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Psychometric development of an instrument for the diagnosis and assessment of anosognosia in Alzheimer's disease

Charles A. Licata
University of Tennessee

To the Graduate Council:

I am submitting herewith a dissertation written by Charles A. Licata entitled "Psychometric development of an instrument for the diagnosis and assessment of anosognosia in Alzheimer's disease." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Comparative and Experimental Medicine.

John H. Dougherty, Major Professor

We have read this dissertation and recommend its acceptance:

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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recommend its acceptance:

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R. Kent Hutson

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Barton Rohrbach

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John Lounsbury

Accepted for the Council:

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(Original signatures are on file in the Graduate Admissions and Records Office.)

Psychometric Development of an Instrument for the Diagnosis and Assessment of Anosognosia in Alzheimer's disease

A Dissertation
Presented for the
Doctor of Philosophy Degree
The University of Tennessee, Knoxville

Charles A Licata
May, 2009

Dedication

This dissertation is dedicated to

Prof. Dr. John H. Dougherty Jr., M.D.

Whose guidance, support, and friendship made this dissertation possible.

Abstract

The purpose this study was to develop a psychometrically sound paper-n-pencil questionnaire for the measuring and diagnosing of anosognosia in Alzheimer's disease (AD). Anosognosia is defined as the lack of awareness one has towards one's own state. It manifests within AD as an unawareness of symptoms the individual is experiencing. The initial 43-item questionnaire was administered to 67 AD patients (age: u = 72.66, SD = 3.40), with 41 females and 26 males. A Cronbach's-alpha of 0.89 was obtained showing the questionnaire had excellent internal reliability.

The 43 items in the original questionnaire were reduced to 10 using the internal reliability analysis. The 10-item questionnaire was administered to a new group of 83 AD patients (age: u = 75.83, SD = 3.83), with 58 females and 25 males. Internal reliability of the new questionnaire remained high with an obtained Cronbach's-alpha of 0.87. Correlations between the sample population 10-item questionnaire score and the Mini Mental State Exam (r = -0.24, $p < 0.05$) and Geriatric Depression Scale (r = -0.30, $p < 0.05$) showed a low but significant correlation. The 8-Point Clock Drawing (r = -0.04, $p > 0.05$), and Zarit's Caregiver Burden Scale (r = 0.04, $p > 0.05$) showed no correlation. Using 19 of the patients a one-way Intraclass Coefficient (ICC) was used to determine inter-rater agreement (alpha = 0.63). Twenty-one of the patients were used for the purpose of test-retest and resulted in a Pearson-r correlation of r = 0.70 ($p < 0.000$).

Forty-three normal subjects were enrolled in the study (age: u = 73.95, SD = 3.90) with 23 females and 20 males. Using the normals mean + 2SD a cutoff score of 12 was obtained as the point where an AD patient was diagnosed as having anosognosia.

Using the cutoff value there were 42 AD patients who had anosognosia which was 51% of the sample population.

The questionnaire was found to be reliable though further studies would be needed to confirm the results by expanding the sample size and using more generalized inclusion criteria. Nevertheless, the questionnaire showed little relationship to the other questionnaires administered during the study. This helps to show the questionnaire is measuring a unique phenomenon which is not related to other standard diagnostic questionnaires used with AD patients.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
AD	Alzheimer's disease
ADL	Activities of Daily Living
AD-Q	Anosognosia Questionnaire-Dementia
APP	Amyloid Precursor Protein
BVRT	Benton Visual Retention Test
CAS-AD	Cole Anosognosia Scale for Alzheimer's disease
CDT-8	8-Point Clock Drawing
DPS	Dementia Psychosis Scale
DSM-IV	Diagnostic and Statistic Manual of Mental Disorders, 4th edition
DSM-IV(R)	Diagnostic and Statistic Manual of Mental Disorders - Revised, 4th edition
FIM	Functional Independence Measure
fMRI	Functional Magnetic Resonance Imaging
FTD	Frontotemporal Dementia
GDS	Geriatric Depression Scale
G.D.S.	Global Deterioration Scale
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Scale
ICC	Intraclass Coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
LM	Logical Memory
MMSE	Mini Mental State Exam
MRI	Functional Magnetic Resonance Imaging
NFT	Neurofibrillary Tangles
NHTSA	National Highway Traffic Safety Administration
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's disease and Related Disorders Association
PA	Paired Associate
PET	Positron Emission Tomography
PLACS	Pathological Laughing and Crying Scale
rCBF	Regional Cerebral Blood Flow
RPM	Raven's Progressive Matrix
SCID	Clinical Interview for Axis 1 DSM-III-R Diagnosis
SD	Standard Deviation
SPECT	Single photon emission computed tomography
ZCBS	Zarit's Caregiver Burden Scale

1. LITERATURE REVIEW

1.1 Alzheimer's disease

In 1901 Auguste D was a 51-year-old patient who was committed to the Frankfurt Asylum with what was considered to be unusual symptoms (Schneider & Dagerman, 2004). Alzheimer, who was a physician on staff, became fascinated with Auguste's state and followed her slow cognitive decline until her death 5 years later. Alzheimer had her brain sent to Kraeplin's laboratory in Munich where the two examined the brain using new staining techniques to identify a large amount of amyloid plaques and neurofibrillary tangles within the brain tissue (Small & Cappai, 2006). The same year Alzheimer presented both his pathological and clinical symptoms of presenile dementia noting Auguste's memory loss, disorientation, hallucinations, and untimely death. Later the disease was unintentionally named when Kraeplin used the term "Alzheimer's disease" in a textbook he authored (Morris & Salmon, 2007).

Alzheimer's disease (AD) has become the most common form of dementia, representing more then 60% of today's current dementia diagnoses (Ferri, et al., 2005). It is estimated that in 2000 over 4 to 4.5 million people in the United States were suffering from AD, and it is estimated that this number may triple or quadruple by 2050 (Kawas, 2003). In 2006, the worldwide estimate for the prevalence of AD was 26.6 million. This number is also expected to increase in relation to the United States estimate, with 1 in 85 persons in the world being afflicted by the disease ((Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007).

AD has a slow onset with the disease classified into 3 stages; mild, moderate, and severe. Mild AD is characterized by small changes in normal cognitive functioning such as the ability to remember recent events or information (Peterson, 2007). As the disease progresses into the moderate stage the individual's cognitive functions deteriorate to where there is a decrease in the level of independence in relation to activities of daily living (ADL). The individual may also require greater assistance in performing more cognitively challenging tasks. The disease will then progress into the severe stage. During the severe stage an individual looses the ability to function on a day-to-day basis. Symptoms can include inability to recognize family members, problems speaking, performing simple daily activities, or changes in personality or behaviors. The 3 stage model is most commonly used though there have been other scales introduced in an effort to stage AD, such as Reisberg's (1982) subjective 7 stage Physician-rated questionnaire called the Global Deterioration Scale (G.D.S.) (Table 1).

Table 1. Global Deterioration Scale (G.D.S.)

7 Stage of decreasing ability

Stage 1: No cognitive decline
Stage 2: Very mild cognitive decline
Stage 3: Mild cognitive decline
Stage 4: Moderate cognitive decline
Stage 5: Moderately severe cognitive decline
Stage 6: Severe cognitive decline
Stage 7: Very severe cognitive decline

Reisberg B, et al. Am J Psychiatry. 1982;139:1136-1139.

The widely accepted diagnosis criterion for probable AD is the National Institute (McKhann, et al., 1984). The criteria states that dementia needs to be established by clinical examination and documented by cognitive tests, confirmed by neuropsychological testing, contain at least two areas of cognition deficit, demonstrate progressive worsening of symptoms, have an onset between 40 and 90 years of age, and an absence of any other systematic or brain disease capable of producing dementia (Cummings, 2007).

Though the previous standard has been used for over 2 decades, today it is common place for a PET scan to also be performed in order to differentiate between AD and frontotemporal dementia (FTD) (Corey-Bloom, et al., 1995). The reasoning for a PET scan is that FTD will often meet the diagnostic criteria for AD (Varma, et al., 1999). The use of a PET scan helps to determine if there is severe hypometabolism in the frontotemporal area of the brain which is an identifying feature of FTD and thereby will rule out AD.

As with staging, the NINCDS-ADRDA is not the only existing diagnostic criteria (Table 2). The International Classification of Disease, 10th revision (ICD-10) criteria includes the presence of dementia, insidious onset, slow deterioration of cognition, absence of clinical or laboratory evidence of a systematic illness or brain disease that can induce dementia, and the absence of a history of sudden onset of neurological signs indicative of focal brain injury. The Diagnostic and Statistic Manual of Mental Disorders, 4th edition (DSM-IV) (APA, 1994) and Diagnostic and Statistic Manual of Mental Disorders - Revised, 4th edition (DSM-IV-TR) (APA, 2000) requires a gradual onset and a

Table 2. Three Criteria for AD Diagnosis

Characteristics	ICD-10	DSM-IV	NINCDS-ADRDA Probably AD
Memory decline	+	+	+
Thinking impairment	+	-	-
Aphasia, apraxia, agnosia or disturbed executive functioning	-	+	-
Impairment of at least one non-memory intellectual function	+	+	+
Dementia established by questionnaire	-	-	+
Dementia confirmed by neuropsychological testing	-	-	+
ADL impairments	+	-	-
Social or occupational impairment	-	+	-
Decline from previous level	+	+	+
Onset between the age of 40 and 90	-	-	+
Insidious onset	+	+	-
Slow deterioration	+	-	+
Continuing deterioration	-	+	+
Absence of clinical or laboratory evidence of another dementing disorder	+	+	+
Absence of sudden onset	+	-	+
Absence of focal neurological signs	+	-	+
Absence of substance abuse	-	+	-
Deficit not limited to delirious period	+	+	+
Absence of another major mental disorder	-	+	-

Cummings, J. (2004). Definitions and diagnostic criteria. In Clinical Diagnosis and Management of Azlheimer's Disease. 3nd Edition. Ed. S. Gauthier. Martin Dunitz, London.

continuing cognitive decline, as well as the absence of other neurological disorders, systematic conditions, or substance abuse sufficient to induce dementia. Furthermore, the condition cannot occur during a delirium and must not be attributable to a major psychiatric disorder.

Unlike the ICD-10 and DSM-IV, the NINCDS-ADRDA criteria does not rely on activities of daily living as a diagnostic criteria, but instead uses it as supportive information. It is considered to be a weakness by some since it can cause the disease to be under diagnosed. However, the NINCDS-ADRDA also has its strength since its criteria excludes sudden onset which is not a conventional occurrence with AD. Also, unlike the DSM-IV criteria, it does not exclude patients who have substance abuse, depression, or schizophrenia (Cummings, 2007).

There are 3 possible diagnostic categories for AD: definite, possible, and probable (Table 3). A definite diagnosis requires the NINCDS-ADRDA criteria to be met together with histopathologic evidence of AD through autopsy or biopsy (Schachter & Davis, 2000). Probable AD requires the dementia to have onset between 40 and 90 years of age; that it be established by clinical examination and documented by cognitive testing; contain deficits in two or more areas of cognition; have a progressively worsening cognitive function; be devoid of any disturbance of consciousness; and the absence of any systematic or brain disease capable of producing a dementia syndrome. Lastly, the criteria for Possible AD includes an atypical onset, presentation, or progression of a dementia syndrome without a known cause; the presence of a systematic or other brain disease capable of producing dementia, but not thought to be the cause of the dementia;

Table 3. Diagnosis Categories for AD

Definite AD

- Clinical criteria for probable AD.
- Histopathologic evidence of AD (autopsy or biopsy).

Probable AD

- Dementia established by clinical examination and documented by mental status questionnaire.
- Dementia confirmed by neuropsychological testing.
- Deficits in two or more areas of cognition.
- Progressive worsening of memory or other cognitive functions.
- No disturbance of consciousness.
- Onset between 40 and 90 years of age.
- Absence of systematic or brain disease capable of producing a dementia syndrome.

Possible AD

- Atypical onset, presentation, or progression of a dementia syndrome without a known cause.
- Presence of a systematic or other brain disease capable of producing dementia, but not thought to be the cause of the dementia.
- Gradually progressive decline in a single intellectual function in the absence of any other identifiable cause.

and the gradual but progressive decline in a single intellectual function in the absence of any other identifiable cause (Lopez , et al., 2000).

1.2 Pathogenesis of AD

AD is considered to be a multifactorial disease (Blass 1993). Associated with the disease are genetic and environmental factors which contribute to inflammatory responses in the brain and the eventual loss of neurons which ultimately lead to the manifestation of AD. Most notable changes to the brain and what are believed to be the primary cause of AD is the presence of beta amyloid plaques and neurofibrillary tangles (NFT).

Beta amyloid plaques are formed from an abnormality with the functioning of Amyloid precursor proteins (APP). APP is normally found in the brain and essential to the brain's development and repair. After use APP is broken down into 37-amino-acid segment and is recycled to create more APP (William & Shankle, 2005). Within the AD patient APP incorrectly breaks down and creates 40- and 42-amino-acid fragments. Called beta amyloid plaques, the fragments are not reused and begin to collect within the brain into protein accumulations called BA42 complexes which cause neuronal death (Selko, 2004).

NFT is a cytoskeletal abnormality found in AD, though it is not unique to the disease itself (Terry & Katzman, 1983). NFT appear to be created by the abnormal accumulation of Tau proteins which are essential to maintaining the shape and structure of the neuron. Due to a mutation of a gene on chromosome 17 the Tau proteins begin to twist causing a neuron's axon to become misshapen (William & Shankle, 2005). The

malformed proteins block the flow of molecules from the cell body to the outer regions of the cell, eventually causing the death of the neuron.

It is uncertain how the two processes are related and it is currently believed AD is the result of multiple factors which produce neuronal death. Whether beta amyloid plaques or NFT are the initial trigger, or if they are independent occurrences causing the disease is still in debate (Belanger, Pearson, & Poirier, 2007).

1.3 Risk Factors

Age is considered the greatest risk factor for developing AD. Ten percent of people over the age of 65 have AD with the risk doubling every 5 years thereafter ("National Institute on Aging", 2006). Some individuals inherit AD (Familial), though this occurs in less then 1% of AD cases with onset occurring before the age of 65. However, almost all people with Down syndrome start to show AD associated changes to the brain after age 40 with onset occurring in their 50s or 60s (Black, Patterson, & Feightner, 2001).

