Reinforcement Learning in Individuals at Risk for Alzheimer's Disease

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by

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ABSTRACT
REINFORCEMENT LEARNING IN INDIVIDUALS AT
RISK FOR ALZHEIMER'S DISEASE

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Explicit memory is the hallmark of impairment in Alzheimer's disease (AD) while implicit memory has mixed task-dependent results. Models of memory processes have posited that hippocampal function is sensitive to reinforcement learning (RL), which involves both explicit and implicit memory. The hippocampus is also vital for the transfer of learned associations to novel situations. Nevertheless, RL paradigms have been underutilized in assessing memory processes in individuals at risk for AD, which may aid in early identification of cognitive decline.

Thirty-six apolipoprotein-E (APOE) genotyped older adults (Male n=8; M_{age}=80; $M_{education}$=15 years) performed word stem completion, word recognition, and RL tasks. The RL task was comprised of an RL phase, an implicit testing phase, and explicit recognition component. Group comparisons were made based on low risk (APOE ε4-; n=16) vs. high risk (APOE ε4+; n=20) for AD. A series of mixed ANOVAs based on task performance indicated that risk groups did not differ on EM measures (RL, word recognition, and RL recognition). However, high risk participants exhibited significantly *poorer IM* performance (RL testing and word stem) than the low risk group, p = .03.

The pattern of results in the present study was counter to prediction in that risk groups did not differ on explicit memory measures, which was strongly supported by existing literature. However, the exhibited performance of poorer implicit memory in the high risk group is consistent with results implicating the hippocampus in the application learned associations to novel environments. RL paradigms may offer high sensitivity for assessing preclinical decline.

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Reinforcement Learning in Individuals at Risk for Alzheimer's Disease

Alzheimer's disease (AD) is the most severe form of dementia, a term referring to a group of symptoms affecting cognitive abilities such as memory, judgment, and behavior. Characterized by hyperphosphorylated tau tangles and amyloid plaques, AD is marked by clinically significant impairment in explicit memory (Fleischman, Wilson, Gabrieli, Schneider, Bienias, & Bennett, 2006). This form of memory refers to conscious recollection of factual information that can be segmented into components accounting for autobiographical experiences (episodic) and general knowledge (semantic; Gong, Tian, Cheng, Chen, Yin, Meng et al., 2010; Blennow, de Leon, & Zetterberg, 2006; Fleischman, Gabrieli, Rinaldi, Reminger, Grinnell, Lange, Shaprio, 1996). Conversely, implicit memory accounts for the performance of a task without declarative recollection (e.g., tying a shoe, riding a bike) or without conscious awareness, such as responding faster to items recently experienced than to novel stimuli (Zillmer, Spiers, & Culbertson, 2008; Jelici, Bonebakker, & Bonke, 1995). Neuropsychological evidence contrasting impairments in various neurodegenerative diseases such as AD, Parkinson's disease (PD), and amnesia supports the independence of these two memory systems (Randolph, Tierney, & Chase, 1995). Results from these studies have shown different patterns indicating that implicit memory processes are impaired in PD while explicit memory processes are impaired in AD and amnesia (Light, Singh, & Capps, 1986; Heindel, Salmon, Shults, Walicke & Butters, 1989; Bondi & Kaszniak, 1991; Huberman, Moscovitch & Freedman, 1994; Maki & Knopman, 1996; Knowlton, Mangels, & Squire,

1996). Implicit memory in AD specifically has a pattern of both preservation and impairment (Fleischamn et al., 2006).

Memory system resource allocation, cognitive demands of the task utilized, disease neuropathology, and different neural circuitry underlying each memory system have all been postulated to account for performance difference across and within distinct neurological profiles (Gabrieli et al.., 1995, Fleischman et al., 2005). The field largely acknowledges dissociable memory composition, rather than a unitary system (Squire, 1987; Poldrack & Packard, 2003; Fleischman et al., 2005; Gabrieli et al., 1995; Randolph et al., 1995). This is supported by evidence showing that damage to the basal ganglia and cerebellum typically produce impairments to different aspects of implicit memory, leaving explicit memory intact, while damage to hippocampus and associated frontal pathways typically produce impairment in explicit but not implicit memory functions. Repetition priming, perceptual priming, and conceptual priming, as well as corresponding recognition tasks, are among those most commonly employed to investigate these memory processes. Investigations into implicit memory are often assessed either via perceptual priming tasks, which target the physical attributes of the stimuli, or conceptual priming tasks, which tap a form of implicit memory by indirectly accessing the meanings of previously studied stimuli (Maki & Knopman, 1996). Recognition tasks are commonly employed after completion of these priming tasks in order to assess explicit memory. Thus, these tasks independently assess explicit and implicit memory.

Explicit Memory

Explicit memory processes have been associated with various brain regions including prefrontal cortex and medial temporal lobe (MTL; Poldrack & Packard, 2003;

Schacter & Badgaiyan, 2001). The role of the hippocampus, a MTL structure responsible for the progression of information into long-term memory, has been well established in explicit memory and its principal role in cognitive decline (Tulving & Markowitsch, 1998). Numerous functional magnetic resonance imaging (fMRI) investigations into the preclinical biomarkers for developing AD have utilized explicit memory tasks. These studies have correlated medial temporal deactivation to episodic memory decline showing that as performance worsens, medial temporal lobe degeneration increases (Twamley et al., 2006). Seidenberg et al. (2009) employed this methodology in conjunction with a semantic memory task to distinguish healthy individuals at various levels of risk for AD. Although no group differences were found behaviorally or neuropsychologically, greater activation in various brain regions including bilateral prefrontal cortex occurred in individuals at high risk for developing AD for famous compared to non-famous names. Individuals at low risk showed greater activation to non-famous vs. famous names. Increased activation in individuals at risk for developing AD is thought to be evidence of compensatory functioning due to declining efficiency of the system (Sugarman, Woodard, Nielson, Seidenberg, Smith, Durgerian, & Rao, 2012). This would account for the comparable performance observed between groups (Bookheimer, Strojwas, Cohen, Saunders, Pericak-Vance, Mazziotta, & Small, 2000; Nielson et al., 2006).

Several studies have found decreased activity in multiple areas in AD patients during episodic encoding tasks (Sperling et al., 2003b, Golby et al., 2005). These studies consistently found decreased activity in the hippocampus and parahippocampal regions compared to healthy controls. Decreased activation in prefrontal cortex (pFC) and

temporal areas was also found. However, Sperling et al., (2003b) and Grady et al., (2003) found increased activation in the prefrontal region in AD patients. Some research groups conducting investigations in genetically at risk but asymptomatic individuals have found that carriers of the apolipoprotein-E (APOE) ε4 allele, a genetic risk factor for the development of AD, had greater activation than ε3 allele and non-carriers (Bookheimer et al., 2000; Bondi et al., 2005; Seidenberg et al., 2009), while a number of studies found decreased activation in carriers vs. non-carriers (Smith et al., 1999; Mondadori et al., 2007).

Implicit Memory

Implicit memory refers to the process by which unintentional or unconscious recollection of previous experiences aids in the facilitation of action or choice (Zillmer et al, 2008; Schacter, Chiu, & Ochsner, 1993). Word-stem completion, a perceptual priming task, has commonly been used to assess implicit memory processes. In this task, participants are presented with the first three letters of a word. The participant is required to complete it with the word that first comes to mind (Graf, Mandler, & Handen, 1982). Word identification tasks, which involve the quick classification of a string of letters as a word or a non-word, have also been used (Heindel et al., 1989). The influence of other recently presented stimuli can cause increased or decreased response times on this type of task.

Implicit memory systems have largely been associated with posterior cortical areas, cerebellum, neocortex, and neostraitum, including the basal ganglia (Squire, 1993). The basal ganglia are subcortical nuclei including the striatum, the caudate and putamen, the globus pallidus, the substantia nigra and the subthalamic nucleus that have been

collectively postulated to be responsible for various learning and decision making processes (Weicki & Frank, 2010; Zillmer et al, 2008). A number of investigations have supported neocortical involvement in implicit memory task performance (Knowlton et al, 1996; Poldrack & Packard, 2003; Bondi & Kaszniak, 1991). On a word-identification task, no differences were found between AD patients and healthy elders (Abbenhuis, Raaijmakers, Raaijmakers, & Woerden, 1990). A number of studies have also supported intact word-stem completion performance in AD (Keane, Gabrieli, Fennema, Goodwin, & Corkin 1991; Shimamura et al.,1987; Christensen & Birrell, 1991). Keane et al., (1991) concluded that normal priming can occur in AD under perceptual learning conditions; that is under implicit instruction. Conversely, reaction times for recognition memory tasks in these same studies documented the typical pattern of impaired explicit memory in AD relative to healthy controls.

While intact priming accuracy has been seen, some studies have revealed generally poor performance in AD across memory tasks. For example, Heindel et al., (1989) investigated word-stem completion performance among six different groups of cognitively intact and impaired elderly individuals. Among these were middle-aged and elderly normal controls, and groups with either HD, AD, PD with dementia or PD without dementia. AD patient performance (accuracy) on this task was poorer compared with all other groups except the PD with dementia patients. They further reported poorer AD performance on explicit memory (recall and recognition) tasks compared to all other groups with the exception of HD. Bondi & Kaszniak (1991) replicated these results, reporting impaired AD relative to PD performance on a word-stem completion task and on free-recall, cued-recall and recognition tasks. Taken together, these studies provide

evidence that impairment in AD can be observed across both explicit and implicit systems. Recognition (i.e., explicit) performance, however, appears to be more consistently impaired across studies than implicit performance.

