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Diagnosing the Prodromal State of Alzheimer's Disease

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Abstract

Mild Cognitive Impairment- Amnesic Subtype (MCIa) is a putative prodromal stage of Alzheimer's Disease (AD) characterized by focal deficits in episodic verbal memory. Less is known about relative deficits in visuospatial learning, although there is ample evidence indicating involvement of the hippocampus in visuospatial learning, as well as hippocampal degeneration in early AD. The aim of this study was to better characterize the components of working memory dysfunction in people with MCIa to increase the ability to reliably diagnose this disease. Fifty-six elderly adults diagnosed with MCIa and 94 healthy elderly completed a hidden maze learning task. Results indicated similar functioning between groups on measures of reasoning, problem solving, and accuracy. However, MCIa subjects were less efficient at learning the hidden path, making more errors per second on average (Cohen's $d = -.78$) and requiring a longer time to complete the maze (Cohen's $d = .77$). The learning curve between the first two trials was four times as steep for healthy elderly compared to MCIa (slopes = 4.9 vs. 1.24, respectively), indicating that MCIa subjects exhibited relative difficulty in holding and making effective use of an internal spatial map in order to improve performance. Our results suggest that MCIa patients have focal deficits in visuospatial working memory, with relative preservation of functioning on other more global measures of cognitive functioning. This particular pattern of results may be specific to the amnesic variant of MCI.

Early symptoms of Alzheimer's disease (AD) include memory complaints such as repeatedly losing items, forgetting names, and forgetting appointments. As the disease progresses, there is increasingly severe memory loss and difficulties with activities of daily living. For example, individuals are unable to dress or clean themselves, become confused by eating utensils, and lose the ability to care for themselves. Eventually the ability to walk, talk or lead a productive life deteriorates. The Diagnostic and Statistical Manual of Mental Disorders (4th edition) lists criteria for diagnosing dementia of the Alzheimer's type, although AD cannot be definitively diagnosed until post-mortem analysis of the neurologic damage. AD dementia includes memory impairment along with impairment in at least one other cognitive domain which includes aphasia, apraxia, agnosia or executive function deficits. Critical to diagnosis is the patient's history of cognitive disturbance and disturbance of daily living through their own account or by a knowledgeable informant. These symptoms cannot be the result of other neurologic or psychiatric disturbances (Kelley & Peterson, 2007). AD ultimately shortens the lifespan and leads to mortality, but disease progression is variable which causes a differential speed of decline in functional ability for each individual (Haupt, Kurz, & Pollmann, 1992).

Memory and Cognitive Change

Many healthy elderly experience a gradual decline in cognitive speed of processing and working memory (Kelley et al., 2007). These normal symptoms of aging can be categorized under the broad domains of learning and memory, and are mediated by the morphological changes in the hippocampus and cortex (Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008). These normative components of healthy aging are similar to those of Mild Cognitive Impairment- Amnesic (MCIa) subtype with the exception of a specific decline in episodic memory in MCIa. The characterization of cognitive profiles for healthy aging and MCIa need to

be more clearly delineated. AD is preceded by a diagnosis of MCIa 80% of the time, which emphasizes the importance of differentiation between healthy aging deficits and MCIa (Kelley et al., 2007). Early intervention in the MCIa disease course is beneficial for a number of reasons. The accurate diagnosis of type of Dementia is necessary for appropriate intervention and treatment options to be utilized. Development of new treatments through research and clinical trials can be useful to individuals with a specific diagnosis, and their participation is vital to the successful creation of new medications and therapies. Understanding the prognosis of a particular dementia diagnosis is helpful for family members to prepare themselves and the individual for future care management.

Empirical studies have shown that cases of MCIa that include a specific decline in social and occupational functioning are a significant predictor of progression to AD. These areas of decline are the first to be noticed by individuals suffering with MCIa, and by the time a diagnosis of AD is made, a broad base of functional decline is evident (Hsiung, Alipour, Jacova, Grand, & Gauthier, 2008). A prospective study conducted with pre-dementia individuals concluded that during the prodromal stage of AD, there is a significant cognitive deficit in the ability to verbally shift from one subcategory of information to another. This executive function deficit was significant only for individuals that developed AD (Raoux, Amieva, Goff, Auriacombe, Carcaillon, 2008). These studies show specific domains of cognitive decline are significantly indicative of an AD diagnosis, which is imperative for early intervention.

