Reinforcement Learning, Error-Related Negativity, and Genetic Risk for Alzheimer's Disease

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by

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ABSTRACT
REINFORCEMENT LEARING, ERROR RELATED NEGATIVITY, AND GENETIC RISK FOR ALZHIEMER'S DISEASE
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Reinforcement learning (RL) has been widely used as a model of animal and human learning and decision-making. The neural networks underlying RL involve many of the same structures primarily affected by Alzheimer's disease (AD) such as the hippocampus. Yet, RL and non-invasive evaluation of its neural underpinnings have been underutilized as a framework for understanding disease pathology and its pre-clinical states. This study aimed to provide a novel approach for assessing subtle changes in asymptomatic apolipoprotein-E (APOE) carriers and non-carriers.

Electroencephalography was collected from forty APOE genotyped older adults (Male n = 11; M_{age} = 79.30; $M_{education}$ = 14.88 years) during an RL task comprised of distinct phases (RL, implicit). Neural components associated with the error detection system involved in RL, the response error-related negativity (ERN) and the feedback error-related negativity (FRN), were examined for individuals at low (APOE ε4-; n=20) and high risk (APOE ε4+; n=20). RL task performance did not differ between risk groups. However, the high-risk group consistently elicited greater peak amplitudes than the low-risk group. The pattern of results indicated that the high-risk group deviated from typical RL processes such that peak amplitudes did not differ between early and late learning. Additionally, despite intact learning, latent hippocampal atrophy is believed to have disrupted the transfer and use of learned information to novel situations thus altering the hippocampal-frontostriatal circuit responsible for adaptive behavior and the corresponding neural signal.

The results indicate that disease related changes can be identified prior to clinical diagnosis or functional decline using RL and a non-invasive assessment of neural function, which may prove to inform clinical conceptualization, assessment, and treatment.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Reinforcement Learning, Error-Related Negativity, and Genetic Risk for Alzheimer's Disease

Reinforcement learning (RL) suggests that individuals navigate their environments through a learning process (Sutton & Barto, 1998). The theoretical principles of learning depend on brain regions heavily affected by disease pathology such as hippocampal atrophy in Alzheimer's disease (AD; e.g., Berger, Alger, & Thompson, 1976; Clark, Manns, & Squire, 2002; Shohamy, Myers, Onlaor, & Gluck, 2004; Shohamy & Wagner, 2008). This disorder, despite being habitually characterized by memory loss, causes widespread cognitive impairments, including aspects of executive function and potential deficits in learning. However, little investigation has applied an RL model to AD or its pre-clinical states. The epidemic prevalence of AD, an estimated 115.4 million cases world wide by 2050 (Bicalho et al., 2013), necessitates such a novel approach of identifying early onset and predicting patterns of progression.

Growing fields of research are showing that the occurrence and progression of disease related atrophy can be detected years before diagnosis, and importantly, at the neuronal level via changes in the brain's synaptic activity (e.g., Coleman, Federoff, & Kurlan, 2004; Davies et al., 1988; Liraz, Boehm-Cagan, & Michaelson, 2013). Indeed, specific neural components have already been found to be sensitive to both RL and genetic risk for AD (Green & Levey, 1999; Mathalon et al., 2003). This means that the first stages of decline from typical to atypical function are invisible to the naked eye, begin well before any maladaptive behaviors are evident, and might be detectable via a measure of synaptic function, such as electroencephalography (EEG). Furthermore, if behavioral changes characteristic of AD are acknowledged to be caused by structural

degeneration of regions important for RL, then investigating how people learn, and the underlying mechanisms that facilitate such learning, may prove fruitful for understanding this condition. By applying an RL framework to the behavioral outcomes and neural underpinnings of AD and risk for AD, the likelihood of early identification and prediction may be dramatically enhanced. New methods of assessment, the development of effective treatments, interventions, and ultimately, the opportunity for prevention might follow. The present study aimed to examine RL in a sample of asymptomatic older adults at low and high risk for developing AD.

Previous research demonstrated that individuals with Parkinson's disease (PD) made significantly more errors during testing using an acquired equivalence paradigm than healthy elders or non-demented individuals with hippocampal atrophy (Myers et al., 2003). Controls and those with hippocampal atrophy did not differ. These findings have also been corroborated in the animal literature (Bonardi, Rey, Richmond, & Hall, 1993; Frank, Rudy, & O'Reilly, 2003). These findings imply that the basal ganglia are involved in processes responsible for initial reinforcement learning, presumably intact in AD and healthy elders 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. 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 RL to novel situations. Myers et al., (2003) concluded that damage to the hippocampus may impact *how* information is learned, which may impact the manner in which information is brought to bear in future situations. It is in this respect that the present study aims to expand based on the neural correlates of RL, specifically on the generation of a prediction error. In

order to understand how a model of RL might be applied to a disease state such as AD, it is important to first understand what learning is and the specific aspects of such a model.

Reinforcement Learning: A Brief Review

In short, learning is a form of change (Thorndike, 1931) produced by synaptic function (Hebb, 1949) and reflected in observable behavior (Pavlov, 1927; Pavlov & Anrep, 2003; Skinner, 1938; Watson, 1913). Building on the principles of associative learning - namely that positive interactions between an agent and the environment are likely to be repeated while actions leading to negative outcomes are not (Kaelbling, Littman, & Moore, 1996; Maia, 2009; Thorndike, 1931) - reinforcement learning was introduced as a computational framework of goal-directed behaviors executed by an agent in a dynamic, non-deterministic environment (Barto, 1992; Sutton & Barto, 1998).

In order to take such action, people acquire information by interacting with their environment. They store that information, generalize it, alter and manipulate it, retrieve it, transmit it, and ultimately, they use it (Münte et al., 2000). RL, therefore, is a framework for understanding what "we" *do* in order to achieve "something" with the goal of adaptively adjusting behavior to maximize the frequency and/or magnitude of outcomes over time (Barto, 1992; Sutton & Barto, 1998). In order to do this, an agent ("we"), must be able to remember (memory) and learn (executive function) from its past experience (Sutton & Barto, 1998). Additionally, a balanced trade-off between repeatedly engaging in actions that have previously been found to be effective and allowing for the discovery of new actions that may be more effective must be established. The establishment of that balance necessitates, 1) that some actions be performed when the outcome is uncertain and, 2) that the environment be frequently monitored (Sutton &

Barto, 1998). Actions can then be appropriately adaptive (Konidaris, Scheidwasser, & Barto, 2012) such that they are used to improve performance.

The adaptability of the learning process greatly depends on the symbolic representation and manipulation of environmental components required for task completion (Gallistel & King, 2011). Memories hold meaningful information, and the accessibility and use of that information is vital for learning and decision making. Medial temporal lobe (MTL) structures are responsible for such processing. In order for present and future goal-directed behavior to be optimized, past behavior and outcomes need to be remembered, making it necessary for memories to carry information forward in time so that it can be accessed and used (Gallistel & King, 2011). Impairment of the MTL, as in AD, would theoretically impact this aspect of the learning process, causing atypical and inefficient RL as opposed to adaptive RL reliant on typical information processing.

Fundamental Mechanisms of Reinforcement Learning

The RL framework contains various mechanisms that work in concert to facilitate learning and produce behavior. These mechanisms include the reward function and value, the environment, probability and uncertainty, and critically, the prediction value and prediction error. A brief discussion of each is provided below.

Reward Function and Reward Value. The reward function of RL maps each perceived state to a reward indicating the desirability of that state within that environment. Indicative of the long-term desirability, the value function of RL specifies the total amount of reward an agent can expect to accumulate over time, beginning from the current state (Sutton & Barto, 1998). RL performs value function learning online through direct interaction with the environment and provides specific predictions of

future outcomes (Konidaris et al., 2012). The value function plays a central role in the agents' propensity to seek out rewards and avoid punishments (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). Within the classic RL model, these functions are closely related; however, as actions are based on the effective estimation of values, values are considered more important (Sutton & Barto, 1998).

Context. The environment, or context, in which actions take place, is another key element of the RL framework. The efficiency of the learning model is directly related to how well it generalizes from past experiences in order to predict future rewards and take action to attain them (Sutton & Barto, 1998).

Probability and Uncertainty. Probability is ever present within the RL framework for the simple reason that there are no certainties in life; outcomes are true or false, right or wrong, only with some measure of probability (Gallistel & King, 2011). Probability in RL measures a degree of belief before and after accounting for evidence (Gallistel & King, 2011). This information ultimately informs the action made based on the predictive value of the possible outcome. An element of uncertainty is inherent in the RL model since the amount of information communicated at any given time can be calculated as the amount of uncertainty in the environment before an event minus the uncertainty after the event (Gallistel & King, 2011; O'Doherty et al., 2003).

Prediction Error. When an agent interacts with its environment in the manner outlined above, an outcome results. This outcome holds either positive (rewards) or negative (non-reward/punishments) valence. Rewarding outcomes tend to maintain, strengthen, and improve the efficacy of (synaptic) connections leading to them while non-rewarding outcomes tend to shift actions toward rewarding ones (Hebb, 1949;

Silvetti & Verguts, 2012; Sutton & Barto, 1998; Thorndike, 1931) facilitating action in the future. The *experience* of learning, that is trial-and-error processing, rewires the brain in such a way that it becomes better suited to its current environment (Gallistel & King, 2011), which is the goal of RL. Importantly, despite response valence, outcomes do not provide explicit information about which action *would have been* most beneficial to long-term interests (Kaelbling et al., 1996). In order to address this, Rescorla and Wagner (1972) modified Thorndike's model of associative learning to add the prediction error (PE), which is the discrepancy between the expected reward or punishment and the actual outcome (O'Doherty et al., 2003). In accordance with the principle of classical conditioning, once it is learned that a reward or punishment follows the presentation of a neutral stimulus, that stimulus has predictive value (O'Doherty, 2004). Prediction value is acquired through a prediction error (O'Doherty, 2004). Critically, in novel situations, the prediction value is equal to zero.

Neural Substrates of Reinforcement Learning

RL (i.e., reward processing) involves a highly interconnected network of brain areas. Such areas include orbital and medial prefrontal cortex, amygdala, the anterior cingulate cortex, striatum, and critically, medial temporal lobe, specifically the hippocampus, and the basal ganglia (O'Doherty, 2004). The orbital frontal cortex (OFC) has been found to be a neural correlate of behavioral choice responsible for coding stimulus reward value (O'Doherty, 2004). The amygdala is also implicated in reward value processing, but is additionally associated with the intensity and/or amount of available reward (O'Doherty, 2004). The anterior cingulate cortex (ACC) is well known to be involved in conflict monitoring, error detection, and reinforcement processing

(Holroyd & Coles, 2002; Silvetti & Verguts, 2012). Impairments, inherent or acquired, in any of these regions would result in altered neural function manifested as deficits in basic behaviors.

Basal Ganglia and Dopamine. The importance of the basal ganglia (BG), a set of subcortical nuclei including the striatum, the caudate and putamen, the globus pallidus, the substantia nigra and the subthalamic nucleus, within the RL framework comes from its mechanistic genesis of the prediction error. In a landmark study by Schultz, Dayan, and Montague (1997), it was discovered that phasic elevations in dopamine (DA), a neurotransmitter vital to BG function, occur when outcomes exceed expectations, resulting in a positive PE. Conversely, DA decreases below tonic baseline when outcomes are worse than anticipated, eliciting a negative PE (Collins & Frank, 2012; Frank, Seeberger, & O'Reilly, 2004; O'Doherty, 2004; Schultz et al., 1997). These findings were subsequently supported by neuroimaging data (cf. O'Doherty et al., 2003). Critically, before learning, the neural processes accounting for the PE, the spike in DA, presents at reward onset. That is, they present at the point at which the valence of the outcome is known (i.e., feedback). After learning, however, the PE shifts backward in time to the onset of the stimulus (O'Doherty et al., 2003). Learning therefore occurs by updating expectations in proportion to the PE, across trials, over time (i.e., generalizing experience) so that expectation converges with actual outcomes (O'Doherty et al., 2003). This coincides with memory processes bringing information forward in time to allow for adaptive responding (Berger et al., 1976).

The DA system originates in subcortical nuclei including the substantia nigra and the ventral tegmental area, which project to the basal ganglia and the cortex (Holroyd &

Coles, 2002). Work previously reported within an RL paradigm has provided a comprehensive mechanistic account of neural processes implicating BG pathways in this framework (Cools, 2006; Frank, Woroch, & Curran, 2005; Shohamy et al., 2004; Shohamy & Wagner, 2008; 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 et al., 2005). This highly complex system has been widely established to be involved in learning, decision making, reward processing, as well as declarative and non-declarative memory.

Reinforcement Learning Assessed by Electroencephalography

One important approach used to study the biological foundations of RL, such as the PE, is electroencephalography (EEG), a coarse index of the electrical potentials that constitute brain activity measured on the surface of the scalp (Dyro, 1989; Luck, 2014; Münte et al., 2000). EEG is collected by use of an electrode cap containing a specified number of sensors (typically 64; Luck, 2014). These sensors are designed to reduce environmental noise and movement artifacts so neural activity can be identified through the use of a conductive gel. Direct contact with the scalp is necessary for the strongest signal to be collected. Activity is detectable via this method because human beings produce electricity via the synaptic potentials throughout the brain; the same ones responsible for learning processes (Hebb, 1949, 2005; Silvetti & Verguts, 2012). The raw, conglomerated nature of EEG resembles noise to the naked, untrained eye; however, this signal reflects small systematically fluctuating oscillations (Dyro, 1989; Holroyd & Coles, 2002; Luck, 2014; Münte et al., 2000) responsible for human cognition. It is

comprised of various rhythms, frequencies, and components that have been correlated in various ways to human behavior.

Overview of EEG.

The electrogenesis of brain activity lies in action potentials and post-synaptic potentials (Luck, 2014; Münte et al., 2000). An action potential is a discrete voltage spike traveling from the axon hillock down the axon terminal (Luck, 2014). These potentials are not typically detectable on the scalp surface (Luck, 2014). Conversely, post-synaptic potentials are those that occur due to the binding of neurotransmitters to post-synaptic cell receptors, causing the ion channels to open or close (Luck, 2014). These are known as local field potentials and are what is reflected in the EEG signal (Luck, 2014). As information processing occurs, the interpretation of that information modulates the plasticity (learning) of the brain via synchronous firing of large populations of dipole pyramidal cells (Münte et al., 2000). The quantity of neurons involved in this process makes the detection and measurement of these processes possible.

