Early detection of Alzheimer's disease

A neuropsychological approach

Why preclinical prediction is important

The aging population in Taiwan has grown rapidly in recent decades. As age is the most important risk factor for developing dementia, the size of the population with dementia is expected to increase, causing substantial societal impacts on health care costs and caregiving. As the dominant paradigm in health care has swung from treatment to prevention, there has been a recent explosion of interest in developing tools and identifying factors that are important for predicting, in healthy and well-functioning populations, which individuals will eventually develop age-related disease or dysfunction. Efficient and accurate prediction of Alzheimer's disease (AD) in the preclinical stage is important for social and medical reasons and can serve as a cornerstone for developing effective interventions to prevent or delay the onset of AD or other age-related diseases or dysfunctions.

Mild cognitive impairment: A risk factor for the development of AD

The concept of *mild cognitive impairment* (MCI) describes patients who have memory or cognitive complaints exceeding those expected from normal aging but who do not satisfy the clinical criteria for dementia. Understanding the relationship between MCI and AD has been complicated by the fact that MCI represents a heterogeneous population, both etiologically and cognitively. For example, some patients with MCI suffer exclusively from symptoms of episodic memory difficulty, while others may have additional cognitive (e.g., language, executive) symptoms that, while present, are not sufficient to warrant a dementia diagnosis. In one of our recent works, our research team demonstrated that comprehensive neuropsychological assessment helps to detect subtle differences between the subgroups of MCI, and neuropsychological approaches can be used to improve biomarker-based predictions. For example, through a comprehensive neuropsychological approach, we were able to identify individuals in the very early stage of MCI (*Chang et al.*, 2015). By applying advanced imaging techniques to those individuals, we further discovered that diminished integrity of select white matter tracts actually appears earlier than the traditional marker, gray matter atrophy in medial temporal regions (Figure 1); this discovery also provides further support for the idea that changes in white matter are independent of changes in gray matter. In another study from our research team (*Chang, Yen, Chen, Yan, & Tseng*, 2016), we successfully applied a comprehensive neuropsychological approach to identify individuals who were not yet in the stage of MCI (i.e., pre-MCI) but who showed subtle behavioral signs predicting their conversion to MCI within two years. In addition, this study extended our previous work by revealing that the same white matter changes can be used as a marker in the early detection of AD. As the two above-mentioned studies suggest, when sound neuropsychological approaches are employed, significant improvements are made in characterizing AD risk phenotypes. These improvements offer the possibility of biomarkers with strengthened connections to phenotypes in expected patterns and may also reveal associations beyond or instead of typical AD pathophysiology (e.g., white matter integrity).

Development of a sensitive tool for preclinical detection

A rapidly expanding body of literature has revealed several biomarkers as well as genetic and neurocognitive risk factors that predict the development of AD. Screening for biochemical, genetic or neuroimaging risk factors is either too expensive or impractical for use at the population level. Neurocognitive measures hold promise, particularly when evaluated in the context of other variables, in predicting which individuals will eventually develop symptoms of dementia. Because it is known that early pathological changes in AD involve medial temporal/limbic structures, evaluation of memory functions has emerged as a useful and recommended approach to identifying at-risk individuals. With the goal of improving sensitivity and specificity in the identification of preclinical AD individuals, our research team recently developed a memory test that more specifically taps the contribution of medial temporal/limbic structures to memory performance by using unique features of the Chinese language. Through a carefully designed experiment, we found that individuals with preclinical AD individuals have

disproportionate deficits in associative memory compared to item memory, and deficits in associative memory were correlated with structural measurements of the hippocampal and surrounding regions, which suggests that our associative memory task is useful in identifying people with prodromal AD (Figure 2). Moreover, we are the first to report elevated rates of a unique error type, namely, orthographic errors related to features specific to Chinese characters, in older adults with MCI, which may be a useful measure in the early detection of AD for Chinese-speaking populations(*Chen & Chang*, 2016).

Summary and conclusions

Neuropsychological evaluation of the elderly across the continuum from normal aging to clinical dementia has proven useful in identifying cognitive variables that predict the eventual development of AD. When such efforts are made to more comprehensively assess neuropsychological functions, they result in improved characterizations of detectable cognitive decline preceding the clinical diagnosis of AD, leading to strengthened associations with clinical outcomes and biomarkers. Further work is needed to identify or develop the minimum efficient battery for the prediction of clinically meaningful cognitive change.