Older adults have been shown to have relatively normal performance on implicit memory tasks (Light et al., 1986; Flieschman et al., 2004, 2005). Studies in patients with Mild Cognitive Impairment (MCI), a condition not severe enough to meet criteria for dementia but is often an early form of it, were found to have impaired explicit and implicit memory performance on a conceptual priming task (Gong et al., 2010). However, Huberman et al., (1994) concluded that this pattern of functioning changes as dementia progresses. They concluded that while repetition effects were likely to be preserved in early stages of AD, conceptual priming may be as profoundly impaired as explicit memory in this population. Amnestic patients, with bilateral damage to the hippocampal formation or diencephalic midline, reportedly have impaired explicit but intact implicit memory functioning, leading to the conclusion that prodromal patterns of implicit memory function may be similar in AD (Knowlton et al., 1996). However, it is important to note that intact implicit memory has also been reported in AD (See Gabrieli et al., 1994; Grafman et al., 1990).

Executive functioning impairments in AD also become more evident with disease progression. Functions attributed to the executive system include planning, flexible problem solving, working memory, attentional allocation, inhibition, and at the highest levels, self-monitoring and self-assessment of behavior (Zillmer et al, 2008). Utilization of an explicit memory decision making task (Game of Dice task), indicated that activation in the dorsolateral pFC, posterior parietal lobe, the anterior cingulate, and the

right lingual gyrus were the result of task information processing (Labudda, Woermann, Mertens, Pholmann-Eden, Markowitsch, & Brand, 2008). Activation was attributed to executive functions such as conflict detection, and that decision-making processes based on explicit conditions depend on dorsolateral pFC activation while decision making under ambiguity has been shown to depend on orbitofrontal and ventromedial pFC.

Investigations of higher order cognitive functions involving pFC mechanisms, such as those in learning and decision making, are limited in participants with AD (Blennow, et al., 2006; Collins & Frank, 2012). Based on the current review of the literature, the function of explicit and implicit memory in reinforcement learning in AD has not been well established. Previous work in reinforcement learning in PD patients on medication, however, showed impaired implicit memory performance (Frank et al., 2004, 2005; Cavanagh et al., 2011). Inquiry into differential processing of these two systems in individuals with varying risk for AD may provide insight into the early pathophysiology and progression of AD, because of the well-established link between learning and memory (Anderson, 1995); such information would aid in the ability to distinguish those at risk for cognitive decline from those who are likely to remain cognitively intact. This type of distinction would assist in accurate and early diagnosis of AD, as well as in efforts to development preventions and treatments. Currently, the only definitive diagnosis of the disease is through neuropathology, which is assessed post-mortem. At autopsy, only about 87.7% of probable AD cases and 54% of MCI cases are typically confirmed as AD, suggesting that 12% of clinically diagnosed AD patients and nearly half of MCI patients may be misdiagnosed (Schneider, Arvanitakis, Leurgans & Bennett,

2009). This is particularly noteworthy as the conversion from MCI to AD is estimated at approximately 30% (Peterson et al., 2001; Twamley et al., 2006).

The presence of APOE ε4 accounts for 50-60% of AD patients examined post-mortem (Twamley et al., 2006; Raber, Huang, & Ashford, 200). The likelihood of disease development in individuals with one copy of the allele is 3 times that of individuals without it, and the likelihood of development in homozygote carriers is 15 times greater than non-carriers (Twamley et al., 2006). The APOE gene is associated with amyloid β protein deposition in the brain leading to the distinguishing plaques and tangles, and the neurological and cognitive deficits in memory found in individuals with AD. This process is commonly known as the amyloid cascade hypothesis (Hardy & Selkoe, 2002). APOE ε4, one among three APOE alleles (ε2, ε3, and ε4), is associated with the greatest risk of AD (Twamley et al., 2006). Other risk factors associated with AD include decreased brain size, reduced mental and physical activity, low education, head injury, and vascular disease related factors such as hypertension, smoking, and diabetes (Twamley e al., 2006). The potential causal relationship of all these factors has yet to be determined. Davies et al., (1988) determined that the neurodegenerative process leading to AD begins approximately 20-30 years prior to clinical diagnosis, a finding supported by a variety of distinct research groups (Selkoe, 2002; Coleman, Federoff, & Kurlan, 2004). This finding has monumental implications for future research avenues as the reliable identification of neural and cognitive biomarkers that confidently distinguish between individuals with and without AD, as postulated in the proposed study with individuals at risk for AD, would greatly impact diagnosis procedures, treatments, and potentially the prognosis of AD.

Clinicians, public health officials and researchers alike have frequently called for consistent and reliable techniques that will predict memory decline and differentiate at-risk individuals (e.g., healthy or those with MCI) who will remain stable from those who will go on to develop AD. Because implicit memory has been overshadowed by explicit memory in the literature on older healthy adults at risk for developing AD, we seek to investigate these processes using a novel task involving prefrontal cortex, dorsolateral striatum, and the hippocampus because of their implication in successful learning (Lee et al., 2012; Simon & Daw, 2011).

Reinforcement Learning

Reinforcement learning is the process by which decisions are made based on the evaluation of past experiences and the expectation of future outcomes that have been mentally created and maintained in working memory (Pennington, 1988; Frank & Claus, 2006; Frank & Kong, 2008). The value placed on a particular choice can be adjusted based on direct experience of rewards and punishments (model-based reinforcement learning) but direct experience is not required to influence subsequent behavior (model-free reinforcement learning; Lee, Seo, & Jung, 2012). Decision making (action selection), occurs after outcome evidence has been mentally created and maintained in working memory (Frank & Claus, 2006). Implicit memory is thus responsible for one's ability to attribute values to future outcomes. Appropriately adjusting behaviors based on outcome feedback (adaptive learning) is facilitated by ventromedial and orbitofrontal cortices (OFC). Action facilitation occurs when information is processed in the striato-orbitofrontal loop and then projected out to pFC and motor cortex. This indicates that learning can occur by one's evaluation and/or experience of the environment. For

example, choosing a restaurant may occur as the result of personal preference and experience or based on the recommendation of others. Decisions are often the result of mixed probabilities of both good and bad outcomes. Thus, a certain amount of ambiguity and risk is involved in these rather basic decisions.

Reinforcement Learning and the Hippocampus

As previously stated, the deterioration of the hippocampus leading to explicit memory deficits in AD is a hallmark of the disease. Within the field of AD research less emphasis has been placed on hippocampal involvement in other cognitive abilities such as learning and decision-making. As one of the primary functions of the hippocampus is the encoding of episodic and spatial memories, and the development of contextual representations (Atallah, Frank, & O'Reilly, 2004), it plays a central role in value function updating exhibited in reinforcement learning (Lee et al., 2012). The hippocampus has been suggested to play a role in the tripartite cognitive architecture model put forth by Atallah et al., 2004. They presented a "trade-off model" in which the hippocampus and posterior cortex play a critical role in the gathering and maintenance of flexible relational representations while the frontal cortex, including the basal ganglia, accounts for working memory and action selection processes. Additionally, computational models in animals have suggested that the hippocampus may alter the weights of individual stimuli during learning (Frank, Rudy, & O'Reilly, 2003). Thus, reinforcement learning paradigms may be sensitive to progressive atrophy of the hippocampus in individuals at risk for AD.

Probabilistic Classification Tasks

Probabilistic classification tasks, such as the Weather Prediction Task, have been employed to assess implicit acquisition of information (Knowlton et al., 1996). In this task, participants are presented with four cards and asked to determine if the pattern presented will lead to “sunshine” or “rain”. Following each presentation, participants are asked to state a specific strategy for determining their choice (Knowlton et al., 1996; Frank, 2005). During this form of task, healthy individuals learn the outcomes of the presented choices over multiple trials. Information across multiple trials is thus more valuable than information from a single trial; a process dependent on dorsal striatum (Knowlton et al., 1996). Amnesic patients exhibited normal performance on the learning portion of this task but showed severe declarative memory impairment for the training episode of the task (Knowlton et al., 1996).

Probabilistic Selection Task

An adaptation of the Weather Prediction Task, dubbed the Probabilistic Selection (PS) Task, has been used to investigate learning and decision making in PD patients and other psychopathologies (Frank et al., 2004; Frank, 2005). The PS task employs feedback (e.g., correct) following a forced-choice trial, similar to the Weather Prediction Task. However, in the PS task participants are not asked to declare a strategy for the choices they make, even though many participants attempt to develop one. Briefly, the PS task is a forced-choice reinforcement learning paradigm comprised of two phases: a training phase and a test phase (Frank, Seeberger, & O’Reilly, 2004; Frank, 2006). In the training phase, participants are presented with three pairs of figures (basic geometric shapes of varying colors; A:B, C:D, E:F) presented in random order. Participants are asked to select one figure of each pair. Feedback is given after each choice (i.e., “correct” or “incorrect”

using a probabilistic reinforcement schedule that varies for each stimulus (80%(A), 70%(C), 60%(E), 40%(F), 30%(D), and 20%(B); Frank et al., 2004). Performance criteria are imposed during the training phase (i.e., 70% of the 80:20 pair, 60% of the 70:30 pair, and 50% of the 60:40 pair), which must be met prior to moving on to testing. In the testing phase, novel pairs are presented (e.g., 80:70, 30:40), which are used to evaluate whether choices were more influenced by positive or negative feedback. Subjects make a choice for each pair, but no feedback is given.