EEG is comprised of rhythms classified by the number of cycles per second (oscillations): delta (0.5-4 Hz), theta (4-7.5 Hz), alpha (7.5-14 Hz), sigma (14-15), beta (14-40 Hz), and gamma (40+ Hz; Münte et al., 2000). The amplitude of these frequency bands is a measure of power (Luck, 2014); that is, the strength of the signal. Muscular activity, such as tension in the jaw or eye blinks, is also an electrical phenomenon detectable via EEG (Luck, 2014; Münte et al., 2000). These generally represent artifacts and are typically isolated and removed from the EEG signal in data analysis pre-processing.

The major benefit of EEG is its temporal precision. However, EEG is not best suited to answer all questions for that reason alone. Its spatial resolution, for example, pales in comparison to functional magnetic resonance imaging or magnetoencephalography. The electrical signal produced by the dipole field (a field with positive and negative charges; Rugg & Coles, 1995) diffuses throughout the brain at nearly the speed of light (Luck, 2014). This is necessary because all human function is enabled by neural firing. This, however, makes identifying the origin of that signal difficult via EEG. Yet, knowing *where* something originates does not equate to knowledge about *how* it originated or, perhaps more importantly, what it means (Luck, 2014). The prediction error of the RL model, for example, provides meaningful information for adaptive learning and decision making measurable via EEG, independent of spatial precision.

Event-Related Potentials. Within the raw EEG signal, specific neural responses to external or internal stimuli can be extracted (Luck, 2014; Münte et al., 2000). These responses are referred to as event-related potentials (ERPs); they provide a real-time measure of task-related neural processing (Luck, 2014), and are particularly important for examining the more precise neural foundations of RL. EEG acquisition can be linked to behavior through the use of coded trigger values such that neural processes corresponding to various events can be identified (i.e., viewing stimuli, making a response, receiving feedback). ERPs are identified by segmenting (i.e., epoching) raw data surrounding an event of interest and creating a grand average (Luck, 2014). The amplitude of all ERP waves can be interpreted as an indication of power, such that larger amplitudes indicate larger effects (Luck, 2014). The peak amplitude is simply the maximum amplitude of the

wave within a given window of time (Luck, 2014). Amplitude is measured relative to the baseline average voltage (Luck, 2014). The latency of the component is defined as the interval, measured in milliseconds, from event onset until the beginning of the component (Handy, 2005; Luck, 2014). The amplitude and latency of the ERP depend on the physical properties of the relevant tissues (e.g., neurons, membranes, ions, intracellular fluid, bone, skin, etc.) and the measurement tool (Münte et al., 2000). Conventionally, and for no apparent reason, negative peaks are oriented *upward* (Luck, 2014). However, figures presented here show intuitive orientation such that negative peaks are downward facing.

Many ERPs have been identified over decades of empirical research, each identified by its deflection – either positive (P) or negative (N) – and its latency within the waveform following the event of interest. Among the most widely known and studied components are N1, N2, N400, P1, P2, P3, P600 and P50. P1 is an "obligatory sensory response" meaning that it is indiscriminately elicited by visual stimuli (Luck, 2014, p. 11). This is the first positive-going peak of the waveform. As the neural waveform contains an endless cycle of peaks and troughs, each positive peak is followed by a negative peak at a later latency of onset. Thus, P1 is followed by the N2, which has been found to be elicited by non-target stimuli that repeat (Luck, 2014). Each of the waveforms listed above has been associated with various cognitive processes.

The monitoring of such cognitive processes is routine in research and in clinical care. EEG has a long history of being used as a tool for differential diagnosis of epilepsy and seizures, for example. ERPs specifically have been used as clinical markers for various psychiatric and neurological disorders, including AD. The assessment of ERPs

(e.g., P3, N1, P50, N400, etc.) has successfully discriminated older adults with AD from healthy elders with 100% sensitivity and 6% specificity using pattern recognition statistics (Benvenuto, Jin, Casale, Lynch, & Granger, 2002; Katada, Sato, Ojika, & Ueda, 2004). The most predictive ERPs occurred between 200-400 ms and 800-1000 ms. Importantly, additive predictive power was found in the use of visual cognitive tasks eliciting simple forms of learning (Benvenuto et al., 2002), similar to the task employed in the present study.

Reinforcement Learning as a Predictor of Alzheimer's disease

The cognitive and behavioral symptoms of AD result from a progressive degradation of the integrity of functional neural networks and altered synaptic functioning. Although AD is classically a disorder of memory resulting from selective loss in medial limbic regions (Weintraub, Wicklund, & Salmon, 2012), as the disease progresses deterioration extends to neocortical regions, eventually causing deficits across multiple cognitive domains (Weintraub et al., 2012). Importantly, these profound and progressive impairments of episodic memory in AD have implications for RL even very early in the disease process. Specifically, individuals with AD exhibit rapid forgetting over time, accompanied by impairment in recognition and free recall of learned material (Weintraub et al., 2012), which indicates a deficit in memory consolidation. An important result of such deficits would be a drastic influence on RL, because the prediction value is formulated by evaluation and recognition of past experiences in the construction of a model of the environment. However, empirical research in this area is lacking. Furthermore, executive functions (EF), which broadly refer to the ability to mentally manipulate information, plan, pay attention, solve problems, and shift course under

changing demands, also exhibit deficits early in the course of AD (Albert, 1996; Hazlett, Figueroa, & Nielson, 2015; Weintraub et al., 2012).

RL theory would suggest extensive alterations occur in how one would engage in goal-directed behavior as AD pathology progresses. For example, if one cannot attend to a task, the integration of all RL elements would be compromised, such that adaptive and optimal behaviors would likely not lead to maximization of rewards. Similar deficits would result from an inability in problem solving, multi-step planning, or recall. Thus, RL might be very sensitive to early changes in AD. Yet, it has received very little attention in the literature. A closer examination of AD, its mechanisms and risk factors is needed in the context of RL.

Overview of AD Relative to Learning and Memory. The clinical presentation of AD was first described a century ago as "a peculiar disease of the cerebral cortex" (Alzheimer, 1907a; Strassnig & Ganguli, 2005, p. 32). In his report, Alzheimer described a disoriented woman with rapid memory loss, language impairment, and personality changes (Alzheimer, 1907b; Strassnig & Ganguli, 2005). Her symptoms led to an inability to carry out activities of daily living (ADLs) independently. Today, AD is characterized by difficulty remembering conversations, names, and/or events, apathy and/or depression, impaired communication skills, disorientation, confusion, poor judgment, behavioral changes, and, in later stages, difficulty speaking, swallowing, and walking (American Psychiatric Association, 2013). Diagnostic criteria include evidence of significant cognitive decline (e.g., in memory, language, or *learning*) that interferes with independently carrying out ADLs.

Memory Systems and AD. The memory system is, in and of itself, complex. It is comprised of different brain regions accounting for different abilities (Clark et al., 2002), including the distinction between declarative (i.e., conscious) memory (DM) and nondeclarative (i.e., non-conscious) memory (NDM). AD is marked by clinically significant impairment in DM (Fleischman et al., 2005), referring to conscious recollection of factual information that can be segmented into components accounting for autobiographical experiences (episodic) and general knowledge (semantic; Blennow, de Leon, & Zetterberg, 2006; Fleischman et al., 1997; Gong et al., 2010). DM memory processes have been associated with various brain regions such as prefrontal cortex and medial temporal lobe, including the hippocampus (Poldrack & Packard, 2003; Schacter & Badgaiyan, 2001). The role of the hippocampus, important at least for consolidation of consciously learned information into long-term storage, is well established in DM (Eichenbaum, 2004) and in cognitive decline in AD (Jack et al., 2000; Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Tulving & Markowitsch, 1998).

NDM accounts for the performance of a task without intentional recollection or without conscious awareness (Jelicic, Bonebakker, & Bonke, 1995; Zillmer, Spiers, & Culbertson, 2007). These systems have largely been associated with posterior cortical areas, cerebellum, neocortex, and neostraitum, including the basal ganglia (Squire, Knowlton, & Musen, 1993). Neuropsychological evidence contrasting impairments in various neurodegenerative diseases such as AD, PD, and amnesia supports the independence of these two memory systems (Randolph, Tierney, & Chase, 1995). NDM processes have been shown to be impaired in PD while DM processes are impaired in AD and amnesia (Bondi & Kaszniak, 1991; Heindel, Salmon, Shults, Walicke, & Butters,

1989; Huberman, Moscovitch, & Freedman, 1994; Knowlton, Mangels, & Squire, 1996; Light, Singh, & Capps, 1986; Maki & Knopman, 1996). Different neural circuitry underlying each memory system has all been postulated to account for performance differences across and within distinct neurological profiles (Fleischman et al., 2005; Gabrieli, Fleischman, Keane, Reminger, & Morrell, 1995).

Learning Mechanisms and AD. It has been postulated that as pathology increases, the brain compensates for structural changes and atrophy until the damage and/or loss of neurons becomes so significant, it manifests in observable alterations in cognition and behavior. Most notable are impairments in memory caused by the deterioration of the hippocampus and its associated networks, along with a decline in executive functions (e.g., attention, inhibition, planning, processing speed, etc.). Behaviorally, this might be evident in the forgetting of conversations/tasks or impulsively making decisions, respectively.

Outlined as a learning mechanism (Berger et al., 1976; Gluck & Myers, 2001; O'Reilly & Rudy, 2001), the hippocampus has input and output through the fornix, a bundle of fibers connecting it with subcortical structures, such as BG (Martinez Jr & Kesner, 1998), which modulates the flow of information (Martinez Jr & Kesner, 1998). Through its projects to the thalamus, the fornix ultimately projects to the cingulate, which has been established to be responsible for the generation of the prediction error. Because 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 updating the value functions of RL (Lee, Seo, & Jung, 2012).

More specifically, 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 BG, 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 et al., 2003). Without an intact network, the DA pathways of the BG are altered, which results in observable behavioral deficits due to maladaptive prediction error processing.

Because memories hold meaningful information for goal-directed behavior, memory process failures inhibit the formation of an adaptive RL model of the environment. This is important because the model is used to predict the probability of future outcomes, such as failing to remember the order of multi-step task. It is postulated here that a RL model may be able to explain deficits currently attributed solely to other cognitive domains. Despite the established role of the hippocampus (memory) in RL, it is only recently beginning to be studied (Shohamy & Wagner, 2008). Similarly, and critically, RL has not been well studied in AD, despite the critical role of the hippocampus to AD pathology.

Risk for AD: Apolipoprotein-E.

Risk factors are an additional consideration for studying RL as a predictor of AD. Because AD pathology begins years before functional decline and clinical diagnosis, assessing RL processes among individuals with risk factors for the disease may provide insight into its etiology. Apolipoprotein-E (APOE) is a well-established risk factor that

has been studied in relation to various cognitive and neural changes associated with AD (Selkoe, Mandelkow, & Holtzman, 2012). APOE has been extensively shown to distinguish individuals with AD from those without. It is known to influence the deposition of β-amyloid protein that forms the plaques that are hallmarks of AD (Kang et al., 1987; Maurer, Volk, & Gerbaldo, 1997). Critically, the precursor protein of β-amyloid plays a key role in multiple neuronal and synaptic processes, including neuron formation (cf. Müller & Zheng, 2012). Synaptogenesis and the maintenance of the synaptic connections are also supported by APOE (Pfrieger, 2003); both central to learning processes.

APOE has three polymorphisms (i.e., alleles) and six phenotypes, combinations of the two alleles; one allele is inherited from each parent (Mahley & Rall Jr, 2000). The variants of APOE include epsilon (ε) 2, ε3, and ε4 (Selkoe et al., 2012). Each isoform differs by only *one or two* amino acids (arginine and cysteine; Mahley, 1988; Mahley & Rall Jr, 2000; Zhong & Weisgraber, 2009); however, these seemingly minuscule alterations cause drastic structural and functional differences. APOE ε4 is associated with increased risk for cardiovascular disease, poor traumatic brain injury outcomes, and cognitive impairment with advancing age (Filippini et al., 2009). Global cognitive functioning, episodic memory, and executive function have all been found to be negatively impacted by ε4 (Small, Rosnick, Fratiglioni, & Bäckman, 2004); all of which are vital for an adaptive learning model.

While APOE ε4 is found in only one-fifth of the population (Mahley, Weisgraber, & Huang, 2009), 50-60% of AD patients examined post-mortem have it (Raber, Huang, & Ashford, 2004; Twamley, Ropacki, & Bondi, 2006). The likelihood of

disease development in individuals with one copy of ε4 is triple that of individuals who do not carry it, and the likelihood of development in homozygote carriers (i.e., ε4/ε4) is 15 times greater than in non-carriers (Kim, Basak, & Holtzman, 2009; Twamley et al., 2006). These statistics indicate that individuals who are at risk for the development of AD, as well as those with a diagnosis, are likely to experience the cognitive deficits leading to impaired RL.

Reinforcement Learning, AD, and APOE. Despite the utility of studying RL, its systematic study in APOE ε4 carriers has not yet been undertaken. Such studies are needed to evaluate whether RL can contribute to characterizing and predicting AD in novel ways. The previous phase of this study utilized a probabilistic selection (PS) task, which is a reinforcement learning task that employs feedback following a forced-choice trial, similar to the Weather Prediction Task (cf. Knowlton et al., 1996). Work on the PS task has provided a comprehensive mechanistic account of neural processes highlighting basal ganglia pathways in RL and decision-making (Cools, 2006; Frank, 2005; Wiecki & Frank, 2010).

Previous studies examining APOE differences in neural functioning found that EEG coherence – that is functional connectivity – was disrupted in ε4 carriers in temporaparietal and occipitoparietal regions (Jelicic et al., 1995). Additionally, EEG slowing was evident in carriers compared to controls. Decreased alpha and increased theta power have been shown consistently in AD (Jackson & Snyder, 2008; Jeong, 2004; Olichney, Yang, Taylor, & Kutas, 2011; Ponomareva, Korovaitseva, & Rogaev, 2008). More recently, theta power distinguished carriers from non-carriers in samples of 6-15 year olds (Alexander et al., 2007) and infants (Dean et al., 2014).

