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Development of a neurocognitive test battery to accurately predict driving ability in patients with Mild Cognitive Impairment and early Alzheimer's disease

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Abstract

Alzheimer's disease is a devastating progressive neurodegenerative disease that is becoming increasingly common in the United States. This disease presents many difficulties for both those diagnosed and their families, not the least of which is whether the patient should continue to drive. Due to the extreme conflict this decision and its enforcement can cause, doctors are often called upon to make a recommendation. At this point, physicians have no proven clinical tool at their disposal for use in deciding whether to recommend that a patient cease to drive. This study attempted to develop a model to predict driving ability using a variety of neurocognitive tests and to validate the Computerized Self Test for use in differentiating between normal aging, Mild Cognitive Impairment, and Early Alzheimer's disease. This study examined the results of driving simulations for 66 participants, split into three groups, and the ability of neurocognitive tests to predict them. The study found that the neurocognitive tests were unable to accurately predict driving performance and the CST was able to differentiate between MCI and EAD but not between normal aging and MCI. The negative results of this study should not serve as a deterrent for future study in the area, as several significant sources of error were present in the design and execution of the study.

Introduction

Alzheimer's disease is a progressive neurodegenerative disease that affects nearly 5.2 million people in the United States today and is growing quickly, up from an estimated 2.4 million people in the United States in 2002 (Alzheimer's Association, 2013; Plassman et al., 2007). It represents the 6th leading cause of death among Americans, placing it in the spotlight of public attention (Alzheimer's Association, 2013).

Alzheimer's is characterized by insidious onset and cognitive decline. Cognitive decline can occur in one or several domains, including verbal fluency, short-term memory, executive functions, and attention (Dougherty et al., 2012). This disease is devastating and many aspects of it are the subject of intense study. The ability of patients with Alzheimer's disease to drive is one of these aspects. Another, less known, source of cognitive decline among older adults is mild cognitive impairment (MCI). Mild cognitive impairment is a clinical syndrome that is defined as cognitive decline which exceeds that expected for an individual of a given age and education but is not extreme enough to cause problems with that individual's day to day life (Gauthier et al., 2006). MCI is often considered a prodromal phase of Alzheimer's disease and it has an annual conversion rate between 10-15%, with more than half progressing to dementia within 5 years (Spulber et al., 2010; Petersen et al., 1999; Gauthier et al., 2006). Given MCI's intermediate position between the severity of Alzheimer's disease and normal aging and its propensity for becoming Alzheimer's, it is often difficult to distinguish it from either normal aging or very early Alzheimer's disease, though the task remains important nonetheless (Gauthier et al., 2006). However, even though MCI often develops into Alzheimer's disease and usually mimics its symptomology, few studies have addressed driving ability in patients with MCI.

The relationship between driving and dementia is well studied. With the Baby Boomers reaching retirement age, the number of people with Alzheimer's disease is predicted to increase by 40% by the year 2025 (Alzheimer's Association, 2013). Numerous studies have shown that dementia is a significant risk factor for impaired driving ability, including decreased car-following distance, decreased speed, inability to

navigate, and increased frequency of crashes (Brown & Ott, 2004; Uchiyama et al., 2003; Horikawa et al., 2004). The importance of an increased understanding of how cognitive decline, especially the decline seen in Alzheimer's disease, affects a person's ability to drive cannot be overstated.

Even with the increased risk of dangerous driving behavior in dementia, the decision about whether or not to recommend that a patient not drive cannot be easily made. A person's ability to drive has a significant impact on their perceived autonomy, which is almost universally acknowledged as extremely important by those doctors, nurses, and caregivers that provide care to older adults. Restrictions of autonomy can result in increases in negative affect and decreases in self-esteem and trust (Deci & Ryan, 1987). In some situations, restriction of an elder's driving privileges can result in serious transportation difficulties (Taylor & Tripodes, 2001). Needless to say, attempting to restrict a family member's driving can be very difficult for the family. Because of this, doctors are often asked to make this recommendation to the patient themselves. Doctors, however, must also consider the psychological ramifications of such a recommendation. It must also be considered that not all drivers with dementia are dangerous (Rizzo, 1996). If the diagnosis of dementia is not a definite sign that a person is unable to drive, a careful balance between safety and autonomy must be established by a physician when determining whether or not a patient should drive (Snyder, 2005). Thus far, there have been very few studies that make recommendations as to signs that clinicians can use to predict whether a person with dementia can drive safely. Driving has been shown to be a task which requires a variety of cognitive abilities to be used simultaneously (Just, Keller, & Cynkar, 2008). Thus, it has been proposed that driving

ability may be predictable if it is addressed as a complex combination of cognitive domains, including visuospatial reasoning, memory, verbal fluency, and attention (Spiers & McGuire, 2007).