Work on the PS task has provided a comprehensive mechanistic account of neural processes implicating basal ganglia pathways, direct and indirect, in reinforcement learning and decision-making (Frank, 2005; Cools, 2006; Wiecki & Frank, 2010). These regions of the brain have strong and well-established projections to the thalamus, prefrontal cortex, and motor cortex (Frank et al., 2004; Frank, 2005). This highly complex system has been widely established to be involved in learning, decision making, reward processing, as well as explicit and implicit memory (Frank et al., 2004). These processes are highly governed by the striatum, specifically associated with executive function. Further investigation of the cortico-basal-ganglia circuitry conventionally acknowledged to account for cognitive and reward processing, requires the close examination of the direct and indirect pathways of the basal ganglia (Frank, 2005). Thus, in learning and decision making processes, stimuli are processed through the motor cortex and are projected to the basal ganglia (Wiecki & Frank, 2010; Frank et al., 2006). The basal ganglia then act as a decision making center comprised of the two pathways, direct and indirect, that facilitate action (Frank et al., 2004; Wiecki & Frank, 2010; Frank et al., 2006). These pathways correspond to inhibitory and disinhibitory processes, which

are analogous to “putting on the break” and “releasing the break” for a particular action, respectively (Frank et al., 2004). Understanding this system, and being able to accurately assess it from a behavioral or psychophysiological standpoint, presents one of the biggest obstacles in identifying etiological underpinnings for neurodegenerative disorders impairing memory systems. It is important to note that in contrast to classic explicit and implicit memory tasks, such as word-stem completion and recognition, reinforcement learning involves both explicit and implicit memory processes that are not entirely separable due to the integrated function of the hippocampus and the basal ganglia outlined by the “trade-off model” (Wiecki & Frank, 2010; Atallah et al., 2004).

Results of investigations on PD patients on and off medication have shown that low levels of dopamine lead to better learning to avoid choices that lead to negative outcomes (“No-go”; Frank et al., 2004). Conversely, PD patients on medication, with higher levels of dopamine, exhibit enhanced learning to seek choices that lead to positive outcomes (“Go”). This differential pattern of learning is accounted for the by the increase in striatal dopamine before and after medication is introduced into the system. Thus, on the reinforcement learning task proposed for the current study, individuals off medication implicitly learned to avoid-B (the least rewarding stimuli) better than they learned to choose-A (the most rewarding stimuli) although they are given explicit feedback regarding choices made. Understanding why individuals choose one stimulus over another is important because of the implications it has for cognitive processes, which allow for adaptive environmental adaptation (Frank, 2005).

Hypotheses

As previous work in AD has employed use of various implicit and explicit memory tasks, this cross-sectional non-equivalent comparison group investigation assessed for possible memory system dysfunction in individuals at risk for AD with a different methodology than has previously been reported. The proposed study aimed to compare memory functioning during a reinforcement learning task (i.e., trial-and-error decision making) in healthy elders at low vs. high risk for developing Alzheimer's disease. By using this particular reinforcement learning task (probabilistic selection (PS) task described below), we were able to assess the consistency or inconsistency of memory system function within the same task. The primary goal of this study was to develop an approach that would detect differences between AD risk groups, which may then be useful in differentiating those more likely to develop AD from those who will remain healthy.

Specifically, this study aimed to:

1. Assess accuracy differences between AD risk groups. Although there is some variability across studies, the preponderance of the literature suggests generally intact implicit but impaired explicit memory in individuals with AD. Therefore, it was hypothesized that high and low AD risk groups would differ on the PS task in accuracy during the training phase (i.e., reinforcement learning) but not the testing phase (i.e., implicit memory). Specifically, individuals at high risk for AD were expected to exhibit lower training accuracy than low risk individuals, but were not expected to significantly differ in the testing phase of the task.

2. Test for the possible explicit/implicit memory differential within risk groups. No significant difference was expected for individuals at low risk. However, if AD risk leads to greater impact on explicit than implicit memory, it was expected that high risk participants would exhibit worse performance during training than during testing as a result of the explicit component of the training phase.
3. Compare accuracy on the training phase of the reinforcement learning task to that on a post-task recognition test, an extension of the original PS task developed for the current study. As both measures involve explicit memory processes, it was expected that significant differences in performance would be evident for individuals at high risk but not low risk individuals.
4. Examine between-group performance on a word-stem completion and word-recognition task. Implicit memory (priming) is evidenced by faster responding to previously viewed stimuli, thus the assessment of reaction time was necessary to assess group differences. Review of the findings on this classic implicit memory task in AD indicated inconsistent results. However, based on previous hypotheses of intact implicit performance on the probabilistic selection task and on the pre-clinical status of the sample, it was hypothesized that individuals at high risk for AD would not significantly differ from those at low risk on the word-stem completion task. Based on findings of stable recognition impairment in AD, however, individuals at high risk were expected to perform more poorly on recognition of previously presented words than individuals at low risk.

5. Compare performance in at-risk individuals on traditional explicit and implicit memory tasks, as compared to the PS task in order to further examine explicit memory performance in individuals at high risk. As reinforcement learning involves both explicit and implicit memory process, successful learning of the PS task training phase involves a great deal less conscious awareness than traditional explicit tasks. While participants develop strategies for accurate responding, whether learning is occurring and what is being learned is unclear to them. Thus, by contrasting these two, which allow for the assessment of the theoretical difference in learning processes between them, insight into the nuances of explicit memory in AD risk may be gained. Differences observed between groups may thus be observed in the degree to which individuals are able to consciously express what they have learned. While individuals may not be able to declaratively state that they have learned, performance on the probabilistic task was hoped to provide evidence that they have indeed learned the task parameters. Thus, it was hypothesized that all participants would differ between these recognition measures but that high risk individuals would exhibit poorer performance on both measures than low risk individuals.

The overarching objective of the proposed study was to take advantage of an existing longitudinal study to add to the existing etiological literature of memory processes in asymptomatic individuals at risk for the development of AD.

Methods

Participants. 36 healthy older cognitively intact adult participants (Age_M = 80; Female n = 28) were included in the study. Participants were recruited from an ongoing

longitudinal study that examines various biomarkers and cognitive indices of risk for AD. Participants recruited were known carriers (n = 20) and non-carriers (n =16) of the APOE ε4 allele, a genetic risk factor for developing AD. Individuals in the longitudinal study were originally screened for neurological, psychological and drug histories that might complicate study interpretations. Yet, those recruited for the current study were assessed again for medical and health conditions. Significant neurological medical history (e.g. stroke, head injury with significant loss of consciousness, dementia, epilepsy), current psychological illness such as schizophrenia, major depression, anxiety, etc. with symptoms including but not limited to psychosis, mania, delusional thinking, hallucinations, use of psychoactive medications, and documented or suspected history of drug abuse and/or alcoholism were assessed. No significant conditions were reported. No participants were excluded from analyses based on specific medical histories. One participant had a Dementia Rating Scale-2 total score equal to 121 (less than 123; 2 standard deviations below the mean) but was not exclude from analysis.

Measures.

Health status. Health status was assessed using a survey from our laboratory that includes questions regarding past and current diagnoses, surgeries, medications, and physical conditions. This measure was completed by participants at home and brought to the session. It was expected to take approximately 15 minutes to complete.

The Dementia Rating Scale (DRS; Mattis, 1976, 1988) is a brief experimenter-administered measure that assesses five areas of cognitive functioning in elderly individuals. It produces five subscale scores: Attention, Initiation-Perseveration, Construction, Conceptualization, and Memory. The DRS has been shown to have a valid

measure of constructs within mild to moderate AD with criterion correlations to widely used instruments, such as the Wechsler Adult Intelligence Scales. It is scored by summing the raw number of correctly answered items corresponding to each subscale for a total score. The DRS has been shown to have a sensitivity of 98% and a specificity of 97% (Monsch et al. 1995). This measure was used to provide a measure of cognitive status. It took approximately 20-40 minutes to complete.

The Word Stem Completion Task (WSC; Graf, Mandler, & Haden, 1982) is a perceptual priming task commonly used to assess implicit memory. Participants viewed a list of twenty words presented one at a time for three seconds each. The words were specifically chosen to have similar usage frequency and the same number of common completions after a 3-letter stem (Graf, Mandler, & Haden, 1982). Participants were instructed to remember the words in anticipation of a later test. After a brief delay, participants began the word-stem completion task. The first three letters of a word (21 words total) were presented on the computer screen. Participants were instructed to complete the word-stem with the first word that came to mind. Priming in a word-stem completion task was assessed, as typically done, by examining the accuracy of stem completion for primed words relative to unprimed words.

Word Recognition. Recognition of the words studied prior to the WSC task was tested in standard format. Fifty words (16 targets and 34 distractors, randomly ordered) were presented one at a time. Participants were instructed to respond by pushing the keyboard confirming the word was previously presented on the word list or if it is new. The task was self-paced but took approximately 5 minutes to complete. Word recognition performance was assessed in a manner that examined discrimination (i.e., corrected for

guessing) but kept the scores in the metric of percent correct, allowing direct comparison with the word stem data. Thus, Corrected Percent Correct = (1-Error Rate) X (Hit Rate), where the Hit Rate = Hits/total targets and Error Rate = false alarms/total foils (Nielson & Lorber, 2009; Nielson & Powless, 2007).

The Probabilistic Selection Task (PS) is a forced-choice reinforcement learning paradigm comprised of two phases: a training phase and a test phase (Frank, Seeberger, & O'Reilly, 2004; Frank, 2006). In the training phase, participants were presented with three pairs of figures (basic geometric shapes of varying colors; A:B, C:D, E:F) presented in random order. Participants were asked to select one of the figures by pressing a key on the corresponding side of the keyboard (left key, left stimulus). Figures appeared on both sides of the screen according to randomization of pairs. Choices were probabilistically reinforced with either positive ("Correct" printed in green) or negative ("Incorrect" printed in red) feedback (Frank et al., 2004). If no response was made within 5 seconds, the words "No Response Detected" appeared on the screen in white for 1.5 seconds. Probability percentages of reinforcement were set at 80%(A), 70%(C), 60%(E), 40%(F), 30%(D), and 20%(B) respectively for the six different stimuli presented. Performance criteria in the training phase (set to 70% optimal responding of the 80:20 stimulus pair, 60% of the 70:30 pair, and 50% of the 60:40 pair), was evaluated after each block of 60 trials, for a maximum of 6 blocks (360 trials). Once the learning criteria were met, participants proceeded to a test phase where novel stimulus pairs (e.g., 80:70, 30:40) were used to evaluate whether choices were more influenced by positive or negative feedback. No feedback will be given in this phase of the task. The length of the task

varied between approximately 10 and 40 minutes, depending on individual trial response times and how quickly the learning criteria were met.