The use of EEG power to highlight neural differences in asymptomatic individuals is an important advancement in the field. The identification of specific neural ERP components has been similarly beneficial, though it is far less studied. Katada et al. (2004) and Benvenuto et al. (2002) demonstrated that ERPs can effectively distinguish between AD and controls, even when behavioral differences were not present. Such findings are vitally important because they indicate what while behavioral function was intact, evidence of pathology was detected neurally.

The broad implications of using ERPs to investigate risk for AD lie in the fact that individuals in the early-to-mid stages of AD have been found to have 30% less synaptic density and 25% fewer synapses (Jack et al., 2010; Olichney et al., 2011) than healthy controls. This is consistent with an observed decrease in EEG power among older adults (Polich, 1997). Hippocampal damage has also been shown to be reflected in ERP indices of encoding (Grunwald, Elger, Lehnertz, Van Roost, & Heinze, 1995) and larger hippocampal volumes were associated with changes in ERP components (Schiltz et al., 2006). Furthermore, because the neural response to negative and positive feedback are different (Nieuwenhuis, Holroyd, Mol, & Coles, 2004), ERPs reflect the RL prediction error. ERPs and RL are thus both extremely sensitive to AD neuropathology and disease progression (Olichney et al., 2011).

Evidence suggests that the power of the EEG decreases with age, but neural processes also become slower (Goodin & Aminoff, 1986). Abnormalities, such as longer latencies and reduced amplitudes in neural activity have be identified approximately 10 years prior to the clinical presentation of dementia (Golob et al., 2009) and have been shown to be present in the absence of behavioral differences (Alexander et al., 2007).

These findings are consistent with those of Benvenuto et al. (2002) who examined ERPs in AD using pattern recognition. These results are important because they indicate that, on a molecular and biochemical level, neuropathology impeding synaptic function and RL mechanisms are measurable via an ERP methodology (Polich & Kok, 1995). In order to understand the learning process of RL specifically, however, more sensitive and error processing-related components are necessary. The error-related negativities described below are two such components.

Reinforcement Learning and Error-Related Negativity. In a landmark article, Holroyd and Coles (2002) proposed that reward processing (e.g., reward prediction and prediction error), is reflected by specific neural components, which are generated by a "high-level, generic, error processing system" (p. 680). These ERPs are referred to as the response-error-related negativity (ERN) and the feedback-error-related negativity (FRN; Eppinger, Kray, Mock, & Mecklinger, 2008; Holroyd & Coles, 2002; Nieuwenhuis et al., 2002). Both are negative deflections in response-locked and feedback-locked averaged EEG peaking approximately 80 milliseconds (ms) after response and 200 ms post-feedback (Holroyd & Coles, 2002; Luck, 2014). Maximal amplitude has been found in frontal sites (i.e., FCz and Cz, on the 10-20 system for EEG placement; Eppinger et al., 2008; Homan, Herman, & Purdy, 1987; Mathewson, Dywan, & Segalowitz, 2005).

Good support exists for the generation of these components by activity in the mesencephalic dopamine system (Hajcak, Holroyd, Moser, & Simons, 2005; Holroyd & Coles, 2002), which underlies RL. Source localization techniques have also been used to identify that the ERN is generated in the dorsal part of the anterior cingulate cortex (ACC) and medial prefrontal areas (Eppinger et al., 2008; Holroyd & Coles, 2002;

Holroyd, Dien, & Coles, 1998; Mathalon et al., 2003; Mathewson et al., 2005). The interaction of these systems were hypothesized and subsequently confirmed by Holroyd and Coles (2002), who postulated that when errors are made, the DA system conveys a negative reinforcement learning signal, (a negative prediction error) in the frontal cortex where the ERN facilitates adaptive motor responses (Holroyd & Coles, 2002). Additional evidence supports the role of DA in long-term potentiation and long-term depression at the synapse terminals (Holroyd & Coles, 2002), influencing the learning signal.

The RL theory of the ERN states that modulation of its amplitude occurs via motor-related regions of the ACC such that phasic decreases in DA are associated with larger ERNs and phasic increases in DA are associated with decreased ERNs (Hajcak et al., 2005; Holroyd & Coles, 2002; Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003). The phasic decrease in DA was reflective of negative prediction error, indicating that outcomes were worse than anticipated; they were inconsistent with prediction. This elicits a larger ERN because the amplitude of the ERP denotes its power. Conversely, the phasic increase in DA elicits a smaller ERN because outcomes converged more closely to actual outcomes; the degree of error was less.

Temporally, the FRN is evident when explicit knowledge is gained about the outcome of a response (i.e., whether is it was correct or incorrect). Conversely, the ERN is evident at the first detection of error and perceived degree of error (Holroyd & Coles, 2002; Luck, 2014). Error awareness, as opposed to error detection has been found to be associated with a closely related component called the error-positivity (cf. Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). Use of the information associated with the error to evade future mistakes has also been associated with the ERN (Holroyd & Coles, 2002);

the degree of error (i.e., small mistakes vs. big ones) is evidenced by the magnitude of the ERN (Hajcak et al., 2005). The error signal associated with detection is used (processed) to teach the motor system to be consistent with neural network implementations of RL principles and adaptively improve actions over time (Holroyd & Coles, 2002). This is an important piece of the RL puzzle because, although learning (i.e., navigating the world) can occur without action selection (i.e., without movement), functioning independently, a standard of mental health, in the world cannot. The beauty of the neural network lies, perhaps, in how seamlessly it performs its complex functions absent of anomalous conditions. It is the sensitivity of the system to the presence of anomalies, however, that allows for detection of neuropathology.

In order to effectively carry out daily functions, the ERN is necessarily flexible (generic), being elicited by various modalities (e.g., auditory, visual, olfactory, and motor), and involved in higher-order processes (Holroyd & Coles, 2002). Frontal systems, responsible for executive control such as response monitoring, are an inherent part of RL (Holroyd & Coles, 2002). The ERN thus contributes to the regulating global aspects of human behavior (Holroyd & Coles, 2002). As was discussed regarding RL, DA neurons are sensitive to changes in prediction such that positive outcomes elicit positive DA signals and negative outcomes elicit negative signals (Hajcak et al., 2005). In the classic RL model, the DA prediction error increases the proclivity of rewarding actions, thereby acting as the reinforcing element in Thorndike's associative learning theory (Daw, Gershman, Seymour, Dayan, & Dolan, 2011; Maia, 2009; Suri & Schultz, 1999).

With regard to neural mechanisms, and DA in particular, it has long been established that receptor density in the caudate, putamen, and frontal cortex decline between the ages of 19 and 73 (Wong et al., 1984). In tasks that elicit various kinds of errors (e.g., visual, auditory) amplitude of the ERN was reduced in 54-65 year olds compared to 19-25 year olds (Falkenstein, Hoormann, & Hohnsbein, 2001). Somewhat recent findings from neurocompuational models have indicated that the attenuation of the ERN in older adults can in fact be accounted for by decreased phasic activity within the mesencephalic DA system as prescribed by the RL theory (Nieuwenhuis et al., 2002). Age-related deficits in the mesencephalic DA system in older age may be evident in error-processing impairment due to the systems' projections to the prefrontal cortex affecting cognitive control (Eppinger et al., 2008), which again have been found to decline with age. Findings suggesting midbrain DA modulation of the ERN in the elderly are indicative of AD related changes in the error processing system both behaviorally and neurally (Mathalon et al., 2003).

As the ERN has been shown to be sensitive to RL processes independent of neural dysfunction or atrophy, as well as to age and the neuropathology of AD, the next logical step of empirical research is to investigate *preclinical* stages among those individuals at risk for developing the disease. To our knowledge, no studies have investigated this connection. However, in a study using the aforementioned probabilistic selection task (Frank, 2005; Frank et al., 2005), the ERN was sensitive to adaptive responding such that avoiding negative outcomes elicited larger ERNs in learners with a positive bias (i.e., those learning from positive feedback). In other words, those individuals who learned to adaptively adjust behavior based on rewarding outcomes exhibited enhanced neural

activity in response to negative outcomes. Larger ERNs were also elicited by positive learners than by those learning to avoid negative feedback when presented with high conflict (win/win; lose/lose) situations. These findings support the role of DA and the ACC in generation of the ERN as well as the phasic dips enabling direct and indirect DA pathways in decision-making. Combining the behavioral findings Frank et al. (2005) and in light of findings from Mathalon et al. (2003) indicating ERN sensitivity to AD, may provide an important step toward testing whether neuropathology can be predicted by examining RL in asymptomatic, at-risk older adults.

Hypotheses

Previous work in risk for AD has employed use of various implicit and explicit memory tasks, but has failed to investigate RL processes reliant on both forms of memory. The present investigation aimed to address this gap by examining the neural substrates of RL. Because neural changes occur prior to behavioral deficits, this investigation hoped to provide a method of detecting pre-clinical differences in an asymptomatic sample at genetic risk for AD. To that end, the proposed study aimed to compare specific event-related potentials between healthy elders at low vs. high risk for developing AD.

Specifically, the present study assessed response-ERN and feedback-ERN differences in the training phase.

1. The amplitude of the feedback-ERN was expected to be greater early in the learning phase of the PS task compared to later in learning. The opposite was expected for the response-ERN such that it would be greater in the later stages of learning. This pattern was expected to be evident in both risk groups.

   a. Furthermore, larger response-ERNs were expected to be exhibited on pairs with greater probability differences (e.g., 80:20) when compared to pairs with more similar probabilities (e.g., 60:40). The difference between these pairs was anticipated to be less for individuals in the high-risk group.

2. The amplitude of the response-ERN later in learning was anticipated to be reduced in the high-risk group compared to the low-risk group.

This theoretically driven comparison was based on the prediction value being equal to zero in novel situations. This is due to its reliance on the prediction error, which is acquired over the course of learning. In early stages of learning, the prediction error presents at the feedback-ERN, not at the response-ERN. This is due to a lack of previous experiences to generalize from early in learning. As learning occurs, the prediction error propagates back in time to the onset of the response; to the time when detection or perception of an error occurs.

This pattern of results was expected to be dependent on trial type (i.e., the probability pairing of the stimuli). This was due to the uncertainty inherent in the less discrepant pairs (60:40). While predictive value has been established for each choice (because learning has occurred), the certainty of those choices is close to chance (50:50) leading individuals to continue to seek out options leading to maximum rewards. This is in contrast to the more discrepant pairs (80:20) in which certainty of reward is nearly 100%. The establishment of the prediction error is also reliant on the transfer of learned information into storage where it can be accessed and applied to novel situations. Presumed insipid hippocampal atrophy in the high-risk group would theoretically impact

learning such that a disturbance in information transfer was predicted to affect the prediction error evident by the response-ERN.

In addition to examining processes within the training phase of the task, the present study aimed to assess the testing phase (implicit learning) in order to examine the application of learned information independent of feedback.

3. It was expected that individuals at high risk would exhibit diminished response-ERN peak amplitudes compared to low risk on incorrect compared to correct trials. In order to appropriately compare the training and testing phases, it was also necessary to investigate the probability pairings of novel stimuli.

By design, this phase lacks feedback. The temporal difference mechanism of the feedback-ERN can therefore not be assessed during this phase. However, a group comparison of the response-ERN in the PS task was proposed to assess the neural correlates of novel performance independent of feedback. Theoretically, the ERN should be greater for trials that are inconsistent with the prediction error (i.e., trials on which individuals select the less correct stimulus) because at this phase of the task appropriate learning of the probabilistic parameters has occurred.

Method

This cross-sectional non-equivalent comparison group design study assessed differential learning and memory impairments in asymptomatic individuals at low vs. high risk for developing AD using a RL paradigm.

Participants. A total of 49 healthy older adult participants were included in the study. Participants were recruited from an ongoing longitudinal study that examined

various biomarkers and cognitive indices of risk for AD. They were known carriers and non-carriers of the APOE ε4 allele, a genetic risk factor for developing AD. They were initially screened for neurological, psychological, and substance use histories that might complicate study interpretations. Those recruited for the current study, however, 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, use of psychoactive medications, and documented or suspected history of substance abuse and/or alcoholism were evaluated for all participants in order to control for possible confounding variables. Overall health of the sample included in analyses ranged from fair to excellent. Participants whose Dementia Rating Scale-2 total score was less than 123 (2 standard deviations below the mean) were tested, but were excluded from analyses in order to limit sample to healthy, intact elders. Range of DRS-2 total scores for the sample analyzed was 130-144.

Measures.

Health status. Health was assessed using a survey from our laboratory that included questions regarding past and current diagnoses, surgeries, medications, and physical conditions.

The Dementia Rating Scale-2 (DRS; Jurica, Leitten, & Mattis, 2004; Mattis, 1976) is a brief experimenter-administered measure that assesses five areas of cognitive functioning in elderly individuals. 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 produces five subscale scores: Attention, Initiation-Perseveration, Construction, Conceptualization, and Memory. It is scored by summing the raw number of correctly answered items corresponding to each subscale, which is summed to make a total score. The DRS has been shown to have a sensitivity of 98% and a specificity of 97% (Monsch et al., 1995).

The Probabilistic Selection Task (PS Task) is a forced-choice reinforcement learning paradigm comprised of two phases: a training phase and a test phase (Frank, 2006; Frank et al., 2004). The training phase consists of three pairs of figures (basic geometric shapes of varying colors; A:B, C:D, E:F) presented in random order, 20 trials of each pair for a total of 60 trials per training block. 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 throughout the task 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. A maximum of 6 blocks (360 trials) was set. Once learning criteria was met, participants proceeded to a test phase consisting of 120 trials of novel stimulus pairs (e.g., 80:70, 30:40).

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., 2009). Participants were sent a packet of information regarding the study, which included the medical health survey. Upon arrival to the first session, survey materials were collected and informed consent was completed. After initial study procedures were complete, participants took part in a series of tasks including the DRS-2. The version of the DRS-2 administered was dependent on previous testing parameters; however, the alternate version was administered to the majority of participants. After completing session one, participants were dismissed and returned for a second session approximately one week later.