In early AD, cognitive deficits are apparent in divided attention tasks, however the ability to selectively allocate resources is still intact (Rapp, Krampe, & Baltes, 2006). A specific study by Rapp et al. showed that participants with mild AD selectively maintained postural control at the cost of memory performance. Another study by Graham, Simons, Pratt, Patterson, & Hodges

(2000) showed how participants with AD exhibited no difference between severity of deficits when testing their semantic and episodic memory. However, medial temporal lobe (MTL) damage has been shown to be associated with “semantization” of autobiographical information that was once remembered as an episodic memory with spatio-temporal and phenomenological details. A vivid memory complete with details of time, place, duration and an understanding of what was learned is decreased into knowledge of what was learned without any memory of the event in which the learning took place. In healthy elderly, working memory tends to become slower; in MCIa, neuronal damage begins to effect the MTL and there is a specific deficit in episodic memory, and in AD, episodic memories begin to fade into less vibrant more factual semantic memories (Ciaramelli, Lauro-Grotto, & Treves, 2006). This somewhat contradicts the previous study that showed how episodic and semantic memory deficits did not differ in severity. More research needs to be done to better understand the trajectory of the destruction of memories caused by AD so that appropriate and successful interventions can be implemented.

Biological Causes

AD is characterized by Central Nervous System (CNS) plaques (deposits of amyloid B-peptide which causes damage to the surrounding neurons) and tangles (twisted intracellular microtubules, associated with the protein tau, which causes oxidative modifications) (Mattson, 2004). These plaques and tangles are in high concentration in brain areas involving learning, memory and emotional behaviors including the entorhinal cortex, hippocampus, basal forebrain and amygdala. They start out in the entorhinal cortex and hippocampus causing memory deficits as the first symptom of AD. As the disease progresses the plaques and tangles invade the basal forebrain and amygdala, and eventually the entire neo-cortex. These brain regions reduce in size

as the disease progresses because of the extensive neuronal death that they incur. The cause of these plaques and tangles is currently debated (Mattson, 2004).

Epidemiology

AD is the most common cause of dementia and affects as many as 5.2 million people in the United States in 2008 (Alzheimer's Association, 2008). It costs around \$47,000 per year to care for one person suffering with AD, whether in home care or institutionalized (Trabucchi, 1999). The prevalence of this disease is increasing and estimated to reach 106.8 million by 2050 worldwide (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). At 85 years of age, the incidence of dementia falls between 15-40% (Ankri, & Poupard, 2003). It is estimated that 62% of those diagnosed with AD are women relative to men, which likely reflects their longevity (Brookmeyer et al., 2007). Oestrogen levels in pre-menopausal women have also been shown to have a neuroprotective effect against AD (Ankri et al., 2003). Modifiable risk factors for AD include smoking, hypertension, homocysteine, type 2 diabetes, insulin resistance, and obesity. Some preventative methods of AD include stress reduction, toxin avoidance, mental and physical exercise, and a diet rich in omega-3 fatty acids and antioxidants (Kidd, 2008).

Although multiple genetic risk factors have been identified, one gene in particular that codes for creation of the beta-amyloid protein in the brain, the APOE e4 allele, has been of special interest. Individuals that carry at least one copy of the APOE e4 allele are at significantly increased risk for developing AD (Tierney, Szalai, Snow, Fisher, & Tsuda, 1996). Still, possessing this risk factor does not guarantee development of AD and the only way to definitively diagnose this disease is by post-mortem analysis of plaques and tangles in the brain (Mattson, 2004).

Treatment

Current medications for AD include acetylcholinesterase inhibitors but these only treat symptoms and do not slow disease progression. There is no treatment available to prevent or reverse the progress of AD, therefore researchers are currently focusing on finding treatments to prevent the onset of AD (Winblad, & Jelic, 2004). If disease onset were delayed by two years, the worldwide prevalence would decrease by 22.8 million individuals, and delaying it by only 1 year would decrease the incidence by 11.8 million individuals worldwide (Brookmeyer et al., 2007). Several new therapy approaches are currently being explored including the development of passive immunotherapy and gene expression therapies (Foster, Verdile, Bates, & Martins, 2008; Tomanin, & Scarpa, 2004).

Other treatments for AD patients focus on secondary symptoms. Depression is highly comorbid with AD and is the most frequent psychiatric complication in AD sufferers. As many as 50% of AD patients suffer with depression, and can be treated for both neurologic illnesses simultaneously. Treatments include pharmacologic agents, patient focused behavioral therapy and electroconvulsive therapy (ECT) (Lyketsos, & Olin, 2002).

