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Error Related Negativity in Parkinson's Disease: A Test of the Validity of MesencephalicDopamine Contributions to ERN

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ABSTRACT

A model proposed by Holroyd and Coles (2002) stating that error related negativity (ERN) is caused by a decrease in mesencephalic dopamine output to the ACC was tested. A group of individuals with Parkinson's disease (N = 16) and an age and education matched group free from neurological disorder (N = 16) completed a card guessing task where the magnitude of monetary penalties and rewards for incorrect and correct answers was varied by block. Individuals with Parkinson's disease were tested after an overnight washout from dopamingeric medications.

The amplitude of the mid-frontal negativity elicited by feedback was analyzed with spatial and temporal principal components analyses. Dipole source analyses were also performed. Analyses revealed no significant differences in the mid-frontal negativity amplitude between the two groups. In addition, the magnitude of consequence and the validity of response had no significant effects on fERN amplitude although there was a trend for higher magnitude consequences to be associated with larger fERN amplitude. Dipole analyses indicated the source of the mid-frontal negativity fell into the cingulate, specifically the cingulate gyrus. The results suggest that the mid-frontal negativity elicited by feedback indicating an error was made remains intact in individuals

with Parkinson's disease. This does not support predictions made by Holroyd and Coles' model in regard to this group unless disruptions to the system that produces the fERN do not occur until later stages in the disease. An additional finding was a late positive potential for the error trials which began approximately 450 milliseconds after feedback and continued throughout the epoch. The ramifications of this wave are discussed.

Introduction

The purpose of the present study is to test a proposal by Holroyd and Coles (2002) that attempts to explain the function of a component of brain electrical activity that occurs when an error is committed. This activity, commonly referred to as error related negativity (ERN), may have significant ramifications on how organisms alter behavior in order to maintain optimal functioning in the face of constantly shifting environmental contingencies. However, before discussing the procedures that will be used to test some of the assumptions of this model, a comprehensive review of the function and characteristics of ERN and other pertinent topics will be presented.

Error Processing and Subsequent Behavior Change

Cognitive scientists have been studying behavior and brain activity related to performance on various cognitive tasks. Recently, there has been a growing interest in behavior and neural systems associated with error processing, presumably because the ability to properly adjust behavior when an error is made is crucial for optimal performance and adaptation to changing environmental contingencies. Rabbit (1966) conducted one of the first empirical studies focusing on error commission. While completing reaction time tasks, participants' reaction times were significantly shorter on trials where errors were made. In addition, a novel observation of this study was that trials following errors were associated with significantly longer reaction times. Rabbit hypothesized that after committing an error, participants responded more slowly, presumably in order to decrease the probability of future errors.

More recently, there has been an increased attention to the electrical brain activity elicited when errors are committed. Primarily, this research is concerned with various components of neural electrical activity and subsequent behavior changes that occur after the presentation of information indicating an erroneous response was made. Before reviewing this research, a brief description of the techniques used to quantify aspects of this brain electrical activity is provided.

Event Related Potentials

Event related potentials (ERP's) are small voltage fluctuations resulting from neural activity, presumably elicited by mental activity or an outside event (Fisch, 1999). This activity is reflective of the collective effect of multiple post synaptic potentials on the extracellular environment. It is not due to the firing of individuals neurons as changes in voltage inside the cell are too weak and too brief to be measured from non-invasive procedures. It is thought that the activity most likely to cause the voltage changes in the extracellular environment that are readily measured are due to the summated activity of multiple neurons firing in synchrony in response to some external or internal event that elicits mental activity (Fisch).

The voltage fluctuations can be measured from sensors placed on the scalp. Deflections in the resulting reading, commonly referred to as components, can be identified. Unfortunately, ERP components that are of interest are often much smaller than other unrelated voltage fluctuations that are picked up in the recording from the scalp (Fisch, 1999). Thus, these components of interest can not be readily observed from the unprocessed EEG record. One popular method of extracting the ERP components from ongoing activity is by averaging the signal across multiple trials of some form of

repeated manipulation. During this procedure, small portions of the record (segments) are oriented or locked to a repeated event such as the presentation of a stimulus (stimulus locked) or an elicited response (response locked). Events that are unrelated in time to this event will take place at different times during the segment while the activity elicited by the repeated event that the timing of the segments are locked to should take place at approximately the same time within each segment. Multiple segments are averaged together so that the activity that is unrelated to the event the segment is locked to will occur at different times in the segment. Because of this, unrelated activity will average out such that their summated activity will approach zero as the number of segments that are averaged is increased. In contrast, a voltage deflection related to the event the segment is locked to occur at the same time in each segment. Since the voltage deflection occurs at the same time in each segment, it will not average out to zero when multiple segments are averaged together.

A number of ERP components typically appear in response to stimuli presented in certain manners across studies and have thus been identified. ERP components may be distinguished on the basis of whether they represent mere sensory processing or further cognitive processing of an event (Coles & Rugg, 1995). Various researchers within the field have posited that components that take place100 milliseconds or less after the eliciting event most often represent the former while processes that are delayed by more than 100 milliseconds typically represent the later. ERP components are usually defined based on polarity (positive or negative), timing (delay in milliseconds the waveform appears after the eliciting event), scalp topography, and response to experimental

manipulations. At times, ERP components of similar polarity and duration are also identified by letter which specifies the temporal order in which they occur.

Among the primary advantages of using an electroencephalogram (EEG) is that it is able to take hundreds of readings each second. Thus, this method provides a technique with excellent temporal resolution. Specifically, EEG can detect changes in brain electrical activity over a very small period of time. However, the method is prone to poor spatial resolution because there is not a perfect correspondence to the scalp distribution and the location of the source of the electrical activity. In fact, because the scalp distribution represents the collective activity of any number of possible neural generators active at a given time, there are multiple possible combinations of activity from neural generators that may account for the same scalp distribution.

Error Related Negativity

Two research labs nearly simultaneously reported that during error trials, a negative deflection wave commonly referred to as error related negativity (ERN) occurs. The timing of and nomenclature of the ERN varies according to whether or not the participant has immediate access to information regarding the validity of their response. The first studies to report ERN used tasks where the validity of response was immediately known. In this case, the ERN, begins almost immediately and peaks approximately 80 milliseconds later (Falkenstein, 1991; Gehring et al., 1990; 1993). Several years later Miltner and colleagues (1997) became the first to demonstrate the ERN on errors during a task where the validity of response was not immediately known. In this case, the negativity associated with the error, commonly referred to as feedback related negativity (FRN) (Miltner et al., 1997) or feedback error related negativity

(fERN) (Holroyd, Hajcak, & Larsen, 2006) occurs approximately 280 milliseconds after a participant receives information that indicates their action was in some way an error (Miltner et al., 1997). Subsequently, the fERN was observed during the performance of a variety of tasks where participants do not know the validity of their response until they are told. Examples include time estimation tasks (Donkers, Nieuwenhuis, & Boxtel, 2005; Holroyd, Hajcak, & Larsen, 2006; Miltner et al.), guessing tasks (Hajcak, Moser, Holroyd, & Simons, 2006; Holroyd et al., 2006; Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003; Ruchsow, Grothe, Spitzer, & Kiefer, 2002; Yasuda, Sato, Miyawaki, Kumano, & Kuboki, 2004), gambling or strategy tasks (Cohen, Elger, & Ranganath, 2006; Cohen & Ranganath, 2007; Gehring & Willoughby, 2002; Gehring & Willoughby, 2004; Hewig et al., 2004; Nieuwenhuis, Yeung, Holroyd, Schurger, & Cohen, 2004), tasks where participants learn stimulus response mapping (Holroyd & Coles, 2002) or even during passive designs where participants makes no action but merely view stimuli indicating that monetary compensation for participation will be decreased (Donkers et al.; Potts, Martin, Burton, & Montague, 2006). The fERN is generally larger for feedback indicating an error or negative outcome than feedback indicating correct responses although exceptions to this have been reported (Donkers et al.; Miltner et al.). Additionally, one study noted that feedback indicating neither a monetary loss or gain (neutral outcome) was followed by fERN that was equal in size to feedback indicating a monetary loss (Holroyd et al) leading to the conclusion that fERN may indicate whether or not a goal has been satisfied rather than whether an error has occurred.

Both ERN and fERN are distributed over the frontal-central regions of the scalp. There is strong consensus that both types of negativity originate in the rostal portion of

the anterior cingulate cortex (ACC). Studies exploring the ERN using dipole source localization analyses (Dehaene, Posner, & Tucker, 1994; Gehring, Himle & Nisenson, 2000; Hewig et al., 2007; Holroyd, Dien, & Coles, 1998) or fMRI (Carter et al., 1998; Laurens, Ngan, Bates, Kiehl, & Liddle, 2003; Miltner et al; Ruchsow et al., 2002; Ullsperger & von Cramon, 2001) support this conclusion. However, several studies have reported some divergence between ERN and fERN in terms of scalp topography and source localization. Specifically, these studies indicated that the fERN is more right lateralized at the frontal sites than the response ERN (Donkers et al., 2005; Gehring & Willoughby, 2004; Nieuwenhuis et al., 2001). In terms of dipole source localization two studies comparing ERN and fERN in the same participants indicated that fERN is more posterior than the negativity generated during a response ERN (Badgaiyan & Posner, 1998; Muller, Moller, Rodriquez-Fornells & Munte, 2005). Another subtle dissimilarity between ERN and fERN is that negativity for fERN is larger for trials where feedback indicates a correct response (Donkers et al.).

Characteristics of ERN

Considerable research has been performed to ascertain the function and characteristics of the ERN. These efforts have revealed that the ERN is independent of sensory modality in that it is generated after errors on tasks where the stimulus is presented orally (Falkenstein, Hoorman, & Hohnsbein, 2001) or responses are made orally (Ganushchak & Schiller, 2006; Masaki, Tanaka, Takasawa & Yamazaki, 2001) as well as visually. Thus, the ERN is generated by a system that is generalized to stimuli of multiple senses suggesting mediation by secondary structures that process information after it is integrated from its sensory specific components (Falkenstein et al.). In

addition, ERN is not specific to errors committed by certain areas of the body in that it is generated when responses are made with the feet (Gehring & Fencsik, 2001) or with eye gaze (Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001) as well as with hands or fingers. The ERN can occur even when participants do not indicate conscious awareness of error (Endrass et al., 2007; Nieuwenhuis et al., 2001) but it is not present when errors are intentional (Stemmer, Witzke, & Schonle, 2001). There is strong empirical evidence that the ERN amplitude becomes smaller with age. This effect has been demonstrated on a switching task (Themanson, Hillman, & Curtain, 2006) a picture naming task (Mathalon et al., 2003) and a Stroop task (West, 2004) although this effect was attenuated for older participants reporting they are highly physically active (Themanson et al., 2006).

