AN EVENT-RELATED POTENTIAL (ERP) STUDY EXAMINING REWARD PROCESSING AND MOOD IN PARKINSON'S DISEASE AND HEALTHY AGING

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2010

To those who might benefit from this project

ACKNOWLEDGMENTS

I would like to acknowledge my dissertation chair and mentor, William M. Perlstein, Ph.D. for his encouragement and support of this project. I would also thank to thank my committee members, Russell M. Bauer, Ph.D., W. Keith Berg, Ph.D., Michael Marsiske, Ph.D., John C. Rosenbek, Ph.D., and Frank Skidmore, M.D. for their helpful advice and feedback. Finally, I express gratitude to Chris Sozda, M.S., Sarah Key-DeLyria, M.A., David Stigge-Kaufman, Ph.D. and Michael Larson, Ph.D. for their invaluable assistance, generosity, humor, and kindness throughout this process. This research was supported by a scholarship awarded by the American Psychological Foundation.

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August 2010

Chair: William M. Perlstein
Major: Psychology

The ability to appropriately respond to environmental feedback is crucial for successful living. Positive and negative feedback differentially activate reinforcement learning systems in the brain and reliance on external feedback changes adaptively over the course of learning so that the probability of success or failure can be predicted prior to action. Despite significant advances in our understanding of the reinforcement learning system, questions remain, particularly regarding outcomes of damage to the system. Older age and Parkinson's disease (PD) are known to be associated with impairments in reinforcement learning and damage to the neural networks underlying the processing of errors and feedback. In order to better understand the nature of these impairments, two event-related potential (ERP) experiments were conducted in young adults, community-dwelling older adults, and PD patients. The experiments used a probabilistic learning task that manipulated valence and feedback probability in order to investigate differential valence-related reactivity, error detection, and feedback processing, as measured by response-locked and feedback-locked ERP components.

Within the young adult control group, predictions from the reinforcement learning theory were generally upheld for both error-related and feedback-related processing,

providing a basis of comparison for examination of age-related changes. Evidence for age-related changes was primarily found in error-related processing. Interpreted within the context of reinforcement learning theory, this was attributed to failure to develop internalized representations of responses with learning in the older adult controls. Consistent with predictions, some evidence was found for relative preservation of activity related to positive outcomes as compared to negative outcomes of actions.

Contrary to expectations, patients with Parkinson's disease did not demonstrate impairments in reinforcement learning compared to older adult controls with respect to accuracy or ERP reflections of error- and feedback-processing. In fact, some evidence was found for increased response-related activity in PD patients versus controls. Based on valence-related patterns found in the data, hypotheses were generated based on reinforcement learning theory and the effects of aging, Parkinson's disease and dopaminergic medication on positive and negative feedback processing.

Taken together, the results of these experiments provide support for the reinforcement learning theory of the ERN and bolster the validity of requests for inclusion of the role of positive information processing in the theory. Moreover, these results help to clarify the impact of aging and Parkinson's disease on learning and decision-making and have implications for designing and improving interventions for cognitive impairments.

CHAPTER 1
GENERAL INTRODUCTION AND METHODS

General Introduction

Monitoring performance in order to appropriately and flexibly adapt decision-making in response to environmental feedback is crucial for survival. The process of responding to both positive and negative environmental feedback has been called "reinforcement learning" (Holroyd & Coles, 2002); the key principle behind this type of learning is that behavior followed by positive or rewarding outcomes is more likely to recur, whereas behavior followed by negative or punishing outcomes is less likely to recur.

The process of predicting, evaluating and responding to such rewards and punishments is complex, and involves dopaminergic activity in frontal and subcortical regions of the brain (Schultz, Tremblay, & Hollerman, 2000). Unfortunately, despite the apparent importance of this process for learning and successful living, it has been hypothesized that frontal regions of the brain subserving them may be particularly susceptible to dysfunction as we age (West, 2000); in addition, declines in dopaminergic activity that occur in older age may negatively impact problem-solving, decision-making, and other related aspects of executive function (Band, Ridderinkhof, & Segalowitz, 2002; Woodruff-Pak, 1997).Similarly, the more pathological depletion of dopaminergic neurons in the substantia nigra that occurs in Parkinson's disease (PD) also leads to dysfunction of frontal-subcortical circuitry, resulting in deficits in frontal executive function (Zgaljardic et al., 2006) including aspects of performance monitoring such as error detection and feedback processing (Band et al., 2002; Schmitt-Eliassen, Ferstl, Wiesner, Deuschl, & Witt, 2007; Schott et al., 2007) as well as mood symptoms (e.g.,

depression and apathy). Reports of impairments in reinforcement learning are inconsistent in both aging and PD. Moreover, no studies have examined relationships between aspects of reinforcement learning (i.e., error detection and feedback monitoring) and emotional symptoms (i.e., apathy and depression) reported by patients with Parkinson's disease, despite the fact that associations have been found between these symptoms and other elements of executive dysfunction (Isella et al., 2002; Pluck & Brown, 2002; Starkstein et al., 1992).

The overall goal of this dissertation study is to examine the neurophysiological and neuropsychological underpinnings of error detection, feedback processing, and mood (i.e., apathy and depression) by comparing a community-dwelling group of older adults with suspected subclinical dopaminergic dysfunction to a PD group with clinical dopaminergic dysfunction. The study of Parkinson's disease in addition to healthy aging may provide a useful model for understanding relative levels of impairment and preserved ability in performance monitoring between these groups, and how aspects of performance monitoring (i.e., error detection and reinforcement learning) relate to emotional symptoms. Specifically, the following research questions will be addressed:

1. What effect do feedback valence and probability have on reinforcement learning (i.e., error detection and feedback processing) over time?
2. How do aging and Parkinson's disease affect the ability to detect errors and process positive and negative feedback?
3. How are error detection and feedback processing related to other aspects of cognitive and emotional functioning in young adults, community-dwelling older adults, and patients with Parkinson's disease?

Although aspects of executive function such as performance monitoring (e.g., the ability to problem-solve using examiner feedback) are commonly assessed clinically by the use of neuropsychological tests, behavioral assessment of performance monitoring

is difficult and complicated by the fact that these functions require multiple overlapping skills. As a result, use of a more direct measurement instrument may be necessary to elucidate dysfunctional component processes that may contribute to impairments in performance monitoring. The field of cognitive neuroscience provides one such method, namely the use of high-density electroencephalography to measure rapid changes in scalp-recorded brain event-related potentials (ERPs). ERPs have been used to examine two aspects of performance monitoring relevant to reinforcement learning (i.e., error detection and feedback monitoring).

This chapter will discuss neuroanatomical and electrophysiological models of reinforcement learning, review the use of ERPs for studying error detection and feedback processing in aging and PD, and conclude with an introduction to the general methods used in this study.

Neuroanatomical Model of Reinforcement Learning

Structures involved in reward processing have been identified through human fMRI studies and animal studies using single cell recording. Areas consistently demonstrating activation include the ventral striatum, regions of the frontal lobe (i.e., the orbitofrontal cortex, or OFC, and the anterior cingulate cortex, or ACC), and the amygdala (Knutson & Cooper, 2005; Knutson, Fong, Adams, Varner, & Hommer, 2001).

Ventral striatum and dopamine

Based on animal studies, it has been proposed that dopaminergic (DA) signals from the ventral tegmental area and substantia nigra to the ventral striatum/nucleus accumbens aid in the prediction of rewards by increasing in response to received rewards and decreasing when an expected reward is not received. In this way, DA neurons are thought to create stimulus-reward associations by generating a “prediction

error signal," which codes the difference between expectations and actual outcomes, indicating whether events are "better" (positive prediction error) or "worse" (negative prediction error) than expected (Schultz, 2002; Schultz et al., 2000). Over repeated interactions, as stimulus-reward associations are learned, the increased DA response "propagates backward" in time so that it becomes associated with the conditioned stimulus rather than the reward, thereby aiding in the prediction of reward (Holroyd & Coles, 2002).

Anterior cingulate cortex

The dorsal anterior cingulate cortex (dACC) is believed to contribute to attention, motivation and cognitive control (Bokura, Yamaguchi, & Kobayashi, 2001; Botvinick, Cohen, & Carter, 2004; Kerns et al., 2004; Ridderinkhof, Nieuwenhuis, & Bashore, 2003). The ACC is also involved in reward processing and error information (Amador, Schlag-Rey, & Schlag, 2000; Shidara & Richmond, 2002) via its projections from the mesencephalic DA system (Paus, 2001). It has been theorized that the commission of errors causes decreased dopaminergic activity that subsequently disinhibits neuronal activity in the ACC (Holroyd & Coles, 2002); however, the precise contribution of the ACC to performance monitoring is still unclear. Recently, two positions on the topic have been outlined (Holroyd & Coles, 2008): Those who believe that the dACC has an evaluative function suggest that it monitors performance in order to determine success and detect errors (Dehaene, Kerszberg, & Changeux, 1998; Holroyd, Nieuwenhuis et al., 2004; Knutson, Westdorp, Kaiser, & Hommer, 2000) or conflict (Yeung, Botvinick, & Cohen, 2004). On the other hand, those who believe that the dACC is involved in response selection hypothesize that performance monitoring occurs in other brain regions, e.g., the basal ganglia (Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003; Holroyd,

Yeung, Coles, & Cohen, 2005) and the dACC plays a more direct role in the decision making process (Holroyd & Coles, 2002, 2008; Holroyd, Larsen, & Cohen, 2004). This more direct role involves the use of the reward prediction errors signaled by the midbrain dopamine system for action selection (Gibson, 2006; Holroyd & Krigolson, 2007; Schultz, 2002; Schultz et al., 2000), implying the use of information from reward history to adjust future behavioral choices, rather than simply evaluating them. Consistent with the latter hypothesis, activations in the ACC have been seen following receipt of expected rewards (Knutson et al., 2001) and during the anticipation of reward (Knutson & Cooper, 2005); it has been proposed that the ACC codes for the probability of expected outcomes (Knutson & Cooper, 2005; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005).

The ventral portion (or affective subdivision) of the ACC is part of the limbic system, making the ACC part of a circuit that regulates both cognitive and emotional processing, with these two types of information processed separately (Bush, Luu, & Posner, 2000). Because the ventral ACC is connected to the amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus and OFC, it is believed to be involved in the affective evaluation of the valence of feedback as positive or negative.

Orbitofrontal cortex and amygdala

The orbitofrontal cortex (OFC) and amygdala also contribute to the affective aspect of feedback processing. Specifically, the amygdala signals the level of arousal and reward intensity (Anderson et al., 2003), and the OFC, which receives input from primary taste and olfactory cortices, determines the value of the reward and the strength of the behavioral response (Rolls, 2000).

Electrophysiological Model of Reinforcement Learning

Over the last four decades, advances in electrophysiology have enabled new kinds of questions to be addressed regarding neural systems and processes that underlie cognition. Electroencephalography (EEG) records volume-conducted electrical activity of the brain using electrodes placed non-invasively on the scalp (Davidson, Jackson, & Larson, 2000). Electrical activity recorded from EEG can be averaged in association with the presentation of specific events of interest. Initially, the event-related response associated with the presentation of a stimulus is embedded in the ongoing EEG activity. An event-related potential (ERP) waveform associated with a specific stimulus is extracted by averaging multiple samples of the EEG that are time-locked to repeated occurrences of the stimulus (Fabiani, Gratton, & Coles, 2000). Assuming that the underlying brain activity remains constant during the same conditions of an experiment, the benefit of averaging is that the ERPs should remain relatively consistent from trial to trial, while at the same time the ongoing random background EEG is averaged out of the resulting waveform (Otten & Rugg, 2005).

ERPs are highly sensitive to changes in neural activity on the level of milliseconds (ms), making them the “gold standard” among noninvasive imaging methods with respect to temporal resolution (Fabiani et al., 2000). ERP waveforms usually consist of discrete voltage deflections that can either be positive- or negative-going. Specific “components” of ERP waveforms are usually named in accordance with their polarity (positive or negative) and peak latency (in ms). Two examples of negative-going ERP waveforms are the ERN (error-related negativity) and the FRN (feedback-related negativity).

Measuring error detection and feedback processing using ERPs

In the past ten to fifteen years, investigation of the mechanisms involved in performance monitoring has been informed by the study of ERP components sensitive to performance feedback (i.e., the "feedback-related negativity" or FRN; (Holroyd & Krigolson, 2007; Miltner, Braun, & Coles, 1997) and error detection (i.e., the "error-related negativity" or ERN; (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). These potentials are thought to be associated with reward prediction signals generated by dopamine signaling to the ACC.

The FRN is maximal over frontal areas, has an average amplitude between 5 and 10 μV, and a peak latency around 300 ms (Hajcak, Holroyd, Moser, & Simons, 2005; Nieuwenhuis, Holroyd, Mol, & Coles, 2004). Findings from ERP source modeling, functional magnetic resonance imaging, and single-unit recording studies suggest that the FRN is generated in the medial frontal cortex, most likely the ACC (Amiez, Joseph, & Procyk, 2005; Brown & Braver, 2005; W. J. Gehring & Willoughby, 2002; Holroyd & Coles, 2002; Ridderinkhof et al., 2003; Shidara & Richmond, 2002). Although the FRN was initially used to study negative reinforcement, it is also reliably elicited by positive feedback (Hajcak et al., 2005; Holroyd & Coles, 2008; Oliveira, McDonald, & Goodman, 2007), when it appears as a less negative-going ERP deflection (compared to that elicited by negative feedback; see Figure 1-1 and Nieuwenhuis et al., 2004 for reviews). The FRN also appears to be modulated by feedback probability, such that lower probability events elicit higher amplitudes and higher probability events elicit lower amplitudes (Bellebaum & Daum, 2008; Hajcak, Moser, Holroyd, & Simons, 2007).

The identification of the ACC as the source of the FRN suggests that it may be related to the error-related negativity (ERN), a putative reflection of the evaluative

process of performance monitoring that becomes more negative with awareness of errors. The ERN, which is a response-locked deflection, has a peak latency within 100 ms of an error response, is distributed medial-frontally, and also appears to be generated by the ACC (Holroyd, Larsen et al., 2004; Holroyd, Nieuwenhuis et al., 2004; Yeung et al., 2004). The ERN was initially identified for its relationship to error detection, and it was suggested that the ERN was elicited when a mismatch occurred between the internal representation of a correct response and the actual response (Falkenstein et al., 1991; W.J. Gehring, Goss, Coles, Meyer, & Donchin, 1993). An alternate view developed positing that the ERN is a manifestation of conflict between competing responses (Yeung et al., 2004) that can also occur on correct trials; on correct trials it is referred to as the correct-response negativity, or CRN (Ford, Roth, Menon, & Pfefferbaum, 1999). The CRN is less negative in amplitude than the ERN. It has been suggested that the similarity between the ERN and FRN indicates that they reflect activation of a reinforcement learning system that evaluates outcomes in order to direct future reward-seeking behavior (Holroyd & Coles, 2002; Nieuwenhuis et al., 2004). This evaluation of outcomes as either better or worse than expected is coded as a “reward prediction error” (Schultz, 2002).

Reinforcement learning theory of the ERN

The reinforcement learning theory of the functional significance of the ERN has been gaining increasing support (Holroyd & Coles, 2002). This theory combines the role of the mesencephalic DA system in learning with the error detection and feedback processing function of the ACC (see Nieuwenhuis et al., 2002 for review). Particularly relevant to a discussion of PD, this theory is also based on early research of the basal ganglia that indicates that the basal ganglia monitor and evaluate ongoing events and

predict whether they will result in success or failure. When predictions are revised positively, the basal ganglia signal a phasic increase in dopaminergic activity, and when predictions are revised negatively, they signal a phasic decrease in dopaminergic activity (see Schultz, 2002 for review). A decrease in DA causes a disinhibition of ACC neurons that generates a larger ERN, reflecting larger discrepancies between expectation and outcome (i.e., a negative prediction error), and increases in dopamine activity are associated with smaller ERNs (Holroyd & Coles, 2002). Prior to learning, only feedback (reflected in the FRN) provides information about the correctness of a response; with learning, however, the ERN should propagate back in time and be elicited at the time of the response (Pietschmann, Simon, Endrass, & Kathmann, 2008). Thus, the feedback processing system improves future performance by using DA signals to learn the earliest predictors of reward or punishment.

Predictions from the reinforcement learning theory

Importantly, the reinforcement learning theory is the only theory of the ERN that also makes predictions for changes in FRN amplitude (Nieuwenhuis et al., 2004). With learning, as individuals become better able to predict outcomes of their actions, the amplitude of the response ERN should increase (because errors become more "surprising" reflected in larger differences between expected and received outcomes) whereas the FRN amplitude should decrease, as individuals rely less and less on feedback to shape their behavior (Holroyd & Coles, 2002). These changes in ERN and FRN amplitudes over time should also be related to behavioral changes (i.e., reduced errors over time).

Executive Function and Reinforcement Learning in Aging

Though it is a matter of much debate, there is some evidence that the frontal regions are selectively and differentially affected by aging (West, 2000). Reduced blood flow (Rabbitt et al., 2006), volume (Raz, Rodrigue, Head, Kennedy, & Acker, 2004) and metabolism (Greenwood, 2000) are reported in frontal areas in older adults. Markers of white matter integrity are also reduced, with maximal changes noted in anterior white matter; this loss of white matter fibers may play an important role in cognitive dysfunction with aging, perhaps due to cortical "disconnection" (Shenkin et al., 2005). In fact, such physiological changes in frontal regions have been shown to correlate with scores on tests of executive function in older adults (O'Sullivan, Barrick, Morris, Clark, & Markus, 2005; O'Sullivan et al., 2001).

Executive dysfunction in older adults has been observed as impairments in behavioral flexibility, or the ability to adapt behavior based on rewards and punishments (Deakin, Aitken, Robbins, & Sahakian, 2004; MacPherson, Phillips, & Della Sala, 2002; Mell et al., 2005; Ridderinkhof, Span, & van der Molen, 2002). Reduction of behavioral flexibility in older age is likely caused by structural declines in the frontal regions just mentioned, as well as by chemical alterations of the reward system, including loss of serotonergic receptors (Wang et al., 1995) and dopaminergic midbrain neurons located in the ventral tegmental area (VTA), ventral striatum, amygdala, and prefrontal cortex (Schultz et al., 2000) as well as the substantia nigra (Przuntek, Muller, & Riederer, 2004). Such alterations of the "reward system" lead to impairments in feedback processing, learning of stimulus-reinforcement associations, and reward based decision making (Marschner et al., 2005).

Of note, it appears that the integrity of the response to feedback in older adults may be altered based on the valence of the feedback. For example, Eppinger and colleagues (Eppinger, Kray, Mock, & Mecklinger, 2008) reported reduced amplitude ERPs reflecting negative feedback processing in older adults, and concluded that older adults appear to be less affected by negative feedback than positive feedback as compared to young controls. In addition, a recent event-related fMRI study measuring activation in mesolimbic regions during a monetary incentive delay task found evidence for intact activation of brain regions involved in gain anticipation, but a reduction in activation during loss anticipation in older adults compared to young adults (Samanez-Larkin et al., 2007). Differential response to feedback based on valence may be due to disruption of distinct systems underlying processing of positive and negative feedback since it has been shown that positive feedback is processed in medial OFC and striatum (Liu et al., 2007; Nieuwenhuis, Slagter, von Geusau, Heslenfeld, & Holroyd, 2005; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001), whereas negative feedback is processed in lateral OFC, ACC and insula (G. K. Frank et al., 2005; Liu et al., 2007; O'Doherty et al., 2001).

ERP Studies of Reinforcement Learning in Older Adults

As detailed above, behavioral investigations have concluded that older adults often demonstrate impairments in aspects of reinforcement learning (Deakin et al., 2004; MacPherson et al., 2002; Mell et al., 2005; Ridderinkhof et al., 2002); however, ERP studies of error detection and feedback processing in healthy aging have not consistently supported these conclusions.

Based on the reinforcement learning theory, the amplitude of the ERN should increase with learning and the FRN should decrease with learning as participants rely

less on feedback. Using a reinforcement learning paradigm that manipulated the validity of feedback, Nieuwenhuis and colleagues (2002) provided evidence for the theory when they found the expected increases in ERN amplitude and decreases in FRN amplitude as learning progressed in young adults. They reported that older adults demonstrated reduced ERNs and FRNs when compared to healthy young controls, consistent with reports of a dysfunctional reinforcement learning system in older adults. Using a slightly different paradigm, Pietschmann and colleagues (2008) also found evidence for a dysfunctional reinforcement learning system in older adults when they reported no ERN amplitude increase over time in older adults despite similar ERN amplitudes between groups at the beginning of the learning process. Importantly, they also found that FRN amplitudes decreased with learning in both age groups and were reduced in older relative to younger adults, but only in response to negative feedback.

According to Eppinger and colleagues (2008), the Nieuwenhuis study was limited because it did not account for slowed processing speed in older adults, which placed greater time pressure on them, possibly impairing their ability to learn from feedback. Thus, in order to account for age-related changes in response speed, Eppinger and colleagues (2008) used a probabilistic learning task in which validity of feedback was manipulated and response time was adjusted based on performance differences. In contrast to the studies described above, they did not find evidence for an age-related reduction of the ERN when controlling for performance differences between age groups, challenging the hypothesis that older adults are generally impaired in error processing. Like Pietschmann and colleagues (2008), Eppinger and colleagues (2008) reported a reduction of the non-reward related FRN in the elderly. Eppinger and colleagues

suggested that their study provided evidence for an age-related asymmetry in the processing of feedback valence (with more attention paid to positive than negative feedback) and age-related reductions in activity of structures involved in the processing of negative feedback (e.g., ACC and OFC). Interestingly, they explained these findings within the framework of the "socioemotional selectivity theory of aging," which describes a "positivity effect" such that older adults focus more on emotion regulation and use cognitive control mechanisms to increase attention to positive information and decrease attention to negative information. Recent fMRI findings (Samanez-Larkin et al., 2007) using a gain and loss anticipation task seem to support this view by showing that older adults are less affected by potential losses than younger adults, whereas both age groups are equally affected by potential gains. Taken together, these studies suggest that older adults exhibit signs of a dysfunctional reinforcement learning system characterized by valence-dependent impairments in feedback processing; however, these studies do not provide consistent information on changes in the ERN with aging.

Executive Function and Reinforcement Learning in Parkinson's Disease

Although PD is a movement disorder, it is important to recognize that it is not only physically debilitating (causing slowed movements, postural instability, rigidity, muscle weakness and tremor), but also psychologically debilitating (causing increased prevalence of depression, anxiety, and apathy) (Fahn, 2003) and cognitively debilitating (with increased prevalence of dementia and executive dysfunction). Neuropathological processes distinguishing cognitive and emotional dysfunction from motor dysfunction in PD have been clarified with the discovery of reciprocal and distinct circuits connecting cortical and subcortical areas (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000). Three non-motor loops originating in the dorsolateral prefrontal cortex, lateral

orbitofrontal cortex, and anterior cingulate/medial orbitofrontal cortices have been identified. Although dysfunction in all of these areas is likely in PD (Zgaljardic et al., 2006), the loops originating in the lateral orbitofrontal cortex and the ACC/medial orbitofrontal cortex are most relevant to the current project. The lateral loop is thought to be responsible for mediating reward processing and mood, whereas the medial loop is thought to be responsible for conflict monitoring (Zgaljardic, Borod, Foldi, & Mattis, 2003). There appears to be increasing evidence that the medial loop (including the ACC) is also involved in emotional processing and the processing of both negative and positive feedback (i.e., rewards). Identifying relationships between the debilitating cognitive and emotional problems associated with these circuits may be critical for the development of appropriate treatments (McDonald, Richard, & DeLong, 2003).

PD patients often demonstrate declines in executive functions similar to those seen in normal aging, such as inhibition, planning (Owen, 2004), sequencing and set-shifting (Gotham, Brown, & Marsden, 1988; Owen, Iddon, Hodges, Summers, & Robbins, 1997) and response monitoring (Cooper, Sagar, Tidswell, & Jordan, 1994). These various aspects of executive dysfunction may contribute to difficulties initiating goal-directed behavior and impairments in performance monitoring. The mechanism responsible for these cognitive deficits in PD is still unclear but likely includes structures such as the striatum, areas of the frontal cortex, or connections between the two. Functional neuroimaging studies examining cognitive deficits in PD point to disruption of the major dopaminergic pathways including the nigrostriatal (involved in the production of movement), mesolimbic (involved in reward), and mesocortical (involved in motivation and emotion) pathways (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Dagher,

Owen, Boecker, & Brooks, 2001; Goldman-Rakic, Bates, & Chafee, 1992; Mattay et al., 2002).

Due to the disruption of the mesolimbic dopaminergic pathway, it is not surprising that patients with PD demonstrate executive dysfunction in the area of reward processing (i.e., reinforcement learning); however, the precise nature of these impairments is still unclear. As in older adults, patients with PD are more impaired than healthy young adults at learning stimulus-reward associations (M. J. Frank, Seeberger, & O'Reilly R, 2004; Marschner et al., 2005). Non-demented, non-depressed and medicated PD patients have also been found to make disadvantageous choices on a test used to measure the ability to adjust performance and learn stimulus-response associations based on monetary feedback (Iowa Gambling Task; (Kobayakawa, Koyama, Mimura, & Kawamura, 2008; Pagonabarraga et al., 2007). Although this suggests a failure to appropriately learn from feedback, it is not known whether this impairment is due to dysfunction of the mesolimbic reward prediction system, which involves accurate detection of errors, or to dysfunction in processing the rewards/feedback themselves (Schott et al., 2007). Dysfunction in either of these areas is possible in PD since ventral striatal areas are important for the prediction and anticipation of reward, and ventromedial frontal cortex is important for the processing of rewards; either (or both) of these regions may be dysfunctional in PD (Knutson et al., 2001). As described above, these two aspects of performance monitoring are thought to be dissociable using EEG.

In light of the fact that feedback processing systems depend on dopaminergic transmission, the medication status of patients with PD is important to consider during

assessment of feedback-based learning. Studies examining dopaminergic medication effects on feedback processing are contradictory or counterintuitive, with some studies reporting impairments in feedback-based learning when patients are on medication versus off medication (Cools, Altamirano, & D'Esposito, 2006; Czernecki et al., 2002; Swainson et al., 2006), and others reporting contrasting results (M. J. Frank et al., 2004; Shohamy, Myers, Grossman, Sage, & Gluck, 2005; Swainson et al., 2006). These differences may be related to factors such as demographic variables, disease variables, or task difficulty or task demands (Cools, Barker, Sahakian, & Robbins, 2001; Mattay et al., 2002; Swainson et al., 2006). Alternatively, it has been hypothesized that conflicting results demonstrated by medicated and unmedicated patients on feedback-based tasks are due to differences in the processing of positive versus negative feedback (Cools et al., 2006; M. J. Frank et al., 2004), but a consistent pattern of results has not been found. Some studies have reported that patients ON medication demonstrate impairments on feedback-based tasks when they are required to learn from negative feedback or outcomes; in contrast, when learning based on unexpected rewards or positive outcomes, patients ON medications perform as well as patients OFF medications and healthy older adults (Cools et al., 2006; M. J. Frank et al., 2004). Other investigators have reported that patients OFF medication demonstrate impairments when learning from positive feedback (Schott et al., 2007).

ERP and fMRI Studies of Reinforcement Learning in Parkinson's Disease

Some EEG studies suggest that patients with PD demonstrate dysfunction in the error detection system. As in "healthy" aging, examinations of the ERN in patients with PD have reported conflicting results: Some studies of medicated and unmedicated PD patients have reported reduced amplitude ERNs when compared to older adult controls

(Falkenstein et al., 2001; Stemmer, Segalowitz, Dywan, Panisset, & Melmed, 2007) and others have found no difference between medicated patients (tested off medication) and older adult controls (Holroyd, Praamstra, Plat, & Coles, 2002). Recently, reduced ERN amplitudes were observed in both on- and off-medication conditions in the same group of patients when compared to older adult controls (Willemssen, Muller, Schwarz, Hohnsbein, & Falkenstein, 2008).

