國立臺灣大學理學院心理學研究所

碩士論文

Graduate Institute of Psychology

College of Science

National Taiwan University

Master Thesis

主觀認知缺損個體在視覺和聽覺事件記憶上的知感能力

Visual- and Auditory-Based Episodic Memory Feeling-of-Knowing in Individuals with Subjective Cognitive Decline

孫鈺玹

Yu-Hsuan Sun

指導教授：花茂棪 博士、張玉玲 博士

Advisors: Mau-Sun Hua, Ph.D., Yu-Ling Chang, Ph.D.

中華民國 108 年 1 月

January 2019

doi: 10.6342/NTU201900062

致謝

這次的論文得以生產，首先要感謝我的指導教授花茂琴老師，總是不厭其煩地細心指導，讓我在研究的路上得以有個方向徐徐前行。另外，也要感謝張玉玲老師在不少地方的大力相助。而爽快地答應在繁忙十二月擔任口委的邱銘章醫師和楊啟正老師，亦給予我不少研究上面的實用建議。

在收案過程中，受到陳達夫醫師和沛齡的頃力相助，這個研究才得以在短時間內收集到足夠的資料；不管是研究上還是臨床上，都因為這次的診間之旅而大有斬獲。另外，也要感謝神經部門診的護理師們、神經電子診斷科的醫檢師們和志工，以及爽快幫忙的婷文學姊、拳拳到肉的雅嵋學姊、正向充滿的星恬學姊還有鼓勵我繼續留言的織羽，於公於私上都受到不少實質及心靈上的照顧。當然，還有一起收案的夥伴們，猷祥和祐蓁。感謝你們在 IRB 初期的肩膀，還容忍我在收案過程中的各種吐槽和怒火，祝願我們未來都能夠平順一點。

生活上，要感謝老媽願意容忍我持續地著迷於沒什麼前途的學術圈，讓我不愁吃住，還老用他看不懂的語言寫令人費解的大腦活動。另外，因為太對不起一手籌辦新加坡之旅的高中同學們，所以在這邊一併感謝，雖然你們跟我的論文沒什麼關聯。也要感謝淯惇的陪伴，我也就含蓄地說到這邊。

最後，我想要感謝參與這個研究的所有參加者和家屬。感謝你們願意花費人生中寶貴的時間與精力，來參與這個不知道對人類能有什麼貢獻的研究，也要感謝你們願意分享人生中的吉光片羽，讓我得以窺見生命的美麗與哀愁。祝願這個疾病帶走你們所有不好的回憶，讓你們的生活停滯在那些珍貴美好的時光中。

“Do not go gentle into that good night.
Rage, rage against the dying of the light.”
--Dylan Thomas

孫釭玹

2019.01.11

doi: 10.6342/NTU201900062

CONTENTS

Abstract…… 1

Introduction…….…... 4

Methods…….…. 10

Participants…….…. 10

Criteria for groups…….…... 11

FOK paradigm…….…. 13

Neurocognitive measures…….…. 14

Data collection…….…. 16

Statistical analyses……... 16

Results……..... 17

Demogrphic characteristics……. 17

FOK paradigm test performances……. 18

Neurocognitive performances……. 23

FOK judgment and neurocognitive performances……. 24

Discussion…… 26

References…….. 33

Tables…… 51

Figures……..... 58

doi: 10.6342/NTU201900062

摘要

背景 具有主觀認知衰退（Subjective Cognitive Decline）的成年人，被認為是未來可能轉化為輕度認知障礙（Mild Cognitive Impairment）和阿茲海默型失智症（Alzheimer's Disease）的群體。近期研究指出，主觀認知衰退個體在與自主感受和後設記憶有關的腦區，有異常表現。因此，本研究旨在事件記憶中使用知感作業（Feeling-of-Knowing）來檢測主觀認知衰退個體在後設記憶上的表現，是否與輕度認知障礙和阿茲海默型失智症的病人相似，以及其表現是否受視覺或聽覺作業型態影響。

方法 本研究納入年齡範圍在 50 至 85 歲的八十八位受試者，包含健康控制組、主觀認知衰退組、輕度認知障礙組以及阿茲海默型失智症組。每位受試者接受視覺和聽覺事件記憶下的知感作業，以及神經心理測驗套組。

結果 在視覺知感測驗中，主觀認知衰退組的分數表現與健康控制組、輕度認知障礙組間無顯著差異，僅與阿茲海默型失智症組的分數有顯著差異。而健康控制組的表現顯著好於輕度認知障礙組、阿茲海默型失智症組。在聽覺知感測驗中，健康控制組與主觀認知衰退組間無顯著差異，但兩組的表現皆與兩組病人組有顯著差異。

結論 根據本研究在記憶監控功能上的結果，具主觀認知衰退的個體可能處於健康老化與病態老化之間的階段。建議未來針對此議題的研究可納入大量樣本與不同的記憶測驗。

doi: 10.6342/NTU201900062

ABSTRACT

Background Subjective Cognitive Decline (SCD) in cognitively unimpaired individuals has been recognized as a possible sign predicting future decline to mild cognitive impairment (MCI) and Alzhemier's Disease (AD). Individuals with SCD showed atypical findings in brain regions that are associated with subjective feeling and memory monitoring. Thus, the current study aimed to examine whether the performance pattern on the episodic memory feeling of knowing (FOK) paradigm measures in individuals with SCD is comparable to that of patients with MCI and AD, and whether individuals with SCD exhibit different performance pattern on visual- and auditory-modality FOK tests. **Methods** A total of 88 adult participants (aged 50 to 85), including 4 groups**,** healthy control (HC), SCD, MCI and AD, were recruited in the present study. Each participant received visually and aurally episodic memory feeling-of-knowing (FOK) paradigm and a battery of neuropsychological tests. **Results** On the visual FOK test, the performance scores were not significantly different between SCD and HC, and between SCD and MCI while the score differences between SCD and AD were remarkable. The HC's performance significantly overpowered the two patient

doi: 10.6342/NTU201900062

groups. On the auditory FOK test, the performance scores between participants of HC and SCD were not significantly different while the scores of both HC and SCD were significantly different from the two patients groups. **Conclusion.** Based on the present results of meta-memory functioning study, we suggest that individuals with SCD may be placed on the stage between health aging and pathological aging. However, further study on a large scale and different memory tests on this issue is necessary.

Keywords: subjective cognitive decline, feeling-of-knowing, memory monitoring, episodic memory, Alzheimer's disease, mild cognitive impairment

doi: 10.6342/NTU201900062

INTRODUCTION

Alzheimer's disease (AD), characterized by a primary deficit in episodic memory that gradually progresses to a global impairment (Backman, Jones, Berger, Laukka, & Small, 2004, 2005; Dubois et al., 2007; Weintraub, Wicklund, & Salmon, 2012), is the most common cause of elderly dementia. Its neurodegenerative process is thought to begin years before the symptoms surface (Jack et al., 2013; Villemagne et al., 2013). It is thus crucial to identify people at risk for developing AD and provide early intervention to slow down disease progression. Therefore, concepts such as "preclinical AD" or "asymptomatic AD" have been proposed based on evident AD biomarkers in cognitively normal people (Dubois et al., 2010; Sperling et al., 2011). However, in addition to the AD biomarkers, recent studies have suggested that subjective cognitive decline (SCD) in individuals with unimpaired performances on cognitive tests might serve as a sign of preclinical AD (Jessen et al., 2014; Perrotin, Mormino, Madison, Hayenga, & Jagust, 2012), predicting future memory decline (Koppara et al., 2015; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007).

Emerging evidence suggests that SCD is related to AD in multiple domains. A

doi: 10.6342/NTU201900062

seven-year follow-up study reported that most individuals with SCD decline faster than those without such concerns regarding cognitive and functional performances (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Moreover, greater self-reported concern regarding SCD is significantly associated with Abeta deposition, one of the distinctive neuropathological features of AD patients (Nelson et al., 2012), after controlling for objective memory performance (Amariglio et al., 2015). One study also suggested that the reduced confidence in one's general memory performance is correlated with greater Abeta deposition in the right medial prefrontal cortex, anterior cingulate cortex, and precuneus and posterior cingulate cortex in cognitively normal individuals (Perrotin et al., 2012). Similar finding in tau aggregation has been reported recently as well (Swinford, Risacher, Charil, Schwarz, & Saykin, 2018). These regions, known as parts of the default mode network (DMN) (Raichle, 2015), are recognized to be associated with subjective experience and memory monitoring (Chua, Schacter, Rand-Giovannetti, & Sperling, 2006). Functionally, individuals with SCD show abnormal activity in these regions, leading to disintegrations between anterior and posterior regions as well as hippocampal decoupling from the posterior DMN (Dillen et al., 2017; Erk et al., 2011; Sheline et al., 2010). Similar connectivity dysfunctions have been observed in

doi: 10.6342/NTU201900062

individuals with dementia due to AD and those with high-risk mild cognitive impairment (MCI) (Nellessen et al., 2015; Wang et al., 2015).