The function of ERN

Although research regarding the characteristics of the ERN has yielded considerable information, there are still differences of opinion in terms of the mechanism or mechanisms by which the ERN is generated. One of the earliest proposals was articulated by Falkenstein et al. (1990) where they stated that the ERN is elicited when a neural representation of the correct response and a representation of the actual response do not match. Gehring and colleagues (1993) stated similar speculations by pointing out their data were consistent with models postulating the existence of a system used for error detection and compensation. These authors further state that since the ERN is generated almost immediately, it is unlikely that the system involved in ERN production uses sensory or propioceptive information. Instead, the expediency of the onset is consistent with models that suggest the existence of an internal error monitoring system with access

to a neural representation of the correct response and that ERN is generated when there is a discrepancy between the current response and a neural motor record of the correct response. A second theory describing the function of ERN is termed the response conflict theory and has emerged because of observations that ERN generation is not limited to the commission of an error (Carter et al., 1998). This theory states that the ERN is generated when the ACC receives conflicting input from different brain structures.

ERN as an error detection/compensation mechanism. Support for theories endorsing that ERN is generated by a discrepancy between the efference copy of a response and the actual response may be derived from studies that measure ERN amplitude and the magnitude of error. If the ERN is caused by a signal that indicates a mismatch between a response and the efference copy of the correct response, a larger discrepancy between the response and the correct response might result in larger ERN amplitudes if ERN is graded in regard to magnitude of error. This hypothesis may be tested in a 4-choice reaction time test where the four choices are represented with the index and middle fingers of both the left and right hands. An error involving the wrong hand would produce a larger discrepancy between the correct response and an error response than an error involving the wrong finger. In addition, responding with the wrong hand and finger represents an error of the highest magnitude (Falkenstein et al., 2000). The ERN appears to be associated with magnitude of error such that "wrong hand" errors yield larger ERN amplitudes than "wrong finger" errors (Bernstein, Scheffers, & Coles 1995; Falkenstein, Hohnsbein & Hoorman, 1996) and errors involving the wrong hand and finger are associated with larger ERN amplitudes than

"wrong finger only" or "wrong hand only" errors (Falkenstein et al., 1996). This result was not evident, however, during one study where the procedures required participants to respond with their hands and feet (Gehring & Fencsik, 2001). Instead, errors where participants responded with the wrong hand and foot were associated with smaller ERN amplitudes than errors trials involving either the incorrect side or incorrect limb only.

Squeeze force used to initiate the incorrect response may also be conceptualized as a representation of the magnitude of error and thus, squeeze force is expected to be positively correlated with the amplitude of ERN. However, studies that have measured the squeeze force of error responses have yielded inconsistent results. ERN amplitude and squeeze force of the incorrect response demonstrated a positive correlation on a 4-choice go/no-go reaction time task (Scheffers et al., 1996). However, ERN amplitude and squeeze force of the incorrect response were negatively correlated on the Eriksen's Flanker Test (Gehring et al., 1993).

A number of established characteristics of ERN provide the strongest support for error detection/compensation theories. First, although there is often a negative deflection observed during correct trials (CRN), the amplitude of the negative deflection during an ERN is consistently larger than the negative deflection during a CRN. Proponents of the response competition model argue that errors are associated with a higher level of response competition (Carter et al., 1998) but empirical evidence counteracts this assumption (Luu et al., 2000). Consistent with the idea that error detection is a component of ERN, studies have demonstrated that larger ERN amplitudes are correlated with smaller reaction time differences between error trials and correct responses, reflecting a more controlled response strategy (Pailing, Segalowitz, Dywan & Davies,

2002). In addition, ERN amplitudes on a given trial are positively correlated with reaction time, the probability of initiating a correct response immediately after an error (Gehring et al., 1993) and the probability of responding correctly on the trial immediately following an error (Falkenstein, Hoormann, & Hohnsbein, 2001). Gehring and colleagues noted that errors on trials where experimenters stress the importance of accuracy are associated with larger ERN amplitudes than error on trials where speed is emphasized. Subsequent studies confirmed this observation in a flankers task using shapes (Morris, Yee, & Nuechterlein, 2006) and a verbal go/no go task (Ganushchak & Schiller, 2006). Gehring and colleagues stated that this observation provides support for error detection/compensation theories because this system should be more active when it is increasingly important to avoid error commission.

It is important to note that some authors have hypothesized that ERN represents only part of the error detection/compensation process. For example, ERN may be the result of the comparison between the actual response and efferance copy only (Falkenstein, Hoorman, Christ & Hohnsbein, 2000) or it may represent an error detection component specifically (Scheffers et al., 1996). Perhaps the most damaging research to response conflict theory are the studies described above that report ERN is elicited by feedback indicating an error was committed (Holroyd & Coles, 2002; Miltner et al., 1997; Ruchsow et al., 2002). Since feedback occurs after the response is made, the ERN generated occurs in absence of response conflict.

Scheffer and colleagues provide data supporting the notion that the ERN is a function of error detection and not error compensation by demonstrating that that ERN is generated on errors during "go/no-go" tasks. On these tasks, a stimulus indicates whether

the participant is instructed to either initiate a response (go trial) or simply do nothing (no-go trial). For an error on a "no go trial", the correct response is to simply do nothing. Thus, there is no action that will correct an error on a “no go trial.” Despite the absence of a method of error compensation, the ERN is still present following a "no go trial" error (Scheffers et al., 1996). Therefore, ERN is present even when error compensation is not possible. However, ERN may represent a compensatory mechanism that prepares the participant to respond correctly on future trials. In support of this argument is the observation by Gehring and colleagues (1993) that larger ERN amplitudes are associated with behavioral changes consistent with error related compensatory behavior.

ERN as response competition. As stated above, a proposed mechanism for the function of ERN is that ERN is generated by response competition rather than the commission of an error. Specifically, this proposal states that ERN is generated when there are conflicting messages sent to the ACC (Carter et al., 1998). Authors propose that this theory is supported by demonstrations that correct responses during conditions defined by authors as having high conflict will result in increased ACC activity (Carter et al.) and ERN generation (Dikman & Allan, 2000; Falkenstein et al., 2000; Gehring & Knight, 2000; Luu et al., 2000; Vidal, Hasbroucq, Grapperon & Bonnet, 2000).

Further support is derived for the response conflict theory by studies that compare ERN amplitudes that result from errors on tasks where either compatible or conflicting information is presented. On tasks where conflicting information that elicits different responses is presented, a greater amount of response competition should occur. Thus, according to the response competition model, tasks using stimuli with conflicting information will be associated with larger ERN amplitudes. Consistent with this notion,

an fMRI study demonstrated increased ACC activity during incongruent trials on a modified Eriksen's Flanker Task (van Veen, Cohen, Botvinick, Stenger & Carter, 2001). Likewise larger ERN amplitudes are associated with errors on trials with incompatible information for the Eriksen's Flanker Task than with errors during trials where compatible information is presented (van Veen & Carter, 2002).

Investigators have used lateralized readiness potentials (LRP) as an indication of response competition. LRP is defined as the difference between the EEG over the contralateral motor cortex minus the EEG over the ipsilateral motor cortex (Luu, Flaisch, & Tucker, 2000) of the limb that makes a response. Some researchers propose that less asymmetry during tasks where two response choices are represented by movement in either the left or right hands indicate simultaneous activation of both responses, resulting in more response competition.

Some studies measuring LRP have yielded results that support the response conflict model while other studies and refute it. Support for the response conflict model was derived in one EEG study where participants where asked to correct errors that were made on an Eriksen's Flankers Task. Researchers measured temporal overlap between electrical activity associated with the incorrect response and subsequent movement to correct the response with LRP's. Authors state that a longer period of overlap is indicative of greater response competition because motor cortices of each hemisphere are relaying competing motor commands. As predicted, longer temporal overlap was associated with larger ERN amplitudes (Rodriguez-Fornells, Kurzbuch, & Munte, 2002). However, in contrast to the response competition model, one EEG study measured LRP activity associated with errors caused from responding later than a set criteria and errors

caused from responding incorrectly. During correct responses that were considered errors because they were not quick enough, both LRP activity and ERN amplitude were positively correlated with the severity of response latency. This supports the response competition model because ERN amplitude was higher in conditions of increased response competition. However, errors caused by an incorrect response were associated with the largest amount of LRP asymmetry, indicating little response competition. Incorrect responses were also associated with the largest ERN amplitudes. This refutes predictions made by the response competition model because the largest ERN amplitudes were associated with a condition where very little response competition occurs (Luu, et al., 2000).

Hybrid ERN models. Several authors have addressed the possibility that ERN may reflect both response competition and error monitoring. Ullsperger and von Cramon (2001) used fMRI to measure brain activity in participants as they completed a modified Eriksen flanker task. Correct trials involving incompatible information were associated with significantly greater activity in the mesial superior frontal gyrus, the supplementary motor cortex, the posterior cingulate cortex and the anterior cingulate sulcus when compared to correct trials with compatible information. Authors state that this comparison allows an analysis of structures that contribute to the response competition portion of the ERN. The activity in the anterior insula, intraparietal sulcus, and rostal portion of the ACC was significantly greater after commission of an error during incompatible incorrect trials than incompatible trials that were responded to correctly. The authors state that this comparison denotes activity involved in error monitoring. They conclude that both response competition and error monitoring processes contribute

to the amplitude of the ERN but that these elements are separable and distinct from each other.

Swick & Turken (2002) used ERP data to measure activity in a participant with a lesion in the rostal portion of the ACC to determine whether they would display typical components of the ERN associated with response competition and error monitoring. The participant demonstrated larger ERN amplitudes during trials with a higher level of response competition but did not demonstrate an enhanced negativity during error trials. Authors conclude that this provides evidence for a dissociation between ERN amplitude associated with response competition, which is hypothesized to be located in the caudal portion of the ACC and the error monitoring portion of the ERN which is theoretically located in the rostal ACC.

