The Use of Operant Tasks to Assess Cognition in Persons with Alzheimer’s Disease

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Abstract

Objective: Many interventions that exhibit therapeutic potential in preclinical Alzheimer’s disease (AD) research have not been proven effective clinically. One reason for this lack of translatability between animals and humans might be due to a failure to employ measures in animals that generalize to humans. The National Center for Toxicological Research (NCTR) has developed an operant test battery (OTB) designed to generate translational markers of complex brain function in rats, monkeys, and humans. The NCTR OTB has not, as yet, been used to assess cognitive function in persons with a diagnosis of AD. Thus, the purpose of this study was to assess the utility of the NCTR OTB to detect cognitive impairments in individuals with a diagnosis of AD.

Methods: Seven participants with an AD diagnosis and 12 healthy adults (age ≥ 60), completed three operant tasks: Temporal Response Differentiation (TRD); Delayed Matching to Sample (DMTS); and Incremental Repeated Acquisition (IRA). These tasks were used to measure aspects of timing ability, short-term nonverbal memory and attention, and learning, respectively.

Results: Persons with a diagnosis of Alzheimer’s disease performed significantly worse on all three tasks, displaying marked deficits in several areas of cognitive function.

Conclusion: These results suggest that the NCTR OTB is capable of detecting cognitive impairments in individuals with AD and, therefore, is a useful tool for monitoring disease severity and progression and for screening compounds for cognitive enhancing effects in both preclinical and clinical research.

Keywords: Alzheimer’s Disease; Time Perception; Short-term Memory; Learning; Operant Tasks

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by a progressive decline in cognitive function. Most notably impaired in AD are memory and language; however, other features...
include impairment in learning, attention, time perception, and planning (Buck et al., 1997; Coubard et al., 2011; O'Brien et al., 2009). Studies in animal models have identified numerous interventions that have demonstrated potential to attenuate some of the cognitive deficits associated with AD, (Abd-El-Fattah et al., 2014; Ekctjall et al., 2013; Ismail et al., 2013; Liu et al., 2014; Long et al., 2013; Nagakura et al., 2013; Sierksma et al., 2013). Unfortunately, many of these interventions have not been proven effective in humans (Day et al., 2008; Franco & Cedazo-Minguez, 2014; Zeiss, 2014). In fact, in a review by Zeiss (2014), out of the 25 interventions examined, only two pharmacological interventions, donepezil and memantine, consistently produced positive outcomes in both animal and human studies.

One reason for this lack of translatability between the animal and human findings might be due to a failure to employ measures in animals that generalize to the human condition. A common way to assess novel compounds for therapeutic utility in the treatment of AD is to use preclinical behavioral screening procedures in nonhuman subjects that are thought to measure aspects of cognition typically impaired in persons with AD (Porsolt et al., 1993). In other words, the tests designed for use in animal subjects are thought to have predictive validity, suggesting that if a compound is assessed using these nonhuman procedures and is able to improve the performance in animal models of AD, then the compound should also possess therapeutic potential for persons with Alzheimer’s disease. Many of these behavioral assays, however, have not been assessed for their translatability to measures of cognition in humans (Mennenga et al., 2014; Talpos & Steckler, 2013; Webster et al., 2014), and this may account for the lack of generalizability of test results across species.

Clinical AD studies commonly rely on questionnaires and verbally mediated screening measures to assess multiple areas of cognition, whereas preclinical rodent studies have predominately focused on assessing aspects of spatial memory through the use of a variety of maze paradigms, such as the Radial Arm Maze (RAM), Barnes Maze, Y-Maze, and Morris Water Maze (MWM) (Webster et al., 2014). These behavioral tasks require animals to navigate mazes in order to obtain food reinforcers, or in the case of the MWM, escape aversive stimuli. In contrast, human clinical studies commonly use brief neuropsychological measures to assess various aspects of cognition, especially memory (see Cummings et al., 2016; Harrison et al., 2007; Ibarria et al., 2016). Two measures commonly used to screen for cognitive impairments are the Mini-Mental Status Examination (MMSE; Folstein et al., 1975) and the Alzheimer’s Disease Assessment Scale (ADAS; Lin et al., 2013; Rosen et al., 1984). The MMSE is a brief 5-10 min questionnaire that assesses multiple areas of cognition such as attention, memory, and orientation to time and space (Tombaugh & McIntyre, 1992). The ADAS is also a brief measure (~ 30 min) which consists of a series of tasks that measure various aspects of cognition such as word recognition, comprehension of commands, recall of instruction, expressive language, praxis, and memory (Graham et al., 2004). These exams rely heavily on the use of language and, thus, cannot be adapted for use in animals. Furthermore, both the MMSE and the ADAS assess memory for words or numbers which may have little or no relation to spatial memory.