At the beginning of the second session, informed consent was again granted by all participants. This session involved EEG collection. Scalp voltage was measured using Brain Products 64-active electrode cap referenced online to a site immediately posterior to Cz, namely FCz, using a NeuroScan Synamps2 system. Participants were informed about the process of EEG cap hook-up to reduce anxiety with the unfamiliar process. Based on a measurement of the head taken at session one, the appropriate size cap was selected for each participant. Cap placement on the head was in accordance with the 10-20 system such that the front bridge of the cap was placed at 10% of the nasion-to-inion measurement. A chin strap was used to minimize movement of the cap during this process. A conductive gel was then placed between each of the 64 electrodes and the scalp for signal acquisition. Impedance, a measure of signal strength, was held < 50 kΩ. This process took approximately 20 minutes to complete. Participants filled out

questionnaires during this time. All participants were instructed to try to minimize gross motor movements that would interfere with data collection (e.g., resting the head against the back of the chair, pulling away from the amplifier; excessive or exaggerated movement). All data was collected at a sampling rate of 500 Hz. Four minutes of baseline resting EEG was collected (2 minutes eyes open, 2 minutes eyes closed) followed by the completion of 4 counterbalanced computer based tasks including the probabilistic selection task.

At the beginning of the PS task, participants were instructed that two figures would appear simultaneously on the computer screen, one on each side. They were told that one figure would be correct and one would be incorrect, however, at first, they would not know which is which. The instructions indicated that there was no absolute right answer but that some figures had a higher chance of being correct. Participants were instructed to respond as quickly as possible by selecting the keyboard key that corresponded to figure they believed to have the highest chance of being correct. Participants were told that once they performed well enough in the training phase, they would advance to the testing phase. A practice phase was given to all participants to ensure a sufficient understanding of the task. This practice phase was repeated for 8 participants to ensure understanding of the task procedures prior to beginning. Rest breaks were embedded into the task after completion of 2 and 4 blocks with the intention of reducing fatigue and maintaining/increasing attention.

Once participants met learning criteria, they completed the test phase. Prior to beginning this phase, they were instructed to continue to select the image they felt had the

highest chance of being correct. They were also informed that feedback would no longer be given.

At the completion of the task, the EEG cap was removed and participants were given a recognition sheet which required them to assign a value from 0-100 to each of 6 figures according to their belief of how correct it was. Participants were allowed to freely assign percentages to each figure. If a participant assigned the same value to any 2 or more figures, there were asked to provide a rank order of them. Following completion of the recognition sheet, the session continued according to study protocol until dismal.

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 a flat-fee of $20 per session.

Analyses

Sample size justification. An a priori power analysis using G*Power 3.0 (Faul, Erdfelder, Lang, & Buchner, 2007) conducted for a 2 (group) X 2 (learning phase) X 3 (electrode) repeated measures ANOVA, indicated that a total sample size of 14 was needed with the resulting statistical power of .95. It was concluded that this sample size should be sufficient for providing evidence for the significant difference between at-risk participants with a large effect size (0.40), indicating that the current sample size was more than sufficient.

Statistical analyses were conducted using SPSS version 21 (Corp, 2012) and Matlab (MathWorks, 2004). All data were screened for normality. With the exception of

one individual, all participants were Caucasian, and the sample was 72.5% female (see Table 1). A total of 9 participants were eliminated from all data analyses due to failure to meet learning criteria on the PS task (5), computer error or poor EEG data (4) that could not be corrected through various processing methods. A total of 40 healthy, cognitively intact individuals – 20 low risk, 20 high risk – were included in analysis of the training phase. Three participants were removed from testing analyses due to poor behavioral performance in the testing phase.

In order to assess for significant relationships between dependent variables (i.e., accuracy) and demographic characteristics such as age and education, Pearson's correlations were conducted (see Table 2). Age was significantly correlated with the accuracy of the 60:40 pair throughout training ($r = -.327$, $p = .040$). Age was not significantly correlated with any of the ERP variables (p-values ± .255). Importantly, risk groups did not significantly differ by age ($t(38) = .514$, $p = .611$), and age was not consistently correlated with variables of interest. It was, therefore, not included as a covariate in analyses. Education was not significantly correlated with any of the task variables (p-values ± .078). It was, however, inconsistently correlated with ERP variables (p-values range from .012 to .002). Independent samples t-test revealed a significant difference in education between the risk groups ($t(38) = -2.44$, $p = .019$) such that the high-risk group had significantly more years of education than the low-risk group ($M_{High} = 15.90$, SD = 2.62; $M_{Low} = 13.85$, SD = 1.84). Although risk groups did significantly differ in years of education, education is widely considered a *protective* factor against cognitive decline and would not account for any deficits observed in the high-risk group.

It was therefore not included as a covariate. Risk groups did not significantly differ on the MMSE ($t(37) = 1.33$, $p = .192$) or DRS ($t(38) = 1.70$, $p = .099$).

PS Task Analyses.

Performance on the PS task was assessed via overall accuracy, that is by the participants' choice of a figure associated with a high probability of correct feedback (optimal) over one with low probability (suboptimal). For example, the optimal selection of 80% in the 80:20 pair vs. the suboptimal selection of 20% in the same pair. While reaction time was collected, analysis of this performance index was beyond the scope of the present study. Training performance was also more sensitively assessed in a number of ways (see Table 3). Overall training performance included all trial types across all blocks performed. Performance on each trial type, hereafter referred to as trial type 1 (80:20), trial type 2 (70:30), and trial type 3 (60:40) were also assessed across all blocks performed. Performance was divided into overall early (first block) and late (last block) learning, as well as performance on each of the three trial types within each of these blocks. Learning phase (early and late) was deemed to reflect the earliest and latest stages of learning for all participants regardless of the number of training blocks performed, and to allow for an appropriate number of trials for ERP analyses. Importantly, the number of blocks completed did not significantly differ between risk groups ($M_{Low} = 3.35$, $SD = 1.66$; $M_{High} = 3.50$, $SD = 1.61$; $t(38) = -.290$, $p = .773$). The number of trials included in each learning phase was comparable across subjects.

Testing performance was determined by participant's ability to choose the highest probability (optimal) stimuli and avoid the lowest probability (suboptimal) stimuli such that choices should correspond to the 80(A) > 70(C) > 60(E) > 40(F) > 30(D) > 20(B) probability scale. Testing trials pairs were selected and grouped into low, intermediate, and high conflict based on the difference of the probabilities, with 3 pairs in each group. The high conflict group consisted of trials with a probability difference of 10 (80:70; 70:60; 30:20); intermediate conflict consisted of trials with probability differences of 20 or 30 (80:60; 70:40, 40:20); and low conflict consisted of pairs with a probability difference of 40 or 50 (80:30; 70:20; 80:40; see Table 5). Number of training blocks performed was not significantly related to testing performance.

ERP Analyses.

EEG data was analyzed using custom Matlab scripts for Matlab toolboxes, EEGLab (Delorme & Makeig, 2004) and ERPLab (Lopez-Calderon & Luck, 2014). Preprocessing and processing were conducted in stages, each with various parts:

1. Set files (raw data) were loaded and the electrode cap locations were added. Data was referenced using a whole head average, and FCz was retained for analyses.
2. By design, raw data files were divided into multiple files for ease of data collection. For each subject these files were combined. Prior to combining the raw files, however, EEG data was manually compared to the behavioral data to ensure that the two appropriately aligned. Corrections were made if/when necessary, including the removal of unwanted triggers, and raw set files were

concatenated such that each participant had one file with training and testing data. This file was saved and used for subsequent processing.

3. Behavioral triggers were designed to account for all unique combinations of stimuli presented. For example, AB was coded independently of BA. For the purpose of ERP analyses, these were combined and recoded to a single trigger value. This was completed for all trial types. Similar coding was conducted for accuracy and feedback triggers. Trials during which participants did not respond were removed from analyses. This process was repeated for testing data according to its unique trigger values. The files were saved and used for additional processing.
4. Individual subject files were assessed for number of channels, sampling rate (500 Hz), and trigger information to ensure that analyses were comparable across all subjects. This was completed and saved in order to be used for future individual breakdown of data based on condition or trial type.
5. For all participants, a notch filter (59 61/250) was applied. A low pass filter of 100 Hz and a high pass filter of 0.5 Hz was also applied. This is consistent with the literature. For reference, a low pass filter attenuates signals above the specified frequency, while a high pass filter attenuates signals below the cutoff frequency (Luck, 2005). Individual channels were rejected by manual inspection.
6. Independent component analysis (ICA) was conducted for all participants. This is a commonly used method of decomposing the data (Stone, 2004) such that correlations between individual electrodes is removed, leaving a more

unique signal for each electrode. ICA was also used to aid in artifact removal such as blinks. Adaptive Mixture Independent Component Analysis (AMICA) analysis (Palmer, Makeig, Kreutz-Delgado, & Rao, 2008) was implemented to decompose signals for each trial into 64 individual components, and then artifact components were identified for removal using the ADJUST plugin (Mognon, Jovicich, Bruzzone, & Buiatti, 2011) to EEGLAB. This was also used to aid in the manual rejection of components.

7. Interpolation of channels was completed if necessary.
8. Data was epoched 1 second pre-stimulus and 2 seconds post-stimulus onset for triggers of interest (response and feedback). Epochs were manually examined and rejected. Rejections at every stage were completed to reduce artifacts and signal noise in order to best assess the underlying neural signal.
9. Remaining epochs were baseline corrected to the 100 ms pre-stimulus.
10. A low pass filter of 20 Hz was applied.
11. Specific features were extracted to allow for analysis of specific hypotheses. Like trial types were averaged for each participant and then across all participants in each risk group in order to create the grand average which were used in all analyses. Three primary electrodes from the midline - Fz, FCz, Cz - were analyzed due to evidence supporting the peak distribution of the ERPs of interest over these regions (Holroyd & Coles, 2002). Resulting grand averaged ERPs were assessed for all subjects and used in different pair combinations in repeated measures analyses.

12. Peak amplitudes were exported to excel and imported into SPSS for statistical analyses. Plots of the data were created in Matlab (see Figures). Significance was held at $p < 0.05$ throughout.

Results

Behavioral Results

Independent samples t-tests indicated that risk groups did not significantly differ on behavioral measures of learning. Performance throughout the training phase did not differ between risk groups. Risk groups did not significantly differ in early or late learning. They also performed similarly during the testing phase of the task. See Tables 4 and 5.

ERP Results.

Specific Aim #1. The purpose of Aim 1 was to compare response-ERN and feedback-ERN peak amplitudes in the training phase of the PS task on probabilistically discrepant trial types, at early and late stages of learning. It was hypothesized that the peak amplitude of the feedback-ERN would be larger early in learning compared to later in learning, while the response-ERN would be larger later in learning compared to early in learning. It was further anticipated that peak amplitudes would be largest for trial types with more discrepant probability parameters compared less discrepant trial types. This pattern was expected to be evident in both risk groups. Thus, a main effect of learning phase as well as a main effect of ERP amplitude was expected, along with a significant 3-

way interaction, indicating that the response-ERN was most reduced early in learning on 60:40 trials.

Data analytic plan. This aim was assessed in two steps with corresponding post-hoc analyses. First, 2 separate repeated measures ANOVAs were conducted for the feedback-ERN and the response-ERN. This was done because while the two components are part of the same error-related system, they are not dependent/reliant on each other and required independent examination. A 2 (learning phase: early, late) X 3 (electrode: Fz, FCz, Cz) design was first used to assess overall learning (across all blocks of training).

Feedback-ERN Results for Aim 1.

Results examining the feedback-ERN revealed that there was a significant main effect of phase ($F(1,38) = 9.56$, $p = .004$) indicating that total peak amplitudes of the FRN were greater in early learning ($M_{Early} = -5.70$; $M_{Late} = -5.34$) which was consistent with prediction that the prediction error presents at the time of feedback early and becomes smaller over the course of learning. There was also a main effect of electrode ($F(2,76) = 9.14$, $p < .001$), though specific predictions for electrode were not made. The interaction was not significant ($p = .642$).

Pairwise comparisons of electrodes indicated a significant difference between Fz and FCz ($p < .001$) as well as Fz and Cz ($p = .003$). There was not a significant difference between FCz and Cz ($p = .554$). Again, specific predictions for electrode were not made. Estimated marginal means also revealed a significant risk by phase interaction within the low-risk group ($p < .001$), but not the high-risk group ($p = .365$), which was inconsistent with expectation that this phase difference would be significant for both risk groups (Low-Risk: $M_{Early} = -5.62$, $M_{Late} = -5.05$; High-Risk: $M_{Early} = -5.78$, $M_{Late} = -5.63$). A

significant 3-way interaction (risk x learning phase x electrode) within the low-risk group was also observed across all three electrodes (Fz p = .004; FCz p = .005; Cz p = .011) indicating a significant phase difference. Although specific electrode differences were not predicted, results are consistent with the literature indicating greater amplitudes in frontal sites. This interaction was not significant for the high-risk group (p's ± .160).

In order to examine the unique effect of risk, post-hoc analyses were conducted. Results of the FRN analyses revealed a main effect of phase within the low-risk group (F(1, 19) = 10.71, p = .004) and electrode (F(2, 38) = 18.63, p < .001). This is consistent with results outlined above. The interaction was not significant (p = .537). Pairwise comparisons of electrode indicated significant differences between Fz and FCz (p < .001) as well as Fz and Cz (p < .001) and FCz and Cz (p = .012). There was also a significant interaction between phase and electrode indicating that peak amplitude of the FRN was greater in early learning compared to late learning, which was consistent with previous results and with prediction. Importantly, analyses did not reveal any significant findings within the high-risk group (p's > .233).

Response-ERN Results for Aim 1.