Background for Holroyd and Coles' Model Proposing a Function of ERN

Holroyd and Coles (2002) have proposed a merger between the error detection/compensation model of ERN and literature regarding a learning algorithm called the method of temporal differences. Specifically, this hypothesis states that the ACC generates an ERN wave when the basal ganglia decreases dopamine output to the ACC when the consequence of an action is worse than the expected consequence. The discrepancy between expected outcome and actual outcome is termed a temporal difference error. Holroyd and Coles propose that temporal difference errors are relayed to the ACC through mesencephalic dopamine activity. In order to fully appreciate Holroyd and Cole's model, a basic knowledge of the mesencephalic dopamine system and the method of temporal differences model is necessary. Therefore, the following two sections will provide a brief summary of the dopaminergic pathways and their primary

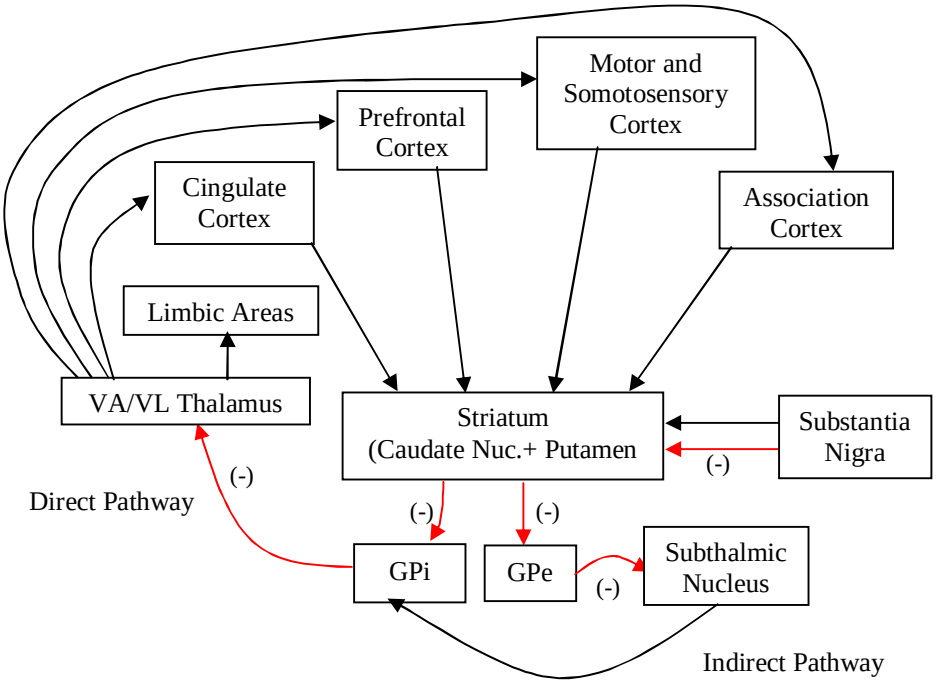
target areas along with a description of the method of temporal differences model and supporting research.

Mesencephalic dopamine system. The majority of the dopaminergic cell bodies of the mesencephalon are located in either the substantia nigra or the adjacent ventral tegmentum (Yelnik, 2002). The substantia nigra is comprised of two parts, the pars compacta and the pars reticula. Dopamine metabolism within the substantia nigra produces melatonin, a substance responsible for the pigmented color of this structure. The dopamine neurons of the substantia nigra project to the striatum which consists of the caudate nucleus and putamen. Additional dopamine projections provide dopamine innervation to the globus pallidus but they are much fewer in number than the projections to the striatum.

The striatum, globus pallidus and subthalamic nucleus together form the basal ganglia (Yelnik, 2002). The structures of the basal ganglia receive input from a variety of cortical and subcortical structures. The ventral portion of the striatum receives input from the amygdala, cingulate cortex, prefrontal cortex, and ventral tegmentum. Information from the motor cortex and somatosensory cortex synapse on the putamen while the caudate nuclei receive information from the association areas of the frontal, parietal, temporal and occipital cortices (Yelnik).

Information is projected to the efferent structures of the basal ganglia through a direct pathway and an indirect pathway (see figure 1). The direct pathway starts with an inhibitory projection from the striatum to the internal division of the globus pallidus (GPi). The GPi provides inhibitory input to the ventral anterior and ventral lateral nuclei of the thalamus (VA/VL thalamus) which in turn projects to the cortex (Albin, Young &

Figure 1. The basal ganglia influences cognitive functioning through a balance of activity of the indirect and direct pathways of three cortico-cortical loops.



Penney, 1989). Information is also relayed through an indirect pathway that originates in the striatum and extends to the external division of the globus pallidus (GPe). From the GPe, information is directed to the subthalamic nucleus and then back to the Gpi.

The VA/VL thalamus projects to a vast number of cortical structures including the premotor, motor, supplementary motor, prefrontal, parietal, temporal, and anterior cingulate cortices as well as the entorhinal cortex and the insula (Berger, Gaspar & Verney, 1991). Cortical projections synapse back to areas of the striatum in a manner outlined above and form three parallel closed cortico-cortical loops that give the basal ganglia the opportunity to influence many cognitive activities. Activation of the direct pathway provides excitatory input to the projection from the VA/VL thalamus to the

cortex while the indirect pathway results in inhibitory input. Efficient motor control is achieved through a balance in activity of these two pathways (Yelnik, 2002).

The ventral tegmentum is the origin of two major dopaminergic projections referred to as the mesolimbic and mesocortical pathways (Ungerstedt, 1971). The ventral tegmentum receives most of its input from limbic structures including the septum, hypothalamus, and amygdala and other areas including the orbitofrontal cortex, the nucleus of the diagonal band, and lateral preoptic nucleus (Domesick, 1988). Efferent projections of the mesolimbic system include the amygdala, septum, bed nucleus of the stria terminalis, and nucleus accumbens. The projection to the nucleus accumbens has gained special attention in that it is thought to play a role in instrumental learning or the signaling of reward. Efferent projections that comprise the mesocortical system include the anterior cingulate cortex and the frontal cortex (Domesick).

Temporal difference error. The method of temporal differences model is an algorithm meant to describe and explain the mechanics of reinforcement learning (Sutton, 1988). This algorithm has roots within the well known Rescorla Wagner model (1972) that states an organism learns about a conditioned stimulus when, through pairing with an unconditioned stimulus, the consequence or outcome associated with the conditioned stimulus is either more positive or less positive than expected.

Consistent with the Rescorla Wagner model, the method of temporal differences model predicts that learning occurs when an outcome differs from what is expected and not because of the presentation of an unconditioned stimulus or a reward. However, the method of temporal differences algorithm adds to the Rescorla Wagner model by taking into account the temporal relationship between stimuli that signal a reward and the

presentation of reward. Specifically, the method of temporal differences model states that with repeated pairing of environmental stimuli and unconditioned stimuli or reinforcers, the organism is able to predict the presentation of reward as it learns the temporal relationship between signaling stimuli and reward delivery. After the temporal relationship between signaling stimuli and reward is learned, the organism divides the time period between the signaling stimuli and reward presentation into equal segments and assigns a value of expected reward to each time segment. This expectation value gradually increases during the time between the presentation of the signaling stimulus and the presentation the reward.

A discrepancy between expected reward and the actual reward that is presented is termed a temporal difference error. Temporal difference errors occur when an outcome is better than expected such as when a reward is presented sooner than predicted or when outcomes that are worse than expected such as the absence of an expected reward or an unexpected delay in the presentation of a reward. Changes in behavior are most likely to be necessary when temporal difference errors occur (Sutton, 1988).

Another caveat of the method of temporal differences model is that after the temporal relationship between signaling stimuli and reward is learned, the organism can alter its behavioral repertoire when a signaling stimulus is presented in order to maximize the probability of future presentation of reward. By doing this, the organism responds to the signaling stimulus instead of merely responding to the outcome itself. Thus, responding is pushed backwards in time as the organism learns to anticipate an unconditioned stimulus or reward before it is presented (Sutton, 1988).

Sutton's (1988) temporal difference theory states that temporal difference errors are detected by a neural structure termed "the critic" that continuously compares expected reward with actual consequences of action. If the critic structure detects a temporal difference error, it relays the information to another structure termed "the actor" which uses the information to adjust ongoing behavior in order to maximize the probability of obtaining a predicted reward.

A number of studies have supported assumptions made by the temporal difference theory by observing that animals (Sutton & Barto, 1990) demonstrate learning behavior corresponding to predictions by the algorithm. Temporal difference theory has gained in popularity with the discovery that its predictions regarding neural activity during operant learning are similar to the firing rate of dopamine neurons (Schultz, 1998; Suri & Schultz, 1998; 1999) or activity of structures that are part of the mesencephalic dopamine system (Berns, McClure, Pagnoni, & Montague, 2001; O'Deherty, Dayan, Riston, Critchley & Dolan, 2003) The timing of dopamine neuron firing has lead to a substantial revision of theories regarding the role of dopamine in reward. Originally, researchers proposed that dopamine firing increases in response to the subjective pleasure associated with the presentation of reward. Numerous animal studies that reported increased dopamine firing during the presentation of reward supported this hypothesis (Hyland, Reynolds, Hay, Perk & Miller, 2002; Ljungberg et al., 1992; Nishino, Ono, Muramoto, Fukuda & Sasaki, 1987). In addition, animals will engage in behaviors that result in electrical stimulation via an electrode to various areas of the brain (Olds & Milner, 1954). Increases in self-stimulation are most frequent when electrodes are attached to important regions along the dopamine tracts such as the substantia nigra, ventral tegmentum, (Zacharko et al., 1990)

medial forebrain bundle (Yavich & Tiihonen, 2000; Zacharko et al.) and nucleus accumbens (Garris et al., 1999; Yavich & Tiihonen; Zacharko et al.).

Studies that have observed the pattern of dopamine firing throughout learning via operant conditioning confirmed that dopamine firing increases during presentation of reward for early learning trials (Suri & Schultz, 1998). However, in a study by Ljungberg and colleagues (1992), monkeys that were conditioned to reach for a lever in order to receive a drop of juice when a light is turned on demonstrated increased dopamine activity upon presentation of the light and not the reward itself after the association between the light and reward was established. Thus, when an organism learns that certain stimuli are associated with the future presentation of a reward, the timing of increased dopamine firing moves back such that the increase corresponds to the presentation of signaling stimuli and not the reward itself. Schutz, Apicella and Ljungberg (1993) obtained similar results in an experiment where primates completed a two choice reaction time test. In this study, a green light above each choice signaled the correct solution. Increases in dopamine cell firing were observed during the presentation of a juice reward during early trials but after a relationship between the signal light and reward was established, the increased firing occurred when the signal light was turned on.