In an attempt to reduce this translational gap between human and nonhuman research, computer simulations of several nonhuman behavioral assays have been developed for use in humans. In particular, virtual radial arm mazes have been devised (Astur et al., 2005; Bohbot et al., 2007; Iaria et al., 2003; Marsh et al., 2010; Spieker et al., 2012) with certain versions capable of detecting
impairments in working and reference memory in persons with a diagnosis of AD (Lee et al., 2014). Virtual reality and real-space human versions that model aspects of the rodent Morris Water Maze have also been developed (Astur et al., 2002; Laczo et al., 2009; Moffat et al., 2001). These tasks require participants to locate a hidden goal positioned within a circular arena. These human versions have been shown to detect performance deficits in individuals with mild cognitive impairment (MCI) and AD (Laczo et al., 2010; Laczo et al., 2009; Nedelska et al., 2012). Nevertheless, computer simulations cannot directly replicate all of the stimuli or variables available when using real world maze paradigms in rodents, and the real-space human version of the Morris Water Maze does not use water as an aversive stimulus to motivate performance as does the rodent MWM. To our knowledge, the effects of potential AD treatments have not been extensively assessed in humans using these tasks; therefore, the generalizability of task performance to preclinical research is unclear.

The majority of preclinical AD studies have focused primarily on reference and working memory, with much less emphasis on other important cognitive functions that are also impaired in individuals with AD, such as attention, time perception, and learning (Forstl, 2008; Webster et al., 2014). It has been demonstrated that attention may be among the first non-memory domains that is adversely affected in persons with a diagnosis of AD, and impaired attention may contribute directly to the functional deterioration characteristic of persons with AD (Coubard et al., 2011; Perry & Hodges, 1999; Romberg et al., 2013). For example, impaired attention has been shown to be highly predictive of increased inability to make financial and medical decisions independently in older adults with AD (Bassett, 1999). Likewise, it has also been demonstrated that individuals with AD suffer from time distortion related to a failure to appropriately track the passage of time (Buck et al., 1997; Carrasco et al., 2000; Shomaker, 1989). Magnetic resonance imaging has shown that AD is correlated with atrophy in the bilateral posterior cingulate cortex (Boccia et al., 2015), an area of the brain suggested to play a direct role in the regulation of attention (Leech & Sharp, 2013). Further, persons with a diagnosis of AD have deficits in learning as demonstrated by impairments in skill acquisition (Merbah et al., 2011) and the ability to learn associations between stimuli (Boespflug et al., 2014; Bodi et al., 2011). Thus, it is imperative that preclinical studies also include tests that measure these important aspects of cognition.

The National Center for Toxicological Research (NCTR) has developed an operant test battery (OTB) designed to measure translational markers of complex brain function, including motivation, simple visual discrimination, time perception, nonverbal memory, and procedural learning. The same behavioral endpoints can be acquired from a variety of species including laboratory animals and humans (Paule et al., 2001), thus, facilitating the extrapolation of preclinical findings to the human condition. This test battery has proven to be a reliable tool for assessing the effects of drugs and toxicants on cognition in rodents and nonhuman primates (Ferguson et al., 1994; Mayorga et al., 2000; Paule, 2000; Paule et al., 2012; Paule et al., 2011; Rodriguez et al., 2010). It has also been used in children to characterize age-appropriate task performance (Baldwin et al., 2012; Chelonis et al., 2000; 2004; 2011a), to study cognitive function and medication effects in persons with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; Baldwin et al., 2004; Chelonis et al., 2011b; Paule et al., 2000), and to examine the effects of pediatric anesthetics (Gleich et al., 2015). Further, several measures from the OTB have been shown to correlate with IQ scores in children (Paule et al., 1999). This battery of tasks is exemplary of translational research tools in that the tasks used in humans are very similar to those NCTR has used with rats (Ferguson et al., 1994;
Mayorga et al., 2000) and nearly identical to those NCTR has used with monkeys. Importantly, human performance on specific tasks from the battery is often indistinguishable from that of monkeys (Chelonis et al., 2014; Paule, 1988; Paule, 2001).