Results examining the response-ERN revealed a significant main effect of phase (F(1,38) = 4.48 , p = .041) indicating that the total peak amplitudes of the ERN across three electrodes was greater in late learning (M_{Early} = -5.15; M_{Late} = -5.36), consistent with prediction that the prediction error is smaller early and becomes greater over the course of learning. Main effect of electrode and interaction were n.s. In order to examine the unique effect of risk on peak amplitude, post-hoc analyses were conducted, but did

not reveal significant differences in the low or high-risk groups, which was consistent with prediction that all participants would exhibit this shift in amplitude.

Trial Type Analyses for Aim 1.

In order to address the second step of aim 1, analyses were conducted accounting for the three training trial types. Thus, a 2 (learning phase: early, late) x 3 (trial type: 1, 2, 3) x 3 (electrode: Fz, FCz, Cz) RM ANOVA was conducted with risk as the between-subjects variable.

Feedback-ERN x Trial Type Results for Aim 1.

Analysis of the FRN across unique trial types revealed a significant main effect of phase ($F(1, 38) = 10.47$, $p = .003$), consistent with previous results reported and with the predicted waveform dynamics that the amplitude would differ between early and late learning across all participants. There was a main effect of electrode ($F(2, 76) = 9.02$, $p < .001$) and a trending phase x gene interaction ($F(1, 38) = 3.29$, $p = .078$). Four-way interaction was not significant ($p = .662$). Thus, results examining the FRN x trial type were not consistent with prediction that risk groups would elicit different peak amplitudes.

Response-ERN x Trial Type Results for Aim 1.

Results examining the ERN x trial type revealed the anticipated main effect of phase ($F(1,38) = 4.56$, $p = .039$) and a trending interaction between trial type and gene ($F(2, 76) = 2.73$, $p = .072$). Pairwise comparisons indicated a significant difference of peak amplitude within the low-risk group between trial types 2 (70:30) and 3 (60:40; $p = .045$). Differences in peak amplitude within the high-risk group were not significant. Specific within-group difference predictions were not made. There was also a significant

interaction between phase and trial type ($F(2,76) = 5.10$, p = .008); in early learning, there was a trending difference between trial types 1 and 2 ($p = .070$) and significant difference between trial types 2 and 3 ($p = .014$). There was a trending difference between trial types 2 and 3 in late learning ($p = .067$).

Estimated marginal means also revealed a significant 4-way (gene x phase x trial type x electrode) interaction. Results were not entirely consistent with prediction such that risk differences were exhibited on trial type 2 rather than trial type 3. In early learning, there was a significant risk difference in peak amplitudes of trial type 2 at Fz ($M_{Diff} = 1.56$, $p = .001$) and FCz ($M_{Diff} = .985$, $p = .041$). In late learning, there was a significant risk difference in the peak amplitudes for trial type 2 at Fz ($M_{Diff} = 1.02$, $p = .042$) and trial type 3 at Fz ($M_{Diff} = .883$, $p = .030$). Results in late learning were consistent with initial prediction of a difference for trial type 3.

Specific Aim #2. The purpose of Aim 2 was to compare the response-ERN by risk group in late learning. Peak amplitude of the response-ERN between trial types was expected to be reduced in the high-risk group compared to the low-risk group.

Data analytic plan. This aim was addressed utilizing the same RM ANOVA pairwise comparison used for Specific Aim 1.

Results indicated that in late learning, there was a significant risk difference in the peak amplitudes for trial type 2 and trial type 3 (trial type 2 $M_{Diff} = 1.02$, $p = .042$; trial type 3 $M_{Diff} = .883$, $p = .030$). However, peak amplitudes elicited by the high-risk group were *greater* than the low-risk group ($M_{High} = -5.66$; $M_{Low} = -4.85$), which is inconsistent with prediction that amplitudes would be smaller for the high-risk group.

Specific Aim #3. The purpose of Aim 3 was to compare the response-ERN by risk group in testing phase of the PS task. Within the testing phase, it was expected that ERNs elicited on trials where the probabilistically incorrect (suboptimal) stimulus was chosen would be greater than those where the probabilistically correct (optimal) stimulus was chosen. It was hypothesized that individuals at high risk would exhibit diminished response-ERN peak amplitudes compared to low risk individuals on both trial types.

Data analytic plan. A mixed analysis of variance was conducted using a 2 (group) X 2 (selection type: optimal, suboptimal) design where selection type was defined by the stimulus chosen. A main effect of incorrect stimulus selection was anticipated. A significant interaction effect was expected for the between group comparison such that peak response-ERN amplitude on incorrect trials would be diminished for the high-risk group.

The results did not reveal significant differences between risk groups. However, in order to appropriately compare testing trial types, trials were grouped into conflict groups based on the difference of assigned probability between the two stimuli; low, intermediate, and high conflict groups resulted. A 3 (trial type) x 3 (electrode) repeated measures ANOVA was conducted to assess group differences of the ERN in testing by trial type.

There was not a significant main effect (p = .903) or 3-way interaction (p = .977). However, pairwise comparisons of group differences indicated a significant 3-way interaction such that the peak ERN amplitude of trial type 2 was significantly greater for the high-risk group than for the low-risk group (M_{Low} = -4.65; M_{High} = -6.10; p = .028). Risk differences for this particular trail type were not predicted. There was also a

trending difference for trial type 1 (p = .092), also indicating greater amplitude within the high-risk group (M_{Low} = -4.93; M_{High} = -5.97). This trend was consistent with the general prediction that the high-risk group would exhibit a deficit in novel portions of the task.

Discussion

This study aimed to apply a model of learning to AD as a novel approach to understanding disease pathology and identifying a way of detecting very sensitive cognitive changes among individuals at genetic risk for developing the disease. EEG was used as a method of assessing neural function because various studies have shown it to be sensitive to disease-related changes prior to clinical decline (Liraz et al., 2013). For example, middle-aged individuals with a family history of AD and APOE ε4+ were found to have prolonged latencies of the P3, N2 and P2 components on an auditory odd-ball paradigm in the absence of neuropsychological deficits (Green & Levey, 1999). A learning paradigm was chosen for the current study because it was believed to be an ideal framework for real-world functioning (Sutton & Barto, 1998) and because it allows for the examination of the dynamic interaction of the frontostriatal-hippocampal network (Seger & Cincotta, 2005). This paradigm has been successful in elucidating cognitive processes in other neurodegenerative disorders such as Parkinson's disease (Cavanagh et al., 2011; Frank, 2006; Frank et al., 2004; Pizzagalli et al., 2008) and affective disorders such as depression (Holmes & Pizzagalli, 2008; Santesso et al., 2008).

The current study proposed that two groups of cognitively intact, high-functioning individuals differing only by genetic risk for AD, would deviate in their RL-related neural signals, thus demonstrating evidence of early, disease-related pathology (e.g.,

Coleman et al., 2004). Two components of the error detection system, specifically the FRN and the ERN (Miltner, Brauer, Hecht, Trippe, & Coles, 2004; Miltner, Braun, & Coles, 1997), were examined because they reflect activity of a reinforcement learning system (Hajcak et al., 2005; Holroyd & Coles, 2002). Results revealed that the groups did indeed differ in peak amplitudes of the ERN and the FRN, at various stages of learning and in the generalization of that learning in an implicit learning phase.

Feedback-Error Related Negativity

Based on the literature indicating that the prediction error occurs at the time of feedback early in learning (Holroyd & Coles, 2002), it was predicted that peak amplitude of the feedback-ERN would be greater (i.e., more negative) within the first block of the PS task compared to the last block (late learning). This shift from early to late was indeed significant for the low-risk group, and was observed across all frontal and medial electrodes assessed. This is consistent with the literature outlining the generation of the error-related system in dorsal ACC (Holroyd & Coles, 2002; Mars et al., 2005; Miltner et al., 2003) and studies indicating that frontal activity is highest early in learning (Seger & Cincotta, 2005). However, this shift was not observed in the high-risk group.

Examination of peak amplitudes of the FRN for the 3 training trial types revealed that the risk groups did not differ. The lack of difference is perhaps not surprising given that this particular ERP is feedback-locked and that feedback did not differ across trial types. Consistent with the analytical approach in the current study, previous studies have assessed FRN and RL processes by collapsing across trials with correct and incorrect feedback (Hajcak et al., 2005). A difference in peak amplitude by trial type would have suggested differences in additional processes not examined here, such as possible

differences in neural responses to positive and negative feedback and specific learning biases (Frank et al., 2005; Holroyd & Coles, 2002; Miltner et al., 1997). Amplitude differences comparing correct with incorrect feedback trials were not assessed here because these processes are primarily mediated by the basal ganglia; deficits in basal ganglia function were not expected within this sample. Furthermore, studies have indicated that the amplitude of the FRN is insensitive to the expectation of negative feedback and that it is negligible on trials with positive feedback (Hajcak et al., 2005). It is therefore reasonable to conclude that amplitude differences on correct and incorrect trials would not be present within this sample. However, because this is an *error-related* system, examination of feedback differences may provide further insight into the observed pattern of results.

Importantly, when examining the FRN by trial type, there was an expected significant phase difference indicating greater FRN amplitude in early compared to late learning for the low-risk group. Again, no such shift occurred for the high-risk group. The lack of shift in the high-risk group can be taken as a deviation from typical, adaptive RL-related information processing. Consistent with previous findings, this is believed to be the result of impaired transfer of the acquired knowledge (Myers et al., 2003). Moreover, this was unexpectedly evident over the course of the training phase, not solely in the testing (novel) phase. It is important to keep in mind that the training phase of the task is RL, which utilizes both explicit and implicit memory systems (Eichenbaum, 2004; Maren & Holt, 2000; Tulving & Markowitsch, 1998). Thus, the pattern of results may speak to the role hippocampally driven implicit memory (Atallah et al., 2004; Cavanagh,

Zambrano-Vazquez, & Allen, 2012; Myers et al., 2003) and how this form of memory impacts adaptive RL in individuals at risk for AD.

With regard to the observed differences between electrodes examined, it is important to note that given the poor spatial resolution of EEG and that source localization analyses were well beyond the scope of this study, it is difficult, if not impossible, to interpret differences between electrodes as theoretically or clinically meaningful, despite statistical significance. Examination of these specific electrodes was based on thorough review of the literature, therefore, significant findings were expected and likely do not reflect specific genetic differences. However, these results support previous findings that the diffuse EEG signal is relatively consistent within the midline, over supplemental motor area (Hajcak et al., 2005; Holroyd & Coles, 2002). It also suggests that source localization analyses may prove fruitful in future studies.

Response-Error Related Negativity

According to the RL model, the PE presents at feedback in early learning but back-propagates to the moment of error detection or perception as learning occurs (Holroyd & Coles, 2002). For the present task, that moment was the time of response. At this point in the task, the basal ganglia are continuously evaluating events and predicting outcomes (reward prediction; (reward prediction; Hajcak et al., 2005; Holroyd & Coles, 2002). This evaluative processes results in phasic modulation of midbrain dopamine, which in turn modulates the amplitude of the ERN (Hajcak et al., 2005).

Consistent with the literature and with FRN dynamics, the amplitude of the response-ERN in the current study was predicted to be smaller in early learning compared to late learning (Holroyd & Coles, 2002). Similar to analyses of the FRN, both

correct and incorrect training trials were analyzed indiscriminately. Despite the fact that the ERN is part of an error detection system, studies have indicated that this component is elicited for both correct and incorrect trials (Hajcak et al., 2005). This has also been found in fMRI studies showing that the ACC is activated for both types of responses (e.g., Carter et al., 1998; Kiehl, Liddle, & Hopfinger, 2000; Menon, Adleman, White, Glover, & Reiss, 2001). Moreover, we anticipated the ERN would be activated by both types of trials in the current task because the evaluation of feedback is probabilistic, meaning that participants are likely to perceive the accuracy of their responses on a continuum rather than dichotomously.

Results revealed a trending main effect of phase such that amplitudes were greater in the last block of learning compared to the first block. This was observed in both groups as expected.

The high-risk group was expected to exhibit smaller amplitudes than the low-risk group in all analyses. However, the opposite pattern emerged indicating that the high-risk group consistently had greater amplitudes than the low-risk group. Interestingly, examination of the unique effect of individual probability differences revealed a significant 4-way interaction. The high-risk group elicited greater peak amplitudes (Fz and FCz) on intermediate conflict trials in early learning, and greater amplitudes (Fz) on trials of intermediate and high conflict in late learning. Results suggest that all participants performed and exhibited similar neural responses on the low conflict trials; that is, the one closet to 100:0 probability. However, group differences were observed on the intermediate trial types in early and late learning; differences for high conflict trial types were observed only in late learning.

Greater amplitudes on the intermediate conditions in both early and late learning in the high-risk group may indicate that these individuals had more difficulty finding an adaptive trade-off between exploring and exploiting options in order to optimize learning. The greater amplitudes indicate that for this pair in particular, outcomes were consistently worse than participants expected, leading to more negative peak amplitudes of the ERN. Findings related to the intermediate pair are particularly important because they indicate that the cognitive demand was optimal for observing RL dynamics whereas the high conflict pair may have been too challenging and the low conflict pair not challenging enough for these mechanisms to be observed.

The finding that the risk groups differed from each other in late learning for the high conflict pair may indicate that the initial stages of learning of the trial pair closest to 50:50 was difficult for all participants, and elicited similar neural responses. However, the low-risk group appears to have adaptively learned over the course of the training phase while the high-risk group did not. Thus, the low conflict trials were not demanding enough to observe differences and the high conflict trials were too demanding.

Error Related Negativity in Novel RL

The hippocampus is traditionally thought of as being responsible for explicit memory. However, it has been outlined as a learning mechanism (Gluck & Myers, 2001; O'Reilly & Rudy, 2001) with specific roles in procedural learning (Atallah et al., 2004), and has been shown to play a vital part in the updating of the value function in RL (Lee et al., 2012). This medial temporal lobe structure is responsible for the flexible and generalized use of information in novel situations (Eichenbaum, Stewart, & Morris, 1990; Myers et al., 2003). Because of its role in both explicit and implicit processes, it was

proposed here that RL processes it would be uniquely sensitive to AD related pathology (Shohamy & Wagner, 2008) such that individuals at high risk for the disease would exhibit altered patterns of RL.