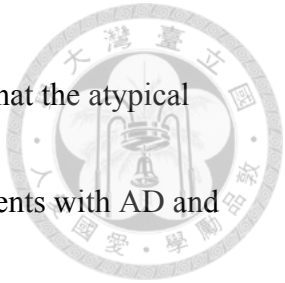
A growing body of literature has reported impaired memory monitoring, along with salient deficits in episodic memory, in patients with AD (Dodson et al., 2011; Galeone, Pappalardo, Chieffi, Iavarone, & Carlomagno, 2011; Souchay, Isingrini, & Gil, 2002), as well as in individuals with MCI (Galeone et al., 2011; Perrotin, Belleville, & Isingrini, 2007; Souchay, 2007; Y.-L. Wang, Hua, Chang, & Lu, 2007). While some researchers have reported that both individuals with AD and MCI exhibit a tendency to overestimate their memory performance on tests (Galeone et al., 2011; Perrotin et al., 2007), others suggest that the impaired memory monitoring of overestimation is limited to the general memory performance in daily living (Gallo, Cramer, Wong, & Bennett, 2012). Moreover, recent studies have revealed that tasks involving self-related information induced abnormal prefrontal activity in patients with AD and MCI (Genon et al., 2014; Zamboni et al., 2013). A similar disadvantage regarding the processing of self-related information in individuals with SCD has been reported, suggesting a weakness in memory monitoring. One study reported that compared to their counterparts of the same age, individuals with SCD tend to have lower confidence

doi: 10.6342/NTU201900062

regarding general memory performance (Perrotin et al., 2012). Moreover, research has found discrepant memory-specific observations between individuals with SCD and their informants; informants' observations tend to be better at predicting cognitive and functional declines (Slavin et al., 2015). However, no study directly measures the memory monitoring function in SCD.

Regardless of the memory-related deficit, some studies suggest that the nature of the materials that constitute memory may lead to different forgetting rates in patients with AD and MCI (Ally, Hussey, Ko, & Molitor, 2013; Vallet et al., 2016). Vallet et al. (2016) used learning items incorporating different abstraction levels of information and recorded their forgetting rates in healthy controls (HCs) and individuals with AD and MCI. They found that despite the fact that patients with AD tended to have the fastest forgetting rate compared to the other two groups, an exceptionally fast rate for items that embodied abstract visual features was revealed. Patients with MCI also exhibited a faster decline rate in recognizing abstract visual items. Although contradictory findings were reported by another research team, according to whom patients with AD and MCI demonstrate better memory for pictures (Ally, 2012; Ally, Gold, & Budson, 2009; Ally et al., 2013), it is possible that the difference was mainly due to the level of abstraction

doi: 10.6342/NTU201900062



of the stimuli used. Accumulative research has documented the fact that the atypical neural activities in processing visual and auditory stimuli among patients with AD and MCI stem not from fundamental elements processing but from the information integration levels (Bender et al., 2014; Golden et al., 2015; Golden et al., 2016; Hao et al., 2005; Kurimoto et al., 2012). Thus, in terms of a preference for visual or auditory memory in patients with AD and MCI, the results might reflect their impaired functions in dealing with memory composed of items at higher levels of abstraction.

To our knowledge, few studies have explored the memory-related characteristics of individuals with SCD. Despite a self-reported experience of memory decline in such individuals, no study has directly measured their memory monitoring functioning through objective methods. Traditional cognitive tests for studying pre-clinical AD were those used to diagnose dementia; therefore, it is possible that they lacked the sensitivity to detect the subtle cognitive changes that correlate to AD pathology progression at the preclinical stage (Mortamais et al., 2017). Such change might be more likely to be detected by tasks conducted prospectively; that is, tasks that demand high execution abilities (Bisiacchi, Tarantino, & Ciccola, 2008). The feeling-of-knowing (FOK) paradigm (Hart, 1965) reflects the memory monitoring prospectively with respect to

doi: 10.6342/NTU201900062

subsequent memory recognition (Chua, Schacter, & Sperling, 2009). An imaging study demonstrated that the FOK paradigm is correlated with activity in the prefrontal, medial parietal, and hippocampal formation regions (Chua et al., 2009), which have been found to exhibit atypical activity and salient Abeta deposition in individuals with SCD (Dillen et al., 2017; Erk et al., 2011; Sheline et al., 2010). Moreover, previous studies have suggested that the aging-related decline in memory monitoring is associated with change in executive function (Isingrini, Perrotin, & Souchay, 2008; Souchay & Isingrini, 2004; Souchay, Isingrini, & Espagnet, 2000), whereas the declined performance in patients with AD and MCI exhibits a correlation with episodic memory (Cosentino, 2014; Perrotin et al., 2007; Souchay et al., 2002). Regarding patients with MCI, a study suggested that, along with the episodic memory deficit, the existence of executive dysfunction might predict the decline from MCI to AD (Bisiacchi, Borella, Bergamaschi, Carretti, & Mondini, 2008).

Thus, the current study aimed to examine 1) whether individuals with SCD share similar performance pattern on episodic memory FOK measures with those with MCI and AD, and 2) whether individuals with SCD exhibit different performance pattern on visual- and auditory-based episodic memory FOK tests.

doi: 10.6342/NTU201900062

METHODS

PARTICIPANTS

A total of 100 participants (50 to 85 years old) were recruited from the Neurology Clinics of the National Taiwan University Hospital (NTUH) or from the communities in the present study. Exclusive criteria were applied to exclude individuals with alcohol or substance abuse, intellectual disability, brain injury, stroke, endocrine dysfunction, neurological disorders, or psychiatric disorders. All participants had a normal or corrected-to-normal vision and hearing abilities. Participants with diagnoses of dementia or mild cognitive impairment other than Alzheimer's origin were excluded as well. Twelve participants were excluded from further analyses due to other demented origins ($N = 6$), psychiatric conditions ($N = 2$), intelligent disability ($N = 1$), and non-diagnostic demented conditions ($N = 3$). A total of 88 participants were recruited in the final analyses.

All participants received a thorough explanation of the research purpose and signed an informed consent form. The Institutional Review Board (IRB) of the National

doi: 10.6342/NTU201900062

Taiwan University Hospital approved the current study. Detailed demographic data were shown in **Table 1**.

(INSERT TABLE 1 HERE)

CRITERIA FOR GROUPS

Participants recruited from the Clinics, prior to participating in the study, firstly received an examination by a physician who performed a medical history review, Mini-Mental Status Examination (MMSE), and neurologic examination. Then, a neuropsychologist conducted the neurocognitive assessment, including an interview with participant's informant for the Clinical Dementia Rating (CDR). The final diagnosis was made upon a primary attending physician after reviewing all examination results, including results of brain imaging, neuropsychological assessment, and lab examinations. With respect to their episodic memory performance for research classification purpose, Taiwan version of Wechsler Memory Scale-III (WMS-III) (Hua et al., 2005) Logical Memory I and II were performed. Participants were later classified into the following groups.

doi: 10.6342/NTU201900062

SCD Group. Individuals who performed normally across cognitive domains in neuropsychological tests and had a subjective decline in memory within the last five years (Jessen et al., 2014) were classified into the SCD group.

MCI Group. Individuals with episodic memory scores of approximately 1.0 SD or greater below the mean in the general population were considered for possible memory impairment (Albert et al., 2011). However, no algorithm was used to simply determine the diagnosis of MCI; study coordinators, neuropsychologists, and physicians who had examined the individual assigned the diagnosis based on their discussion regarding the examinations and published criteria (Albert et al., 2011). For the purpose of the study, only individuals with primary memory impairment were recruited in the MCI group.

AD Group. Individuals who had a CDR score of 0.5 and met the published criteria of the National Institute on Aging and the Alzheimer's Association (NIA-AA) (McKhann et al., 2011) were classified into dementia due to AD.

HC Group. Individuals in the HC group volunteered from the communities. Before attending the study, volunteers received a thorough neuropsychological examination performed by a study coordinator to determine their neurocognitive

doi: 10.6342/NTU201900062

functions and other conditions. Information regarding medical history, family history, and medication were collected during the process. Individuals who performed without 1.0 SD below age- and education-matched norms in all cognitive domains were recruited and matched to the SCD group in terms of demographics.