The NCTR OTB has not yet been used to study cognitive function in persons with a diagnosis of AD. If the NCTR OTB is able to detect cognitive impairments in individuals with a diagnosis of AD, this would serve to validate the use of the OTB as a tool for assessing cognition in animal models of AD. Then, the use of the OTB in animal models might also strengthen the ability of future preclinical AD research to identify treatments likely to translate to the clinic. Thus, the purpose of this study was to determine whether tasks from the NCTR OTB could detect cognitive impairments in humans diagnosed with AD. Given that previous research has demonstrated attention, time perception, learning, and memory to be impaired in persons with AD (Baddeley et al., 1999; Forstl, 2008; Perry & Hodges, 1999; Romberg et al., 2013), specific tasks were selected from the OTB that are believed to measure each of these cognitive domains. Specifically, the Temporal Response Differentiation (TRD), Delayed Matching-to-Sample (DMTS), and Incremental Repeated Acquisition (IRA) tasks were used to assess aspects of timing ability, short-term nonverbal memory and attention, and procedural learning, respectively, in persons with a diagnosis of AD.

2. Methods

2.1 Participants

Participants with a consensus diagnosis of AD were recruited from the Memory Research Center at the University of Arkansas for Medical Sciences. All study procedures were approved by the Research Involving Human Subjects Committee for the Food and Drug Administration and by the Institutional Review Board for the University of Arkansas for Medical Sciences. Informed consent was obtained from each participant prior to their participation in the study. The procedure for obtaining a consensus diagnosis of AD began with the acquisition of a medical history by a behavioral neurologist followed by a two part neurological examination. The first part of this examination consisted of the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981), the Wechsler Memory Scale–Revised (Wechsler, 1987), and the Auditory Verbal Learning Test (Rey, 1964). The second part of this examination, used for research categorization, included the Mini Mental State Examination (MMSE; Folstein et al., 1975), the Clinical Dementia Rating Scale (Hughes et al., 1982; Morris, 1993), the Free and Cued Selective Reminding Test (Buschke, 1984), and the Boston Naming Test (Kaplan et al., 1983). After necessary information was obtained, a consensus committee consisting of behavioral neurologists, geriatricians, neurophysiologists, nurses, and other personnel made a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Revised 4th Edition, and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders measure (McKhann et al., 1984).

Once a consensus diagnosis of AD was obtained, participants were contacted by the study staff and asked if they would be willing to participate in the research project. During the experimental session, participants in the AD group were excluded if they scored greater than or equal to 27 or less than 10 on the MMSE. They were also excluded if they scored 85 or below on the North American Adult Reading Test (NAART) (Uttl, 2002). Further, participants who were diagnosed with Parkinson’s disease, Huntington’s disease, brain masses, or Multiple Sclerosis were also excluded.
Control participants were recruited from the Memory Research Center at a University of Arkansas for Medical Sciences and the surrounding community of Little Rock, Arkansas. These participants were healthy elderly individuals with no history of AD and were included in this group if they scored 28 or above on the MMSE during the testing session. Control participants were excluded if they scored 85 or below on the NAART or were diagnosed with Parkinson's disease, Huntington's disease, brain masses, or Multiple Sclerosis. The final sample of participants included 19 adults who were 60 years of age or older. There were 8 males and 11 females; 15 were Caucasian and 4 were African American. Seven of the participants were diagnosed with AD and 12 were controls. All participants were asked to refrain from consuming alcoholic beverages for at least 8 hours prior to testing and all provided informed consent.