PST Recognition was presented following completion of the probabilistic selection task. The test sheet contained all six task stimuli with a blank space provided next to each one. Participants were instructed to assign a percentage next to each one reflecting their assessment of how often the stimulus was correct. For example, the assignment of 25% to a figure reflected a perception of low correct probability. Participants were instructed to assign percentages ranging from 0 to 100. Percentages assigned were not required to add up to 100%. This task was specifically added to the original PS task protocol to provide a measure of explicit memory recognition functioning that would support the hypothesized group differences. This measure took approximately 2-5 minutes.

Procedures.

Study procedures. Participants were recruited by telephone from an existing pool of participants in a longitudinal study being conducted by our research group (Seidenberg et al., 2009; Woodard et al., 2010). Participants were sent a packet of information regarding the study which included the medical health survey. Upon arrival, survey materials were collected and informed consent was completed.

After initial study procedures were completed, participants viewed a twenty item word list. After a delay, participants viewed twenty-one word stems on the computer screen and were asked to complete the stem with the first word that comes to mind. After the word-stem completion was administered, the DRS (alternate or standard) was administered. The version of the DRS administered was dependent on previous testing

parameters. The standard version was administered to only 3 participants. Next, participants began the word recognition task. They were presented with words on the computer screen and asked to indicate if the word was one previously shown or not. After completing this task (and a variety of others not included in this study), participants were dismissed and returned for a second session approximately one week later.

At the beginning of the second session, informed consent was again procured. Participants then completed the probabilistic selection task. They were instructed that two figures were going to appear simultaneously on the computer screen, one on each side of the screen. They are told that one figure was going to be correct and one would be incorrect, however, at first, which is which was unknown. The instructions indicated that there is no absolute right answer but that some figures had a higher chance of being correct. They were asked to respond by selecting the key that corresponds with the figure they believe to have the highest chance of being correct. Participants were told that there were several training phases to the task and that their performance during that phase would advance them to a test phase. Participants were then instructed on the response keys and time limitation for each trial (5 seconds). These instructions were followed by a practice section that was repeated at most 2 times when necessary (n = 8). Of those individuals, only 1 was not included in analysis, but that was the result of not meeting learning criteria.

After the experimenter was satisfied that the participant understood the task well enough to proceed, the training phase of the task started. Rest breaks are embedded into the task after completion of 2 and 4 blocks. These breaks were intended to reduce fatigue and increase attention. Once participants met learning criteria, they were instructed that

they were entering a testing phase. During this phase, they were instructed to continue selecting the image they felt had the highest chance of being correct; however, feedback would not be given. At the completion of the task, participants were immediately given the recognition task. On this sheet, they were instructed to place a percentage next to each figure corresponding to their perception of the figure's correctness.

Participants were not provided individual performance feedback nor made aware of the probabilistic parameters of the task in order to ensure their ability to participate in continuing research. However, general feedback on cognitive function was offered (as is generally done for participants in this long-term study). Participants were compensated $20 per session (Sabbatical Fellowship to KAN). Compensation was not performance dependent.

Sample size justification. An a priori power analysis using G*Power (G*Power 3.0: Erdfelder, Faul, & Buchner, 1996) conducted for a 2 (group) X 2 (test) repeated measures ANOVA, indicated that a total sample size of 26 was needed with the resulting statistical power of .80 for a medium effect size. Thus, it was concluded that that sample size should have be sufficient for providing evidence for the significant difference between at-risk participants. Based on previous study outcomes, recruitment exceeded the proposed sample size by approximately 38% (n = 36) to account for the estimate of individuals who would not meet learning criteria on the PS task, and therefore be excluded from analysis.

Results

This study was conducted to determine if healthy elders (see Tables 1 and 2 for Demographic Summary) at high and low risk for developing AD, as determined by

APOE ε4 gene inheritance, exhibit performance differences on a reinforcement learning task, a word-stem completion task, and associated recognition tasks. Preliminary data analyses were conducted in Matlab R2011b (The MathWorks, Natick, MA) and Microsoft Excel 2010 (Microsoft). Statistical tests were analyzed at $p < .05$ in SPSS 19 (SPSS, 2010).

Pearson correlations were performed to assess the relationship between demographic and task variables. No significant relationships were found. A Spearman correlation was performed to assess the relationship between education and risk group. There was a strong, positive correlation between years of education and risk group, *rho* = 0.46, $p = 0.004$, with the high risk group completing more years of formal education than the low risk group. However, education was not significantly correlated to PS task variables (training, $r = -.16$, $p = 0.40$; testing, $r = -.05$, $p = .78$; PS recognition, $r = .15$, $p = .43$), word-stem completion ($r = -.02$, $p = .94$), or word-recognition ($r = .14$, $p = .45$). It was therefore, not included as a covariate in analyses; while it did differ between groups, it did not correlate with the outcome variables. Additionally, a significant, negative correlation between PS training and PS recognition performance was found, $r = -.36$, $p = .02$, indicating that better reinforcement learning was associated with poorer explicit awareness of the reinforcement schedule. Thus, recognition of adaptive learning was not aided by better initial learning performance (indeed, if anything, it was impaired by better learning).

Sex, age, and risk were not significantly correlated with task variables (See Table 1.4). Additionally, the average number of training blocks performed (M = 3.13; *SD* = 1.68) was not significantly correlated to task performance, $r = -.27$, $p = .14$ (training), *r*

= .07, p = .68 (testing), r = .02, p = .90 (PS recognition; see Table 1.4) It was also not significantly different between groups, $t(2,28)$ = -.82, p = .42 Risk group was held as the categorical independent variable for all analyses. Total sample analyzed for PS task n = 30, n = 29 for PS recognition task due to one participant's failure to complete this portion of the protocol.

Probabilistic Selection Task Analysis

Individual participant data were analyzed to assess overall learning of task parameters. Data were analyzed on a block-by-block basis to ensure participants met the learning criteria in the training phase (set to 70% optimal responding of the 80:20 stimulus pair, 60% of the 70:30 pair, and 50% of the 60:40 pair). Six participants (n = 3 each risk group) were excluded due to failure to meet these criteria. Additionally, one participant was excluded from recognition performance analyses due to failure to complete the task. Examination of the distributions revealed no underlying problems with the assumptions of normality (skew; kurtosis).

Task accuracy in the training phase was assessed by the calculating the average of participants selecting the most probabilistically rewarding stimulus over the least probabilistically rewarding stimulus (i.e., selection of A(80%) in the A(80):B(20) pair). In the testing phase, accuracy was determined by the average of each participant's ability to choose the highest probability (Choose-A) and avoid the lowest probability (Avoid-B) in novel combinations of stimuli such that choices corresponded to the 80(A) > 70(C) > 60(E) > 40(F) > 30(D) > 20(B) probability scale.

PS recognition performance was computed by calculating the absolute value of the difference between the task-assigned probability for stimulus A (80) and the

participant assigned probability for the same stimulus (any value between 0-100). The same difference score was computed for task-assigned probability of 20 for stimulus B. This difference was then divided by the total possible difference of 160 (80 for each stimulus given the highest probabilistic value). For example, if a participant assigned 20 as the probability of stimulus A being correct and 10 as the probability of stimulus B being correct, the difference measure of 80-20 for A (60) and 20-10 for B (10) divided by the total possible would result in an overall recognition performance measure of 43.7% ((|80-20| + |20-10|)/160 = .437)). This measure provides an indication of how accurately each participant was able to assess and explicitly state the probabilities of task stimuli.

Specific Aim #1: Accuracy differences between the risk groups.

It was hypothesized that accuracy would differ between high and low risk individuals during the training phase of the probabilistic selection task. Individuals at high risk for AD were expected to be less accurate than low risk participants. In contrast, significant differences were not expected during the testing phase of the task.

A mixed analysis of variance was conducted using a 2 (group) X 2 (task) design, where task was PS training and testing performance. A significant main effect of task, $F(1,28) = 8.35$, $p = .01$, $\eta_p^2 = .23$, was found, reflecting differences in overall performance between the conditions. The interaction was not significant, $F(1,28) = 1.41$, $p = .24$, $\eta_p^2 = .05$. The between subjects group effect was also not significant, $F(1,28) = 1.03$, $p = .32$, $\eta_p^2 = .04$. A priori contrasts showed that training performance was not significantly different between low and high risk groups ($M_{Diff} = -.004$, $p = .94$) nor was performance on the PS recognition task ($M_{Diff} = .11$, $p = .22$).

Specific Aim #2: PS training vs. testing within risk groups.

It was expected that high risk participants would exhibit poorer performance during PS training than during testing, while no such difference was expected for low risk participants.

The same mixed ANOVA used for Aim #1 was used for Aim 2. Pairwise comparisons indicated no significant difference on training (M = 80.0, SD = 11.0) versus testing (M = 72.2, SD = 22.1) portions of the reinforcement learning task for low risk participants, p = .27. However, among high risk participants, training performance (M = 80.4, SD = 13.7) was significantly *better* than testing performance (M = 61.7, SD = 23.1), p = .004, opposite of the predicted effect (see Figure 3).

Specific Aim #3: Group differences on PS task training phase vs. recognition test.

It was hypothesized that significant differences in performance would be evident for high risk but not low risk participants between PS training and PS recognition, as both measures include, to some degree, explicit memory processing.

A mixed analysis of variance was performed using a 2 (group) X 2 (task) analysis, where task was PS training and PS recognition. A significant main effect of task was observed $F(1,27) = 127.73$, $p < .001$, $\eta_p^2 = 0.83$; overall training performance (M = 80.1, SD = 12.6) was significantly greater than recognition performance (M = 33.6, SD = 13.2). No significant interaction was found, $F(1,27) = .12$, $p = .73$, $\eta_p^2 = .004$. The between subjects group effect was also not significant, $F(1,27) = .39$, $p = .54$, $\eta_p^2 = .01$. A priori contrasts showed that PS training performance was not significantly different between risk groups ($M_{Diff} = -.003$, $p = .96$), nor was performance on the PS recognition task ($M_{Diff} = -.031$, $p = .54$; see Figure 4).