FOK PARADIGM

The memory monitoring ability was assessed by FOK paradigm with a recall-judgment-recognition fashion in episodic memory tests, in which studies suggested that were better in revealing the impaired abilities of the AD patients (Cosentino, 2014; Souchay, 2007). The episodic memory tests with FOK paradigm were the Rey Complex Figure Test and Recognition Trials (RCFT) (Meyers & Meyers, 1995) for visual episodic memory, and the Word List subtest in the WMS-III for auditory episodic memory. The FOK judgments were embodied after delayed recall phase and before recognition for each presenting item. That is, participants were asked to answer the FOK question of "Do you feel like you can accurately recognize the item" in a binary fashion before giving the "Yes/No" answer for recognition. The traditional

doi: 10.6342/NTU201900062

FOK paradigm asked participants to judge their responses toward unrecalled items (Hart, 1965; Nelson, 1990). However, the current study following the FOK paradigm used by Souchay et al. (2002) that participants were asked to make FOK judgments for each item during the recognition phases. In this way, their responses, in combination of recognition accuracy and FOK judgment, were coded into four categories for further calculation of the Hamann coefficient (Schraw, 1995; Souchay et al., 2002); please refer to **Table 2** for the equation. Hamann coefficient was used to represent FOK accuracy.

(INSERT TABLE 2 HERE)

NEUROCOGNITIVE MEASUREMENTS

In consideration of the influences of episodic memory and executive function in the FOK judgment, visual- and auditory-based tests relative to these functions were selected.

Episodic Memory. Participants received the Visual Reproduction I and II, and the Verbal Paired Associates I and II subtest of the WMS-III for constructing the scores for episodic memory. A study suggested that immediate and delayed recall performances in

doi: 10.6342/NTU201900062

episodic memory might involve different brain regions in the DMN (Huo, Li, Wang, Zheng, & Li, 2018), scores were used separately to calculate into "Immediate Recall" and "Delayed Recall" measures. In order to avoid the visuospatial deficit that interfered participants' performances on visual episodic memory, the Copy and the Discrimination phases of the Visual Reproduction subtest were used as the reference.

Executive Function. Two subtests from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) were used as indicators of executive function; they were the Matrix Reasoning and the Digit Span Backward.

General Intellectual Ability. In order to rule out the possibility that the intellectual ability might interfere with participants' learning ability, their IQ performances on the WAIS-III or WAIS-IV were collected through their record of recent neuropsychological examination. For those without previous examination record, the project coordinator estimated their full-scale IQ by performances on the Similarities, the Arithmetic, the Matrix Reasoning, and the Digit Symbol Substitution subtests from the WAIS-III (Chen, Hua, Zhu, & Chen, 2008).

doi: 10.6342/NTU201900062

DATA COLLECTION

Participants who had cardiovascular risk factors in groups other than HC, Hachinski Ischemic Score (HIS) (Hachinski et al., 1975; Rosen, Terry, Fuld, Katzman, & Peck, 1980) was used to rule out individuals with a score of 4 or greater. In consideration of the influence of possible confounding variables, each participant was asked to fill out the Taiwan Geriatric Depression Scale-15 (GDS-15) (Liao et al., 2004; Liu et al., 1997; Sheikh, Yesavage, & Health, 1986). All participants were also asked to report the cognitive decline as comparing to self, or to others.

STATISTICAL ANALYSES

Data were explored by scatterplot, the Shapiro-Wilk test and the Levene's test to determine the analysis method. Different analysis methods were applied based on the characteristic of data. All statistical tests were performed through SPSS version 25 on the macOS system version 10.14.

doi: 10.6342/NTU201900062

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Regarding to demographic characteristics among groups, analysis of variance showed a main effect of age ($F(3, 84) = 5.722$, $p = .001$, $d = .68$) across four groups. Post-hoc pairwise-comparison analyses using Scheffe indicated that HC was younger than MCI ($p = .029$, $d = .849$) and AD ($p = .01$, $d = 1.41$), whereas SCD did not differ significantly with other groups ($p > .05$). Due to the failure to meet the assumptions of parametric methods, non-parametric method was used for comparing the years of education between four groups. An independent-samples Kruskal-Wallis H test showed that four groups did not differ significantly in years of education ($H = 7.635$, $p = .054$, $d = .483$).

Performances in episodic memory and general cognitive tests. Analysis of variance showed a main effect of the Logical Memory II ($F(3,30) = 23.737$, $p < .001$, $d = .92$) across four groups. Post hoc pairwise-comparison analyses using Scheffe indicated that the performance of AD was worse than HC ($p < .001$, $d = 3.564$), SCD (p

doi: 10.6342/NTU201900062

< .001, d = 4.02) and MCI (p = .012, d = 1.866), and MCI was worse than SCD (p < .001, d = 1.496) and HC (p < .001, d = 1.515). The memory performance did not differ significantly between HC and SCD (p = .728, d = .20).

Independent-samples Kruskal-Wallis H tests showed significant differences in the MMSE (H = 26.752, p < .001, d = 1.256) and the FSIQ (H = 11.012, p = .012, d = .649) among four groups. However, an independent-samples t-test indicated no difference in the FSIQ between SCD and HC (t(61) = .391, p = .697, d = .099). No additional analysis of the MMSE was done given its nature of cognitive screening. Please refer to **Table 1** for detailed information regarding demographic characteristics of four groups.

(INSERT TABLE 1 HERE)

FOK PARADIGM TEST PERFORMANCE

The proportion (%) of overall "yes" and "no" FOK judgments was computed to determine whether four groups utilized the FOK category in a similar fashion. Kruskal-Wallis H tests indicated no significant difference was found on the "yes" and "no" judgment in the visual episodic memory among four groups (H = 2.258, p = .521, d = .189), but significant in the auditory episodic memory (H = 9.083, p = .028, d

doi: 10.6342/NTU201900062

= .559). However, Post-hoc pairwise-contrast analyses using Dunn-Bonferroni method for performance in the auditory episodic memory did not reveal any difference among these groups.

Given the fact that no significant difference of "yes/no" preference in FOK judgment among four groups, further analyses were done for exploring the group differences in FOK performance. The one-way ANCOVA was conducted to compare the visual FOK accuracy of four groups whilst controlling for age. Results indicated a significant group difference on the visual FOK accuracy ($F(3, 83) = 12.443$, $p < .001$, partial eta squared = .310). Post-hoc pairwise-comparison analyses using the Dunn-Bonferroni procedure indicated that AD performed significantly worse than other groups (AD-HC: $p < .001$, $d = 10.987$; AD-SCD: $p < .001$, $d = 10.708$; AD-MCI: $p > .05$, $d = 5.859$); despite no significant difference between HC and SCD ($p = .157$, $d = 1.232$), SCD did not differ from MCI ($p = .157$, $d = 3.385$) while HC outperformed MCI ($p = .033$, $d = 4.263$).

Regarding FOK performances on auditory-based episodic memory test, the Kruskal-Wallis H test showed a significant difference ($H = 37.613$, $p < .001$, $d = 1.674$)

doi: 10.6342/NTU201900062

among four groups. Post-hoc pairwise-comparison analyses using Dunn-Bonferroni method revealed that HC performed significantly better than MCI ($p < .001$, $d = 1.991$) and AD ($p < .001$, $d = 2.674$), SCD also performed better than MCI ($p < .001$, $d = 1.366$) and AD ($p < .001$, $d = 2.145$). Please refer to **Table 3** for details.

(INSERT TABLE 3 HERE)

Subcomponents of FOK performance. The percentage of hits and misses relative to yes/no FOK judgment was used as indicators of whether overestimation and underestimation happen in the level of groups (Souchay et al., 2002). Given the restriction of data pattern, the Kruskal-Wallis *H* test was used to detect differences at the group level.

Results revealed a significant group difference for hits and misses on the "yes" judgments of both visual and auditory episodic memory tasks (see **Table 4**). However, further post-hoc pairwise-comparison analyses using Dunn-Bonferroni method indicated different significant pattern in each condition. Comparisons on the auditory task revealed a consistent pattern that patient groups made significant fewer hits for "yes" judgment (AD-SCD: $p = .001$, $d = 1.987$; AD-HC: $p < .001$, $d = 2.751$; MCI-SCD:

doi: 10.6342/NTU201900062

p = .001, d = 1.267; MCI-HC: p < .001, d = 1.768) and more misses (AD-SCD: p = .019, d = 1.046; AD-HC: p = .003, d = 1.345; MCI-SCD: p = .019, d = .858; MCI-HC: p < .001, d = 1.102) than HC and SCD. On the visual task, patient groups still made significant fewer hits (AD-HC: p < .001, d = 2.287; MCI-HC: p = .005, d = 1.276) and more misses (AD-HC: p = .004, d = 1.322; MCI-HC: p = .022, d = .788) than the HC, but different pattern emerged while comparing to SCD. That is, no significant difference was reported between MCI and SCD regardless of hits or misses; AD only committed fewer hits than SCD (p = .001, d = 2.112), but no difference between for misses (p = .44, d = 1.082).