2.2 Apparatus

Participants performed the tasks in a private 15’ X 20’ room with a 5 ft high solid partition separating the experimenter and the participant. The experimenter remained in a different section of the room throughout the tasks and did not interact with the participant during the tasks. The other section of the room where the participant performed the tasks contained the experimental apparatus which was adjacent to a video monitor, on which task instructions were presented. Audio and visual directions were played on this monitor prior to starting the task [as described previously (Paule et al., 1998)]. The experimental apparatus was attached to the center of the wall adjacent to where the monitor was located. The apparatus consisted of a large wooden cabinet that was 182 cm tall by 60.8 cm wide by 50.4 cm deep, a response panel, and a nickel dispenser. The response panel was mounted on the front surface of the cabinet and the nickel dispenser was located inside the cabinet, above the level of the response panel. Figure 1 is a diagram of the 65.4 cm high, 55.6 cm wide response panel that was located on the front of the apparatus 60.8 cm above the floor. A round speaker, 6 cm in diameter was located 7.3 cm below the top edge of the panel. White noise was delivered through this speaker to mask extraneous sounds during testing. The panel contained two types of response manipulanda and a variety of stimulus lights. Each response lever was 5 cm wide and extended 3 cm from the apparatus when activated. The response levers were centered in a horizontal row, each 3.5 cm apart. Positioned 22 cm below the response panel and 15 cm from the left edge of the apparatus was a tray where reinforcers (nickels) were delivered. The tray was 15 cm wide, 10 cm deep and 7.5 cm tall. The activation and presentation of the retractable levers and recording of responses were automated using a computerized system developed at the FDA’s National Center for Toxicological Research.

2.3 Procedure

Each participant performed three tasks for money (nickel) reinforcers; all participants were allowed to keep all nickels earned during the test session. The tasks were presented in the following order: the time estimation or temporal response differentiation (TRD) task; the short-term nonverbal memory or delayed matching-to-sample (DMTS) task, and the procedural learning or incremental repeated acquisition (IRA) task. Before each task, the participant viewed pre-recorded audio and visual instructions for that task. After the participant finished watching the instructions, the videotape was turned off and the participant was asked if he/she understood the instructions. If the participant did not, the research assistant replayed the videotape until the
participant understood the task. Initial descriptions of these procedures have been described elsewhere (Paule et al., 1988).

![Diagram of the operant test panel.](image)

**Fig. 1.** The operant test panel.

### 2.4 Time Estimation or Temporal Response Differentiation (TRD) Task

For this task only the far left retractable lever was used (Fig. 1). The participant was instructed to hold this lever in the depressed position for at least 10 but no more than 14 seconds to receive a nickel. A trial began when the participant pressed the lever and ended when the participant released it. The task lasted for 10 minutes or until the participant earned 30 nickels. This task is identical to that used for both rats (Ferguson et al., 1994; Mayorga et al., 2000) and monkeys (Buffalo et al., 1994; Ferguson & Paule, 1993).

The dependent variables for the TRD task included two types of lever holds, called bursts and timing holds. Bursts consisted of lever holds that lasted less than 2 seconds while timing holds lasted 2 or more seconds. In order to be included in the analyses a minimum of 10 lever holds must have been initiated, two of which had to be of 2 s or greater in duration. One participant from the AD group was excluded from this analysis based on these criteria. The distribution of lever hold durations was determined by assigning each lever hold duration to an appropriate 1 s time bin for each participant. For example, 2 s lever hold durations would be any lever hold duration that was 2 s or greater but less than 3 s. Lever hold durations greater than or equal to 20 s were combined into a single, 20 s time bin. The number of lever holds made in each 1 s bin was averaged across participants in each group so the frequency distributions of lever hold durations for each group could be generated and visually compared across groups. These lever holds were used to calculate the means (accuracies) and standard deviations (precision) of timing holds. Specifically, the means
and standard deviations of the duration of timing holds were computed using the raw timing hold data for each participant and these data were compared across groups. In addition, the number of correct (reinforced) lever holds, mean timing hold durations, and variability of mean timing hold durations (standard deviations) were also determined.

2.5 Short-term memory or Delayed Matching-to-Sample (DMTS) task.

For this task, a white sample stimulus on a black background (a circle, square, triangle, plus sign, vertical bar, horizontal bar, or X) appeared on the center plate of the three press-plates (see Figure 1). After viewing this sample stimulus, the participant pressed the center press-plate and the stimulus was immediately extinguished. Following the random presentation of 1 of 6 delays (1, 2, 4, 8, 16, and 32 sec), each press-plate was illuminated with a different stimulus, pseudo-randomly presented, one of which matched the sample stimulus displayed earlier. If the participant pressed the plate that matched the initial sample stimulus, she or he received a nickel and the next trial began immediately. If the participant pressed one of the two plates that did not match the sample, the participant did not earn a nickel and the next trial began following a 10-second timeout (all press-plates dark). The session lasted 15 minutes or until the participant earned 60 nickels.

