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Different mechanisms of episodic memory failure in mild cognitive impairment

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Abstract

Mild cognitive impairment (MCI), defined as episodic memory impairment beyond what is expected in normal aging, is often associated with hippocampal atrophy (HA) and may represent incipient Alzheimer's disease. However, recent studies suggest that MCI is very heterogeneous and multiple etiologies likely exist. One possibility is small vessel cerebrovascular disease (CVD). Specifically, we hypothesized that white matter hyperintensities (WMH), an MRI marker for CVD, would lead to impairments in executive control processes critical for working memory that may, in turn, result in episodic memory impairment. To test this hypothesis, we examined a group of subjects clinically diagnosed with MCI and used MRI to further subcategorize individuals as either MCI with severe white matter hyperintensities (MCI-WMH) or MCI with severe hippocampal atrophy (MCI-HA). MCI-WMH, MCI-HA, and matched control subjects each performed a battery of working memory and episodic memory tasks. Results showed that MCI-HA and MCI-WMH were equally impaired on the episodic memory task relative to controls, but MCI-WMH were additionally impaired on tests tapping verbal and spatial working memory abilities and attentional control processes. These results suggest that CVD and hippocampal dysfunction are associated with distinct neuropsychological profiles. Although both syndromes are associated with episodic memory deficits, CVD is additionally associated with working memory and executive control deficits.

Keywords: Aging; Dementia; White matter hyperintensities; Working memory; Cerebrovascular disease; Hippocampus

1. Introduction

Even in the absence of dementia, many elderly persons develop a degree of cognitive loss beyond what is expected in normal aging. There are many characterizations of this intermediate stage of cognition, one of which is mild cognitive impairment (MCI) (Petersen et al., 1999). Individuals diagnosed with MCI typically have severe episodic memory deficits with otherwise relatively preserved cognitive and functional abilities. MCI was originally defined to identify individuals who are in the preclinical stage of Alzheimer's disease (AD). Given that the hippocampus plays a central role in episodic memory and is the initial target of AD pathology, many studies have focused on hippocampal dysfunction as an etiology of MCI. Indeed, there is evidence that individuals with MCI show distinct hippocampal activation patterns (Machulda et al., 2003; Small, Perera, DeLaPaz, Mayeux, & Stern, 1999) and that individuals with MCI and hippocampal atrophy (HA) have greatly increased risk of developing AD (Jack et al., 1999). Such results suggest a strong link between hippocampal dysfunction and MCI.

However, it is has also become clear that some individuals diagnosed with MCI do not have hippocampal atrophy and

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are not in the preclinical stages of AD, suggesting that other pathological processes are at work. Epidemiological studies suggest that MCI is heterogeneous and likely arises from multiple etiologies (DeCarli, 2003a). One possible etiology is small vessel cerebrovascular disease (CVD). Small vessel CVD is commonly seen in elderly individuals and has been associated with increased risk for MCI (DeCarli et al., 2001; Lopez et al., 2003). Rather than causing large cortical strokes, small vessel CVD is associated with small subcortical infarcts and white matter abnormalities.

These white matter changes appear on MRI as white matter hyperintensities (WMH) and are used as a marker for small vessel CVD severity in this study. WMH appear as areas of high signal intensity in deep or periventricular white matter on proton density and T2-weighted MRIs. The underlying pathology is non-specific and includes multiple types of injury to white matter such as reduction in myelination of axons, narrowing of small vessels, and gliosis (see Bronge, 2002, for review). WMH have been associated with hypertension, diabetes mellitus, and history of stroke, three risk factors for CVD (Breteler et al., 1994b; DeCarli et al., 1995).

We propose that WMH related to small vessel CVD may play a role in the episodic memory impairment characteristic of MCI. Given the evidence that WMH may be associated with frontal lobe dysfunction (Breteler et al., 1994a; DeCarli et al., 1995; Gunning-Dixon & Raz, 2003), we predicted that WMH may compromise executive control processes that are critical for working memory, which in turn may lead to episodic memory deficits and a diagnosis of MCI. This theory presupposes that if information cannot be actively maintained and manipulated at an immediate or short-term level, episodic encoding and retrieval impairments may arise. Thus, whereas hippocampal dysfunction may be associated with isolated episodic memory impairments, small vessel CVD may lead to a distinct pattern of deficits that includes both episodic memory impairment and deficits in executive control processes.

To test our hypothesis, we examined a group of individuals who were clinically diagnosed with MCI and used MRI to identify two subgroups of subjects: (1) those with severe WMH without hippocampal atrophy (MCI-WMH), and (2) those with severe hippocampal atrophy without extensive WMH (MCI-HA). Cognitive performance for each of these groups was compared to a group of age-matched control subjects. Importantly, these specific subgroups of MCI subjects were selected for the purpose of trying to understand the different mechanisms by which WMH and HA may lead to episodic memory impairment in MCI. Although there is increasing evidence suggesting that cerebrovascular disease and degenerative processes associated with AD often co-occur, the nature of the interaction is unclear and complex to study due to the difficulty of disentangling the two in standard clinical samples. Thus, we examined a highly selected sample in order to begin to understand the separate roles that each type of brain lesion may play in producing memory impairment.

The study is divided into two parts. First, we compared performance of MCI patients and controls on the neuropsychological tests that were used to diagnose MCI. This allowed us to determine whether standard neuropsychological tests used widely in clinical practice could distinguish between two MCI groups with different underlying brain pathologies. Second, we compared the performance of these subjects on a battery of behavioral tasks used widely in the cognitive neuroscience literature. The purpose of using these tasks was to attempt to understand the different cognitive mechanisms that underlie memory loss in MCI. The battery included an episodic memory task, two working memory tasks, and a version of the continuous performance test (CPT). We predicted that both groups of MCI participants would show deficits on the episodic memory task, but that the MCI-WMH group would show additional impairments on the working memory tasks and on the CPT.

2. Methods

2.1. Participant selection

This study was approved by the UC Davis IRB. All participants were recruited from the UC Davis Alzheimer's Disease Center (ADC) and were over the age of 65 years, in stable health. Exclusion criteria were limited to clinical depression, history of cortical strokes, and red–green color blindness. Five of the 11 MCI-HA participants and 6 of the 11 MCI-WMH were on stable doses of cholinesterase inhibitors. All participants received a clinical diagnosis through the ADC of either normal cognition or mild cognitive impairment based on neurological exams and neuropsychological evaluations. The diagnoses of either normal or MCI were adjudicated at a multidisciplinary case conference, based upon all available clinical information. Subjects with MCI all met criteria for an amnestic form of MCI (Petersen et al., 1999) as all had memory complaints (usually verified by an informant), performed poorly on neuropsychological tests of verbal memory (Memory Assessment Scales (MAS) List Learning, Logical Memory I and II, see below), had normal general cognitive function, and intact activities of daily living. All of these MCI subjects were recruited from a pool of individuals who presented to the ADC for cognitive evaluation of their memory complaints. Control subjects were recruited either from the community through advertising or word of mouth, or from spouses of patients seen at the ADC. MRIs obtained within 6 months (mean = 121 days) of clinical diagnosis were then used to categorize participants in the MCI group as either MCI-WMH or MCI-HA. After examination of MRIs, out of a total of 30 individuals clinically diagnosed with MCI, 3 were excluded based on having neither severe HA or severe WMH and 5 were excluded based on the presence of both severe HA and severe WMH. As an additional measure to confirm the presence of cerebrovascular disease in the MCI-WMH group, we also exam-