While on the FOK "no" judgment, results showed significant group differences for both hits and misses on the auditory task, but group difference was only reported for misses (H = 9.4, p = .024, d = .574) on the visual task (see **Table 4**). However, further post-hoc pairwise-contrast analyses on the auditory task showed that only AD made more misses than HC (p = .019, d = 1.701). No group difference was found in other conditions, including those for misses on the visual task.

(INSERT TABLE 4 HERE)

doi: 10.6342/NTU201900062

Individuals in each group that below the 5% performance in HC. In order to examine whether the insignificance results between SCD and patient groups indicate data homogeneity or difference that was statistically not detectable, a chi-square test was performed. Individuals in the HC group were sorted based on their miss performance on the visual FOK "yes" judgment. The percentage score of individual who ranked at the five percentile was used in the following analyses as cutoff score. Results showed that 12.1% of SCD, 33.3% of MCI, and 57.1% of AD were below that cutoff score, 25. A likelihood ratio chi-squared test showed that performances in four groups were not equally distributed, $\chi^2 = (3, N = 88) = 14.743$, $p = .002$, phi = .425. Same procedure was applied on performance on the misses in the auditory FOK "yes" judgment, and the cutoff score was 8.33. Results showed that 15.2% of SCD, 61.1% of MCI, and 71.4% of AD were below the cutoff score. A likelihood ratio chi-squared test showed that performances in four groups were not equally distributed, $\chi^2 = (3, N = 88) = 29.698$, $p < .001$, phi = .582.

Figure 1 shows the participant proportion with "a poor-level performance," which was based on a cut-off score below five-percentile rank of the HC group performance

doi: 10.6342/NTU201900062

score, distribution on both visual- and aural-FOK tests. On **Figure 1a,** based on such a criterion, only AD group had a higher proportion of participants with poor-level performance than normal-level performance; it was not the case for HC, SCD and MCI groups. Nonetheless, the participant proportion with poor-level performance tended to gradually increase from the HC, SCD, MCI to AD groups. **Figure 1b** shows that both HC and SCD groups exhibited a lower proportion of participants with poor-level performance scores on the auditory test while both patient groups evidenced the reverse picture.

(INSERT FIGURE 1 HERE)

NEUROCOGNITIVE PERFORMANCES

Analysis of variance showed a main effect of group on delayed recall ($F(3, 81) = 7.422$, $p < .001$, partial eta squared = .216) and immediate recall ($F(3, 81) = 4.831$, $p = .004$, partial eta squared = .152) measures after controlling age and the FSIQ. However, no significant main effect of group was found in executive function measure ($F(3, 81) = .157$, $p = .925$, partial eta squared = .152). Independent-samples t-tests

doi: 10.6342/NTU201900062

showed no significant difference between HC and SCD in all three neurocognitive measures. Detailed information was in **Table 5**.

(INSERT TABLE 5 HERE)

FOK JUDGMENT AND NEUROCOGNITIVE PERFORMANCES

In order to examine the relationship between FOK judgment and neurocognitive performance, correlations were calculated (see **Table 6**). Previous analyses revealed the misses on the FOK "yes" judgment was sensitive in distinguishing HC from other groups. Thus, special attention was paid on the relationships between misses on the FOK "yes" judgment and three neurocognitive measures. Pearson's *r* correlation was performed. However, the relationship with neurocognitive measures did not examine in the auditory-based FOK performance due to violation to the assumption of Pearson's.

The misses on the "yes" judgment was negatively correlated with executive function in both HC ($r(30) = -.370$, $p = .044$) and SCD ($r(33) = -.420$, $p = .015$); no correlation was found in MCI ($r(18) = .118$, $p = .641$) and AD ($r(7) = -.347$, $p = .445$). In addition to executive function, the misses was also negatively correlated with

doi: 10.6342/NTU201900062

immediate recall in HC ($r(30) = -.572$, $p = .001$). Contrary to the results of Souchay et al. (2002), no correlation with memory score was found in all four groups.

Since literature has suggested that the aging-related decline of executive function and episodic memory behaving similarly and being strongly correlated to each other (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010), further correlations were done to examine the relationship between executive function and other two measures. Pearson's *r* correlations showed that executive function measure was positively correlated with immediate recall measure in both HC ($r(30) = .782$, $p < .001$) and SCD ($r(33) = .453$, $p = .008$). A z-test was conducted (Eid, Gollwitzer, & Schmitt, 2017) comparing the correlations in SCD and HC. The result was statistically significant ($z = 2.119$, $p = .017$, one-tailed) that the HC group showed a stronger correlation between executive function and immediate recall when compared to SCD. Positive correlations between executive function and delayed recall were also found in both HC ($r(30) = .694$, $p < .001$) and SCD ($r(33) = .409$, $p = .018$). However, no significant correlation difference was reported ($z = 1.588$, $p = .056$, one-tailed).

(INSERT TABLE 6 HERE).

doi: 10.6342/NTU201900062

DISCUSSION

The present study examined memory monitoring performance in individuals with SCD by applying the FOK paradigm in episodic memory tests, which examined whether individuals with SCD exhibit differences across different modalities.

Individuals with SCD did not exhibit differences on the overall performance of making memory-monitoring judgment as compared to healthy elders in the present study. This finding supports a previous study wherein individuals with SCD judged their memory performance no worse than did healthy elders (Perrotin et al., 2012). However, the current study revealed the difference between individuals with SCD and healthy elders while comparing them to patients with MCI and AD. While healthy elders consistently exhibited significantly better memory monitoring performances than did patients across domains, individuals with SCD only excelled on the auditory-based test. That is, despite no statistical difference was reported between healthy elders and individuals with SCD, our results also demonstrated insignificant differences between individuals with SCD and patients with MCI and AD on visual-based test. A possible

doi: 10.6342/NTU201900062

explanation for the aforementioned results is that the subtle cognitive changes in individuals with SCD were compensated for by other neurocognitive mechanisms (Erk et al., 2011), leading to a decline that was not detectable when compared to healthy elders (Koppara et al., 2015). This is in line with the cognitive decline depicted in the study of Jessen et al. (2014); the slope of cognitive decline did not steeply drop during the preclinical phase. In other words, our finding might suggest individuals with SCD lying at the intermediate position between healthy elders and patients with MCI, as **Figure 1a** showed a gradually increasing trend in the proportion of poor performance from healthy elders, individuals with SCD, to pathological patients. Moreover, a recent study has addressed the relationship between SCD and MCI from a different perspective. It stated that the boundary between MCI and SCD is artificial in nature, and thus the issue requires further study establishing an optimal distinction (Molinuevo et al., 2017).

Our results support the idea that auditory-based tests are better in the context of detecting episodic memory deficits (Albert et al., 2011; Mortamais et al., 2017). However, our discoveries in the visual-based test contradict previous findings of the picture superiority effect in patients with AD and MCI (Ally, 2012; Ally et al., 2009;

doi: 10.6342/NTU201900062

Embree, Budson, & Ally, 2012). The reasons might be multifold. First, the visual stimuli we used in this study were highly abstract, without concrete general concept that was familiar to participants. The figure placed a high demand on information processing (Shin, Park, Park, Seol, & Kwon, 2006), differing from concrete pictures used in previous studies. Therefore, instead of an unequal performance caused by test modality, it is possible that the difference was created by the level of abstraction embodied in the information (Vallet et al., 2016). Recent research has also indicated that patients with mild AD exhibit a relatively intact cued performance when the cues are focused on distinctive conceptual information related to the target item (Deason, Hussey, Flannery, & Ally, 2015). Second, our study mainly focused on the accuracy of monitoring memory prospectively in relation to subsequent recognition. Despite a previous study reporting that patients with MCI demonstrate a coherent performance on rating their confidence and recognizing presented picture is new or old (Embree et al., 2012), our results from the comparison with healthy elders provide evidence that MCI patients' ability to deal with visual items is not superior than auditory item at memory monitoring. Third, the tests selected for the FOK paradigm might have been of varying levels from

doi: 10.6342/NTU201900062

their cognitive substrates to test procedures. For example, RCFT requires attentive learning during encoding phase (Shin et al., 2006) whereas Word list subtest of WMS-III uses semantically-associated learning during encoding (Chang et al., 2018). Thus, these memory tests require different cognitive abilities while processing provided stimuli. Moreover, it is unlikely that these tests were comparable given the fact that they use different approaches to measure the memory performance other than visual versus auditory stimulus difference only. Therefore, the discrepant results between our study and previous literature might need further studies to clarify given the possibility that FOK performances in two selected tests might actually reflect different cognitive components.