The dependent variables for the DMTS task included overall accuracy, percent task completed, observing response latency, and overall choice response latency. Overall measures were obtained by collapsing each variable across delays and provided general measures of DMTS behavior. Overall accuracy was the number of correct choices divided by the total number of choices times 100. Percent task completed was the total number of nickels earned divided by the total number possible times 100. Observing response latency was the average time it took to press the initial target (sample) stimulus after it appeared on the center press-plate. Overall choice response latency was the average time it took to press one of the three choice stimuli after they appeared on the three press-plates. Accuracy and choice response latency at each delay were also determined. This method of analysis provided a more detailed examination of the data and could be used to examine decay curves and interactions between recall delay and other variables. Accuracy was the percentage of correct choice responses at each delay. Choice response latency was the average time it took to press one of the three choice stimuli after they appeared on the three press-plates for each delay. For the data to be included in the analyses, the participant had to have completed at least one trial at each delay. Two participants from the AD group were excluded from this analysis based on these criteria.

2.6 Learning or Incremental Repeated Acquisition (IRA) Task

This task utilized all four retractable levers and began with the illumination of the right-most of the six serial position indicator lights (see Figure 1), which was colored red. Initially, the participant's task was to determine which lever was correct in the presence of the red stimulus light (task level IRA1). When the participant pressed incorrect levers, an incorrect response indicator light was illuminated for two seconds, and the participant could not make another effective response. When the participant pressed the correct lever, a nickel was immediately dispensed into the reinforcer tray (see Figure 1), and the correct response indicator light was illuminated for one second. The correct response indicator light and the red stimulus light were extinguished for two seconds after dispensing the nickel, then the red stimulus light was re-illuminated, and the participant could then
make another response. After three correct responses at IRA1, regardless of the number of incorrect responses, the red stimulus light was extinguished for a delay of 30 seconds and the task difficulty was incremented to IRA2, a 2-lever sequence. IRA2 began with the illumination of the second serial position indicator light (green). The participant's task was to determine which lever was correct in the presence of the new green light. When the participant pressed the correct lever, the green stimulus light was extinguished and the red stimulus light was illuminated. The participant then was required to press the lever that was correct in the presence of the red light to receive a nickel. The participant repeated the procedure until she or he produced three errorless response sequences after which all stimulus lights were extinguished for 30 seconds, the task difficulty was increased to IRA3 (a 3-lever sequence), and the third serial position indicator light was illuminated. The process continued in like fashion for IRA4, IRA5, and IRA6. If the participant made an incorrect response within a sequence, the participant was allowed to complete that sequence and obtain a nickel (error correction was permitted). Participants continued until they completed IRA 6 or until fifteen minutes elapsed.

The dependent variables for IRA were percent task completed, accuracy, and response rate. Percent task completed was the total number of errorless sequences completed divided by the total possible (3 at each of 6 levels for a total of 18). Accuracy was the number of correct lever presses divided by the total number of lever presses. Response rate was the number of responses made during the time allotted for responses (minus timeout periods). Since only one of the participants in the AD group was able to complete three errorless sequences at IRA3, only data for IRA levels one through three were analyzed for both AD participants and controls. Data for one control participant was not included in the analysis because that person made no responses during the session.

2.7 Data Analysis

Statistical analyses were conducted using Graphpad Prism 6. For the TRD task, independent samples t-tests were used to compare differences between groups in bursts, timing holds, correct lever holds, average hold duration, and the standard deviation of average hold duration. For the IRA task, independent samples t-tests were used to compare differences between groups in percent task completed, accuracy, and response rate. For the DMTS task, independent samples t-tests were conducted to compare differences between groups in percent task completed, accuracy, choice latency, and observing response latency. Additionally, split-plot ANOVAs were conducted to examine differences between accuracy and choice response latency at each delay. Planned comparisons using a t-test were performed following each ANOVA. In order to control for multiple comparisons, the Bonferroni Correction was used to calculate the threshold value for each individual comparison (Abdi, 2007).

3. Results

3.1 Time Perception Task: Temporal Response Differentiation

The AD group made significantly more burst responses (lever holds that lasted less than 2 sec; \( t(15) = 2.77, p < .05 \)) and fewer correct responses (\( t(15) = 2.47, p < .05 \)) than the control group. In contrast, both groups initiated a similar number of timing holds (Fig. 2A). For the number of timing lever holds in each 1-second bin, the AD group exhibited a well-defined peak of lever holds at 8
seconds. In contrast, lever hold durations in the 10-14 second reinforced time window (10-13 second bins) were elevated compared to every other bin for the control group. These results indicate that persons with AD seemingly over-estimate the passage of time (Fig. 2B). For the mean duration of timed lever holds, participants in the AD group were significantly shorter than for controls ($t(15) = 2.98, p < .01$; Fig. 2C). In contrast, the precision or variability (standard deviation) of timed lever hold durations was not significantly different between groups.