O'Doherty and colleagues (2003) used fMRI to measure activity during a classical conditioning procedure to determine whether the pattern of activity matched predictions made by Sutton's model. One of three visual displays was paired with a pleasant sweet taste, a neutral taste, or a display that meant that the pleasant taste would not be presented. During early trials, the presentation of the pleasant taste elicited increased activity in the ventral striatum and the prefrontal cortex. However, after

conditioning was established this increased activity occurred during the presentation of the visual displays that signaled the future presentation of the pleasant tastes.

Mesencephalic dopamine activity is also associated with the occurrence of temporal difference errors. Specifically, a temporal difference error that results from a reward that is presented sooner than predicted is associated with increased dopamine neuronal firing (Hollerman & Schultz, 1998; Suri & Schultz, 1999). Likewise, temporal difference errors corresponding to the omission of an expected reward are associated with decreases in dopamine neuron firing (Montague, Dayan, & Sejnowski, 1996; Suri & Schultz, 1999). For example, Suri and Schultz trained primates to make a reaching movement with their arm in response to either a visual or audio stimulus in order to receive a few drops of apple juice. A constant time delay between reaching movement and reward delivery was implemented. During later trials, the time delay was varied. Delivery of the juice before the established time delay resulted in increased dopaminergic activity while a longer delay was associated with decreased activity.

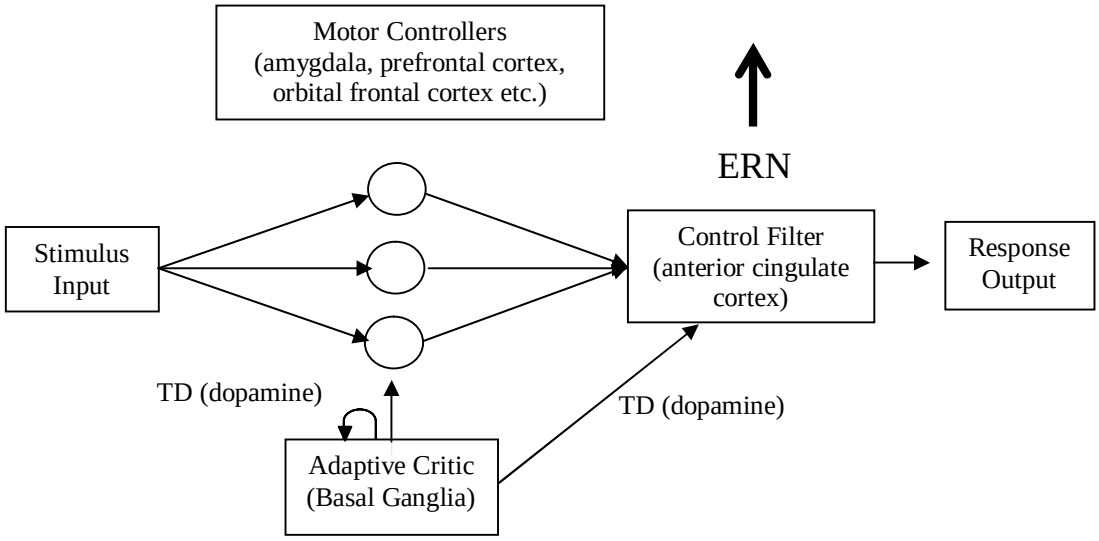
A number of models have been proposed based on theories regarding the physiological correlate of the theoretical critic. Most researchers agree that the critic is located in the basal ganglia (Contreras-Vidal & Schultz, 1999; Houk, Adams & Barto, 1995; Joel, Niv & Ruppin, 2002). Cells within the basal ganglia function by providing excitatory and inhibitory input to the dopaminergic system such that phasic dopamine activity is increased by presentation of reward signaling stimuli and decreased after a time duration that corresponds to the presentation of reward. Other mechanisms cause an increase in firing after a reward is presented but this is counteracted by inhibitory input from the critic. If the reward is not presented, there is no excitatory dopamine input and

the inhibition from the critic is not countered, resulting in decreased dopamine activity. Other models have proposed different mechanisms by which the basal ganglia functions as the physiological representation of the critic through regulation of dopaminergic activity (Contreras-Vidal & Schultz; Joel et al.). However, there is a strong consensus that the basal ganglia represents the critic in the method of temporal differences model.

Holroyd and Coles' (2002) Model for the Function of ERN

Holroyd and Coles (2002) propose that when the central nervous system receives stimulus input, multiple structures send response commands to the motor system. However, information that is sent from motor controllers to the motor system must first pass through the ACC. Since the commands sent by differing motor controllers often conflict, the ACC acts as a filter by deciding which controllers will be given control of

Figure 2. Holroyd and Cole's model on how ERN is generated when the basal ganglia relays a message to the anterior cingulate cortex via dopamine activity that a TD error has occurred. Model and figure are taken from Holroyd and Coles (2002).



the motor system. In order to ensure that ongoing behavior will yield the maximum amount of reinforcement, the ACC must have access to information about the consequence of a motor response. Fluctuations of mesecephalic dopamine innervation to the cortex provide this information. Specifically, the basal ganglia serves as an "adaptive critic" that determines whether a response has led to a discrepancy between the expected consequence and actual outcome (ie. a temporal difference error). Outcomes that are more or less positive than expected result in an increase or decrease in dopaminergic input to the ACC respectively. Errors produce decreases in dopaminergic activity because they result in outcomes that are worse than expected. The resulting decrease in dopamine cortical input disinhibits neurons in the ACC, leading to the generation of ERN.

Empirical Testing of the Model

Effect of outcome/expectation discrepancies on ERN. A number of studies have been conducted to test some of the assumptions that the model proposes. Specifically, researchers have built on the assumption that the ERN is created by a discrepancy between the expected and actual outcome of an action by testing how ERN amplitude varies when this discrepancy is manipulated. The two variables commonly used in this manipulation are strength of participant expectation for a reward or “positive” outcome and the magnitude of the consequence for action. These studies are an attempt to ascertain whether ERN simply classifies events into two outcomes: good versus bad or if the ERN is graded based on level of discrepancy between the expected consequence and the actual outcome.

Studies that manipulate the discrepancy between expected and actual outcome by presenting trials with varying probability of reward for correct responses have yielded mixed results. Several studies report larger ERN amplitudes when errors are made after trials associated with higher probably of a correct answer as opposed to trials associated with a low probably of correct answer when probability is manipulated trial by trial (Holroyd et al., 2003) or between blocks of trials (Hewig et al., 2006; Yasuda et al., 2004). However, other studies report no effect of reward probability on ERN amplitude for either mode of presentation (Hajcak et al., 2005) or that greater reward probability enlarged CRN amplitude only (Cohen et al., 2007).

Effect of magnitude of consequence on ERN. Studies addressing magnitude of consequences for correct and incorrect responses have yielded mixed results. In support of the assumption that ERN amplitude would vary with magnitude of consequence for correct or incorrect responses, some studies report ERN amplitude that is larger when errors lead to absence of monetary reward instead of an unpleasant auditory stimulus (Dikman and Allan, 2000), or when a larger number of points are offered for a correct response on a trial by trial basis (Hajcak et al., 2005) or on blocked trial format (Pailing & Segalowitz, 2004) even when the accuracy levels were the same for each condition (Hajcak et al.). In contrast to this, two studies report that varying the size of reward or penalties based on correct and incorrect guesses respectively had no effect on ERN magnitude (Hajcak et al., 2006; Holroyd et al., 2006). In two of the studies reporting correlations between ERN amplitude and magnitude of consequence, the effect was only observed for participants who scored low on measures of consciousness (Dikman & Allan) or sociability (Pailing & Segalowitz). Authors suggest that those who score high

on these traits failed to display a fluctuation in ERN amplitude because they are equally motivated to respond correctly even when external incentives are small. This conclusion would also suggest that differential discrepancy between expected outcome and true consequence of response is not sufficient for creating a change in ERN amplitude but that a differential affective reaction to greater or lesser discrepancies is also necessary.

Error related negativity and compromised dopamine systems. Given that Holroyd and Coles suggest that the ERN is dependent on communication of the mesencephalic dopamine system with cortical areas, damage to critical areas or connections proposed to be involved in the generation of the ERN or conditions that alter dopaminergic activity may in turn alter the ERN. Several lines of research have been conducted in recent years which do explore changes in the ERN after a compromise to the system occurs. Specifically, studies have compared ERN characteristics of brain lesioned, schizophrenic, or Parkinson's disease suffering participants with age and education matched controls to assess what changes resulting in a compromise to the system.

Patients with lesions of the lateral prefrontal cortex (Gehring & Knight, 2000) or medial prefrontal cortex including the ACC (Stemmer, Segalowitz, Witzke, & Schonle, 2004) demonstrated reduced ERN amplitude but intact CRN when compared to neurologically intact participants or neurologically intact siblings. Interestingly, three of the five participants in the study by Stemmer and colleagues were aware of their errors even when they did not generate an ERN. Patients with frontal white matter lesions demonstrated the same pattern such that there was no significant difference between the CRN and ERN for this group (Hogan, Vargha-Khadem, Saunders, Kirkham, & Baldeweg, 2006).

Researchers have studied the morphology of the ERN in patients with schizophrenia in order to assess whether alterations in dopaminergic function would be associated with an absent or attenuated ERN. Presumably, a reduced or attenuated ERN within this population would provide evidence that support the assumption of a dopamergic contribution to the generation of this waveform. Compared to the participants with no neurological disorder, medicated participants with schizophrenia displayed smaller ERN amplitudes than a group free of psychological disorder when compared on an Eriksen flanker task involving shapes (Morris et al., 2006), a stroop color-word naming task (Alain, McNeely, Christensen, & West, 2002) and a go/no go task (Bates, Kiehl, Laurens, & Liddle, 2002; Laurens et al., 2003). There was one exception in that there was no difference between the groups in the flanker task study when speed was emphasized over accuracy (Morris et al.). In addition, unlike participants free of psychological disorder, schizophrenic participants did not have increased activity of the rostal ACC during commission of an error but do show hyperactivity in the parietal cortex in both the right and left hemispheres (Laurens et al., 2003). Another interesting finding was that the negativity associated with correct trials was larger in the participants with schizophrenia in all of these studies to the point where there was no significant difference between their ERN and CRN.