In comparison with healthy elders, further analyses suggest a discrepant relationship between memory monitoring and neurocognitive functions in individuals with SCD. Unlike the finding in patients with AD (Souchay et al., 2002), executive function was negatively correlated with the overestimation of accuracy in both healthy elders and individuals with SCD. This finding supports previous studies that found memory monitoring performance measured by the FOK paradigm to be associated with

doi: 10.6342/NTU201900062

executive function in aging-related decline (Isingrini et al., 2008; Souchay & Isingrini, 2004). However, a negative correlation between the immediate recall score indicating learning functioning and the accuracy overestimation of the FOK task was only evident in our HC group. As the learning index indicated participants' ability to learn new information, reflecting a partial characteristic of episodic memory (Albert et al., 2011), our results might suggest that individuals with SCD has a tendency to less use memory resources in proceeding memory monitoring compared to healthy elders. Such findings appear to be in line with a recent proposal suggesting that within-person variability across cognitive domains is more valuable in predicting late-life cognitive decline (Salthouse & Soubelet, 2014). However, further follow-up studies on this issue are needed.

Several limitations were noted in the current study. First, our study used a relatively small sample size in each group, particularly the patient groups. In order to obtain sufficient information to examine differences between groups, it is advised that future studies involve larger sample sizes. Second, we are aware of the debate about the influence of recruiting sites for individuals with SCD (Perrotin et al., 2017;

doi: 10.6342/NTU201900062

Rodriguez-Gomez, Abdelnour, Jessen, Valero, & Boada, 2015). Thus, information regarding depressive mood, medical records, and judgment regarding one's own memory decline were collected to eliminate possible confounding variables. Third, it is likely that our results were biased by participants' response preference in the FOK paradigm. In other words, all participants tended to state "yes," firmly assured of their following accuracy, which the base rate for "yes" judgment was enlarged enough to show variation. However, this tendency was observed across groups, and no significant difference was reported between groups. Thus, this is unlikely to have led to the final results. Another similar statistical limitation was from our data distribution. That is, the selected auditory episodic memory test had items with high familiarity or high semantic association to help memorizing. According to our data, it is clear that cognitively normal participants almost excelled in every trial in the auditory-based test, leading to a violation of the parametric assumption. This makes data analysis problematic as some useful kits could not be performed. Fourth, our study requires extra caution while explaining the FOK test results between SCD and HC given the fact that no direct differences were observed. It is possible that the insignificance, other than the gradual

doi: 10.6342/NTU201900062

decline during the AD pathology, is rooted from the visual stimulus item lacking in sensitivity differentiating SCD from HC. Future study on this issue is merited.

However, to our knowledge, the current study is the first to use an objective method to examine how individuals with SCD monitor their memory. Despite the fact that there was no significant difference in comparison with healthy elders, our results suggest that individuals with SCD are at the intermediate position between normal aging and pathological aging. This finding is in line with a recent hypothesis depicting AD as a continuum (Jack et al., 2018). Moreover, a recent study simulated the AD disease progression through data-driven model and found multifactorial interactions, rather than linear cascade event, are responsible for the progression (Veitch et al., In press). In addition, out study might provide an objective measure targeting individuals with SCD who might be in risk for pathological change. Future follow-up study on this issue is thus needed.

doi: 10.6342/NTU201900062

REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*, 270-279. doi:10.1016/j.jalz.2011.03.008

Ally, B. A. (2012). Using pictures and words to understand recognition memory deterioration in amnestic mild cognitive impairment and Alzheimer's disease: A review. *Current Neurology and Neuroscience Reports, 12*, 687-694. doi:10.1007/s11910-012-0310-7

Ally, B. A., Gold, C. A., & Budson, A. E. (2009). The picture superiority effect in patients with Alzheimer's disease and mild cognitive impairment. *Neuropsychologia, 47*, 595-598. doi:10.1016/j.neuropsychologia.2008.10.010

Ally, B. A., Hussey, E. P., Ko, P. C., & Molitor, R. J. (2013). Pattern separation and

doi: 10.6342/NTU201900062

pattern completion in Alzheimer's disease: Evidence of rapid forgetting in amnestic mild cognitive impairment. *Hippocampus, 23*, 1246-1258. doi:10.1002/hipo.22162

Amariglio, R. E., Mormino, E. C., Pietras, A. C., Marshall, G. A., Vannini, P., Johnson, K. A., . . . Rentz, D. M. (2015). Subjective cognitive concerns, amyloid-beta, and neurodegeneration in clinically normal elderly. *Neurology, 85*, 56-62. doi:10.1212/WNL.0000000000001712

Backman, L., Jones, S., Berger, A.-K., Laukka, E. J., & Small, B. J. (2004). Multuple cognitive deficits during the transition to Alzheimer's Disease. *Journal of Internal Medicine, 256*, 195-204.

Backman, L., Jones, S., Berger, A.-K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's Disease: A meta-analysis. *Neuropsychology, 19*, 520-531. doi:10.1037/0894-4105.19.4.520.supp

Bender, S., Bluschke, A., Dippel, G., Rupp, A., Weisbrod, M., & Thomas, C. (2014). Auditory post-processing in a passive listening task is deficient in Alzheimer's disease. *Clinical Neurophysiology, 125*, 53-62. doi:10.1016/j.clinph.2013.05.026

doi: 10.6342/NTU201900062

Bisiacchi, P. S., Borella, E., Bergamaschi, S., Carretti, B., & Mondini, S. (2008). Interplay between memory and executive functions in normal and pathological aging. *Journal of Clinical and Experimental Neuropsychology, 30*, 723-733. doi:10.1080/13803390701689587

Bisiacchi, P. S., Tarantino, V., & Ciccola, A. (2008). Aging and prospective memory: The role of working memory and monitoring processes. *Aging Clinical and Experimental Research, 20*, 569-577.

Chang, H. T., Chen, T. F., Cheng, T. W., Lai, Y. M., & Hua, M. S. (2018). Arbitrary and semantic associations in subjective memory impairment and amnestic mild cognitive impairment among Taiwanese individuals: A cross-sectional study. *Journal Formosan Medical Association, 117*, 427-433. doi:10.1016/j.jfma.2017.05.014

Chen, H.-Y., Hua, M.-S., Zhu, J.-J., & Chen, Y.-H. J. (2008). Selection of factor-based WAIS-III tetrads in the Taiwan standardization sample: A Guide to Clinical Practice. *Chinese Journal of Psychology, 50*, 91-109.

Chua, E. F., Schacter, D. L., Rand-Giovannetti, E., & Sperling, R. A. (2006).

doi: 10.6342/NTU201900062

Understanding metamemory: Neural correlates of the cognitive process and subjective level of confidence in recognition memory. *Neuroimage, 29*, 1150-1160. doi:10.1016/j.neuroimage.2005.09.058

Chua, E. F., Schacter, D. L., & Sperling, R. A. (2009). Neural correlates of metamemory: A comparison of feeling-of-knowing and retrospective confidence judgments. *Journal of Cognitive Neuroscience, 21*, 1751-1765. doi:10.1162/jocn.2009.21123

Cosentino, S. (2014). Metacognition in Alzheimer's Disease. In S. M. Fleming & C. D. Frith (Eds.), *The cognitive neuroscience of metacognition* (pp. 389-407). New York, NY, US: Springer-Verlag Publishing. doi.org/10.1007/978-3-642-45190-4_17

Deason, R. G., Hussey, E. P., Flannery, S., & Ally, B. A. (2015). Preserved conceptual implicit memory for pictures in patients with Alzheimer's disease. *Brain and Cognition, 99*, 112-117. doi:10.1016/j.bandc.2015.07.008

Dillen, K. N. H., Jacobs, H. I. L., Kukolja, J., Richter, N., von Reutern, B., Onur, O. A., . . . Fink, G. R. (2017). Functional disintegration of the default mode

doi: 10.6342/NTU201900062

network in prodromal Alzheimer's Disease. *Journal of Alzheimer's Disease, 59*, 169-187. doi:10.3233/JAD-161120

Dodson, C. S., Spaniol, M., O'Connor, M. K., Deason, R. G., Ally, B. A., & Budson, A. E. (2011). Alzheimer's disease and memory-monitoring impairment: Alzheimer's patients show a monitoring deficit that is greater than their accuracy deficit. *Neuropsychologia, 49*, 2609-2618. doi:10.1016/j.neuropsychologia.2011.05.008

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., . . . Scheltens, P. (2010). Revising the definition of Alzheimer's disease: A new lexicon. *The Lancet Neurology, 9*, 1118-1127. doi:10.1016/S1474-4422(10)70223-4

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., . . . Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS–ADRDA criteria. *The Lancet Neurology, 6*, 734-746. doi:10.1016/s1474-4422(07)70178-3

Embree, L. M., Budson, A. E., & Ally, B. A. (2012). Memorial familiarity remains

doi: 10.6342/NTU201900062

intact for pictures but not for words in patients with amnestic mild cognitive impairment. *Neuropsychologia, 50*, 2333-2340. doi:10.1016/j.neuropsychologia.2012.06.001

Erk, S., Spottke, A., Meisen, A., Wagner, M., Walter, H., & Jessen, F. (2011). Evidence of neuronal compensation during episodic memory in subjective memory impairment. *Archives Of General Psychiatry, 68*, 845-852.