Consistent with reduced ERN amplitudes in patients with PD, another EEG study found amplitude reductions of a brain potential reflecting reward anticipation (i.e., the stimulus-preceding negativity) in PD patients when compared to older adult controls (Mattox, Valle-Inclan, & Hackley, 2006). Similarly, a recent fMRI study showed that, whereas young adults exhibited midbrain and ventral striatal activation during reward prediction and no mesolimbic response to the reward itself, unmedicated patients with Parkinson's disease demonstrated no mesolimbic activity during reward prediction, but rather during feedback processing (Schott et al., 2007). This seems to suggest that PD patients demonstrate impairment in learning the predictive value of the rewards, despite intact ability to process rewards themselves. Surprisingly, no studies to date have exploited the temporal sensitivity of electrophysiological reflections to differentiate whether impairments occur in reward anticipation or in the ability to process feedback itself (i.e., by measuring the FRN) to bolster these findings in PD.

Because there are no published studies examining the FRN in PD, in order to identify reasonable predictions regarding the FRN in this population, it might be useful to consider ERP evidence of error detection and reward-processing impairments in patients diagnosed with schizophrenia, another neurological population characterized

by a dysfunctional dopaminergic system. Like PD patients, patients with schizophrenia demonstrate diminished ERN amplitude compared to “healthy” subjects in a variety of experimental tasks (Alain, McNeely, He, Christensen, & West, 2002; Kopp & Rist, 1999; Mathalon et al., 2002; Morris, Heerey, Gold, & Holroyd, 2008; Morris, Yee, & Nuechterlein, 2006). In the only study examining FRN amplitude in patients with schizophrenia, Morris and colleagues (Morris et al., 2008) reported reduced FRN amplitude during early trials of a probabilistic learning task in which feedback was necessary for accurate performance. As in studies of older adults, this reduction was seen only in response to negative feedback.

Emotional Symptoms in Parkinson’s Disease

Due to disruption of mesocortical pathways involved in motivation and emotion, it is not surprising that mood symptoms are common among PD patients. In comparison to the estimated prevalence of depression in the general population (15%), the prevalence of depression in PD is quite high, with approximately 40-50% of PD patients reporting these symptoms (Cummings, 1992; McDonald et al., 2003).

Depressive symptoms reported in PD may be explained as a psychological reaction to stress and loss of function associated with the disease. On the other hand, these symptoms may be explained by physiological outcomes resulting from degeneration of brain regions including the substantia nigra and ventral tegmental area (McDonald et al., 2003); reduced metabolism in the caudate, orbitofrontal cortex, and medial frontal lobes (Mayberg et al., 1990; Ring et al., 1994); or changes in neurotransmitter levels such as serotonin (Mayeux, Stern, Cote, & Williams, 1984).

In addition to depression, an estimated 15-42% of PD patients report symptoms of apathy (Cummings, 1997; Zgaljardic et al., 2003). An “apathy syndrome” has been

defined as a primary lack of motivation exhibited in behavioral, cognitive, and emotional domains (Marin, 1991). According to this model, the behavioral domain includes symptoms such as lack of effort, lack of productivity, and lack of initiative (or diminished goal-directed behavior); the cognitive domain includes symptoms such as loss of interest in new experiences and lack of concern about one's personal problems; and the affective domain includes symptoms of flattened affect and lack of response to positive or negative events.

Historically, differentiation of depressive symptoms from apathy symptoms has been difficult; however, more recently, the importance of this distinction has become the focus of research. For example, it has been reported that up to 29% of PD patients meet criteria for apathy without significant depression (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006; Starkstein et al., 1992), suggesting that different mechanisms may underlie apathy, (e.g., orbitomedial or ACC/VTA connections) (Tekin & Cummings, 2002) and depression (e.g., orbitofrontal/subcortical connections) (Cummings & Masterman, 1999). The identification of different mechanisms underlying these disorders may signal the need for different treatments.

Unfortunately, there are currently no pharmacologic treatments for apathy. Like executive dysfunction, however, apathy may respond to dopaminergic agents, implying a similar mechanism associated with the loss of DA (Pedersen et al.). Thus, hypothesized mechanisms of apathy in PD may be similar to the mechanisms of executive dysfunction, consistent with a "frontal lobe syndrome."

Interactions Between Cognition and Emotion – Importance of the ACC

Indeed, studies have reported correlations between apathy and executive functioning in PD such that increasing apathy is related to worse executive functioning

(Isella et al., 2002; Pluck & Brown, 2002; Starkstein et al., 1992). The mechanism underlying this relationship could be dysfunction of the ACC. Lesions of the ACC have produced a host of symptoms, including apathy, dysregulation of autonomic functions, akinetic mutism and emotional instability (Bush et al., 2000); as described in the preceding review, impairments in performance monitoring have also been linked with dysfunction of the ACC. In addition, patients with Alzheimer's disease who exhibit apathy are more likely to show damage to the medial frontal and ACC regions (Craig et al., 1996; Migneco et al., 2001; Rosen et al., 2005).

In light of the behavioral and affective components of an "apathy syndrome," and given the close connections between brain regions subserving emotional symptoms of apathy and regions subserving cognitive executive functions such as performance monitoring and reinforcement learning, it seems plausible that apathy may be related to decreased sensitivity to reinforcement. In fact, a relationship has been found between negative symptom severity and reduced FRN amplitude (Morris et al., 2008) in a sample of patients with schizophrenia (a population also affected by dysregulated dopamine). In addition, reduced ventral striatal activation during reward anticipation was associated with an increase in severity of the negative symptoms (e.g., apathy) in an unmedicated sample of patients with schizophrenia (Juckel et al., 2006). Because PD also negatively impacts these regions, patients with Parkinson disease represent an ideal population for examining relationships between these cognitive and affective symptoms. Surprisingly, one previous study comparing non-demented and non-depressed patients with PD on and off dopaminergic medications found no relationship between mood and stimulus-reward learning (using a task similar to the Wisconsin Card Sorting Task and a

gambling task) (Czernecki et al., 2002). These investigators found that levodopa medication improved subjectively reported motivation (i.e., apathy), but increased perseverative errors, suggesting a positive influence of medication on the subjective evaluation of motivation, but negative effects on feedback sensitivity. Unfortunately, the measures used in this study did not allow for a precise examination of component processes of stimulus-reward learning, such as error detection and feedback processing, which could be assessed using EEG.

The negative effects of depression on cognition are well documented. Depressive symptoms are correlated with an increased risk of dementia (McDonald et al., 2003) and memory as measured by the Dementia Rating Scale has been found to be worse in depressed patients with PD than in non-depressed patients with PD or healthy controls (Norman, Troster, Fields, & Brooks, 2002). There is a vast literature on the association between executive dysfunction and depressive symptoms in otherwise healthy individuals (e.g., (Veiel, 1997). A relationship between executive impairment (e.g., in problem-solving, set-shifting, phonemic fluency) and depression has also been reported in PD, but it is not clear if the deficits are specific to depression in PD, the disease itself, or simply an aspect of global cognitive deterioration, or overall clinical severity (Troster et al., 1995).

Studies of the impact of depression on aspects of performance monitoring such as error detection and feedback processing are generally consistent with theories that depression is accompanied by increased attention to errors (Davidson, 1998). Based on reports of enhanced reactivity to errors evidenced by elevated ERN amplitude in patients with major depressive disorder, it has been suggested that these patients may

have exaggerated early error-detection processes (Chiu & Deldin, 2007). Depressed individuals are seen as being highly sensitive to negative feedback, demonstrated by increased activation in the anterior cingulate cortex in response to negative stimuli (Anand et al., 2005). In addition, depressed and dysphoric individuals are less responsive to positive stimuli and rewards such as monetary incentives (Naranjo, Tremblay, & Busto, 2001). Studies of the responsivity to negative feedback using EEG to examine the FRN are less clear, and report enhanced amplitudes in moderately depressed patients and attenuated amplitudes in severely depressed patients (Tucker, Luu, Frishkoff, Quiring, & Poulsen, 2003).

Summary and Rationale for the Present Study

Impairments in executive functioning and aspects of performance monitoring including error detection and feedback processing have been reported in both “healthy” aging and Parkinson’s disease. These impairments likely result from varying degrees of decline in the integrity of frontal lobe structures including the ACC and OFC; dysfunctional connections between these frontal structures and subcortical structures (e.g., the striatum); and disruptions in dopaminergic transmission. Failure to appropriately adapt decision-making in response to environmental feedback may result in an increase in negative outcomes associated with behavioral choices and a decrease in positive outcomes, which in turn may lead to increased negative emotion (e.g., depression) and amotivation (i.e., apathy). Alternatively, depression and apathy may exacerbate difficulties with learning from feedback, creating a cycle of maladaptive behavior choices.

Although progress has been made with respect to understanding the brain structures and neurotransmitters involved in feedback-related decision making,

questions remain regarding the effects of aging and Parkinson disease on feedback processing, and regarding relationships between cognitive and affective components of this process. Because evaluating component processes of feedback-based decision-making using traditional neuropsychological tests is difficult, event-related potentials may provide a more direct method of assessing the neural processes involved.

Increased attention is being paid to the differential effects of valence on the processing of feedback in older adults, with converging evidence pointing to specific impairments in the processing of negative feedback. Continued support for the finding of preserved positive feedback processing could have implications for cognitive rehabilitation. Moreover, despite strong support for modulation of the ERN and FRN components by affect (i.e., depression), only one study (Morris et al., 2008) has examined the relationship between negative symptoms (including apathy) and the FRN. Because PD patients exhibit relatively high rates of apathy, understanding the degree to which this motivational disorder is associated with ERP reflections of impairments in error detection and decreased sensitivity to reinforcement may also be important for intervention planning. This research could demonstrate a relationship between affective processing and performance monitoring in PD, adding to our understanding of models of reinforcement learning and dopamine-related aging processes in general.

This dissertation will investigate the following specific aims and hypotheses:

1) **Specific Aim 1:** Provide support for the reinforcement learning theory by examining the effects of manipulation of feedback probability and valence on ERP components during the course of the experiment.

    - **Hypothesis 1:** The ERN will be of greater (more negative) amplitude than the CRN in all probability conditions and that the greatest (most negative) ERN amplitude will be observed in the least ambiguous (i.e., most probable) condition, reflecting greater awareness of errors in this condition.

- **Hypothesis 2:** ERN amplitude should become more negative over time, reflecting the idea that awareness of errors increases with learning; this change will be most apparent in the least ambiguous condition.

- **Hypothesis 3:** FRN amplitude will be greater in response to negative feedback than to positive feedback in all probability conditions; the most negative FRN amplitude will be observed in the most ambiguous condition, reflecting the idea that reliance on feedback increases under conditions of greater ambiguity.

- **Hypothesis 4:** FRN amplitude will decrease (become less negative) over time, reflecting the idea that reliance on feedback decreases with learning.

2) **Specific Aim 2:** Examine the effects of aging and Parkinson's disease on reinforcement learning (i.e., error detection and feedback processing).

- **Hypothesis 5:** At the start of the experiment, older controls will demonstrate smaller ERN amplitudes than younger controls; however, over subsequent trial blocks, ERN amplitudes of older controls will be similar to younger controls.

- **Hypothesis 6:** ERN amplitudes of older adults and patients with PD will not differ at the start of the experiment; however, over subsequent blocks, ERN amplitudes of patients with PD will be smaller than those of older controls.

- **Hypothesis 7:** With respect to the amplitude of the FRN following positive feedback, older adult controls will not differ from younger controls.

- **Hypothesis 8:** In turn, the amplitude of the FRN following positive feedback for patients with PD will not differ from that of older controls.

- **Hypothesis 9:** With respect to the processing of negative feedback, older adult controls will exhibit reduced amplitude FRNs compared to younger controls across blocks.

- **Hypothesis 10:** In turn, PD patients will exhibit reduced amplitude FRNs compared to older adult controls.

3) **Specific Aim 3:** *Exploratory analyses* will investigate the relationships between feedback processing, emotional symptoms and other aspects of executive dysfunction.

- **Hypothesis 11:** Participants from all groups will demonstrate relationships between measures of executive functioning and ERP reflections of negative feedback processing after controlling for positive feedback processing. In addition, feedback processing will be associated with emotional symptoms, particularly apathy.

General Methods

Because the testing procedure and ERP methods were identical across the studies, the task stimuli and procedures, as well as the ERP acquisition, reduction, and analysis methods are described below.

ERP Task Stimuli and Procedures

Task stimuli

Stimuli and procedures for the task were modified from Eppinger et al (2008). Stimuli consisted of 18 black and white images of objects taken from the Snodgrass and Vanderwart picture database (Snodgrass & Vanderwart, 1980). Each stimulus belonged to one of three learning conditions in which validity of feedback was manipulated. In the "100% validity" condition (i.e., feedback is always valid), stimulus A was mapped to the right response key and stimulus B to the left response key. Thus, if participants pressed the right button in response to stimulus A, they always received positive feedback; if they responded to stimulus A with a left button press, they always received negative feedback (and the reverse for stimulus B). Two different stimuli (C and D) were used in the "80% validity" condition. If participants responded to C with a left button press, they received positive feedback 80% of the time and negative feedback 20% of the time. If they responded with a right button press, they received negative feedback 80% of the time and positive feedback 20% of the time (and vice versa for Stimulus D). A similar procedure was followed in the "60% validity" condition. In each block of 240 trials, 80 "100% valid" trials, 80 "80% valid" trials, and 80 "60% valid" trials were presented in mixed order (i.e., not in blocks).

Prior to starting the experiment, participants completed one practice block of eight "100% valid" trials and one practice block of 70 trials from all three validity

conditions in order to familiarize themselves with the experiment. These practice stimuli were different from those used in the experimental blocks. There were three blocks in the experiment; each block used a new set of stimuli from the six stimulus categories. In each experimental block, each of the six stimuli was presented 40 times in random order. Thus, each participant completed 240 trials per block, for a total of 720 trials.

Participants were instructed to press one of two keys on a keyboard as quickly as possible in response to each stimulus and to determine the correct stimulus–response associations using trial and error based on feedback that they were given. Positive feedback was "$$$$" printed in green against a black background, and negative feedback was "XXXX" printed in red against a black background. When a participant responded too slowly, they saw the words "too slow." To increase motivation and interest in the task, they were informed that they could win up to ten extra dollars for their participation, depending on their performance. Following completion of the ERP task, participants completed a post-task questionnaire assessing their level of engagement in the task and their perceived emotional reactivity to the task.

Trial procedure

At the beginning of each trial, a fixation cross appeared for 500 ms, followed by a stimulus picture for 500 ms. In an effort to ensure an equal number of trials from which to learn, we adjusted for age- and disease-related slowing by adapting the response deadline in 100 ms steps in a range of 600 – 1000 ms depending on the proportion of time-out trials relative to performed trials (see Eppinger et al., 2008). Each participant began with a response deadline of 700 ms. After the first trial, an algorithm monitored the proportion of time-out trials (number of time-out trials relative to the trials performed). If the proportion of time-out trials was smaller than 2%, a response deadline

of 600 ms was applied. For every time-out rate increase of 2%, the response deadline was increased by 100 ms, with a maximum deadline of 1000 ms (for over 8% of time-out trials). This was done in order to make sure that all subjects produced a similar proportion of time-out trials. After responding to the stimulus picture, a blank screen appeared for 500 ms followed by the feedback stimulus for 500 ms. Then participants began the next trial.

Neuropsychological Measures

Participants completed a short battery of neuropsychological tests focused primarily on the assessment of executive functions. The Mini-Mental State Exam (MMSE; (Folstein, Folstein, & McHugh, 1975) and the Dementia Rating Scale (DRS; (Mattis, 1988) were used to screen for dementia and estimate overall cognitive functioning. All participants completed the MMSE, but only older adults (controls and patients with PD) completed the DRS. Full scale intelligence quotients (FSIQs) were estimated using the National Adult Reading Test. Participants also completed Trail Making Tests A and B (Reitan & Wolfson, 1995), the Digit Span subtest from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; (Wechsler, 1997), the Controlled Oral Word Association Test (COWA; (Benton & Hamsher, 1989), the Stroop Color and Word Test (Golden, 1978), and the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Each of these tests measures a slightly different form of cognitive/ executive functioning. Trails A and B provide a measure of attention and cognitive flexibility, Digit Span measures attention and working memory, the Stroop Color and Word Test measures inhibition, selective attention, and response conflict, and the Wisconsin Card Sorting Test measures abstract problem-solving and set-shifting using examiner feedback (Lezak, Howieson, & Loring, 2004). COWA is a

measure of speeded verbal output, an ability that has been shown to be impaired in PD and is related to ACC functioning (Abrahams et al., 2003).

Emotional Measures

Participants also completed self-report questionnaires assessing emotional functioning. Depression was assessed using both the Beck Depression Inventory-Second Edition (BDI-II; (Beck, 1996) and the Geriatric Depression Scale (GDS; (Yesavage et al., 1983). The GDS was used in addition to the BDI-II because it accounts for somatic symptoms often experienced by older adults that may artificially inflate the likelihood of depression diagnosis (Blazer, 2002). A modified version of the Apathy Evaluation Scale (Starkstein et al., 1992) as well as the Lille Apathy Rating Scale (LARS; (Sockeel et al., 2006) were used to assess apathy symptoms. The State-Trait Anxiety Inventory (STAI; (Speilberger, Gorusch, Lushene, Vagg, & Jacobs, 1983) was used to provide information regarding the participants' general levels of anxiety as manifested in temporary states of distress and more long-term personality traits.

EEG Data Acquisition and Reduction

EEG was recorded from 64 scalp sites using a 64-channel geodesic sensor net and Electrical Geodesics Incorporated (EGI; Eugene, Oregon, USA) amplifier system (amplification 20K, nominal bandpass .10 – 100Hz). EEG was referenced to Cz and digitized continuously at 250 Hz with a 16-bit analog-to-digital converter. Electrode placements enabled recording vertical and horizontal eye movements reflected in electro-oculographic (EOG) activity. A right posterior electrode approximately two inches behind the right mastoid served as common ground. Electrode impedance was generally maintained below 50 kΩ, consistent with procedures suggested by the manufacturer.

EEG data were analyzed using Brain Electric Source Analysis (BESA) software (MEGIS Software, GmbH, Gräfelfing, Germany). Eyeblink artifacts were identified with a template-based method (Ille, Berg, & Scherg, 2002) and corrected using the adaptive artifact correction (Ille et al., 2002). Continuous EEG was then segmented into condition-related epochs. Using the BESA artifact scan tool, single-trial epochs were discarded using threshold criteria that maximized the number of trials accepted from each individual. The average voltage threshold that was used for excluding trials was 121.7 μV (SD: 6.3, range: 120-150). Point-to-point transitions were not allowed to exceed 75 μV. Single-trial EEG was then digitally re-referenced to an average reference (Bertrand, Perrin, & Pernier, 1985). Prior to analyses, EEG was digitally low-pass filtered at 30 Hz (zero phase).

The individual-subject event-related potentials (ERPs) were extracted and averaged from the ongoing EEG recording in discrete temporal windows that coincided with response and feedback onset to obtain response- and feedback-locked ERPs, respectively. Individual-subject *response-locked* averages were derived separately for correct (CRN) and incorrect (ERN) trials for the 100%, 80% and 60% conditions, spanning 200ms prior to and 500ms following response and baseline corrected using the 200ms pre-response window. To ensure accurate characterization of ERN/CRN amplitude and prevent spurious findings that might result from potential groupwise latency differences, the response-locked components were measured as the mean amplitude within a 60 ms time window centered on the peak of the ERN/CRN at electrode FCz in each group. ERP trials containing errors of omission were excluded from averages.

Individual-subject feedback-locked ERPs were derived separately for reward and non-reward trials for the 100%, 80% and 60% feedback blocks spanning 100 ms before- and 800 ms following-feedback and were baseline corrected using the 100 ms pre-feedback stimulus window. In light of previous findings that measurement of the FRN can be confounded by potential overlap with other components (e.g., P300; (Holroyd, Larsen et al., 2004; Holroyd et al., 2003), initial quantification of the FRN will be completed by calculating difference waves subtracting the mean amplitude of the ERP associated with reward feedback from the ERP associated with non-reward feedback. The "non-reward minus reward" difference waves will also be calculated for the three probability conditions. The feedback-locked components were measured as the mean amplitude within a 60 ms time window centered on the peak of the FRN at electrode FCz in each group.

As mentioned above, the ERP components of interest – ERN/CRN and FRN – were quantified at electrode FCz. This location was chosen based on previous studies showing that they are maximal at this medio-frontal site (Hajcak et al., 2005; Holroyd, Larsen et al., 2004; Holroyd et al., 2003; Larson, Kelly, Stigge-Kaufman, Schmalfuss, & Perlstein, 2007) and because both components were largest at that site on examination of grand-averaged waveforms.

Data Analysis

Independent samples t-tests were performed to examine between-group differences on neuropsychological data. The accuracy data from the feedback-based learning task was analyzed by averaging mean accuracy rates individually for each subject and validity condition into three "bins" (of 240 trials), reflecting the three learning blocks. Trials for which no response was given were removed before calculating

accuracy. The mean accuracy rates (% correct), as well as ERP component mean amplitudes, were analyzed using separate repeated measures analyses of variance (ANOVAs). ANOVAs included the between-subjects factor of group (younger vs. older; older vs. PD), and within-subject factors of validity (100%, 80%, 60%), bin (1, 2, 3), and valence (positive or negative). Partial-eta^2 is reported as a measure of effect size. In accordance with a priori hypotheses, planned contrasts with polynomial comparisons were used to decompose interaction effects. In addition to planned contrasts, follow-up post-hoc comparisons were made using Bonferroni corrections for multiple comparisons. The Greenhouse-Geisser epsilon adjustment (Greenhouse & Geisser, 1959) was applied for ANOVAs with more than two levels of a within-subject factor to correct for possible violations of sphericity; corrected *p*-values are reported where the assumption of sphericity is violated. Pearson-product correlation coefficients were used to examine the relationships between difference wave amplitudes and neuropsychological data of interest.

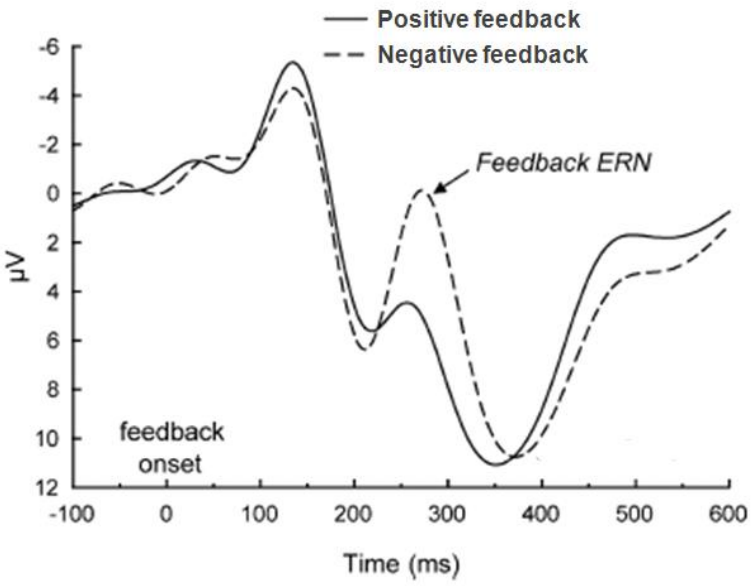


Figure 1-1. Typical example of event-related brain potentials associated with negative and positive feedback recorded from electrode FCz. Note that here the FRN is called the “feedback ERN.” Adapted from Nieuwenhuis et al. (2002).

CHAPTER 2
EXPERIMENT 1: THE EFFECT OF AGING ON ERROR DETECTION AND FEEDBACK PROCESSING

Overview and Predictions

Experiment 1 was conducted in order to replicate the results reported by Eppinger and colleagues (2008) using a modified version of their task. More specifically, this experiment examined whether electrophysiological correlates of error detection (as reflected in the fronto-central ERN) and feedback processing (as reflected in the fronto-central FRN) reflect changes in reinforcement learning abilities and differential sensitivity to feedback valence in younger versus older adults by using a probabilistic learning task in which feedback validity was manipulated. In addition, exploratory analyses examined relationships between ERP amplitudes, neuropsychological test results, and self-reported emotional symptoms.

For the young adult group, in accordance with the predictions from the reinforcement learning theory of the ERN/FRN (Holroyd & Coles, 2002; Nieuwenhuis et al., 2004), it was expected that the amplitude of the ERN would be larger than the CRN across learning conditions, and that the amplitude of the ERN would increase over time as errors become more “surprising” with learning. The increase was expected to be most apparent in the 100% condition, followed by the 80% condition. Thus the amplitude of the incorrect minus correct difference wave for the ERN should be greatest the more valid the feedback. Similarly, the amplitude of the FRN for negative feedback (i.e., non-reward) was expected to be larger than the amplitude for positive feedback (i.e., reward), but the amplitude of the FRN should decrease over time as participants rely less and less on feedback. The amplitude of the incorrect minus correct difference wave for the FRN should increase the more invalid the feedback in both groups.

In accordance with previous results in an older adult sample (Eppinger et al., 2008), it was predicted that older adults would also demonstrate the largest ERN/CRNs in the 100% condition, followed by the 80% and 60% conditions. Although larger incorrect minus correct difference waves were expected with increasing validity for the response-related activity, it was predicted that these increased amplitudes would be more pronounced in the younger than older participants. Older subjects should demonstrate reductions of the ERN/CRN early in the course of the experiment; however, by the end of the experiment their amplitudes should not differ from younger adults, suggesting that older adults are not impaired in error detection; rather, they are slower to learn stimulus-response mappings. The FRNs for both groups were expected to be maximal in the 60% condition, followed by the 80% and 100% conditions. Age-related reductions in the FRN were predicted for incorrect trials but not for correct trials, regardless of validity condition, suggesting that older adults rely more on positive than negative feedback valence during learning. Finally, in exploratory analyses, participants were expected to show correlations between FRN incorrect-minus-correct difference waves and scores on cognitive measures thought to be dependent on functioning of frontal brain regions. In particular, relationships were expected between FRN difference waves and performance on neuropsychological tests of problem solving using feedback (WCST) and working memory (Digits Backwards).

Methods

Participants

Forty-three participants were recruited from the community for this study. Three younger and two older adults were excluded from data analysis due to technical difficulties during data acquisition. The final sample included nineteen young

participants (ages 19-35) and nineteen older participants (ages 56-76). Table 2-1 provides demographic and neuropsychological data for the participants. The two groups were matched for gender (χ^2 = 1.31, p > .20) and handedness (χ^2 = .36, p > .50). Although older subjects had a higher mean level of education compared to those in the younger group, t(36) = -3.3, p = .002, the two groups were well-matched with respect to premorbid estimated FSIQ, t(36) = -.84, p > .40. All participants completed all cognitive measures. All participants denied histories of learning disability, traumatic brain injury, and neurological disease.

Procedures

After informed consent was obtained, participants began an experimental session which lasted approximately 3 hours. All individuals completed all tasks in one session. Subjects received financial compensation ($20 + $10 bonus) for their participation.

Results

Behavioral Data

Reinforcement learning task performance

Although an attempt was made to equate the number of no-response trials and both groups had a relatively low percentage of such trials (M = .01, SD = .01, for younger adults, M = .02, SD = .02, for older adults), this difference was significant such that older adults had a greater number of timed-out trials in the 80% [F (1, 36) = 6.3, p < .05] and 60% [F (1,36) = 5.0, p < .05] validity conditions compared to the younger adults. There were no significant correlations between number of timed-out trials and accuracy in any of the validity conditions. See Table 2-2 for a summary of median response times.

Accuracy data for each group in the three validity conditions and three bins are presented in Table 2-3 and displayed in Figure 2-1. The accuracy data were analyzed using an ANOVA with a between-subject factor of age group (younger, older) and within-subjects factors of validity condition (100%, 80% and 60%) and bin (1, 2, 3). The ANOVA revealed a significant main effect of age group, $F(1, 36) = 9.89$, $p < 0.01$, reflecting increased accuracy in the younger compared to older adults. There was also a significant main effect of validity condition, $F(2, 72) = 162.54$, $p < .001$, partial-eta^2 = .82, and a significant interaction between age group and validity, $F(2, 72) = 8.15$, $p < 0.01$, partial-eta^2 = .19. Contrasts for each level of the validity factor showed a higher accuracy for the 100% compared to the 80% validity condition and for the 80% compared to the 60% validity condition (*p*s < .001). Separate ANOVAs for each of the validity conditions revealed a significant age difference only in the 100% validity condition, $F(1, 36) = 15.14$, $p < .001$, such that older adults also performed worse than younger adults in this condition. The difference between groups was marginally significant for the 80% condition $F(1, 36) = 3.02$, $p = .09$; older adults tended to perform worse than younger adults in this condition.