Many studies have recently been published revealing that certain brain regions, including the parieto-occipital cortices, cerebellum, and cortical regions associated with perception and motor control, are activated by driving (Uchiyama et al., 2003; Horikawa et al., 2004; Mader et al., 2009). These regions, particularly the parieto-occipital cortices, are associated with visuospatial integration and coordination, motor control, and vision. Consequently, this study seeks to investigate the utility of visuospatial and other executive function tasks for predicting driving ability.

A group led by John Dougherty, Jr. has recently created a test which assesses many of the different cognitive domains mentioned above and call it the Computerized Self Test (CST). This test, which is completed entirely on a computer, has tasks that examine visuospatial organization, memory, verbal fluency, attention, and orientation. In a 2012 study, the group found that the CST could distinguish between normal aging, MCI, and early Alzheimer's disease patients with a specificity of 99% (Dougherty et al., 2012). This finding is reexamined here.

The aim of this study was to determine the most robust combination of neurocognitive measures for predicting the ability of a person with mild cognitive impairment or early Alzheimer's disease to successfully navigate a route in a driving simulator. This study also intended to test the utility of the Computerized Self Test in differentiating between normal aging, mild cognitive impairment, and early Alzheimer's disease.

Methods

Participants

The participants for this study included 68 people (age 19-88) who were split into groups based on age and diagnosis of cognitive impairment. Four groups total were included. Group 1 consisted of 17 college students between the ages of 18 and 25 from the University of Tennessee. Group 2 consisted of 16 people without cognitive impairment aged 55 and over. Group 3 consisted of 20 people aged 55 and over who carried a clinical diagnosis of MCI. Group 4 consisted of 15 people aged 55 and over who carried a clinical diagnosis of Alzheimer's disease. Diagnosis of Alzheimer's disease and MCI was made based on NINCDS-ADRDA criteria and were made by a board certified neurologist or specialist in Geriatric Medicine. Groups 2, 3, and 4 did not differ significantly in age. Cognitively impaired participants were recruited during normal visits to Cole Neuroscience Center where, if they met the inclusion criteria, they were given an overview of the study and offered the chance to participate. Control participants were recruited either through Cole Neuroscience Center (spouses of patients, etc.) or through direct recruitment by research assistants at the University of Tennessee. Each participant signed an informed consent document and, for the cognitively impaired participants, caregivers and spouses also signed informed consent documents. All participants were required to have been driving within two years of testing. Exclusion criteria included recent drug or alcohol use, a history of substance abuse, a history of psychiatric illness, a history of neurological difficulties other than MCI or early AD, and a history of head injury. The study was reviewed and approved by the

University of Tennessee campus IRB and the University of Tennessee Graduate School of Medicine IRB.

Group	Size	Mean Age	Range	Standard Deviation
Young Controls	17	22.1	19-25	1.65
Normal Aging	16	70.9	56-86	8.76
MCI	20	72.1	61-80	5.24
Alzheimer's Disease	15	76	63-88	7.36

Table 1 – Demographics of the study samples. Groups 2, 3, and 4 did not differ significantly in age.(Deci, 1987)