Specific Aim #4: Group differences in word-stem completion vs. word-recognition.

It was hypothesized that word-stem completion performance would not differ between participant groups, but low risk participants were expected to outperform high risk participants on the word-recognition task.

A paired-samples t-test was conducted as a manipulation check to assure that a priming effect occurred for word-stem completion. There was a statistically significant difference in response time for correctly completed stems (M = 1.51, SD = 0.79) and incorrectly completed primed stems (M = 2.65, SD = 1.35), $t(34) = -4.98$, $p < 0.001$ indicating that individuals completed word-stems for primed words faster than for unprimed words. This was demonstrated for both the high, $t(19) = 4.26$, $p = .001$ and low, $t(14) = 2.35$, $p = .034$, groups. A priming effect was also validated for overall performance by computing the percentage of correctly completed primed stems relative to the percentage of unprimed stems completed with the 'expected' word (i.e., chance performance). Priming was demonstrated; performance was significantly greater than chance, $t(34) = 4.07$, $p < .001$. This was also demonstrated for both high $t(19) = -3.37$, $p = .003$) and low, $t(14) = -4.46$, $p < .001$ risk groups.

A mixed analysis of variance was conducted using a 2 (group) X 2 (task) analysis, where task was word-stem completion and word-recognition performance. A significant main effect of task was observed, $F(1,33) = 135.55$, $p < .001$, $\eta_p^2 = 0.80$. As is typical, word-stem completion performance (M = 16.3; SD = 14.1) was significantly poorer than word-recognition performance (M = 55.7; SD = 21.1), but there was no significant interaction, $F(1,33) = .35$, $p = .56$, $\eta_p^2 = .01$, or main effect of group, $F(1,33) = 1.04$, $p = .31$, $\eta_p^2 = .03$. Word-stem completion performance was not significantly different

between risk groups (M_{Diff} = .07, p = .13) nor was performance on the word-recognition task (M_{Diff} = .03, p = .65; see Figure 5).

Specific Aim #5: Explicit vs. implicit performance between groups.

Interactions between task and group were hypothesized such that performance would differ between word and PS recognition measures generally, consistent with differences predicted in Aim 3, but also that high risk participants would exhibit poorer performance on both measures than low risk participants. In contrast, no significant differences were expected in either group on measures of implicit memory.

Mixed analysis of variance was conducted using a 2 (group) X 2 (task) analysis, where the tasks were word-recognition and PS recognition performance. A significant main effect of task was observed, $F(1,28) = 26.53$, $p < .001$, $\eta_p^2 = 0.49$, such that word-recognition (M = 56.3; SD = 21.8) was significantly better than PS recognition (M = 33.9; SD = 13.1). However, no significant interaction, $F(1,28) = .47$, $p = .50$, $\eta_p^2 = .07$, or group main effect was found, $F(1,28) = .19$, $p = .67$, $\eta_p^2 = .007$. Word-recognition performance was not significantly different between risk groups (M_{Diff} = -.01, p = .85), nor was performance on the PS recognition task (M_{Diff} = .05, p = .51; see Figure 6).

Mixed analysis of variance was conducted using a 2 (group) X 2 (task) analysis, where the tasks were word-stem completion and PS task testing performance. A significant main effect of task was observed, $F(1,28) = 79.98$, $p < .001$, $\eta_p^2 = 0.74$, where word-stem performance (M = 16.4; SD = 14.9) was significantly poorer than PS testing performance (M = 66.2; SD = 22.9). No significant interaction was found, $F(1,28) = .02$, $p = .90$, $\eta_p^2 = .001$. However, the between subjects group effect was significant, $F(1,28) = 5.32$, $p = .03$, $\eta_p^2 = .16$. Levene's test of equality of error variances was significant, p =

.008 for word-stem completion performance. This was addressed by evaluating the results with a more conservative alpha level, $p = .001$; however, the pattern of significance was maintained. Performance of the high risk group was significantly poorer on word-stem completion ($M = 12.5$; $SD = 8.1$) and PS testing ($M = 61.7$; $SD = 20.0$) than the performance of the low risk group (word-stem: $M = 21.7$; $SD = 23.1$; PS testing: $M = 72.2$; $SD = 22.1$), $p < .001$, see Figure 7.

Discussion

Based on a review of the literature on memory system function in individuals with Alzheimer's disease and on the existing ability to identify preclinical biomarkers for cognitive decline, the current study aimed to contribute novel predictions that would elucidate the pattern of memory function in asymptomatic carriers of the APOE ε4 allele, a genetic risk factor for AD. It was expected that individuals at risk would exhibit differential patterns of performance on reinforcement learning, explicit, and implicit tasks reliant on these memory systems. Broadly, this aim was achieved. However, the pattern of results supporting the differentiation was not as predicted. Importantly, the pattern of results motivated a reconceptualization of the PS task, giving greater consideration for the role of explicit and implicit processes in reinforcement learning. Specifically, the training phase of the PS task involves reinforcement learning that requires both explicit and implicit processes, and a requirement for learning to a specific minimum criterion. Thus, it assesses learning quite differently than the other explicit memory measures employed. As such, the PS training phase is conceptualized heretofore as reinforcement learning reliant on explicit and implicit processes, while PS testing is conceptualized as reliant on implicit memory processes, and the PS recognition task is conceptualized as

reliant on explicit memory processes. As traditional tests, word-stem completion continued to be viewed as an implicit memory measure and word-recognition as an explicit measure.

It was hypothesized that individuals at high risk for developing AD would exhibit poorer reinforcement learning performance, as assessed by the training phase of the PS task, than individuals at low risk, but would not differ from low risk individuals in the implicit application of memory (Hypothesis 1 and 2). Results indicated that risk groups did not differ in reinforcement learning performance (training) or implicit retrieval of that learning (testing). However, individuals at high risk were significantly *better* at learning than they were at the application of that reinforcement learning at testing. Thus, this finding was opposite of what was predicted.

Differences between reinforcement learning and explicit memory (PS recognition) were also predicted for individuals at high risk but not at low risk (Hypothesis 3). Results indicated that independent of genetic risk, reinforcement learning performance was significantly better than the ability to explicitly identify the relationships that were learned. Yet, neither task differentiated the risk groups.

Traditional memory measures, word-stem completion (implicit) and word-recognition (explicit), were examined to assess the pattern of memory function in high- vs. low AD risk groups (Hypothesis 4). As is typical, word recognition was significantly better than word-stem completion. However, the lack of significant interaction indicated that risk did not differentiate performance for either measure. Moreover, comparisons of these traditional measures with the reinforcement learning task phases and recognition showed that risk did not differentiate explicit memory measure performance. Yet, word-

stem completion did differentiate risk; high risk participants had significantly poorer stem completion than low risk participants (Hypothesis 5).

Breakdown of the analyses revealed that the risk groups, based on APOE ε4 status, did not significantly differ on learning and implicit portions of the reinforcement learning task (i.e., PS training and PS testing, respectively). Instead, participants in both groups exhibited comparable patterns of performance. However, while the high risk group exhibited adaptive learning (a process heavily reliant on both explicit and implicit memory processes) to a comparable degree as the low risk group, they exhibited *poorer* implicit memory overall than individuals at low risk. This result was robust, with a moderately large effect size ($\eta_p^2 = .16$) and significance maintained after adjusting alpha to $p < .001$ to account for unequal variances. This was contrary to prediction and to the literature, which generally suggests explicit memory impairment, and largely intact implicit memory in AD (Heindel et al.,1989; Bondi & Kaszniak, 1991).

Although the past literature makes interpreting the present results somewhat perplexing, results comparable to the present findings were shown using an acquired equivalence paradigm that distinguished hippocampal and basal ganglia functions in healthy elders, PD patients and non-demented individuals with hippocampal atrophy (Myer et al., 2003). In the acquired equivalence task, participants perform a training phase in which A1 is associated with X1, subsequently followed by the association of A2 and X1. A second pairing of B1 and B2 is made with Y1 in a similar fashion. During a second training phase, A1 is associated with X2 and B1 with Y2. In a transfer phase, similar to PS testing, no feedback is provided and participants are asked to assess the association between A2 and X2, and B2 with Y2. The results indicated that during the

training phase, PD patients made significantly more errors than the other two groups, while controls and those with hippocampal atrophy did *not* differ (Myer et al., 2003). These findings have also been corroborated in the animal literature (Bonardi, Rey, Richmond, & Hall, 1993; Frank & O'Reilly, 2003).

The Myer et al. (2003) findings are largely similar to the current PS task findings. That is, participants at high AD risk (analogous to hippocampal atrophy) did not differ from low AD risk (analogous to controls) in the training phase. However, in Myer et al. during the transfer phase of the acquired equivalence task, there was a trend ($p = .059$) for differences between hippocampal atrophy and PD participants, which is quite comparable to the current results. Individuals at low risk performed similarly to high risk individuals on the word-recognition and PS acquisition and recognition (explicit) tasks. However, their implicit memory performance (PS testing, word-stem completion) was significantly better than in the high risk group. As these individuals were presumed to lack latent neuropathology, their pattern of performance suggests they have intact ability to transfer learned information to contextually novel situations (Myer et al., 2003), in contrast to high risk participants. Myer et al. concluded that the basal ganglia, not the hippocampus, disrupted initial learning in the training phase, while the hippocampus, not the basal ganglia, disrupted information transfer (Myer et al., 2003).