Examination of effects of learning over time revealed a significant main effect of bin $F(2, 72) = 45.41$, $p < .0001$, partial-eta^2 = .56. Post hoc pairwise comparisons of accuracy during each bin revealed significantly better performance in the last bin compared to the first bin and in the second bin compared to the first bin (*p*s < .0001); however, the improvement between the second and third bins was only marginally significant ($p = .06$). There were no significant bin x group [$F(2, 72) = .45$, $p = .64$, partial-eta^2 = .01, observed power = .12, Cohen's $f = .11$] or validity x bin x group [$F(4,$

144) = 1.63, p = .18, partial-eta^2 = .04, observed power = .43, Cohen's f = .21] interactions. Sensitivity analysis of the within-subjects factor "bin" and associated interactions (alpha = .05, power = .80, mean correlation between repeated measures = .55) revealed that this design should be able to detect effects up to f = .20. There was a significant interaction between validity and bin $F(4, 144) = 10.47$, $p < .0001$, partial-eta^2 = .23. In the 100% valid condition, both groups improved significantly from bin 1 to bin 2 (ps < .0001), but not from bin 2 to bin 3 (ps > .05). In the 80% condition, the younger group demonstrated significant improvements from bin 1 to bin 2 ($p < .05$) and marginally significant improvements from bin 2 to bin 3 (p = .09); likewise for the older group, significant improvements in accuracy could be seen from bin 1 to bin 2 ($p < .05$), but not from bin 2 to bin 3. As expected, there were no significant learning-related changes in the 60% condition for either group.

These results are generally consistent with those reported previously by Eppinger and colleagues (2008), with two important differences: 1) The current study observed a significant difference in accuracy between age groups at all time points (i.e., bins) in the 100% condition, despite a similar number of trials attempted in this condition, and 2) this study observed the opposite effects of learning over time in the 80% condition such that older adults demonstrated similar accuracy to younger adults early in the experiment in this condition, but did not improve from the second to third bins, resulting in worse performance in the third bin.

Neuropsychological and emotional functioning

The younger and older groups performed comparably on the MMSE, NART FSIQ, Digit Span, and the Wisconsin Card Sorting Test, and endorsed similar levels of apathy and depression symptoms. Older adults out-performed younger subjects on the

Boston Naming Test. Not surprisingly, younger adults out-performed the older adults on timed tests requiring speeded responses, including phonemic and semantic verbal fluency, Trails A and B_1, and Stroop Color-Word Naming (ps < .05). Although no individuals met diagnostic criteria for any psychiatric disorder, one member of the younger group obtained a score on the AES that was above the conventional clinical cutoff for apathy (14), one member of the older group obtained a score on the BDI-II that was in the range for mild depression (>14) and the young subjects endorsed a greater level of trait anxiety (p < .05).

Event-Related Potential Data

See Table 2-4 for the number of trials comprising the ERP waveforms in each condition for the two groups. In line with the accuracy data, the two age groups differed in numbers of trials per waveform in the 100% condition such that the ERN and non-reward FRN waveforms ($p < .0001$) for older adults contained more trials than those of younger adults, and the CRN waveforms ($p < .01$) for younger adults had more trials than those of older adults. No significant group differences were observed in the other probability conditions.

Response-locked ERPs (ERN/CRN)

In the first step, incorrect minus correct difference waves were calculated. These difference waves showed maximal negative amplitudes with a latency of approximately 60 ms in both groups. Spline-interpolated voltage maps are shown in Figure 2-2. This roughly corresponds to the latencies of the peak amplitude seen in the original ERN and CRN waveforms. Mean amplitudes of these difference waves were calculated using a

[1] When Trails A was used as a covariate in order to control for the effects of generalized slowing, the difference between groups for Trails B was no longer significant ($p = .46$).

time window from 30-90 ms. A comparison of the mean amplitudes of the difference waves was conducted using a repeated-measures ANOVA (2-group x 3-validity condition x 3-bin). There was a significant main effect of group $F(1, 35) = 15.67$, $p < .001$, reflecting greater amplitudes for the younger versus the older adults. There was also a significant main effect of validity $F(2, 70) = 9.77$, $p = .001$, partial-eta$^2 = .22$, and a significant interaction between age group and validity $F(2, 70) = 6.50$, $p = .003$, partial-eta$^2 = .16$. Contrasts for each of the validity conditions showed that the mean amplitude of the difference wave was greater for the 100% condition compared to the 80% and 60% conditions (ps < .05); however, we did not detect a significant difference in amplitude in the 80% condition compared to the 60% condition ($p = .19$). The younger group exhibited greater amplitudes of the difference waves than older adults in the 100% and 80% conditions (ps < .01), but not the 60% condition. Analyses of each group separately revealed that the younger group showed the expected declines in amplitude with decreasing probability (ps < .05), whereas no significant differences in amplitude between conditions were found in the older group.

Results of the repeated measures analysis of amplitudes of the difference waves also revealed significant learning-related effects across bins (see Figure 2-3). There was a main effect of bin $F(2, 70) = 3.86$, $p < .05$, partial-eta$^2 = .10$, such that the amplitude of the difference wave increased significantly from bin 1 to bin 3 ($p < .05$), but not from bin 1 to bin 2 or from bin 2 to bin 3. There were also significant interactions between group and bin $F(2, 70) = 4.05$, $p < .05$, partial-eta$^2 = .10$, validity and bin $F(4, 140) = 3.02$, $p < .05$, partial-eta$^2 = .08$, and group, validity, and bin $F(4, 140) = 3.45$, $p = .01$, partial-eta$^2 = .09$. Separate analyses for the factor validity showed that for the

younger adults, the amplitude of the difference wave in the 100% condition increased from bin 2 to bin 3 ($p < .05$) and bin 1 to bin 3 ($p = .002$), but not from bin 1 to bin 2 ($p = .08$). Younger adults failed to demonstrate significant increases in amplitude across bins in the 80% or 60% conditions. Interestingly, although the older adults demonstrated learning effects across bins in terms of increased accuracy, this was not reflected in increased amplitudes of the difference waves in any validity condition (all *p*s > .25).

Follow-up ANOVAs of the amplitude of the difference wave in each validity condition and each bin showed that the amplitude of the difference wave was significantly more negative for the younger adults compared to the older adults in bins 2 and 3 for the 100% condition (*p*'s < .05) and in bin 2 for the 80% condition ($p < .05$). There were also trends for the younger adults to exhibit more negative amplitudes than older adults in bins 1 ($p = .06$) and 3 ($p < .06$) for the 80% condition. As expected, there were no significant differences for the 60% condition.

In the second step, the response-locked components were examined separately in order to examine the effects of age and validity condition on changes in mean amplitude by response type (correct or incorrect). The response-locked components were measured as the mean amplitude within a 60 ms time window centered on the peak of the ERN at electrode FCz. A 2 (age group) x 2 (response type) x 3 (validity) x 3 (bin) repeated measures ANOVA was conducted. One younger adult was excluded from the ERN/CRN analysis because he did not commit any errors in the third bin for the 100% valid condition. Response-locked ERP waveforms from the probabilistic learning task can be seen in Figure 2-4. Mean ERP amplitude data are presented in Tables 2-5 and 2-6. In line with Eppinger et al (2008), we did not find a main effect of group [$F(1, 36) =$

2.67, p = .11, partial-eta^2 = .07, observed power = .36, Cohen's f = .27]. Sensitivity analysis indicated that this design should be able to detect effects up to f = .34 (alpha = .05, power = .80, mean correlation between repeated measures = .28). As expected, there was a significant main effect of response type $F(1,35) = 17.54$, p = .001, such that the ERN was more negative than the CRN. This main effect was qualified by interactions between group and response type $F(1, 35) = 19.77$, $p < .001$, partial-eta^2 = .36, validity and response type $F(2, 70) = 14.75$, $p < .001$, partial-eta^2 = .29 and group, validity, and response type $F(2, 70) = 7.57$, p = .001, partial-eta^2 = .17. The validity x response type interaction reflected linear relationships such that the mean amplitude of the ERN was largest in the 100% condition, followed by the 80% and 60% conditions; in contrast, the mean amplitude of the CRN was largest in the 60% condition followed by the 80% and 100% conditions. These linear relationships were observed in the younger adult group, but not the older adult group. There were no significant quadratic relationships. Follow-up ANOVAs of the group x validity x response type interaction revealed significant differences such that the mean amplitude of the CRN was smaller for the younger adults compared to the older adults in the 100% and 60% conditions (p's < .05); however, there were no significant group differences in the amplitude of the ERN in any condition.

See Table 2-7 for a summary of the ANOVA results. When examining effects of learning over time, we did not find a main effect of bin [$F(2, 70) = 1.66$, p = .20, partial-eta^2 = .05, observed power = .33, Cohen's f = .22]. Sensitivity analysis indicated that this design should be able to detect significant effects up to f = .19 (alpha = .05, power = .80, mean correlation between repeated measures = .59). We did find a significant bin x

group interaction $F(2, 70) = 9.70$, $p < .001$, partial-eta^2= .22 and a significant bin x response type interaction $F(2, 70) = 4.77$, $p < .05$, partial-eta^2 = .12. There was also a significant group x response type x bin interaction $F(2, 70) = 6.00$, $p < .01$, partial-eta^2 = .15, a significant group x validity x bin interaction $F(4, 140) = 2.96$, $p < .05$, partial-eta^2 = .08, a significant response type x validity x bin interaction $F(4, 140) = 4.36$, $p < .01$, partial-eta^2 = .11 and a significant group x response type x validity x bin interaction $F(4, 140) = 3.63$, $p < .01$, partial-eta^2 = .09. Follow-up analyses for the group x response type x validity x bin interaction revealed that, during bin 2, the mean amplitudes of the CRN were smaller for the younger adults than the older adults in all conditions. During bin 3, they were smaller in the 100% ($p < .001$) and 60% ($p < .05$) conditions only. In contrast, during bin 2, the mean amplitude of the ERN was larger for the older adults compared to the younger adults for the 80% and 60% conditions (*ps* < .05). During bin 3, the mean amplitude of the ERN was larger for the younger adults compared to the older adults in the 100% condition only ($p < .01$).

Within-group analyses showed that for the younger adults, the mean amplitude of the CRN became significantly smaller from bin 1 to bin 2 ($p = .002$) and bin 1 to bin 3 ($p < .001$) in the 100% condition. In the 80% condition, the mean amplitude of the CRN became *smaller* from bin 1 to bin 2 ($p < .001$) and from bin 1 to bin 3 ($p < .05$), but became *larger* from bin 2 to bin 3 ($p = .002$). For the older adults, the mean amplitude of the CRN became significantly smaller from bin 2 to bin 3 in the 100% condition ($p < .01$). For the younger adults, the mean amplitude of the ERN significantly increased from bin 2 to bin 3 and from bin 1 to bin 3 in the 100% condition (*p's* < .05; see Figure 2-5). In the 80% condition, the mean amplitude of the ERN decreased from bin 1 to bin 2

(p = .003) and increased from bin 2 to bin 3 (p < .05). The older adults did not show any learning-related changes in the mean amplitude of the ERN (see Figure 2-6).

Feedback-locked ERPs (FRN)

In the first step, non-reward-minus-reward difference waves were calculated. These difference waves showed maximal negative amplitudes with a latency of approximately 280 ms for younger adults, and 290 ms for older adults as shown in Figure 2-7. This roughly corresponds with latencies of the peak amplitude seen in the original reward- and non-reward-related FRN waveforms. Mean amplitudes of these difference waves were calculated using a time window from 250-310 ms for younger adults and 260-320 ms for older adults.

As with the error-related activity, a comparison of the mean amplitudes of the difference waves for feedback-related activity was conducted using a repeated-measures ANOVA (2-groups x 3-validity conditions x 3-bins). In contrast to the results of Eppinger et al., 2007, a significant main effect of group was not detected [F(1, 36) = .001, p = .98, partial-eta^2 < .001, observed power = .05, Cohen's f < .01]. Sensitivity analysis suggested that this design should be able to detect significant effects up to f = .40 (alpha = .05, power = .80, mean correlation between repeated measures = .61). There was a significant main effect of validity F(2, 72) = 11.60, p < .001, partial-eta^2 = .24, and a significant interaction between age group and validity F(2, 72) = 7.85, p = .001, partial-eta^2 = .18. Contrasts for each of the validity conditions showed a significant linear trend such that the mean amplitude of the difference wave was greater (more negative) for the 60% condition compared to the 100% and 80% conditions (ps < .05); in turn, the mean amplitude of the difference wave for the 80% condition was greater than that for the 100% condition (p < .05). Consistent with Eppinger et al. (2008), separate

within group analyses showed that these relationships were observed for the younger adults (*ps* < .05), but not for older adults (*ps* > .50).

Analysis of amplitudes of the difference waves also revealed significant learning-related effects across bins (see Figure 2-8). There was a main effect of bin $F(2, 72) = 3.99$, $p < .05$, partial-eta$^2 = .10$; pairwise comparisons showed trends toward decreased amplitude of the difference wave from bin 1 to bin 2 ($p = .09$) and from bin 1 to bin 3 ($p = .06$) but not from bin 2 to bin 3. There was also a significant quadratic interaction between group and bin $F(2, 72) = 5.08$, $p < .01$, partial-eta$^2 = .12$, and a marginally significant interaction between validity and bin $F(4, 140) = 2.47$, $p = .07$, partial-eta$^2 = .06$. Separate within-groups analyses showed that for the younger group, the amplitude of the difference wave decreased as expected from bin 1 to bin 2 in both the 100% and 80% conditions (ps < .05). For the older adult group, significant decreases in FRN amplitude over time could not be detected, although there was a marginally significant decrease from bin 1 to bin 3 in the 100% condition ($p = .07$).

In the second step, the feedback-locked components were examined separately in order to examine the effects of age on changes in mean amplitude by feedback type (reward or non-reward). The feedback-locked components were measured as the mean amplitude within a 60 ms time window centered on the peak of the FRN at electrode FCz (238 ms in younger adults and 260 ms in older adults). A 2 (age group) x 2 (feedback type) x 3 (validity) x 3 (bin) repeated measures ANOVA was conducted. Feedback-locked ERP waveforms from the probabilistic learning task can be seen in Figure 2-9. Mean ERP amplitude data are presented in Tables 2-8 and 2-9. In contrast to Eppinger et al, we did not find a main effect of group [$F(1, 36) = .99$, $p = .33$, partial-

eta^2 = .03, observed power = .16, Cohen's *f* = .17] or a significant interaction between group and feedback type [*F*(1, 36) = .45, *p* = .51, partial-eta^2 = .01, observed power = .10, Cohen's *f* = .10]. Sensitivity analyses indicated that this design should be able to detect significant between-group effects up to *f* = .44 and a significant interaction up to *f* = .11 (alpha = .05, power = .80, mean correlation between repeated measures = .86). There was a significant main effect of validity *F* (2, 72) = 3.60, *p* < .05, partial-eta^2 = .09. Pairwise comparisons revealed a trend towards greater amplitudes for the 100% condition compared to the 60% condition (*p* = .07). There was also a main effect of feedback type *F*(1, 36) = 8.89, *p* < .01, such that the FRN related to non-reward was more negative than the FRN related to reward. These main effects were qualified by interactions between validity and feedback type *F*(2, 72) = 6.52, *p* < .01, partial-eta^2 = .15 and group, validity, and feedback type *F*(2, 72) = 5.33, *p* < .01, partial-eta^2 = .13. Separate within-group analyses showed that for the younger adults, the FRN to reward was larger in the 100% condition compared to the 80% condition (*p* = .01) and in the 80% condition compared to the 60% condition (*p* = .001). There were no significant differences in mean amplitude for the FRN to non-reward in any condition. When comparing the mean amplitudes between valences and within condition, there was a trend for the FRN to non-reward to be larger than the FRN to reward in the 80% condition (*p* = .08). Similarly, in the 60% condition, the FRN to non-reward was larger than the FRN to reward (*p* = .001). In the older adult group, no significant differences could be found.

With respect to effects of learning over time, we did not find a main effect of bin [*F*(2, 72) = 1.03, *p* = .36, partial-eta^2 = .03, observed power = .21, Cohen's *f* = .17] or a

significant interaction between feedback type, validity, and bin (see Table 2-10). Sensitivity analysis suggested that this design should be able to detect a significant effect of bin up to *f* = .20 (alpha = .05, power = .80, mean correlation between repeated measures = .60). There was a significant interaction of bin by feedback type $F(2, 72) = 3.22$, $p < .05$, partial-eta^2 = .08, which was qualified by a significant group x feedback type x bin interaction $F(2, 72) = 7.77$, $p = .001$, partial-eta^2 = .18. When the two groups were analyzed separately, the younger adults exhibited significantly larger mean amplitudes of the FRN to reward for the 100% and 80% conditions in bin 2 compared to bin 1 (ps < .01) and in bin 3 compared to bin 1 (ps < .05). For older adults, the amplitude of the reward-related FRN increased from bin 2 to bin 3 in the 100% condition ($p < .01$). There were no significant changes over time for the mean amplitude of the FRN to non-reward in any validity condition for either group (see Figures 2-10 and 2-11).

Follow-up ANOVAs showed group differences such that the mean amplitude of the FRN to reward was larger for the younger adults compared to the older adults in the 100% condition during bin 2 ($p < .05$). The mean amplitude of the FRN to non-reward was larger for the younger adults compared to the older adults in the 80% condition during bin 1 ($p < .05$).

Relationship to performance on neuropsychological tests

Several demographic and neuropsychological variables correlated with FRN difference wave amplitudes (see Table 2-11). In the 100% valid condition, scores on the LARS were negatively correlated with the FRN difference wave in bin 2 only ($r = -.351$, $p < .05$) and BNT scores were negatively correlated with the FRN difference wave in bin 1 only ($r = -.373$, $p < .05$). In the 80% valid condition, phonemic fluency (i.e., COWA)

performance was positively correlated with the FRN difference wave for bin 2 only (r = .361, p < .05) and the Trails B raw score was negatively correlated with the difference wave in bin 2 (r = -.330, p < .05). In the 60% valid condition, the number of errors on Trails A was positively correlated with the difference wave in bin 1 (r = .339, p < .05).

Discussion

This study had three primary goals. The first was to verify predictions from the reinforcement learning theory by measuring the effects of feedback valence and probability on ERP reflections of error detection and feedback processing over time; the second was to investigate how and whether aging affects reinforcement learning (i.e., error detection and feedback processing abilities) believed to be mediated by the mesencephalic dopamine system; and the third was to explore how ERP reflections of error detection and feedback processing are related to other aspects of cognitive functioning thought to be dependent on frontal brain regions.

Although some evidence has suggested that older adults exhibit impairments in error detection that negatively impact learning (Nieuwenhuis et al., 2002), recent counter-evidence has demonstrated that when older adults are given equivalent opportunity to learn from errors, reflections of error detection are not affected by aging; rather, older adults demonstrate valence-specific differences in feedback processing such that they are less affected by negative than positive feedback (Eppinger et al., 2008), consistent with the “socioemotional selectivity theory of aging,” which posits that older adults use emotion regulation and cognitive control to increase attention to positive information and decrease attention to negative information (Mather & Carstensen, 2005). The current study intended to replicate the latter findings using a modified version of a probabilistic learning paradigm in which positive and negative

feedback were provided in three validity conditions (100%, 80%, and 60%), and an attempt was made to equate the number of trials contributing to learning in both groups. Differences in reinforcement learning were measured as a function of changes in ERP amplitude as well as changes in performance (i.e., accuracy) over time. In addition, exploratory analyses investigated relationships between electrophysiological reflections of feedback processing and neuropsychological measures of theoretically related cognitive constructs.

Specific Aim 1: Support for the Reinforcement Learning Theory

Behavioral data

Although we were unsuccessful in our attempt to equate the number of trials retained between groups by using an adaptive response deadline in the 80% and 60% conditions, a similar number of trials was retained for the 100% condition. Despite an equivalent number of trials attempted in the 100% condition, the younger adults out-performed the older adults; in addition, they demonstrated a trend toward better performance in the 80% condition, consistent with previous reports suggesting that older adults exhibit impairments in reinforcement learning (Deakin et al., 2004; MacPherson et al., 2002; Mell et al., 2005; Ridderinkhof et al., 2002; Nieuwenhuis et al., 2002; Pietschmann et al., 2008).

Despite the evidence for an impaired reinforcement learning system in older adults provided above, both groups demonstrated better performance in the 100% condition compared to the 80% condition and in the 80% condition compared to the 60% condition, suggesting that older adults benefit to some extent from increasing condition validity. As expected, both groups improved over time in the two learning conditions (i.e., 100% and 80%), but did not exhibit learning over time in the 60%

condition. Importantly, in both groups, the significant changes in learning occurred from bin 1 to bin 2; learning appeared to plateau from bin 2 to bin 3 such that no significant learning effects were found. Based on this trend, it is unclear whether older adults would have been able to improve to the level of younger adults if given more time, as was previously reported (Eppinger et al., 2008).

Response-locked ERPs (ERN/CRN)

Consistent with predictions derived from the reinforcement learning theory (Eppinger et al., 2008; Holroyd & Coles, 2002; Nieuwenhuis et al., 2002), for the younger control group, the ERN was larger than the CRN in all validity conditions. The mean amplitude of the ERN increased with increasing validity, such that the largest amplitude was observed in the 100% valid condition, reflecting the idea that awareness of error commission is greatest under conditions in which correctness of response is the least ambiguous.

Support for learning-related changes in the response-related ERPs was most clear when examining the mean amplitude of the ERN – CRN difference waves. Within the younger group, the amplitude of the difference wave increased over time in the least ambiguous learning condition, providing support for the idea that as internal representations of correct and incorrect responses become more fixed with learning, greater conflict occurs when erroneous responses are made. Learning-related effects were also found for younger adults in the 100% condition when looking at the mean amplitude of the ERN and CRN separately, such that the mean amplitude of the ERN increased over time and the mean amplitude of the CRN decreased over time. Learning effects in the 80% condition were less clear, but essentially paralleled those from the 100% condition. It is possible that ERN amplitudes in the 80% condition were

affected to some degree by the use of a variable response deadline. Younger adults may not have experienced necessary time pressure to elicit greater amplitude ERNs in the more ambiguous condition.

Overall, these results support predictions from the reinforcement learning theory, including recent suggestions that correct-response activity (i.e., positive prediction errors), in addition to error activity (i.e., negative prediction errors), contributes to reinforcement learning (Eppinger et al., 2008; Pietschmann et al., 2008). Although conflicting theories have been generated regarding the function of the CRN, these results suggest that the CRN is a correct-response analogue to the ERN; in other words, as commission of errors becomes more "surprising" with learning, commission of correct responses is less "surprising" with learning, resulting in smaller amplitudes of the CRN.

Feedback-locked ERPs (FRN)

Analysis of the feedback-locked difference waves within the younger control group also provided some support for the reinforcement learning theory. As expected, the mean amplitude of the non-reward – reward difference wave decreased with increasing feedback validity, reflecting the idea that reliance on feedback is greatest in the most ambiguous situations (Eppinger et al., 2008; Holroyd & Coles, 2002). As previously reported (Eppinger et al., 2008; Nieuwenhuis et al., 2002), older adults in the present study did not exhibit variations in amplitude based on feedback validity. Learning-related effects on the difference waves appeared to be consistent with the theory; the mean amplitude of the difference wave decreased from bin 1 to bin 2 in both learning conditions, providing some evidence that reliance on feedback decreases with learning (Holroyd & Coles, 2002).

Separate analyses of the FRN to non-reward and the FRN to reward revealed results that were somewhat contrary to expectations. Although the non-reward related FRN was larger than the reward-related FRN in the 80% and 60% conditions as expected, we were unable to find differences in the amplitude of the non-reward related FRN across conditions. Although there were no predictions from the reinforcement learning theory with respect to changes in reward-related activity, the reward-related FRN became larger with increasing feedback validity such that it was most negative in the 100% condition, followed by the 80% and 60% conditions, contrary to predictions for the non-reward related activity. Similar results have been reported previously in an older adult group (Nieuwenhuis et al., 2002). Learning-related effects observed in the reward-related FRN for younger adults were also unexpected: the reward related FRN became more negative over time in both the 100% and 80% conditions, suggesting that reactivity to positive feedback did not decrease over time as hypothesized. There were no learning-related effects observed for the non-reward related FRN, in keeping with prior research (Eppinger et al., 2008). These results are interesting and may indicate preferential reliance on positive feedback over time even in healthy young adults, particularly in less ambiguous learning conditions.

In summary, the younger adult data support both condition-related and learning-related predictions from the reinforcement learning theory with respect to the ERN/CRN. Predictions related to feedback-locked activity were generally supported when examining difference waves; however, separate analysis of reward-related activity yielded unexpected results.

Specific Aim 2: Effects of Aging on ERP Reflections of Reinforcement Learning

Response-locked ERPs (ERN/CRN)

In consideration of predictions from the electrophysiological model of the reinforcement learning theory, we attempted to discern whether the behavioral impairments observed in older adults were a result of dysfunction in the error-detection phase of learning, the feedback processing phase, or both. Consistent with Eppinger and colleagues (2008), our younger control group exhibited greater amplitude ERN-CRN difference waves than those of older adults in both learning conditions, providing initial support for the hypothesis that older adults exhibit impairments in the error-detection phase of learning. In order to investigate whether these impairments are valence-specific, as reported previously (Eppinger et al., 2008; Pietschmann et al., 2008), we examined ERN and CRN amplitudes separately. In line with these two previous reports, we found no difference between groups in the amplitude of the ERN in any condition when all time points (i.e., bins across trials) were combined. These results conflict with several previous studies that reported smaller ERN amplitudes in older adults (Band & Kok, 2000; Falkenstein et al., 2001; Mathewson, Dywan, & Segalowitz, 2005; Nieuwenhuis et al., 2002; Themanson, Hillman, & Curtin, 2006). One salient difference between studies finding comparable ERNs between groups and studies finding differences is that the former either reduced time pressure on older adults (Eppinger et al., 2008) or did not apply time pressure at all (Pietschmann et al., 2008). Although reduced time pressure was the intended aspect of the current study, it is possible that relieving the time pressure on both groups resulted in less response conflict in younger adults, artificially reducing their ERN amplitudes.

With regard to learning-related changes of the ERN, it was predicted that earlier in the experiment, older controls would demonstrate smaller ERN amplitudes than younger controls, but that these differences would not be observed later in the experiment, suggesting that older adults require more time to develop internal representations of appropriate responses. Instead, ERNs did not differ between groups during bin 1, and the ERN of older adults was smaller than that of younger adults by the end of the experiment in the least ambiguous condition. Based on the reinforcement learning theory, it might be concluded that older adults failed to create an internal representation of the appropriate response, or developed a weak representation, resulting in uncertainty and reduced amplitude ERNs (Band & Kok, 2000).

We anticipated that the amplitude of the CRN would also be equivalent between groups (Falkenstein et al., 2001); however, the amplitude of the CRN was unexpectedly smaller for the younger adults compared to the older adults in the 100% and 60% conditions. Within the older adult group, the amplitude of the CRN decreased from bin 2 to bin 3 in the least ambiguous condition; similarly, within the younger adult group, the amplitude of the CRN decreased over time in both learning conditions. Importantly, initial interpretations of the error-detection system focused on events that are “worse than expected;” there was no role for activity on correct trials, except that it was subtracted from incorrect trials to form difference waves as an internal control. Although this view is increasingly being challenged (Band & Kok, 2000; Bartholow et al., 2005; Falkenstein et al., 2001; W. J. Gehring & Knight, 2000; Mathewson et al., 2005), the function of the CRN is still a matter of much debate. One theory is that the CRN increases when uncertainty about the correct response is high. It seems reasonable,

then, that the CRN should decrease when uncertainty is low (e.g., as learning progresses). This hypothesis fits well with the current study; however, another group who found significant reductions of the CRN with learning in a young control group (Pietschmann et al., 2008) concluded that CRN reductions signified that performance monitoring becomes error-specific with advanced learning. It has also been surmised that the "CRN" results from overlapping stimulus-evoked components in the response-locked ERP (Coles, Scheffers, & Holroyd, 2001). In general, for the older participants, ERN/CRN mean amplitudes were not altered by validity condition and changed very little over the course of the entire experiment, consistent with previous research (Pietschmann et al., 2008).