Procedure

Participants in groups 2, 3, and 4 arrived at the University of Tennessee Medical Center, where they were administered a series of neurocognitive tests. These tests were given in the same order for every participant, which was CST, MMSE, MoCA, followed by Trail Making 1 and 4, Verbal Fluency, and Stroop Color Word Interference test from the Delis-Kaplan Executive Function System. Participants from group 1 were tested on the University of Tennessee campus. All participants then reported to the driving simulator, where they were given a driving knowledge evaluation developed from the Tennessee Driver's Manual. After completing the evaluation, a 3 minute warm-up simulation was performed to acclimate the participant to the simulator. Once completed, the participant was shown a map with a highlighted route and given three minutes to memorize the route. The four turn route was on a map with street names clearly labeled. Written directions were provided in the top corner of the map (Appendix I). After

three minutes, the participant was asked to enter the simulator and drive the route that had been memorized. A research assistant recorded the participant's driving behavior on a driving evaluation to supplement the data recorded by the simulator itself (Appendix I). Upon completion of the route, participants were given up to five minutes to rest. Soft drinks and potato chips were offered as refreshments. At the end of the five minute break, the same procedure was completed for two additional routes. Occasionally, participants would experience discomfort in the simulator, at which point they were escorted from the simulator, given water, and allowed to rest. Participants who experienced discomfort were not allowed to continue in the driving task.

Tests

MMSE:

The MMSE, or Mini-Mental State Exam, is the most widely used multi-domain cognitive test. It contains tasks that assess orientation, working memory, attention, and visuospatial organization (Folstein, Folstein, & McHugh, 1975).

MoCA:

The MoCA, or Montreal Cognitive Assessment, was developed in 2005 as a screening tool for MCI. It contains tasks that assess visuospatial organization, executive functioning, memory, verbal fluency, orientation, and attention (Nasreddine et al., 2005).

Trail Making 1:

A part of the Delis-Kaplan Executive Function System (DKEFS), the Trail Making 1 task presents participants with two pages consisting of multiple circles. Enclosed in these circles are numbers and participants are asked to cross of each circle that contains the number 3. This test is designed to assess visuospatial ability.

Trail Making 4:

Another part of the DKEFS, the Trail Making 4 tasks presents participants with two pages with circles containing numbers and letters. Participants are asked to draw a line connecting all the circles, alternating between numbers and letters in ascending order.

Verbal Fluency:

Consisting of multiple tasks, the verbal fluency portion of the DKEFS requires participants to name as many words as they can that fit into certain categories or start with certain letters. This test assesses verbal fluency.

Stroop Color-Word Interference:

Consisting of four separate tasks, the Stroop test portion of the DKEFS requires participants to read color words written in different color ink. This test assesses executive control with an emphasis on inhibitory control.

Statistics

All data were analyzed using JMP Pro 10 for Windows. An Incomplete variable was created, with 0 meaning that the participant completed the route successfully and 1 meaning that the participant did not complete the route successfully.

To create a model to predict driving ability, JMP Pro 10's partitioning algorithm utilized the various tests to predict Incomplete.

Results

Groups 2, 3, and 4 did not differ significantly on the Incomplete variable, meaning that normal aging participants were no more likely to complete the route successfully than were participants with MCI or Alzheimer's disease. The CST was able to differentiate between participants with MCI and participants with Alzheimer's disease ($p=.027$) but not between normal aging and MCI ($p=.356$). The MMSE and MoCA could differentiate between normal, MCI, and Alzheimer's groups ($p<.04$). See Appendix II for more details.

The results of JMP Pro 10's partitioning algorithm can be found in Figure 1. The tests utilized were all from the DKEFS, including verbal fluency, Stroop color-word interference, and the Trailmaking tasks. This partitioning result was subjected to a 10-fold crossvalidation, which yielded a crossvalidation R^2 of .3158.

Discussion

The CST is an effective test for distinguishing between MCI and early Alzheimer's disease. This partially confirms the findings in Dougherty et al.'s 2012 study. However, the current study failed to replicate the CST's ability to distinguish between normal aging and MCI. Unfortunately, this portion of the current study was subject to error. During the course of the study, a miscommunication occurred which resulted in Group 1 participants, tested at the University of Tennessee campus, taking the CST by themselves instead of being given it by a trained test administrator. This led to corruption of the CST scores for Group 1, which excluded them from the data analysis. It is possible that this error masked the significance of the difference between the normal aging group and the MCI group (the two groups differed by more than 1 point). It is also possible that the CST is most useful with certain dementias. Since the difference between the CST and the MMSE is primarily in verbal fluency measures, it is possible that the CST's advantage is optimized in dementia patterns that are characterized by verbal fluency deficits. Future studies may then examine the CST's efficacy in different types of dementia, such as frontotemporal dementia or semantic dementia, or different subtypes of Alzheimer's disease, such as logopenic aphasia.