Mild Cognitive Impairment Amnesic Subtype (MCIa)

Mild cognitive impairment amnesic subtype (MCIa) is the prodromal stage of AD, and is characterized by mild memory impairment but a lack of dementia: cognitive decline severe enough to compromise daily function (Kelley et al., 2007). A major limitation of diagnosing MCIa is the lack of a universally agreed upon diagnostic tool. The Clinical Dementia Rating Scale (CDR) and the Global Deterioration Scale (GDS) are both used in conjunction with clinical observation to diagnose MCIa, although the qualifying scores for MCIa verses AD differ among professionals (Peterson, Smith, Waring, Ivnik, & Tangalos, 1999; Peterson, Doody, Kurz, Mohs,

& Morris, 2001). Currently, the Peterson criteria are a widely used tool for diagnosing MCIa. The diagnosis includes: 1) cognitive complaint (usually memory), preferably corroborated by an informant 2) cognitive impairment (usually memory) for age and education 3) essentially normal general cognitive function 4) largely preserved activities of daily living and 5) no dementia (Peterson et al., 1999, 2001). A universally accepted method of diagnosis for MCIa, such as a biomarker, would allow more time to explore novel treatment options that may have the potential to delay AD.

Related to this goal, there has been much controversy over research on cognitive decline observed in healthy aging, because of the likelihood that many samples of subjects have been contaminated by the inclusion of individuals with MCIa. With the somewhat recent discovery of MCIa and the lack of a universally accepted diagnostic tool, researchers now doubt the validity of their healthy aging sample (Kelley et al., 2007). Research will continue to uncover aspects of MCIa, like episodic memory decline and specific executive function deficits that differ from healthy aging deficits like general cognitive slowing (Tapia-Arancibia, et al., 2008; Kelley, et al., 2007).

Biomarkers

The next step for researchers is to find an early biomarker that detects a change in cognition specifying the neurological state of MCIa, indicating an increased risk of developing AD. A variety of biomarkers have been explored, including proteins found in blood plasma or cerebrospinal fluid (CSF). Neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) have all been used to detect pathology and track disease progression. There are many limitations to these technologically

based methods including the lack of a baseline scan to estimate individual change over time with the costs involved. Appropriate neuropsychological examination may be a more easily administered and cost effective way of detecting early deficits in executive function and memory impairments. However, a biomarker that detects AD based on the cognitive pathology which occurs prior to the onset of more profound symptoms would be ideal. A biomarker may be found in the utilization of multiple technologies since multiple pathological events could be occurring simultaneously to cause AD (Aisen, Albert, Breitner, Buckholtz, & Corey-Bloom, et al., 2008).

Groton Maze Learning Test (GMLT)

A diagnostic tool that is sensitive and specific enough to diagnose MCIa is a necessary step to prolonging the onset of AD. The Groton Maze Learning Test (GMLT) is a computerized neuropsychological measure that tests immediate and short-term memory for visuospatial information (Pietrzak, Maruff, Mayes, Roman, & Sosa, et al., 2008). The GMLT has been shown to be sensitive enough to differentiate between healthy older adults and young adults in terms of spatial learning efficiency and error monitoring (Pietrzak et al., 2008). The GMLT is also sensitive enough to detect deficits in problem solving and working memory with the induction of pharmacologic challenges (Thomas, Snyder, Pietrzak, Jackson, & Bednar, et al., in press). The decline in speed and accuracy of spatial cognitive functions induced by scopolamine (a cholinergic antagonist) and the reversal of these effects with the induction of donepezil (a cholinergic reuptake inhibitor) was accurately measured by the GMLT (Thomas, et al., in press).

This study sought to determine whether the GMLT is sensitive and specific enough to differentiate between MCIa and healthy elderly. The importance of this distinction is to more clearly understand what characterizes the cognitive decline associated with healthy aging, versus

the more severely debilitating MCI and the fatal AD. Knowing the individual characteristics of each of these cognitive states will enhance early diagnostic ability.

