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Cellular, synaptic, and biochemical features of resilient cognition in Alzheimer's disease

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Abstract

Although neuritic plaques and neurofibrillary tangles in older adults are correlated with cognitive impairment and severity of dementia, it has long been recognized that the relationship is imperfect, as some people exhibit normal cognition despite high levels of Alzheimer's disease (AD) pathology. We compared the cellular, synaptic, and biochemical composition of midfrontal cortices in female subjects from the Religious Orders Study who were stratified into three subgroups: (1) pathological AD with normal cognition ("AD-Resilient"), (2) pathological AD with AD-typical dementia ("AD-Dementia"), and (3) pathologically normal with normal cognition ("Normal Comparison"). The AD-Resilient group exhibited preserved densities of synaptophysin-labeled presynaptic terminals and synaptopodin-labeled dendritic spines compared with the AD-Dementia group, and increased densities of glial fibrillary acidic protein astrocytes compared with both the AD-Dementia and Normal Comparison groups. Further, in a discovery-type antibody microarray protein analysis, we identified a number of candidate protein abnormalities that were associated with a particular diagnostic group. These data characterize cellular and synaptic features and identify novel biochemical targets that may be associated with resilient cognitive brain aging in the setting of pathological AD.

Keywords: Cognitive reserve; Synapse; Synaptophysin; Synaptopodin; Glial fibrillary acidic protein; Antibody microarray

1. Introduction

Beta-amyloid (Aβ) plaques and hyperphosphorylated tau neurofibrillary tangles are common age-related lesions that are presumed to play primary pathophysiological roles in Alzheimer's disease (AD) dementia (Jellinger, 2009). However, it is also recognized that the correlation between these neuropathological lesions and cognition is modest and accounts for a limited amount of the variance of cognition among older adults. Normal cognition despite pathological AD was recognized > 80 years ago and has been described in case reports and series (Tomlinson et al., 1968; Terry et al., 1991). More recently, there has been increasing interest in cognitive "resilience" or "reserve" in large-scale epidemiological studies. For example, the Nun Study has shown discordance of cognition with pathology and the important effects of education, diet, linguistic ability, and childhood positive emotion on cognitive function in late life (Tyas et al., 2007; Iacono et al., 2009). The Baltimore Longitudinal Study of Aging (BLSA) (O'Brien et al., 2009), the Honolulu-Asia Aging Study (White, 2009), and the Medical Research Council Cognitive Function and Ageing Study (Savva et al., 2009) have similarly reported dissociations

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between plaques, tangles, or other pathological lesions and cognition. This relatively poor correlation may become even more pronounced in the oldest old (Haroutunian et al., 2008; Ewbank and Arnold, 2009).

In the Religious Orders Study (ROS) and its companion study, the Rush Memory and Aging Project (Bennett, 2006), we found that a third of older people with normal cognition have densities of plaques and tangles that meet National Institute on Aging–Reagan Institute criteria for intermediate or even high likelihood of AD, as well as infarctions and Lewy bodies (Bennett et al., 2006b; Schneider et al., 2007). Although such cases may be the minority, it is evident that healthy cognition occurs amid a spectrum of brain pathology: from those who remain cognitively intact and whose brains are relatively free of neurodegenerative disease or other pathological lesions to those who remain resilient even with significant accumulations of pathology.

Aside from noting such discordance in clinicopathological studies, there has been little pursuant postmortem investigation of neurobiological factors that might confer or be associated with resilient brain aging. Here, we describe neuropathological, cellular, synaptic, and molecular features associated with resilient cognition in the face of AD pathology in participants from the well-characterized ROS cohort.

2. Methods

2.1. Case materials

2.1.1. Clinical characterization

The ROS cohort consists of $>$ 1100 older Catholic nuns, priests, and brothers who agreed to annual clinical evaluations and signed an informed consent and an Anatomic Gift Act, donating their brains for research at the time of death (Wilson et al., 2004). The ROS is conducted by the Rush Alzheimer's Disease Center in Chicago with approval of the Institutional Review Board at Rush University. Participants were seen annually and had up to 18 clinical evaluations documenting level of cognition and clinical diagnoses of mild cognitive impairment (MCI), AD, and other types of dementia (Bennett et al., 2006a), with clinical diagnoses conforming to common established criteria (McKhann et al., 1984; American Psychiatric Association, 2000; Petersen and Negash, 2008). Annual evaluations included a uniform structured interview and examination consisting of medical history, neurological examination, and cognitive testing by trained personnel who are blind to previous evaluations, as previously described (Bennett et al., 2002). Twenty-one cognitive tests assessed a broad range of abilities commonly impaired in older persons with and without dementia. Neuropsychological indices of cognition were summarized as a global measure based on the average z-score of all tests, using the mean and standard deviation from the measures of the baseline assessments, encompassing measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. Detailed information on the individual tests and on the derivation and correlates of composite measures is contained in previous publications (Wilson et al., 2002, 2004).

2.1.2. Neuropathological processing and diagnosis

Brain autopsies were conducted in a standardized fashion, as previously described (Mufson et al., 1999; Bennett et al., 2004). Briefly, after macroscopic inspection and photodocumentation, precise 1-cm coronal slabs were alternately fixed in 4% paraformaldehyde for 24–48 hours or frozen. The hemisphere used for diagnostic and frozen blocks alternated randomly between cases. Diagnostic blocks were dissected from fixed slabs and included midfrontal, superior or middle temporal, inferior parietal cortex, entorhinal cortex, hippocampus, anterior basal ganglia, anterior thalamus, and midbrain. These were embedded in paraffin, cut into 6-μm sections, and mounted on glass slides. Bielschowsky silver staining was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in the frontal, temporal, parietal, and entorhinal cortices, and the hippocampus. Immunohistochemistry for α-synuclein was used to identify any Lewy bodies (Schneider et al., 2007). Macroscopic infarctions identified at the time of brain dissection were verified by histopathology, and microinfarcts were documented on inspection of hematoxylin-and-eosin-stained tissue sections (Arvanitakis et al., 2011). Neuropathologic diagnoses of AD were established by a board-certified neuropathologist blinded to age and all clinical data according to National Institute on Aging–Reagan Institute (Hyman and Trojanowski, 1997), Braak (Braak and Braak, 1995), and Consortium to Establish a Registry for Alzheimer's Disease (Mirra et al., 1991) classifications.

2.1.3. Stratification for final case selection

To contrast neuropathological AD with and without dementia with semiquantitative neurohistological and proteomic analyses, we applied an a priori stepwise stratification strategy and selected 10 "AD-Resilient" cases, 10 AD-Dementia cases, and 10 cognitively and pathologically "Normal Comparison" (NC) cases. This yielded well-matched subgroups of cases that highlighted contrasts of cognition and pathology while minimizing demographic and other residual factors. We first limited our selection to female participants in the ROS cohort, thus minimizing sex and major lifestyle differences (given relatively similar lifestyle activities, diet, habits, and health care of Catholic female clergy). We excluded any cases with clinical or pathological diagnoses other than normal, MCI, or AD that potentially contributed to cognitive impairment (e.g., abundant Lewy body pathology, infarcts, hippocampal sclerosis). Cases with coincidental minor pathologies that were not deemed to contribute to cognition were allowed. We next stratified according to composite cognition scores from