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Longitudinal assessment of global and regional atrophy rates in Alzheimer's disease and dementia with Lewy bodies

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ABSTRACT

Background & objective: Percent whole brain volume change (PBVC) measured from serial MRI scans is widely accepted as a sensitive marker of disease progression in Alzheimer's disease (AD). However, the utility of PBVC in the differential diagnosis of dementia remains to be established. We compared PBVC in AD and dementia with Lewy bodies (DLB), and investigated associations with clinical measures.
Methods: 72 participants (14 DLBs, 25 ADs, and 33 healthy controls (HCs)) underwent clinical assessment and 3 Tesla T1-weighted MRI at baseline and repeated at 12 months. We used FSL-SIENA to estimate PBVC for each subject. Voxelwise analyses and ANCOVA compared PBVC between DLB and AD, while correlational tests examined associations of PBVC with clinical measures.
Results: AD had significantly greater atrophy over 1 year (1.8%) compared to DLB (1.0%; $p = 0.01$) and HC (0.9%; $p < 0.01$) in widespread regions of the brain including periventricular areas. PBVC was not significantly different between DLB and HC ($p = 0.95$). There were no differences in cognitive decline between DLB and AD. In the combined dementia group (AD and DLB), younger age was associated with higher atrophy rates ($r = 0.49$, $p < 0.01$).
Conclusions: AD showed a faster rate of global brain atrophy compared to DLB, which had similar rates of atrophy to HC. Among dementia subjects, younger age was associated with accelerated atrophy, reflecting more aggressive disease in younger people. PBVC could aid in differentiating between DLB and AD, however its utility as an outcome marker in DLB is limited.

1. Introduction

Dementia with Lewy bodies (DLB) is the second leading cause of degenerative dementia in older people after Alzheimer's disease (AD), accounting for up to 15% of cases confirmed at autopsy (McKeith et al., 1996). DLB shares common clinical, neuropsychological and pathological features with other dementia subtypes such as AD and Parkinson's disease with dementia, making differentiation between these disorders challenging. Despite the development of consensus diagnostic criteria, the sensitivity for differential diagnosis of DLB in clinical practice remains low and many DLB patients could be misdiagnosed. In light of this uncertainty, and with important implications for subsequent patient management, there is growing emphasis on the development of reliable imaging markers to help distinguish DLB from other subtypes of dementia.

The majority of imaging studies in AD and DLB have been cross-sectional, while there has been a paucity of longitudinal studies in DLB (O'Brien et al., 2001; Whitwell et al., 2007), which might be more sensitive to detect early pathological changes than measurements at a single time point (Smith et al., 2007). Furthermore, a longitudinal design can reduce the confounding effect of inter-individual morphological variability as each subject serves as his or her own control. The rate of whole brain atrophy on serial MRI is increasingly recognized as a sensitive and objective marker of disease progression in neurodegenerative diseases (Fox and Freeborough, 1997). Reported whole brain atrophy rates in AD range from 1% to 4% per year (Cover et al., 2011), while atrophy rates in similarly aged non-demented people range from 0.3% to 0.7% per year (Cover et al., 2011; Henneman et al., 2009; Sluimer et al., 2008). As such, longitudinal assessment of brain atrophy in

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different subtypes of dementia and healthy controls may allow us to distinguish pathological rates of brain atrophy from normal age-related changes. The clinical relevance of atrophy rates has been supported by previous studies showing the relationship with cognitive dysfunctions (Sluimer et al., 2008). In light of this evidence, global atrophy rates are used as a secondary outcome marker in phase III trials of potentially disease-modifying interventions in AD (Frisoni et al., 2010).

Previous studies using serial MRI to investigate atrophy rates in DLB have yielded conflicting findings, with some studies showing similar rates in subjects with DLB and AD (O'Brien et al., 2001), while slower atrophy rates in DLB have been reported (Whitwell et al., 2007). Thus, the clinical implications of whole brain atrophy rates in DLB remain poorly understood, and further studies are warranted.

The aims of the present study were to use serial MRI to investigate whole brain atrophy rates over a 12-month period in clinically diagnosed subjects with AD and DLB, and similarly aged HC, as well as to investigate the associations between percent brain volume change (PBVC) and clinical measures. Based on earlier cross-sectional findings of reduced whole brain atrophy and relative structural preservation of the medial temporal lobes (Mak et al., 2014; R. Watson et al., 2012a), we hypothesized that subjects with DLB would have significantly lower rates of whole brain atrophy compared to AD.

2. Methods

2.1. Subjects, assessment and diagnosis

At baseline, seventy one subjects with dementia over the age of 60 (36 subjects with probable AD (McKhann et al., 1984) and 35 with probable DLB (McKeith et al., 2005)) were recruited from a community dwelling population of patients referred to local Old Age Psychiatry, Geriatric Medicine or Neurology Services in the North East of England, UK, as previously described (R. Watson et al., 2012a). Consensus on diagnosis was made with 3 experienced clinicians. Subjects underwent clinical and neuropsychological evaluations at baseline and follow-up at 1 year. Thirty-five similarly aged control subjects were recruited from relatives and friends of subjects with dementia or volunteered via advertisements in local community newsletters.