Method

Participants

There were a total of 156 participants in this study: 97 healthy elderly (HE) and 62 with diagnosed Mild Cognitive Impairment- Amnesic Subtype (MCIa). (see *Table 1*) The diagnosis of MCIa was based on the Peterson criteria described above. Each participant completed the Mini Mental Status Exam (MMSE) and the average score for the HE and MCIa participants' was 29 and 27 out of a possible 30, respectively. The total number of years of education was also collected and totaled an average of 13 for the HE participants and 12 for the MCIa participants. This study included 87 females, 60 HE and 27 with MCIa, and 69 males, 34 HE and 35 with MCIa. The HE females had an average age of 68 years (Standard Deviation (SD)=8, Range (R)=30) and the HE males had an average age of 67 years (SD=9, R=35). The females diagnosed with MCI had an average age of 69 years (SD=9, R=25) and the males had an average age of 71 years (SD=9, R=29). The HE participants had a total average age of 67 years (SD= 8, R=40) and the participants with MCIa had a total average age of 70 years (SD= 8 years, R=29).

Participants were pooled from the control arms of four separate pharmaceutical trials occurring between 2003-2007 with sites in Syracuse NY, Toronto Canada, Austin Texas, and Melbourne Australia.

Table 1
Demographics

	MMSE Score	Years of Ed.	Mean Age	% Male
HE	29 (SD=1.05)	13 (SD=4.06)	67 (SD=8, R=40)	36%
MCI	27 (SD=1.33)	12 (SD=3.00)	70 (SD=8, R=29)	56%
Total	28 (SD=1.19)	12.5 (SD=3.57)	69 (SD=9, R=36)	44%

Note. HE = Healthy Elderly; MCI = Mild Cognitive Impairment; SD = standard deviation; R= range; MMSE = Mini Mental Status Exam; Ed.= Education.

Inclusion/Exclusion Criteria

Participants with a history of any clinically significant diseases or unstable medical conditions like cancer or insulin dependent diabetes were excluded from the study. Also, any participant with depression, a psychiatric disorder, or insomnia was excluded. Increased alcohol consumption or tobacco use, treatment with an investigational drug or antidepressants, or hospitalization during the study qualified for exclusion from the study.

Participants were included if they were 55 to 90 years of age, had normal physical examination results, and were able to give written informed consent. Their Body Mass Index (BMI) was between 18 and 34 kg/m² and had a total body weight of more than 50kg. A head CT or MRI must have been collected within the past 12 months. Also, a score of 12 or less on the Hamilton Depression Rating Scale and a Modified Hachinski score of less than or equal to 4 was necessary. No participants were diagnosed with AD. For MCIa participants, memory complaints were verified by a reliable informant in frequent contact with the participant.

Materials/Procedures

The Neuropsychological Measures that were given to each participant included the Rey-Osterrieth Complex Figure Test (ROCF), the Wechsler Memory Scale (WMS), the Rey Auditory

Verbal Learning test (RAVLT), the Weschler Adult Intelligence Scale (WAIS-III) Digit Symbol, and the Trail Making Test Part A and B.

The ROCF test assesses visuospatial abilities such as hand to eye coordination, as well as memory, attention and planning abilities. In this assessment, participants are asked to copy a drawing, draw it again from memory after a 5 minute delay, and again after a 30 minute delay.

The WMS assesses learning, working memory and attention capabilities using auditory and visual stimuli. This is done by asking participants to recall specific information about the stimuli after a delay period.

The RAVLT asks participants to listen to words, and to read a different set of words. Later, they are asked to recall which words were spoken and which were read. In the delay version, participants are again asked 20-30 minutes later. This tests memory, both immediate and delayed, and the efficiency of learning.

The Weschler Adult Intelligence Scale (WAIS-III) Digit Symbol test assesses general adult intelligence, and the Trail Making Test Part A and B assesses executive control, such as initiating action and abstract thinking.

The participants also completed experimental measures including The Time Chase Test (TCT) and the Groton Maze Learning Test (GMLT) to assess visuomotor speed and working memory. The TCT was first completed by each participant to measure his/her visual motor function. In this test, participants were asked to use a stylus to follow a moving target on a 10X10 grid using a hand-held Compaq iPAQ touch screen computer (see *Figure 1* below).