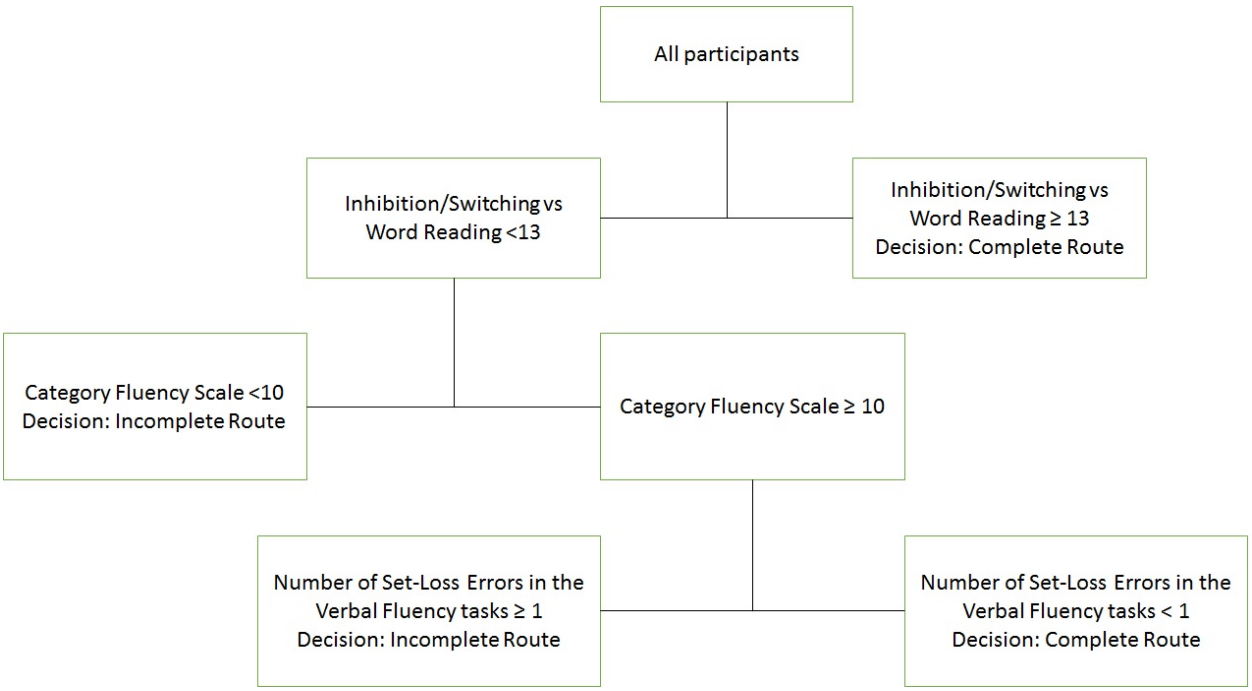

Figure 1 – Results of the partitioning algorithm in JMP Pro 10. The first split involves the Stroop test contrast score of Inhibition/Switching vs Word Reading scaled scores. The next split involves the category fluency scaled score from the verbal fluency test. The final split involves the number of set-loss errors in the verbal fluency task. This decision tree had a 10-fold crossvalidation R^2=0.3158 and a misclassification rate of 12.5%.

While the attempt to derive a robust set of neurocognitive tests resulted in a fairly simple decision tree that could predict whether or not a participant could successfully complete the driving task with 87.5% accuracy, the crossvalidation R^2 is only 0.3158. This means that the decision tree is in danger of having overfit the data and may not be generalizable. Further evidence for this conclusion comes from the seemingly unlikely combination of tests used, including the number of set-loss errors in the second trial of the verbal fluency task, a contrast score from the Stroop interference task, and category fluency from the verbal fluency task. These seemingly disparate indicators may yield promising direction for further study, however. They all have in common a focus on verbal fluency and executive functioning. Further study on the pursuit of a predictive

model for driving ability should focus on these domains specifically, using a wide range of tests to get the most accurate picture possible of these domains. This may be the best way to achieve a successful model predicting driving behavior using neurocognitive tests.