Galeone, F., Pappalardo, S., Chieffi, S., Iavarone, A., & Carlomagno, S. (2011). Anosognosia for memory deficit in amnestic mild cognitive impairment and Alzheimer's disease. *International Journal of Geriatric Psychiatry, 26*, 695-701. doi:10.1002/gps.2583

Gallo, D. A., Cramer, S. J., Wong, J. T., & Bennett, D. A. (2012). Alzheimer's disease can spare local metacognition despite global anosognosia: Revisiting the confidence-accuracy relationship in episodic memory. *Neuropsychologia, 50*, 2356-2364. doi:10.1016/j.neuropsychologia.2012.06.005

Genon, S., Bahri, M. A., Collette, F., Angel, L., d'Argembeau, A., Clarys, D., . . . Bastin, C. (2014). Cognitive and neuroimaging evidence of impaired interaction

doi: 10.6342/NTU201900062

between self and memory in Alzheimer's disease. *Cortex, 51*, 11-24. doi:10.1016/j.cortex.2013.06.009

Golden, H. L., Agustus, J. L., Goll, J. C., Downey, L. E., Mummery, C. J., Schott, J. M., . . . Warren, J. D. (2015). Functional neuroanatomy of auditory scene analysis in Alzheimer's disease. *Neuroimage: Clinical, 7*, 699-708. doi:10.1016/j.nicl.2015.02.019

Golden, H. L., Agustus, J. L., Nicholas, J. M., Schott, J. M., Crutch, S. J., Mancini, L., & Warren, J. D. (2016). Functional neuroanatomy of spatial sound processing in Alzheimer's disease. *Neurobiology of Aging, 39*, 154-164. doi:10.1016/j.neurobiolaging.2015.12.006

Hachinski, V. C., Iliff, L. D., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., . . . Symon, L. (1975). Cerebral blood flow in dementia. *Archives of Neurology, 32*, 632-637.

Hao, J., Li, K., Li, K., Zhang, D., Wang, W., Yang, Y., . . . Zhou, X. (2005). Visual attention deficits in Alzheimer's disease: an fMRI study. *Neuroscience Letters, 385*, 18-23. doi:10.1016/j.neulet.2005.05.028

doi: 10.6342/NTU201900062

Hart, J. T. (1965). Memory and the feeling-of-knowing experience. *Journal of Educational Psychology, 56*, 208-216.

Hua, M., Chang, B., Lin, K., Yang, J., Lu, S., & Chen, H. (2005). *Wechsler Memory Scale Third Edition (WMS-III) Manual for Taiwan*. Taipei, Taiwan: The Chinese Behavioral Science Corporation.

Huo, L., Li, R., Wang, P., Zheng, Z., & Li, J. (2018). The default mode network supports episodic memory in cognitively unimpaired elderly individuals: Different contributions to immediate recall and delayed recall. *Frontiers in Aging Neuroscience, 10*, 6. doi:10.3389/fnagi.2018.00006

Isingrini, M., Perrotin, A., & Souchay, C. (2008). Aging, metamemory regulation and executive functioning. *Progress in Brain Research, 169*, 377-392. doi:10.1016/S0079-6123(07)00024-6

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., . . . Contributors. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia, 14*, 535-562. doi:10.1016/j.jalz.2018.02.018

doi: 10.6342/NTU201900062

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., . . . Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *The Lancet Neurology, 12*, 207-216. doi:10.1016/S1474-4422(12)70291-0

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chetelat, G., . . . Subjective Cognitive Decline Initiative Working, G. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia, 10*, 844-852. doi:10.1016/j.jalz.2014.01.001

Koppara, A., Wagner, M., Lange, C., Ernst, A., Wiese, B., Konig, H. H., . . . Jessen, F. (2015). Cognitive performance before and after the onset of subjective cognitive decline in old age. *Alzheimer's & Dementia (Amsterdam), 1*, 194-205. doi:10.1016/j.dadm.2015.02.005

Kurimoto, R., Ishii, R., Canuet, L., Ikezawa, K., Iwase, M., Azechi, M., . . . Takeda, M. (2012). Induced oscillatory responses during the Sternberg's visual memory task in patients with Alzheimer's disease and mild cognitive impairment. *Neuroimage,*

doi: 10.6342/NTU201900062

59, 4132-4140. doi:10.1016/j.neuroimage.2011.10.061

Liao, Y., Yeh, T., Yang, Y., Lu, F., Chang, C., Ko, H., & Lo, C. J. T. J. o. P. (2004). Reliability and validation of the Taiwan geriatric depression scale. *Taiwanese Journal of Psychiatry, 18*, 30-41.

Liu, C., Wang, S., Teng, E., Fuh, J., Lin, C., Lin, K., . . . Yang, Y. J. P. M. (1997). Depressive disorders among older residents in a Chinese rural community. *Psychological Medicine, 27*, 943-949.

McCabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: Evidence for a common executive attention construct. *Neuropsychology, 24*, 222-243. doi:10.1037/a0017619

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*, 263-269. doi:10.1016/j.jalz.2011.03.005

doi: 10.6342/NTU201900062

Meyers, J. E., & Meyers, K. R. (1995). *Rey Complex Figure Test and recognition trial professional manual.* Odessa, FL, US: Psychological Assessment Resources.

Molinuevo, J. L., Rabin, L. A., Amariglio, R., Buckley, R., Dubois, B., Ellis, K. A., . . . Subjective Cognitive Decline Initiative Working, G. (2017). Implementation of subjective cognitive decline criteria in research studies. *Alzheimer's & Demeniat, 13*, 296-311. doi:10.1016/j.jalz.2016.09.012

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., . . . Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimer's & Dementia, 13*, 468-492. doi:10.1016/j.jalz.2016.06.2365

Nellessen, N., Rottschy, C., Eickhoff, S. B., Ketteler, S. T., Kuhn, H., Shah, N. J., . . . Reetz, K. (2015). Specific and disease stage-dependent episodic memory-related brain activation patterns in Alzheimer's disease: A coordinate-based meta-analysis. *Brain Structure and Function, 220*, 1555-1571. doi:10.1007/s00429-014-0744-6

Nelson, P. T., Alafuzoff, I., Bigio, E. H., Bouras, C., Braak, H., Cairns, N. J., . . . Beach,

doi: 10.6342/NTU201900062

T. G. (2012). Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *Journal of Neuropathology & Experimental Neurology, 71*, 362-381. doi:10.1097/NEN.0b013e31825018f7

Nelson, T. O. (1990). Metamemory: A theoretical framework and new findings. In B. H. Ross (Ed.) *Psychology of learning and motivation* (Vol. 26, pp. 125-173). Cambridge, MA, US: Academic Press.

Perrotin, A., Belleville, S., & Isingrini, M. (2007). Metamemory monitoring in mild cognitive impairment: Evidence of a less accurate episodic feeling-of-knowing. *Neuropsychologia, 45*, 2811-2826. doi:10.1016/j.neuropsychologia.2007.05.003

Perrotin, A., La Joie, R., de La Sayette, V., Barre, L., Mezenge, F., Mutlu, J., . . . Chetelat, G. (2017). Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's & Dementia, 13*, 550-560. doi:10.1016/j.jalz.2016.08.011

Perrotin, A., Mormino, E. C., Madison, C. M., Hayenga, A. O., & Jagust, W. J. (2012). Subjective cognition and amyloid deposition imaging: A Pittsburgh Compound

doi: 10.6342/NTU201900062

B positron emission tomography study in normal elderly individuals. *Archives of Neurology, 69*, 223-229. doi:10.1001/archneurol.2011.666

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience, 38*, 433-447. doi:10.1146/annurev-neuro-071013-014030

Reisberg, B., Shulman, M. B., Torossian, C., Leng, L., & Zhu, W. (2010). Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimer's & Dementia, 6*, 11-24. doi:10.1016/j.jalz.2009.10.002

Rodriguez-Gomez, O., Abdelnour, C., Jessen, F., Valero, S., & Boada, M. (2015). Influence of sampling and recruitment methods in studies of subjective cognitive decline. *Journal of Alzheimer's Disease, 48*, 99-107. doi:10.3233/JAD-150189

Rosen, W. G., Terry, R. D., Fuld, P. A., Katzman, R., & Peck, A. (1980). Pathological verification of ischemic score in differentiation of dementias. *Annals of Neurology, 7*, 486-488. doi:10.1002/ana.410070516

Salthouse, T. A., & Soubelet, A. (2014). Heterogeneous ability profiles may be a unique indicator of impending cognitive decline. *Neuropsychology, 28*, 812-818. doi:10.1037/neu0000100

doi: 10.6342/NTU201900062

Schraw, G. (1995). Measures of feeling‐of‐knowing accuracy: A new look at an old problem. *Applied Cognitive Psychology, 9*, 321-332.