Feedback-locked ERPs (FRN)

In contrast to predictions from the reinforcement learning theory, we were unable to find group differences in the mean amplitudes of the FRN difference waves in any condition. In line with our hypotheses, when we compared the mean amplitudes of the reward-related FRN between groups, collapsing across bins, there were no group differences; however, contrary to expectations, we also found little evidence for reduced non-reward related FRNs in the older adults compared to younger adults. It has previously been reported that, whereas older adults do not demonstrate a reduction in reward-related FRN amplitude, they do exhibit a reduction in reactivity to negative feedback, contributing to the theory that older adults preferentially rely on positive feedback for learning (Eppinger et al., 2008; Pietschmann et al., 2008). Reasons for these disparate results may be related to differences in study design. For example, one study did not manipulate feedback validity (Pietschmann et al., 2008) which may have reduced the need for reliance on feedback, resulting in reductions in the non-reward

related FRN (Pietschmann et al., 2008). This explanation seems unlikely, however, since reductions in the reward-related FRN would also have been expected and were not found. It is also possible that high functioning in our group of older adults served as a protective factor and obscured "normal" age-related changes seen in structures underlying the processing of negative feedback (to be discussed in the next chapter). Overall, our data suggest that the feedback-processing system is relatively intact as compared to the error-processing system in this group of older adults; however, it should be noted that, as with the error-related activity, older adults demonstrated very little expected variability as a function of probability condition.

We also failed to find evidence for learning-related effects for the non-reward related FRN in either group, consistent with previous reports (Eppinger et al., 2008; Nieuwenhuis et al., 2002). The reward-related FRN increased over time for younger adults as has been reported previously (Pietschmann et al., 2008). Interestingly, for the older adults, the reward-related FRN increased as the CRN decreased from bin 2 to bin 3 in the 100% condition only.

Taken together, the most striking pattern found in these data is that the younger adults exhibited at least some degree of condition-, valence-, and learning-related modulations in electrophysiological reflections of error-detection and feedback processing consistent with the reinforcement learning theory, but the older adults generally did not, in keeping with their poorer behavioral performance. Importantly, we found fewer differences between groups with respect to feedback processing; however, older adults exhibited clear impairments with respect to error- and correct-response detection with learning as compared to younger adults (see Figure 2-12). Interpreted

within the context of the reinforcement learning theory, we could conclude dopaminergic signaling is relatively intact early in the course of learning (i.e., when learning is dependent on feedback); however, there is a failure of the system to both appropriately modulate the signal based on probability of reinforcement and "propagate" it back in time so that it becomes associated with the response, rather than the stimulus. Thus, an internalized representation of the response is not created, resulting in greater uncertainty regarding whether the outcome is better or worse than expected.

One notable exception to the lack of learning-related change seen in the older adults' data was the increase in reward-related FRN amplitude over time and decrease in CRN amplitude at the end of the experiment in the least ambiguous condition. Perhaps this provides some support for the contention that the positive feedback processing system is relatively intact in older adults as compared to the negative feedback processing system. In any case, it is difficult to see how reports of decreased non-reward related FRNs in the context of similar reward-related FRNs has contributed to arguments for an "enhanced positivity effect" in aging, rather than an argument for dysregulated reactivity to punishment. This is especially unclear in light of the fact that this "positivity effect" appears to be viewed as an adaptive cognitive control mechanism despite evidence for poorer performance on reinforcement learning tasks.

Specific Aim 3: Relationship to Neuropsychological Test Performance

Feedback related activity correlated with estimated IQ, verbal fluency, visuomotor sequencing and set-switching, symptoms of apathy, and performance on a language measure. We expected larger (more negative) values of the FRN difference waves to be correlated with higher scores on measures of executive function. Unfortunately, several of the relationships were in the counter-intuitive direction. For example, better

verbal fluency and set-switching performances were related to smaller (more positive*)* amplitudes of the FRN difference wave as were higher IQ and lower levels of apathy. In contrast, better naming ability and fewer errors on an attention measure were related to more negative amplitudes. The reason for unexpected correlation patterns is not clear, but it is possible that performance on the probabilistic learning task did not generalize well to performance on other tests of frontal-executive functioning. Like other “executive functions,” feedback processing is likely dependent on extremely complex cognitive systems not encompassed by these exploratory hypotheses.

Table 2-1. Means and standard deviations (*SD*) of demographic and neuropsychological data for younger and older participants.

	Younger (n = 19)		Older (n = 19)		
	Mean	(*SD*)	Mean	(*SD*)	*p*
Demographics					
Age (years)	23.9	(5.2)	66.9	(6.7)	< .001
Education (years)	14.4	(1.8)	16.5	(2.1)	.002
Female (%)	15.8	--	31.6	--	*ns*
Right-Handed (%)	89.5	--	94.7	--	*ns*
Cognitive Functioning					
MMSE	28.2	(1.5)	28.3	(1.7)	*ns*
NART FSIQ	112.9	(6.5)	114.8	(7.4)	*ns*
Boston Naming Test	55.8	(2.2)	56.8	(5.0)	< .01
COWA (FAS)	47.7	(11.7)	39.0	(8.9)	< .05
Semantic Fluency (Animals)	25.5	(4.0)	20.4	(3.7)	< .001
Digit Span Forward	12.4	(2.0)	11.0	(2.6)	*ns*
Digit Span Backward	7.9	(2.6)	6.7	(2.1)	*ns*
Trails A (sec)	18.2	(5.7)	31.8	(9.1)	< .001
Trails B (sec)	41.5	(14.2)	71.0	(26.8)	< .001
Stroop Word Reading	113.8	(19.1)	108.1	(17.1)	*ns*
Stroop Color Naming	80.6	(16.5)	74.8	(12.4)	*ns*
Stroop Color Word Naming	53.5	(12.8)	45.5	(11.0)	< .05
Stroop Interference	5.2	(8.9)	2.5	(8.9)	*ns*
WCST Categories Completed	5.2	(1.5)	5.6	(1.0)	*ns*
WCST Perseverative Errors	12.3	(10.4)	12.5	(9.6)	*ns*
WCST Failure to Maintain Set	.5	(1.1)	.6	(.7)	*ns*
Emotional Functioning					
BDI-II	5.2	(3.9)	3.6	(4.9)	*ns*
AES	6.7	(4.8)	5.7	(3.0)	*ns*
LARS	-26.6	(6.0)	-24.8	(3.6)	*ns*
STAI - State	29.4	(9.0)	26.9	(9.4)	*ns*
STAI - Trait	33.9	(9.1)	27.6	(8.3)	< .05

Table 2-2. Mean response time (*SD*) in the three validity conditions (100%, 80%, and 60%), displayed separately for the three bins and two age groups.

Bin	Response time in milliseconds, validity					
	Young Adults (n = 19)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
1	522 (133)	525 (143)	539 (136)	595 (165)	591 (167)	586 (157)
2	510 (119)	518 (133)	518 (144)	577 (154)	579 (157)	580 (164)
3	511 (122)	513 (126)	527 (124)	573 (164)	587 (150)	591 (155)

Table 2-3. Mean accuracy (SD) in the three validity conditions (100%, 80%, and 60%), displayed separately for the three bins and two age groups.

Bin	Accuracy in % correct, validity					
	Young Adults (n = 19)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
1	.74 (.09)	.61 (.08)	.47 (.06)	.63 (.10)	.57 (.10)	.47 (.06)
2	.85 (.10)	.65 (.10)	.49 (.06)	.72 (.10)	.61 (.09)	.48 (.06)
3	.86 (.09)	.68 (.08)	.50 (.05)	.75 (.12)	.60 (.11)	.52 (.06)

Table 2-4. Mean (*SD*) number of trials per condition in each age group.

ERP	Young Adults (n = 19)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
ERN	38 (16)	76 (15)	109 (14)	62 (21)	85 (20)	108 (11)
CRN	174 (26)	136 (23)	103 (12)	149 (26)	127 (25)	107 (14)
FRN(neg)	35 (17)	72 (19)	103 (22)	60 (23)	84 (25)	105 (18)
FRN(pos)	161 (35)	126 (30)	96 (18)	143 (33)	122 (26)	100 (20)

Table 2-5. Mean amplitudes (μV) of the ERN in the three validity conditions (100%, 80%, and 60%), displayed separately for the three bins and two age groups.

Bin	Young Adults (n = 18)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
1	- .01 (1.9)	- .22 (1.6)	.63 (1.8)	- .09 (1.3)	.18 (1.2)	- .15 (1.4)
2	- .19 (3.1)	.67 (1.6)	.80 (1.6)	- .03 (1.0)	- .11 (1.2)	- .07 (1.3)
3	- 2.0 (3.0)	- .01 (1.6)	.59 (1.4)	.23 (1.4)	.18 (1.2)	.04 (1.8)

Table 2-6. Mean amplitudes (μV) of the CRN in the three validity conditions (100%, 80%, and 60% validity), displayed separately for the three bins and two age groups.

Bin	Young Adults (n = 18)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
1	.77 (1.6)	.19 (1.8)	.29 (1.6)	.21 (1.3)	.11 (1.4)	- .13 (1.4)
2	1.65 (1.3)	1.31 (1.8)	.83 (1.7)	- .17 (1.2)	- .37 (1.8)	- .32 (1.5)
3	2.05 (1.2)	.75 (1.5)	.73 (1.4)	.47 (1.3)	.15 (1.7)	- .25 (1.1)

Table 2-7. Summary of the 2-Group x 2-Response Type x 3-Validity x 3-Bin repeated measures ANOVA conducted on the ERN/CRN mean amplitude data.

	F	*p*	partial-eta^2
Group[a]			
Response Type[a]	17.5	.001	.27
Validity[b]			
Bin[b]			
Group x Response Type[a]	19.8	< .001	.36
Group x Validity[b]			
Group x Bin[b]	9.7	< .001	.22
Response Type x Validity[b]	14.8	< .001	.29
Response Type x Bin[b]	4.8	< .05	.12
Validity x Bin[c]			
Group x Response Type x Validity[b]	7.6	.001	.17
Group x Response Type x Bin[b]	6.0	< .01	.15
Group x Validity x Bin[c]	3.0	< .05	.08
Response Type x Validity x Bin[c]	4.4	< .01	.11
Group x Response Type x Validity x Bin[c]	3.6	< .01	.09

[a] df = 1,35 [b] df = 2,70 [c] df = 4,140

Table 2-8. Mean amplitudes (μV) of the non-reward related FRN in the three validity conditions (100%, 80%, and 60% validity), displayed separately for the three bins and two age groups.

Bin	Young Adults (n = 19)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
1	- 1.0 (2.8)	- 1.2 (3.2)	- 1.0 (3.6)	- .3 (2.4)	.7 (2.2)	.3 (1.9)
2	.1 (4.2)	- .6 (2.5)	- .7 (2.6)	.04 (2.2)	.01 (2.5)	- .3 (3.3)
3	- .3 (2.9)	- .7 (2.5)	- 1.3 (2.7)	- .01 (2.3)	- .1 (2.8)	.2 (3.0)

Table 2-9. Mean amplitudes (μV) of the reward related FRN in the three validity conditions (100%, 80%, and 60% validity), displayed separately for the three bins and two age groups.

Bin	Young Adults (n = 19)			Older Adults (n = 19)		
	100%	80%	60%	100%	80%	60%
1	- .2 (2.2)	.4 (2.3)	.8 (2.4)	.4 (2.6)	.5 (2.8)	.4 (4.1)
2	-1.2 (2.3)	-.7 (2.4)	.5 (2.6)	.6 (2.4)	.6 (3.0)	.8 (3.0)
3	-1.3 (2.2)	-.7 (2.1)	.4 (2.2)	- .4 (3.2)	.6 (2.5)	.2 (3.9)

Table 2-10. Summary of the 2-Group x 2-Feedback Type x 3-Validity x 3-Bin ANOVA conducted on the reward- and non-reward FRN mean amplitude data.

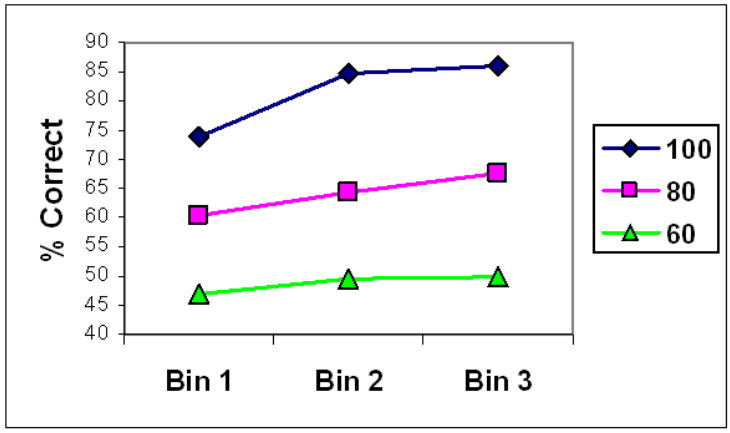
	F	*p*	partial-eta^2
Group[a]			
Feedback Type[a]	8.9	< .01	.15
Validity[b]	3.6	< .05	
Bin[b]			
Group x Feedback Type[a]			
Group x Validity[b]			
Group x Bin[b]			
Feedback Type x Validity[b]	6.5	< .01	.15
Feedback Type x Bin[b]	3.2	< .05	.08
Validity x Bin[c]			
Group x Feedback Type x Validity[b]	5.3	< .01	.13
Group x Feedback Type x Bin[b]	7.8	.001	.18
Group x Validity x Bin[c]			
Feedback Type x Validity x Bin[c]			
Group x Feedback Type x Validity x Bin[c]			

[a] df = 1,36 [b] df = 2,72 [c] df = 4, 144

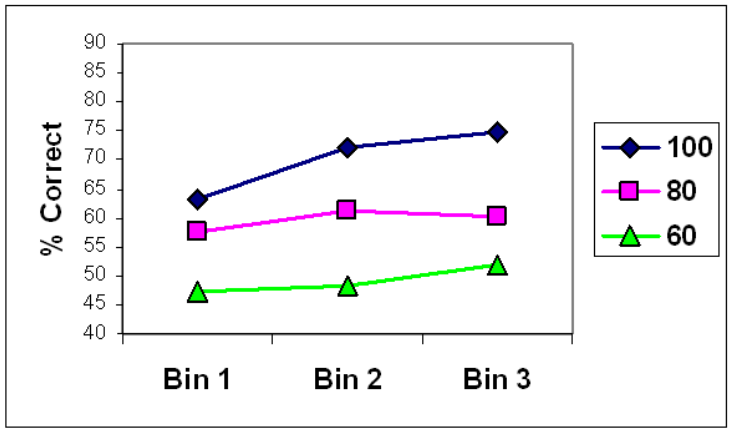
Table 2-11. Significant correlations between FRN difference waves and neuropsychological measures for younger and older groups combined.

	100%			80%			60%		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
NART									.33*
COWA					.36*				
BNT	-.37*								
Trails A Errors							.34*		
Trails B					-.33*				
LARS		-.35*							

* $p < .05$ (two-tailed)



A



B

Figure 2-1. Accuracy over time in each of the three validity conditions displayed separately for A) younger and B) older adults.

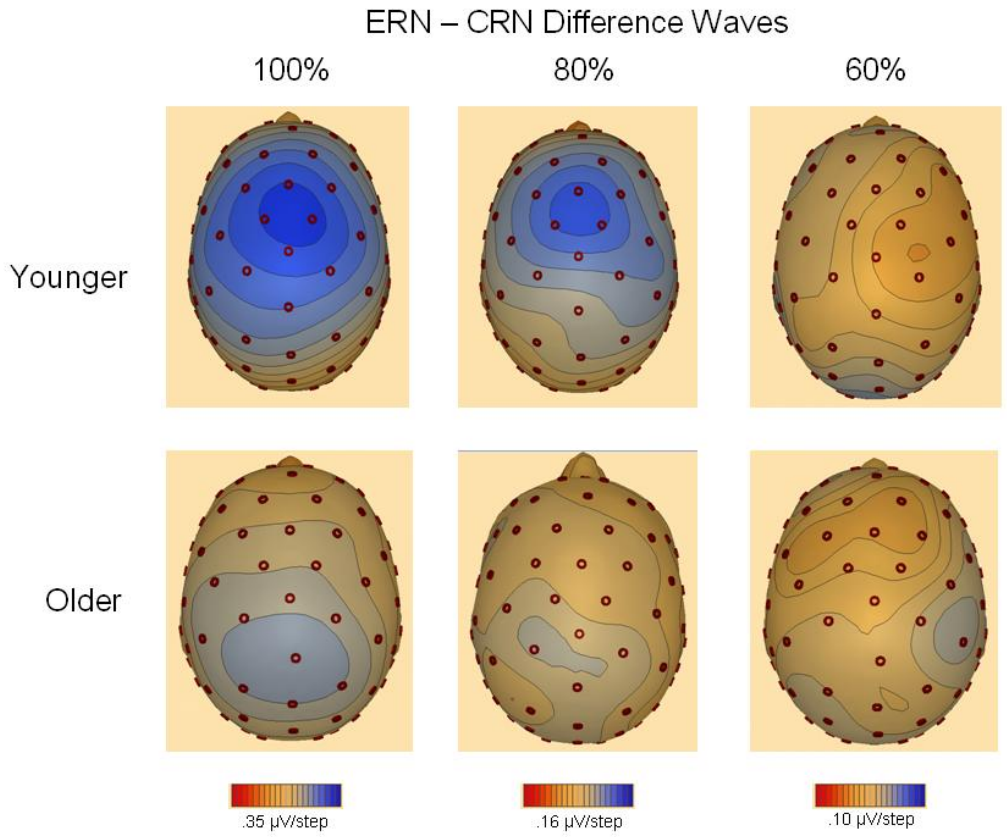


Figure 2-2. Spherical spline voltage maps for the ERN – CRN difference waves in both groups, taken at 60 ms. (Note different voltage scale ranges for the different probability conditions.)

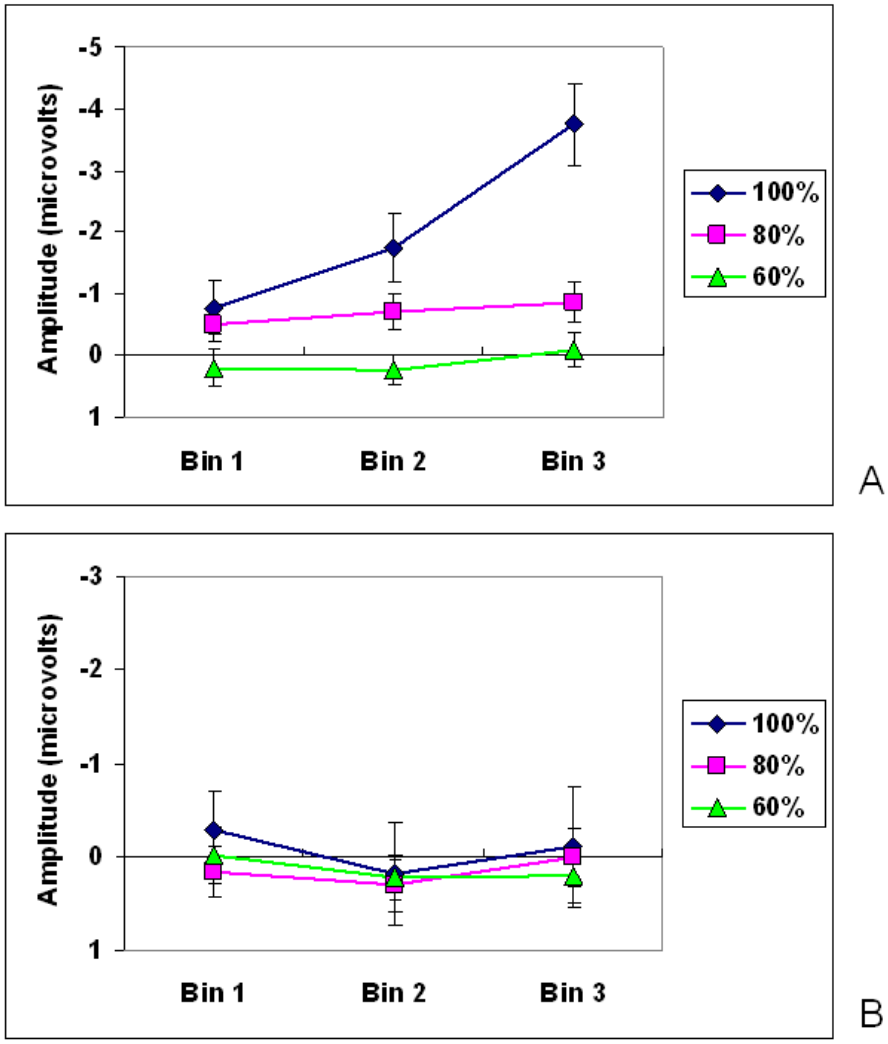


Figure 2-3. Amplitude of the ERN-CRN difference wave in each condition over time displayed separately for A) younger and B) older adults. Error bars represent standard error of the mean (SEM). (Note that y-axis scales differ between groups.)

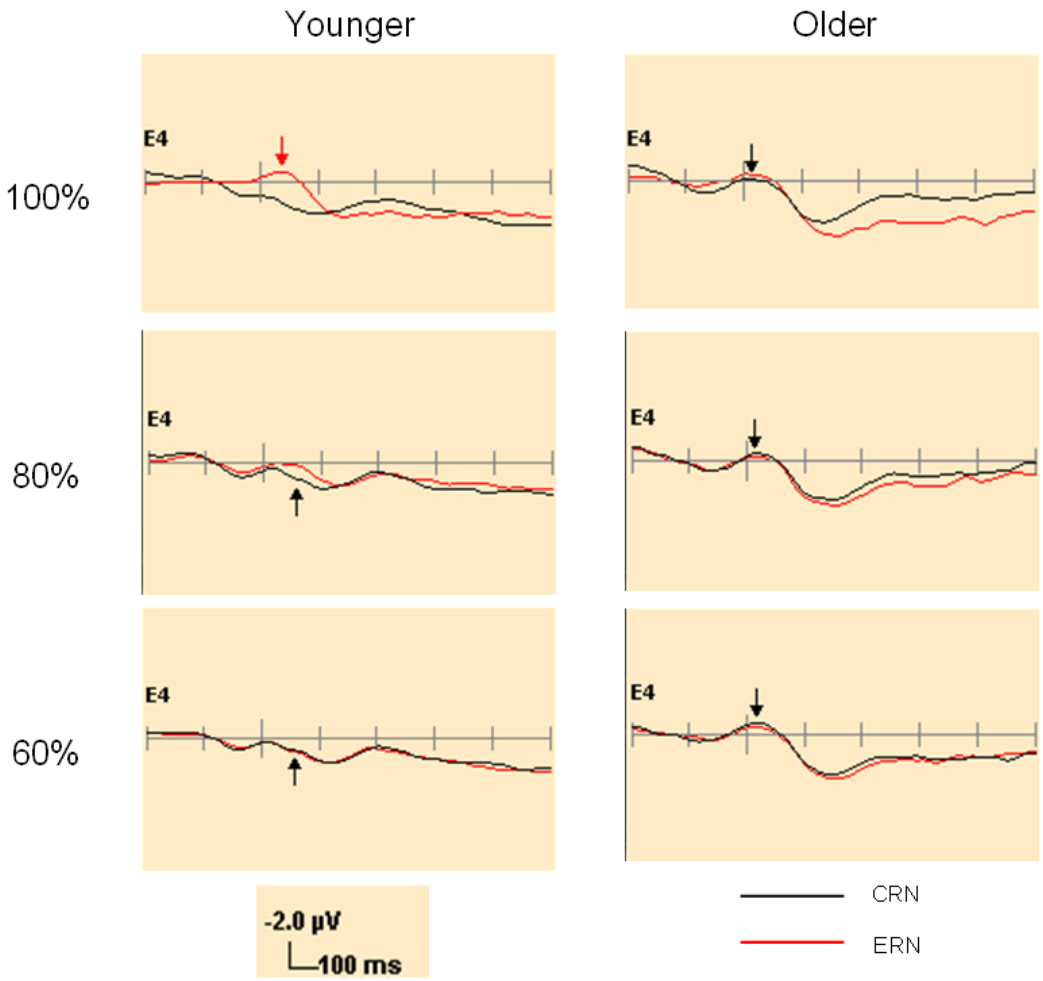


Figure 2-4. Grand-averaged response-locked ERPs taken from electrode FCz displayed separately for each group in each validity condition collapsed across all three bins. Arrows indicate approximate location of the ERP component. Microvolts on the *y*-axis, milliseconds on the *x*-axis. Negative is plotted up by convention.

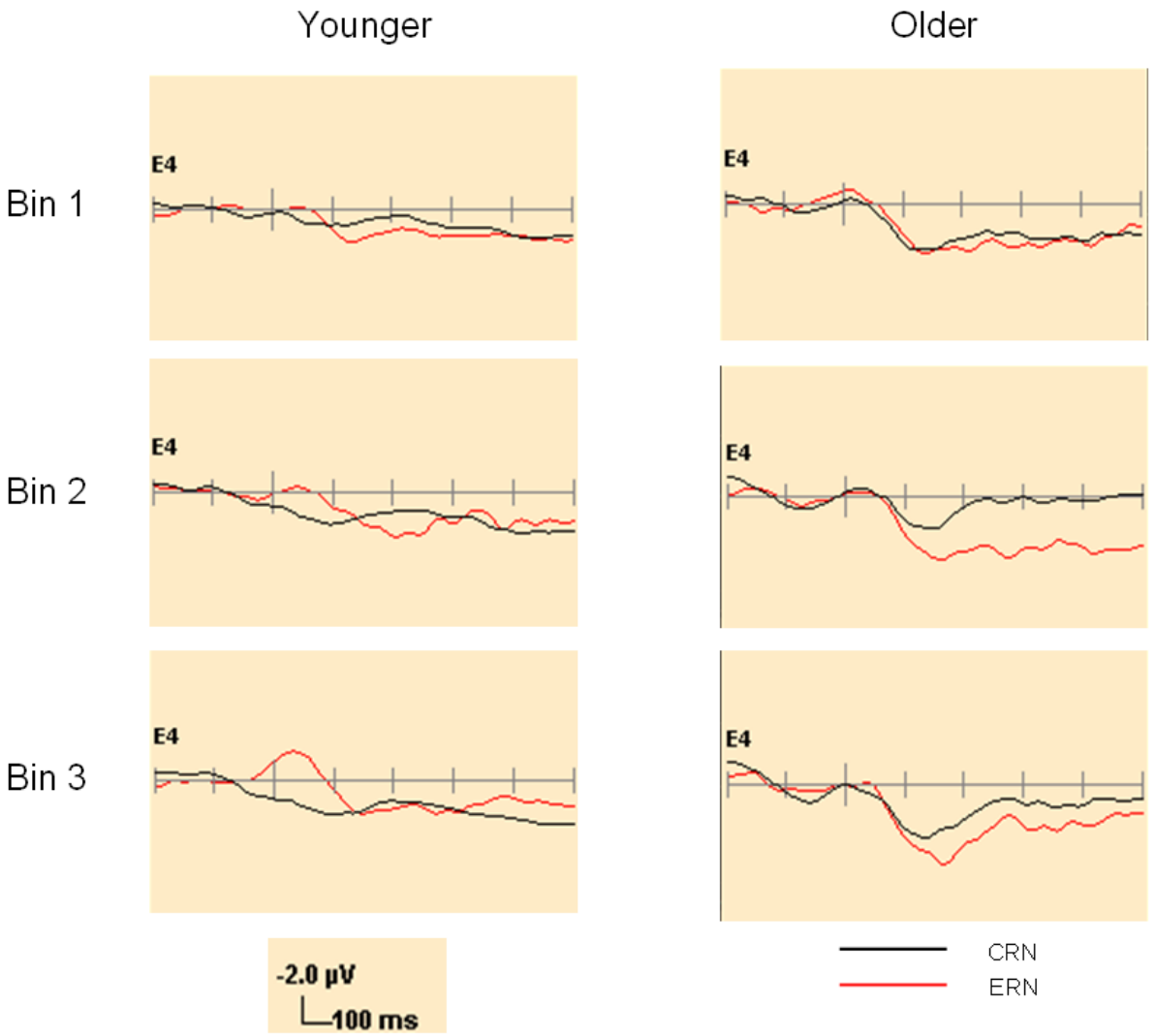


Figure 2-5. Grand-averaged response-locked ERPs at electrode FCz demonstrating learning-related effects for each group in the 100% validity condition. Microvolts on the *y*-axis, milliseconds on the *x*-axis. Negative is plotted up by convention.