Gender has not been found to be a risk factor among AD patients in the United States, however females in Europe and Asia have are reported to be at a higher risk then males (Feinberg et al., 2000). Though the reasons are not yet fully understood, some investigators believe the cause may be the greater longevity of woman, difficulty in diagnosing males since there is a higher prevalence of cerebrovascular disease with men, and unexpected hormonal effects brought on by menopause and low testosterone levels (Belanger, et al., 2007).

Lower education level has been linked to an increased risk in AD (Karp et al., 2004), while other studies failed to show an association, or an association was only demonstrated within subgroups. (Letenneur et al., 2000). It is hypothesized that higher level of education creates improved abilities in thinking, learning, and memory which result in the constantly challenged brain creating a cognitive reserve. The reserve allows the brain to adapt to the damages caused by AD (Roe, Xiong, Miller, & Morris, 2007). An analogy often used is how the body accrues benefits to fight disease when regular physical exercise is performed.

Other additional documented risk factors include chronic inflammatory conditions, clinical depression, strokes, high cholesterol, high blood pressure, stress, obesity, and toxins (Ampuero et. al., 2008). Though documented they have note been shown to be significant risk factors, but are believed to contribute to the overall chance of being afflicted with the disease.

1.4 Anosognosia and Alzheimer's disease

The term commonly used for AD awareness deficits is anosognosia, though the term is also used to describe both neurological and psychological conditions. Gabriel Anton first recorded a description of anosognosia in 1893 (McGlynn & Schacter, 1989). Gabriel reported a patient's unwavering belief that his daughter was constantly lying by his left side. The term , however, was also applied to a disorder by Babinski (1914) when describing the lack of awareness in two hemiplegic patients that denied their left hemiplegias after suffering a stroke (Feinberg et al., 2000).

Anosognosia as described by Babinski is directly referring to a lack of awareness of motor deficits, and not to any cognitive deficit within the patient (Anderson & Tranel, 1989). Unfortunately, the term has come to identify a variety of conditions in which the patient experiences a lack of awareness and this has been partially responsible for the many hypotheses relating to the cause of the disorder. As previously mentioned anosognosia was originally associated with left-hemisphere neglect. Currently it has also been used to describe the denial of symptoms in cognitive disorders and more recently it was used to refer to a parent, caregiver, or teacher's inability to recognize the cognitive decline of children they care for (Butler & Light, 2003).

Within the AD population, anosognosia was first used to describe the cognitive deficits of an individual. Physicians have widely identified a lack of awareness among patient's suffering from Alzheimer's disease. The most noticeable deficit is a patient's ability to recognize their cognitive limitations; however, the patient may also fail to realize changes that occur in their behavior, as well as physical limitations they experience. With these deficits in mind, investigators and clinicians have been actively studying the physiological, psychological, and maintenance issues of AD patients who present symptoms of anosognosia. Present research has shown the number of AD patient's suffering from anosognosia is approximately 20% (Migliorelli, et al., 1995), though the number is believed by some investigators and clinicians to be as high as 75% (Antoine et al., 2004).

Anosognosia can have a direct effect on the diagnosis, intervention, treatment, and management of patients inflicted with the AD (Cotrell, 1997). Important to the care

of the AD patient is the ability of clinicians, staff, and social workers to be able to guide caregivers to effective means of managing patient activities. Giving the caregiver an insight into the extent of anosognosia being experienced by the patient can help to alleviate caregiver stress by giving them information as to why a patient may not be able to understand what they can and can not do. By doing so the quality of life for the patient and caregiver can be enhanced.

The diagnosis of anosognosia in hemiplegic patients is simple since it requires the physician only to observe a patient's response to a number of straight forward questions regarding the left side of the patient's environment (McGlynn & Schacter, 1989). Ramachandran and Blakeslee (1998) presented a clear example with his description of Mrs. Dodds, a patient who had a stroke that resulted in paralysis of her left arm. Whenever she was asked questions to perform an activity that required the use of her left arm, she would give a response that allowed her to avoid acknowledging her paralysis. The response would center on her unwillingness to perform a task she had already been asked to do, or that she was too tired to perform the task.

The diagnosis in the preceding case was readily made; however, the etiology of anosognosia is far more complex and not greatly understood (McGlynn & Schacter, 1989). In some cases the patient may believe they are actually performing a task requiring the use of a paralyzed limb, such as clapping their hands together, when in reality the affected limb is not responding at all. Furthermore, there have been observations of patients who will altogether deny the ownership of their affected limbs,

claiming it belongs to someone else even though the person may not be present in the room or no longer alive.

There have been a number of theories to explain anosognosia in the hemiplegic patient with most falling into two categories (Ramachandran and Blakeslee, 1998). The first category involves the Freudian concepts of coping. It occurs when a patient is unable to come to terms with their illness and they attempt to cope with the situation by relying on the defense mechanism of denial. The second category takes on a neurological view with the denial being a direct consequence of left-hemisphere neglect. When anosognosia occurs it is in relation to damage to the right hemisphere of the brain which supports the neurological theory.

The cognitive deficit seen in AD patients with anosognosia involves denial of common AD symptoms such as memory and executive functioning impairment. Executive functioning consists of, but is not limited too, actions involving planning, decision making, error correction, or situations to resist a strong habitual response. One of the earliest empirical studies on AD anosognosia was performed by Reisberg and colleagues (1985). The study reported significantly less awareness of cognitive deficits in moderate to severe AD cases when compared to mild cases. The investigators proposed that anosognosia may be the result of a defense mechanism that attempts to protect the individual from knowledge of their illness and thereby avoiding possible depression. To explore this idea, there have been numerous attempts designed to examine the correlation between patient severity of AD and depression. Feher and associates (1991) reported a weak negative correlation between anosognosia and

depression, while in a separate study by Sevush and Leve (1993) reported a significant negative correlation between the two. A third study by Reed and associates (1993) failed to find any significant correlation between depression and anosognosia in their subject population.

Other investigators have moved away from searching for a psychological mechanism for anosognosia and instead looked at neurological damage in the frontal lobe. In separate studies conducted by Lopez and associates (1994), and Michon and associates (1994), AD patients with anosognosia were found to have significantly greater cognitive deficits when compared to AD patients without anosognosia. Both investigators suggested frontal lobe damage as being the cause of the anosognosia since the anosognosia group did worse at performing tasks related to tapping into frontal lobe functions. The frontal lobes are involved in problem solving, spontaneity, memory, language, judgment, impulse control, and social behavior. Damage to the region may cause the patient not to process fully the ramifications of actions they take. There has been difficulty in replication of the studies. The reason may be caused by many studies relying on a cognitive domain relating to items of memory, or spatial and temporal orientation, while others included a behavioral domain which includes irritability, selfishness, inappropriate emotional display, and lack of inhibition (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996).

In 1996 Starkstein and associates addressed the issue of differing domains by examining 186 AD patients. The patients were administered the Anosognosia Questionnaire-Dementia (AD-Q) and a battery of tests geared towards determining their

cognitive and behavioral states. To access behavior, subjects were given the clinical interview for axis 1 DSM-III-R diagnosis (SCID), the Hamilton Depression Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), Bech Mania Scale, Pathological Laughing and Crying Scale (PLACS), Apathy Scale, Irritability Scale, Dementia Psychosis Scale (DPS), and Functional Independence Measure (FIM). To access cognitive abilities the Mini-Mental Status Examination (MMS), Raven's Progressive Matrix (RPM), Wisconsin Card Sorting Test, Controlled Oral Word Association Test, Digit Span, Buschke Selective Reminding Test, Token Test, Block Design, and Similarities Test were administered. The results indicated that cognitive deficits were positively correlated with severe intellectual decline, a higher frequency of delusions, severe apathy, and a decrease in depression. Lack of awareness of behavioral changes positively correlated with lack of inhibition scores and severe pathological laughing. An important finding was a very weak positive correlation between lack of behavioral awareness and neuropsychological test scores. The authors point to these findings as further evidence to show that anosognosia within AD has two distinct domains with very different mechanisms.

Concurrent studies performed with neuropsychological questionnaires on AD patients with anosognosia have shown significantly more deficits related to the frontal lobe (Lopez, Becher, Somsak, Dew, and DeKosky, 1993); (Michon, Deweer, Pillon, Agid, and Dubois, 1994) when compared to AD patients without anosognosia. These findings suggest AD anosognosia is the result of damage to the frontal lobes, and this view has become readily accepted by many investigators although these studies could not be replicated (Bech, Kastrup, and Rafaelsen, 1986).

By far, the greatest problem relating to the study of anosognosia in AD patients stems from the heterogeneity of the population. The progression of AD has a highly variable duration of disease, rate of cognitive decline, and appearance of symptoms. Studies designed to determine correlations between phenomena within AD and anosognosia often fail due to the variability found within the population. An example of the problem was identified in a study performed on AD patients by Feher and associates (1991). Thirty-eight AD patient were administered a battery of memory tests which included the Logical Memory (LM) and Paired Associate (PA) module from the Wechsler Memory Scale, and the Benton Visual Retention Test (BVRT). They determined the level of denial by administering a standard memory questionnaire to the patient and caregiver. The investigators were surprised to find only weak correlations between a patient's level of denial and the severity of memory impairment.

Reed and associates (1993), and Michon and associates (1994), reported similar findings when studying AD and anosognosia. Reed and associates found the ability of mild and moderate AD patients to accurately report personal memory impairments had no direct relationship to the severity of their dementia. Michon compared the memory of AD patients with mild and moderate dementia and found a high variability in self rated memory skills within each group. Michon suggested that the variability was due to a defense mechanism caused by the patient's depression about their illness; however, he quickly points out that none of the study patients were diagnosed with depression. He further suggests that the amount of information an individual patient receives from caregivers and family may lead to a greater recognition of their deficits. Supporting this

idea are studies suggesting an AD patient's awareness of deficits may be influenced by the treatments they receive, the quality of available psychiatric services and social support, and the amount of illness related information they obtain (Johnson & Orrell, 1995). It has been suggested indirect interventions can help a patient to recognize the facets of their illness.

Feher (1991) pointed out that AD patients have the ability to learn more complex insight in regards to self-awareness. Insight is retained in many AD patients without regard to the level of diseases severity. Given the variability of anosognosia in the population, some individuals are more likely than others to benefit from awareness enhancing interventions. The specific effects anosognosia is having on the patient's ability to understand their personality, behavior, and cognitive abilities need to identified and understood before clinicians are able to determine if a patient is likely to benefit from an awareness intervention.

Another difficulty with insight intervention is the possibility that a newly acquired insight will be bound to a specific outcome of one of the diseases symptoms (Glisky & Schacter, 1987). The overall learned insight might be confused or lost if the status or environment of the associated symptom changes. A patient who is helped to gain insight into not wandering away from the house may not maintain the behavior when moved to a new living location. Butters and associates (1993) provide an opposing point of view stating that repetition of tasks, ideas, and concepts can cause successful learning in most memory-impaired patients. Their findings showed a positive correlation between increased repetition of tasks and the amount of learning in patients. These authors also

assert that a task must be meaningful to the individual patient for successful learning to take place.

Regnier and Pynoos (1992) provide guidelines to allow caregivers, working along with clinicians, to create an environment designed to foster insight in elderly patients with dementia. In this scenario, the caregiver develops different strategies to cue behaviors important to everyday activities of the patient. Examples of this strategy include placing the patient's medication next to meals or making sure a comb is easily visible when the patient stands at the bathroom sink. Though not a solution to all the problems encountered with the AD patient, the situation exemplifies the need for caregiver education to identify anosognosia and is important as they will be directly involved with the tasks necessary to try and help a patient compensate for their lack of awareness (Barco, Crosson, Bolesta, Werts, & Stout, 1991).

There is still a lot to be understood about AD anosognosia. Currently there is no gold standard for measuring anosognosia. Investigators and clinicians have used different means to gauge anosognosia from non-validated questionnaires of their creation, modified versions of other scales, or basing the degree of anosognosia buy using clinician observation (Cotrell, 1997). Though it is only part of the disease its can have a significant impact on the quality of life of the patient and caregiver. The ability of a caregiver and clinician to manage the patient relies heavily on the patient being aware of the presenting symptoms and careful monitoring can improve the quality of life for the AD patient, caregiver, and family. Necessary to accomplish this goal is easily

administered questionnaires capable of capturing the broad effects of the awareness deficit and producing results that can be easily explained to a caregiver.

1.5 Driving, Dementia, and Alzheimer's disease

In 1999, there were more than 18.5 million licensed drivers over the age of 65, comprising 10 percent of all licensed drivers (U.S. Department of Transportation, 2000). This number is projected to grow to over 17 percent by the year 2020 (Marottoli, 2000). However, it is believed that the proportion of elderly drivers will be even greater than this estimate due to the increasing number of women drivers this group. Elderly drivers travel fewer miles than any other age group, on average less than 2600 miles per year after age 80 (Dubinsky, Stein, & Lyons, 2000). However, per mile driven, elderly drivers have higher rates of traffic violations, collisions, and fatalities than all age groups over age 25 (Beers & Berkow, 2000).

While society recognizes the importance of maintaining the autonomy and independence for the elderly that are granted by driving privileges, there are inherent risks associated with driving that increase with age. According to the NHTSA, in 2000, six percent of all people injured in traffic accidents were elderly. They made up 13 percent of all traffic fatalities and 12 percent of all vehicle occupant fatalities. Most traffic fatalities involving the elderly occurred during the daytime (81 percent), on weekdays (71 percent), and involved another vehicle (76 percent). In two-vehicle crashes, the car driven by the elderly individual was more than three times as likely to be struck and more often involved maneuvers such as yielding right-of-way, heeding stop

signs or red lights, and negotiating intersections (U.S. Department of Transportation, 2000); (Beers & Berkow, 2000).

Driving performance among older adults is affected by numerous age-related changes in physiology and cognition. Medical conditions and medications can affect vision, hearing, vehicle control, and attention. However, the single most important medical diagnosis affecting driving performance has been dementia, particularly AD, where crash rates as high as three times that of the general elderly population have been (Dubinsky, et al., 2000).