![Fig. 2. Temporal Results Differentiation (TRD) Task.](image)

3.2 Short-term Memory Task: Delayed Matching-to-Sample

The control group was significantly more accurate ($t(15) = 6.26, p < .0001$, for overall accuracy) and completed more of the task ($t(15) = 6.79, p < .0001$) than the AD group (Fig. 3A). Participants with AD had significantly longer observing response latencies ($t(15) = 5.74, p < .0001$) and overall choice response latencies ($t(15) = 3.74, p < .01$) than controls (Fig. 3B). The accuracy of the control group approached 100% at each recall delay, but the AD group performed well below that level. In fact, at delays of two seconds and longer, performance of the AD group was not significantly greater than chance (33%; Fig. 3C). A two-way ANOVA revealed a significant effect of group ($F(1,15) = 39.5, p < .0001$) on overall accuracy.
delay, \((F(5,75) = 3.7, p < .01)\), and interaction, \((F(5,75) = 3.3, p < .01)\). Independent t-tests revealed that the accuracy of the AD group was significantly lower than that of the control group at each delay (Fig. 3C).

The AD group also exhibited longer choice response latencies than the control group at each delay (see Figure 3D). A two-way ANOVA revealed a significant effect of group \((F(1,15) = 15.8, p < .01)\) but no significant effect of delay or interaction. Independent t-tests revealed that the choice response latencies for the AD group were significantly longer than those of the controls at almost every delay (Figure 3D).

**Fig. 3.** Delayed Matching-to-Sample (DMTS) Task. (A) The average percent task completed (PTC, left) and accuracy (right) for the DMTS task for AD and control participants. (B) The average overall observing response latency (left) and average overall choice response latency (right) for the DMTS task for AD and control participants. (C) The average accuracy for AD group and controls for each recall delay interval for the DMTS task. (D) The average choice response latencies for AD group and controls across each recall delay interval for the DMTS task. For graphs A and B, ** indicates different from control with \(p < .01\); **** indicates different from control with \(p < .0001\). For graphs C and D, * indicates \(p < \text{Bonferroni-} \text{adjusted } p\)-value (.0083).

### 3.3 Learning Task: Incremental Repeated Acquisition

Participants in the AD group were less accurate \((t(16) = 5.309, p < .0001)\) and completed less of the
task \( (t(16) = 5.07, p < .001) \) than controls (Fig. 4A). A percent task completed (PTC) of 33.3\%, 50\%, 66.7\%, 83.3\%, and 100\% indicated completion of IRA Levels 2, 3, 4, 5, and 6 respectively. On average, participants in the AD group obtained a PTC of 34.13\%, whereas controls had an average PTC of 78.28\%. This indicates that participants in the AD group were rarely ever able to master a 3-lever sequence whereas controls generally completed 5-lever sequences. In fact, only one individual with AD completed IRA level three (IRA3), whereas, all of the controls completed IRA3. Additionally, even though participants in the AD group completed less of the task than controls, their response rate was not significantly different than that of controls (Fig. 4B).

![Fig. 4. Incremental Repeated Acquisition (IRA) Task. (A) The average percent task completed (PTC) and accuracy for the IRA task for AD and control participants. *** indicates different from control with \( p < .001 \) and **** indicates different from control with \( p < .0001 \). (B) The average rate of responding for the IRA task for AD and control participants.](image)

4. Discussion

The purpose of this study was to determine whether three tasks from the NCTR OTB could detect cognitive impairments in persons diagnosed with AD. The results clearly demonstrate that automated cognitive assessment using the NCTR OTB can be effective in elderly persons with and without a diagnosis of AD. Persons with a diagnosis of AD performed significantly worse than controls on all three OTB tasks. These tasks possess high translatability between human and nonhuman animal models and similar tasks have been used to assess cognition in transgenic mouse models of AD (Blackshear et al., 2011; Roddick et al. 2014; Woolley & Ballard, 2005). Further, the NCTR OTB assesses multiple areas of cognition and shows potential for identifying cognitive markers for AD in its early stages. Given the translational capabilities of these tasks, the data suggest that the NCTR OTB is a valid tool for use both preclinically and clinically in studies to assess the effectiveness of pharmacological and other treatment strategies in ameliorating the cognitive deficits characteristic of AD.