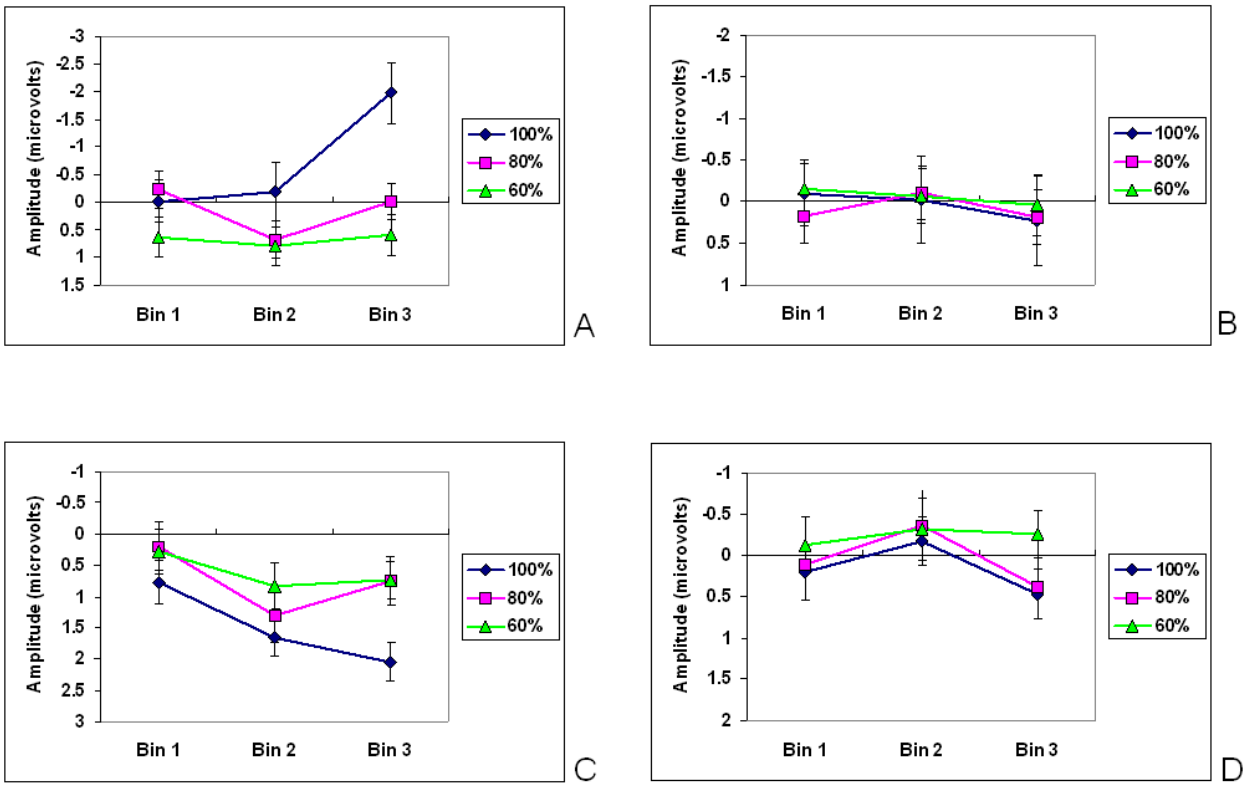


Figure 2-6. ERN amplitudes in each condition over time displayed separately for A) younger and B) older adults. CRN amplitudes in each condition over time displayed separately for C) younger and D) older adults. Error bars represent SEM. (Note that y-axis scales differ between groups.)

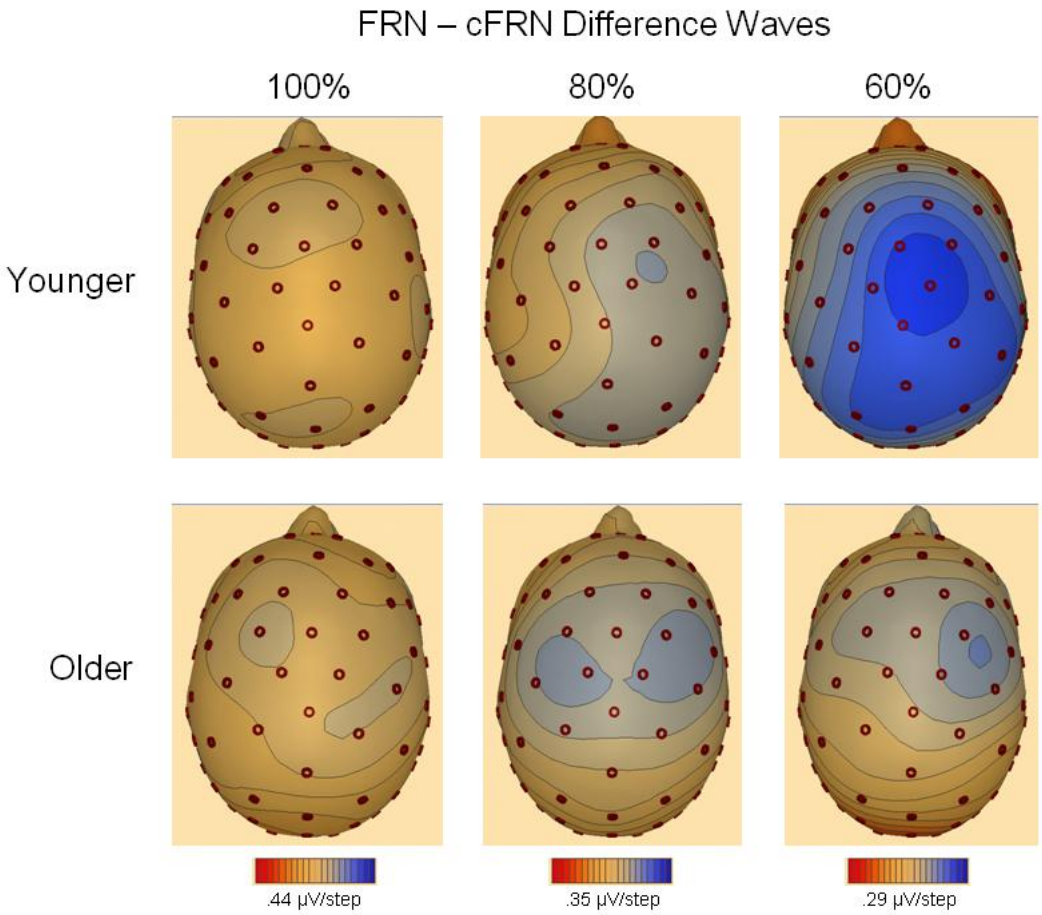


Figure 2-7. Spherical spline voltage maps for the FRN – cFRN difference waves in both groups. (cFRN = FRN to reward. Note different voltage scale ranges for the different probability conditions.)

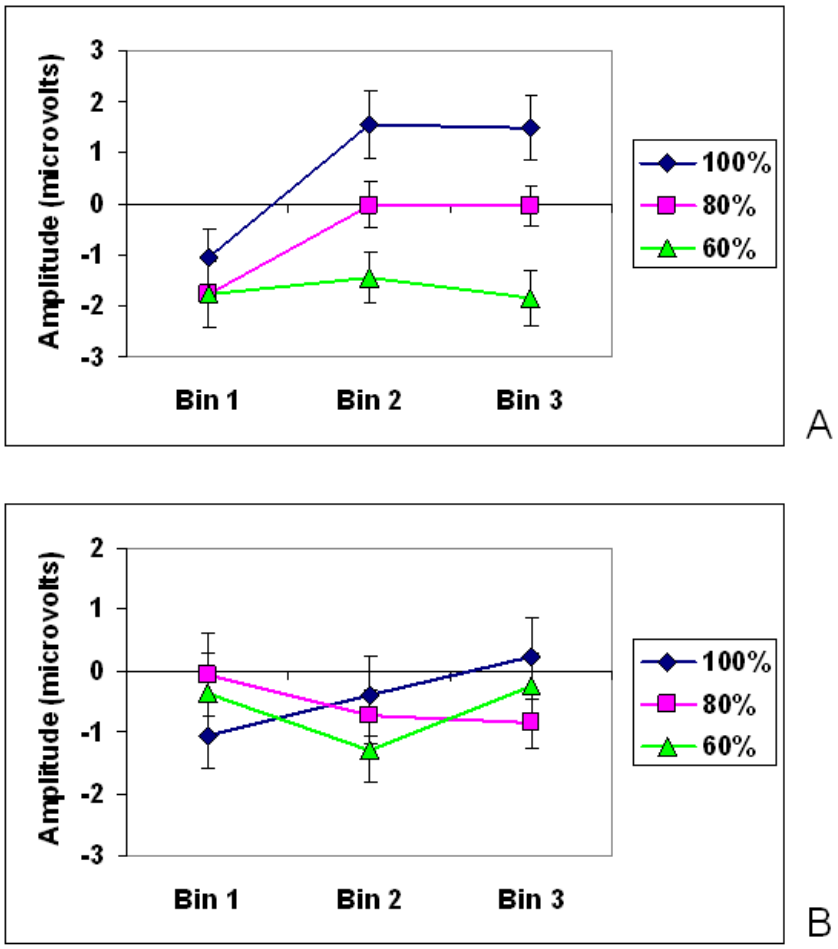


Figure 2-8. Amplitude of the non-reward minus reward FRN difference wave in each condition over time displayed separately for A) younger and B) older adults. Error bars represent standard error of the mean (SEM). (Note that y-axis scales differ between groups.)

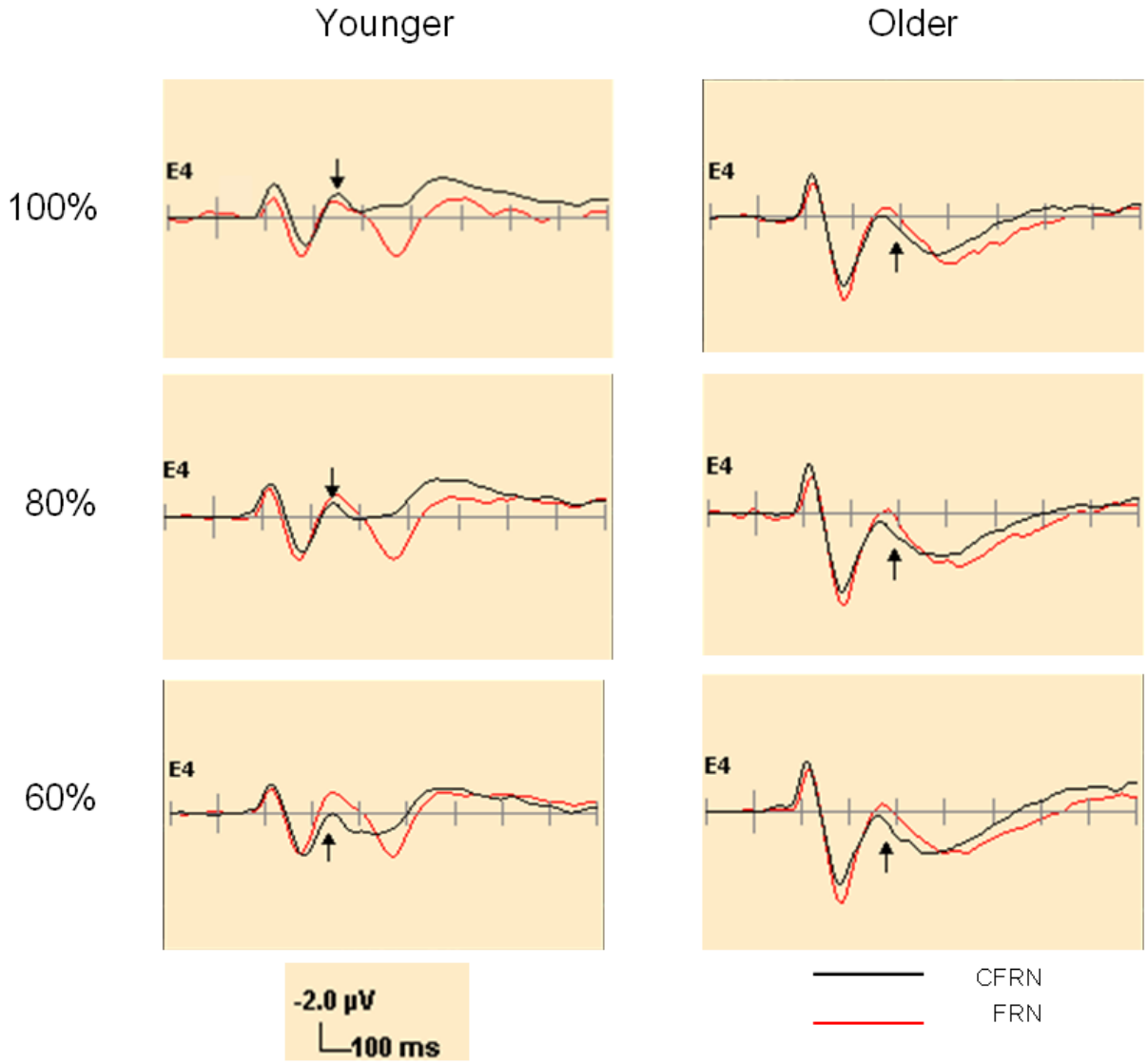


Figure 2-9. Grand-averaged feedback-locked ERPs taken from electrode FCz displayed separately for each group in each validity condition collapsed across the bins. Arrows indicate approximate location of the ERP component. Microvolts on the *y*-axis, milliseconds on the *x*-axis. Negative is plotted up by convention. (CFRN = reward-related FRN.)

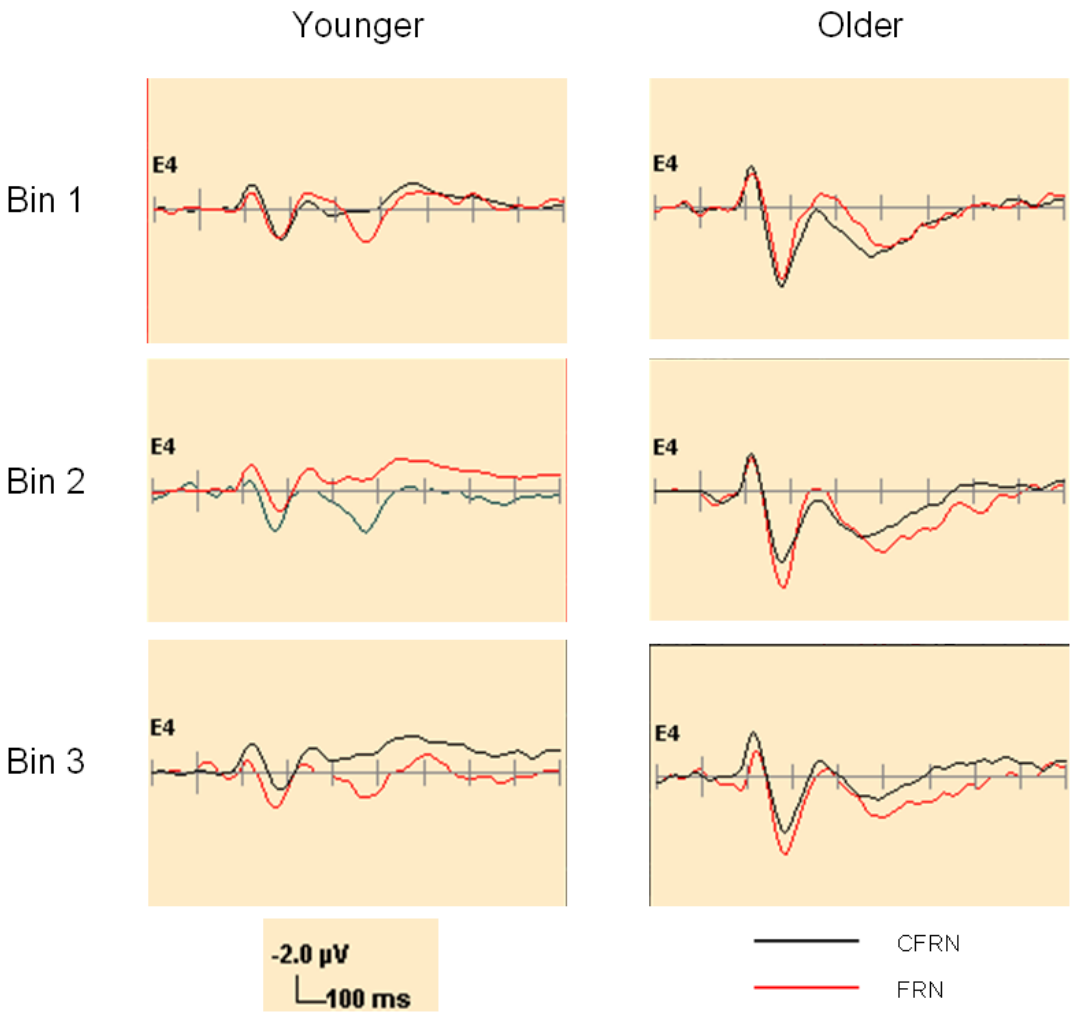


Figure 2-10. Grand-averaged feedback-related ERPs taken from electrode FCz demonstrating learning-related effects for each group in the 100% validity condition. Microvolts on the *y*-axis, milliseconds on the *x*-axis. (CFRN = reward-related FRN.)

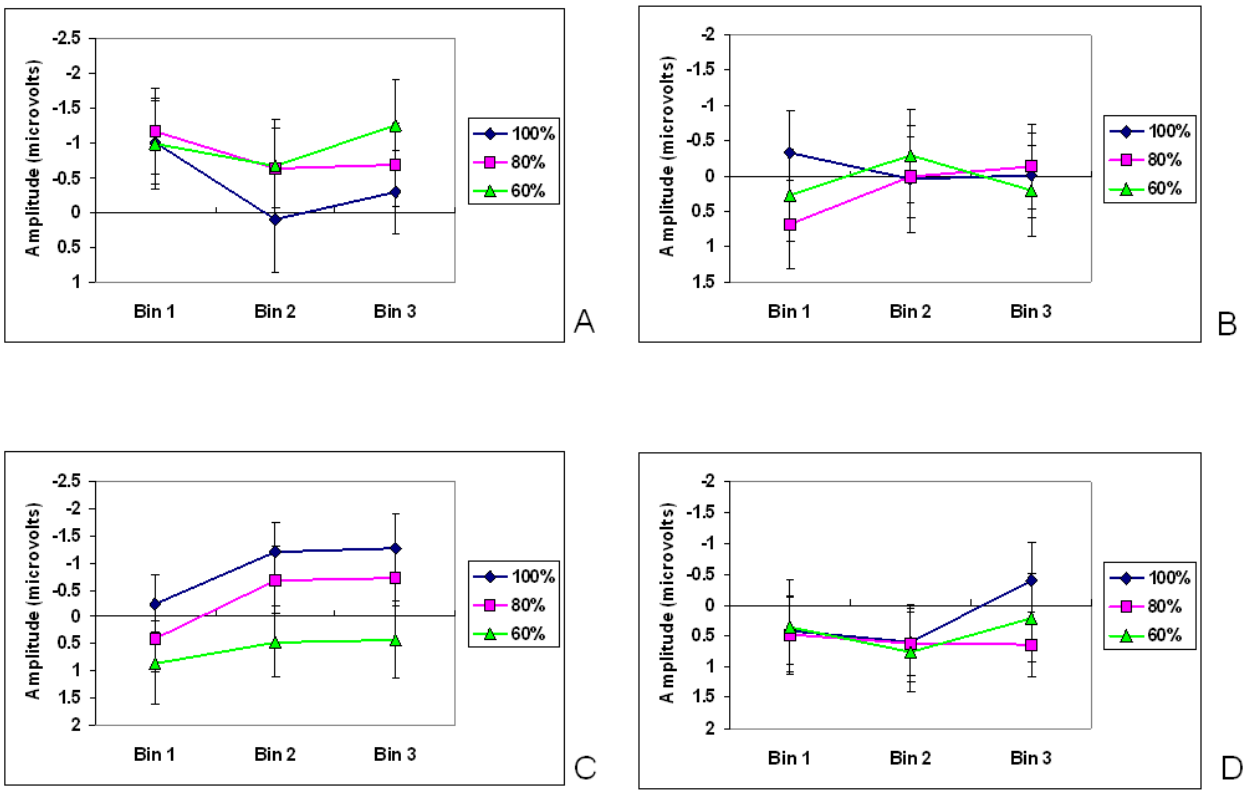


Figure 2-11. Non-reward related FRN amplitudes in each condition over time displayed separately for A) younger and B) older adults. Reward-related FRN amplitudes in each condition over time displayed separately for C) younger and D) older adults. Error bars represent SEM. (Note that y-axis scales differ between groups.)

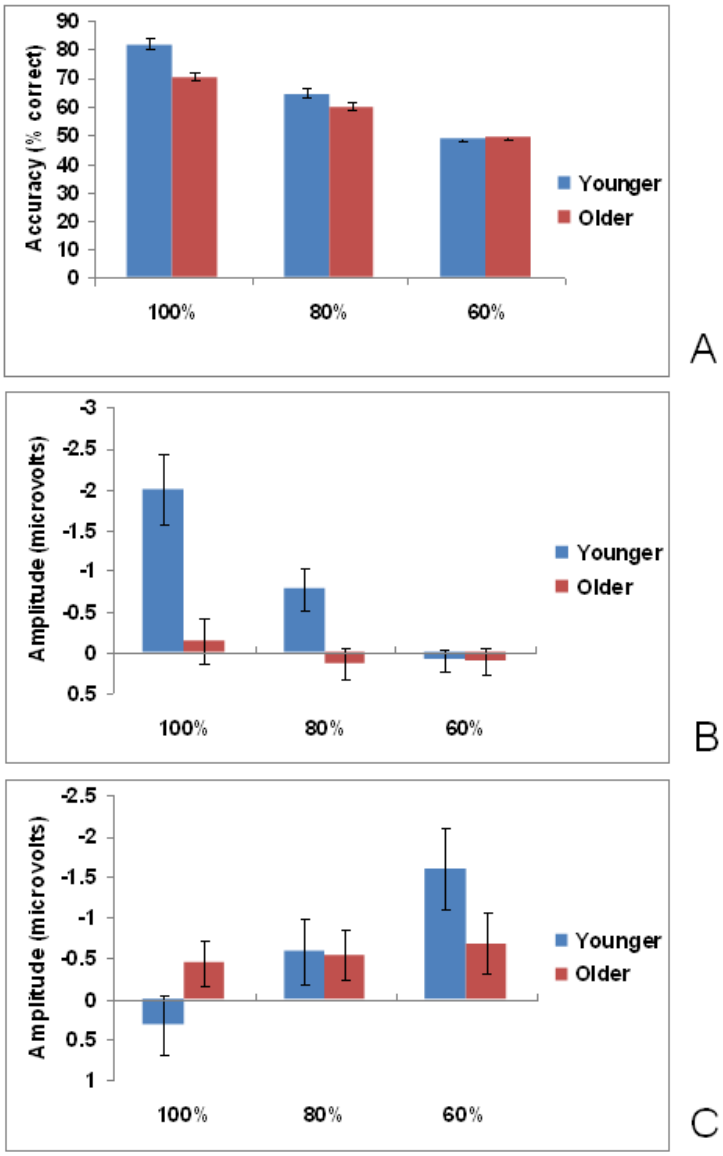


Figure 2-12. A) Mean accuracy in each condition. B) Mean amplitude of the ERN-CRN difference wave in each condition. C) Mean amplitude of the FRN to non-reward minus the FRN to reward difference wave in each condition. Error bars represent SEM.

CHAPTER 3
EXPERIMENT 2: THE EFFECT OF PARKINSON'S DISEASE ON ERROR DETECTION AND FEEDBACK PROCESSING

Overview and Predictions

Experiment 2 was conducted in order to examine the effects of Parkinson's disease on ERP reflections of error detection and feedback processing. Because these aspects of cognitive functioning are thought to be related to integrity of the frontal lobe and its connections to other brain regions, it was expected that the greater degree of fronto-striatal dysfunction in PD would result in greater impairments than those seen in community-dwelling older adults who presumably exhibit a lesser degree of disruption to these regions. Thus, it was predicted that medicated patients with PD would perform more poorly on the probabilistic learning task. Consistent with some previous reports (Falkenstein et al., 2001; Stemmer et al., 2007), it was initially anticipated that PD patients would exhibit decreased ERNs compared to older adult controls and that the older adult controls would exhibit greater increases in error-related activity over time compared to medicated patients with PD; thus group differences in ERP reflections of error detection should be most apparent at the end of the experiment. Because ERN amplitude increases over time were not detected in the older adults during Experiment 1, however, predictions were revised to reflect similar ERN amplitudes in medicated PD patients compared to older adult controls as reported elsewhere (Holroyd et al., 2002).

In light of previous reports of intact positive feedback processing in medicated PD patients using purely behavioral measures (Cools et al., 2006; Frank et al., 2004), it was expected that patients with PD would demonstrate similar amplitudes as older controls for the FRN to reward; however, in keeping with the prediction of greater disruption to frontally-mediated cognitive functioning in PD, it was anticipated that patients with PD

would demonstrate reductions in the amplitude of the FRN to non-reward compared to older controls.

In exploratory analyses, relationships between ERP component amplitudes, performance on neuropsychological tests, and self-reported mood symptoms were examined. In addition to the expected relationships between FRN difference waves and performance on measures of executive functioning, particularly Digits Backward, verbal fluency (COWA) and the Wisconsin Card Sorting Test, it was expected that FRN amplitudes would correlate with self-reported symptoms of apathy (AES, LARS).

Methods

Participants

Data from the older adult sample recruited for Experiment 1 were used in Experiment 2. PD patients for Experiment 2 were recruited through the community and through the Neurology Clinic at the Malcom Randall VA Medical Center in Gainesville, Florida. Of the thirty-five participants recruited, two older adults and four patients with PD were excluded from data analysis due to technical difficulties during data acquisition or for excessive noise in the EEG data. Exclusionary criteria for the control participants included a history of learning disability, neurological disease, or head injury. To be included in the PD group, patients had to be non-demented and meet diagnostic criteria for PD. Clinical criteria for PD diagnosis included at least two of four cardinal motor signs (akinesia, bradykinesia, resting tremor, and rigidity; (Hughes, Ben-Shlomo, Daniel, & Lees, 1992) and a history of demonstrated therapeutic response to dopamine replacement therapy as measured by improvement in motor signs on the United Parkinson Disease Rating Scale (UPDRS; (Fahn & Elton, 1987).

In addition to the nineteen older adult controls (ages 56-76) recruited for Experiment 1, the final sample for Experiment 2 included ten age-matched patients with Parkinson's disease (ages 57-78). The two groups did not differ with respect to age $t(27) = -.08$, $p > .90$, gender ($\chi^2 = .44$, $p > .50$), handedness ($\chi^2 = 1.53$, $p > .21$), education $t(27) = -.14$, $p > .88$, or premorbid estimated FSIQ, $t(27) = -.84$, $p > .16$. Due to the small number of participants in the PD group, sensitivity analyses and post-hoc power analyses were conducted using G-Power software (Faul, 2007). By convention, the following interpretations of effect sizes will be used: $f = .1$ (small), $f = .25$ (medium), and $f = .4$ (large) (Cohen, 1992).

All participants in this study obtained scores of 24 or higher on the MMSE (Folstein et al., 1975) and 130 or higher on the Dementia Rating Scale (Mattis, 1988). Patients' scores on standard measures for staging PD motor symptoms and disease course were obtained in the "on" medication state within six months of their participation in this study. All patients were in Hoehn-Yahr stages 1-3 when tested on medication. Of the ten participants with PD, one received a Hoehn-Yahr score of 1, five were given the score of 2, two were scored as 2.5, and two were scored as 3. Demographic and neuropsychological data for the participants are shown in Table 3-1.

Procedures

After informed consent was obtained, participants began an experimental session which lasted approximately three hours. All individuals completed all tasks in one session. Participants received financial compensation ($30) for their participation.

Results

Behavioral Data

Reinforcement learning task performance

The number of timed-out trials did not differ between groups (*M* = .02, *SD* = .01, for older controls, *M* = .03, *SD* = .03, for PD patients). See Table 3-2 for a summary of mean response times.

Accuracy data for each group in the three validity conditions and three bins is presented in Table 3-3 and Figure 3-1. The accuracy data were initially analyzed with an ANOVA design with the factors group (older control, PD) and validity (100%, 80% and 60% validity). Results of a sensitivity analysis (alpha = .05, power = .80, mean correlation between repeated measures = .27) found that this design should be able to detect significant between-group effects up to *f* = .49 and significant group x validity interactions up to *f* = .42. The ANOVA revealed no significant main effect of group, $F(1, 27) = .38$, $p = .54$, partial eta squared = .014, observed power = .09, Cohen's *f* = .11. There was a significant main effect of validity, $F(2, 54) = 51.36$, $p < .001$, partial eta squared = .66. Contrasts for each level of the validity factor showed a higher accuracy for the 100% compared to the 80% validity condition and for the 80% compared to the 60% validity condition (*p*s < .0001). There was no significant interaction between group and validity $F(2, 54) = .10$, $p = .89$, partial eta squared = .004, observed power = .06, Cohen's *f* = .07.