Generally, in the case of medical diagnoses such as diabetes, heart failure or stroke, it has been found that the elderly often compensate well for their physical limitations and will voluntarily limit or relinquish their driving privilege (Carr, 2000). This has not been so with AD patients in whom the presence of anosognosia can adversely impact a patient's ability to recognize poor or worsening driving performance. Rebok and associates (1994) stated that patients with AD tend to continue driving until an accident occurs or someone forcefully intervenes. Dubinsky and colleagues stated that the mean duration of dementia to onset of first crash was 4.0 years with an average MMSE score of 19.9 at the time of crash.

Rebok provided evidence for the role of anosognosia as a contributor to high accident rates with the use of self-appraisal mechanisms. These showed that while controls and AD patients were identical in rating their driving capabilities, the AD group performed significantly worse. AD patients tended to underestimate the severity of their impairments and the skills necessary to avoid accidents while driving.

1.6 Neuroimaging and AD Related Anosognosia

As early as 1995 research was performed using PET, MRI, and SPECT imaging techniques in an attempt to discover brain regions involved in the occurrence of anosognosia (Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005). When investigating the ability of subjects to self-asses their cognitive and behavioral activities the temporoparietal junction has been reported to have high activation (Salmon, et al., 2006); (Ruby & Decety, 2001); (Vogel & Luck, 2002). However, during the last decade more studies have identified other areas of the brain with potential relationships to "self-awareness". These differing results leave open the question of which areas of the brain is responsible for anosognosia.

In 2005 Vogel and associates reported a decreased activity in the right inferior cortex using SPECT imaging techniques. Stanonik (2002) identified other potential regions which included hypoactivation in the right prefrontal lobe and anterior cingulated cortex in subjects with anosognosia.

The cause of these apparently conflicting results is unknown although it has been suggested the diverse methodology among studies may be responsible. The various questionnaires being used to measure anosognosia may be the cause. Several questionnaires have appeared in multiple studies, but they have not gone through thorough psychometric testing, while others are created specifically for a study and have little to no testing of reliability or validity.

2. METHODS

2.1 OVERVIEW OF COLE ANOSOGNOSIA SCALE FOR ALZHEIMER'S DISEASE (CAS-AD)

The development of the Cole Anosognosia Scale for Alzheimer's disease (CAS-AD) had two phases. The first was the development of a 43-Item questionnaire which was administered to patients and caregivers. Collected along with the 43-Item questionnaire were the Mini Mental State Exam (MMSE) and Geriatric Depressions Scale (GDS). The two questionnaires were part of normal routine exams that every patient undergoes at the clinic where subjects were enrolled.

Once sufficient data was collected (n>50) the 43-Item questionnaire was reduced to 10 items using Cronbach's alpha (Cronbach, 1951) to perform item reduction. The resulting questionnaire was administered to a new sample of patients along with the MMSE, GDS, and Clock Drawing Task (CDT-8), Trail-Making Task: Part B (TMT-B). The caregivers were administered the new 10-item questionnaire and the Zarit's Caregiver Burden Scale (ZCBS).

Lastly, the 10-items scale was administered to normal subjects to determine a cutoff score for determining individuals who had anosognosia. The cutoff score was then used to identify the AD patients with anosognosia and analysis performed on their TMT-B when compared to AD patients without anosognosia.

The methods to analyze the data collected are described in the following sections.

2.2 SUBJECT SELECTION

2.2.1 Inclusion/Exclusion Criteria for AD Subjects

The inclusion criteria used for subjects of the 43-item and the 10-item questionnaire were identical. The patient must have had a willingness to participate, diagnosed with AD, scored between 15 and 24 on the MMSE, and had no history of other dementias or any severe psychological disorders, and at least one primary caregiver with the willingness to participate. A patient would be excluded from the study if all primary caregivers had any history of dementia or any severe psychological disorders. All AD patients included in the study were current patients at the Cole Neuroscience Center, University of Tennessee Medical Center, Knoxville, Tennessee. The patients completed all questionnaires during regular visits to the Cole Neuroscience Center Alzheimer's Clinic days.

2.2.2 Inclusion/Exclusion for Normal Subjects

The inclusion criteria for the normal subjects were a willingness to participate, scored between 27 and 30 on the MMSE, no history of other dementias or any severe psychological disorders, and at least one caregiver willing to participate. A subject would be excluded the caregiver acting as a caregiver had a history of dementia or severe psychological disorders. All normal subjects included in the study were obtained from the Cole Neuroscience Center or Sleep Disorder Center (University of Tennessee Medical Center, Knoxville, Tennessee).

2.3 STANDARD QUESTIONNAIRES

2.3.1 Mini Mental Status Exam (MMSE)

The accepted gold standard in cognitive testing for dementia is the MMSE (Folstein, Folstein, & McHugh, 1975)). The MMSE has a score ranging from 0 to 30 point and tests the following categories; orientation (10 points), registration (3 points), attention (5 points), recall (3 points), language (8 points), and visuospatial (1 point) abilities. The questionnaire must be administered by an examiner who asks a series of questions in a specific order. The orientation category has 10 questions about time, date, and locations. Each correct answer is scored 1 point. Registration requires the patient to repeat 3 words the examiner says with 1 point scored for each (this can be done multiple times until the patient answers correctly, though scoring is only done on the first response). Attention requires the patient to concentrate on spelling a 5 letter word backwards or count from 100 backwards by decrements of 7 until they reach 65. One point is scored for each correct response. Recall is tested by asking the patient to repeat the 3 words used in the registration part of the exam with each correct answer scoring 1 point. The language part is a series of 8 questions ranging from naming items to writing a sentence and is worth 8 points total. Finally, the last question asks the patient to copy a design of overlapping figures to test visuospatial ability and is worth 1 point if the patient draws figures resembling the ones on the exam and they overlap appropriately.

2.3.2 Geriatric Depression Scale (GDS)

The GDS is a 30 item questionnaire developed to identify mild and severe depression in the elderly. The questionnaire has been shown to have a strong sensitivity

and specificity (sensitive = 84%, specificity = 95%) (Yesavage, et al., 1982). Each of the 30 items is a simple sentence asking about a person's current satisfaction with life. The GDS is a self-administered questionnaire with each question being answered by circling "no" or "yes". A question has a score of 1 depending on the answer circled ("yes" is worth 1 with some questions and "no" in others). The total score for the questionnaire is 0 to 30 with 0-9 showing no depression, 10-19 mild depression, and 20-30 severe depression.

2.3.3 Zarit's Caregiver Burden Scale (ZCBS)

The ZCBS is a widely used questionnaire measuring the level of burden felt by caregivers (Parks & Novielli, 2000). The questionnaire contains 22 items which are answered by using a Likert scale with 5 responses. The possible responses in order are "never", "rarely", "sometimes", "quite frequently", and "nearly always" with each answer scored from 0 to 4 respectively. The total score ranges from 0 to 88 with a score between 0 and 22 indicating no burden, 23 to 44 mild burden, 45 to 66 moderate burden, and 67 to 88 severe burden.

Clock Drawing: 8-Point Scoring

- Correct Numbering (all numbers (1-12) included and no others).
- Numbers in Correct Position
- Numbers in Clock Circle
- Numbers Spaced Relatively Equally Apart
- Numbers Spaced Relatively Equal from Circle Edge
- One Clock Hand Points to 2
- One Clock Hand Points to 11
- There are only 2 Clock Hands

Fig 1. Clock Drawing: 8-Point Scoring

2.3.4 Clock Drawing Task: 8 Point Scoring (CDT-8)

Clock drawing has become a standard test for visuospatial problems in individuals. The patient is asked to draw a clock with the hands pointing to 10 after 11. The clock drawing portion of the Self Test II (STII) (de Leonni Stanonik et al., 2005) is used to obtain the CDT-8. There have been a number of scoring methods suggested; however the 8-point scoring was used for the study since it has been shown to highly correlate with driver safety (U.S. Department of Transportation, 2000) (Fig 1).

2.3.5 Trail Making Test – Part B (TMT-B)

Numerous studies have been performed showing the TMT-B significantly correlates to driver performance and safety (Stutts, Stewart, & Martell, 1998). The questionnaire is an administered test and asks an individual to draw a continuous line starting at the number 1 and ending with the letter L. The line has to alternate from the next number in the sequence to the next letter and then again to the next number (1 to A, A to 2, 2 to B, etc.). The person is corrected and helped by the administrator if mistakes or confusion occurs. Not completing the test within 3 minutes indicates a higher chance of being in a car accident or displaying poor performance on a driving test.

2.4 DATA COLLECTION PROCEDURES

2.3.4 AD Subject Data Collection

All patients and caregivers enrolled in the study were required to read and sign an Informed Consent approved by the University of Tennessee Graduate School of Medicine Institutional Review Board (IRB #2232) (Appendix C). The questionnaires administered to each patient enrolled in the 43-item part of the study were the 43-Item CAS-AD,

MMSE, and GDS. The caregiver was only asked to complete the caregiver version of the CAS-AD. The questionnaires administered to each patient enrolled in the 10-item part of the study were the 10-item CAS-AD, MMSE, GDS, CDT-8, and TMT-B. The caregiver also filled out the ZCBS and the caregiver version of the CAS-AD. The MMSE, GDS, TMT-B, CDT-8, and ZCBS were administered as part of the patient's normal visit to the Cole Neuroscience Center. The questionnaires are routinely administered to the majority of the patients seen at the clinic. The MMSE and TMT-B were required to be administered by staff at the Cole Neuroscience Center, while the GDS, CDT-8, and ZCBS did not require any supervision by staff members. All questionnaires were scored by the Cole Neuroscience staff or research assistants, except for the CAS-AD which was scored using command syntax written in SPSS v16. The scores from the MMSE, GDS, ZCBS, CDT-8, and TMT-B were recorded on a top sheet and attached to the patient's and caregiver's completed CAS-AD questionnaires. All data collected was entered into SPSS v16 where each subject was given a unique identifier to maintain subject privacy.

2.4.1 Normal Subject Data Collection

All normal subjects and caregivers enrolled in the study were required to read and sign an Informed Consent approved by the University of Tennessee Graduate School of Medicine Institutional Review Board (IRB #2232) (Appendix C). The questionnaires administered to each subject enrolled in the MMSE and the 10-item CAS-AD. The MMSE were required to be administered by investigators at the Cole Neuroscience Center and University of Tennessee Sleep Center. All questionnaires were scored by the Cole Neuroscience staff or research assistants, except for the CAS-AD which was scored

Common Changes in Mild AD	Common Changes in Moderate AD	Common Changes in Severe AD
• Loses spark or zest for life - does not start anything. • Loses recent memory without a change in appearance or casual conversation. • Loses judgment about money. • Has difficulty with new learning and making new memories. • Has trouble finding words - may substitute or make up words that sound like or mean something like the forgotten word. • May stop talking to avoid making mistakes. • Has shorter attention span and less motivation to stay with an activity. • Easily loses way going to familiar places. • Resists change or new things. • Has trouble organizing and thinking logically. • Asks repetitive questions. • Withdraws, loses interest, is irritable, not as sensitive to others' feelings, uncharacteristically angry when frustrated or tired. • Won't make decisions. For example, when asked what she wants to eat, says "I'll have what she is having." • Takes longer to do routine chores and becomes upset if rushed or if something unexpected happens. • Forgets to pay, pays too much, or forgets how to pay - may hand the checkout person a wallet instead of the correct amount of money. • Forgets to eat, eats only one kind of food, or eats constantly. • Loses or misplaces things by hiding them in odd places or forgets where things go, such as putting clothes in the dishwasher. • Constantly checks, searches or hoards things of no value.	• Changes in behavior, concern for appearance, hygiene, and sleep become more noticeable. • Mixes up identity of people, such as thinking a son is a brother or that a wife is a stranger. • Poor judgment creates safety issues when left alone - may wander and risk exposure, poisoning, falls, self-neglect or exploitation. • Has trouble recognizing familiar people and own objects; may take things that belong to others. • Continuously repeats stories, favorite words, statements, or motions like tearing tissues. • Has restless, repetitive movements in late afternoon or evening, such as pacing, trying doorknobs, fingering draperies. • Cannot organize thoughts or follow logical explanations. • Has trouble following written notes or completing tasks. • Makes up stories to fill in gaps in memory. For example might say, "Mama will come for me when she gets off work." • May be able to read but cannot formulate the correct response to a written request. • May accuse, threaten, curse, fidget or behave inappropriately, such as kicking, hitting, biting, screaming or grabbing. • May become sloppy or forget manners. • May see, hear, smell, or taste things that are not there. • May accuse spouse of an affair or family members of stealing. • Naps frequently or awakens at night believing it is time to go to work. • Has more difficulty positioning the body to use the toilet or sit in a chair. • May think mirror image is following him or television story is happening to her. • Needs help finding the toilet, using the shower, remembering to drink, and dressing for the weather or occasion. • Exhibits inappropriate sexual behavior, such as mistaking another individual for a spouse. Forgets what is private behavior, and may disrobe or masturbate in public.	• Doesn't recognize self or close family. • Speaks in gibberish, is mute, or is difficult to understand. • May refuse to eat, chokes, or forgets to swallow. • May repetitively cry out, pat or touch everything. • Loses control of bowel and bladder. • Loses weight and skin becomes thin and tears easily. • May look uncomfortable or cry out when transferred or touched. • Forgets how to walk or is too unsteady or weak to stand alone. • May have seizures, frequent infections, falls. • May groan, scream or mumble loudly. • Sleeps more. • Needs total assistance for all activities of daily living.

Fig 2. Caring for People with Alzheimer's Disease: A Manual for Facility Staff
(Gwyther, 2001)

using command syntax written in SPSS v16. All data collected was entered into SPSS v16 where each subject was given a unique identifier to maintain subject privacy.

2.5 CAS-AD Development

2.5.1 43-Item CAS-AD Development

Two Physicians and 2 Research Associates with Masters in Experimental Psychology developed the initial 43-item questionnaire. Item topics where based on the observations of investigators while seeing patients at the Cole Neuroscience Center's Alzheimer's clinic and adapted from a list of symptoms cited in *Caring for People with Alzheimer's Disease: A Manual for Facility Staff* (Gwyther, 2001) (Fig. 2). The symptoms listed by Gwyther have been accepted by the National Institute of Aging (2007). Items created for the questionnaire were designed to reflect a broad range of symptoms observed throughout the course of the disease.