Morris and colleagues (2007) also studied fERN in a group of participants with schizophrenia in a task that replicated the procedure in a study by Holroyd and Coles (2002). In this task, participants learn stimulus-response pairs by feedback which is either accurate all the time, 80 percent of the time or random. When feedback is accurate, the feedback becomes unnecessary after participants learn stimulus response

pairs and ERN moves from the time of feedback to the time of the response. When feedback is random there is no method to determine accuracy of response until the feedback is given. Schizophrenic participants had reduced fERN amplitudes compared to controls. They did not show a reduction in fERN amplitude and response ERN increase that is characteristic for participants who learn the stimulus response mapping for this task. In addition, unlike the neurologically intact participants, in the participants with schizophrenia, there was no significant difference in the amplitude of the fERN and CRN during the condition where feedback was accurate. This would indicate these patients have suffered damage to the system that generates the ERN such that it is treating errors and correct responses similarly. In addition, the patients are failing to learn stimulus response mappings so that unlike the control participants, the system is dependent on feedback to validate their response, even throughout the later trials.

Holroyd and Coles Model and Participants with Parkinson's Disease

Holroyd and Coles (2002) have suggested that testing individuals with Parkinson's disease would also provide a method to test models that endorse a role of dopamine in the system that generates the ERN. In order to understand the rationale behind this suggestion, a brief review of the neurological and behavioral consequences of Parkinson's disease is provided.

Parkinson's disease. Parkinson's disease is a neurodegenerative disorder that results in widespread cell necrosis of the dopaminergic neurons of the substantia nigra (Bernheimer, Birkmayer, Hornykiewcz, Jelliger & Seitelberger, 1973; Freedman, 1990; Kish, Shannak, & Hornykiewicz, 1988). Thus, the function of the nigrostriatal dopamine path is hindered because the input to the striatum from the substantia nigra is drastically

decreased. At autopsy there is less than one percent of dopamine remaining in the putamen and four percent left in some areas of the caudate nucleus (Kish et al.). As a result of compromised function of this pathway, a number of motor difficulties occur including bradykinesia (slowness of movement), resting tremor, shuffling gate, posture irregularities, and rigidity. Further difficulties associated with fine motor control of facial muscles include dystharthia, monotone voice, and an emotionless mask-like facial expression (Freedman, 1990).

Unfortunately, decreased substantia nigra mediated dopaminergic innervation to the basal ganglia also aversely effects ascending cortical projections. Since dopaminergic ascending fibers from the nigrostriatal pathway connect to a large distribution of cortical areas including the prefrontal cortex, anterior cingulate cortex, limbic cortex and orbital frontal cortex, a number of cognitive and behavioral difficulties emerge. Impaired performance on tasks that depend on frontal lobe functioning occur early and are among the most common forms of cognitive impairment that accompany Parkinson's disease (Levy et al., 2002). These tasks involve skills associated with executive functioning which are defined as "higher order" abilities used in the self-regulation, problem solving strategies, or goal directed behavior (Marie et al., 1999). Parkinson's disease participants have demonstrated impaired performance on several tests of executive functioning including an Object Alternation Task (Marie et al.), the Wisconsin Card Sorting Test (Aleviadou, Katsarou, Bostantjopoulou, Kiosseoglou & Mentenopoulos, 1999; Starkstein et al., 1996; Van Spaendonck, Berger, Horstink, Buytenhujs & Cools, 1996), word fluency (Van Spaendonck et al.) the Odd Man Out Test (Richards, Cote & Stern, 1993) the Stroop Task (Alegret et al., 2001), the Trail Making test (Alegret et al.),

and a go/no-go task (Tamaru, 1997). Furthermore, executive dysfunction in participants with Parkinson's disease is correlated with disease progression variables such as dopamine activity of the caudate nucleus (Marie et al.), UPDRS score, severity of rigidity (Alevriadou et al.; Van Spaendonck et al., 1996) and degree of extra pyramidal symptoms (Richards et al.).

Parkinson's disease is also associated with damage to dopamine pathways other than the nigrostriatal pathway. Uhl, Hedreen and Price (1985) observed a 45% percent depletion of dopamine neurons in the ventral tegmentum in a sample of Parkinson's disease patients who were receiving surgery. Autopsy cases revealed a 40 to 60 percent dopamine loss to various limbic and cortical areas that receive input from the ventral tegmentum (Jellinger, 1991).

Additional evidence indicates that Parkinson's disease may be detrimental to the functioning of cholinergic, noradrenergic, and serotonergic neurotransmitter systems as well. For example, Parkinson's disease is associated with a 32 to 90 percent neuronal loss in the Nucleus Basalis of Meynert (Jellinger, 1991; Zweig, Cardillo, Cohen, Giere & Hedreen, 1993) as well as a 50 to 60 percent reduction of cholinergic metabolite concentration in the cortex and hippocampus (Jellinger). Significant neuronal loss also occurs in the locus coeruleus (Jellinger; Zweig et al.), denoting marked noradrenergic cell loss. Finally, observations that Parkinson's disease is associated with dorsal raphe nucleus cell loss (Jellinger), reduced cerebral spinal fluid concentrations of 5-HIAA and a 20 to 60 percent reduction in the concentration of serotonin in the cortex, (Mayeux, Stern, Cote & Williams, 1984) provides strong support that disease symptoms include serotonergic dysfunction.

The diffuse damage of dopamine systems other than the nigrostriatal pathway may also be associated with behavioral symptoms. A high prevalence of comorbid depression (Slaughter, Slaughter, Nichols, Holmes & Martens, 2001; Schrag, Jahanshahi & Quinn, 2001; Tandberg et al., 1996), apathy (Isella et al., 2002; Pluck & Brown, 2002) and anxiety (Walsh & Bennett, 2001) is associated with Parkinson's disease. Researchers have suggested that mood alterations are caused by impairment of the mesolimbic system because reduced activity of this pathway alters the ability to experience the pleasant mood that accompany rewards (Mayberg & Solomon, 1995). Studies that demonstrate a positive correlation between presence of comorbid depression among individuals with Parkinson's disease and both atrophy of the ventral tegmental area (Torack & Morris, 1988) and decreased glucose metabolism in frontal areas that receive input from the ventral tegmentum (Mayberg et al., 1990) support this hypothesis. In addition, patients with Parkinson's disease endorse a lower level of novelty seeking than a group of patients diagnosed with osteoarthritis that are matched for disability scores (Menza et al., 1993; 1994). Cloninger (1987) proposed that certain personality traits are related to neurotransmitter functioning. Specifically, novelty seeking is related to dopamingeric mediated reward systems while harm avoidance is related to serotonin systems.

Behavioral symptoms may be related to serotonin fluctuations in Parkinson's disease as well. Depression level is positively correlated with harm avoidance among participants with Parkinson's disease (Jacobs, Heberlein, Vieregge & Vieregge, 2001; Menza et al., 1993) suggesting that depression is due to altered serotonin functioning. In addition, depression in Parkinson's disease often responds to SSRI's (Tesei et al., 2000).

Impaired executive performance in Parkinson's disease has been conceptualized as difficulty with shifting set or inability to inhibit a behavior, cognition or response strategy (Richard et al., 1993). Studies that disseminate executive functioning into multiple skills have demonstrated an association between severity of Parkinson's disease related symptoms and set shifting. For example, Marie and colleagues (1999) reported a significant correlation between performance on a task that involves shifting set (object alternation task) and dopamine activity of the caudate nucleus. Two other tests of executive functioning that evaluate planning and attention/working memory demonstrated no such relationship. Similarly, Richards and colleagues (1993) found a correlation between set shifting ability and both extrapyramidal symptoms and perseverative errors on an Odd Man Out test but found no association between disease severity and ability to maintain set. In a sample of participants with Parkinson's disease tested by Van Spaendonck and colleagues (1996), UPDRS scores were significantly correlated with performance on the Wisconsin Card Sort, but not with fluency scores.

Thus, although severity of Parkinson's disease symptoms is correlated with impairment on a variety of tests of executive functioning, only performance on tests that involve set shifting/inhibition are correlated with disease severity. Impairment of the above mentioned tasks that tap executive functioning occur because these tasks involve switching response strategies and inhibiting old strategies that were useful earlier in the task. For example, during the Wisconsin Card Sort, an examinee is instructed to sort cards into piles based on examiner feedback pertaining whether the sort was correct or incorrect. Cards may are sorted by color, form, and number but only one of these strategies is correct at a certain point in the test. The proper response strategy is switched

during the task so that if sorting by color is the correct strategy at the beginning of the task, sorting by form or number will be correct later in the task (Grant & Berg, 1948). Multiples studies demonstrated that participants with Parkinson's disease make significantly more errors that involve the continuation of using an old strategy after being told that the strategy is not correct (Aleviadou, et al., 1999; Van Spaendonck, et al., 1996).

The errors made on the Wisconsin Card Sort task and other tasks that tap ability to inhibit behavior and shift set may be also be conceptualized as a decreased ability to change behavior in response to feedback indicating that an error as been made. Participants with Parkinson's disease exhibit an inability to inhibit the incorrect strategy, even after coming in contact with negative contingencies for using the incorrect response. This behavioral pattern is similar to what would be expected by decreased ERN amplitudes if the ERN is a mechanism by which structures involved in motor action are able to utilize contingencies to change ongoing behavior.

Evaluation of Holroyd and Coles' Model with PD participants. Holroyd and Coles (2002) propose that ERN amplitudes should be diminished for individuals with Parkinson's disease because there is reduced dopaminergic activity in the projections from the substantia nigra to the basal ganglia. Severe basal ganglia dysfunction resulting from damage to this pathway should hinder the ability to detect a temporal difference error. Since ERN generation by the ACC occurs in response to a temporal difference error, ERN's should be reduced in strength or eliminated within individuals with Parkinson's disease.

The several studies testing this line of reasoning have yielded inconsistent results. Falkenstein et al. (2001) observed the ERN characteristics of a group of Parkinson's disease participants and a group of neurologically intact control participants while they completed an Eriksen's flanker task, a go/no go task and a Simon-type task. During the Simon-type task, the participants were asked to press a button with their left index finger if the presented stimulus is red or to press a different button with their right index finger if the presented stimulus is green. In half the trials, the colored objects are arrows that point to either the same or opposite direction of the key that participants are instructed press. The Parkinson's afflicted group consisted of medicated individuals with mild symptomology who scored a mean of 25 on the Unified Parkinson's Disease Rating Scale (UPDRS) and demonstrated no significant cognitive impairment on a Wisconsin Card Sort Task or word fluency test. Analyses revealed that during all three tasks, ERN amplitude was significantly smaller within the group with Parkinson's disease while there were no differences in CRN amplitude. ERN latencies for the Parkinson's disease group were significantly shorter in the Simon and go/no go task.