The GMLT was then administered using the same touch screen computer. The participants used a stylus to navigate their way through a 29-step maze that is hidden below a 10x10 grid of squares on the computer screen, with the goal of learning the specific path from

start to finish. Each time the participant makes a correct move they can continue on, but if they make a mistake and touch the wrong square it is recorded as a “legal error.” The participant is then instructed to touch the last correct square, and then try again by touching a different square. If the participant touches the wrong square again prior to touching the last correct square, it is recorded as a “perseverative error.” If the participant fails to return to the last correct square again, this is recorded as a “rule break error.” The maze is completed 5 times and a 6th time after a delay period; scores are gathered during every trial on the total time to completion of the maze (in msec), total number of moves, total number of wrong moves, and the total number of perseverative and rule-break errors.

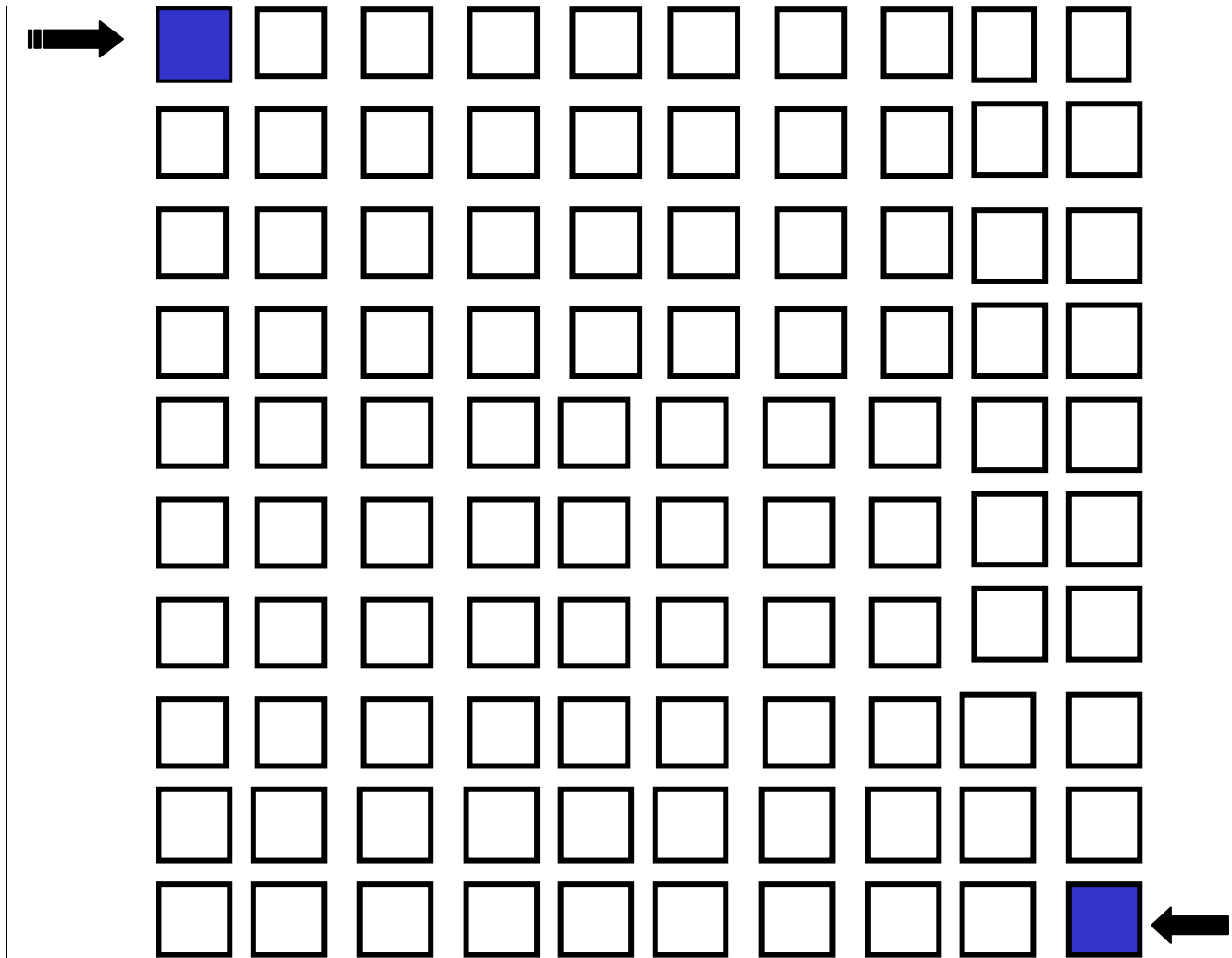


Figure 1. Groton Learning Maze Test: 10 X 10 Grid

Results

Table 2 below shows the similarities and differences between the Healthy Elderly (HE) group and the Mild Cognitive Impairment- amnesic subtype (MCIa) group on established neuropsychological measures. The HE and MCIa groups did not differ on the (WAIS-III) Digit Symbol or the Trail Making Test Part A and B. As participants with MCIa are only expected to have deficits in memory it is logical that their results would not differ significantly from the HE participants in tests of general adult intelligence and executive control.