The patient questionnaire had a seven page format. The caregiver questionnaire had the same items as the patient form; however questions were reworded to ask about the patient. Answers to items were closed ended using a 5-response Likert scale. The possible responses were "Never", "Almost Never", "Sometimes", "Almost Always", and "Always". A response header was printed at the top and bottom of the page to remind patients and caregivers of the 5 possible responses.

Administrators were asked to note recurring misunderstandings, confusion, or frustrations with items with the first 30 patients and caregivers who completed the questionnaire. Those items were reviewed and modified by the investigators, and the questionnaire was updated to reflect any changes. An example would be "I often wander

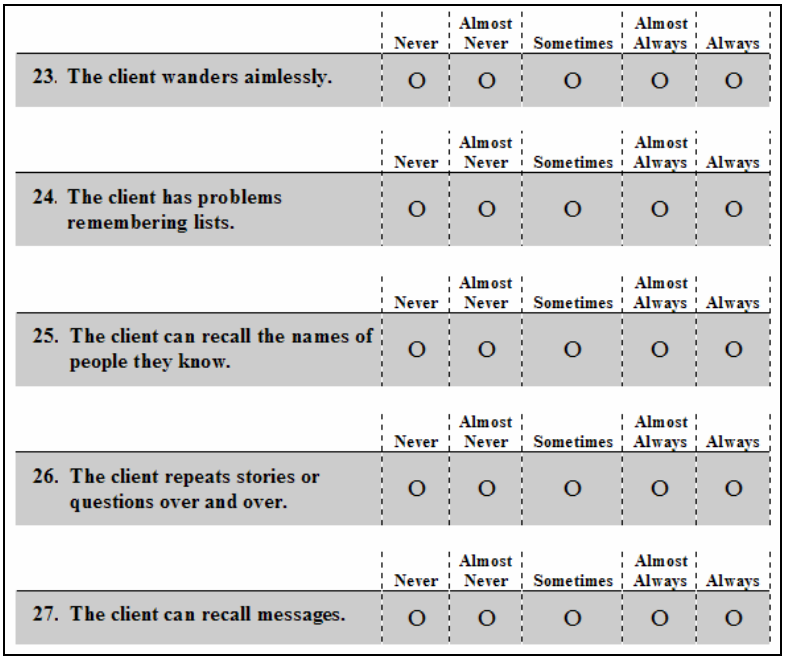
Questions:	Never	Almost Never	Sometimes	Almost Always	Always
1. I am able to do house cleaning or chores.	O	O	O	O	O
2. I enjoy performing my favorite activities.	O	O	O	O	O
3. I can remember the dates of important events.	O	O	O	O	O
4. I can recall lists of items.	O	O	O	O	O
5. I can follow story lines or movie plots.	O	O	O	O	O

Fig 3. Portion of Original 43-Item Questionnaire Layout

without any purpose". A number of patients loosely interpreted the question to mean "to wander about with nothing to do" so the question was reworded to "I wander aimlessly" which prevented any further confusion reported.

While administering the 43-item questionnaire, administrators also uncovered a visuospatial problem with some AD patients not being able to correctly line up items to the matching response line (Fig 3). To correct for the problem the questionnaire was reformatted by placing a response header over every item and separating each header/item with white space (Fig 4). This made it easier for participants to line up the items with corresponding responses; however, it also caused the questionnaire to be expanded to from 4 to 7 pages.

Once modifications were complete the questionnaire was administered to 23 new patients who completed the questionnaire without assistance of an administrator. The first 30 patients used for the development of the questionnaire were not included in the



	Never	Almost Never	Sometimes	Almost Always	Always
23. The client wanders aimlessly.	O	O	O	O	O
24. The client has problems remembering lists.	O	O	O	O	O
25. The client can recall the names of people they know.	O	O	O	O	O
26. The client repeats stories or questions over and over.	O	O	O	O	O
27. The client can recall messages.	O	O	O	O	O

Fig 4. Portion of Revised 43-Item Questionnaire Layout

data analysis since the format of the questionnaire differed from that administered to patients enrolled after changes in the questionnaire format.

2.5.2 Scoring the 43-Item CAS-AD

The 43-Item CAS-AD was scored by assigning a value of 1 to 5 respectively to each item response ("Never", "Almost Never", "Sometimes", "Almost Always", and "Always"). The absolute value of each patient's item response score minus the caregiver's item response score was totaled. For the 43-Item scale the resulting score was divided by 43 for a result of 0 to 4.

2.5.3 10-Item CAS-AD Development

When sufficient data was collected the questionnaire's internal reliability was determined using Cronbach's-alpha and item reduction of the 43-tiem questionnaire was performed.

2.5.4 Scoring for the Administration of 10-Item CAS-AD to AD Subjects

For the 10-Item questionnaire the sum of the item scores were not divided by 10. This resulted in a score of 0 to 40. The reason for using a different scoring method was to allow for a score consisting of integers which are easily interpretable by individuals in a clinic setting.

2.6 Statistical Analysis

All independent t-test were 2-tailed and used an alpha of 0.05. A distribution would be considered normal if the skewness and kurtosis fell between the range of ±2 (George & Mallery, 2003).

2.6.1 Descriptive Statistics of 43-Item CAS-AD Administered to Preliminary AD Subjects

Descriptive statistics were performed on the patient's gender and age. The patients were then divided into two groups by gender, and descriptive statistics for age were obtained, as well as skewness and kurtosis to determine if the ages of each gender were normally distributed. An independent t-test was used to determine if the ages between genders were significantly different. A Leven's Test of Equality of Variance was used to determine if the age between genders were similar (Levene, 1960).

Descriptive statistics were performed on the 43-item questionnaire score for the total group and for each gender. The descriptive statistics contained skewness and kurtosis to determine if the scores were distributed normally. A Leven's Test was used to test the Equality of Variance of scores between genders and an independent t-test was used to determine whether scores between genders were statistically different.

2.6.2 43-Item CAS-AD Reduction Analysis

Cronbach's-alpha was used to determine the internal reliability of the questionnaire. The analysis was then used to remove items from the questionnaire with the goal of having a 10-item questionnaire displaying Cronbach's-alpha between 0.8 and 0.9. Items were removed one at a time if their removal would keep the remaining items Cronbach-alpha as close to 0.9 as possible. If there were two or more items whose removal would result in the same Cronbach's-alpha, the investigators removed the item which was perceived as the least important to the content validity of the questionnaire. The removal process was continued until only 10 items remained. The resulting 10 items were rescored using the method described for the 43-item questionnaire and a Pearson's correlation coefficient (Rodgers, & Nicewander, 1988) was obtained to determine how well the scores of the 43-item and 10-item questionnaire relate.

2.6.3 Descriptive Statistics for the Administration of 10-Item CAS-AD to AD Subjects

Descriptive statistics were performed on the patient's gender and age. The patients were then divided into two groups by gender, and descriptive statistics for age were obtained, as well as skewness and kurtosis to determine if the ages of each gender

were normally distributed. An independent t-test was used to determine if the ages between genders were significantly different. A Leven's Test of Equality of Variance was used to determine if the age between genders were similar.

Descriptive statistics were performed on the 10-item questionnaire score for the total group and for each gender. The descriptive statistics contained skewness and kurtosis to determine if the scores were distributed normally. A Leven's Test was used to test the Equality of Variance of scores between genders and an independent t-test was used to determine whether scores between genders were statistically different.

Reliability of the 10-item questionnaire was determined using three different statistical methods. A Cronbach's-alpha was performed to determine the internal reliability of the questionnaire. A Pearson's-r correlation coefficient was used to determine test-retest reliability of the questionnaire and a One-way Intraclass Coefficient (ICC) (Koch, 1982) was used to determine inter-rater agreement. A split-half reliability analysis was use to obtain a spearman-brown coefficient for equal length parts (Brown, 1910); (Spearman, 1910).

Descriptive statistics for the MMSE, GDS, CDT-8, TMT-B, and ZCBS were determined for the patient population and the population divided by gender. A Pearson's-r was used to determine if significant correlations exist between afore mentioned questionnaires and the 10-item questionnaire score for the patient population total and by gender. A 2-tailed independent t-test was performed for each questionnaire to determine if any significant difference existed between genders.

2.6.4 Descriptive Statistics for the Administration of 10-Item Questionnaire to Normal Subjects

The statistical process used in section 2.6.1 was used to analyze the group of normal subjects enrolled for the 10-item administration of the questionnaire. A 2-tail independent t-test was performed for ages between the AD patients and normals who took the 10-Item questionnaire to make sure the groups were of similar age (de Leonni Stanonik, et al., 2005).

2.6.5 Analysis of AD Subjects with and without anosognosia based on Administered 10-item CAS-AD

A cutoff score for the 10-Item CAS-AD was determined to define anosognosia among AD patients. The cutoff score was calculated as 2 SD above the mean of the normal population. The 10-item AD group was divided into two groups; those without and with anosognosia. A one-tail independent t-test was performed to determine if any significantly lower mean score on the TMT-B existed for the group with anosognosia.

3. RESULTS

3.1 Descriptive Statistics of 43-Item CAS-AD Administered to Preliminary AD Subjects

One-hundred and six Alzheimer patients who met the inclusion criteria were enrolled in the study. Thirty-nine were excluded due to incomplete questionnaires with the final number being 67 (age: u = 72.66, SD = 3.40), with 41 females (age: u = 72.39, SD = 4.58) and 26 males (age: u = 73.08, SD = 4.14). The age between genders showed no significant difference existing ($t(65)$ = 0.537, p = 0.593) (Table 4).

The 43-Item Questionnaire score for the population had a mean of 0.87 (SD = 0.42) with the mean score for females being .87 (SD = 0.42) and males .87 (SD = 0.36). Since the kurtosis of the scores for females was 2.68 (female: median = 0.76, range =

Table 4. 43-Item Subject Statistics

43-Item Subjects						
Age	*n*	*u*	*SD*	*df*	*t*	*p*
Total	67	72.66	3.40			
Female	41	72.39	4.58			
Male	26	73.08	4.14			
t-test * gender				65	0.537	0.593

Questionnaire Scores	*n*	*u*	*SD*	*df*	*t*	*p*
Total	67	.871	.420			
Female	41	.873	.420			
Male	26	.867	.358			
t-test * gender				65	0.142	0.887

Table 5. 43-Item Subjects Statistics with 10-Item Scoring

43-Item Subjects with 10-Item Scoring						
Questionnaire Scores	*n*	*u*	*SD*	*df*	*t*	*p*
Total	67	1.199	.631			
Female	41	1.129	.636			
Male	26	1.050	.631			
t-test * gender				65	-0.498	0.620

Table 6. 10-Items After Item Reduction

10-Item Questionnaire	Corrected Item Total Correlation
1. I am able to do house cleaning or chores.	.385
2. I enjoy performing my favorite activities.	.546
3. I can remember the dates of important events.	.714
4. I can recall lists of items.	.728
5. I can follow story lines or movie plots.	.474
6. I am able to make accurate plans about future events (birthdays, vacation, anniversaries, etc).	.647
7. I always remember appointments.	.663
8. I find it easy to create and write down lists.	.581
9. I know where I place items around the house.	.539
10. I always know where I placed my keys, wallet, or pocketbook.	.533

2.10; male: median = 0.81, range = 1.36) the scores were transformed using log10 to create a normal distribution. The females mean was -0.10 (*SD* = 0.20) and males -0.10 (*SD* = 0.18). Using the transformed scores between genders equal no significant difference was found (*t(65)* = 0.142, *p* = 0.887).

3.2 43-Item CAS-AD Reduction Analysis

The 43-item questionnaire had a Cronbach's-alpha of 0.89 was obtained showing the questionnaire had excellent internal reliability. The 10-Items left after reduction were scored using the sum of item scores divided by 10. The mean score was 1.10 (*SD* = 0.63) with the mean score for females being 1.13 (*SD* = 0.64) and males 1.05 (*SD* =0.63). The 10-item scores between genders showed no significant difference (*t(65)* = -0.498, *p* = 0.620) (Table 5). The reduction of the questionnaire to 10-items produced a Cronbach's-alpha of 0.84 (Table 6). A significantly high correlation (*r* =0.90, *p* < 0.000) was found when the final 10 items identified were rescored and compared to the original 43-item questionnaire scores.

3.3 The Administration of 10-Item CAS-AD to AD Subjects

Of the eighty-four new AD patients enrolled in the second phase of the study using the 10-item questionnaire; one patient dropped out citing privacy concerns (Table 7). The total number of patients used was 83 (age: *u* = 75.53, *SD* = 3.83), with 58 females (age: *u* = 75.21, *SD* = 3.80) and 25 males (age: *u* = 76.28, *SD* = 3.89). The patients age between genders showed no significant (*t(81)* = -1.176, *p* = 0.243). The mean 10-item score was 12.94 (*SD* = 6.94), with females mean score of 12.81 (*SD* =

7.21) and males 13.24 (*SD* = 6.39). The scores between genders showed no significant difference (*t(81)* = -0.257, *p* = 0.798).

Internal reliability of the new questionnaire remained high with an obtained Cronbach's-alpha of 0.87 (Table 6). Nineteen of the 83 patients who each had 2 caregivers acting as informants were used to determine the inter-rater agreement. The ICC single measure alpha was 0.63 ($p < 0.000$). Twenty-one of the 83 patients were used to evaluate the test-retest over time using scores from initial enrollment and 3 month follow up visit. Results showed a significantly high correlation ($r = 0.70$, $p < 0.000$). Using the 83 patients split-half reliability was found to be significantly high ($n = 83$, $r = 0.86$, $p < 0.000$).

For the patient population the mean for the MMSE (*u* = 21.30, *SD* = 2.59), GDS (*u* =6.29, *SD* = 4.93), CDT-8 (*u* = 5.12, *SD* = 2.58), and ZCBS (*u* = 29.37, *SD* = 17.36) Mean scores for the questionnaires were obtained for females (MMSE: *u* = 21.10, *SD* = 2.75; GDS: *u* = 6.41, *SD* = 5.29; CDT-8: *u* = 4.83, *SD* = 3.32; ZCBS: *u* = 28.12, *SD* = 16.61), and males (MMSE: *u* = 21.76, *SD* = 2.17; GDS: *u* = 6.00, *SD* = 4.03; CDT-8: *u* = 32.28, *SD* = 3.81; ZCBS: *u* = 5.80, *SD* = 2.63).