Sheikh, J. I., Yesavage, J. A. J. C. G. T. J. o. A., & Health, M. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health, 5*, 165-173.

Sheline, Y. I., Raichle, M. E., Snyder, A. Z., Morris, J. C., Head, D., Wang, S., & Mintun, M. A. (2010). Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biological Psychiatry, 67*, 584-587. doi:10.1016/j.biopsych.2009.08.024

Shin, M. S., Park, S. Y., Park, S. R., Seol, S. H., & Kwon, J. S. (2006). Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nature Protocols, 1*, 892-899. doi:10.1038/nprot.2006.115

Slavin, M. J., Sachdev, P. S., Kochan, N. A., Woolf, C., Crawford, J. D., Giskes, K., . . . Brodaty, H. (2015). Predicting cognitive, functional, and diagnostic change over 4 years using baseline subjective cognitive complaints in the Sydney Memory

doi: 10.6342/NTU201900062

and Ageing Study. *The American Journal of Geriatric Psychiatry, 23*, 906-914. doi:10.1016/j.jagp.2014.09.001

Souchay, C. (2007). Metamemory in Alzheimer's Disease. *Cortex, 43*, 987-1003. doi:10.1016/s0010-9452(08)70696-8

Souchay, C., & Isingrini, M. (2004). Age related differences in metacognitive control: Role of executive functioning. *Brain and Cognition, 56*, 89-99. doi:10.1016/j.bandc.2004.06.002

Souchay, C., Isingrini, M., & Espagnet, L. (2000). Aging, episodic memory feeling-of-knowing, and frontal functioning. *Neuropsychology, 14*, 299-309. doi:10.1037/0894-4105.14.2.299

Souchay, C., Isingrini, M., & Gil, R. (2002). Alzheimer's Disease and Feeling-of-Knowing in episodic memory. *Neuropsychologia, 1442*, 1-11.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., . . . Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

doi: 10.6342/NTU201900062

Alzheimer's & Dementia, 7, 280-292. doi:10.1016/j.jalz.2011.03.003

Swinford, C. G., Risacher, S. L., Charil, A., Schwarz, A. J., & Saykin, A. J. (2018). Memory concerns in the early Alzheimer's disease prodrome: Regional association with tau deposition. *Alzheimer's & Dementia (Amsterdam), 10*, 322-331. doi:10.1016/j.dadm.2018.03.001

Vallet, G. T., Rouleau, I., Benoit, S., Langlois, R., Barbeau, E. J., & Joubert, S. (2016). Alzheimer's disease and memory strength: Gradual decline of memory traces as a function of their strength. *Journal of Clinical and Experimental Neuropsychology, 38*, 648-660. doi:10.1080/13803395.2016.1147530

van Oijen, M., de Jong, F. J., Hofman, A., Koudstaal, P. J., & Breteler, M. M. (2007). Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimer's & Dementia, 3*, 92-97. doi:10.1016/j.jalz.2007.01.011

Veitch, D. P., Weiner, M. W., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., . . . Alzheimer's Disease Neuroimaging, I. (In press). Understanding disease progression and improving Alzheimer's disease clinical trials: Recent highlights from the Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's & Dementia.*

doi: 10.6342/NTU201900062

doi:10.1016/j.jalz.2018.08.005

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., . . . Lifestyle Research, G. (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *The Lancet Neurology, 12*, 357-367. doi:10.1016/S1474-4422(13)70044-9

Wang, P., Zhou, B., Yao, H., Zhan, Y., Zhang, Z., Cui, Y., . . . Jiang, T. (2015). Aberrant intra- and inter-network connectivity architectures in Alzheimer's disease and mild cognitive impairment. *Scientific Reports, 5*, 14824. doi:10.1038/srep14824

Wang, Y.-L., Hua, M.-S., Chang, W.-N., & Lu, C.-H. (2007). Episodic memory Feeling-of-Knowing in early demented Ppatients with Alzheimer's Disease. *Chinese Journal of Psychology, 49*, 365-382.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine, 2*, a006171. doi:10.1101/cshperspect.a006171

Youden, W. J. (1950). Index for rating diagnostic tests. *Cancer, 3*, 32-35.

doi: 10.6342/NTU201900062

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., . . . Wilcock, G. K. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex, 49*, 668-678. doi:10.1016/j.cortex.2012.04.011

doi: 10.6342/NTU201900062

TABLES

Table 1

Demographic Characteristics of Four Groups

Variables	HC ($N = 30$)	SCD ($N = 33$)	MCI ($N = 18$)	AD ($N = 7$)
Female, No. (%)	24 (80)	20 (61)	9 (50)	3 (43)
Age, Mean (SD)*	63.37 (7.55)	66.09 (6.44)	69.72 (7.35)[a]	73.43 (4.65)[a]
Education, Mean (SD)	14.20 (3.25)	14.61 (3.36)	12.5 (2.81)	14.14 (2.73)
Education, Median (Range)	15 (6-20)	16 (6-20)	12 (6-18)	16 (9-16)
Estimated full scaled IQ, Mean (SD)	119.27 (12.91)	118.06 (11.6)	111.11 (9.18)	107.43 (11.75)
Estimated full scaled IQ, Median (Range)*	121.5 (49)	120 (50)	114.5 (29)	109 (35)
MMSE, Mean (SD)	28.73 (1.41)	28.82 (1.1)	27.11 (2.22)	23.57 (1.51)
MMSE, Median (Range)*	29 (24-30)	29 (26-30)	27.5 (22-30)	23 (22-26)
Logical Memory, Mean (SD)*	13.93 (3.07)	13.36 (2.52)	9.17 (3.29)[a,b]	6.75 (.957)[a,b]
GDS, Mean (SD)	1.03 (1.19)	2.12 (1.56)	1.33 (1.03)	.86 (1.47)
GDS, Median (Range)	1 (0-5)	2 (0-5)	1 (0-4)	0 (0-4)

Note. *significant difference between groups; [a] significantly different from HC; [b] significantly different from SCD.

doi: 10.6342/NTU201900062

Table 2

The data array and the equation for the Hamann Index

Conditions	Recognition performance	
	Correct	Incorrect
FOK 'Yes' judgment	a	b
FOK 'No' judgment	c	d
Hamann Index = [(a+d)-(b+c)]/[(a+d)+(b+c)]		

doi: 10.6342/NTU201900062

Table 3

Percentage (%) of FOK Judgment and Episodic Memory Performance on Visual- and Auditory-Based Episodic Memory

Performances	HC (*N* = 30)		SCD (*N* = 33)		MCI (*N* = 18)		AD (*N* = 7)	
	Visual	Auditory	Visual	Auditory	Visual	Auditory	Visual	Auditory
Feeling-of-knowing ratings								
Judgments 'yes'	95.83 (62.5-100)	100 (62.5-100)	95.83 (54.17-100)	100 (70.83-100)	93.75 (58.33-100)	95.83 (33.33-100)	70.83 (37.5-100)	75 (16.67-100)
Judgments 'no'	4.17 (0-37.5)	0.00 (0-37.5)	4.17 (0-45.83)	0.00 (0-29.17)	6.25 (0-41.67)	4.17 (0-66.67)	29.17 (0-62.5)	25 (0-83.33)
Feeling-of-knowing accuracy								
Hits for yes judgment	79.17 (50-95.83)	95.83 (62.5-100)	79.17 (45.83-100)	95.83 (66.67-100)	66.67 (37.5-87.5)[a]	75.00[a,b] (33.33-100)	41.67[a,b] (25-66.67)	62.50[a,b] (12.5-79.17)
Misses for yes judgment	12.50 (0-33.33)	0.00 (0-16.67)	16.67 (0-37.5)	0.00 (0 -29.17)	20.83[a] (8.33-41.67)	18.75[a,b] (0-50)	33.33[a] (12.5-45.83)	20.83[a,b] (0-33.33)
Hits for no judgment	4.17 (0-29.17)	0.00 (0-33.33)	0.00 (0-29.17)	0.00 (0 -25.00)	2.08 (0 -29.17)	0.00 (0-50)	20.83 (0-29.17)	8.33 (0-50)
Misses for no judgment	0.00 (0-8.33)	0.00 (0-4.17)	0.00 (0-20.83)	0.00 (0 -12.50)	4.17 (0 -16.67)	0.00 (0-16.67)	8.33 (0-33.33)	8.33[a] (0-33.33)

doi: 10.6342/NTU201900062

Table 3 *(Continued)*

Percentage (%) of FOK Judgment and Episodic Memory Performance on Visual- and Auditory-Based Episodic Memory