For the purpose of the present study, we included only subjects with MRI assessments from both baseline and 1-year follow-up. Of the 36 AD subjects, 25 were included after 11 were unable to participate in the follow-up assessment. Of the 35 DLB subjects, 14 were included after 12 declined to participate as they or their carers felt they were too unwell and 9 subjects had died. Half the DLB subjects ($n = 7$) had abnormal dopamine transporter scans as part of the clinical work-up before entering the study. Of the 35 HC subjects, 33 were included in the present analyses after 2 declined to participate due to other reasons. The research was approved by the local ethics committee. All subjects or, where appropriate, their nearest relative, provided written informed consent. Assessment of global cognitive measures at both baseline and follow-up assessments, included the Cambridge Cognitive Examination (CAMCOG) (Huppert et al., 1995), which incorporates the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Motor parkinsonism was evaluated with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). For subjects with dementia, neuropsychiatric features were examined with the Neuropsychiatric Inventory (Cummings et al., 1994), and cognitive fluctuations were assessed with the cognitive fluctuation scale (Walker et al., 2000).

2.2. MRI acquisition

Subjects underwent both baseline and repeat MR imaging with a 12-month interval. At each time point, subjects underwent T1 weighted MR scanning on the same 3 T MRI system using an 8 channel head coil (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands) within 2 months of the clinical assessments as previously described (R. Watson et al., 2012a). The sequence was a standard T1 weighted volumetric sequence covering the whole brain (3D MPRAGE, sagittal acquisition, 1 mm isotropic resolution and matrix size of 240 (anterior–posterior) × 240 (superior–inferior) × 180 (right–left); repetition time (TR) = 9.6 ms; echo time (TE) = 4.6 ms; flip angle = 8°; SENSE factor = 2). The acquired volume was angulated such that the axial slice orientation was standardized to align with the AC–PC line.

2.3. Image analysis

2.3.1. Estimation of whole brain atrophy rate

Whole brain atrophy rate was estimated with SIENA (Smith et al., 2001), part of the FSL software package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Firstly, brain extraction was performed in acquired images at both of the two time points (Smith et al., 2002). For each individual subject, the baseline and follow-up brain images were aligned to each other (Jenkinson and Smith, 2001) using the skull images to constrain the registration scaling, and both brain images were then resampled into the space halfway. Next, tissue-type segmentation was carried out (Zhang et al., 2001) in order to find brain/non-brain edge points, and then perpendicular edge displacement (between the two time points) was estimated at these edge points. Finally, the mean edge displacement across the whole brain was converted into a global estimate of PBVC between the two time-points.

2.3.2. Voxel-wise assessment of atrophy over time

Next, we performed a voxelwise statistical analysis of atrophy across subjects using SIENAr, an extension of SIENA from the FSL package (Bartsch et al., 2004). Built upon the result of the previous SIENA analysis, the edge displacement image was dilated for each subject, transformed into MNI152 space, and masked by a standard MNI152-space brain edge image. In this way the edge displacement values were warped onto the standard brain edge. Next, voxelwise statistical analysis was performed on the resulting images from all subjects to test for significant differences in atrophy over time among the AD, DLB and HC groups. In all voxelwise comparisons, age and gender were included as covariates in the General Linear Model (GLM). The threshold free cluster enhancement (TCFE) algorithm (Nichols and Holmes, 2002) was used to correct for multiple comparisons across the whole brain at $p < 0.05$ based on permutation testing (5000 permutations for each contrast in order to build an empirically derived null distribution against which to compare observed effects). The anatomical locations of the significant cortical GM clusters were determined by using the standard Harvard–Oxford cortical structural atlas (see http://www.fmrib.ox.ac.uk/fsl/) containing 48 regions for each hemisphere.

2.4. Statistical analysis

Statistical analyses were performed with the STATA13 (http://www.stata.com) software. The distribution of continuous variables was tested for normality using the Skewness–Kurtosis test and visual inspection of histograms. Parametric data were assessed using either t-tests or analysis of variance (ANOVA) for continuous variables. For non-parametric data, Kruskal–Wallis was used. χ^2 tests were used to examine differences between categorical measures. Group effects in PBVC were tested with analysis of covariance (ANCOVA) controlling for age and gender, followed by post-hoc comparisons using the Tukey–Kramer tests. Associations of PBVC with clinical measures were evaluated with Spearman's rank order correlation coefficient or Pearson's correlations depending on the distribution of the data. These correlational tests were further adjusted by applying Bonferroni correction for multiple