Differences between groups were found on recall memory after a delay on the ROCF,

WMS, and RAVLT. On the ROCF test, the MCIa group was able to copy a drawing accurately, and draw it again from memory after a 5 minute delay, but were unable to draw it from memory after a 30 minute delay. The HE group was able to draw the picture correctly, including after the 30 minute delay.

When completing the WMS, the MCIa participants had difficulty remembering enough of the auditory and visual stimuli after a delay period to accurately complete the task. The HE group was able to successfully complete the task after the delay period.

The RAVLT results showed that the MCIa participants had more difficulty learning and remembering the list of words spoken to them and the list of words that they read compared with the HE participants, while the HE participants had less difficulty.

Table 2
Neuropsychological Outcome Measures

	Mean (Standard Deviation)		Effect Size Cohen's <i>d</i>
	Healthy Elderly	MCIa	
Weschler Adult Intelligence Scale (WAIS-III) Digit Symbol	11 (2.4)	10 (2.78)	.39
Trail Making Test Part A	36 (11.49)	39 (15.96)	.22
Trail Making Test Part B	83 (27.0)	103 (40.02)	.61
Rey Osterrieth Complex Figure (ROCF) Copy	33 (2.43)	31 (4.75)	.57
ROCF 3 min delay	19 (6.14)	17 (5.39)	.34
ROCF 30 min delay**	18 (4.59)	13 (4.0)	1.15
Wechsler Memory Scale (WMS) Logical Memory Delayed**	12 (2.11)	8 (2.57)	1.74
Rey Auditory Verbal Learning (RAVLT) List A- Immediate**	10 (2.75)	6 (2.93)	1.42
RAVLT List A- Delayed**	10 (2.76)	6 (3.24)	1.35

In completing the Groton Maze Learning Test (GMLT) the HE participants worked at a faster rate and with fewer errors than the participants diagnosed with MCIa. A MANCOVA was performed, co-varying for age, with the Time Chase Test (TCT) correct moves [$F(1, 3) = 16.9, p < .05$] and mean correct moves per second [$F(1, 3) = 22.4, p < .05$]. The HE group made more correct moves on the TCT and more mean correct moves per second when compared to the MCIa group. This shows the MCIa group was less proficient at visually tracking a moving

stimulus, and tapping a touch- screen in the correct location at the correct time in response to the stimulus compared with the HE group. The MCIa group took a longer amount of time to complete the GMLT than the HE group, [$F(1, 3) = 30.2, p < .05$], indicating the HE group was able to work more quickly.

The HE group made fewer exploratory errors (erroneously tapping an incorrect box for the first time) in each trial when compared with the MCIa group [$t(154) = 2.33, p > .05$]. This shows that the MCIa group had difficulty remembering which squares were correct after learning this information from the previous trial. The number of exploratory errors should decrease as the hidden maze becomes more familiar after every trial. The HE group was better at remembering which correct squares they tapped in the previous trial and avoided tapping incorrect squares on the succeeding trials, causing them to have fewer exploratory errors than the MCIa group.

The MCIa group made significantly more errors in trial 5, the final trial, when compared to the HE group [$t(154) = 2.11, p > .05$]. This again shows that the MCIa group had difficulty accurately learning and remembering the correct squares to tap, even after 4 previous trials.

Figure 2 below depicts the accuracy with which the HE and MCIa participants learned the hidden maze across the five trials in the GMLT. The MCIa participants' learning curve from trial 1 to trial 2 is 1.24, while the HE participants' learning curve from trial 1 to trial 2 is much more efficient at 4.9. From trial 3 to trial 5 the learning curve for the MCIa participants is 2.61 and for the HE participants is again more efficient at 2.09. The HE group's slope is consistently more steep than the MCIa group, indicating they are learning the hidden maze at a faster rate.