Examination of the testing (novel) phase of the task revealed that group peak amplitudes did not significantly differ on optimal and suboptimal choices. Behaviorally, this was expected because such choices are the overall measure of accuracy. However, a few things should be considered when interpreting these results. First, this phase lacked feedback. Participants were therefore essentially blind to their performance and were unable to accurately assess their performance on a trial-to-trial basis. In other words, participants were unable to detect or largely perceive a difference in error such that it would elicit a different neural response. However, the ERN has been shown to be sensitive to participant expectancy (Cavanagh et al., 2011; Hajcak et al., 2005). Therefore, the lack of difference in ERN by risk group suggests that genetic risk for AD did not play a role in altering the expectancy of rewards and non-rewards. Risk differences in the neural signal were, therefore, hidden when examined based on optimal and suboptimal choices. A previous study of the PS task in PD patients treated with deep brain stimulation similarly found undifferentiated responses to optimal and suboptimal choices (Cavanagh et al., 2012).

However, an important aspect of RL is an agent's evaluation of conflict. The probabilistic nature of the task allows for the possibility of win-win (a choice between two highly rewarding options), lose-lose (a choice between to non-rewarding options), and win-lose (a choice between a reward and a non-rewarding option) situations. The ACC is widely implicated in conflict monitoring during information processing (Yeung,

Botvinick, & Cohen, 2004). A previous study of the PS task in PD assessed conflict trials and found neural response differences on high conflict trials when on vs. off deep brain stimulation (Cavanagh et al., 2012). Theta-band power, the same frequency elicited by the ERP components examined here, was found to predict reaction time on these trials. In short, previous findings have demonstrated that there is a relationship between conflict in RL and its associated neural signals. When trial types in current study were grouped into conflict conditions equivalent to those in the training phase (i.e., low, intermediate, high), differences were observed.

The high-risk group exhibited significantly greater amplitudes than the low-risk group on intermediate conflict trials. This is consistent with learning results in that not only was the high-risk group less efficient at learning this pair, they were also less efficient at applying that learned information to novel situations. This is perhaps not surprising. What is very interesting, however, is that there was a trending difference in peak amplitude of the low conflict trials, those closest to 100:0. It should be kept in mind that there were not significant differences between risk groups for the corresponding pair in training. It should also be noted that while the low conflict group resembles absolute certainty, it is not, in fact; it required appropriate learning of a 40- or 50- point difference in probability.

Taken together, the present results are believed to provide evidence that despite efficient learning, high AD risk individuals were not as effective in adaptive learning or in applying learned information to a novel environment. This is consistent with literature supporting the role of the hippocampus in the flexible use and transfer of acquired knowledge to novel situations (Atallah et al., 2004; Myers et al., 2003) as well as the

overall theory proposed here that latent hippocampal atrophy negatively impacts adaptive RL. Importantly, the current study was comprised of elders who lacked objective deficits in explicit or implicit memory that could otherwise account for the observed pattern of results. Thus, the pattern of results is most consistent with an AD risk-related difference in hippocampal integrity thereby affecting its ability to adaptively learn or to transfer or apply previously learned information for future use.

RL Performance

Throughout the course of this study, the current sample has been conceptualized as 'the best of the best' indicating that the high and low risk individuals did not differ by behavior or ability to carry out activities of daily living. They also did not objectively differ by age or measures shown to be sensitive to cognitive decline; indeed, the high-risk group had greater educational attainment than the low-risk group, which if influential at all, would confer protection (Arenaza-Urquijo, Wirth, & Chételat, 2015; Dekhtyar et al., 2015; Katzman, 1993). Results indicated that groups did not differ from each other on behavioral indices of learning. As such, the lack of task performance differences could be considered another indication of the cognitively intact nature of the sample, which adds strength to the implications of the neural differences observed in the current study.

Several studies investigating ERPs have shown neural activity differences when behavioral differences were not evident. Among of large sample of 415 participants ranging across the lifespan, behavioral analyses revealed no cognitive differences between apolipoprotein allele groups; indeed, ε4 carriers had better verbal fluency than ε3/ε3 controls (Alexander et al., 2007). Moreover, ERPs have been utilized without behavioral assessment altogether in order to distinguish those with AD from matched

controls using an extended projection pursuit method. This approach was able to identify 100% of those with AD, while incorrectly classifying only one control (6.1% false-alarm rate; Benvenuto et al., 2002; see also Katada et al., 2004). Previous investigations utilizing the PS task in other disorders such as depression and obsessive-compulsive disorder have also found neural differences when behavioral differences were not present (Cavanagh, Gründler, Frank, & Allen, 2010).

Taken together, these results indicate that the neural network responsible for adaptive, goal-directed behavior differs among cognitively intact individuals at risk for the development of AD compared to those at low risk. The neural signal associated with error detection is used to teach the motor system to be consistent with neural network implementations of RL principles and adaptively improve actions over time (Cavanagh et al., 2011; Holroyd & Coles, 2002). This is evident in the low-risk group, as indicated by the shift in response-ERN and feedback-ERN peak amplitudes from early to late learning. In contrast, the high-risk group did not demonstrate this process. We contend that the difference is due to disruption of the dynamic frontostriatal-hippocampal circuit in those with AD risk that results in a deficit in communication between the basal ganglia and the hippocampus, and projection to the motor cortex (Cavanagh et al., 2011; Hajcak et al., 2005). This information processing system is vital to the ability to effectively carry out activities of daily living. The current results provide very early evidence that underlying disease pathology can be detected among asymptomatic individuals via a noninvasive and inexpensive measure of neural activity during RL.

Limitations

Anticipated limitations of the study were largely avoided as the recruitment of APOE ε4 carriers, sample size and equality of groups, task difficulty, and EEG signal artifact were not problematic. Indeed, the sample size was large and equal between risk groups. Furthermore, only four participants had to be excluded for technical error or poor quality EEG signal. Instead, the primary reason for exclusion from analysis was failure to meet the learning criteria on the PS task. A larger sample would potentially increase power to add to the observed trends, but the results are supported by adequate power. Moreover, the intact cognitive status of the sample proved extremely valuable toward isolating subtle neural distinctions between risk groups. A more sensitive analysis of the PS behavioral data had previously been suggested and was ultimately carried out. This was, however, not due to limitations in the proposed analyses but rather necessary for appropriate comparison of the two phases of the task.

Future studies could consider some additions that could improve on this study. The current sample is not representative of a racially diverse population, and it consisted largely of women. It will be important to replicate findings with a more generalizable sample. Additionally, the current study did not examine the unique impact of negative vs. positive feedback in the amplitude of the FRN. It is possible that the difference in feedback type is impacting the overall results such that one group is more sensitive to positive or negative feedback. The current study also did not examine ERP latencies, other ERPs within the waveform, or reaction time in the behavioral task. Any, or all, of these metrics may prove useful in further understanding learning within this group of cognitively intact individuals at genetic risk for AD. Lastly, the results have been interpreted assuming future hippocampal atrophy in the high-risk group. Confirmation of

this would rule out the possibility of alternate explanations for the risk differences observed herein. In addition, future studies including participants diagnosed with AD, and perhaps other dementia etiologies such as frontotemporal dementia, would be valuable in contributing to the understanding of how regional disease pathology impacts a RL model.

Conclusions

The current study provided the first evidence that RL-related ERPs are sensitive to AD risk among cognitively intact individuals wher e no behavioral differences were apparent. We contend that subtle disruption of hippocampal-frontostriatal network communication results in early changes that alter and disrupt adaptive learning. These findings provide a framework for identifying pre-clinical markers of risk for future cognitive decline and AD that is economically viable and widely accessible.

RL is an ideal model with which to assess subtle neural changes prior to clinical and functional decline because it requires the simultaneous and unobstructed utilization of the frontostriatal-hippocampal network (Atallah et al., 2004; Maia, 2009; Seger & Cincotta, 2005). Clinical assessment typically promotes the isolation of cognitive domains to assist with differential diagnosis, such as using neuropsychological tests that examine executive function independent of memory, visuospatial skills independent of language function, etc. This approach is extremely useful once a certain degree of impairment has been reached. However, individuals who are in early states of the disease process often perform “normally” on these measures, or perform too similarly across domains for differential diagnosis or etiological determination to be achieved. Converging evidence suggests that disease related neural pathology begins years to

decades prior to impairment (Lazarczyk, Hof, Bouras, & Giannakopoulos, 2012; Morris, 2005; Sperling et al., 2011). While the onset of clinically significant behavioral impairment is difficult to pinpoint based on individual factors, more recent findings have shown that neural differences between infant APOE ε4 carriers and non-carriers have been observed (Dean et al., 2014). As such, the opportunities for early classification, and possibly intervention or prevention, may span across the lifespan so long as a method of identification exists.

Although, the current approach to clinical assessment is effective in later stages of the disease, it does not fully assess neural function. That is to say that the brain is a highly interconnected network of structures working in concert to carry out activities of daily living. Individuals do not solely use memory when cooking or shopping; they do not just use executive functions when driving or working. Thus, to best understand these networks and to best predict when they might by degenerating, it is essential to assess them interactively. RL does so, and thus it can provide a novel clinical conceptualization of AD and other neurologic disorders.

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Table 1.

Demographic Variables

	Total Sample n = 40		Low Risk n = 20		High Risk n = 20		
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	*p*
Sex	11M, 29F	-	5M, 15F	-	6M, 14F	-	-
Age (yrs)	79.3 (4.9)	72-89	79.7 (5.2)	72-89	78.9 (4.6)	72-86	0.61
Education (yrs)	14.7 (2.4)	12-20	13.9 (1.8)	12-18	15.6 (2.6)	12-20	0.02*
MMSE	28.1 (1.8)	24-30	28.5 (1.7)	24-30	27.7 (1.9)	24-30	0.19
DRS-2	138.0 (3.3)	130-144	138.9 (3.2)	132-144	137.2 (3.2)	130-144	0.10

Note. Low Risk = APOE ε4-/± Family History; High Risk = APOE ε4+/± Family History; M = Male; F = Female; MMSE = Mini Mental State Exam, possible range 0-30; MMSE *n* = 19 Low-risk group; DRS = Dementia Rating Scale-2, possible 0-144; *p < .05

Table 2.

Correlations of Demographic Variables

	Age	Education	APOE ε4±	MMSE	DRS
Age	-	-.023	-.083	-.101	-.087
Education	-.023	-	.368*	.090	.115
APOE ε4±	-.083	.368	-	-.214	-.265
MMSE	-.101	.090	-.214	-	.619**
DRS-2	-.087	.115	-.265	.619**	-

Note. APOE ε4± = Apolipoprotein carriers and non-carriers ± Family History; MMSE = Mini Mental State Exam; DRS = Dementia Rating Scale-2; Ethnicity of the entire sample was Caucasian; *p < .05 **p < .001

Table 3.

PS Task Variable Composition

Training	
Overall Accuracy	Average of all training trials
Trial Type 1 accuracy	Average all 80:20 pairs
Trial Type 2 accuracy	Average all 70:30 pairs
Trial Type 3 accuracy	Average all 60:40 pairs
Early Learning	Average of all training trials within the first block
First block Trial Type 1	Average all 80:20 pairs within the first block
First block Trial Type 2	Average all 70:30 pairs within the first block
First block Trial Type 3	Average all 60:40 pairs within the first block
Late Learning	Average of all training trials within the last block
Last block Trial Type 1	Average all 80:20 pairs within the last block
Last block Trial Type 2	Average all 70:30 pairs within the last block
Last block Trial Type 3	Average all 60:40 pairs within the last block
Testing	
Overall	Average of optimal and suboptimal
Low Conflict	Average 80:70, 70:60, 30:20
Intermediate Conflict	Average 80:60, 70:40, 40:20
High Conflict	Average 80:30, 80:40, 70:20

Note. The composition of performance variables by task phase, learning phase, training
trial type, and testing conflict type.

Table 4.

PS Task Variable Means and Standard Deviations

	Overall Sample n = 40		Low Risk n = 20		High Risk n = 20	
	Mean	SD	Mean	SD	Mean	SD
Blocks Performed	3.42	1.61	3.35	1.66	3.50	1.61
Training						
Overall Training						
Overall accuracy	68.14	0.86	67.53	6.86	68.74	0.62
Trial Type 1	78.33	1.27	77.42	1.35	79.24	1.21
Trial Type 2	65.28	1.11	65.27	1.17	65.29	1.05
Trial Type 3	60.80	1.58	59.92	1.65	61.67	1.54
Early Learning (First Block)						
Overall accuracy	62.08	1.24	61.67	1.23	62.50	1.28
Trial Type 1	71.88	2.00	70.00	1.71	73.75	2.24
Trial Type 2	58.13	1.53	57.50	1.46	58.75	1.63
Trial Type 3	57.13	2.40	57.50	2.20	56.75	2.62
Late Learning (Last Block)						
Overall accuracy	75.83	1.05	75.33	1.28	76.33	0.80
Trial Type 1	86.13	1.36	85.75	1.59	86.50	1.12
Trial Type 2	74.50	1.40	74.25	1.41	74.75	1.42
Trial Type 3	66.88	1.90	66.00	2.21	67.75	1.60
Testing						
Overall Accuracy	62.31	1.42	62.25	1.45	62.37	1.43
Low Conflict	74.26	1.80	75.82	1.91	72.70	1.71
Intermediate Conflict	61.99	1.65	65.49	1.71	58.48	1.56
High Conflict	55.00	1.71	56.76	1.97	52.34	1.42

Note. Low Risk = APOE ε4-/± Family History; High Risk = APOE ε4+/± Family History; Training: Overall accuracy = accuracy across trial types; Trial Type 1 = 80:20; Trial Type 2 = 70:30; Trial Type 3 = 60:40; Testing: Overall accuracy = accuracy across all trial types; Low Conflict = pairs discrepant by 40- to 50-points; Intermediate Conflict = pairs discrepant by 20- to 30-points; High Conflict = pairs discrepant by 10 points.

Table 5.

