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Neuropsychologia 46 (2008) 1597–1612

NEUROPSYCHOLOGIA

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Mapping progressive brain structural changes in early Alzheimer's disease and mild cognitive impairment

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Received 3 July 2007; received in revised form 3 October 2007; accepted 31 October 2007
Available online 14 December 2007

Abstract

Alzheimer's disease (AD), the most common neurodegenerative disorder of the elderly, ranks third in health care cost after heart disease and cancer. Given the disproportionate aging of the population in all developed countries, the socio-economic impact of AD will continue to rise. Mild cognitive impairment (MCI), a transitional state between normal aging and dementia, carries a four- to sixfold increased risk of future diagnosis of dementia. As complete drug-induced reversal of AD symptoms seems unlikely, researchers are now focusing on the earliest stages of AD where a therapeutic intervention is likely to realize the greatest impact. Recently neuroimaging has received significant scientific consideration as a promising *in vivo* disease-tracking modality that can also provide potential surrogate biomarkers for therapeutic trials. While several volumetric techniques laid the foundation of the neuroimaging research in AD and MCI, more precise computational anatomy techniques have recently become available. This new technology detects and visualizes discrete changes in cortical and hippocampal integrity and tracks the spread of AD pathology throughout the living brain. Related methods can visualize regionally specific correlations between brain atrophy and important proxy measures of disease such as neuropsychological tests, age of onset or factors that may influence disease progression. We describe extensively validated cortical and hippocampal mapping techniques that are sensitive to clinically relevant changes even in the single individual, and can identify group differences in epidemiological studies or clinical treatment trials. We give an overview of some recent neuroimaging advances in AD and MCI and discuss strengths and weaknesses of the various analytic approaches.
Published by Elsevier Ltd.

Keywords: Alzheimer's disease; Mild cognitive impairment (MCI); Neuroimaging; Brain mapping; MRI; Cortical atrophy; Hippocampal atrophy; Ventricular expansion

1. Introduction

Alzheimer's disease (AD), the most common cause of degenerative dementia, causes progressive brain atrophy. These atrophic changes are readily observed with structural neuroimaging. In the past three decades, several important technological leaps have allowed us to study the brain, as degeneration progresses. Magnetic resonance imaging (MRI), currently the structural neuroimaging method of choice for diagnostic and research efforts, revolutionized the field several decades ago. More recently, advanced analytic techniques have become available further empowering our ability to discover disease associated pathologic changes and clinical correlations *in vivo*. In this review we will provide a comprehensive overview of recent advances in MRI research on AD and related diseases, while critically appraising the methodology.

1.1. Alzheimer's disease

AD is the commonest form of dementia worldwide—it currently affects 4.9 million elderly over the age of 65 and as many as 500,000 people under the age of 65 in the United States alone (Alzheimer Association, 2007). It manifests with relentlessly progressive cognitive decline presenting initially as memory loss and then spreads to affect all other cognitive faculties and the patients' ability to conduct an independent lifestyle. Pre-mortem, AD-associated brain changes can be clinically eval-

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0028-3932/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.neuropsychologia.2007.10.026

uated with the help of neuroimaging. They consist of global atrophy with an early predilection for the hippocampal region and the temporo-parietal cortical areas. Post-mortem examination reveals abundant cortical and hippocampal neuritic plaques (NP) and neurofibrillary tangles (NFT) as well as pancerebellar atrophy upon gross inspection of the brain.

Several risk factors influence the prevalence of AD. Age is by far the greatest risk factor: at the age of 65, one in eight elderly individuals carries the diagnosis, but after the age of 85, the ratio is close to one in every two persons. Genetic predisposition for late-onset sporadic AD seems to be primarily conveyed by the presence of the apolipoprotein E4 (ApoE4) allele in a dose-dependent fashion—subjects with one ApoE4 copy have increased risk (odds ratio, OR = 2.6–3.2), and those with two copies have greatly increased risk (OR = 14.9) for developing AD, while the ApoE2 allele appears to be protective (OR = 0.6) (Farrer et al., 1997; Graff-Radford et al., 2002). Rare genetic variants of fully penetrant autosomal dominant forms of AD also exist and have been attributed to presenilin 1 and presenilin 2 gene mutations on chromosomes 14 and 1 and to an amyloid protein precursor gene mutation on chromosome 21. Even so, these autosomal dominant forms account for only 2% of all AD cases (Campion et al., 1999).The societal cost of AD is immense. AD is the 5th leading cause of death among the elderly. The total number of deaths caused by AD has increased by 33% between 2000 and 2004, but those from other major etiologies, such as heart disease, breast cancer, prostate cancer and stroke, have decreased by 3-10% each (Alzheimer Association, 2007). More than $148 billion is spent on AD related healthcare costs annually (Alzheimer Association, 2007).

