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In vivo imaging of neurodegeneration in dementia with Lewy bodies (DLB)

Chiadi U. Onyike and **Gwenn S. Smith**

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

For almost two decades, O'Brien and colleagues have investigated virtually every facet of dementia with Lewy bodies (DLB), phenomenology, treatment, and neurobiology, ranging from genetics to post-mortem and *in vivo* imaging studies. The latest study from this group, reported here, describes differences in regional grey matter volumes using magnetic resonance (MR) imaging and an automated segmentation analysis method in a well-characterized sample of patients with Alzheimer disease (AD), DLB, and a healthy control group (Watson *et al.*, 2015). The study incorporated detailed psychometric assessments of cognitive and motor functions for correlation with the grey matter volumes, and age, gender and dementia severity were included as covariates in the statistical analysis. The key observations are relatively greater hippocampal volumes and lower subcortical volumes in DLB compared to AD, but it is to be noted that most of these differences in subcortical volume were demonstrated indirectly through comparisons of the disease groups with age-matched healthy control subjects. Thus, replication in studies that make direct comparisons between DLB and AD subjects, perhaps in a larger sample size, is necessary. Still, these results highlight the potential for MR imaging to provide indicators of the extent of the neurodegenerative process in DLB. Furthermore, the results underscore the importance of correcting molecular imaging data for the effects of cerebral atrophy (partial volume correction) that may further enhance the ability of these methods to reveal pathophysiological processes.

In the past decade, there has been unprecedented progress in the development of molecular imaging radiotracers. The development and validation of the Pittsburgh B Compound for *in vivo* imaging of beta-amyloid deposition has had the most impact on the *in vivo* diagnosis of AD and its preclinical conditions since cerebral glucose metabolism studies identified the changes in neural function associated with diagnosis, progression, and genetic risk of AD (Klunk *et al.*, 2004; Jagust *et al.*, 1985; Smith *et al.*, 1992; Reiman *et al.*, 2004). More recently, radiotracers for tau have been developed that are increasingly being applied to the investigation of AD and other dementia types (Chien *et al.*, 2013). In a recent effort led by the Michael J. Fox Foundation, a consortium of radiochemists and basic scientists are collaborating to develop a radiotracer for alpha-synuclein (Neal *et al.*, 2013). The development of an alpha-synuclein radiotracer will have the same impact on DLB as the

Conflict of interest

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beta-amyloid and tau radiotracer have had for AD. Finally, molecular imaging studies have consistently shown monoamine dysfunction in DLB, consistent with post-mortem studies (as reviewed by Mak *et al.*, 2014). Neuroimaging findings including striatal dopamine transporter loss, global and regional perfusion, and metabolic deficits have been incorporated into the revised diagnostic criteria for DLB (Mckeith *et al.*, 2005). The availability of these *in vivo* molecular imaging methods, especially in study designs involving multi-modality imaging have the great potential in the earlier diagnosis of DLB and the development of more effective treatments.

The differential diagnosis of DLB from AD is sometimes difficult, especially in the earliest stages of illness where patients may not have fully developed clinical syndromes. This is an important issue, given the imperative of earlier diagnosis for treatment and research. The findings in this study do not yet have clinical utility for bedside diagnosis. More work is required to identify and operationalize differences in atrophy patterns for the differential diagnosis of DLB from AD. Nevertheless, the findings from this study, together with earlier work, show atrophy patterns that may show close correspondence to the distribution of neuropathology in DLB. Therefore, finer description of brain atrophy patterns in DLB can facilitate the validation of an alpha-synuclein tracer. Also, detailed structural mapping of neurodegeneration in DLB will be needed for the interpretation of future multimodal imaging studies that utilize amyloid, tau, and alpha-synuclein tracers to investigate neurodegenerative changes in DLB.

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