We conducted a sensitivity analysis for the main effect of bin and the interaction between bin and group (alpha = .05, power = .80, mean correlation between repeated measures = .51) and found that this design should be able to detect effects up to *f* = .31. Examination of effects of learning over time using a repeated measures ANOVA (2-

group x 3-conditions x 3-bins) revealed a significant main effect of bin $F(2, 54) = 19.48$, $p < .0001$, partial eta squared = .42. Post hoc pairwise comparisons of accuracy during each bin revealed significantly better performance in the last bin compared to the first bin and in the second bin compared to the first bin (*p*s < .0001); however, the improvement between the second and third bins was not significant. There was a significant interaction between validity and bin $F(2.74, 74.10) = 3.15$, $p < .05$, partial eta squared = .11, observed power = .68. In the 100% valid condition, the older adult control group improved significantly from bin 1 to bin 2 and from bin 1 to bin 3 (*p*s < .0001), and demonstrated a marginally significant improvement from bin 2 to bin 3 ($p = .08$). In contrast, the PD group only demonstrated significant improvement in accuracy from bin 1 to bin 3 ($p < .05$). In the 80% condition, the older adult control group showed significant improvements in accuracy from bin 1 to bin 2 ($p < .05$), but not from bin 2 to bin 3. PD patients did not show significant improvements between any of the bins in this condition. As expected, there were no significant learning-related changes in the 60% condition for either group. There were no significant bin x group [$F(2, 54) = .03$, $p = .97$, partial eta squared = .001, observed power = .06, Cohen's $f = .06$] or validity x bin x group interactions.

Cognitive and emotional functioning

The groups performed comparably on all neuropsychological tests except Digit Span forward and Stroop Word Reading (see Table 3-1). The patients with PD performed more poorly than the older adult control participants on these two tasks (*ps* < .05). The PD patients also demonstrated trends toward slower performance on Stroop Color Reading ($p = .09$) and more errors committed on Trails B ($p = .07$). Both groups endorsed similar levels of symptoms of anxiety and depression. PD patients endorsed

a higher level of apathy symptoms than older adult control subjects on the AES; however, they endorsed similar levels of apathy symptomatology on the LARS. Although no individuals met diagnostic criteria for any psychiatric disorder currently, three members of the PD group obtained scores on the AES above the conventional clinical cutoff for apathy (14), and one member of the older group and two members of the PD group obtained scores on the BDI-II in the range for mild depression (>14).

Event Related Potential Data

Table 3-4 presents the number of trials comprising the ERP waveforms in each condition for the two groups. The two groups differed in numbers of trials per waveform in the 60% condition such that the incorrect-feedback FRN waveforms ($p < .05$) for PD patients had more trials than those of controls. No significant group differences were observed in the other probability conditions.

Response-locked ERPs (ERN/CRN)

In the first step, incorrect minus correct difference waves were calculated. These difference waves showed maximal negative amplitudes with a latency of approximately 45 ms in the PD group and 60 ms in the control group, shown in Figure 3-2. This roughly corresponds to the latencies of the peak amplitude seen in the original ERN and CRN waveforms. Mean amplitudes of these difference waves were calculated using a time window from 15-75 ms for the PD group and 30-90 ms for the control group, with each window centered on the peak amplitude as observed in the grand means for each group. An initial comparison of the mean amplitudes of the difference waves was conducted using a repeated-measures ANOVA (2-group x 3-validity condition x 3-bin). We also conducted a sensitivity analysis (alpha = .05, power = .80, mean correlation between repeated measures = .36) and found that this design should be able to detect

significant between-group effects up to *f* = .52, significant effect of condition up to *f* = .36 and significant group x validity interactions up to *f* = .38. We did not detect any significant main effects or interactions. [Main effect of group: *F*(1, 27) = .03, *p* = .87, partial eta squared = .001, observed power = .05, Cohen's *f* = .03; main effect of validity condition: *F*(2, 54) = .49, *p* = .61, partial eta squared = .018, observed power = .13, Cohen's *f* = .14; interaction: *F*(2, 54) = .33, *p* = .72, partial eta squared = .012, observed power = .10, Cohen's *f* = .11].

We also failed to detect any significant learning-related effects on amplitude across bins [*F*(2, 54) = 1.0, *p* = .38, partial eta squared = .036, observed power = .22, Cohen's *f* = .19] (see Figure 3-3). Sensitivity analysis of the within-subjects factor "bin" and associated interactions (alpha = .05, power = .80, mean correlation between repeated measures = .12) revealed that this design should be able to detect significant effects of *f* = .32. There was no significant bin x group interaction [*F*(2, 54) = .84, *p* = .44, partial eta squared = .03, observed power = .19, Cohen's f = .18] or bin x condition interaction [*F*(4, 108) = .55, *p* = .70, partial eta squared = .02, observed power = .18, Cohen's *f* = .14].

In the second step, the response-locked components were examined separately in order to examine the effects of disease status on changes in mean amplitude by response type (correct or incorrect). The response-locked components were measured as the mean amplitude within a 60 ms time window centered on the peak of the ERN at electrode FCz. A 2 (group) x 2 (response type) x 3 (validity) x 3 (bin) repeated measures ANOVA was conducted. Response-locked ERP waveforms from the probabilistic learning task can be seen in Figure 3-4. Mean ERP amplitude and latency

data are presented in Tables 3-5 through 3-6. Sensitivity analysis (alpha = .05, power = .80, mean correlation between repeated measures = .76 for valence and .80 for condition) revealed that this design should be able to detect a significant group main effect up to *f* = .64, main effect of valence up to *f* = .24, main effect of condition up to .20, a significant group x valence interaction up to *f* = .19, and a significant group x validity interaction up to *f* = .16. In line with the results from the analysis of difference waves, we detected no significant main effects or interactions [main effect of group: $F(1, 27) = 2.58$, $p = .12$, partial eta squared = .09, observed power = .34, Cohen's $f = .31$; main effect of valence: $F(1, 27) = .18$, $p = .68$, partial eta squared < .01, observed power = .07, Cohen's $f = .08$; main effect of validity condition: $F(2, 54) = .45$, $p = .64$, partial eta squared = .016, observed power = .12, Cohen's $f = .13$; group x valence interaction: $F(1, 27) = .009$, $p = .93$, partial eta squared < .0001, observed power = .05, Cohen's $f = .01$; group x validity condition interaction: (2, 54) = 1.37, $p = .26$, partial eta squared = .05, observed power = .28, Cohen's $f = .23$]. Examination of tests of within-subjects contrasts revealed a marginally significant group x condition interaction ($p = .09$). Follow-up ANOVAs demonstrated that these differences occurred in the 100% condition for both the ERN [$F(1, 27) = 3.34$, $p < .09$] and the CRN [$F(1, 27) = 4.03$, $p < .06$] such that the mean amplitudes of the response-locked ERPs were larger for the PD group than for the control group.

We were unable to detect any significant effects of learning over time [main effect of bin: [$F(2, 54) = 1.74$, $p = .19$, partial eta squared = .06, observed power = .35, Cohen's $f = .25$] see Figure 3-5 and 3-6. Sensitivity analyses of the within-subjects factor "bin" and associated interactions (alpha = .05, power = .80, mean correlation

between repeated measures in the 100% condition = .59) revealed that this design should be able to detect significant effects up to *f* = .23. We detected no significant bin x group [*F*(2, 54) = 1.25, *p* = .29, partial eta squared = .044, observed power = .26, Cohen's *f* = .21], bin x valence [*F*(2, 54) = .99, *p* = .38, partial eta squared = .04, observed power = .21, Cohen's *f* = .19] or bin x validity condition [*F*(4, 108) = .55, *p* = .70, partial eta squared = .02, observed power = .18, Cohen's *f* = .14] interactions.

Feedback-locked ERPs (FRN)

In the first step, non-reward-minus-reward difference waves were calculated. These difference waves showed maximal negative amplitudes with a latency of approximately 290 ms for older controls and 312 ms for PD patients as shown in Figure 3-7. This roughly corresponds with latencies of the peak amplitude seen in the original reward- and non-reward-related FRN waveforms. Mean amplitudes of these difference waves were calculated using a time window from 260-320 ms for older controls and 282-342 ms for PD patients.

As with the response-related activity, the mean amplitudes of the difference waves for feedback-related activity were compared using a repeated-measures ANOVA (2-group x 3-validity condition). We conducted a sensitivity analysis (alpha = .05, power = .80, mean correlation between repeated measures = .64) and found that this design should be able to detect significant between-group effects up to *f* = .59, a significant effect of validity condition up to *f* = .31 and a significant group x validity condition interaction up to *f* = .23. No significant main effect of group was detected [*F*(1, 27) = .63, *p* = .44, partial-eta^2 = .02, observed power = .12, Cohen's *f* = .15]. There was no significant main effect of condition [*F*(2, 54) = 2.41, *p* = .12, partial-eta^2 = .08, observed power = .40, Cohen's *f* = .30]. The group x validity condition interaction was not

significant [$F(2, 54) = .99$, $p = .38$, partial-eta^2 = .04, observed power = .21, Cohen's $f = .19$].

Sensitivity analyses of the within-subjects factor "bin" and associated interactions (alpha = .05, power = .80, mean correlation between repeated measures = .15) revealed that this design should be able to detect significant effects up to $f = .33$. Examination of effects of learning over time revealed no main effect of bin [$F(2, 54) = 1.27$, $p = .29$, partial-eta^2 = .05, observed power = .26, Cohen's $f = .22$]. There was a marginally significant bin x group interaction [$F(2, 54) = 2.49$, $p = .09$, partial-eta^2 = .08, observed power = .48, Cohen's $f = .30$]. This was a quadratic trend such that PD patients exhibited the largest amplitudes in the first bin, followed by the third bin, then the second bin. In contrast, the control group exhibited the largest amplitudes in the second bin followed by the first bin, then the third bin (see Figure 3-8). A significant bin x condition interaction was not detected [$F(4, 108) = 1.50$, $p = .22$, partial-eta^2 = .05, observed power = .39, Cohen's $f = .23$].

In the second step, the feedback-locked components were examined separately in order to investigate the effects of group on changes in mean amplitude by feedback type (reward or non-reward). The feedback-locked components were measured as the mean amplitude within a 60 ms time window centered on the peak of the FRN at electrode FCz (260 ms in older controls and 282 for PD patients). A 2 (group) x 2 (feedback type) x 3 (validity) repeated measures ANOVA was conducted as well as a sensitivity analysis (alpha = .05, power = .80, mean correlation between the repeated measure valence = .89; mean correlation between the repeated measure condition = .90). Based on the analysis, this design should be able to detect significant between-

group effects up to f = .52, significant within-group effects up to f = .32 and significant within-between interactions up to f = .17. Feedback-locked ERP waveforms from the probabilistic learning task can be seen in Figures 3-9 and 3-10. Mean ERP amplitude data are presented in Tables 3-7 through 3-8. Although we did not find main effects of group [$F(1,27) = .009$, $p = .92$, partial eta^2 < .0001, observed power = .05, Cohen's f < .03] or validity condition [$F(2, 54) = 2.08$, $p = .15$, partial eta^2 = .072, observed power = .35, Cohen's f = .28], there was a significant main effect of feedback type [$F(1,27) = 6.50$, $p < .05$, partial eta^2 = .19, observed power = .69, Cohen's f = .48] such that the FRN to non-reward was more negative than the FRN related to reward. We were unable to detect any significant group x validity [$F(2, 54) = 1.51$, $p = .23$, partial eta^2 = .05, observed power = .31, Cohen's f = .24], group x feedback type [$F(1, 27) = .57$, p = .46, partial eta^2 = .021, observed power = .11, Cohen's f = .15], or validity x feedback type interactions [$F(2, 54) = .86$, $p = .40$, partial eta^2 = .03, observed power = .17, Cohen's f = .15].

When we added the effect of bin, we were unable to detect any significant main effect of bin [$F(2, 54) = .27$, $p = .71$, partial eta squared = .01, observed power = .09, Cohen's f = .10]. We were also unable to detect significant bin x group [$F(2, 54) = .22$, p = .81, partial eta^2 = .01, observed power = .08, Cohen's f = .09], bin x validity condition [$F(4, 108) = .93$, $p = .42$, partial eta^2 = .033, observed power = .35, Cohen's f = .18], or bin x feedback type [$F(2, 54) = 1.04$, $p = .35$, partial eta^2 = .037, observed power = .21, Cohen's f = .20] interactions, but the main effect of feedback type was qualified by a marginally significant interaction between group, bin, and feedback type [$F(2, 54)$ =

2.95, p = .06, partial-eta^2 = .10, observed power = .55, Cohen's f = .33] (see Figure 3-11).

Relationship to performance on neuropsychological tests and disease variables

When both groups were combined, several neuropsychological variables correlated with FRN difference wave amplitudes (see Table 3-9). In the 100% valid condition, performance on Digit Span Backwards was positively correlated with the FRN difference wave in bin 1 (r = .37, p < .05); time to complete Trails B was positively correlated with the FRN difference wave in bin 2 (r = .40, p < .05); number of categories completed on the WCST was negatively correlated with the FRN difference wave in bin 1 (r = -.37, p < .05); number of perseverative errors on the WCST was positively correlated with the FRN difference wave in bin 2 (r = .43, p < .05), and performance on the BNT was negatively correlated with the FRN difference wave in bins 1 and 2 (r = -.45, p < .05). In the 80% valid condition, the amplitude of the FRN difference wave in bin 3 was positively correlated with age (r = .37, p < .05) and time to complete Trails B (r = .38, p < .05), and negatively correlated with number of categories completed on the WCST (r = -.31, p < .05).

Within the PD group, duration of PD symptoms was negatively correlated with the FRN difference wave in the 100% condition across the entire experiment (r = -.63, p < .05.) and Hoehn-Yahr stage was positively correlated with the FRN difference wave in the 80% condition in bin 3 (r = .86, p < .001).

Discussion

The purpose of Experiment 2 was to use the same experimental paradigm used in Experiment 1 to investigate the effects of Parkinson's disease on error detection and feedback processing. Of particular interest was the question of whether differences

existed with respect to valence. Thus, in addition to feedback probability, feedback valence was manipulated and ERP reflections of error detection and feedback processing were compared between patients with Parkinson's disease and age-matched controls. As in the first experiment, a secondary (exploratory) goal was to explore relationships between feedback processing, emotional symptoms and executive functioning.

Effects of Aging and PD on ERP Reflections of Reinforcement Learning

Behavioral data

The groups performed comparably on the reinforcement learning task and demonstrated better performance in the 100% condition compared to the 80% condition and in the 80% condition compared to the 60% condition. Both groups generally improved over time in the least ambiguous (i.e., 100%) learning condition; however, only the older adult control group improved in the more ambiguous (i.e., 80%) condition from the first to second bins. As expected, neither group exhibited learning in the 60% condition. Although we predicted that PD patients would perform more poorly than the control group, equivalent performance on feedback-based learning tasks between older adult controls and medicated patients with PD has been reported previously (Shohamy et al., 2005; Swainson et al., 2006) and could be due to factors such as demographic and disease variables, or task difficulty and demands. For example, both groups in our sample were premorbidly high functioning, and PD patients were generally in mild to moderate stages of disease. Moreover, in the current study, the use of an adaptive response deadline successfully equated the number of trials attempted between groups, providing equivalent opportunity to learn from feedback. In addition, it has previously been reported that PD patients perform comparably to controls on similar tasks

requiring learning under ambiguous conditions; this has been attributed to relative sparing of limbic-dependent processes as compared to processes more dependent on dorsolateral prefrontal function (Euteneuer et al., 2009).

Response-locked ERPs (ERN/CRN)

In line with the revised hypothesis that accounted for the unexpectedly reduced ERN amplitudes in older adult controls found in Experiment 1, significant group differences were not found in the amplitude of the ERN-CRN difference wave, nor did we find amplitude differences by condition, or increased amplitude over time. These null findings are in contrast to studies reporting reduced amplitude ERNs in medicated (Falkenstein et al., 2001; Ito & Kitagawa, 2006) and unmedicated (drug-naïve) (Falkenstein et al., 2001; Stemmer et al., 2007) patients with PD as well as in the same patients tested both on- and off-medication (Willemssen et al., 2008) when compared to older adult controls. Previous reports of reduced amplitude ERNs in PD patients fit well with the dopamine hypothesis of the reinforcement learning theory, by suggesting that degeneration of dopaminergic neurons leads to disrupted signaling and reduced activation of the ACC; however, as with behavioral data, reasons for disparate results between studies could be due to several factors. For example, it is possible that the ERNs of our older adults were unusually small, contributing to the appearance of equivalent amplitudes between older adults and patients with Parkinson's disease. The amplitude of ERP waveforms can be measured in many ways, often with disparate effects. ERN amplitude has been measured variously using peak-to-peak scoring, difference wave calculations, mean amplitudes, and base-to-peak scoring approaches. In the present study, mean amplitudes were used because it has been suggested that this method helps to account for artificially increased maximum amplitude that can occur

in “noisy” waveforms (e.g., when testing patients with Parkinson’s disease), or bias due to unequal number of trials per waveform (Luck, 2005). Difference wave calculations were also used based on the work of previous investigators (e.g., Eppinger et al., 2008). Differences in paradigm design may also impact results, such as use of tasks that are more complex and/or contain a smaller number of trials (Falkenstein et al., 2001; Stemmer et al., 2007), which may not allow patients to learn and develop increased ERN amplitudes. Finally, differences in patient sample characteristics, such as inclusion of patients in more severe stages of disease (e.g., Ito & Kitagawa, 2006), may also contribute to differences in results. In support of our data, Holroyd and colleagues (Holroyd et al., 2002) have previously reported spared error-related potentials in a group of PD patients in mild-to-moderate stages of disease tested “off medication,” suggesting perhaps that early stage Parkinson’s disease does not negatively impact the error processing system over and above the effects of “normal” aging.

When mean amplitudes of the ERN and CRN were measured separately, results were surprising. Though findings of the current study should be interpreted with caution in light of the small sample size and relative lack of power, PD patients exhibited *greater* amplitude ERNs and CRNs than controls in the least ambiguous condition. Moreover, although we did not find significant learning-related changes in amplitude, examination of data patterns suggested that the ERN and CRN amplitudes of the PD patients began to dissociate (i.e., the ERN became larger as the CRN became smaller) over time as has been observed in a group of healthy young controls (Pietschmann et al., 2008). To our knowledge, these relationships have not been reported previously in a group of PD patients, though similar CRN amplitudes have been found between patients and

controls (Falkenstein et al., 2001; Willemssen et al., 2008). Interpreted within the dopamine hypothesis of the reinforcement learning theory, perhaps dopaminergic medication was able to restore the error-processing system to levels found in "normal" aging. Because patients in published studies are often taking a variety of different medications for treatment of Parkinson's disease, and reports suggest that dopamine agonists increase ERN amplitude (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004), it would be worthwhile to test whether different medications affect the error processing system in different ways. The results of the current study are interesting in light of suggestions that medicating "healthy" older adults with dopaminergic agents might improve their performance on reinforcement learning tasks. Of note, even if dopaminergic medication contributes to appropriate signaling to the ACC (and corresponding generation of ERNs and CRNs), it is not clear that this activation improves behavioral outcomes in terms of increased accuracy; many previous reports describe lack of cognitive enhancement with dopaminergic medication (Cools, 2008).

Feedback-locked ERPs (FRN)

A small amount of support for FRN-related predictions of the reinforcement learning theory was found in the data from the older adult controls and PD patients. Marginally significant results suggested greater amplitudes of the difference waves in the more ambiguous learning condition compared to the least ambiguous learning condition. In addition, generally decreasing amplitudes of the difference wave were observed over time, though decline was not clearly demonstrated because it was a quadratic trend.

One of the most important hypotheses of the current study was the prediction that aging and PD would have differential effects on the processing of feedback depending

on valence, such that PD patients would exhibit similar FRN amplitudes to reward, but reduced amplitude FRNs to non-reward compared to controls. In line with our hypotheses, no differences between groups were found with respect to the amplitude of the FRN to reward. If increased sample size and power were to uphold these findings, the current study would provide support for spared positive feedback processing systems in medicated patients with Parkinson's disease (Cools et al., 2006). Consistent with widely held accounts of the relative amplitude of the two feedback-related components, the amplitude of the FRN to non-reward was greater than the amplitude of the FRN to reward. Although this outcome is positive since it suggests that the feedback processing system is relatively intact in these two groups, it also contributed to our failure to find predicted group differences in the ability to process negative feedback.

It is possible that low statistical power contributed to these null findings since support for impaired reactivity to negative feedback in medicated PD patients is mounting. For example, a recent behavioral study concluded that reactivity to positive and negative feedback is differentially affected by Parkinson's disease and by particular dopaminergic medications used to treat its symptoms (Bodi et al., 2009). Bodi and colleagues (2009) found that treatment-naïve patients demonstrated selective deficits in positive feedback (i.e., reward) processing, but when patients were treated with dopamine agonists (pramipexole and ropinerole) these deficits were remediated, and the ability to process negative feedback became impaired. In addition, evidence has been found for blunted electrodermal responses to losses, but not to gains, in medicated patients with PD compared to older controls (Euteneuer et al., 2009).

An explanation for these differential valence effects based on recent neuroimaging findings suggests that PD patients recruit a compensatory system which shifts reward processing activity from more dysfunctional striatal systems to relatively better functioning frontal regions (Keitz et al., 2008). In healthy controls, increased activation in the left putamen is observed when provided monetary feedback compared to positive and neutral feedback; however, medicated PD patients exhibit increased activation in the left putamen in response to neutral feedback compared to both types of positive feedback (Keitz et al., 2008; Kunig et al., 2000). In addition, PD patients exhibit increased activation in medial prefrontal cortex (Keitz et al., 2008; Schott et al., 2007), dorsolateral prefrontal cortex (Kunig et al., 2000) and ACC (Kunig et al., 2000; Schott et al., 2007) in positive feedback conditions, which is not observed in controls.

An alternative to this "compensatory mechanism" hypothesis was previously outlined explaining the differential response to feedback based on valence. Frank and colleagues (M. J. Frank & Claus, 2006; M. J. Frank et al., 2004) developed an elegant neurobiologically-based computational model of the role of the basal ganglia in learning and decision-making. This model suggests that phasic dopamine bursts generated in response to rewards increase synaptic plasticity in the direct pathway (which connects the striatum to the substantia nigra pars reticulata and the internal segment of the globus pallidus) and decrease activity in the indirect pathway (which connects the striatum via the external segment of the globus pallidus to the substantia nigra pars reticulata and the internal segment of the globus pallidus). Thus, increased synaptic plasticity in the direct pathway is thought to reinforce rewarding behavior. In contrast, in response to negative or punishing feedback, phasic decreases in dopamine have the

opposite effect, leading to avoidance of harmful or bad decisions. Based on this model, it is thought that decreased dopamine in regions underlying processing of positive feedback (e.g., striatum) (Liu et al., 2007; Nieuwenhuis et al., 2005; O'Doherty et al., 2001) leads to impaired reward-related learning in non-medicated patients. On the other hand, when patients are treated with dopaminergic medication, these regions are "replenished," leading to improved reactivity to positive feedback; however, reactivity to negative feedback is impaired, either because the medication "blocks the effects of normal dopamine dips" (Euteneuer et al., 2009), or because regions underlying negative feedback processing (e.g., lateral OFC, ACC, and insula) (G. K. Frank et al., 2005; Liu et al., 2007; O'Doherty et al., 2001) become "overdosed" and dysregulated. In light of these hypotheses, it is possible that impairments in positive or negative feedback processing were not detected because medication levels were appropriately balanced in our sample such that frontal regions were not overdosed. Alternatively, as suggested in the discussion of Experiment 1, it is possible that feedback processing mechanisms were relatively spared in this high-functioning group of PD patients.

Relationship to Neuropsychological Test Performance

Consistent with expectations, feedback-related activity correlated with age and performance on measures of executive functioning. Because the reinforcement learning task required problem solving using feedback, it is not surprising that FRN amplitude was associated with better performance on the WCST as measured by a greater number of categories completed and fewer perseverative errors. Interestingly, it has previously been reported that performance on the WCST was not related to ERN amplitude in PD patients and older adult controls (Falkenstein et al., 2001; Willemssen et al., 2008), perhaps suggesting that performance on the WCST relies more on

feedback than error processing. Intact feedback processing was also related to visuomotor sequencing and set switching, which may reflect reliance on cognitive flexibility for success on the reinforcement learning task and subsequent appropriate changes in FRN amplitude. Increased age was associated with smaller amplitudes of the difference wave. As in Experiment 1, better performance on a language measure was associated with intact feedback processing. The fact that this relationship appeared in both experiments is somewhat surprising considering the restricted range of scores resulting from universally high performance on this measure. Counter-intuitively, better working memory was associated with smaller amplitudes of the difference wave. This result is particularly unexpected since a wealth of evidence supports a relationship between dopaminergic signaling and working memory; however, it is possible (as hypothesized above), that dopaminergic medication resulted in appropriate signaling as reflected by the FRN, but the medication caused an "overdosing" effect on working memory (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008; Cools, Lewis, Clark, Barker, & Robbins, 2007). Unfortunately, as in Experiment 1, we did not find expected relationships between feedback processing and emotional symptoms (e.g., apathy). This null finding was likely due to the small sample size, as well as to a small range of scores on these measures. The inclusion of patients in more advanced stages of disease would be necessary for required levels of apathy.

Within the PD group, feedback processing was related to several disease variables. Smaller FRN amplitudes were related to greater disease severity as measured by Hoehn-Yahr stage in keeping with well-known relationships between dopamine uptake and disease severity (Benamer et al., 2000; Berding et al., 2003).

There was a trend toward relationships between larger FRN amplitudes and levodopa equivalent dosage, which might support the hypothesis that appropriate medication management in our sample contributed to evidence for intact feedback processing. Somewhat surprisingly, shorter duration of symptoms was related to smaller amplitude difference waves; however, duration of symptoms is often an inaccurate marker of disease severity since variations exist not only with respect to progression of symptoms, but also with respect to how long symptoms were present prior to their identification.

Table 3-1. Demographic and neuropsychological data for older adults and patients with Parkinson's disease.

	Older (n = 19)		PD (n = 10)		
	Mean	(*SD*)	Mean	(*SD*)	*p*
Demographics					
Age (years)	66.9	(6.7)	67.1	(6.5)	*ns*
Education (years)	16.5	(2.1)	16.6	(2.7)	*ns*
Female (%)	31.6	--	20.0	--	*ns*
Right-Handed (%)	94.7	--	80.0	--	*ns*
Cognitive Functioning					
MMSE	28.3	(1.7)	29.0	(1.0)	*ns*
Dementia Rating Scale	140.7	(3.1)	140.1	(3.9)	*ns*
NART FSIQ	114.8	(7.4)	109.4	(13.0)	*ns*
Boston Naming Test	56.8	(5.0)	57.5	(2.8)	*ns*
COWA (FAS)	39.0	(8.9)	35.7	(11.8)	*ns*
Semantic Fluency (Animals)	20.4	(3.7)	20.5	(6.1)	*ns*
Digit Span Forward	11.0	(2.6)	8.4	(2.3)	< .05
Digit Span Backward	6.7	(2.1)	6.9	(2.6)	*ns*
Trails A (sec)	31.8	(9.1)	33.8	(11.1)	*ns*
Trails A (errors)	.1	(.3)	.1	(.3)	*ns*
Trails B (sec)	71.0	(26.8)	85.7	(33.2)	*ns*
Trails B (errors)	.3	(.7)	.9	(1.0)	.07
Stroop Word Reading	108.1	(17.1)	93.1	(9.0)	< .05
Stroop Color Naming	74.8	(12.4)	67.2	(8.3)	.09
Stroop Color Word Naming	45.5	(11.0)	45.7	(9.0)	*ns*
Stroop Interference	2.5	(8.9)	3.8	(5.8)	*ns*
WCST Categories Completed	5.6	(1.0)	5.1	(1.9)	*ns*
WCST Perseverative Errors	12.5	(9.6)	11.5	(10.5)	*ns*
WCST Failure to Maintain Set	.6	(.7)	.7	(1.9)	*ns*
Emotional Functioning					
BDI-II	3.6	(4.9)	5.7	(6.0)	*ns*
GDS	1.9	(3.6)	4.0	(6.3)	*ns*
AES	5.7	(3.0)	10.1	(6.0)	< .05
LARS	-24.8	(3.6)	-26.9	(4.9)	*ns*
STAI - State	26.9	(9.4)	25.8	(4.5)	*ns*
STAI - Trait	27.6	(8.3)	29.7	(7.7)	*ns*
Disease Characteristics					
Duration of Symptoms (years)	--	--	7.9	(4.0)	--
UPDRS Motor - On Meds	--	--	25.4	(10.2)	--
Hoehn-Yahr Scale – On Meds	--	--	2.2	(.6)	--
Levodopa equivalent dosage (mg)	--	--	754.4	(251.9)	--
Antidepressant Medications (%)	5	--	40	--	< .05

Table 3-2. Mean response time (SD) in the three validity conditions (100%, 80%, and 60%), displayed separately for the three bins and two groups.