A significant differences was not found among male and female study patients for any of the questionnaires (MMSE: *t(81)* = -1.06, *p* = 0.292; GDS: *t(81)* = 0.35, *p* > 0.728; CDT-8: *t(81)* = -1.00, *p* > 0.320; ZCBS: *t(81)* = -1.59, *p* > 0.116). Correlations between the sample population 10-item questionnaire score and the MMSE ($r = -0.24$, $p = 0.032$), and GDS ($r = -0.30$, $p = 0.006$) were significant though weak, where the

Table 7. 10-Item Statistics: Administration to AD Subjects

Instrument Statistics for 10-Item Administration to AD Subjects
(n = 83, Females = 58, Male = 25)

Descriptive Statistic for Instruments								
	MMSE		GDS		CDT-8		ZCBS	
	u	*SD*	*u*	*SD*	*u*	*SD*	*u*	*SD*
Total	21.30	2.59	6.29	4.93	5.12	2.58	29.27	17.36
Female	21.10	2.75	6.41	5.29	4.83	3.32	28.12	16.61
Male	21.76	2.17	6.00	4.03	3.28	3.81	5.80	2.63

Independent t-test								
	MMSE		GDS		CDT-8		ZCBS	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*
By gender	-1.06	0.292	0.35	0.728	-1.00	0.320	-1.59	0.116

Pearson's r Correlation 10-Item Questionnaire Score * Instruments								
	MMSE		GDS		CDT-8		ZCBS	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Total	-0.24	0.032	-0.30	0.006	-0.04	0.743	0.04	0.699

correlation with the CDT-8 (r = -0.04, p = 0.743), and ZCBS (r = 0.04, p = 0.699) showed no significance (Table 7).

3.4 Descriptive Statistics for the Administration of 10-Item CAS-AD to Normal Subjects

There were 43 normal subjects enrolled in the study (age: u = 73.95, SD = 3.90) with 23 females (age: u = 73.83, SD = 4.23) and 20 males (u = 74.10, SD = 3.60). Age between genders showed no significant difference ($t(41)$ = 0.227, p = 0.822) (Table 8). The mean MMSE score for the sample population was 29.67 (SD = 0.75). The distribution does not have a normal curve, however this is expected since the MMSE scores of the normal population are expected to not have adequate variance. The age between the AD Patients administered the 10-item questionnaire and normal subjects showed no significant

Table 8. Normal Subject Statistics

Normal Subject						
Age	*n*	*u*	*SD*	*df*	*t*	*p*
Total	43	73.95	3.90			
Female	23	73.83	4.23			
Male	20	74.10	3.60			
t-test * gender				41	0.227	0.822

Questionnaire Scores	*n*	*u*	*SD*	*df*	*t*	*p*
Total	43	7.19	2.22			
Female	23	7.26	2.24			
Male	20	7.10	2.25			
t-test * gender				41	-0.235	0.816

Table 9. Statistics for Patients Defined With and Without Anosognosia

Statistics for Patients Defined With and Without Anosognosia
(n = 83, Females = 58, Male = 25)

Age	*u*	*SD*	*df*	*t*	*p*
Without	74.23	8.05			
With	77.41	7.72			
t-test * without/with			81	-1.839	0.070

Descriptive Statistic for Instruments								
	MMSE		GDS		CDT-8		ZCBS	
	u	*SD*	*u*	*SD*	*u*	*SD*	*u*	*SD*
Without	21.46	2.51	7.54	5.70	5.00	2.48	28.95	18.01
With	21.14	2.68	5.12	3.78	5.19	2.70	31.12	17.26

Independent t-test								
	MMSE		GDS		CDT-8		ZCBS	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*
t-test * without/with	0.562	0.576	2.273	0.026	-0.335	0.738	-0.560	.577

difference in age. The ages between groups had unequal variance ($F = 15.330$, $p < 0.000$), with the t-test result for unequal variance showing significant difference in age between groups ($t(123.68) = 1.778$, $p = 0.078$). The mean CAS-AD score for the normal subjects was 7.19 ($SD = 2.22$) with females having a mean of 7.26 ($SD = 2.24$) and males 7.10 ($SD = 2.25$). No significant difference in scores was found when comparing between gender ($t(41) = -0.235$, $p = 0.816$).

3.5 Analysis of AD Subjects with and without anosognosia based on Administered 10-item CAS-AD

Using the mean and SD of the normal subjects a cutoff score to define anosognosia was determined to be 12. There were 41 (49%) patients who did not fit the definition for anosognosia (age: $u = 74.23$, $SD = 8.05$) and 42 (51%) with anosognosia (age: $u = 77.41$, $SD = 7.73$). The age between the groups with and without anosognosia showed no significant difference ($t(81) = -1.839$, $p = 0.070$) (Table 9).

For patients without anosognosia the mean score for the MMSE was 21.46 ($SD = 2.51$), GDS was 7.54 ($SD = 7.54$), ZCBS was 28.95 ($SD = 18.01$), and CDT-8 was 5.00 ($SD = 2.48$). For patients with anosognosia the mean score for the MMSE was 21.14 ($SD = 2.68$), GDS was 5.12 ($SD = 3.78$), ZCBS was 31.12 ($SD = 17.26$), and CDT-8 was 5.19 ($SD = 2.70$).

Unequal variance was found between patient groups with and without anosognosia for GDS scores ($F = 7.657$, $p = 0.007$). Patients without anosognosia had a significantly greater GDS score then patients without anosognosia ($t(69.24) = 2.273$, $p = 0.026$). The MMSE (($t(81) = 0.562$, $p = 0.576$), ZCBS (($t(81) = -0.560$, $p = .577$), and CDT-8 (($t(81)$

Table 10. Statistics for TMT-B Grouped by With and Without Anosognosia

Statistics for TMT-B (With and Without Anosognosia)
(n = 22, without = 10, with = 12)

Age	*u*	*SD*	*df*	*t*	*p*
Without	74.00	6.37			
With	77.33	8.55			
t-test * without/with			20	-1.018	0.321

TMT-B	*u*	*SD*	*df*	*t*	*p*
Without	16.67	5.55			
With	14.70	5.95			
t-test * without/with			20	-0.802	0.432

= -0.335, $p = 0.738$) showed no significant differences in mean scores between patients with and without anosognosia.

There were 22 patients willing to complete the TMT-B, ten of which did not meet the criteria for anosognosia (Table 10). Ten were without anosognosia (age: $u = 74.00$, $SD = 6.37$) and 12 with (age: $u = 77.33$, $SD = 8.55$). Age between patients with and without anosognosia showed no significant difference ($t(20) = -1.018$, $p = 0.321$). The mean scores for the TMT-B for patients without anosognosia was 16.67 ($SD = 5.55$) and with was 14.70 ($SD = 5.95$) with no significant difference existing ($t(20) = -0.802$, $p = 0.432$).

4. DISCUSSION

4.1 43-Item CAS-AD

The CAS-AD was begun in 2001 as a companion questionnaire for an fMRI imaging investigation into the possible role the anterior cingulate cortex (ACC) plays in the area of attention and self awareness (Stanonik, 2002). The study consisted of normal controls and AD patients. The AD patients were further divided into with and without anosognosia groups using the 43-Item CAS-AD with a cutoff point of 1. Anosognosia was used as a means of distinguishing subjects who had a deficit of self awareness and the MRI images obtained were analyzed to determine if the ACC activation was significantly different in the Anosognosia subject when compared to the other groups (the study found a significant hypoactivation in the anosognosia group).

At the time of the 2001 study a questionnaire called the Anosognosia Questionnaire for Dementia (AD-Q) (Migliorelli et al., 1995) was going to be used which had been developed for an fMRI study performed in Argentina. After reviewing the material there was concern with problems in translation of the questions since every item was preceded with the negative sounding phrase “Do you have problems”. This concern prompted the investigators to administer the questionnaire to several patients to evaluate how individual’s felt about the questions. It was concluded by the investigators that the patients were feeling potential levels of anxiety due to the questionnaire’s wording and it was the desire of the investigators to minimize as much stress as possible. The investigators decided not to use the AD-Q and instead create a questionnaire for use in the study with specific care taken to make it as minimally evasive as possible.

4.2 Subject Selection for 43-Item and 10-Item CAS-AD

The inclusion and exclusion criteria for the study were a carry over of the original 2001 fMRI study. Due to the nature of the study, the criteria were more rigid than necessary for the psychometric testing and should have been changed in order to include a more culturally diverse group of subjects. The removal of the MMSE score requirements and whether the patient had past psychological disorders would have allowed for the study to be generalized to a larger AD population and increase the statistical power of the study, though it would have added numerous confounding variables.

Another limiting factor to the number of individuals included in the study was the active clinic setting where the data was collected. Data collection occurred during patient visits to the office which limited the time available to administer questionnaires not specific to a patient's visit. The Cole Neuroscience Center does not have a diverse socio-economic or minority population. The current study's population exclusively contained Caucasians. Both of these factors put into question the validity of the questionnaire in the general population, though the simplicity of the questionnaire's items should allow it to span across ethnic groups and education levels.

4.3 43-Item CAS-AD

The items used were meant to capture a broad spectrum of symptoms seen throughout the 3 stages of the AD Mild, Moderate, and Severe. The item creation method used could bring into question the face validity of the questionnaire. Another method would have been to poll the caregiver population to determine common recurring

symptoms and concerns (Streiner & Norman, 1995). To perform data collection in the following manner would have required additional time which was not conducive to the time constraints of the initial ACC study. Nevertheless, the items came from reliable sources and are believed to have adequately reflected common caregiver observations. In order to show internal reliability a Cronbach's-alpha between 0.8 and 0.9 is desired (George & Mallery, 2003). The internal reliability of the questionnaire was high (r = 0.89) showing a significant degree of association between the items.

Though the 43-Item questionnaire could be used on its own, it was the intention of the investigators to create a more accessible 10-Item scale for both research and clinical settings. The significantly strong correlation (r = 0.90) between the 43-tiem and 10-item version of the instrument demonstrates the shorter version is as reliable as its longer version. This allows the shorter version to be ideal for setting where it is important for a questionnaire to be administered in a timely manner.

4.4 10-Item CAS-AD

After being administered to a new sample AD patients the internal reliability of the 10-Item questionnaire remained high (cronbach's-alpha = 0.87) showing the items related well to each other while maintaining adequate variability. The questionnaire allows for anosognosia to be measured in two different ways. First, the score can be used as a measurement of the degree of anosognosia on a continuum. Second, the questionnaire can be used to diagnose anosognosia in the AD patient by using the cutoff score of 12.

As expected, when using the entire sample population there was a statistically

significant, but small correlations found between the total 10-Item CAS-AD and the MMSE (r = -0.24, $p < 0.05$) or GDS (r = -0.30, $p < 0.05$). Though some prior research has shown anosognosia to have a high correlation with cognitive decline and depression (but not necessarily with both together)(Sevush & Leve, 1993), it is believed that anosognosia is its own unique phenomena which is not related to degree of dementia or depression ((Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991); (Reed, Jagust, & Coulter, 1993). The low correlation adds credence to this hypothesis.

To asses the stress associated with caregivers a correlation of the ZCBS was performed using the 10-Item questionnaire AD population with no significant correlation being found (r = -0.04, p = 0.699). The opposite results were expected with caregiver stress increasing as the severity of anosognosia increased. It is expected that the results may be a function of the inclusion criteria using the MMSE score. Excluded from the study were patients with more severe dementia. It is hypothesized caregivers of subjects with more pronounced dementia may increase the mean of the stress for the group with anosognosia and a significant difference would be found. Furthermore, it uncertain if the high level of social work intervention provided at Cole Neuroscience Center may be adding a confounding variable in regard to caregiver stress.

4.5 Inter-rater and Test-retest Reliability of 10-Item CAS-AD

The resulting ICC for the questionnaire was high (r = 0.63, $p < 0.05$), but a result greater then 0.70 is desired. Though not as high as hoped for it is considered to be satisfactory given the nature of the caregivers which are being used in the study. AD patients who attended the clinic with more then one caregiver would have a spouse and a

child with them. The varying contact the caregivers might have with the patient is a confounding factor which could have caused a discrepancy, there by lowering the ICC result.

Results of test-retest analysis among patients yielded a Pearson-r correlation of 0.70 ($p < 0.000$). Like the ICC, this is not as high as would be desired, but good enough to be able to say with confidence that the questionnaire was reliable when administered over time. The target period used was 3 months; however one of the factors which could not be accounted for was the use of pharmaceutical medication during the test-retest period which may increase or maintain a patient's cognitive ability. Though denying drug therapy would be the best way to perform test-retest reliability, it would be unethical to deny treatment.

4.5 AD Subjects with and without anosognosia as Diagnosed by 10-Item CAS-AD

There was no significant difference in age between the AD subjects and normals who took the 10-Item questionnaire ($t(123.68) = 1.78$, $p > 0.05$) which increases the confidence that the normal group appropriately reflected the ages of AD group and allowed for the setting of the cutoff score based on the normals mean and SD (de Leonni Stanonik, et al., 2005).

Fifty-one percent of the AD subjects had anosognosia ($n = 42$) when using the cutoff score of 12. The prevalence of anosognosia among study patients is approximately midway between the reported numbers of 20% to 75% (Migliorelli, et al., 1995); (Antoine, Antoine, Guermonprez, & Frigard, 2004)

Depression scores between AD subjects with and without anosognosia showed

that subjects with anosognosia had a significantly lower level of depression ($t(69.24) = 2.27$, $p < 0.05$). The result was unexpected, but it does show that anosognosia may have a relationship with the levels of patient depression, stressing the importance of the low, but significant correlation between depression scores and the 10-item score of the 83 AD subjects.

Driving

Driving is one of the activities essential to the independent life style of most individuals today. There is a noticeable decrease in driving skill as people age and the effects are worsened with the advent of dementia (U.S. Department of Transportation, 2000). Even though in mild AD patients there is still an ability to control vehicles, they are at increased risk of getting lost, making incorrect turns, and causing at-fault errors on driving simulation tasks (Uc, Rizzo, Anderson, Shi, & Dawson, 2004).