Holroyd and colleagues (2002) also compared a sample of non-medicated individuals with Parkinson's disease with a group free from neurological disorder in regard to ERN amplitude on errors on an Eriksen's flanker task. Parkinson's disease symptom severity was similar to the group in the study by Falkenstein and colleagues (UPDRS mean = 26.9 Hoehn and Yahr mean = 2.5) and participants had normal MMSE scores. Holroyd and colleagues did not observe a significant difference between the ERN amplitudes of the participants with Parkinson's disease and the control group. They suggested that the contrasting results may be due to one of several reasons. First, the

error rate in one of the tasks in the Falkenstein study was significantly higher in the group with Parkinson's disease than the control group and that decreased accuracy on a task will coincide with reduced ERN amplitude. Second, the participants in the study by Holroyd and colleagues completed the procedures after overnight withdraw from dopaminergic medications. They state that at times, individuals with Parkinson's disease function better while off medications. Holroyd and colleagues also point out that they measured responses with squeeze force while the participants in Falkenstein and colleagues pressed a button to indicate their response. By using squeeze force, Holroyd and colleagues were able to use a mathematical algorithm to create segments that were time locked to a point that could readily distinguish the participants' intended responses from noise caused by tremor. They suggest that failure to use this algorithm could result in an attenuation of the ERN because a button press may allow tremor to cause more inconsistency in the time from intended motor onset to the time where a the segments are response locked from, thereby reducing ERN amplitude in the same way latency jitter will artificially reduce the amplitude of a waveform.

Recently, two more studies have continued this inquiry and support the results found by Falkenstein and colleagues (2001). Ito and Kitagawa (2007) tested a medicated group with Parkinson's disease in mild stages (Hoehn and Yahr mean = 2.11) and a group of neurologically intact individuals on a lexical decision task and reported a decreased ERN amplitude for participants with Parkinson's disease. There were no significant differences in ERN latency or CRN between the groups. The ERN amplitude of the group with Parkinson's disease correlated negatively with level of executive functioning as measured by the WCST. Stemmer et al. (2007) addressed the issue of

medications by comparing the ERN properties induced by completion of an Eriken's Flankers task among a group of neurologically intact individuals and two groups of participants with Parkinson's disease, one tested during the on phase of their medication and one group that were tested while not being treated with medications. Compared to the neurologically intact group, both groups suffering from Parkinson's disease displayed attenuated ERN amplitudes in the Cz, FCz, and Fz sites. However, the two Parkinson's disease afflicted groups did not differ in terms of ERN amplitude from each other.

Presently, it is difficult to determine whether Parkinson's disease is associated with decreased ERN amplitude as empirical testing of this hypothesis has yielded inconsistent results and two of the suggested reasons for this discrepancy offered by Holroyd and colleagues were not addressed in subsequent studies. Since Parkinson's disease leads to severely decreased dopaminergic input to the basal ganglia, robust reductions in ERN amplitudes would be expected. All studies tested participants in the mild to moderate stages and a reduction in ERN was observed in three of the four studies. But two of the three reasons Holroyd and colleagues suggested as causes for the discrepancy among studies have not been directly addressed. Therefore, further research would provide useful information regarding the validity of Holroyd and Coles' model.

Purpose of the Present Study

The overarching goal of the present study was to test the some of the assumptions of a model proposed by Holroyd and Coles (2002) stating that error related negativity occurs when an error leads to decreased dopaminergic enervation of the ACC. Participants with Parkinson's disease were recruited for this purpose because if the model proposed by Holroyd and Coles is valid, widespread dopamine cell necrosis should result

in robust changes to ERN. In order to comprehensively explore this question, the analyses conducted during the present study had two distinct purposes.

The first purpose of the present study was to determine whether the presence of Parkinson's disease in moderate stages is associated with an attenuation of the amplitude of the ERN. Holroyd and Coles (2002), add to existing theory regarding the function of ERN by stating that the ACC is able to adjust behavior in response to an error because it received information about the consequence of an action through input from the mesencephalic dopamine system. Because Parkinson's disease is a condition that leads to the death of a large portion of dopamine neurons in the substantia nigra and other dopamine systems such as the ventral tegmentum, an attenuated ERN is expected within this group (Holroyd & Coles). At the time when this study was initiated, only two studies had explored the relationship between ERN magnitude and Parkinson's disease. They yielded conflicting results in that one study reported reduced ERN amplitude among participants with Parkinson's disease (Falkenstein et al., 2001) and one study reported equivalent ERN amplitude for all participants (Holroyd et al., 2002). Since this time, two other studies addressing the issue report attenuated ERN amplitudes within participants with Parkinson's disease (Ito & Katagawa, 2006; Stemmer et al., 2007).

The present study will use two novel approaches in an attempt to derive data that will either support or refute a dopaminergic contribution to ERN and to overcome shortcomings of past studies. First, the present study will implement a guessing task similar to the task used in Ruchsow and colleagues (2002) to measure fERN rather than using a task where segments are time locked to the response. Using a fERN provides several advantages over procedures used in previous studies that measured the ERN

among individuals with Parkinson's disease. First, no study involving participants with Parkinson's disease has used a task that evokes fERN. Second, the guessing task in the present study was implemented so that there were a fixed number of responses deemed correct and incorrect. This will ensure that error rate is fixed between the groups. This eliminates the potential for differential error rate between the groups to become a confound as originally suggested by Holroyd and colleagues (2002). Third, feedback is not dependent on motoric ability unlike reaction time tasks. This should overcome the potential "response jitter" associated with tremor induced variance in the time between the intention to respond and the time a response is registered because the segments where the fERN were observed were locked to the presentation of feedback instead of an action. In addition, since this task did not demand a fast response, it would be easier for participants with Parkinson's disease and therefore allow for recruiting of participants who were in more progressed stages. Every former study of ERN in Parkinson's disease recruited participants in the mild stages and with either minimal indication of cognitive deficits or none at all. Because these participants were in the mild stage, changes in the mesencephalic dopamine system associated with these Parkinson's disease samples may be too subtle to result in alterations in ERN magnitude that would be detected consistently. Inclusion of Parkinson's disease patients that are in more advanced stages may result in a group with more severe attenuation of ERN magnitude. A larger effect size will decrease the probability of committing a Type II error if Parkinson's disease is associated with attenuation of ERN. Thus, results derived from testing the sample in the present study will provide more conclusive evidence that supports or contradicts the idea

that Parkinson's disease is associated with changes in ERN magnitude (Holroyd et al., 2002).

The second purpose of the present study is to implement changes in magnitude of the consequence following a response and observe how these changes alter fERN in participants who are either free from neurological disorder or have Parkinson's disease. Response to changes in the magnitude of the consequence following a response may provide a more sensitive means of detecting changes in ERP associated with Parkinson's disease as well as providing stronger support for theories that endorse dopaminergic influences on ERN and fERN. In addition, manipulation of consequence magnitude provides a method of directly assessing whether changes in the discrepancy between the expected outcome and the consequence of a response are associated with alterations in ERN as suggested by Holroyd and colleagues (2002). Increases in the magnitude of the consequence of a response during some trials will result in a larger net discrepancy between expectation for reward and the larger penalty that follows trials where errors are committed. Thus, "large consequence" trials should result in a larger ERN. This assumption has been confirmed in several studies (Dikman and Allan, 2000; Hajcak et al., 2005; Pailing & Segalowitz, 2004) though this effect was not present in other studies (Hajcak et al., 2006; Holroyd et al., 2006). Assuming that the ERN is mediated by the mesencephalic dopamine system, the increase in ERN size that accompanies larger consequence trials may be attenuated or absent in participants with Parkinson's disease.

Hypotheses and Predictions

Hypotheses and predictions are presented for each of the two purposes in the present study. The validity of the hypotheses made in conjunction these purposes were

analyzed with two principal components analyses (PCA) in order to derive virtual electrode sites representing the location of the fERN and the proper time window containing the fERN peak. The amplitude of the derived fERN waves were subjected to a 2X2X2 mixed ANOVA with fERN amplitude as the dependent variable. In regard to independent variables, group membership (Parkinson's disease versus Neurologically Intact) was the between groups factor and magnitude of consequence following a response (large or small) and validity of response (correct or incorrect) were within subjects factors.

The first purpose of the present study was to observe changes in ERN that result from Parkinson's disease. According to Holroyd and Coles (2002) the ERN is mediated by the fluctuations in mesencephalic dopamine activity associated with a response that produces an outcome that is worse than expected. It was predicted that damage to the mesencephalic dopamine system would be associated with a decrease in the ERN amplitudes generated during error trials. Although past studies involving ERN magnitude and Parkinson's disease have yielded conflicting results, it was thought that the inclusion of participants in moderate stages of the disease would provide a large enough effect to be detected by the statistical procedures employed in this study. This would be manifested by an interaction between group membership and response validity such that participants with Parkinson's disease would demonstrate significantly diminished ERN's during error trials.

The second purpose of the present study was to provide data to determine whether changes in the magnitude of consequences associated with a response results in a subsequent change in ERN amplitude and whether the changes in ERN amplitude will be

attenuated in participants with Parkinson's disease. Two predictions were made in regard to these hypotheses:

1) An increase in the magnitude of the consequence associated with a correct or incorrect response on each trial would result in a larger discrepancy between expected outcome and response consequence on trials where errors are committed. Thus, larger consequences would result in an increase in ERN amplitude during error trials. This hypothesis would be verified with an interaction between the magnitude of the consequence and response validity such that participants will produce significantly larger ERN waves on error trials associated with larger consequences than for error trials associated with smaller consequences.

2) The increase in ERN size within the error trials associated with larger consequences might be attenuated or abolished in participants with Parkinson's disease. This prediction would be supported by a group membership by consequence magnitude by response validity interaction where the participants who are free from neurological disorder demonstrate an increase in the difference in ERN amplitude between large consequence error trials compared to small consequence error trials and that this difference in ERN amplitude between large and small consequence trials will either be attenuated or absent in participants with Parkinson's disease.