The ability to detect differences between persons diagnosed with AD and controls with a quite small sample demonstrates another advantage of the OTB: its sensitivity to cognitive disruption in individuals with AD. This is not particularly surprising given that this battery is derived from work with nonhuman primates that often rely on highly sensitive measures to detect drug effects. Similar
to this study, we have found the OTB to detect drug effects in small samples of monkeys (see for example Buffalo et al., 1994; Frederick et al., 1995) and to detect treatment effects in small samples of children with ADHD (see for example Chelonis et al., 2002).

4.1 Time Estimation

The AD group was significantly less accurate in their performance of the time perception task, with their timed responses being characterized by shorter duration of timing estimates (~8 seconds) than those produced by controls (~14 seconds). These data suggest that individuals with a diagnosis of AD over-estimate the passage of time and perceive 8 seconds as being 10 seconds or longer. This finding is consistent with the general notion that individuals with a diagnosis of AD suffer from a failure to appropriately comprehend the passage of time (Buck et al., 1997; Forstl, 2008; Shomaker, 1989) and have specific deficits on tasks that measure time perception (Bangert & Balota, 2012; Carrasco et al., 2000; Nichelli et al., 1993; Rueda & Schmitter-Edgecombe, 2009). The observation that there was no significant increase in the variability of the time productions generated by individuals in the AD group compared to that of the control group suggests that individuals in the AD group did not exhibit deficits in the precision of their timing responses.

4.2 Short-term Nonverbal Memory

Persons in the AD group completed significantly less of the DMTS task, were significantly less accurate, and took longer to make both observing and choice responses than persons in the control group. These data are consistent with those of others who have shown deficits in DMTS task performance in participants with an AD diagnosis (Fowler et al., 2002; Money et al., 1992; Plaza et al., 2012; Sahakian et al., 1988; Sano et al., 1995). Notable aspects of DMTS task performance seen here in persons with a diagnosis of AD include significantly reduced speed of responding to both the sample stimuli (during which time processes such as encoding and discrimination should be important) and the choice stimuli (which should reflect functions perhaps more related to recall). Reduced speed of responding to the sample and choice stimuli might also reflect deficits in attention. Of note is the observation that even after very short delays of a few seconds, recall accuracy in our participants with a diagnosis of AD was not significantly greater than chance. The pattern of significantly slower choice responses seen in the AD group is very different than what was observed here in the elderly control group as well as from other participant groups performing the same task (Chelonis et al., 2000; 2014; Paule et al., 2004). Taken together, the DMTS data suggest problems not only with aspects of visual discrimination and encoding, but also with attention and recall.

4.3 Procedural Learning

Participants with a diagnosis of AD exhibited decreased IRA accuracies and percent task completed compared to the control group. Individuals in the AD group were rarely able to master the 3 lever task; whereas, controls generally were able to master the 5 lever task. These results, thus, suggest that individuals with a diagnosis of AD have deficits in the ability to acquire and retain new visually presented information. In contrast to the DMTS task, response rates were not significantly different from those of the control group. These deficits seem to be solely based on those cognitive abilities associated with learning and recall and not attributable to any motor dysfunction.
4.3 Conclusion

The present study demonstrated that tasks from the NCTR OTB are able to detect impairments in aspects of timing, short-term nonverbal memory and attention, and procedural learning in individuals with a diagnosis of AD. The same tasks used in this study have been developed for and widely used in nonhuman animal models. In monkey and rat studies conducted in NCTR laboratories using the same tasks used here, results have demonstrated that cognitive-disrupting compounds produce performance deficits similar to those seen here in persons with a diagnosis of AD (Buffalo et al., 1994; Frederick et al., 1995; Mayorga et al., 2000; Popke et al., 2000). These results, thus, suggest that the NCTR OTB is a useful tool for assessing and monitoring AD severity and progression as well as screening compounds for cognitive enhancing effects in both preclinical and clinical research.

Disclosure

This document has been reviewed in accordance with United States Food and Drug Administration (FDA) policy and approved for publication. Approval does not signify that the contents necessarily reflect the position or opinions of the FDA nor does mention of trade names or commercial products constitute endorsement or recommendation for use. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the FDA.

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Conflict of Interest

None

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