Table 3

GMLT Outcome Measures with Statistically Significant Differences Between Groups and Effect Sizes (Cohen's d)

	Mean		Standard Error		t-tests	Effect Size Cohen's <i>d</i>
	HE	MCI	HE	MCI		
Total Time (T1 to T5)	261.2	337.6	10.14	12.5	t(154)=4.75, p < .0001	-.78
Total Exploratory Errors	55.01	62.47	2.02	2.49	t(154)=2.33, p=.0212	-.38
Mean Correct/Sec	.64	.5	.019	.023	t(154)=21.94, p<.0001	.77
Difference in Errors T2-T1	-5.74	-1.56	.69	.85	t(154)=3.57, p = .0006	-.63
Slope Learning (T1 to T3)	-3.74	-1.9	.39	.49	t(154)=8.37, p=.0044	-.62
Delayed Recall Time	40.1	47.8	1.78	2.2	t(154)=2.74, p = .007	-.45
TCT Correct Moves	34.5	27.5	1.03	1.27	T(154)=-4.3,p<.0001	.69
Total Trial 5 Errors	7.86	9.5	0.49	0.6	t(154)= 2.11, p>.05	.34

Note. T=Trial; HE=Healthy Elderly; MCI=Mild Cognitive Impairment; TCT=Time Chase Test.

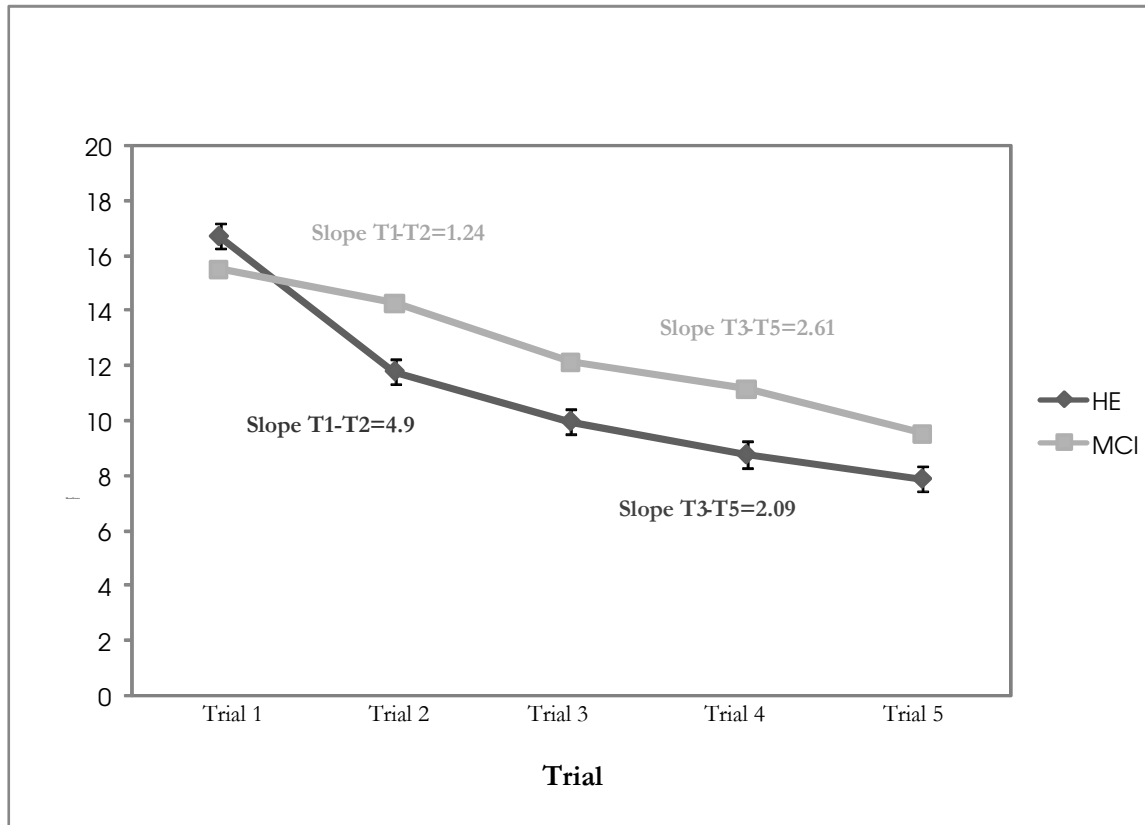


Figure 2: Errors made from trial one to trial five for MCI and HE participants

Because the HE and MCI groups differed significantly on multiple metrics within the GMLT (TCT correct moves, mean correct moves per second, total time in seconds, total exploratory errors) a ROC curve analysis was performed to analyze the ability of the GMLT to differentiate between the two groups. This test shows the sensitivity and specificity of the GMLT to reliably separate HE from those with MCI. TCT correct moves, mean correct moves

per second, total time in seconds, total exploratory errors, total perseverative errors and total rule break errors were all plotted and none were able to reliably differentiate between the two groups.