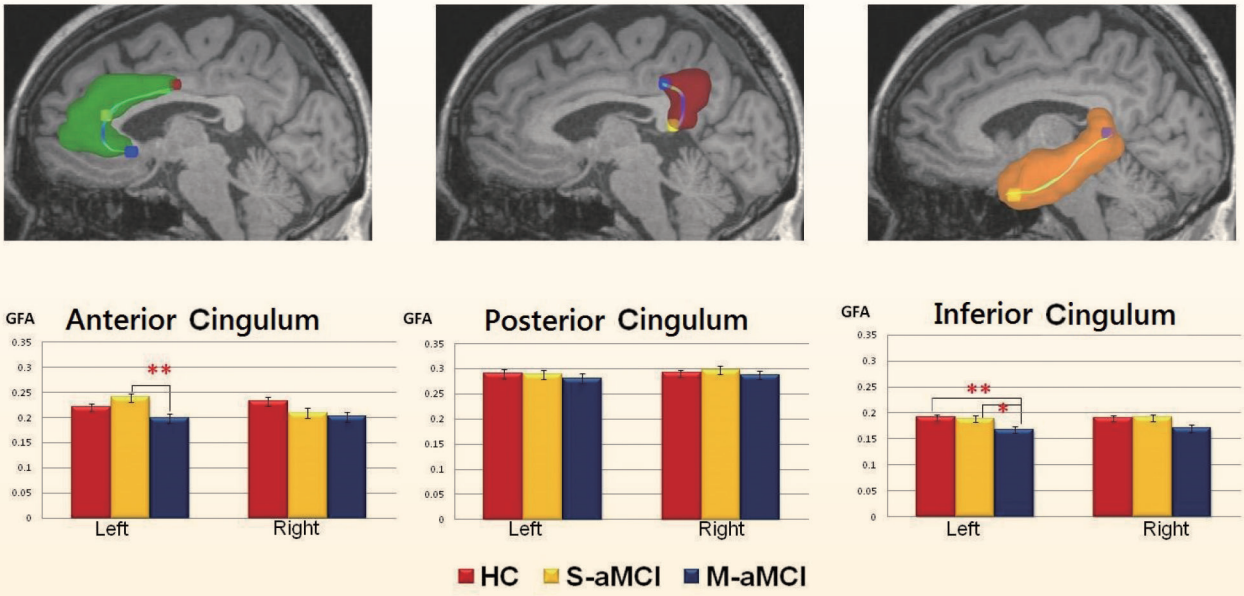

Figure 1. The regions of interest placements, reconstructed tracts, and general fractional anisotropy values derived from diffusion spectrum imaging in the three segments of the cingulum bundle. Abbreviations: HC, healthy controls; S-aMCI, single-domain amnestic mild cognitive impairment; M-aMCI, multidomain amnestic mild cognitive impairment.

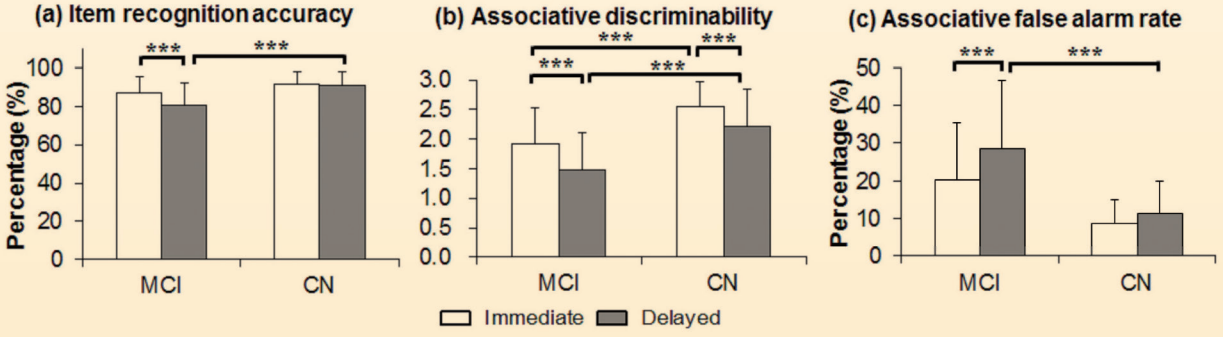

Figure 2. Indices of associative recognition in the cognitive normal (CN) and mild cognitive impairment (MCI) groups: (a) accuracy rate of item recognition, (b) discriminability, and (c) total false alarm rate. Error bars denote the standard deviation. *** $p < 0.001$

References

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Aging mechanism

A critical role of serine protease inhibitor B2 (SerpinB2) in senescence

Normal cells have limited proliferative capacity. They eventually enter a terminal nondividing state termed cellular senescence, which is caused by the incomplete replication of linear chromosomes in cells. Due to the end-replication problem, the telomere (the end of chromosomes) length is shortened upon each cell division. Critically short telomeres are then recognized as DNA strand breaks, and cell cycling is accordingly through a p53-mediated DNA damage response pathway. Although the main players in the process have been identified and characterized, the mechanism of how the DNA damage response pathway is maintained and regulated is less clear.

SerpinB2 is a serine protease inhibitor that binds to both urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA). It is also known as plasminogen activator inhibitor type 2 (PAI-2). Because of its ability to bind uPA and tPA, most research on serpinB2 is related to its extracellular function. Interestingly, it has also been known for over 10 years that the serpinB2 level in senescent cells is increased. However, its role in senescence was not defined. We found that elevating serpinB2 levels is sufficient to induce senescence and that reducing serpinB2 levels greatly decreases the number of senescent cells. These results establish an important role for serpinB2 in senescence. We also showed that senescence induced by serpinB2 is not related to its extracellular function, suggesting an intracellular role of serpinB2.

The mechanism of how serpinB2 is involved in senescence was also analyzed. We found that serpinB2 is a direct target of p53 that can be induced through a DNA damage response pathway in senescent cells (Fig. 1). The induced serpinB2 then binds and stabilizes p21 levels in senescent cells. p21 is an important downstream target of p53. It binds CDKs and inhibits their activities to stop the cell cycle. p21 must be efficiently removed from CDKs for cells to undergo normal cell cycle progression. Thus, the stabilization of p21 by serpinB2 explains how elevated serpinB2 functions in senescent cells. It also provides a novel mechanism for the maintenance of p21 levels in senescent cells.

We also analyzed the expression of serpinB2 under various stresses, including UV irradiation, oxidation damage by hydrogen peroxide exposure, and DNA damage by an anticancer drug, cisplatin. The results showed that the role of serpinB2 is not limited to cellular senescence. SerpinB2 activation might be considered a common stress response that is induced to help cells accommodate stress. The binding and stabilization of p21 by serpinB2 might stop unchecked cell proliferation, providing an opportunity for cells to adjust to various types