Bin	Response time in milliseconds, validity					
	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
1	595 (165)	591 (167)	586 (157)	656 (170)	663 (170)	659 (170)
2	577 (154)	579 (157)	580 (164)	641 (166)	634 (156)	657 (185)
3	573 (164)	587 (150)	591 (155)	629 (166)	654 (157)	657 (156)

Table 3-3. Mean accuracy (SD) in the three validity conditions (100%, 80%, and 60%), displayed separately for the three bins and two groups.

Bin	Accuracy in each validity condition					
	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
1	.63 (.10)	.57 (.10)	.47 (.06)	.64 (.08)	.54 (.05)	.47 (.06)
2	.72 (.10)	.61 (.09)	.48 (.06)	.69 (.16)	.59 (.10)	.50 (.05)
3	.75 (.12)	.60 (.11)	.52 (.06)	.72 (.18)	.61 (.15)	.49 (.05)

Table 3-4. Mean (*SD*) number of trials per condition in each group.

ERP	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
ERN	62 (21)	85 (20)	108 (11)	69 (29)	92 (17)	111 (11)
CRN	149 (26)	127 (25)	107 (14)	154 (36)	126 (24)	105 (11)
FRN(neg)	60 (23)	84 (25)	105 (18)	69 (31)	95 (20)	117 (9)
FRN(pos)	143 (33)	122 (26)	100 (20)	148 (37)	124 (22)	103 (12)

Table 3-5. Mean amplitudes (μV) of the ERN in the three validity conditions displayed separately for the three bins and two groups.

Bin	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
1	- .09 (1.3)	.18 (1.2)	- .15 (1.4)	- .51 (1.2)	- .37 (1.8)	- .38 (.9)
2	- .03 (1.0)	- .11 (1.2)	- .07 (1.3)	- .63 (1.3)	- .56 (1.4)	- .69 (.8)
3	.23 (1.4)	.18 (1.2)	.04 (1.8)	- .95 (1.5)	-1.1 (1.5)	- .49 (.8)

Table 3-6. Mean amplitudes (μV) of the CRN in the three validity conditions displayed separately for the three bins and two groups.

Bin	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
1	.21 (1.3)	.11 (1.4)	- .13 (1.4)	- .90 (.8)	- .53 (1.4)	- .56 (1.4)
2	- .17 (1.2)	- .37 (1.8)	- .32 (1.5)	- .74 (1.4)	- .68 (1.3)	- .93 (1.1)
3	.47 (1.3)	.15 (1.7)	- .25 (1.1)	- .44 (.7)	- .57 (.7)	- .64 (1.1)

Table 3-7. Mean amplitudes (μV) of the non-reward related FRN in the three validity conditions displayed separately for the three bins and two groups.

Bin	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
1	- .3 (2.4)	.7 (2.2)	.3 (1.9)	- .2 (2.4)	- .7 (2.5)	.1 (2.6)
2	.04 (2.2)	.01 (2.5)	- .3 (3.3)	- .2 (2.5)	.2 (2.1)	.4 (2.5)
3	- .01 (2.3)	- .1 (2.8)	.2 (3.0)	.1 (2.4)	- .5 (1.8)	.6 (2.3)

Table 3-8. Mean amplitudes (μV) of the reward related FRN in the three validity conditions (100%, 80%, and 60% validity), displayed separately for the three bins and two groups.

Bin	Older Adults (n = 19)			PD Patients (n = 10)		
	100%	80%	60%	100%	80%	60%
1	.4 (2.6)	.5 (2.8)	.4 (4.1)	.7 (2.2)	.7 (2.5)	1.1 (2.6)
2	.6 (2.4)	.6 (3.0)	.8 (3.0)	.4 (2.0)	.5 (1.6)	.8 (2.3)
3	- .4 (3.2)	.6 (2.5)	.2 (3.9)	- .5 (1.9)	.6 (1.7)	1.5 (3.2)

Table 3-9. Significant correlations between FRN difference waves and neuropsychological measures for PD and older control groups combined.

	100%			80%			60%		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
Age						.37*			
Digits Backward	.37*								
Trails B (raw)		.40*				.38*			
BNT	-.45*	-.45*							
WCST Categories	-.37*					-.31*			
WCST Pers Err		.43*							

*p < .05, **p<.01 (two-tailed)

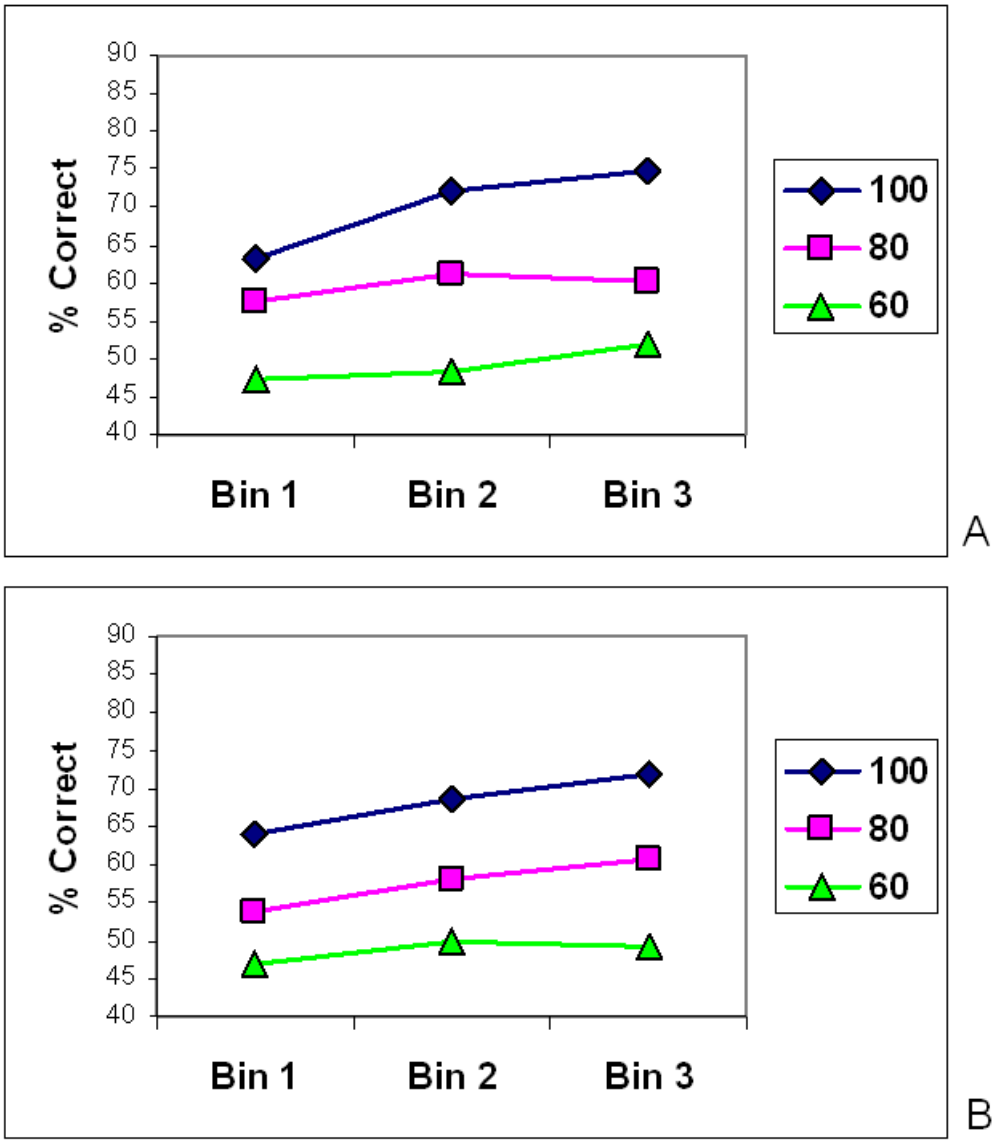


Figure 3-1. Accuracy over time in each of the three validity conditions displayed separately for A) older adult controls and B) patients with PD.

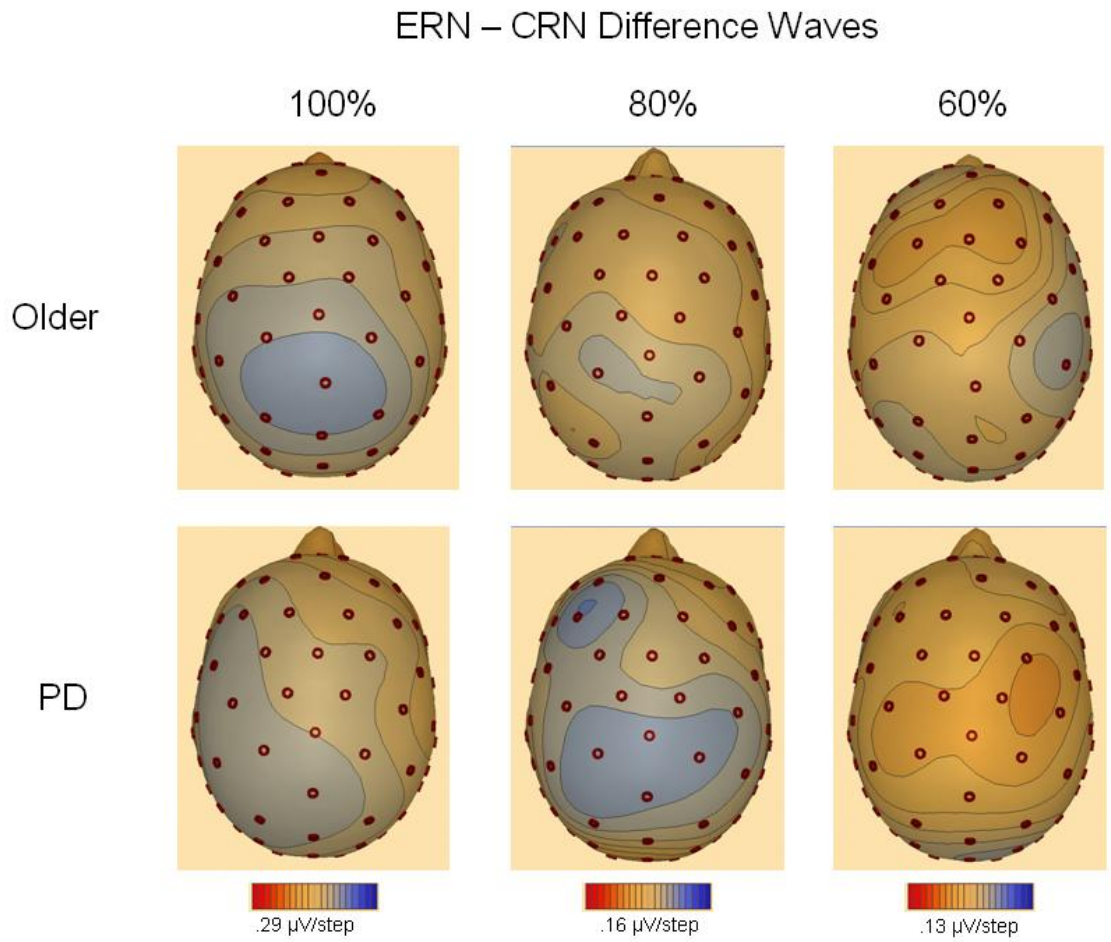


Figure 3-2. Spherical spline voltage maps for the ERN – CRN difference waves in both groups. (Note different voltage scale ranges for the different probability conditions.)

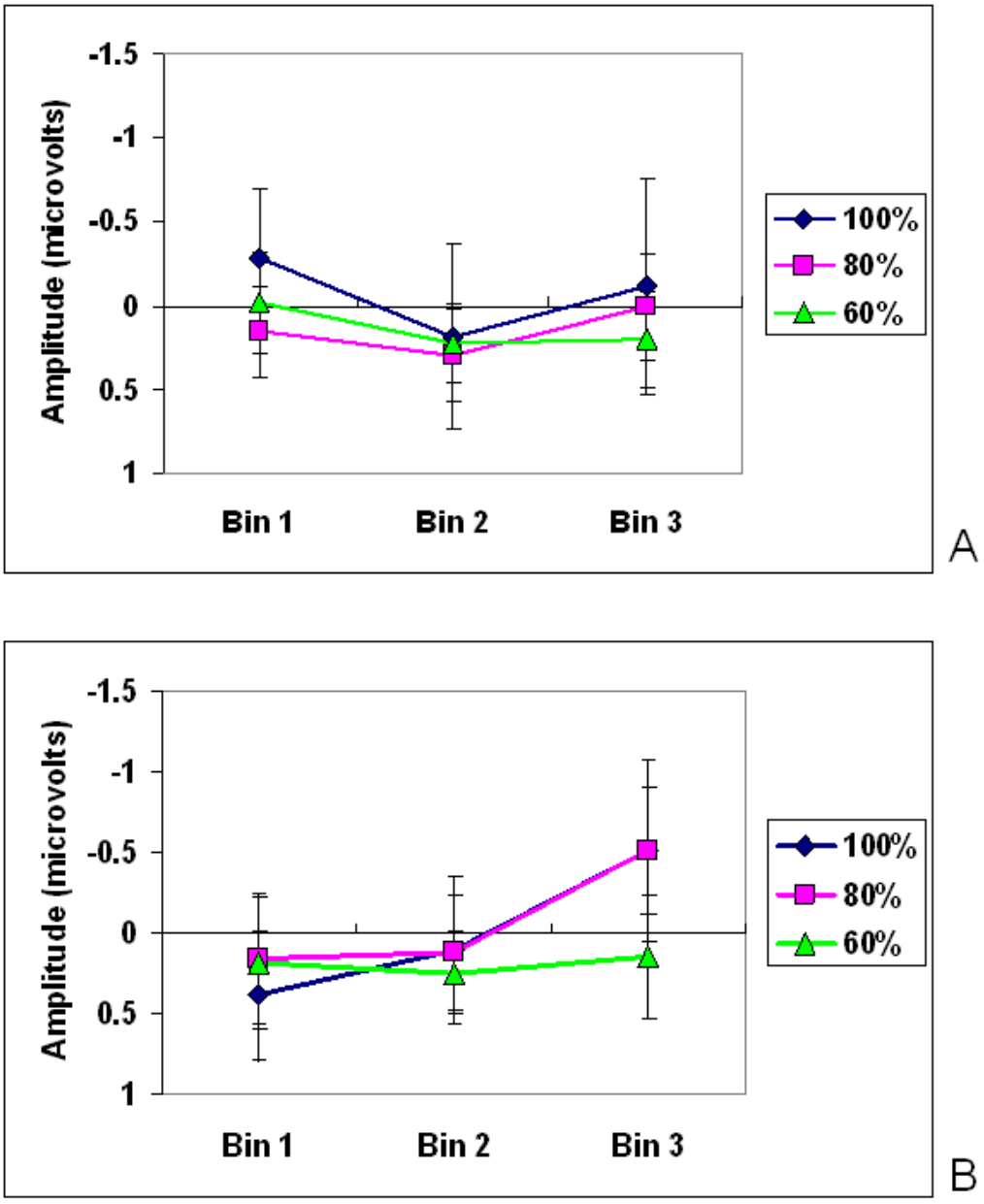


Figure 3-3. Amplitude of the ERN-CRN difference wave in each condition over time displayed separately for A) older controls and B) patients with PD. Error bars represent standard error of the mean (SEM).

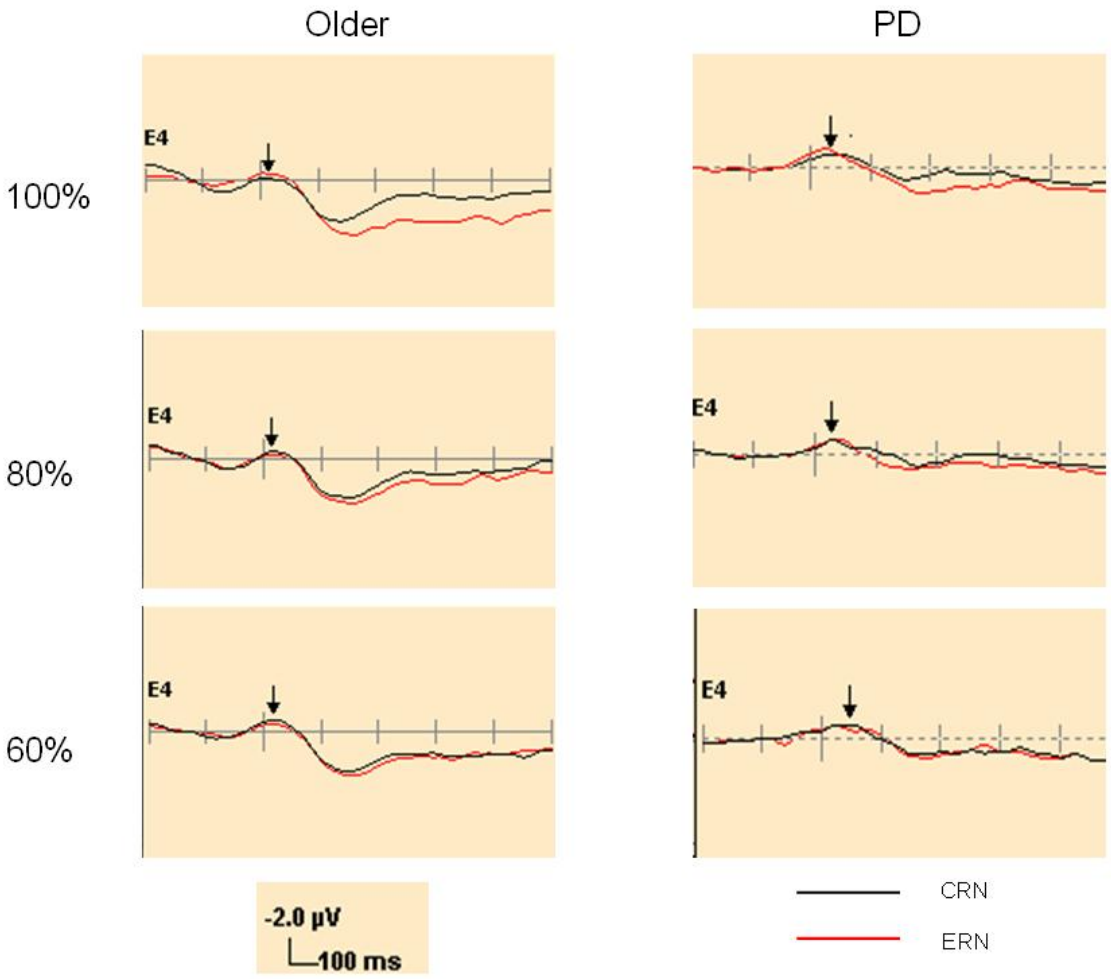


Figure 3-4. Grand-averaged response-locked ERPs taken from electrode FCz displayed separately for each group in each validity condition collapsed across all three bins. Arrows indicate approximate location of the ERP component. Microvolts on the *y*-axis, milliseconds on the *x*-axis. Negative is plotted up by convention.

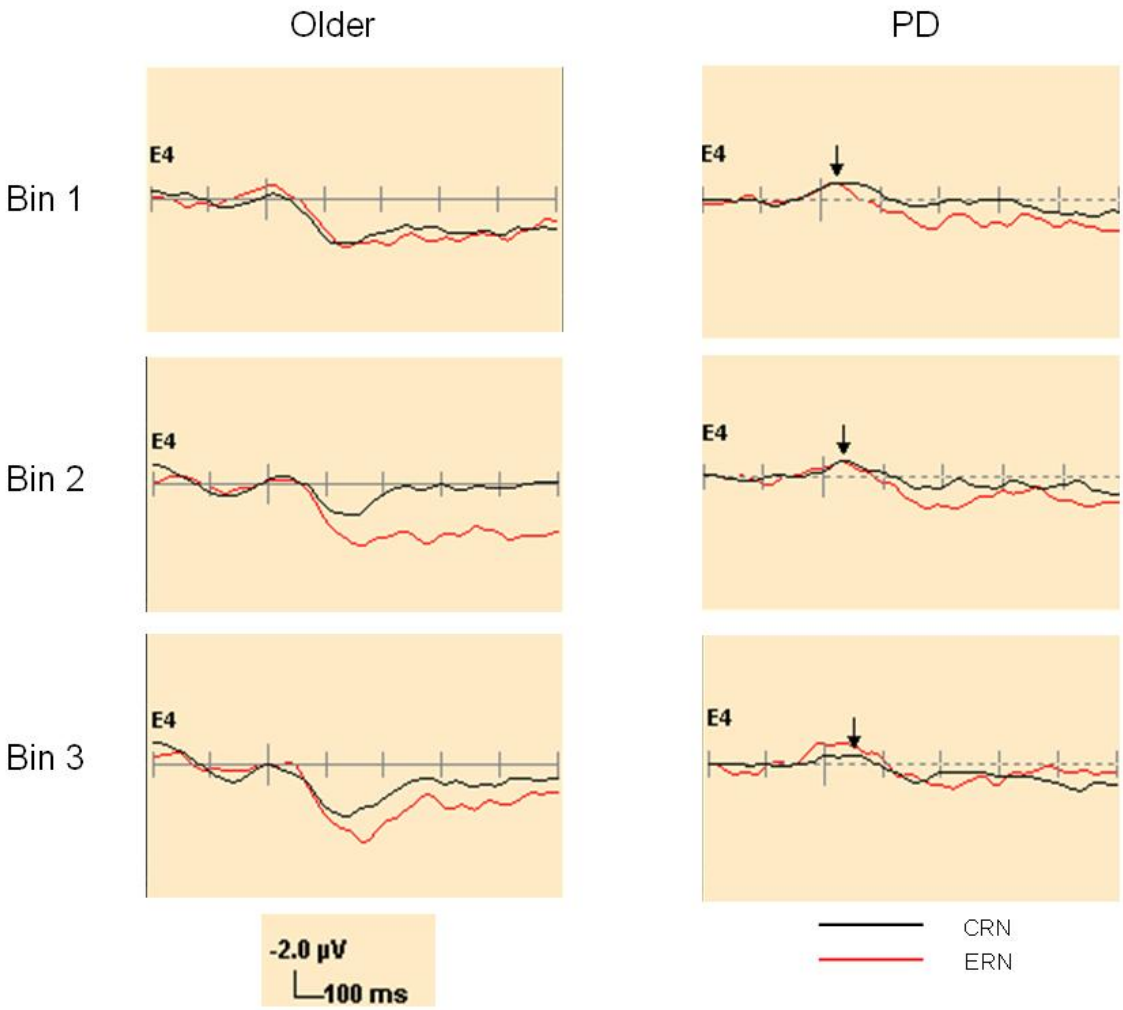


Figure 3-5. Grand-averaged response-locked ERPs at electrode FCz demonstrating learning-related effects for each group in the 100% validity condition. Microvolts on the *y*-axis, milliseconds on the *x*-axis. Negative is plotted up by convention.

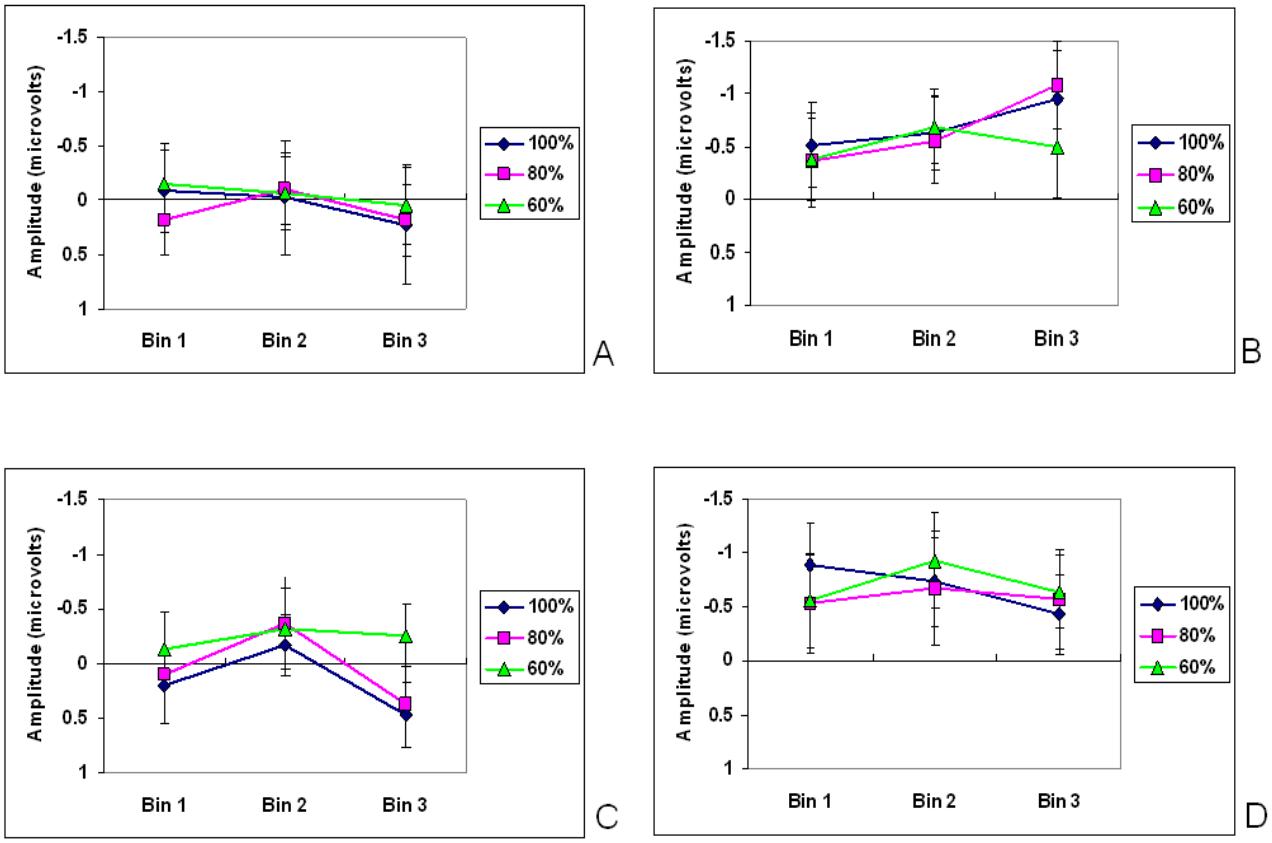


Figure 3-6. ERN amplitudes in each condition over time displayed separately for A) older controls and B) patients with PD. CRN amplitudes in each condition over time displayed separately for C) older controls and D) patients with PD. Error bars represent SEM.