Performances	HC (*N* = 30)		SCD (*N* = 33)		MCI (*N* = 18)		AD (*N* = 7)	
	Visual	Auditory	Visual	Auditory	Visual	Auditory	Visual	Auditory
Hamann index*	0.63 (.17-.92)	0.96 (.33-1)	0.58 (.25-1)	0.92 (.42-1)	0.42[a] (.08-.75)	0.50[a,b] (0-1)	0.08[a,b] (-.08-.33)	0.33[a,b] (-.08-.58)
Episodic memory	RCFT	Word list	RCFT	Word list	RCFT	Word list	RCFT	Word list
Delayed recall, Scaled score, Mean (SD)	9.74 (4.33)	13.23 (2.10)	9.91 (3.90)	11.94 (1.97)	6.13 (3.58)	8.50 (2.09)	1.99 (1.33)	7.00 (0.00)
Recognition, Scaled score, Mean (SD)	10.12 (3.31)	12.40 (1.45)	8.32 (3.25)	11.64 (2.42)	5.20 (3.67)	7.61 (3.13)	1.30 (1.02)	5.29 (1.60)

Note. Median (Range) was reported if not specified. *FOK performance showed significant difference between groups; [a] significantly different from HC; [b] significantly different from SCD.

doi: 10.6342/NTU201900062

Table 4

Results of Subcomponents in FOK Performance

Variables		FOK 'yes' judgment		FOK 'no' judgment	
		Visual	Auditory	Visual	Auditory
Hits	*H*	26.631	37.345	2.182	8.787
	p	< .001**	< .001**	.535	.032*
	d	1.251	1.663	.198	.544
Misses	*H*	16.261	24.888	9.4	12.502
	p	.001**	< .001**	.024*	.006**
	d	.866	1.187	.574	.714

Note. * significant at the level of $p < .05$; ** significant as the level of $p < .01$.

doi: 10.6342/NTU201900062

Table 5

Neurocognitive Performances of Four Groups

Performances	HC (N = 30)	SCD (N = 33)	MCI (N = 18)	AD (N = 7)
Executive Function	9.73 (2.26)	9.42 (1.67)	8.36 (1.53)	8 (1.68)
Matrix Reasoning	13.57 (3.17)	13.03 (2.663)	12.06 (3.019)	11.29 (3.352)
Backward Digit Span	5.9 (1.626)	5.82 (1.685)	4.67 (.97)	4.71 (.951)
Immediate recall	12.6 (2.9)	11.89 (2.46)	9.58 (2.79)	6.58 (1.99)
Visual Reproduction I	12.6 (2.472)	11.67 (2.847)	9.78 (2.777)	7 (3.098)
Word-Pairs I	12.6 (3.892)	12.12 (3.11)	9.39 (3.363)	6.17 (1.941)
Delayed recall	12.05 (2.91)	11.45 (2.19)	7.89 (2.33)	7.42 (3.75)
Visual Reproduction II	11.47 (3.246)	10.52 (2.83)	7.11 (1.967)	9.5 (7.609)
Word-Pair II	12.63 (3.499)	12.39 (2.989)	8.63 (3.162)	5.33 (.516)

Note. Mean (SD) was reported if not specified.

doi: 10.6342/NTU201900062

Table 6

Pearson's r correlation between the misses (%) in the "yes" judgment of visual FOK test and neurocognitive measures

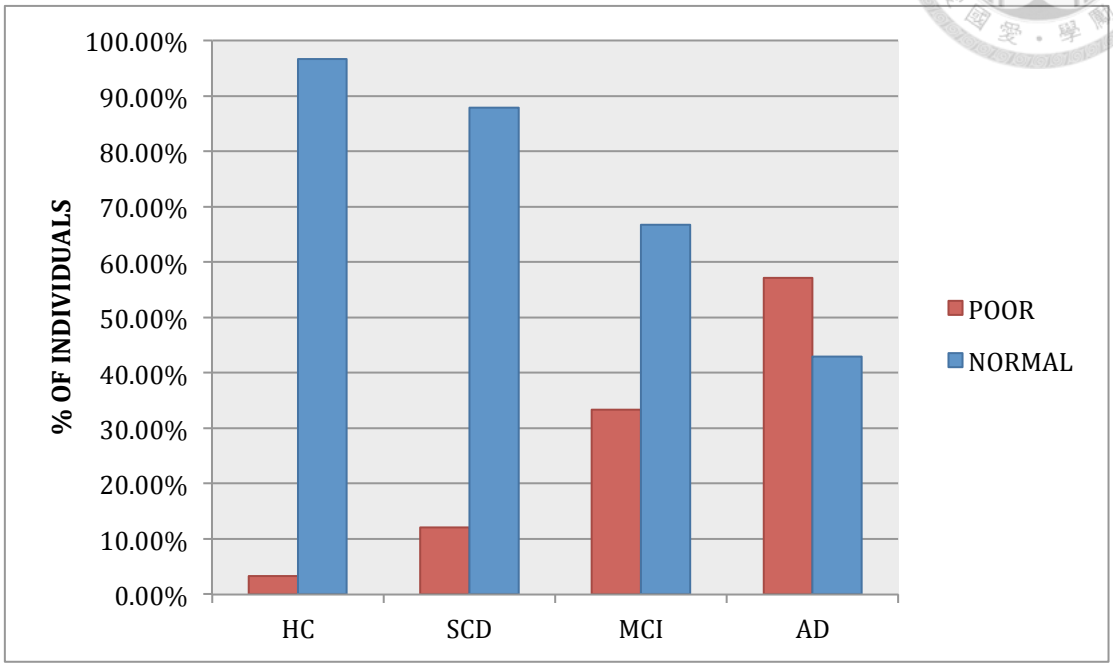
Variables	HC (N = 30)	SCD (N = 33)	MCI (N = 18)	AD (N = 7)
Executive function	-.370*	-.420*	.118	.347
Learning	-.572**	-.292	-.150	-.368
Memory	-.311	-.225	-.134	.464

Note. *significant at the level of $p < .05$; ** significant at the level of $p < .01$.

doi: 10.6342/NTU201900062

FIGURES

(a)



(b)

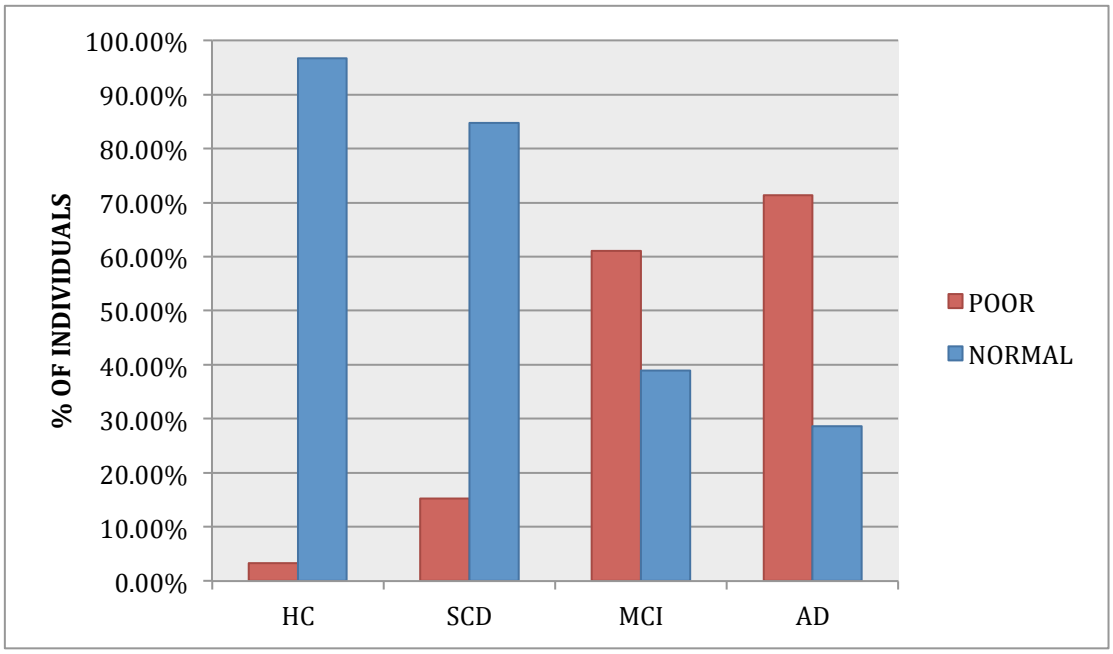


Figure 1. Distributions of individuals (%) with poor or normal performance on the misses of FOK 'yes' judgment on visual-based test (a) and auditory-based test (b).

doi: 10.6342/NTU201900062