Method

Participants

The participants consisted of 53 individuals 30 of which had Parkinson's disease and 23 who were free of neurological disorder. In order to participate, all participants of both groups had to be native English speakers, have normal or corrected vision, and report a history free of neurological disorder (with the exception of Parkinson's disease), psychiatric disorder, stroke, or head injury involving a loss of consciousness for greater than 10 minutes and had to score at least a 24 on the Mini Mental Status Examination (MMSE). Participants that comprised the group with Parkinson's disease were recruited from the University of South Florida clinics, various Parkinson's disease support groups near the Tampa Bay area, or by direct referral from those who participated in the study. Those within the "control group" were recruited from spouses of participants with Parkinson's disease, direct requests made at Parkinson's disease support groups, senior citizen's expos, local malls and stores, or from posting information about the study at local businesses, on internet listing services, local newspapers, a mailing which specializes in advertising, a University email list, several senior citizen's websites, church bulletins, or by direct referral from other participants. This group was selected in a manner so each individual was matched with a member of the Parkinson's disease group in terms of age, years of education, and gender.

Data from 16 (14 male, 2 female) of the 30 participants with Parkinson's disease could be analyzed. For the 14 participants who were not included in data analyzes, three were dropped because the computer task was originally too fast and had to be slowed down from the speed it ran during the collection of pilot data, the program crashed for two participants who decided they did not want to return, four were not analyzed due to excessive movement leaving an insufficient number of trials for analysis, one did not complete the procedures because they were anxious from being in the room and choose to quit after completing an oddball task, two participants gave up and stated the task was too difficult, one participant appeared very impaired and confused while completing an oddball task and so the experimenter choose not to run them, and finally one participant had difficulty physically pressing the buttons required for the task.

Data from 16 (14 male, 2 female) of the 23 participants with no neurological disorder were used to form the control group. For this group, data from three of the participants could not be used because there were too many movement artifacts, two were not analyzed because elastic connectors in the net had broken and their data was not interpretable, one participant was not used because after they had completed all the procedures they mentioned they had a head injury, and one participant was not used because at the end of the experiment, they reported they had experienced symptoms consistent with PTSD during their lifetime.

Table 1 includes demographic data of participants in the Parkinson's disease group and the group with no neurological disorder. Of the 16 participants with Parkinson's disease that were included in the analyses, ages ranged from 51 to 79 (M = 66.81, SD = 7.59) and the years of education they completed ranged from 13 to 22 (M =

16.00, SD = 2.99). The group with no neurological disorder also included 16 participants who were between the ages of 50 and 79 (M = 64.38, SD = 8.27) and had completed between 11 and 23 (M = 16.06, SD = 2.74) years of education. There was no significant difference between the group with Parkinson's disease and the group with participants free of neurological disorder in regard to age (t(30) = .868, p = .392). The mean years of education completed for the group with Parkinson's disease group also did not significantly differ from the neurologically intact group (t(30) = -.062, p = .951).

Table 1

Demographic data of participants

Group	Age	Education	Gender	Hoehn & Yahr Score
Control group	64.38 (8.27)	16.06 (2.74)	14 male, 2 female	NA
Parkinson's disease group	66.81 (7.59)	16.00 (2.99)	14 male, 2 female	2.50 (0.90)

Symptom severity for the participants with Parkinson's disease ranged from mild stage (Stage I) to medium severe (Stage IV) with an average Hoehn and Yahr (1967) score of 2.50 (S.D. = 0.9). Most of the participants were classified into stage II or III. See table 2 for Hoehn and Yahr staging criteria. All the participants with Parkinson's disease were asked to refrain from taking their first morning dose of dopaminergic medications. This ensured an overnight "washout" period so that when they arrived the last dose of dopaminergic medication was taken the night before participation. Procedures for every participant began no later that ten o'clock in the morning. All the

procedures for the experiment could be completed in two hours. Thus, all the participants were finished participating in the experiment by noon.

Table 2

Hoehn and Yahr staging criteria for Parkinson's Disease

Stage of Disease	Description of symptoms
Stage I	Unilateral involvement only, usually with minimal or no functional impairment
Stage II	Bilateral or midline involvement, without impairment of balance
Stage III	First sign of impaired righting reflexes, and unsteadiness. Activities are somewhat restricted. Disability is mild to moderate but still physically independent
Stage IV	Fully developed severely disabling disease; still able to walk and stand unassisted but markedly incapacitated
Stage V	Confinement to bed or wheelchair unless aided

Taken from Hoehn and Yahr (1967)

Apparatus

All stimuli were presented using a DELL Genuine Intel x86 Family 6 model 8 computer and a 21 inch Sony Multiscan 220GS monitor. The presentation of stimuli was programmed through the use of Eprime software version 3.0. Participants' decisions were registered when they used their right or left index fingers to press one of four keys on a computer keyboard.

Evaluation of brain electrophysiology was accomplished through measurement of feedback-locked EEG epochs that were recorded with the Electrical Geodesics Incorporated System 200. Brain activity was recorded with an 128-CHANNEL EGI sensor net using NETSTATION 3.0 acquisition software powered by a Power Mac G4 computer. Data were recorded from 128 electrodes with a 0.1 – 100 Hz bandpass filter and a 60 Hz notch filter and digitalized with 16 bit resolution at a sampling rate of 250

Hz. Placement of sensors was adjusted to ensure that impedance stayed below 50 kΩ for all channels. The first two trials and last two trials of each block were not analyzed.

The techniques used for offline processing and visualization of wave forms were in accordance recommendations with made within the Netstation Waveform Tool Technical Manual published by Electrical Geodesics Inc and were performed using NETSTATION 4.0 software. The data were digitally filtered with a 20 Hz low pass filter and segmented into epochs that began 200 milliseconds before feedback and ended 800 milliseconds after feedback. Artifact detection was performed such that an artifact was defined as any segment where the maximum and minimum amplitude differed by more than 200 μV. Bad channels were replaced according to mathematical estimations made by the procedure on the NETSTATION software. Eye movement artifacts were corrected with the software online correction which applies a regression technique described by Gratton et al. (1988). After the data were subjected to the eye movement correction algorithm, artifact detection and bad channel replacement were performed a second time. The epochs were averaged, re-referenced to the average of the two mastoids and baseline corrected from 200 milliseconds prior to the feedback onset.

Procedure

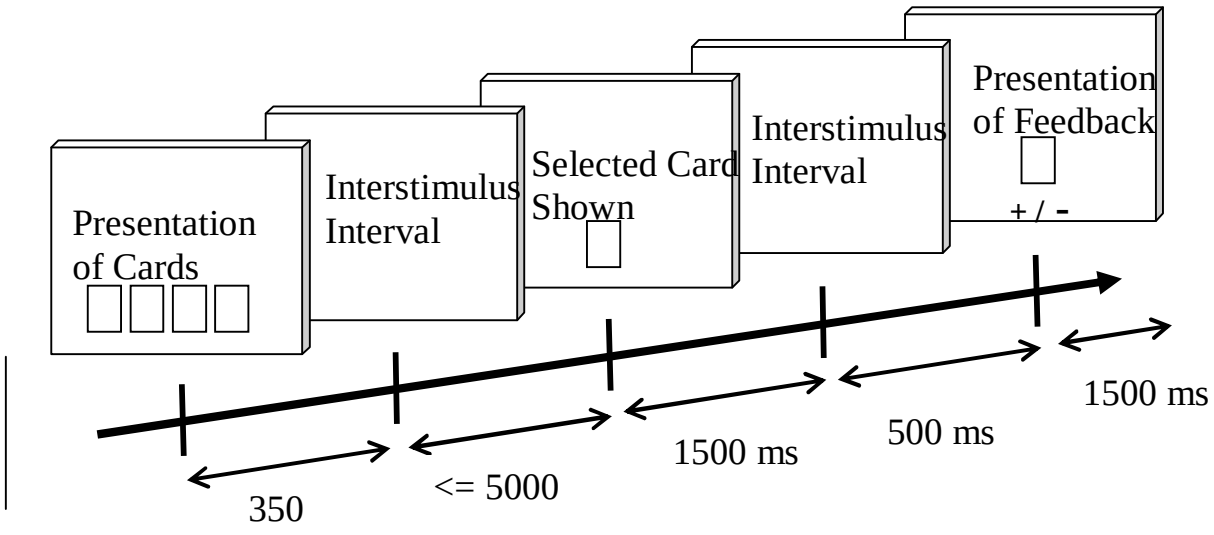
Neuropsychological testing. After reviewing the procedures of the experiment and giving informed consent, participants began by completing a battery of questionnaires consisting of a small demographic questionnaire, the Mini Mental Status Examination (MMSE), the Hopkin's Verbal Learning Test, revised (HVLT-R), the vocabulary subtest of the Shipley Institute of Living Scale, the Beck Depression Inventory 2nd Edition (BDI-2), the 14-item Apathy Evaluation Scale (AES), and the

Stroop Test. Information about symptom severity was obtained from an estimation of disease stage made by a neurologist and was based on the Hoehn and Yahr rating scale.

Measurement of ERP's. Upon completion of the self-report measures, the 128 sensor net described above was placed on each participant and adjusted as needed. The participants were seated in front of the video monitor in a quiet room and the directions for completing the remaining procedures of the experiment were displayed.

The participants completed a modified version of the card selection task used by Ruchsow and colleagues (2002). See Figure 3 for a schematic drawing of the sequence of events during experimental trials. Before the task began, the participants were told that four cards will appear on the computer monitor during each trial. The participants were instructed to attempt to choose the correct card but did not receive instructions about how to determine the correct card. Participants were told to try to implement strategies that lead to correct answers and that they could learn patterns of correct answers in order to do so. They were given an example of using a strategy to guess the

Figure 3. Experimental sequence of events for experimental trials



next card. During this example, the correct solution was to pick cards in succession from left to right starting with the card on the left.

During the performance of the task four cards, each with a colored dot, appeared horizontally aligned across the top of the monitor for 350 milliseconds. From left to right, the colored dots within the cards were red, blue, yellow and black respectively. The participants choose a card by pressing a key that corresponded to that card. After the 350 millisecond presentation of the four horizontally aligned cards, participants were shown a blank screen for up to five seconds. Participants could select a card either during the initial 350 millisecond presentation of the four horizontally aligned cards or anytime during the five second presentation of the blank screen. Immediately after a selection, the computer monitor displayed the selected card centered in the middle of the monitor for 1500 milliseconds. Because the chosen card was displayed when the participant chose a card, the time the previous blank screen was presented could range from 0 milliseconds to 5 seconds depending on when the participant made their card selection. After the presentation of the selected card, a 500 millisecond interstimulus interval occurred. The interstimulus interval was followed by a 1500 millisecond presentation of the correct card centered in the middle of the computer screen and text indicating whether the participant's response was correct. Incorrect responses resulted in feedback with red lettering. Correct responses were displayed with blue lettering. If the participants failed to select a card within the allotted time period the monitor displayed the words "please choose a card faster" in black letters. During the practice trials, the correct response strategy was to select the cards in succession from right to left starting with the card on the right side for trial one. However, during the experimental trials,

correctness was randomly determined with a 66.6% percent chance of the participant's answer being "correct" except for the first and last two trials in each block which were deemed automatically incorrect and correct respectively. After each "correct" response for the experimental trials, a participant's feedback indicated they chose the correct card. However, on trials where the participant's answer was randomly incorrect, one of the other three cards was randomly selected and then subsequently presented as the "correct card".