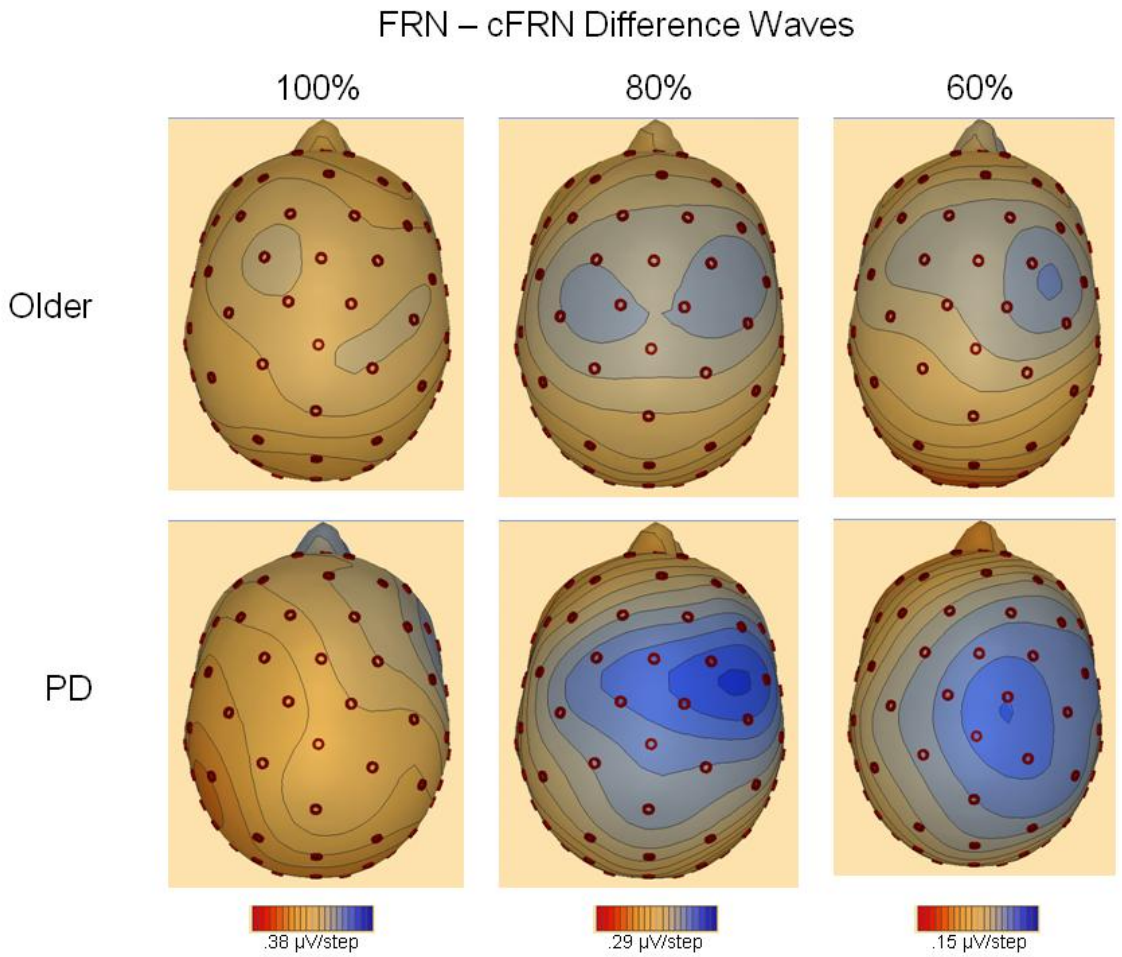


Figure 3-7. Spherical spline voltage maps for the non-reward minus reward difference waves in both groups. (Note different voltage scale ranges for the different probability conditions.)

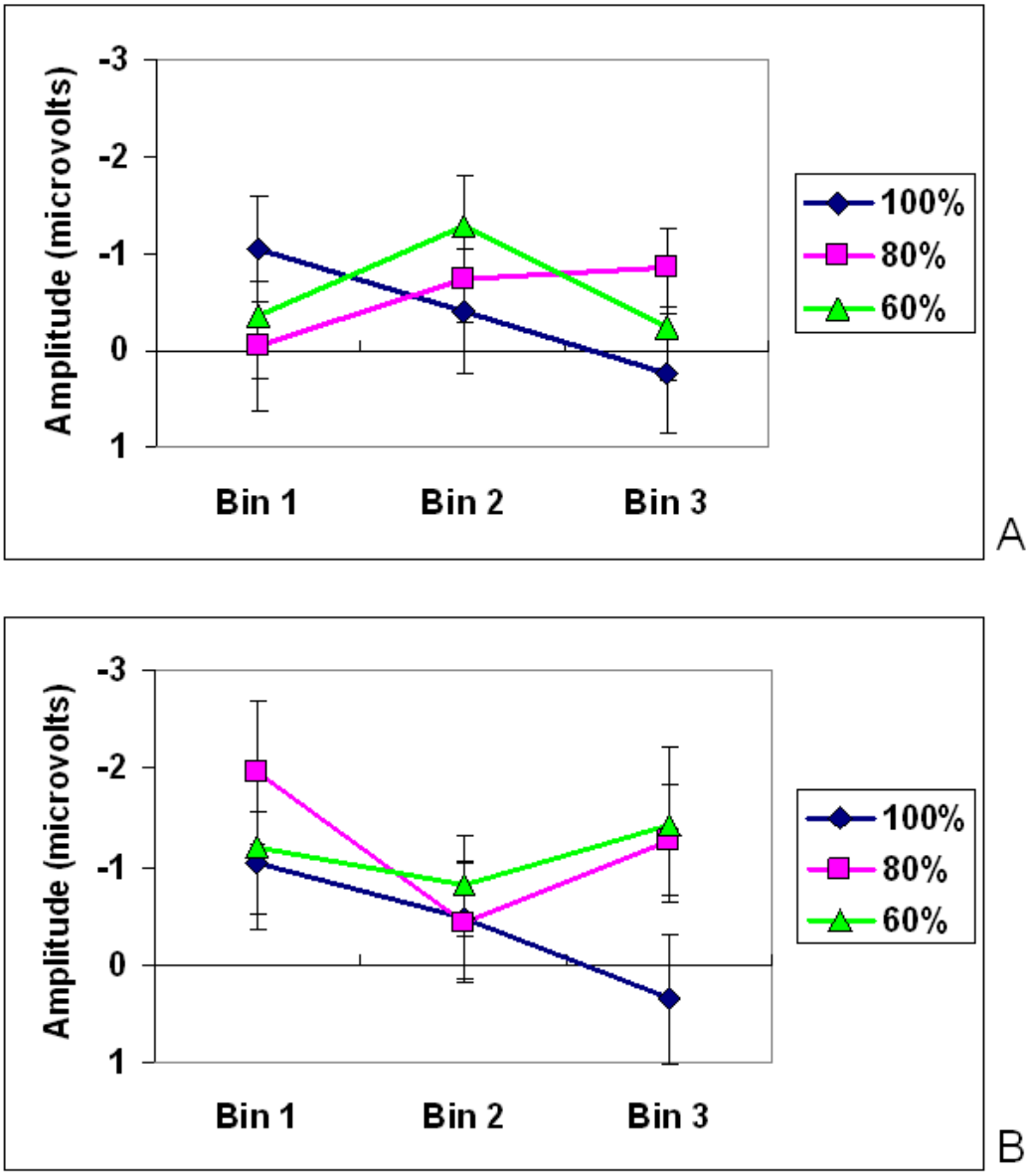


Figure 3-8. Amplitude of the non-reward minus reward FRN difference wave in each condition over time displayed separately for A) older controls and B) patients with PD. Error bars represent standard error of the mean (SEM).

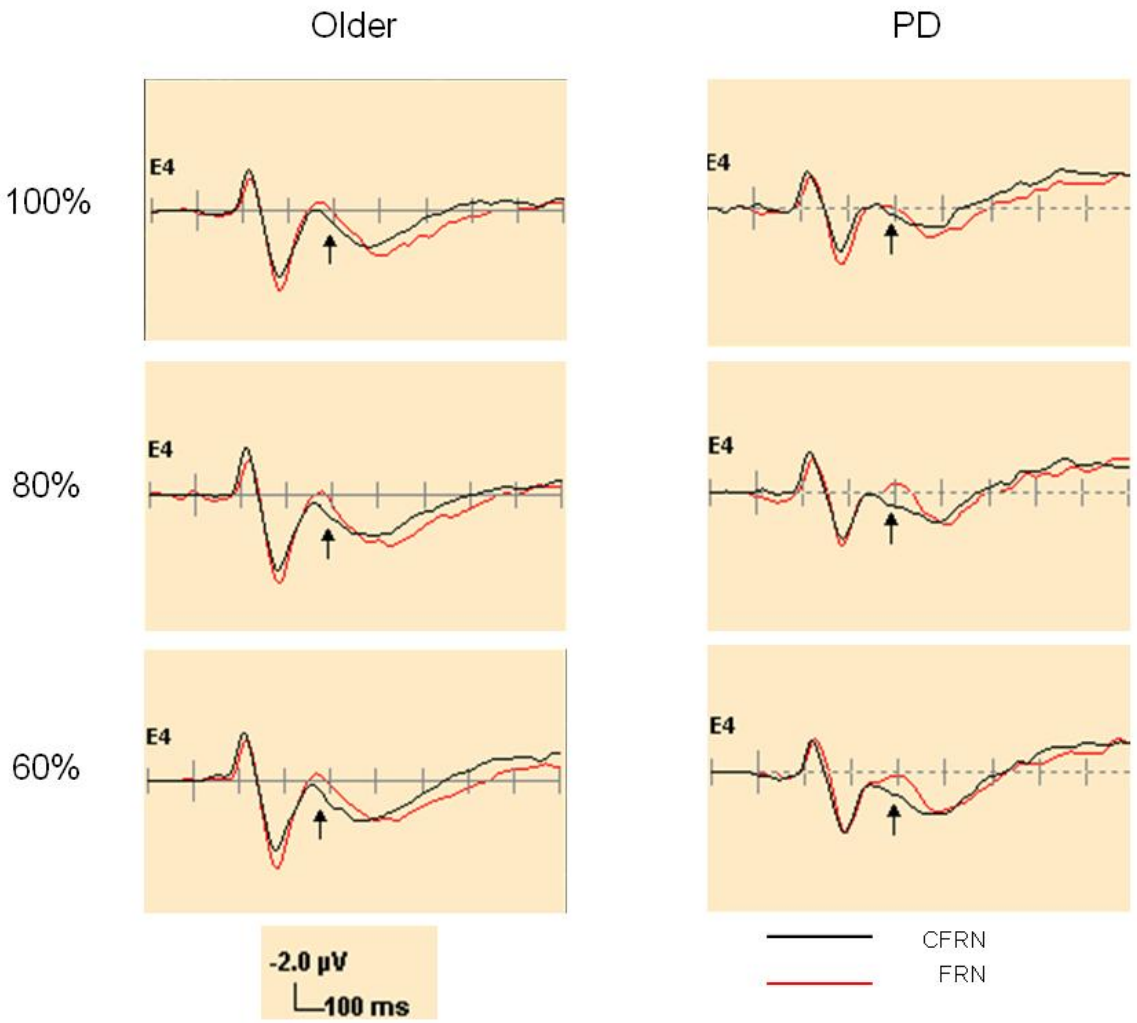


Figure 3-9. Grand-averaged feedback-locked ERPs taken from electrode FCz displayed separately for each group in each validity condition collapsed across the bins. Arrows indicate approximate location of the ERP component. Microvolts on the *y*-axis, milliseconds on the *x*-axis. (CFRN = reward-related FRN.)

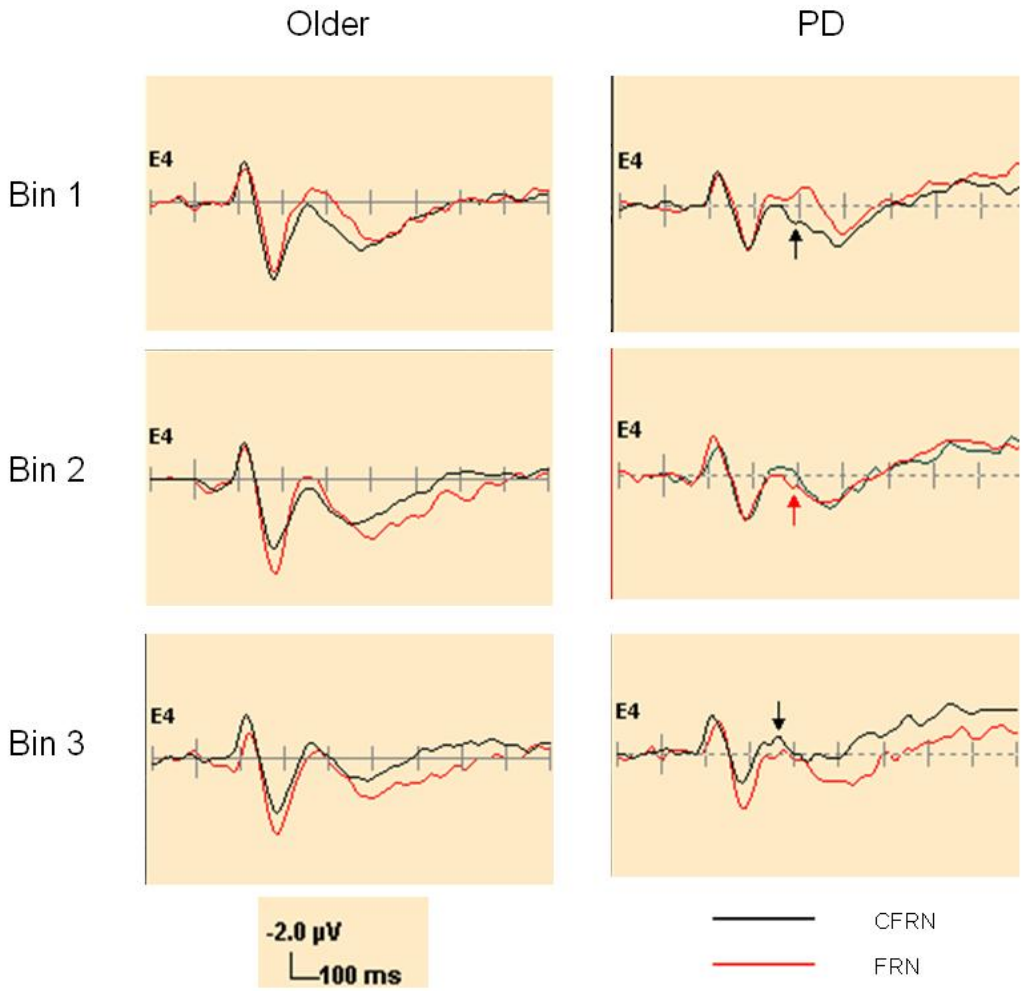


Figure 3-10. Grand-averaged feedback-related ERPs taken from electrode FCz demonstrating learning-related effects for each group in the 100% validity condition. Microvolts on the *y*-axis, milliseconds on the *x*-axis. (CFRN = reward-related FRN.)

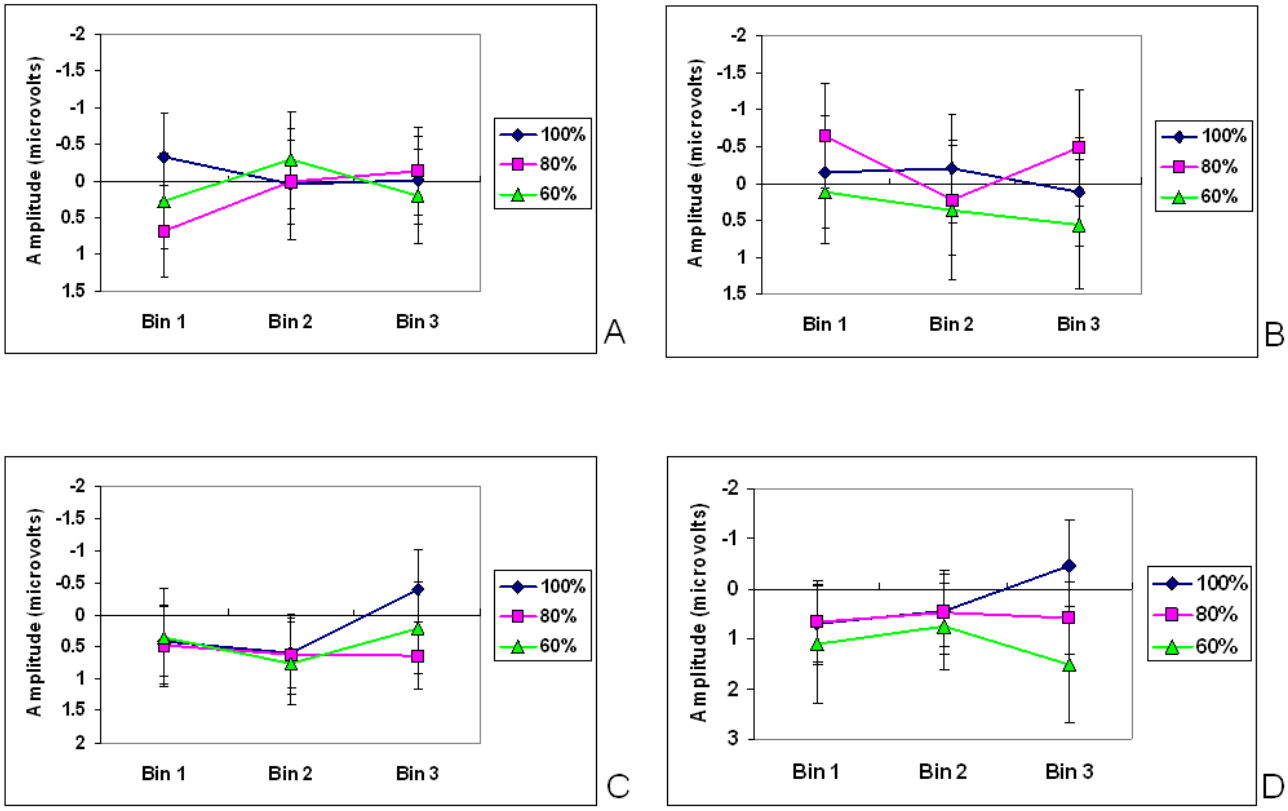


Figure 3-11. Non-reward related FRN amplitudes in each condition over time displayed separately for A) older controls and B) patients with PD. Reward-related FRN amplitudes in each condition over time displayed separately for C) older controls and D) patients with PD. Error bars represent SEM.

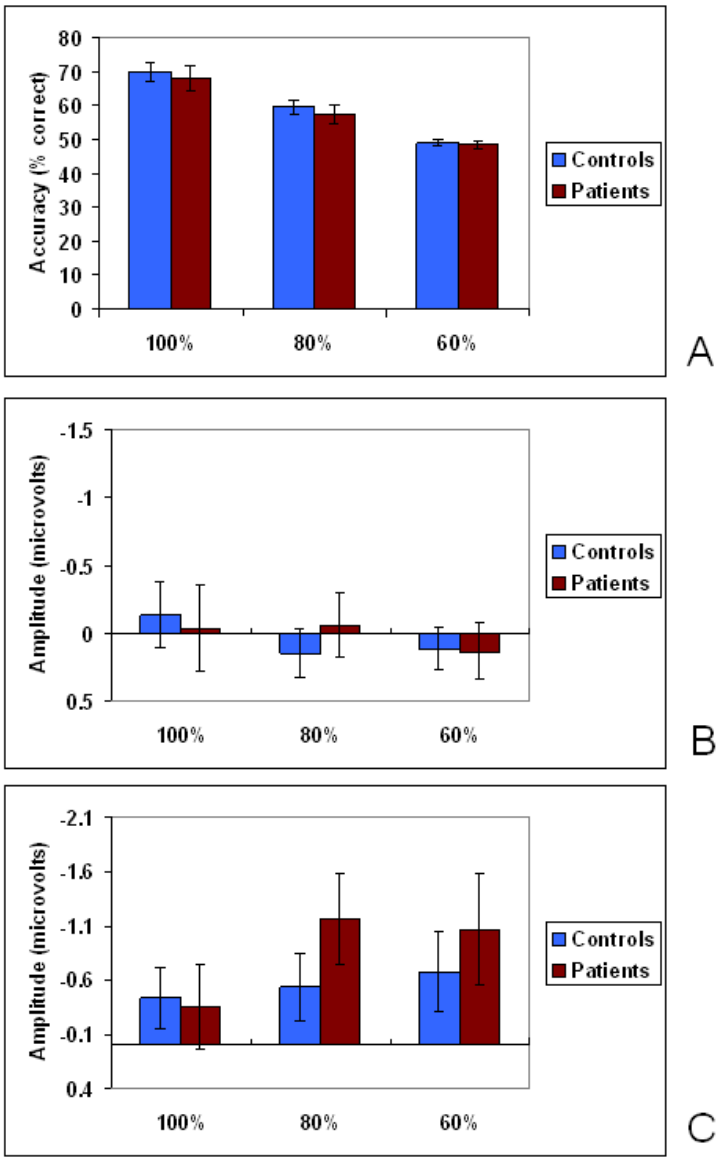


Figure 3-12. A) Mean accuracy in each condition. B) Mean amplitude of the ERN-CRN difference wave in each condition. C) Mean amplitude of the non-reward FRN minus reward FRN difference wave in each condition. Error bars represent SEM.

CHAPTER 4
GENERAL DISCUSSION

Review and Conclusions

These two experiments compared error detection and feedback processing abilities in younger versus older adults, and in patients with Parkinson's disease versus age-matched controls.

The first aim of this project was to provide support for predictions from the reinforcement learning theory by examining the effects of manipulation of feedback probability and valence on ERP reflections of error detection and feedback processing in a sample of healthy young adults. As predicted, the ERN was larger than the CRN and increased with increasing validity, reflecting the idea that awareness of error commission is greatest under conditions in which response selection is the least ambiguous. Also in line with predictions, the mean amplitude of the ERN and the ERN-CRN difference wave increased over time, particularly in the least ambiguous condition, providing support for the idea that as internal representations of correct and incorrect responses become more fixed with learning, greater conflict occurs when erroneous responses are made. Notably, the increase in the difference wave was due, in part, to the fact that the CRN decreased as the ERN increased over time. This finding is important with regard to questions about differential processing of positive and negative valence information and lends support to recent recommendations for the incorporation of a role for correct-response activity in reinforcement learning and theories of the ERN and FRN (Eppinger et al., 2008; Pietschmann et al., 2008).

Predictions from the theory were also supported by analyses of the feedback-related activity. As expected, the non-reward related FRN was larger than the reward-

related FRN. In addition, mean amplitudes of the difference wave decreased with increasing feedback validity, reflecting the idea that reliance on feedback is greatest in the most ambiguous situations (Eppinger et al., 2008; Holroyd & Coles, 2002). Learning-related effects on the difference waves were also consistent with the theory such that mean amplitudes generally decreased over time in both learning conditions, providing evidence that reliance on external feedback decreases with learning as representations of correct responses are internalized (Holroyd & Coles, 2002).

When feedback-related components were examined separately for positive and negative activity, it appeared that predictions from the reinforcement learning theory with respect to non-reward related activity were not supported. Although the theory did not provide predictions for reward-related activity, the reward-related FRN increased with increasing feedback validity and increased over time, in direct contrast to expectations for non-reward related activity. Each of these results has been reported previously; however, they have not been reported simultaneously (Eppinger et al., 2008; Nieuwenhuis et al., 2002). These results also support the role for positive-feedback processing in reinforcement learning and, when combined with the results from analysis of response-locked activity, may suggest that reactivity to positive feedback increases over time as response certainty increases in healthy young adults.

The second aim of the project was to examine the impact of aging and Parkinson's disease on reinforcement learning (i.e., error and feedback processing), with a primary focus on how aging and Parkinson's disease differentially affect processing of negative versus positive feedback. Broadly, dysfunction in the reinforcement learning system in both groups was most clear when examining error-related activity. For the older adult

controls, ERN/CRN mean amplitudes were not altered by validity condition and changed very little over the course of the entire experiment, consistent with previous research (Pietschmann et al., 2008). The only exception to this observation was relatively intact correct-response activity in the least ambiguous condition at the end of the experiment. Interestingly, PD patients tended to exhibit greater amplitudes of response-related activity compared to older adult controls, and amplitudes changed appropriately with learning. Group differences in feedback processing were not detected, contrary to expectations. These results were interpreted within the context of reinforcement learning theory and discussed in relation to medication- and disease-related effects on brain structures underlying the processing of positive and negative information.

An exploratory third aim of this dissertation project was to examine relationships between feedback processing and other aspects of cognitive as well as emotional functioning. In Experiment 1, young and older adults did not demonstrate relationships between measures of executive function and feedback processing. Instead, the most meaningful relationship was between intact feedback processing and attention. In Experiment 2, when the PD patients and older controls were combined, expected relationships emerged between feedback processing and performance on tests of executive function, particularly problem-solving using feedback and cognitive flexibility. Interestingly, better performance on a language measure was associated with intact feedback processing in both experiments. An unexpected relationship between better working memory and smaller amplitudes of the difference wave was found in Experiment 2 and interpreted as reflecting an “overdosing” effect of dopaminergic medication on working memory. Within the PD group, smaller feedback-related

amplitudes were related to greater disease severity. Unfortunately, we did not find expected relationships between feedback processing and emotional symptoms (e.g., apathy), likely due to the small sample size, as well as to a small range of scores on these measures. The inclusion of patients in more advanced stages of disease would be necessary for required levels of apathy. The identification of relationships between feedback processing and psychological functioning could be important for designing interventions and should be explored in future research.

Strengths and Limitations

Unfortunately, recruitment difficulties faced throughout this project not only led to small sample size and decreased power, they also contributed to lack of generalizability of results to the larger population since members of all groups tended to be highly educated.

Moreover, although it was likely necessary to modify this paradigm for use in a population who were expected to suffer from increased fatigability, this adaptation may have clouded interpretation of results. For example, reducing the number of trials may have prevented the development of larger ERNs over time; in addition, reducing the number of bins may have reduced our power to detect learning changes in the latter part of the experiment; and the use of a 60% condition (rather than 50%) may have blurred differences between this “non-learning” condition and the more ambiguous (i.e. 80%) learning condition. In addition, as is often the case when conducting research in aging and Parkinson’s disease, in the former case “healthy” is often loosely defined, and in the latter case, there is a large degree of variability in symptom presentation, which likely added to noise in the data and difficulty finding differences between groups.

A methodological strength of this study was its use of a paradigm that manipulated not only feedback validity, but also valence, which allowed for the testing of predictions from the reinforcement learning theory as well as investigation of distinct mechanisms underlying the processing of reward and punishment. Another strength of the study was its use of an adaptive response deadline in an attempt to equate the number of trials utilized by participants for learning. Although it is possible that the use of the adaptive deadline artificially reduced the amplitude of the ERN component in younger adults by reducing time pressure, it allowed us to flexibly use the same paradigm in two groups for whom cognitive and/or motor slowing were likely to negatively impact performance, thereby potentially artificially decreasing their ERN amplitudes. Finally, this study combined methodology from the disciplines of neuroscience and neuropsychology in an attempt to elucidate behavioral processes broadly (and vaguely) termed "executive functions." ERPs were used to distinguish error detection and feedback processing components of "reinforcement learning" in a manner often indistinguishable using paper-and-pencil based tests alone. Although ERPs have been used in previous studies testing predictions from the reinforcement learning theory, those studies did not attempt to correlate electrophysiological reflections of processes mediated by frontal regions of the brain with more commonly used neuropsychological measures of similar functions. Such correlations may be important when making clinical interpretations of patients' functional capabilities.

Implications and Future Directions

The broad goal of this project was to use EEG to examine the brain mechanisms underlying reinforcement learning and to better understand the way in which "healthy" aging and Parkinson's disease affect error and feedback processing. The results of

these two experiments have provided evidence that correct-response activity plays an important role in reinforcement learning theory, and disruption of frontal-striatal circuitry underlying reinforcement learning causes differential impairments not only with respect to valence (i.e., correct versus error response, positive versus negative feedback), but also with respect to component abilities (i.e., error and feedback processing) contributing to learning.

Because of the apparent complexity underlying these systems, further research is needed in order to clarify the neurological and psychological factors that contribute to impairments in reinforcement learning. Ideally, such research should employ tightly controlled experiments conducted with a large sample of patients closely matched on disease and demographic variables as well as medication regimens. A comparison of patients in different stages of disease (e.g., mild to moderate to severe) might allow for the discovery of informative relationships among demographic, disease, psychological and cognitive variables. Elaboration of comparisons currently being conducted on differential effects of particular treatments for Parkinson's disease (including surgical deep brain stimulation) on reinforcement learning could also prove useful for individualized treatment planning. Most importantly, continued research on the effects of valence on reinforcement learning in these populations will be crucial, not only for improved characterization of the functional significance of these ERP components, but also for determining how impairments in reinforcement learning might be improved, perhaps by using behavioral interventions focused on use of positive environmental feedback. In light of recent reports that decision-making impairments contribute to reduced quality of life in patients with Parkinson's disease, examination of the real-world

functional implications of impaired reinforcement learning in everyday activities would be useful for aiding in the design of such interventions (Delazer et al., 2009).

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BIOGRAPHICAL SKETCH

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