is lost in normal aging and dementia, the volume of cerebral spinal fluid (CSF) in the lateral ventricles and surrounding the brain expands to fill the space, within the fixed volume of the skull (Ferrarini et al., 2008; Nestor et al., 2008; Sullivan et al., 2002; Walhovd et al., 2005). The clear tissue contrast between CSF and brain tissues makes it easier to reliably segment and measure the lateral ventricles in standard T1-weighted anatomic magnetic resonance imaging (MRI) scans, even in populations that present challenges for segmentation of other brain structures (Ferrarini et al., 2008; Qiu et al., 2009). The lateral ventricles can be reliably segmented with semi- or fully-automated methods that measure their overall volume (Jack et al., 2004; Nestor et al., 2008; Resnick et al., 2003), shape (Chou, 2007; Ferrarini et al., 2006; Gong et al., 2011), radial width (Apostolova et al., 2012; Frisoni et al., 2002; Thompson et al., 2004), or boundary shift integral (Ridha et al., 2008; Schott et al., 2005). By comparison, accurate and reliable segmentation of the cortical gray matter surface is somewhat challenging in the brains of older adults, as gray matter (GM) and white matter contrast decreases with age, the cortical surface may also become

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increasingly complex and irregular in shape as more brain tissue is lost. Time-consuming manual editing is often required even with the most sophisticated widely used cortical GM segmentation packages (Fischl and Dale, 2000; Sanchez-Benavides et al., 2010). Some of these issues can be alleviated by collecting scans with specialized protocols to increase the signal-to-noise-ratio at the cortical boundary. Some researchers advocate averaging 2 or more MRI scans within the participant to improve the accuracy of cortical segmentation, although collecting several scans is not always feasible (Perlman, 2007). Relating expansion of the lateral ventricles to detailed 3D maps of cortical GM thinning takes advantage of a subcortical brain structure that is very easily segmented in standard MRI data from older adults, although also allowing interpretations of the likely cortical changes, which have more direct clinical relevance.

Ventricular measures achieve some of the highest possible effect sizes for tracking longitudinal changes in the human brain. Ventricular volume is a powerful MRI biomarker that has been widely used in studies of normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD) (Apostolova et al., 2012; Chou, 2007; Ferrarini et al., 2006; Fleisher et al., 2008; Jack et al., 2004, 2005, 2008a, 2008b; Nestor et al., 2008; Qiu et al., 2009; Thompson et al., 2004; Wang et al., 2002). In comparative studies, fewer participants may be needed (Head-to-head comparisons of effect sizes for brain biomarkers require many caveats as therapeutic interventions may affect each biomarker differently. Also, simply reducing the numerical rate of change for different biomarkers many have different functional or clinical consequences for the patient. Some of these issues are discussed in Hua et al. (2013) to detect statistical effects of disease-modifying interventions in clinical trials using ventricular biomarkers compared with using many other neuroimaging measures. One study demonstrated, for example, that approximately 60 participants are needed to detect a fixed percentage of slowing of ventricular expansion versus 90 participants needed to detect slowing in hippocampal atrophy, and 300 participants needed to detect the same proportional slowing of the rate of decline on neuropsychological tests (Ridha et al., 2008).

Larger or expanding ventricles are linked with a broad range of brain-related health factors in older adults, including current cognitive status and future memory decline (Coffey et al., 2001; Murphy et al., 2010), the brain reserve or general resiliency against neurodegeneration (Cavedo et al., 2012), depression, language scores, CSF measures of amyloid beta, APOE genotype (Chou et al., 2010), poorer cardiovascular health (Isaac et al., 2011), vitamin D deficiency (Annweiler et al., 2013), elevated homocysteine levels (Feng et al., 2013), postoperative cognitive dysfunction (Bourne et al., 2012; Kline et al., 2012), decreased survival in dementia (Olesen et al., 2011), and conversion to MCI and AD (Carmichael et al., 2007b; Fleisher et al., 2008; Jack et al., 2004; Nestor et al., 2008).