Taken together, the current findings and those of Meyer et al. (2003) imply that the basal ganglia are involved in processes responsible for initial reinforcement learning, presumably intact in AD and those at risk for AD, while the hippocampus is involved in the learning of complex tasks that require the application of previously learned associations to novel situations (Myer et al., 2003). Thus, while the hippocampus may not

be critical to habit learning, it does play a vital role in learning that requires the transfer and application of reinforcement learning to novel situations. Myer et al., (2003) concluded that damage to the hippocampus may impact *how* information is learned (i.e., learning in a specific way), which may impact the manner in which information is brought to bear in future situations. This is further supported by the model of memory presented by Atallah et al., (2004), in which the hippocampus and the posterior cortex influence the flexible maintenance of relational information, while the basal ganglia facilitate action selection based on working memory. The structure of the model posited that hippocampal function should be sensitive to reinforcement learning processes. The performance differences resulting from the current investigation are believed to be evidence of such sensitivity as acquisition (reinforcement learning) was not affected within either of the risk groups; only testing (the application of learning) was impacted within the high risk group. Furthermore, as the basal ganglia was not assumed to be impaired within the current sample, as it is in PD, poor reinforcement learning was not anticipated or evidenced.

Additional results of the current study indicated that the overall ability to learn (acquisition) was intact across groups, but the explicit expression (i.e., awareness) of that learning on open-ended pencil and paper task was poor, also across groups. The lack of distinguishable group differences on either of these measures (PS training and recognition), indicate that *overall,* the present sample displayed globally intact explicit performance on the reinforcement learning task.

The inclusion of a reinforcement learning task in the current study was hypothesized to provide a novel approach to identifying patterns of memory function.

However, comparison of it with traditional memory tasks is important for interpreting the results. The results from comparing the traditional measures of memory (i.e., word-stem completion and word-recognition), indicated that individuals at high risk for AD did not significantly differ from those at low risk on the word-stem completion task. Some past studies report no differences in implicit memory on word-identification tasks between individuals with AD and controls (Keane, Gabrieli, Fennema, Goodwin, & Corkin, 1991; Shimamura et al., 1987; Christensen & Birrell, 1991). Importantly, however, Heindel et al., (1989), replicated by Bondi and Kaszniak (1991), did find differences between neurodegenerative groups on the word-stem completion task. The current results trended in the direction of poorer word-stem performance in the high risk group (p = .13). Indeed, when combined with the other implicit memory task, PS testing, there was a main effect of group, showing poorer implicit memory performance in the high risk group. Thus, the present results provide at least weak support for the findings of Heindel et al. and Bondi and Kaszniak. Contrary to prediction, the high risk group did not exhibit significantly poorer performance on the explicit measure (word-recognition) despite the strongly established hallmark of this impairment in AD.

Of the two forms of memory assessed by the tasks, implicit was expected to show a general pattern of stability while explicit was expected to differentiate risk groups. The pattern of results in the present study was relatively opposite to this expectation. That is, the risk groups did not differ on explicit memory tests, but the high risk group exhibited poorer implicit memory performance than the low risk group. The hypothesized differences were largely supported by the existing literature (Randolph, Tierney, & Chase, 1995; Light, Singh, & Capps, 1986; Heindel, Salmon, Shults, Walicke, & Butters,

1989; Huberman, Moscovitch, & Freedman, 1994) and were substantiated also by the neuropsychological literature. For example, learning differences between APOE ε2, ε3, and ε4 carriers on a verbal list learning task (Selective Reminding Task) showed that ε4 carriers, whether hetero- or homozygotes, performed worst of all the allele groups (Helkala et al., 1995). Furthermore, ε4 carriers have also been found to exhibit poorer verbal memory (Soinen and Riekkiner, 1996), as well as Mini Mental State Exam (MMSE), visual attention, logical reasoning, and psychomotor ability (Berr et al., 1996), which collectively impact learning. It is important to note, however, that this pattern is not uncontested in the literature. Chen et al., (2002) conducted a study investigating the differential effect of a family history of AD (positive and negative), and APOE status (hetero- and homozygotes ε4 carriers) on the California Verbal Learning Test (CVLT) among cognitively intact older adults (Age_M = 66.7) Based on previous research indicating decreased performance on this task (Small, Basun, and Backman, 1998; Bondi et al., 1994), Chen et al. hypothesized that ε4 carriers would perform worse than non-carriers. Interestingly, results indicated that age, sex, and education affected performance, but family history and genetic risk did not. The authors posited that these findings were due to either the insensitivity of the CVLT (a dubious conclusion given its strong psychometric properties), or that the detection of risk for future impairment may not be measurable so early by such tests. While differences among cognitively intact ε4 carriers are varied within the neuropsychological literature, the pattern of performance among high risk participants on the implicit memory measures employed in the current sample suggests potential for higher sensitivity to preclinical decline using reinforcement learning paradigms.

Limitations

The anticipated potential limitations were not actually encountered. For example, successful recruitment negated the need to widen the subject pool to community-dwelling individuals and additional genotyping. More, equal group sizes, high and low risk, were easily achieved, negating analytical limitations. However, perhaps the most predominant limitation of the study was the cognitively intact nature of the sample. As participants in a long-term longitudinal sample, we anticipated a broader range of cognitive performance than was achieved. Instead of a range of performance, we encountered the 'best of the best.' That is, we hypothesize that, given the long-term nature of this study, those with the greatest cognitive challenges have been more frequent to withdraw from the study, leaving those who are aging most 'successfully' as participants. Examining participants with a diagnosis of Mild Cognitive Impairment or with age-associated memory impairment, along with APOE alleles, might provide more insight into the hypotheses.

A more sensitive analysis of the PS task may provide insight into behavioral age differences not assessed here. As outlined by investigations using this task in older adults to assess reinforcement learning and working memory (Frank & Kong, 2008), analysis of the training data based on win-stay and lose-switch behaviors may be of value. Based on both this model and the well-established role of dopamine in reinforcement learning, Frank and Kong (2008) postulated the "dopamine hypothesis of aging". This hypothesis proposes that as individuals age, levels of striatal dopamine present in the basal ganglia diminish, leading to a pattern of learning from negative outcomes similar to what is found in PD. Indeed, using the probabilistic selection task employed in the current study, they investigated learning performance among Old-Old (OO; $Age_M = 77$) and Young-Old

(YO; Age_M = 67) participants, finding that the OO group exhibited greater learning from negative feedback. In order to account for the impact of working memory deficits on these findings, the task was analyzed to assess the sensitivity of the basal ganglia to positive and negative feedback. Analysis of trial-by-trial behavior in the first training block of the task revealed that OO individuals had increased switching behavior (avoiding the selection of stimuli previously given negative reinforcement) and impaired learning from positive feedback. High conflict trials, thought to reflect optimization of choices, were also analyzed, which revealed similar results suggestive of increased learning through negative feedback in the older group (Frank & Kong, 2008).

While age was not significantly different between risk groups in the current investigation, a median split approach to investigate Old-Old and Young-Old differences, similar to that employed by Frank and Kong (2008) might be of value. Alternatively, previous investigations employing the PS task have employed Q-learning models to investigate single-trial reward prediction errors (Cavanagh, Frank, Klein, and Allen, 2010). This method of analysis assesses the trial-by-trial learning during the training phase of the PS task. This method requires the computation of Q-learning values (including the learning rate for gains and losses and reinforcer values (correct and incorrect)), which are used to compute the softmax logistic function producing probabilities of responses for each trial (including calculating in a free parameter for inverse gain that accounts for explore and exploit tendencies). The log likelihood estimate is then calculated using a standard hill-climbing search algorithm (see Cavanagh et al., 2010).

Lastly, in addition to a more sensitive analysis of the PS data, an understanding of underlying neural function, as measured by electroencephalography, may be more sensitive to subtle differences between risk groups. In the same investigation referenced previously, Cavanagh et al., (2010), found no behavioral differences between young, healthy participants. However, medial and lateral frontal theta activities were indicative of different behavioral adaptations among participants. Neural correlate differences within the current sample could identify a biomarker for the early detection of cognitive decline. In fact, very recently, neural activity has been used to detect biomarkers for AD. Poil et al., (2013) used resting state EEG to indicate that beta-frequency range (13–30Hz) activity can predict conversion from MCI to AD. More, Schmidt et al., (2013) used alpha/theta frequency range to distinguish AD patients from normal controls. It is being argued within this field that integrating EEG biomarkers into a diagnostic index could greatly improve the ability to identify cognitive decline before it occurs, could be more sensitive than typical behavioral measures of impairment at detecting decline, and could be used to determine when therapeutic interventions should begin (Poil et al., 2013).

In many ways, the findings are clinically encouraging in that they suggest that elders who carry the APOE ε4 allele, thereby having 15 times greater risk for the development of AD, exhibit similar learning and memory function as those at low risk. However, further investigation of the data and examination of neural activity associated with behavioral performance are needed prior to the conclusion that differences between risk groups prior to cognitive decline do not exist beyond those proposed here.