Discussion

Performance on the GMLT allowed for a better characterization of the deficits of the people diagnosed with MCIa and helps to differentiate them from the HE group. Specifically the MCIa group had deficits in visuospatial tasks, such as hand-eye coordination when visually tracking a stimulus and tapping the touch screen at the appropriate time, and had an increased error rate when compared to the HE group. Their increased error rate shows that they were unable to remember the incorrect squares that they tapped in the previous trial, therefore learning from those mistakes, by not tapping those incorrect squares, is impossible.

Hippocampal degeneration, caused by plaques and tangles, is characteristic of Alzheimer's disease (AD) and causes continual memory and learning deficits (Mattson, 2004). These symptoms, when apparent in individuals with diagnosed MCIa, should be taken as a warning sign because 80% of people with MCI do progress to AD (Kelley et al., 2007). The coordination and memory deficits displayed by the results of the MCIa participants on the GMLT could be linked to their possible hippocampal degeneration, which could worsen and lead to AD.

The hippocampus controls working memory, which allows for holding information in memory so it can be manipulated and analyzed as new information is presented (Wisman, Sahin, Maingay, Leanza, & Kirik, 2008). For example, when taking the GMLT the hippocampus controls the memories made as each correct and incorrect square is tapped. This memory can be explained as a cognitive map, or cognitive representation of the hidden maze, which is relied on

each time the hidden maze is completed. One possible explanation for the high number of errors made by the MCIa group could be that their hippocampal degeneration left them unable to keep a cognitive map of the GMLT in their working memory for a long enough period of time to be able to rely on it at each successive trial. Taking each trial of the GMLT would be similar to taking it for the first time.

The number of errors made by the HE group declined as more trials were completed. This could be due to their ability to hold a cognitive representation of the hidden maze in their working memory, and were able to use, and alter it appropriately at each trial.

The ROC analysis performed tested the GMLT on its sensitivity for identifying those with MCIa, and its specificity of only indentifying individuals that truly have MCIa. The analysis showed that the GMLT is not sensitive or specific enough to differentiate between HE and MCIa participants. However, there were significant differences found between the groups, such as error making and visuomotor speed that is useful in the characterization, and identification of individuals with MCIa. Without the GMLT, the cognitive deficit of slowed visuomotor speed in individuals with MCIa would not be known. This test has brought to light another diagnosable criteria for MCIa, which is useful because of its subtle and variable symptoms, especially in relation to healthy aging (Kelley et al., 2007). Now that visuomotor speed has been shown to be a deficit in those with MCIa, this mental illness is closer to being fully characterized, and therefore more easily diagnosed. Alone the GMLT cannot distinguish MCIa from healthy aging; however this hidden maze task can help to create a universally accepted way to reliably characterize MCIa, which is a crucial step in early diagnosis which can help to prevent the onset of AD.

Conclusion

AD is a neurodegenerative illness characterized by cell death, which currently cannot be reversed or cured. The best method to combat this disease is to prevent the cell death from ever beginning, or slowing the process down to a rate in which is unnoticeable clinically. To have the ability to do this, AD needs to be caught at its earliest stages, or even prior to onset. MCI is the prodromal stage of AD and when diagnosed and treated, can delay the onset of AD, thus slows down the rate of cell death. However, diagnosing MCI is complicated as it has yet to be fully characterized with a complete understanding of neuronal degeneration and clinical symptomatology. Also, a universally accepted diagnostic tool is lacking. As this study shows, neurological assessments that focus on testing memory functions, combined with the GMLT have a significant ability to differentiate between healthy elderly and those with diagnosed MCIa. Although the GMLT is not sensitive and specific enough to identify MCIa alone, it has added the vital component of visuospatial deficits to the list of characteristics that distinguish MCIa from healthy aging. With this added understanding of what characterizes MCIa, the GMLT can be added to a battery of neuropsychological measures to increase its diagnostic ability, eventually leading to a universally accepted way to identify MCIa, to help prevent the onset of AD.

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