It is important in the management of an AD patient to limit, or even better, cease driving. Since driving is so empowering to an individual's sense of independence it often becomes difficult to get compliance (Steven W Anderson, Rizzo, Shi, Uc, & Dawson, 2005). Research by Freund and associates (2005) showed elderly drivers without dementia who considered themselves better than other drivers their age were over four times more likely to be unsafe drivers when compared to those who rate themselves as being comparable to or worse than other drivers of their age. Freund specifically points out the problem in determining why the unsafe drivers may over rate their abilities. Though a lack of awareness was mentioned the study was not designed to determine anosognosia was a factor. Nevertheless, even though the subjects of the study did not

have AD or other dementias, it still manages to underscore the importance of AD patients ceasing driving activities.

Important for caregivers to understand is anosognosia does not relieve the patient or their estate of legal liability in the event of a driving accident. In every state public policy forces persons with disabilities to pay for damage they do if they "are to live in the world." The policy clearly indicates how a lack of awareness of driving ability does not break the chain of causation in a liability suite, thereby causing eliminating anosognosia as a valid defense.

The CDT-8 and TMT-B are used to measure driver safety with low scores in both indicating decreased driver ability. Using the entire study sample, the CDT-8 showed no slightly negative, non-significant correlation to the anosognosia scores (r = -0.04, p > 0.05). The t-tests comparing AD subjects with and without anosognosia on the TMT-B produced no significant results ($t(20)$ = 0.43, p > 0.05), though the sample size used for the test was relatively small (with anosognosia: n = 10, u = 14.70, SD = 5.945; without anosognosia: n = 12, u = 16.67, SD = 5.549).

The low negative correlation with the MMSE and the 10-item questionnaire scores administered to AD patients might mean anosognosia occurs independently of cognitive decline which would make the CDT-8 and TMT-B results expected. Further research would need to be performed with more sensitive testing, such as a driving simulator. Though the questionnaire could not be used to make any definitive statement about an AD patient's ability to drive the results would still be beneficial for a clinician to better inform caregivers of the inability of a patient to assess their limitations to drive a

car safely.

4.6 Conclusion

Though anosognosia can be viewed as existing on a continuum it was shown through the use of normal subjects that a cutoff value could be identified. This allows for the scoring of the questionnaire to accurately diagnose a patient as having anosognosia.

The study lacked sufficient sample sizes to come to definitive conclusions about the reliability of the questionnaire. Yet the lack of or significantly low correlations of the 10-item questionnaire scores for the patients (n = 83) with the other questionnaires administered shows the questionnaire is measuring a separate and unique factor associated with AD. Further investigation should include a larger sample size, have greater control over collecting return data and include a greater number of patients with multiple caregivers. In addition, the inclusion/exclusion criteria should be relaxed, allowing for a sample population reflective of most of the population seen at clinics. A comparison of the 43-Item and 10-Item questionnaire would be of interest to determine if questionnaire format has any effect on score outcomes.

The CAS-AD questionnaire is unique since it was designed specifically for the study of patients with AD and not all dementias. It has gone through more rigorous psychometric testing then previous questionnaires. In the past, investigators have developed questionnaires based on the need of an ongoing study and no attempt has been made to assess the reliability or validity of the questionnaire. This situation has resulted in numerous studies that can not be easily compared to one another since it is uncertain if they are measuring the same phenomena. The 10-Item CAS-AD offers investigators a

more accurate way to study AD related anosognosia by using a single reliable questionnaire for diagnosis. The value of the questionnaire within the clinic comes from its ease of administration and the assistance it can give to physicians and social workers in estimating to caregivers the extent of the patient's inability to properly gauge their activities.

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APPENDICES

APPENDIX A: CAS-AD INSTRUMENTS

43-item CAS-AD(P): Patient

CASAD-P

For Study Use: **Date:** _____

Read each question and then mark the circle indicating how you think or feel the question relates to you.

Example #1

	Never	Almost Never	Sometimes	Almost Always	Always
I enjoy reading the paper everyday.	O	O	O	O	O

Example #2

	Never	Almost Never	Sometimes	Almost Always	Always
I wake up early everyday.	O	O	O	O	O

Please turn the page over …

Questions:

	Never	Almost Never	Sometimes	Almost Always	Always
1. I am able to finish a sentence or complete a thought.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
2. I forget the date.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
3. It is easy for me to locate items around the house.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
4. I can remember where I live.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
5. I am able to do house cleaning or chores.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
6. I find it easy to maintain conversations with others.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
7. I enjoy performing my favorite activities.	O	O	O	O	O
	Never	**Almost Never**	**Sometimes**	**Almost Always**	**Always**
8. I often forget where I place items.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
9. I am able to follow instructions.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
10. I bathe or shower regularly.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
11. I can remember the dates of important events.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
12. I am able to tell the time when looking at a clock or watch.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
13. I can recall lists of items.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
14. I am able to get dressed on my own.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
15. I can remember the faces of people I have met in the past.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
16. I am able to follow conversations.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
17. I can follow story lines or movie plots.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
18. I often forget where I live.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
19. I use household items correctly (telephone, TV, radio, etc.).	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
20. I can recognize myself in a mirror.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
21. I am able to make accurate plans about future events (birthdays, vacation, anniversaries, etc).	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
22. I always remember appointments.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
23. I wander aimlessly.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
24. I have problems remembering lists.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
25. I can recall the names of people I know.	O	O	O	O	O
26. I repeat stories or questions over and over.	O	O	O	O	O
27. I can recall messages.	O	O	O	O	O
28. I am able to organize items around the house.	O	O	O	O	O
29. I am able to locate where I live.	O	O	O	O	O
30. I find it easy to create and write down lists.	O	O	O	O	O
31. I can control my bladder.	O	O	O	O	O
32. I know where I place items around the house.	O	O	O	O	O
33. I can drive a car safely.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
34. I can recognize family members.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
35. I cry or laugh inappropriately.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
36. I am able to write notes or letters.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
37. I always know where I placed my keys, wallet, or pocketbook.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
38. I am able to balance my checkbook.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
39. I am able to recognize my home.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
40. I continue to enjoy my hobbies.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
41. I am able to organize items around the house.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
42. I know where my house is located.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
43. I still have an interest in my favorite activities.	O	O	O	O	O

Thank you for completing the questionnaire.

43-Item CAS-AD(C): Informant

CASAD-C

For Study Use: **Date:** _____

Read each question and then mark the circle indicating how you think or feel the question relates to the client.

Example #1

	Never	Almost Never	Sometimes	Almost Always	Always
The client enjoys reading the paper everyday.	O	O	O	O	O

Example #2

	Never	Almost Never	Sometimes	Almost Always	Always
The client wakes up early everyday.	O	O	O	O	O

Please turn the page over …

Questions:

	Never	Almost Never	Sometimes	Almost Always	Always
1. The client is able to finish a sentence or complete a thought.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
2. The client forgets the date.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
3. It is easy for the client to locate items around the house.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
4. The client can remember where they live.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
5. The client is able to do house cleaning or chores.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
6. The client finds it easy to maintain conversations with others.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
7. The client enjoys performing their favorite activities.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
8. The client often forgets where they place items.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
9. The client is able to follow instructions.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
10. The client bathes or showers regularly.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
11. The client can remember the dates of important events.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
12. The client is able to tell the time when looking at a clock or watch.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
13. The client can recall lists of items.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
14. The client is able to get dressed on his/her own.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
15. The client can remember the faces of people they have has met in the past.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
16. The client is able to follow conversations.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
17. The client can follow story lines or movie plots.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
18. The client often forgets where they live.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
19. The client uses household items correctly (telephone, TV, radio, etc.).	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
20. The client can recognize himself/herself in a mirror.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
21. The client is able to make accurate plans about future events (birthdays, vacation, anniversaries, etc).	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
22. The client always remembers appointments.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
23. The client wanders aimlessly.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
24. The client has problems remembering lists.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
25. The client can recall the names of people they know.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
26. The client repeats stories or questions over and over.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
27. The client can recall messages.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
28. The client is able to organize items around the house.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
29. The client is able to locate where they live.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
30. The client finds it easy to create and write down lists.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
31. The client can control their bladder.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
32. The client knows where they place items around the house.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
33. The client can drive a car safely.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
34. The client can recognize family members.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
35. The client cries or laughs inappropriately.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
36. The client is able to write notes or letters.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
37. The client always knows where they placed their keys, wallet, or pocketbook.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
38. The client is able to balance their checkbook.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
39. The client is able to recognize their home.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
40. The client continues to enjoy their hobbies.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
41. The client is able to organize items around the house.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
42. The client knows where their house is located.	O	O	O	O	O

	Never	Almost Never	Sometimes	Almost Always	Always
43. The client still has an interest in their favorite activities.	O	O	O	O	O

Thank you for completing the questionnaire.

10-Item CAS-AD(P): Subject

CASAD-P

Instructions: **Read each question, and then mark the circle indicating how you think or feel the question relates to you. You may answer "Never", "Almost Never", "Sometimes", "Almost Always", or "Always". If you do not normally perform the activity described, answer the question based on "can you do it if you had to."**

Questions:	Never	Almost Never	Sometimes	Almost Always	Always
1. I am able to do house cleaning or chores.	O	O	O	O	O
2. I know where I place items around the house.	O	O	O	O	O
3. I can remember the dates of important events.	O	O	O	O	O
4. I can recall lists of items.	O	O	O	O	O
5. I can follow story lines or movie plots.	O	O	O	O	O
6. I am able to make accurate plans about future events (birthdays, vacation, anniversaries, etc).	O	O	O	O	O
7. I always remember appointments.	O	O	O	O	O
8. I find it easy to create and write down lists.	O	O	O	O	O
9. I enjoy performing my favorite activities.	O	O	O	O	O
10. I always know where I placed my keys, wallet, or pocketbook.	O	O	O	O	O
	Never	Almost Never	Sometimes	Almost Always	Always

Thank you for completing the questionnaire.

10-item CAS-AD(C): Informant

CASAD-C

Instructions: Read each question, and then mark the circle indicating how you think or feel the question relates to the client. You may answer "Never", "Almost Never", "Sometimes", "Almost Always", or "Always". If the client does not normally perform the activity described, answer the question based on "can the client do it if they had to."

Questions:	Never	Almost Never	Sometimes	Almost Always	Always
1. The client is able to do house cleaning or chores.	O	O	O	O	O
2. The client knows where they place items around the house.	O	O	O	O	O
3. The client can remember the dates of important events.	O	O	O	O	O
4. The client can recall lists of items.	O	O	O	O	O
5. The client can follow story lines or movie plots.	O	O	O	O	O
6. The client is able to make accurate plans about future events (birthdays, vacation, anniversaries, etc).	O	O	O	O	O
7. The client always remembers appointments.	O	O	O	O	O
8. The client finds it easy to create and write down lists.	O	O	O	O	O
9. The client enjoys performing their favorite activities.	O	O	O	O	O
10. The client always knows where they have placed their keys, wallet, or pocketbook.	O	O	O	O	O
	Never	Almost Never	Sometimes	Almost Always	Always

What is you relationship with the client (Spouse, Child, etc.) _____

How much contact do you have with the client?

☐ **Everyday** ☐ **Twice-a-week** ☐ **Once-a-week** ☐ **Once-a-month**

Thank you for completing the questionnaire.

APPENDIX B: STANDARD INSTRUMENTS

Mini Mental Status Exam (MMSE)

COGNITIVE CAPACITY SCREENING EXAMINATION

PATIENT NAME: _____ **DATE:** _____

EXAMINER: _____

ORIENTATION SCORE **SCORE**

What is the (year), (season), (month), (date), (day) 5 pts. _____

Where are we: (state), (county), (town), (place), (floor) 5 pts. _____

REGISTRATION

Name three objects: 1 second to say each (hat, car, tree). Then ask the patient all three after you have said them. Give one point for each correct answer. 3 pts. _____
Repeat them until he/she learns all three, count the trials and record. _____

ATTENTION AND CALCULATION

Ask to spell the word "world". Then ask to spell "world" backwards.
d__l__r__o__w__. 1 point for each correct letter. 5 pts. _____

RECALL

Ask for the 3 objects repeated above. 3 pts. _____

LANGUAGE

Name a pencil and a watch. 2 pts. _____

Repeat the following "No ifs, ands, or buts." 1 pt. _____

Follow a three stage command: Take a paper in your right hand, fold it in half, and lay it on the floor. 3 pts. _____
(See Back Page)

Read and obey the following: "Close your eyes." 1 pt. _____

Write a sentence. 1 pt. _____

Copy the design. 1 pt. _____

Reference: MF Folstein, SE Folstein & PR McHugh: "Mini-Mental State." A Practical Method for Grading the Cognitive State of Persons for Clinician. J. Phychiat. Res. 12: 198-198, 1975.

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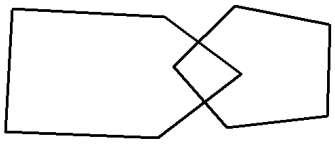
1928 Alcoa Highway
Medical Building B, Suite 102
Knoxville, Tennessee 37920
(865) 544-6740

Close Your Eyes

Write a sentence.

Copy the design.



Geriatric Depression Scale (GDS)

GDS

Name: _____ Date: _____

Think of how you feel towards the following questions. Answer each question by circling one of the answers to the left: "Yes" or "No".

Yes	**No**	Are you basically satisfied with your life?
Yes	No	Have you dropped many of your activities and interests?
Yes	No	Do you feel your life is empty?
Yes	No	Do you often get bored?
Yes	**No**	Are you hopeful about the future?
Yes	No	Are you bothered by thoughts you can't get out of your head?
Yes	**No**	Are you in good spirits most of the time?
Yes	No	Are you afraid that something bad is going to happen to you?
Yes	**No**	Do you feel happy most of the time?
Yes	No	Do you often feel helpless?
Yes	No	Do you often get restless and fidgety?
Yes	No	Do you prefer to stay home at night, rather than go out to do new things?
Yes	No	Do you frequently worry about the future?
Yes	No	Do you feel you have more problems with memory than most people?
Yes	**No**	Do you think it is wonderful to be alive now?
Yes	No	Do you often feel downhearted and blue?
Yes	No	Do you feel pretty worthless the way you are now?
Yes	No	Do you worry a lot about the past?
Yes	**No**	Do you find life very exciting?
Yes	No	Is it hard for you to get started on new projects?
Yes	**No**	Do you feel full of energy?
Yes	No	Do you feel your situation is hopeless?
Yes	No	Do you think that most persons are better off than you are?
Yes	No	Do you frequently get upset over little things?
Yes	No	Do you frequently feel like crying?
Yes	No	Do you have problems concentrating?
Yes	**No**	Do you enjoy getting up in the morning?
Yes	No	Do you prefer to avoid social gatherings?
Yes	**No**	It is easy for you to make decisions?
Yes	**No**	Is your mind as clear as it use to be?