Independent Samples T-Tests of PS Task Variables

	t	df	*p*
Blocks Performed	-.290	38	.773
Overall Training			
Overall accuracy	-.436	38	.666
Trial Type 1	-.450	38	.656
Trial Type 2	-.006	38	.995
Trial Type 3	-.349	38	.729
Early Learning (First Block)			
Overall accuracy	-.210	38	.835
Trial Type 1	-.594	38	.556
Trial Type 2	-.254	38	.800
Trial Type 3	.098	38	.923
Late Learning (Last Block)			
Overall accuracy	-.296	38	.769
Trial Type 1	-.172	38	.864
Trial Type 2	-.112	38	.912
Trial Type 3	-.287	38	.775
Testing			
Overall Accuracy	-.288	35	.775
Low Conflict	.765	35	.449
Intermediate Conflict	1.54	35	.133
High Conflict	.817	35	.420

Note. Low Risk = APOE ε4-/± Family History; High Risk = APOE ε4+/± Family History; Training: Overall accuracy = accuracy across trial types; Trial Type 1 = 80:20; Trial Type 2 = 70:30; Trial Type 3 = 60:40; Testing: Overall accuracy = accuracy across all trial types; Low Conflict = pairs discrepant by 40- to 50-points; Intermediate Conflict = pairs discrepant by 20- to 30-points; High Conflict = pairs discrepant by 10 points. No significant differences were observed.

Table 6.

Peak Amplitude Means of the Response-Error Related Negativity in Early and Late Learning by Trial Type

	Early			Late		
	Fz	FCz	Cz	Fz	FCz	Cz
Overall Sample						
Overall	-5.12	-5.38	-4.95	-5.34	-5.57	-5.17
Trial Type 1	-5.18	-5.42	-4.93	-5.35	-5.53	-5.08
Trial Type 2	-4.94	-5.15	-4.77	-5.49	-5.65	-5.33
Trial Type 3	-5.20	-5.58	-5.16	-5.17	-5.53	-5.12
Low Risk						
Overall	-4.61	-5.04	-4.55	-4.86	-5.27	-4.75
Trial Type 1	-4.82	-5.13	-4.54	-4.88	-5.24	-4.76
Trial Type 2	-4.16	-4.67	-4.17	-5.00	-5.39	-4.81
Trial Type 3	-4.85	-5.36	-4.96	-4.73	-5.19	-4.69
High Risk						
Overall	-5.62	-5.71	-5.34	-5.81	-5.87	-5.59
Trial Type 1	-5.54	-5.71	-5.31	-5.82	-5.82	-5.39
Trial Type 2	-5.72	-5.65	-5.37	-6.00	-5.91	-5.85
Trial Type 3	-5.56	-5.80	-5.37	-5.61	-5.87	-5.55

Note. Low Risk = APOE ε4-/± Family History; High Risk = APOE ε4+/± Family History; Overall accuracy = accuracy across trial types; Trial Type 1 = 80:20; Trial Type 2 = 70:30; Trial Type 3 = 60:40

Table 7.

Peak Amplitude Means of the Feedback-Error Related Negativity in Early and Late Learning by Trial Type

	Early			Late		
	Fz	FCz	Cz	Fz	FCz	Cz
Overall Sample						
Overall	-6.32	-5.50	-5.29	-5.94	-5.10	-5.00
Trial Type 1	-6.31	-5.55	-5.49	-5.89	-5.08	-5.01
Trial Type 2	-6.33	-5.48	-5.15	-6.01	-5.20	-5.01
Trial Type 3	-6.36	-5.48	-5.25	-5.88	-5.00	-4.91
Low Risk						
Overall	-6.47	-5.50	-4.89	-5.83	-4.96	-4.35
Trial Type 1	-6.48	-5.60	-5.14	-5.89	-4.97	-4.41
Trial Type 2	-6.55	-5.55	-4.90	-5.90	-5.13	-4.41
Trial Type 3	-6.41	-5.38	-4.68	-5.68	-4.75	-4.21
High Risk						
Overall	-6.17	-5.50	-5.68	-6.05	-5.23	-5.61
Trial Type 1	-6.14	-5.50	-5.84	-5.90	-5.19	-5.61
Trial Type 2	-6.11	-5.42	-5.40	-6.12	-5.25	-5.61
Trial Type 3	-6.31	-5.58	-5.82	-6.08	-5.24	-5.61

Note. Low Risk = APOE ε4-/± Family History; High Risk = APOE ε4+/± Family History; Overall accuracy = accuracy across trial types; Trial Type 1 = 80:20; Trial Type 2 = 70:30; Trial Type 3 = 60:40

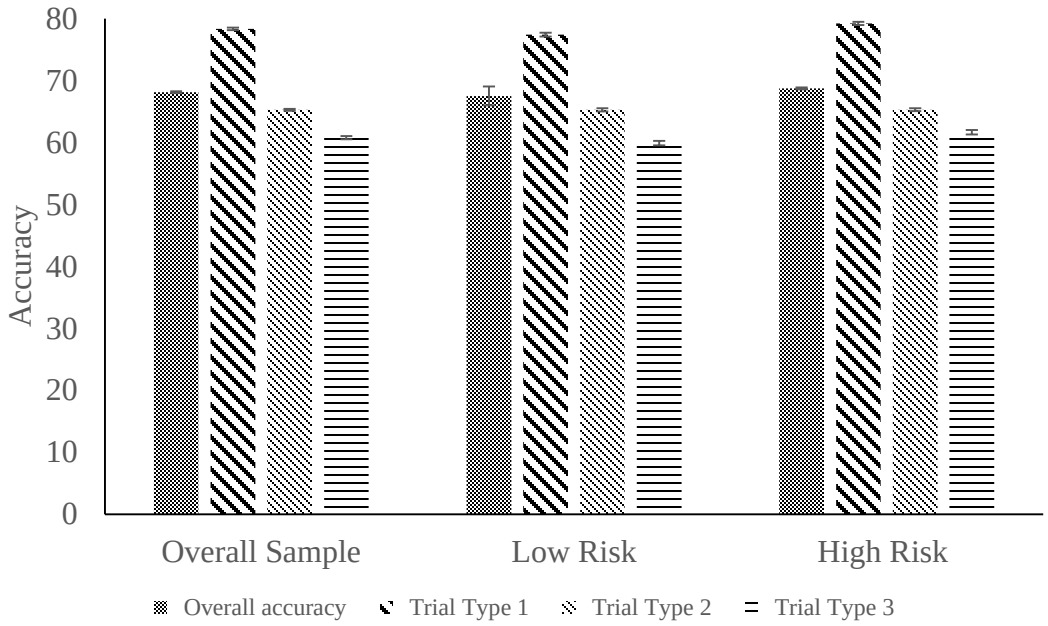


Figure 1. PS Task training phase performance broken down by group (overall sample, risk groups) and accuracy (overall, trial type 1 = low conflict; trial type 2 = intermediate conflict; trial type 3 = high conflict).

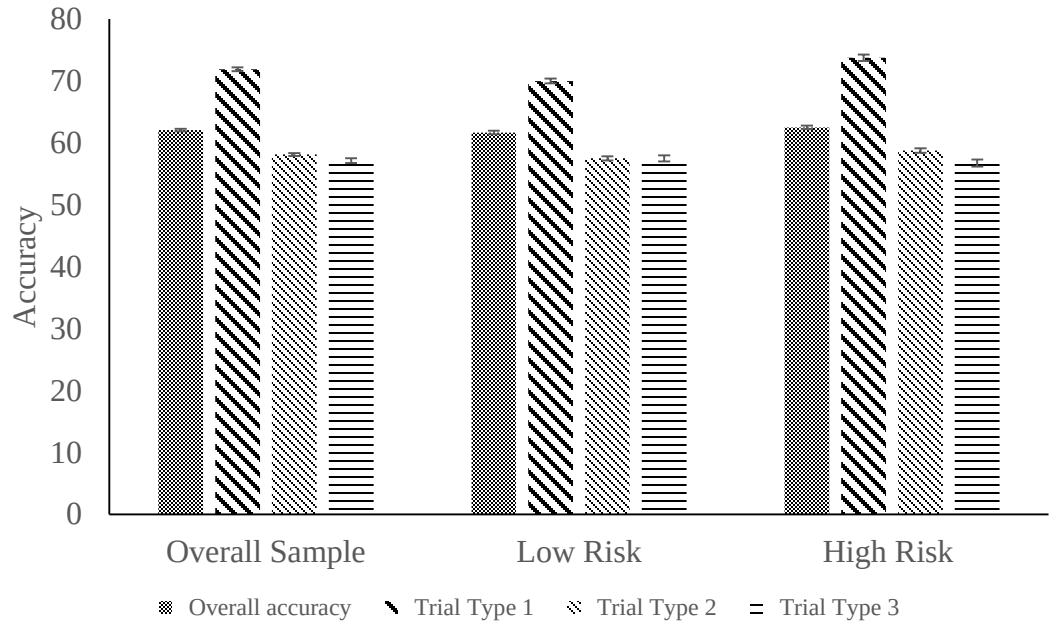


Figure 2. Early learning performance in the training phase of the PS Task broken down by group (overall sample, risk groups) and accuracy (overall, trial type 1 = low conflict; trial type 2 = intermediate conflict; trial type 3 = high conflict).

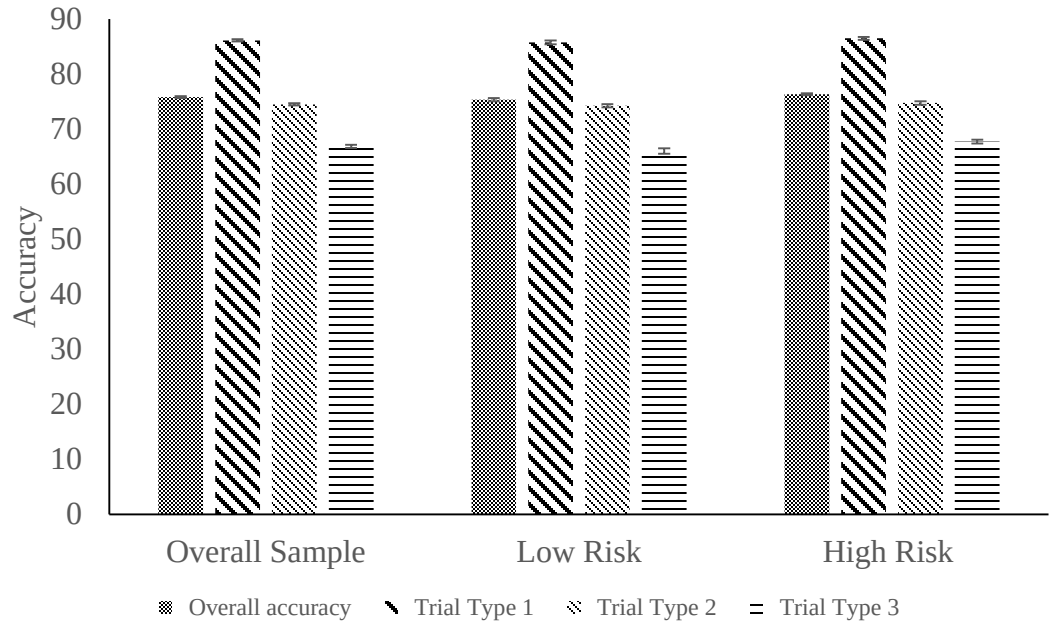


Figure 3. Late learning performance in the training phase of the PS Task broken down by group (overall sample, risk groups) and accuracy (overall, trial type 1 = low conflict; trial type 2 = intermediate conflict; trial type 3 = high conflict).