Although this study was unsuccessful in its attempt to achieve a useful predictive tool for physicians, this failure should not be a deterrent to future study in the area. There were several serious sources of error in this study that lent themselves to its inability to find a significant model for driving ability. The first error was introduced during the use of the driving simulator. Many participants experienced discomfort during the simulations. Standard practice in this situation was to remove the participant from the simulator and discontinue the task. Obviously, this resulted in a large number of incomplete tasks. Accurate records of which patients experienced this discomfort and quit the task prematurely were not kept. Often, participants who stopped the simulation early due to discomfort were indistinguishable, at the data analysis stage, from participants who could simply not remember the route. This introduced a large amount of error into the data analysis, as the Incomplete variable was not a definitive measure of cognitive ability to complete the route but rather a measure of physical ability to withstand the simulation, in some cases. Another source of error came from the simulator itself. Several participants' simulations were not recorded by the simulator due to an unknown error in the machine. Regardless of its cause, this error alone eliminated the data from more the 17 participants in the study. This massive portion of data missing was more than a little damaging to the statistical efforts of this study.

This study, despite its sources of error, revealed several promising possibilities for future research. The first is to test the utility of the CST in differentiating between MCI and other types of dementia, including frontotemporal dementia and logopenic aphasia. Another possibility for research involves correlating driving tests in the simulator with driving tests on the road or on a closed course in older adults. The fact that normal aging adults were no more likely to be able to successfully navigate the route in the simulator, though confounded by the error introduced by simulator-induced discomfort, suggests that performance in the simulator may not be an accurate representation of driving ability in real life. One final idea for further research would be to break down the MMSE, MoCA, and CST into their specific domains, determine which domains are predictive of driving performance and, in conjunction with the further research into the executive function tests and verbal fluency tests, develop a test specifically to predict driving ability.

References

Alzheimer's Association (2013). 2013 Alzheimer's Disease Facts and Figures. *Alzheimer's and Dementia* 9(2).

Brown, L. B. & Ott, B. R. (2004). Driving and dementia: a review of the literature. *J Geriatr Psychiatry Neurol, 17*(4): 232-240.

Deci, E. L., Ryan, R. M. (1987). The support of autonomy and control of behavior. *Journal of Personality and Social Psychology, 53*(6): 1024-1037.

Dougherty, J. H., Jr., Cannon, R. L., Nicholas, C. R., Hall, L., Hare, F., Carr, E., Dougherty, A., Janowitz, J., & Arunthamakun, J. (2010). The computerized self test (CST): an interactive, internet accessible cognitive screening test for dementia. *J Alzheimers Dis, 20*(1): 185-195.

Horikawa, E., Okamura, N., Tashiro, M., Sakurada, Y., Maruyama, M., Arai, H., . . . Itoh, M. (2005). The neural correlates of driving performance identified using positron emission tomography. *Brain Cogn, 58*(2): 166-171.

Just, M. A., Keller, T. A., & Cynkar, J. (2008). A decrease in brain activation associated with driving when listening to someone speak. *Brain Research 1205*: 70-80.

Mader, M., Bresges, A., Topal, R., Busse, A., Forsting, M., & Gizewski, E. R. (2009). Simulated car driving in fMRI--Cerebral activation patterns driving an unfamiliar and a familiar route. *Neuroscience Letters,464*(3): 222-227.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L, & Chertkow, H. (2005). The Montreal Cognitive Assessment (MoCA): A Brief Screening Tool for Mild Cognitive Impairment. *Journal of the American Geriatric Society 53*: 695-699.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., . . . Wallace, R. B. (2007). Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology 29*(1-2): 125-132.

Snyder, C. H. (2005). Dementia and Driving: Autonomy Versus Safety. *Journal of the American Academy of Nurse Practitioners 17*(10): 393-402.

Spiers, H. J., & Maguire, E. A. (2007). Neural substrates of driving behaviour. *Neuroimage 36*(1): 245-255.

Rizzo, M., S. R., McGehee, D., & Dawson, J. (1998). Simulated Car Crashes and Crash Predictors in Drivers With Alzheimer Disease. *Archives of Neurology 54*(5): 545-551.