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Zarit's Caregiver Burden Scale (ZCBS)

Caregiver Interview

Patient Name _____ **Caregiver Name** _____

What is you relationship with the Patient (Spouse, Child, etc.) _____

How much contact do you have with the patient?

☐ **Every day** ☐ **Several times a week** ☐ **Once a week** ☐ **Once a month**

Instructions for caregiver: The questions reflect how persons sometimes feel when they are taking care of another person. After each statement, check the circle that best describes how often you feel that way. There is no right or wrong answer.

	Never	Rarely	Sometimes	Quite Frequently	Nearly Always
1. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	O	O	O	O	O
2. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	O	O	O	O	O
3. Do you feel you have lost control of your life since your relative's illness?	O	O	O	O	O
4. Do you feel uncertain about what to do about your relative?	O	O	O	O	O
5. Do you feel you should be doing more for your relative?	O	O	O	O	O
6. Do you feel you could do a better job in caring for your relative?	O	O	O	O	O
7. Overall, how burdened do you feel in caring for your relative?	O	O	O	O	O
8. Do you feel that your relative asks for more help than he/she needs?	O	O	O	O	O
9. Do you feel your relative is dependent on you?	O	O	O	O	O
	Never	Rarely	Sometimes	Quite Frequently	Nearly Always

Please turn page over to complete the questionnaire.

Caregiver Interview

	Never	Rarely	Sometimes	Quite Frequently	Nearly Always
10. Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?	O	O	O	O	O
11. Are you afraid what the future holds for your relative?	O	O	O	O	O
12. Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	O	O	O	O	O
13. Do you feel that you will be unable to take care of your relative much longer?	O	O	O	O	O
14. Do you wish you could leave the care of your relative to someone else?	O	O	O	O	O
15. Do you feel strained when you are around your relative?	O	O	O	O	O
16. Do you feel angry when you are around your relative?	O	O	O	O	O
17. Do you feel embarrassed over your relative's behavior?	O	O	O	O	O
18. Do you feel uncomfortable about having friends over because of your relative?	O	O	O	O	O
19. Do you feel that your social life has suffered because you are caring for your relative?	O	O	O	O	O
20. Do you feel that your relative currently affects your relationships with other family members or friends in a negative way?	O	O	O	O	O
21. Do you feel your health has suffered because of your involvement with your relative?	O	O	O	O	O
22. Do you feel that you don't have as much privacy as you would like because of your relative?	O	O	O	O	O
	Never	Rarely	Sometimes	Quite Frequently	Nearly Always

Self Test II (STII)

SELF TEST II

Name: _____ **Date:** _____

SIDE 1

Instruction #1:

Complete the questions in order. Complete each question before moving onto the next. You may get help with instructions ONLY.

Questions:

1) In the space below, please draw the face of a clock and put the numbers in the correct positions.
Now, draw in the hands at ten minutes after eleven.

2) Remember these words: (take a few minutes to commit them to memory)

Telephone
Police
River

3) Write down the name of **FIFTEEN** animals.

_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____
_____ _____ _____

Instruction #2:

Turn page over and keep it on Side 2.

SIDE 2

Instruction #3:

DO NOT return to Side 1.

Questions:

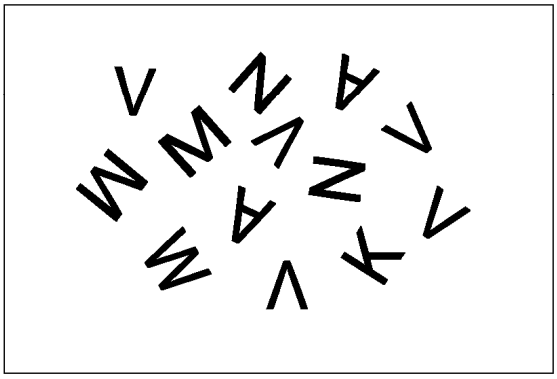
4) What are the three words you were asked to remember?

_____

_____

_____

5) Circle each letter "**V**" in the list of letters below.



6) What is the year? _____

What is the month? _____

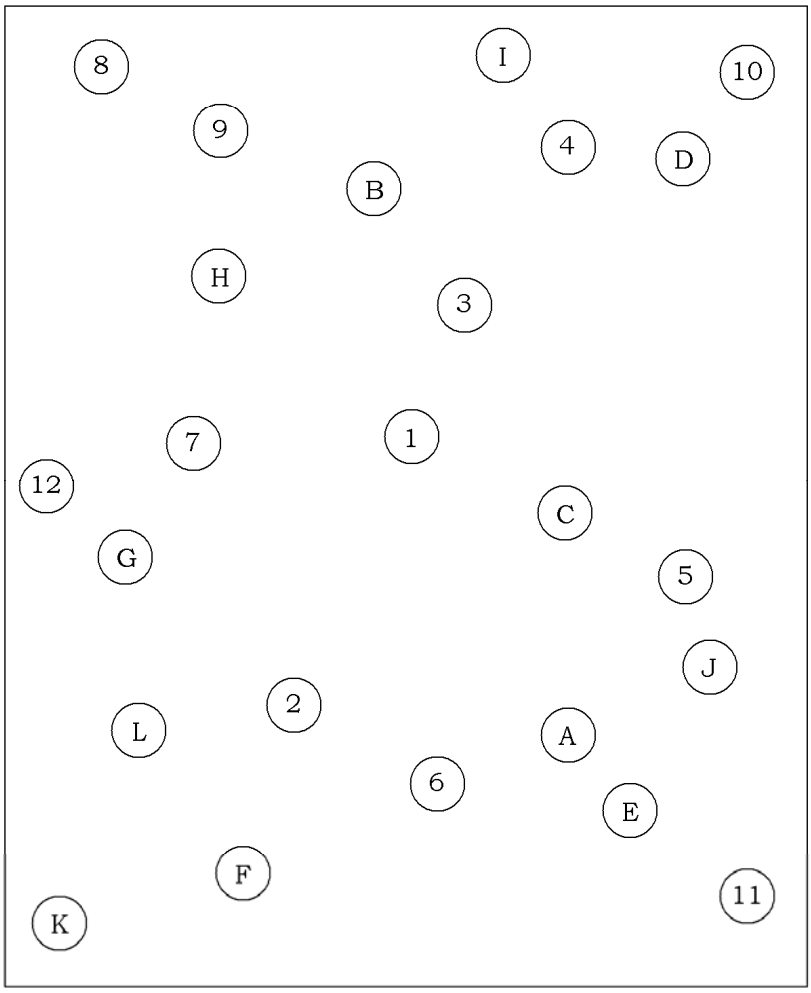
What is the day of the week? _____

Thanks, you are finished!

Trail Making Test – Part B (TMT-B)

Trail-Making Test, Part B

Name: _____ **Date:** _____



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Appendix C: Informed Consent

Alzheimer's Subject

STATEMENT OF INFORMED CONSENT
(Volunteer)
The University of Tennessee Medical Center at Knoxville

Title: Anosognosia Scale Development for Alzheimer's disease (AD) Symptoms.

I have been invited to participate in the above referenced research study. I understand that I will be asked to complete a questionnaire with regards to my daily activities. The nature and purpose of the questionnaire in this study, the risks involved, and the possibilities of complication have been explained to me as follows:

1. The purpose of the inventory is to determine my insight towards activities in my daily life.

2. I understand that I will be administered a 13 question form, the CAS-AD, to determine the awareness of my abilities in short and long-term memory, behavior, and planning. It will take approximately 10 minutes to complete the questionnaire.

3. There will be 240 volunteers enrolled in the study. The study does not have a defined length. During later visits I may be asked to complete further questionnaires, however I do have the right to refuse.

4. Otherwise, access to my records will be limited to principal investigators (Charles Angelo Licata, Dr. John Dougherty), or their assistants, such as the Cole Neuroscience Center's staff. Names will be provided to the UTMCK Institutional Review Board at a later time when those people who will help with the study are specified.

5. If I wish to discuss any concerns regarding the questionnaire, I may contact Charles Licata, Cole Neuroscience Center at 865-544-6742. I may contact the IRB Chairman at (865) 544-9781 if I have any questions about my rights as a participant in this study or my rights as a research subject.

6. I understand that the examiner may terminate the study at any time and that I am free to refuse participation at any time without prejudice to current or future medical care at the University of Tennessee Medical Center, Knoxville.

7. I have read and understand that in the event of injury resulting from the research procedures, financial compensation is not available and medical treatment is not provided free of charge.

8. I understand that I am not waiving any legal rights or releasing the University of Tennessee or its agents from liability or negligence. I understand that, in the event of physical injury resulting from research procedures, the University of Tennessee does not have funds budgeted for compensation either for lost wages or for medical treatment. Therefore, the University does not provide for treatment or reimbursement for such injuries.

9. I understand that I will not be financially compensated for participating in this study.

10. I have read or have had read to me the description of the research study as outlined above. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time. I have been told of the potential risks, discomforts, side effects and adverse reactions as well as the possible benefits (if any) of the study.

11. I freely volunteer to participate in the study. I understand that I do not have to take part in this study and that my refusal to participate will involve no penalty or loss of rights to which I am entitled. I further understand that I am free to later withdraw my consent and discontinue participation in this study at any time. I understand that refusing to participate or later withdrawing from the study will not adversely affect my subsequent medical care.

12. Under federal privacy regulations, you have the right to determine who has access to your personal health information (called "protected health information" or PHI). PHI collected in this study may include your medical history, the results of physical exams, lab tests, x-ray exams,and other diagnostic and treatment procedures, as well as basic demographic information. By signing this consent form, you are authorizing the researchers at the University of Tennessee to have access to your PHI collected in this study (if the study will use PHI in the possession of another covered entity, add) and to receive your PHI from (either) your physician (and/or) facilities where you have received health care. (If any of the following individuals or entities will also be reviewing the PHI collected or received for the study, then add the following sentence.)

    In addition, your PHI may be shared with other persons involved in the conduct or oversight of this research, including (if the study is multi-institutional, add) researchers at (name of the institutions); (if a cooperative group study, add) the (name of the cooperative group); (if the research involves an FDA-regulated drug, device or biologic, add) the Food and Drug Administration (FDA); and (if claims for some of the procedures performed during the study will be submitted to third party payers, add) your medical insurance carrier. (If the research is sponsored, add) Your PHI may also be shared with (name of sponsor), which sponsors and provides funds for this research; (name of CRO, if applicable) which has been hired by the sponsor to coordinate the study; and a Data and Safety Monitoring Committee (if applicable). (If the previous sentence was used, add the following sentence as well.) However, these latter organizations may not have the same obligations to protect your PHI. The Institutional Review Board (IRB) at the UT Graduate School of Medicine may review your PHI as part of its responsibility to protect the rights and welfare of research subjects. Your PHI will not be used or disclosed to any other person or entity, except as required by law, or for authorized oversight of this research study by other regulatory agencies, or for other research for which the use and disclosure of your PHI has been approved by the IRB. Your PHI will be used only for the research purposes described in the Introduction of this consent form. Your PHI will be used (either) until the study is completed (or if the research is FDA regulated) for as long as the sponsor reports study data to the FDA (or if the research is without a foreseeable end-point, such as a repository or a registry) indefinitely. You may cancel this authorization in writing at any time by contacting the principal investigator listed on the first page of the consent form.

    If you cancel the authorization, continued use of your PHI is permitted if it was obtained before the cancellation and its use is necessary in completing the research. However, PHI collected after your cancellation may not be used in the study. If you refuse to provide this authorization, you will not be able to participate in the research study. If you cancel the authorization, then you will be withdrawn from the study. Finally, the federal regulations allow you to obtain access to your PHI collected or used in this study. (If the research study includes treatment of subjects, add the following sentences.) However, in order to complete the research, your access to this PHI may be temporarily suspended while the research is in progress. When the study is completed, your right of access to this information will be reinstated.

_____ _____

Signature of Volunteer Date

_____ _____

Signature of Witness Date

For Study Use: ID: _____

Alzheimer’s Informant

STATEMENT OF INFORMED CONSENT
(Caregiver)
The University of Tennessee Medical Center at Knoxville

Title: Anosognosia Scale Development for Alzheimer's disease (AD) Symptoms.

I have been invited to participate in the above referenced research study. I understand that I will be asked to complete a questionnaire with regards to the volunteer's daily activities. The nature and purpose of the questionnaire in this study, the risks involved, and the possibilities of complication have been explained to me as follows:

1. The purpose of the inventory is to determine the volunteer's insight towards activities in the volunteer's daily life.

2. I understand that I will be administered a 10 question form, the CAS-AD, to determine the awareness of the volunteer's performance of daily activities. It will take approximately 10 minutes to complete. I understand that data will also be used from instruments taken during the volunteer's routine office visit.

3. There will be 240 volunteers enrolled in the study. The study does not have a defined length. During later visits I may be asked to complete further questionnaires, however I do have the right to refuse.

4. Otherwise, access to the volunteer's records will be limited to principal investigators (Charles Angelo Licata, Dr. John Dougherty), or their assistants, such as the Cole Neuroscience Center's staff. Names will be provided to the UTMCK Institutional Review Board at a later time when those people who will help with the study are specified.

5. If I wish to discuss any concerns regarding the questionnaire, I may contact Charles Licata, Cole Neuroscience Center at 865-544-6742. I may contact the IRB Chairman at (865) 544-9781 if I have any questions about my rights as a participant in this study or my rights as a research subject.

6. I understand that the examiner may terminate the study at any time and that I am free to refuse participation at any time without prejudice to current or future medical care at the University of Tennessee Medical Center, Knoxville.

7. I have read and understand that in the event of injury resulting from the research procedures, financial compensation is not available and medical treatment is not provided free of charge.