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Appendix

Tables and Figures

Table 1.1 Summary of Demographic Variables

Variable	N	Mean(SD)	%
Sex			
Male	8		22.2
Female	28		77.8
Age (years)		80.15(4.68)	
72-76	9		25.0
77-79	8		22.2
80-84	11		30.6
85-89	8		22.2
Apolipoprotein-E (APOE) allele			
APOE ε4 positive	20		55.6
APOE ε4 negative	16		44.4
Education (years)		15.00(2.85)	
12	11		30.6
13-16	18		50.0
17-23	7		19.4
Race/Ethnicity			
Caucasian	36		100

Table 1.2 Summary of Cognitive and Task Variables

Variable	N	Mean(SD)	%
Dementia Rating Scale-2	36	137.9(4.40)	
121-123	1		2.8
130-144	35		97.2
Mini Mental State Exam	35	28.34(1.63)	
24-26	6		11.1
27-30	28		86.1
Missing	1		2.8
Probabilistic Selection Task	30		
Blocks Performed		3.13(1.68)	
Training AB		80.02(12.44)	
Testing AB		66.27(22.9)	
Probabilistic Selection Recognition	29	33.96(13.0)	
Word-Stem Priming Effect Proportion Correct	35	16.47(14.9)	
Word-Recognition Proportion Correct	35	56.33(21.8)	

Table 1.3 Summary of Task Variables by Risk Group

	Low Risk		High Risk	
Variable	N	Mean(SD)	N	Mean(SD)
Dementia Rating Scale		139.13(2.96)		136.75(4.59)
121-123	0		1	
130-144	16		19	
Mini Mental State Exam		28.75(1.44)		28.00(1.73)
24-26	2		4	
27-30	16		15	
Missing	0		1	
Probabilistic Selection Task				
Training AB	80.00(11.0)		80.35(13.7)	
Testing AB	72.23(22.1)		61.70(23.1)	
Probabilistic Selection Recognition	31.67(9.50)		33.44((16.9)	
Word-Stem Priming Effect Proportion Correct	21.67(20.0)		12.50(8.10)	
Word-Recognition Proportion Correct	57.60(20.6)		54.30 (22.0)	

Table 1.4 *Pearson Correlations of Demographic and Probabilistic Selection Task Variables.*

	1	2	3	4	5
Sex	-				
Age	.12	-			
Education (years)	.40	.53	-		
Training AB	.90	.23	.40	-	
Testing AB	.29	.85	.77	.59	-
PS Recognition	.70	.83	.43	.02*	.09

*** p < 0.01; * p < 0.05*

Figure 1. *Probabilistic Selection Task Training (Reinforcement Learning) Performance by Risk Groups*

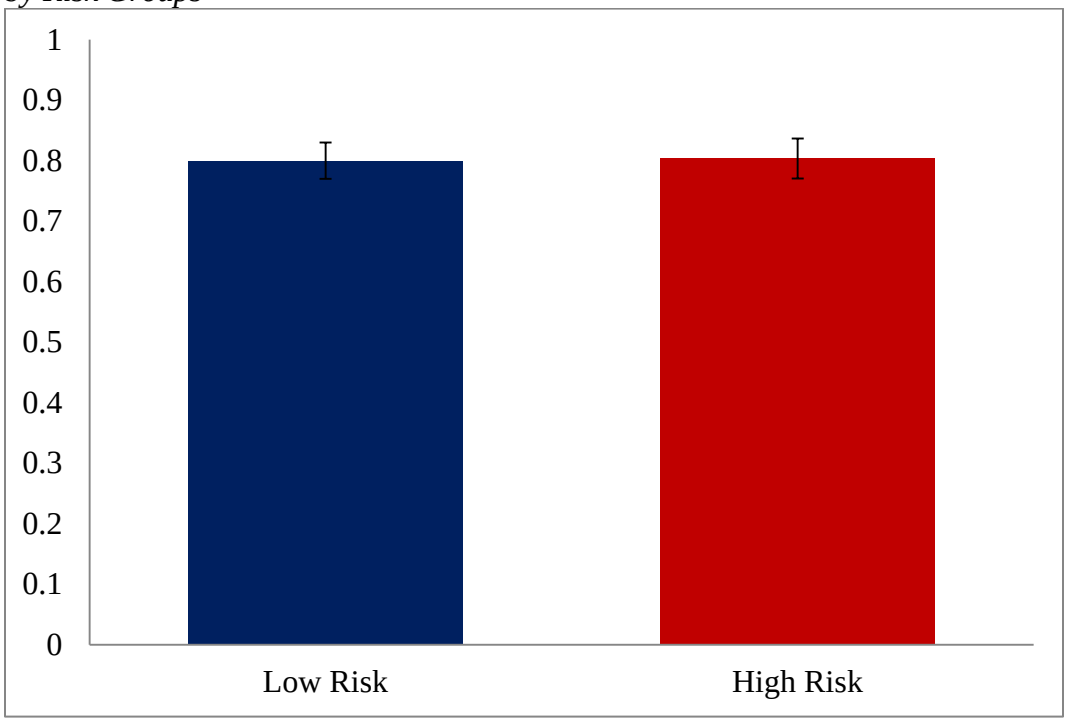


Figure 2. *Probabilistic Selection Task Testing (Implicit) Performance by Risk Groups*

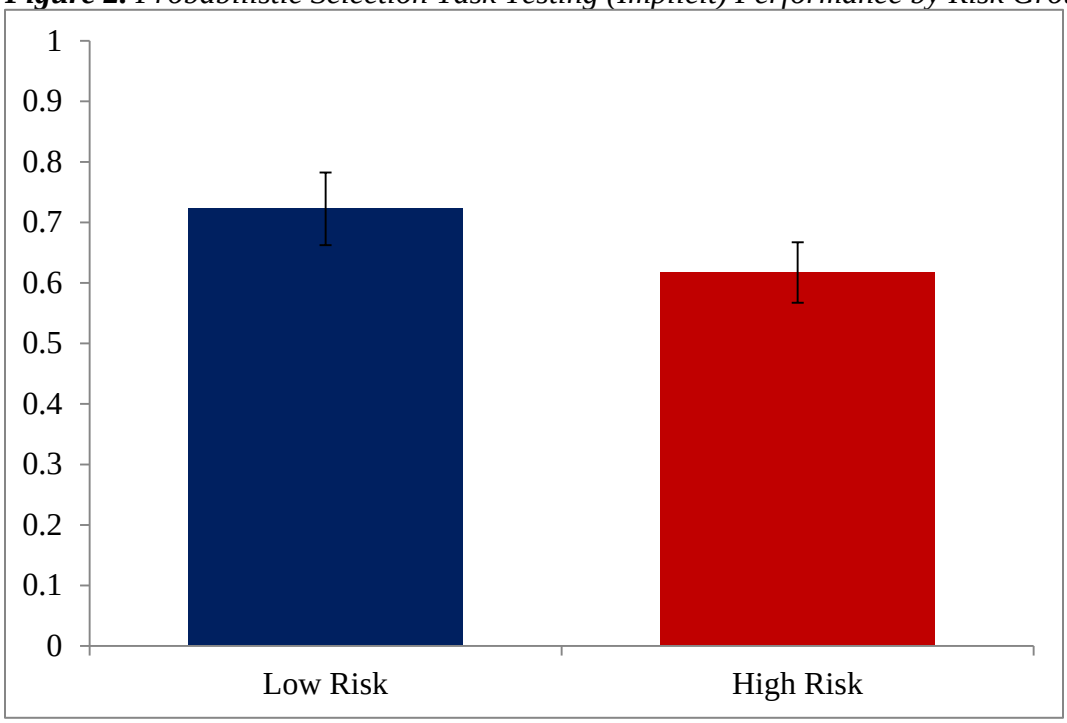
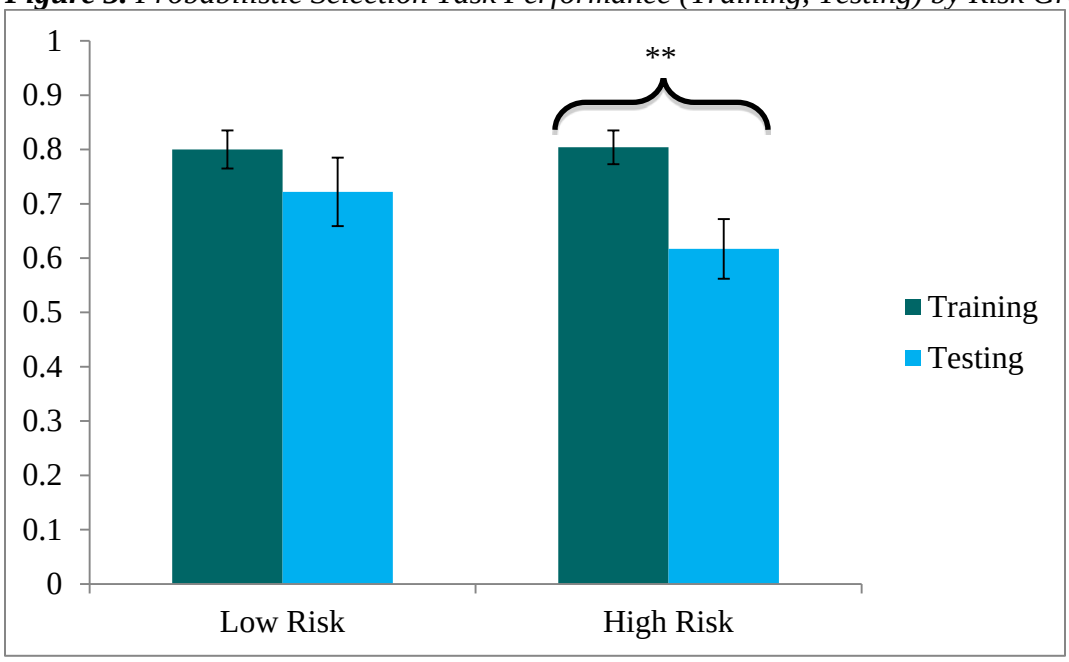
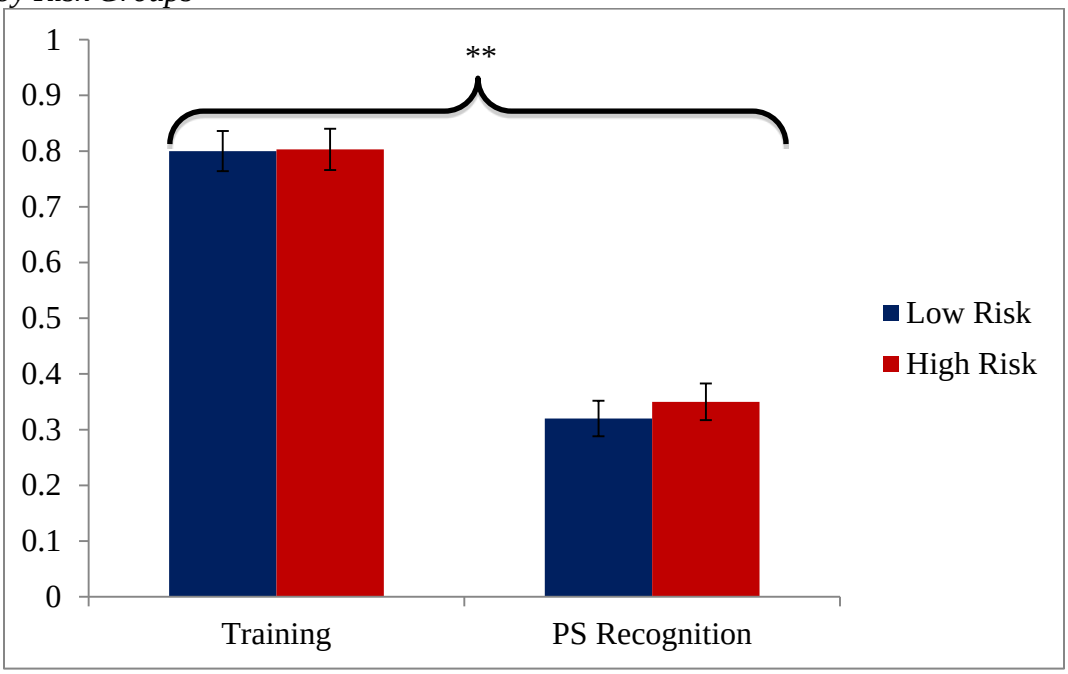