Taylor, B. D. & Tripodes, S. (2001). The effects of driving cessation on the elderly with dementia and their caregivers. *Accident Analysis and Prevention, 33*(4): 519-528.

Uchiyama, Y. (2003). The neural substrates of driving at a safe distance: a functional MRI study. *Neuroscience Letters*.

Appendix I

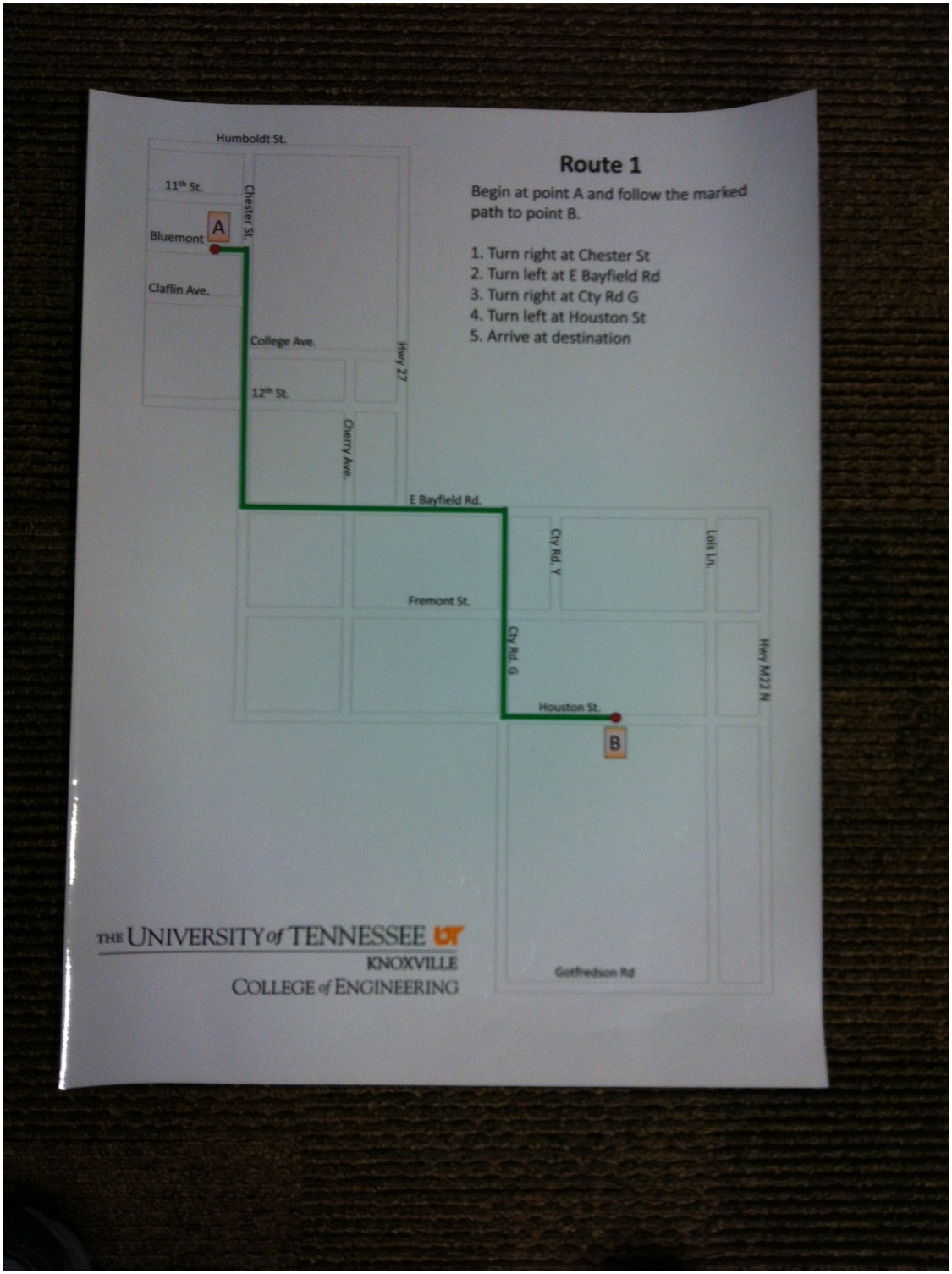

Image 1 – Photograph of the map patients were shown at the driving simulator

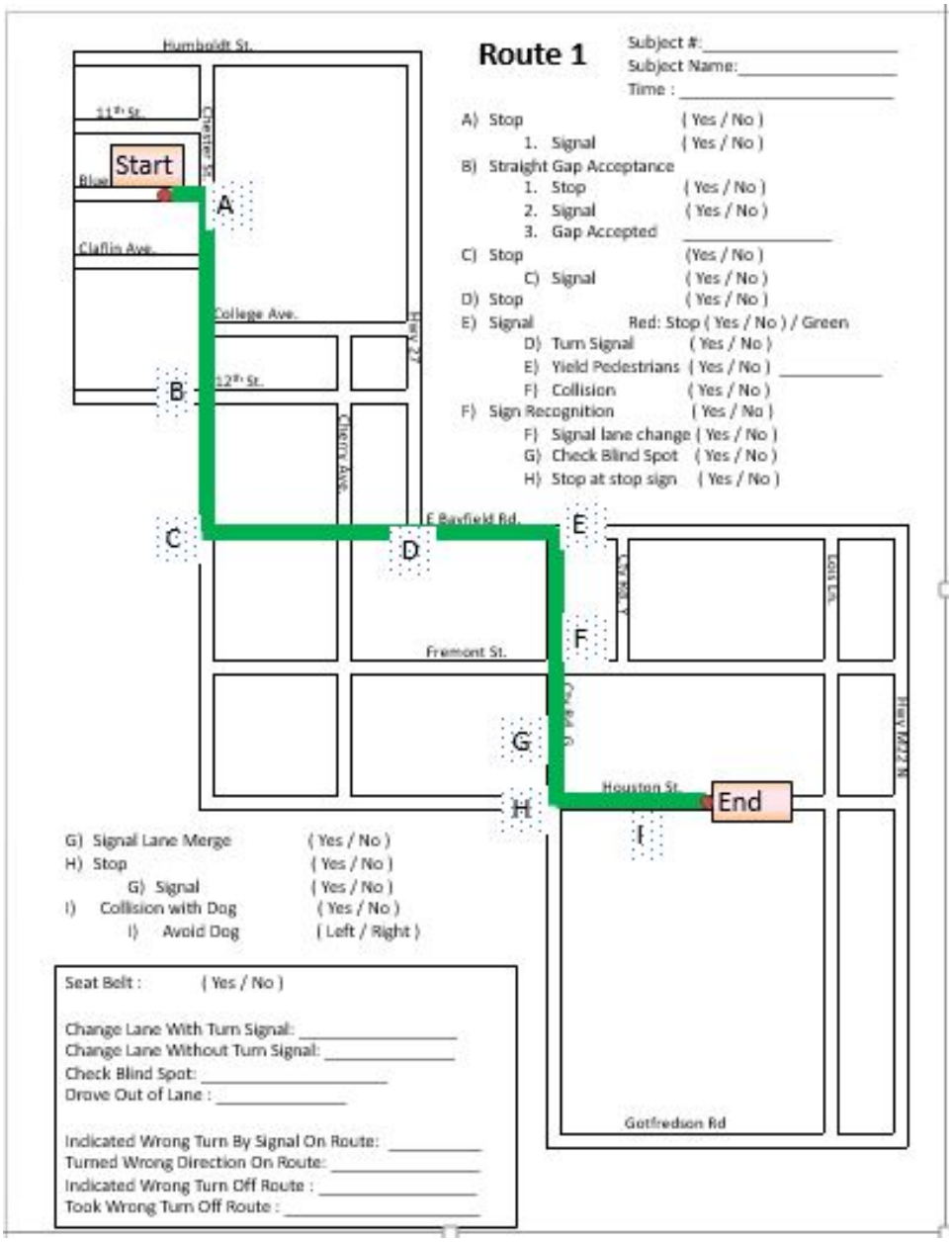

Image 2 – Image of the driving evaluation completed by the driving simulator test administrator