1.2. Mild cognitive impairment

Mild cognitive impairment (MCI) is a relatively recent concept introduced to recognize the intermediate cognitive state where patients are neither cognitively intact nor demented (Winblad et al., 2004). The current prevalence rate for MCI among those 65 years and older is 12–18% (Petersen, 2007) and 10–15% of these patients progress to develop dementia annually (Petersen et al., 2001). Many subjects with MCI have cortical and hippocampal atrophy. Most show unequivocal signs of AD pathology, including plaque and tangle accumulation, postmortem (Haroutunian et al., 1998; Jicha et al., 2006; Price & Morris, 1999). Nevertheless, some MCI patients harbor an alternative pathological diagnosis such as dementia with Lewy bodies, vascular dementia, hippocampal sclerosis, frontotemporal dementia, progressive supranuclear palsy, argyrophilic brain disease or a nonspecific tauopathy (Petersen, 2007). Some MCI cases can also be attributed to nondegenerative pathology (Petersen, 2007).

In recent years, MCI has attracted increasing research interest. It is now widely accepted that MCI is the single most important at-risk state for AD. Two major research questions have captured most attention—how can we predict which MCI patients will develop AD and which treatment would offer neuroprotection from future progression to dementia.

2. Neuroimaging approaches in AD and MCI

Neuroimaging is a powerful tool for creative exploration of the epidemiology, diagnostic sensitivity, progression and therapeutic efficacy in AD and MCI. Reliable biomarkers of the underlying pathology that can also predict disease progression in MCI are needed and several candidate brain measures have been examined in a wealth of cross-sectional and longitudinal neuroimaging studies. Neuroimaging has captured the interest of clinical trialists and may help establish disease-modifying effects in clinical trials by documenting slowing of brain atrophy rates or of amyloid accumulation. Structural measures such as total brain volume, hippocampal and entorhinal cortical volumes have been thoroughly evaluated and used as surrogate markers for clinical trials (Fox, Cousens, Scahill, Harvey, & Rossor, 2000; Fox et al., 2005; Grundman et al., 2002; Jack et al., 2004; Jack, Petersen, et al., 2007; Krishnan et al., 2003). New powerful techniques for more precise 3D disease and treatment effect localization are likewise being explored (Chou et al., 2007; Csernansky, Wang, Miller, Galvin, & Morris, 2005; Thompson et al., 2003, 2004), as are novel positron emission tomography tracers to label the hallmarks of AD in the living brain (Braskie et al., submitted; Protas et al., 2007; Small et al., 2006).

The extent of brain degeneration in dementia can be quantified by purely structural techniques such as MRI and diffusion tensor imaging (which can examine white matter fiber integrity), and tomographic approaches, such as PET and SPECT (Salmon, 2008; Mosconi, 2005), which can quantify cerebral blood flow and metabolism. The structural/functional distinction has been blurred to include PET studies with new ligands that label structural pathology (such as tracer compounds that bind to amyloid) (Kepe, Huang, Small, Satyamurthy, & Barrio, 2006; Klunk et al., 2004; Nordberg, 2008; Small et al., 2006), and MRI variants such as fMRI imaging of blood-oxygenation level dependent (BOLD) contrast (Dickerson & Sperling, 2008), arterial spin labeling (Du et al., 2006), relaxometry (House, St Pierre, Foster, Martins, & Clarnette, 2006), spectroscopy (Kantarci, 2005), and magnetization transfer imaging (van der Flier et al., 2002). For structural MRI scans in particular, the oldest image analysis approach currently used in dementia research is the region of interest (ROI) technique. This measures the overall volume of specific brain substructures. It relies on manual delineation of the structures of interest on each successive image slice, followed by calculating the total volume of the structure, which is then used for statistical analyses. Manual volumetry is a powerful technique and has yielded a wealth of findings, but has several disadvantages. It requires proficient and knowledgeable tracers who can delineate the ROIs with high reliability and consistency. As an operator-dependent technique, the ROI method is most susceptible to subjective bias, although this can be reduced by blinding of analysts to disease status, and periodic assessments to avoid drift in tracing reliability over time. Additionally, it is time consuming and requires an accurate *a priori* hypothesis, so analyses often tend to be limited to one or two structures of interest. The ROI technique also requires a detailed and well-established tracing protocol that unambiguously defines segmentation criteria for