Figure 3. *Probabilistic Selection Task Performance (Training, Testing) by Risk Groups*



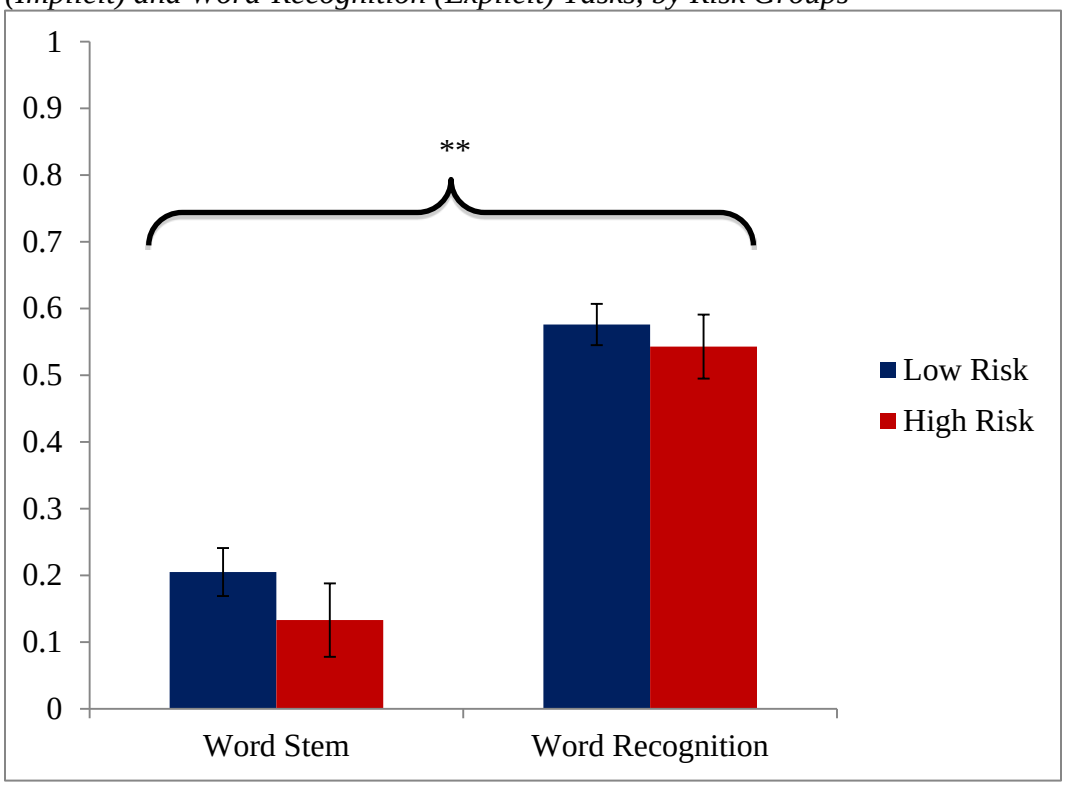
***p* < .001

Figure 4. *Performance on Probabilistic Training (RL) and Recognition (Explicit) Tasks by Risk Groups*



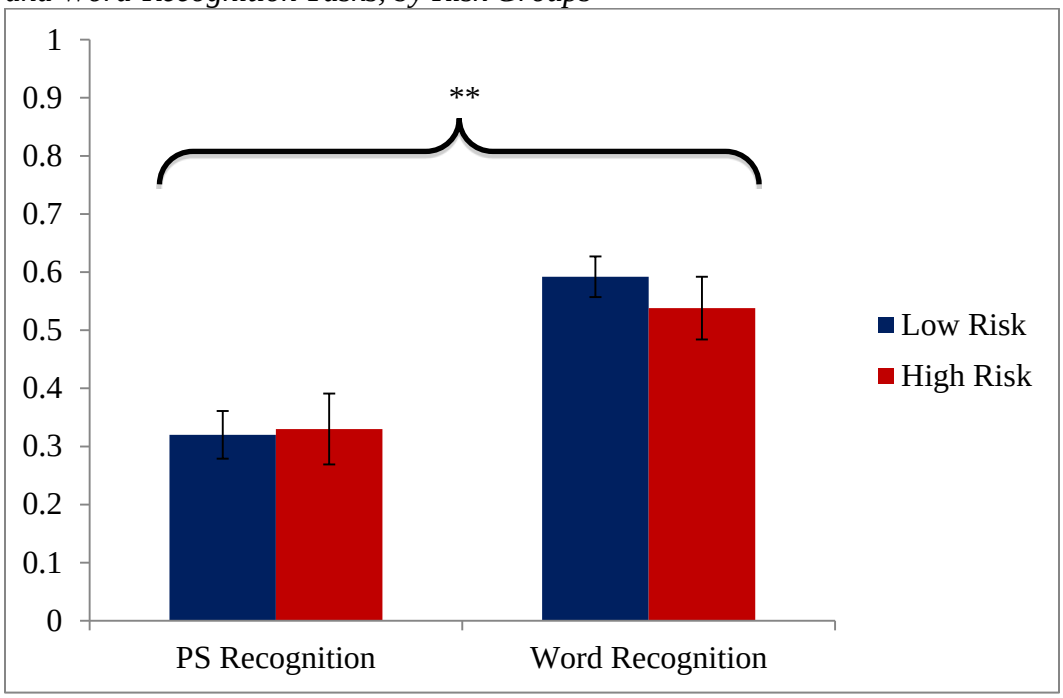
***p* < .001

Figure 5. *Comparison of Traditional Memory Measures, Word-Stem Completion (Implicit) and Word-Recognition (Explicit) Tasks, by Risk Groups*



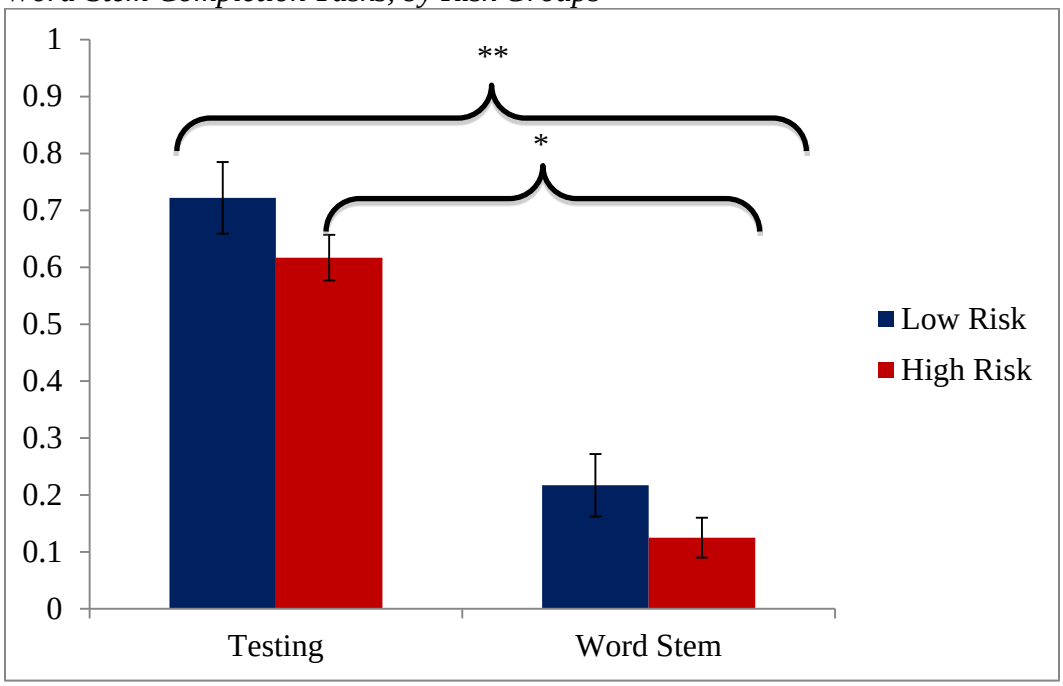
**$p < .001$

Figure 6. *Comparison of Explicit Memory Measures, Probabilistic Selection Recognition and Word-Recognition Tasks, by Risk Groups*



**$p < .001$

Figure 7. *Comparison of Implicit Memory Measures, Probabilistic Selection Testing and Word-Stem Completion Tasks, by Risk Groups*



*$p < .05$; **$p < .001$