Although the ventricles provide several practically useful MRI biomarkers, the structure does not play a direct role in cognition. Therefore, it is vital to determine how the changes in brain regions of functional and cognitive significance in AD relate to expansion in lateral ventricles. Lateral ventricle expansion co-occurs with degeneration of gray and white matter globally and nearby subcortical regions (Ferrarini et al., 2008; Qiu et al., 2009). By associating ventricular expansion with detailed profiles and patterns in cortical GM thickness, we can make good use of the reliability and ease of ventricular segmentation, relating changes to likely differences in cortical structures that are somewhat more difficult or time-consuming to segment but which are more directly susceptible to AD-related pathologies.

2. Methods

2.1. Study population

We analyzed participants that underwent high-resolution, T1-weighted, structural, MRI scanning of the brain, as part of phase 1 of the Alzheimer's Disease Neuroimaging Initiative (ADNI1). Our sample included only participants listed in the standard set of N = 817 baseline, N = 685 one-year follow-up, and N = 544 two-year follow-up scans obtaining during the ADNI1 phase of data collection that was created to promote rigor and more meaningful comparability across ADNI studies (Wyman et al., 2012). In the ventricle analysis, 2 baseline scans and 1 scan from the 1-year follow-up timepoint were not included, although they are currently listed in the standard set, because they were added to the list after we had completed data processing. In the cortical GM analysis, all standard participants were processed.

ADNI was launched in 2004 by the National Institutes of Health, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations to identify and evaluate biomarkers of AD for use in multisite studies. All ADNI data are publicly available at adni.loni.usc.edu. All ADNI studies are conducted in compliance with the Good Clinical Practice guidelines, the Declaration of Helsinki, and the US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards. Written informed consent was obtained from all ADNI participants before the study. ADNI is a multisite longitudinal study of patients with AD, MCI, and healthy older adult control. Standardized protocols maximize consistency across scan sites.

All individuals received a thorough clinical and cognitive evaluation near the time of their scan. The examination included the Mini-Mental State Examination a standardized and widely used 30 point questionnaire with scores of 24–30 typically indicating normal cognition for participants without memory complaints, scores of 24–30 indicating probable MCI for participants with objective memory loss, and scores of 20–26 indicating probable AD; (Folstein et al., 1975) and diagnosis of probable AD, MCI, or cognitively normal. Inclusion and exclusion criteria are detailed in the ADNI protocol (Mueller et al., 2005) and are available online at http://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf.

2.2. Image acquisition

High-resolution structural MRI scans of the brain were acquired for participants included in the standardized ADNI list (Wyman et al., 2012) on 1.5 T scanners from General Electric (Milwaukee, WI, USA), Siemens (Germany), or Philips (the Netherlands) using a standardized MRI protocol for 3-dimensional sagittal magnetization-prepared rapid gradient-echo sequences (Jack et al., 2008a, 2008b).

For lateral ventricle segmentation, we analyzed baseline (N = 834), 1-year (N = 677), and 2-year (N = 536) follow-up brain MRI scans (1.5-Tesla, T1-weighted, 3D, magnetization-prepared rapid gradient-echo, repetition time/echo time = 2400/1000 ms, flip angle = 8°, slice thickness = 1.2 mm, final voxel resolution = $0.9375 \times 0.9375 \times 1.2\ mm^3$). Raw MRI scans were preprocessed to reduce signal inhomogeneity and linearly registered to the ICBM template (Mazziotta et al., 2001) (using 9-parameter registration). Percent change was calculated from both follow-ups compared with baseline, resulting in 1-year (N = 677) and 2-year (N = 536) percent change in ventricular volume.

For cortical GM segmentation, we analyzed baseline (N = 677), 1-year (N = 646), and 2-year (N = 507) follow-up brain MRI scans (1.5-Tesla, T1-weighted, 3D, magnetization-prepared rapid gradient-echo, repetition time/echo time = 2400/1000 ms, flip