8. I understand that I am not waiving any legal rights or releasing the University of Tennessee or its agents from liability or negligence. I understand that, in the event of physical injury resulting from research procedures, the University of Tennessee does not have funds budgeted for compensation either for lost wages or for medical treatment. Therefore, the University does not provide for treatment or reimbursement for such injuries.

9. I understand that I will not be financially compensated for participating in this study.

10. I have read or have had read to me the description of the research study as outlined above. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time. I have been told of the potential risks, discomforts, side effects and adverse reactions as well as the possible benefits (if any) of the study.

11. I freely volunteer to participate in the study. I understand that I do not have to take part in this study and that my refusal to participate will involve no penalty or loss of rights to which I am entitled. I further understand that I am free to later withdraw my consent and discontinue participation in this study at any time. I understand that refusing to participate or later withdrawing from the study will not adversely affect my subsequent medical care.

12. Under federal privacy regulations, you have the right to determine who has access to your personal health information (called "protected health information" or PHI). PHI collected in this study may include your medical history, the results of physical exams, lab tests, x-ray exams,and other diagnostic and treatment procedures, as well as basic demographic information. By signing this consent form, you are authorizing the researchers at the University of Tennessee to have access to your PHI collected in this study (if the study will use PHI in the possession of another covered entity, add) and to receive your PHI from (either) your physician (and/or) facilities where you have received health care. (If any of the following individuals or entities will also be reviewing the PHI collected or received for the study, then add the following sentence.)

    In addition, your PHI may be shared with other persons involved in the conduct or oversight of this research, including (if the study is multi-institutional, add) researchers at (name of the institutions); (if a cooperative group study, add) the (name of the cooperative group); (if the research involves an FDA-regulated drug, device or biologic, add) the Food and Drug Administration (FDA); and (if claims for some of the procedures performed during the study will be submitted to third party payers, add) your medical insurance carrier. (If the research is sponsored, add) Your PHI may also be shared with (name of sponsor), which sponsors and provides funds for this research; (name of CRO, if applicable) which has been hired by the sponsor to coordinate the study; and a Data and Safety Monitoring Committee (if applicable). (If the previous sentence was used, add the following sentence as well.) However, these latter organizations may not have the same obligations to protect your PHI. The Institutional Review Board (IRB) at the UT Graduate School of Medicine may review your PHI as part of its responsibility to protect the rights and welfare of research subjects. Your PHI will not be used or disclosed to any other person or entity, except as required by law, or for authorized oversight of this research study by other regulatory agencies, or for other research for which the use and disclosure of your PHI has been approved by the IRB. Your PHI will be used only for the research purposes described in the Introduction of this consent form. Your PHI will be used (either) until the study is completed (or if the research is FDA regulated) for as long as the sponsor reports study data to the FDA (or if the research is without a foreseeable end-point, such as a repository or a registry) indefinitely. You may cancel this authorization in writing at any time by contacting the principal investigator listed on the first page of the consent form.

    If you cancel the authorization, continued use of your PHI is permitted if it was obtained before the cancellation and its use is necessary in completing the research. However, PHI collected after your cancellation may not be used in the study. If you refuse to provide this authorization, you will not be able to participate in the research study. If you cancel the authorization, then you will be withdrawn from the study. Finally, the federal regulations allow you to obtain access to your PHI collected or used in this study. (If the research study includes treatment of subjects, add the following sentences.) However, in order to complete the research, your access to this PHI may be temporarily suspended while the research is in progress. When the study is completed, your right of access to this information will be reinstated.

_____ _____

Signature of Volunteer Date

_____ _____

Signature of Witness Date

For Study Use: ID: _____

Normal Subject

UT GSM IRB-03
FWA 2301
APPROVED 4/19/07
EXPIRES 4/18/08

Consent to Participate in a Research Study

Study Title: Anosognosia Scale Development for Alzheimer's disease (AD) Symptoms

Principal Investigator: Charles A. Licata, M.A.

Sub Investigator: John H. Dougherty, M.D.

You are being invited to take part the research study named above. The following information is provided to tell you about the study. Please read this form carefully. You will be given a chance to ask questions and have them answered. If you decide to be in the study, you will be given a copy of this consent form for your records.

Your participation in this research study is voluntary. You may choose not to take part in the study and receive other treatments without affecting your healthcare/services or other rights. You are also free to withdraw from this study at any time. In the event new information becomes available that may affect the risks or benefits associated with this research study or your willingness to participate in it, you will be notified so that you can make an informed decision whether or not to continue your participation in this study.

Why is this study being done?
The purpose of this study is to develop a short questionnaire that measures an individual's loss of insight (anosognosia). The goal of the questions is to determine the awareness of your abilities in short and long-term memory, behavior, and planning.

How many people will be in the study?
This study is being conducted through the Cole Neuroscience Center at UT Medical Center. Approximately 240 people will be in this study. The study does not have a defined length, you may be asked to repeat this questionnaire during other visits to this office

What will happen to me during the study?
You will be asked to complete a questionnaire. There are 10 questions. It will take approximately 10 minutes to complete the questionnaire.

What side effects or risks I can expect from being in the study?
There are no physical risks to taking part in this study. There is a slight risk involved in allowing access to your medical records for research purposes. The research staff working on this project will treat your personal information with the utmost care. Your questionnaires will be marked with a number assigned to you rather than your name or personal information. More information about the steps taken to safeguard your personal information is found later in this consent.

UT GSM IRB-03
FWA 2301
APPROVED 4/19/07
EXPIRES 4/18/08

Are there benefits to taking part in the study?
There is no known benefit to you from taking part in this study. However, your participation may help produce a tool that is useful to doctors caring for other patients with Alzheimer's disease.

What if I am injured in this study?
Injuries are not expected in this study. In the unexpected event that you are injured, the UT Medical Center and the Cole Neuroscience Center do not have funds budgeted for compensation either for lost wages or for medical treatment.

You are not waiving any legal rights or releasing the UT Medical Center and the Cole Neuroscience Center from liability for negligence. In the event of physical injury resulting from research procedures

Will I be paid for participating?
No, there is no payment for participating in this study.

Who do I call if I have questions about the study?
For questions about the study call Charles Licata at (865) 544-6742.
For questions about your rights as a research subject: You may contact the Institutional Review Board (IRB) at 865-544-9781. The IRB is a group of people that reviews studies for safety and to protect the rights of study subjects.

Will my medical information be kept private?
All reasonable efforts will be made to keep your protected health information (PHI) private and confidential. PHI is health information that is, or has been, collected or maintained and can be linked back to you. Using or sharing ("disclosure") such information must follow federal privacy guidelines. By signing the consent document for this study, you are giving permission ("authorization") for the uses and disclosures of your personal health information. A decision to participate in this research means that you agree to let the research team use and share your PHI as described below.

As part of the study, Charles Licata, Dr. John Dougherty or their study team may share portions of your medical record, with the groups named below:

- Office for Human Research Protections
- the University of Tennessee Graduate School of Medicine Institutional Review Board

Federal privacy regulations may not apply to these groups; however, they have their own policies and guidelines to assure that all reasonable efforts will be made to keep your personal health information private and confidential.

The study results will be retained in your research record for at least six years after the study is completed. At that time, the research information not already in your medical record will be destroyed. Any research information entered into your medical record will be kept indefinitely.

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EXPIRES 4/18/08

Unless otherwise indicated, this permission to use or share your PHI does not have an expiration date. If you decide to withdraw your permission, we ask that you contact Charles Licata in writing and let him know that you are withdrawing your permission. His mailing address is: Charles Licata, Cole Neuroscience Center 1928 Alcoa Highway, Suite 102, Knoxville TN, 37920. At that time, he will stop further collection of any information about you. However, the health information collected prior to this withdrawal may continue to be used for the purposes of reporting and research quality.

You have the right to see and copy your personal health information related to the research study for as long as the study doctor or research institution holds this information. However, to ensure the scientific quality of the research study, you will not be able to review some of your research information until after the research study has been completed.

Your treatment, payment or enrollment in any health plans or eligibility for benefits will not be affected if you decide not to participate. You will receive a copy of this form after it is signed.

CONSENT OF VOLUNTEER:
I have read or have had read to me the description of the research study as outlined above. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time.

I freely volunteer to participate in the study. I understand that I do not have to take part in this study and that my refusal to participate will involve no penalty or loss of rights to which I am entitled. I further understand that I am free to later withdraw my consent and discontinue participation in this study at any time. I understand that refusing to participate or later withdrawing from the study will not adversely affect my subsequent medical care.

_____ _____ _____
Printed Name of Volunteer Date Time

_____
Signature of Volunteer

_____ _____
Printed Name of Person Obtaining Consent Date

_____
Signature of Person Obtaining Consent

Normal Informant

UT GSM IRB-03
FWA 2301
APPROVED4/19/07
EXPIRES 4/18/08

Consent to Participate in a Research Study

Study Title: Anosognosia Scale Development for Alzheimer's disease (AD) Symptoms

Principal Investigator: Charles A. Licata, M.A.

Sub Investigator: John H. Dougherty, M.D.

You are being invited to take part the research study named above. The following information is provided to tell you about the study. Please read this form carefully. You will be given a chance to ask questions and have them answered. If you decide to be in the study, you will be given a copy of this consent form for your records.

Your participation in this research study is voluntary. You may choose not to take part in the study and receive other treatments without affecting your healthcare/services or other rights. You are also free to withdraw from this study at any time. In the event new information becomes available that may affect the risks or benefits associated with this research study or your willingness to participate in it, you will be notified so that you can make an informed decision whether or not to continue your participation in this study.

Why is this study being done?
The purpose of this study is to develop a short questionnaire that measures an individual's loss of insight (anosognosia). The goal of the questions is to determine the awareness Alzheimer patients have of their abilities in short and long-term memory, behavior, and planning. As a caregiver for a patient with Alzheimer's disease, your answers will be compared to answers the patient gives to the same questions.

How many people will be in the study?
This study is being conducted through the Cole Neuroscience Center at UT Medical Center. Approximately 240 people will be in this study. The study does not have a defined length, you may be asked to repeat this questionnaire during other visits to this office

What will happen to me during the study?
You will be asked to complete a questionnaire. There are 10 questions. It will take approximately 10 minutes to complete the questionnaire.

What side effects or risks I can expect from being in the study?
There are no physical risks to taking part in this study. There is a slight risk involved in allowing access to the patient's medical records for research purposes. The research staff working on this project will treat the personal information with the utmost care. Your questionnaires will be marked with a number assigned to you rather than your

name or personal information. More information about the steps taken to safeguard personal information is found later in this consent.

Are there benefits to taking part in the study?
There is no known benefit to you from taking part in this study. However, your participation may help produce a tool that is useful to doctors caring for patients with Alzheimer's disease.

What if I am injured in this study?
Injuries are not expected in this study. In the unexpected event that you are injured, the UT Medical Center and the Cole Neuroscience Center do not have funds budgeted for compensation either for lost wages or for medical treatment.

You are not waiving any legal rights or releasing the UT Medical Center and the Cole Neuroscience Center from liability for negligence. In the event of physical injury resulting from research procedures

Will I be paid for participating?
No, there is no payment for participating in this study.

Who do I call if I have questions about the study?
For questions about the study call Charles Licata at (865) 544-6742. For questions about your rights as a research subject: You may contact the Institutional Review Board (IRB) at 865-544-9781. The IRB is a group of people that reviews studies for safety and to protect the rights of study subjects.

Will my medical information be kept private?
All reasonable efforts will be made to keep protected health information (PHI) private and confidential. PHI is health information that is, or has been, collected or maintained and can be linked back to you. Using or sharing ("disclosure") such information must follow federal privacy guidelines. By signing the consent document for this study, you are giving permission ("authorization") for the uses and disclosures of your personal health information. A decision to participate in this research means that you agree to let the research team use and share your PHI as described below.

As part of the study, Charles Licata, Dr. John Dougherty or their study team may share portions of your medical record, with the groups named below:

- Office for Human Research Protections
- the University of Tennessee Graduate School of Medicine Institutional Review Board

Federal privacy regulations may not apply to these groups; however, they have their own policies and guidelines to assure that all reasonable efforts will be made to keep your personal health information private and confidential.

The study results will be retained in the volunteer's research record for at least six years after the study is completed. At that time, the research information not already

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in the volunteer's medical record will be destroyed. Any research information entered into the medical record will be kept indefinitely.

Unless otherwise indicated, this permission to use or share your PHI does not have an expiration date. If you decide to withdraw your permission, we ask that you contact Charles Licata in writing and let him know that you are withdrawing your permission. His mailing address is: Charles Licata, Cole Neuroscience Center 1928 Alcoa Highway, Suite 102, Knoxville TN, 37920. At that time, he will stop further collection of any information about you. However, the health information collected prior to this withdrawal may continue to be used for the purposes of reporting and research quality.

You have the right to see and copy your personal health information related to the research study for as long as the study doctor or research institution holds this information. However, to ensure the scientific quality of the research study, you will not be able to review some of your research information until after the research study has been completed.

Your treatment, payment or enrollment in any health plans or eligibility for benefits will not be affected if you decide not to participate. You will receive a copy of this form after it is signed.

CONSENT OF VOLUNTEER:
I have read or have had read to me the description of the research study as outlined above. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time.

I freely volunteer to participate in the study. I understand that I do not have to take part in this study and that my refusal to participate will involve no penalty or loss of rights to which I am entitled. I further understand that I am free to later withdraw my consent and discontinue participation in this study at any time. I understand that refusing to participate or later withdrawing from the study will not adversely affect my subsequent medical care.

Printed Name of Volunteer	Date	Time

Signature of Volunteer

Printed Name of Person Obtaining Consent	Date

Signature of Person Obtaining Consent

VITA

Charles Licata was born in Bay Shore, New York in 1964. In 1985 he obtained his Associates Degree in Data Processing from Suffolk Community College, and then his Bachelors of Science in Computer Information Systems from Dowling College in 1987. He began his corporate career in 1988 with AT&T where he remained for 8 years as a system analyst. In 1996, he began to consult privately in the East Tennessee area while beginning a new academic endeavor. Returning to college full-time in 1997 to obtain a degree in Psychology, Charles attended East Tennessee State College to complete courses in undergraduate psychology. His academic career at the University of Tennessee Psychology department began in the fall of 1999 where he graduated in 2001 with a Masters of Art in Experimental Psychology.