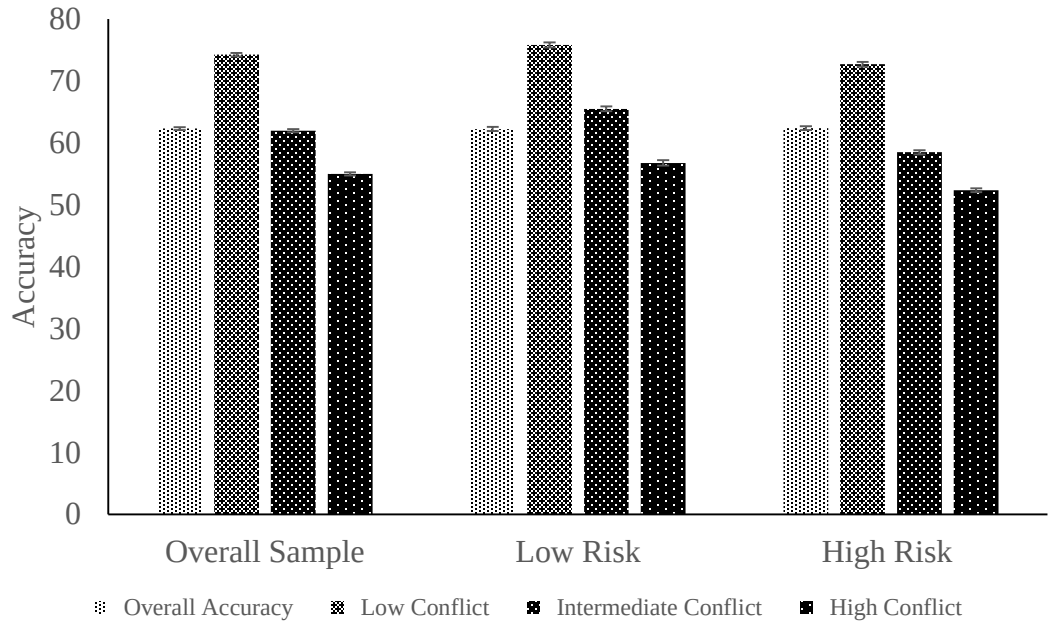
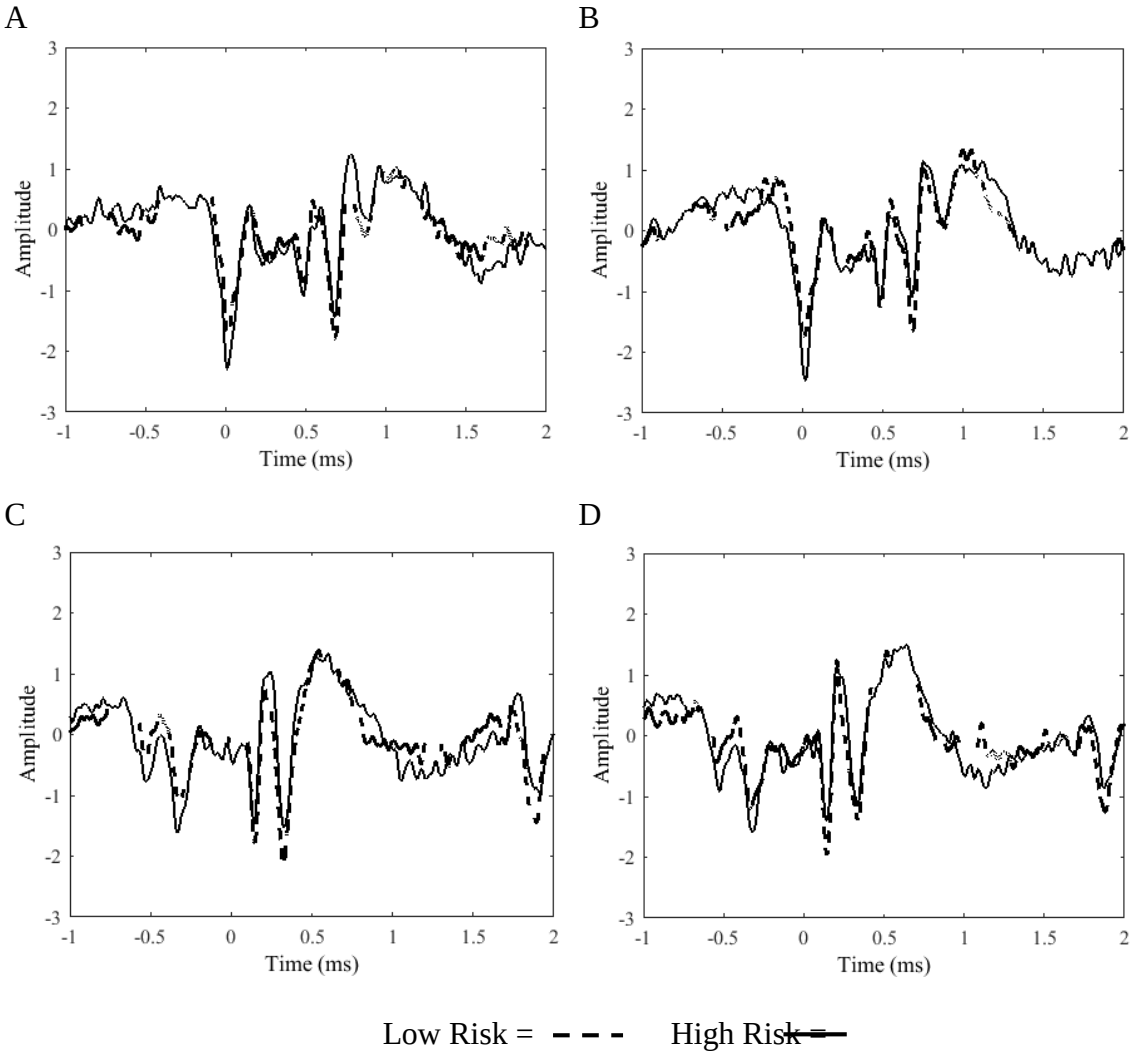


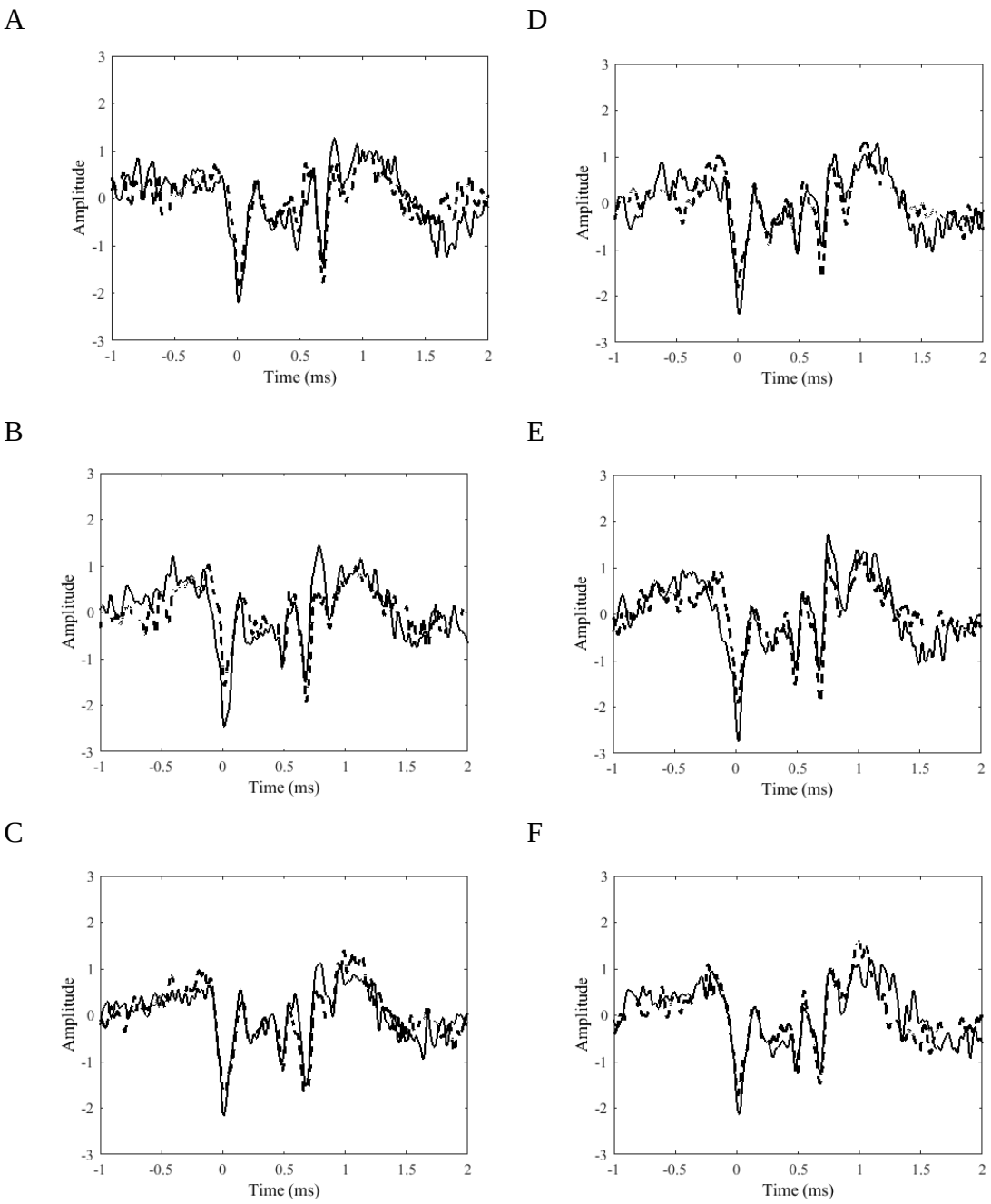
Figure 4. Testing performance of the PS Task broken down by group (overall sample, risk groups) and accuracy (overall, conflict).

Plot 1.



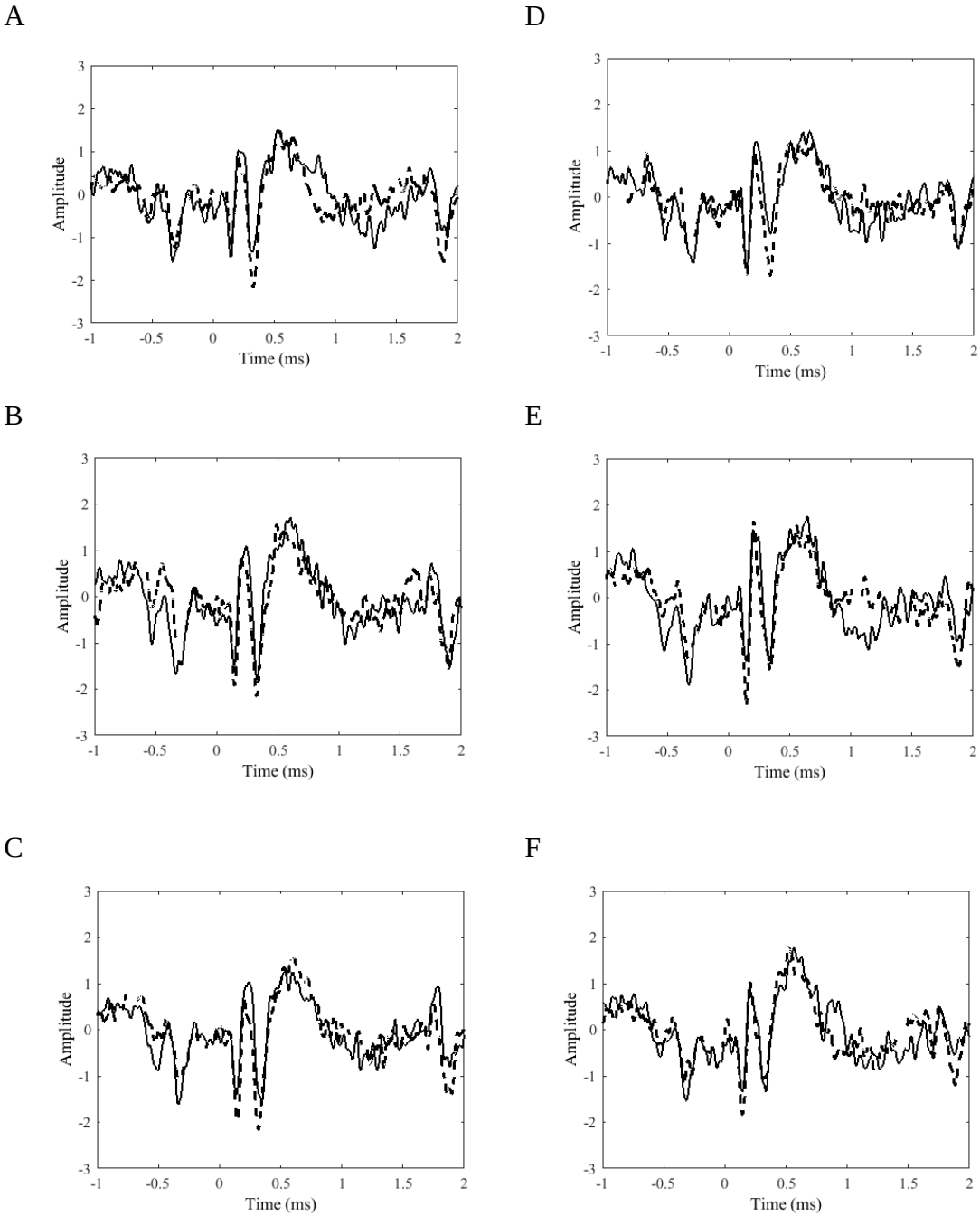
Note. Peak Amplitude at Fz; Response-locked (0 ms) ERN peak amplitudes for early (A) and late (B) learning in the training phase of the PS task. Feedback-locked (~0.4 ms) FRN peak amplitudes for early (C) and late (D) learning in the training phase of the PS Task.

Plot 2.



Note. Peak Amplitudes at Fz; ERN peak amplitudes (0 ms) for early (A, B, C) and late (D, E, F) learning by trial type 1 (80:20), trial type 2 (70:30), and trial type 3 (60:40) in the training phase of the PS task.

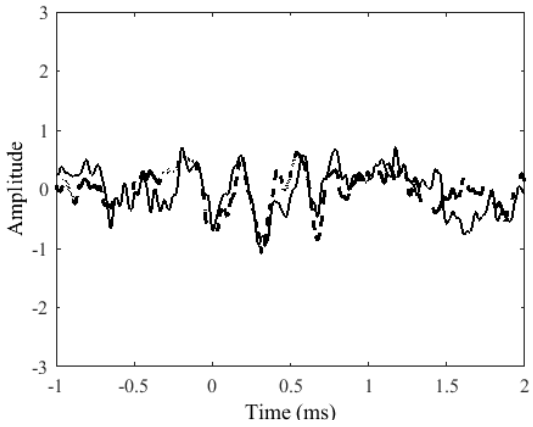
Plot 3.



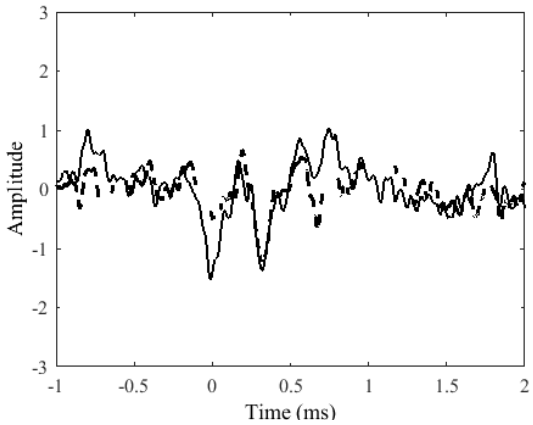
Note. Peak Amplitudes at Fz; FRN peak amplitudes (~0.4 ms) for early (A, B, C) and late (D, E, F) learning by trial type 1 (80:20), trial type 2 (70:30), and trial type 3 (60:40) in the training phase of the PS task.

Plot 4.

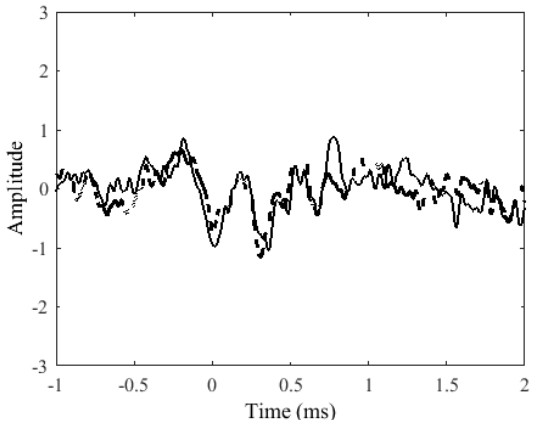
A



B



C



Note. ERN peak amplitudes (0 ms) at Fz for low (A), intermediate (B), and high (C) conflict trial types in the testing phase of the PS task.