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Original Article

# Arbitrary and semantic associations in subjective memory impairment and amnesic mild cognitive impairment among Taiwanese individuals: A cross-sectional study

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## KEYWORDS

Alzheimer's disease;  
Mild cognitive  
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Dementia

**Background/Purpose:** Researchers have recently proposed a preclinical stage of dementia of Alzheimer's type (DAT), referred to as subjective memory impairment (SMI), with the aim of developing methods for the early detection of DAT and subsequent intervention. It has been proposed that the objective memory functions of individuals with SMI are normal; however, arbitrary and semantic associations are both used to describe the processes of memory. No previous studies have investigated these processes among individuals with SMI.

**Methods:** Cross-sectional analysis was used to compare the memory function of individuals with SMI, amnesic mild cognitive impairment (aMCI), or DAT. One hundred and eighty-three participants were recruited from the Memory Clinic of National Taiwan University Hospital and communities in northern Taiwan, including individuals with no memory complaints (HC,  $n = 30$ ) and individuals with SMI ( $n = 61$ ), aMCI-single domain ( $n = 24$ ), aMCI-multiple domain ( $n = 33$ ), or DAT ( $n = 35$ ). The Word Sequence Learning Test (WSLT) was used to assess the formation of arbitrary associations and the Logical Memory subtest of the Wechsler Memory Scale-Third Edition was used to assess the formation of semantic associations.

**Results:** Compared to the HC group, the SMI group performed poorly only on the WSLT, whereas the other groups performed poorly on both of the memory tasks. This study demonstrated that SMI individuals tend to perform poorly in the formation of arbitrary associations.

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**Conclusion:** Our findings suggest that tasks requiring arbitrary associations may provide greater sensitivity in the detection cognitive changes associated with preclinical DAT.

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## Introduction

It has been proposed that subjective memory impairment (SMI) may occur in the absence of objective memory impairment in the preclinical stage of Alzheimer's disease (AD).<sup>1–4</sup> Detecting the first cognitive changes in AD is crucial for early intervention.<sup>1</sup> Memory dysfunction has been identified as the earliest and most telling cognition-related symptom of AD.<sup>5</sup> Unfortunately, researchers have been inconsistent in the assessment of memory among individuals with SMI.<sup>2,6</sup> Previous researchers have argued that challenging memory tasks may provide advantages in the early detection of AD.<sup>7,8</sup> However, limited studies have used a variety of memory tasks to detect memory changes associated with pre-mild cognitive impairment (MCI) stages of AD. This calls into question the validity of previous efforts in early detection.

In addition, memory processes can be differentiated into those involving the formation of arbitrary associations and those involving the formation of semantic associations.<sup>9</sup> Arbitrary associations may involve within-item and item–item connections, whereas semantic associations may involve item-context connections.<sup>10,11</sup> Entities with little semantic linkage (e.g., items in verbal lists) induce a relatively high degree of arbitrary associations. In contrast, pre-established semantic structures in materials may be recruited into the recall process (e.g., prose recall on familiar topics).<sup>9</sup> Deficits in forming arbitrary associations may be more closely related to lesions in the entorhinal and perirhinal cortices,<sup>9–11</sup> the locations identified as having the earliest neuropathological involvement of AD.<sup>12</sup> In contrast, deficits in forming semantic associations may be related to pathologies in the hippocampus and neocortical structures (e.g., inferior temporal cortices).<sup>9,13</sup> Under the assumption that SMI can occur in preclinical stage of AD,<sup>1,2</sup> it would be reasonable to expect individuals in this stage to perform poorly on tasks that depend more heavily on forming arbitrary associations. In contrast, patients with prodromal or clinical AD may suffer from pathologies in the entorhinal and perirhinal cortices, hippocampus, and neocortical structures.<sup>12</sup> Thus, they would be expected to perform poorly on tasks requiring the formation of arbitrary or semantic associations.

The aim of this study was to evaluate the formation of arbitrary and semantic associations among Taiwanese individuals with SMI, amnesic MCI (aMCI) or dementia of Alzheimer's type (DAT) as well as healthy control (HC) individuals without memory complaints using a prose recall test and a verbal list learning test. We hypothesized that individuals with SMI would perform more poorly on the verbal list learning test compared to the prose recall test.

Conversely, we expected that the patient groups would perform similarly poorly on both memory tests.

## Methods

### Participants

This study recruited 161 individuals with memory complaints (>50 years of age) who were seeking help at the Memory Clinic of the National Taiwan University Hospital. The participants were interviewed and screened at the clinic by a neurologist. The participants were then classified as SMI (n = 61) if they performed normally on all tests in the neuropsychological evaluation, as indicated by performance no worse than 1.5 SD below the normative mean in Taiwan, and the duration of their memory complaints was less than 5 years.<sup>1</sup> Participants were classified as having aMCI-single domain (aMCI-sd, n = 24) if their performance on the episodic memory task was 1.5 SD or more below the normative mean with normal performance on other neuropsychological tests.<sup>14</sup> Participants were classified as having aMCI-multiple domain (aMCI-md, n = 33) if they displayed poor performance on the episodic memory task and at least one other cognitive domains, as indicated by a performance of 1.5 SD or more below the norm.<sup>14</sup> Deficit in a given cognitive domain was defined as poor performance on at least one neuropsychological test measuring that domain. Participants were classified as having probable AD dementia (DAT, n = 35) if they met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria<sup>15</sup> and had a Clinical Dementia Rating (CDR) of 0.5 or 1. Among the majority of patients (83%), structural brain imaging data (MRI: 77%; CT scan: 23%; no difference across groups regarding type of imaging data,  $\chi^2_{df=2, N=78} = 0.44, p = 0.80$ ) diagnosed by radiologists were available and approximately half of them revealed a combination of brain atrophy and white matter changes (48%; brain atrophy: 17.9%, white matter changes: 19.2%, no remarkable finding: 21.4%; no difference across the groups,  $\chi^2_{df=6, N=78} = 6.02, p = 0.42$ ). Thirty community-dwelling HC participants without memory complaints were also recruited. They were matched with the SMI individuals in terms of demographics. The community-dwelling volunteers were asked about their memory function using the following question: "Do you feel like your memory function is declining?".<sup>16</sup> Participants who answered "No" were classified as HC. Exclusion criteria for this study included a history of other syndrome, disorder, or disease that could contribute to the current cognitive state

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