For the first few participants in the study, the cards appeared for 350 milliseconds and participants were given 800 milliseconds to select a card. Pilot data run on college students suggested that this time limit was sufficient for participants to respond. However, the participants with Parkinson's disease had great difficulty performing the task within this time limit. Therefore, the time limit was increased until participants seemed able to respond to the majority of trials within the time limit. This resulted in a maximum time limit of five seconds for a selection to be made. This may be due do the mental slowing that is a hallmark of Parkinson's Disease and other subcortical dementias.

The presentation of stimuli began with 32 practice trials during which no monetary reinforcement or monetary penalties for correct and incorrect answers were applied. However, participants were given feedback about the correctness of their response. This gave nearly all the participants enough trials to discover the proper strategy for selecting the correct card, thus encouraging participants to attempt to discover a solution during the experimental trials. Following the practice trials, the experimental trials consisted of 6 blocks with 34 trials each for a total of 204 trials. There was a monetary adjustment of payment for participation associated with each trial.

Specifically, during half of the trials which were designated as "large contingency trials" participants either lost or gained 60 cents for incorrect or correct responses respectively. During the other half of the trials which were designated as "small contingency trials" participants lost or gained 6 cents for incorrect or correct responses respectively. The type of contingency of the trials was varied by block so that each block contained only one type of contingency (large or small). The order of the presentation of large or small contingency blocks was counterbalanced such that half of the participants completed a small contingency block first then large then small, large, small and large. The other half of the participants completed a large contingency block first, then a small contingency block, then large, small, large and small. Participants were informed of the type of contingency associated with each type of block before beginning the block.

Because half the trials were small contingency blocks and half were large contingency blocks, the number of trials for each condition was: 60 large reward correct trials, 60 small reward correct trials, 30 large penalty incorrect trials and 30 small penalty incorrect trials. Thus, total compensation for participants was $19.80 plus compensation mileage associated with driving to the location of the experiment.

Principal components analysis and hypothesis testing. The data were subjected to two principal components analyses (spatial and then temporal) to determine the location, timing and amplitude of the ERN or other waveforms of interest. The factor scores from the spatial and temporal factor deemed to represent the ERN were subjected to a three-way ANOVA with response validity (correct or incorrect answer) and consequence magnitude (large and small) as within subject factors and group membership (Parkinson's disease group or group free from neurological disorder) as a between subjects factor.

In order to familiarize the reader with the application of principal components analyses to ERP data, the procedure will be described in more detail. Raw ERP data comes in the form of an immense number of voltage readings, one at each electrode at each point in time a measurement is taken creating a large array of data. In this experiment, the data consisted of a 129 (electrodes) X 250 (time points) array of averaged voltage readings for each condition of each participant. Hypothesis testing often involves selecting a portion of the data to use as a dependent measure. There are multiple ways to ascertain a measure of the amplitude of the waveform of interest from this dataset. One common method is to take a "base to peak" measure where the researcher selects a single electrode which is recognized to be where the waveform is largest or where it is generally expected to be largest. The base and peak are defined as the most positive and negative points in an arbitrarily defined time interval (Donchin & Heffley, 1978). Similarly, one can define their measurement as the area under selected portion of an arbitrarily chosen ERP curve relative to a chosen baseline. Unfortunately, these methods have several shortcomings. First, it is often difficult to determine the single electrode where the largest peak or area is located. Secondly, determining the time interval where a peak is located can be difficult due to intersubject and intrasubject variability and experimenter biases. Perhaps even more problematic however, is that a single voltage reading may be influenced by multiple underlying components that overlap in time. Thus, dependent variables derived from these methods might not provide an accurate indication of the activity of the waveform of interest (Donchin & Heffley).

Because of the shortcomings of these methods, some researchers advocate applying a series of principal components analyses to the data. The principal components

analysis (PCA) is a method by which orthogonal "components" are derived from a dataset. Deriving these components is a step by step process where the first component is extracted by finding the linear combination of the original variables that accounts for the most variance in the data and the second component is extracted by finding the linear combination of the original variables that account for the most variance in the data but that has no correlation with the first component. Subsequent components are derived by extracting linear combinations of the original variables that account for the most variance in the data but are not correlated with any of the previous components. This method provides a way to reduce the dataset down to fewer dimensions which are more readily interpretable. In addition, the linear combinations are orthogonal so that statistical hypothesis testing can be performed on these linear combinations without the worry of the interaction of other linear combinations that plague peak selection techniques (Spencer, Dien & Donchin, 2001).

When applying this procedure to ERP data it provides a method by which data are reduced to a smaller number of components that may be interpreted more easily. Specifically, the procedure reduces the voltage readings from all participants, across all conditions, at all time points for all the electrodes into a more manageable dataset (Spencer et al., 2001). The first step in this process is to perform a "spatial" PCA on the spatial variance of the data set. In this step the 129 electrodes (128 electrodes + one the reference electrode derived from averaging the two mastoid electrodes) are reduced into a smaller number of factors. These factors represent clusters of electrodes that covary to the extent that one or another could be considered redundant with other electrodes in the cluster. Each factor is thus a linear combination of the original variables that will hold

the information regarding the variance of the original electrodes but present it in a smaller number of more easily understood factors. A varimax rotation is applied to the PCA because it maximizes the variances attributed to each factor while maintaining the factors as orthogonal. The clusters of electrodes termed factors serve as "virtual electrodes" (Spencer et al.)

These "virtual electrodes" can be easily viewed by calculating the correlation scores of the derived virtual electrodes and the original variables which in this case are measurements from actual electrodes, and plotting these correlation coefficients on a topomap. Once virtual electrodes are readily visible, a spatial factor may be selected that is most likely to represent the waveform or waveforms of interest. In this dataset, we are trying to identify error related negativity associated with feedback and thus, a spatial factor where the correlations with the voltage readings from the original electrodes are highest in the electrodes that cluster about the middle frontal portion of the scalp would be identified as the spatial factor of interest. It is important to note that variance accounted for by a spatial factor will be increased if that spatial factor is more "active" during multiple time points or a longer period of time. Thus, the spatial factor of interest might not necessarily be one that accounts for a large amount of the variance in the dataset as a whole.

After completion of the "spatial" PCA a second PCA is performed in order to reduce the time points in the data to a smaller number of "temporal factors." The dependent variable in this procedure is the spatial factor scores derived from the previous spatial PCA. Therefore, the spatial factor scores of all participants, across all experimental conditions, at all time points are subjected to this analysis. The result is a

small number of temporal factors which represent various clusters of time points. A graph that presents the factor loadings of each temporal factor with each time point will show the time where the temporal factor is most "active." Again, the researcher selects a temporal factor that is most consistent with the waveform of interest. In this case, since the feedback error related negativity commonly peaks at approximately 200-350 milliseconds after the feedback, a temporal factor that is most active around this time would be selected. The temporal factor scores within the spatial factor and the temporal factor of interest for each participant and each experimental condition served as the dependent measure for statistical analyses used to test the hypotheses. For the current study, the temporal factor scores of the spatial factor and temporal factor of interest are identified for each participant of each group under each experimental condition. These factor scores are subjected to a three-way ANOVA in order to test the hypotheses described above.

Brain electrical source analysis. In order to further explore and provide verification of correct identification of the waveforms in question, dipole source analyses were conducted on the portion of the data deemed to represent the fERN. All analyses were conducted on BESA version 5.18 from geodesics inc. The analyses were performed on the spatial and temporal component that the principle components analysis identified to be representative of the fERN. The brain electrical source analysis (BESA) was performed on the components rather than the grand averaged data because there was no difference between the trials where answers were deemed incorrect or correct and therefore difference waves could not be used. Difference waves are typically used in BESA because it eliminates much of the variance in the voltage readings associated with

factors other than the factor in question if the extraneous factors are common to both conditions used to construct the difference wave. Therefore, the BESA was performed on the spatial factor and temporal factor representative of the fERN because it was a method to isolate variance in voltage readings attributed to the fERN. Furthermore, a study comparing results obtained from using the PCA components and more traditional methods such as Music-Rap and minimum norm recommends using PCA components as data for the BESA and states several advantages to this method (Dien, Spencer & Donchin, 2003). For the present study, a window of 200 milliseconds to 400 milliseconds after feedback was selected for the BESA analysis because visual inspection of the virtual waveform from spatial factor one suggested the negative deflection deemed to represent the fERN fell within this window.

The first step in this procedure is to calculate the portion of the grand average waveform that is represented by the special and temporal factor that is thought to represent the fERN. This is accomplished by using the results of the PCA to calculate new voltage readings. For a spatial-temporal PCA, one must multiply the factor scores of the temporal factor by the spatial factor loadings and by the standard deviations of the variables of the temporal step (Dien et al., 2003). This is multiplied by the spatial factor loading and by the standard deviations of the spatial variables (the channels). The full equation to calculate the voltage value for a specific channel (c) at a specific time point (t) is: L1*V1*L2*S2*V2 where L1 is the spatial PCA factor loading for c, V1 is the standard deviation of c, L2 is the temporal PCA factor loading for t, S2 is the mean factor scores for the temporal factor, and V2 is the standard deviation of the spatial factor scores at t. This equation can be used to construct a matrix of voltage readings which indicate

the portion of the grand average that is represented by the spatial and temporal factor in question. In the present study, four matrices of data were constructed for four separate dipole analyses. The four conditions were: trials with control participants where feedback indicated the response was correct, trials with control participants where feedback indicated the response was incorrect, trials with Parkinson's diseased participants where the feedback indicated the response was correct and trials with Parkinson's diseased participants where the feedback indicated the response was incorrect.

Dipole analyses were conducted using a four-shell elliptical head model. No constraints were set on dipole orientations. An algorithm was used where dipoles are placed until a position of maximum fit is found. Resulting solutions were converted to a Talairach coordinate system and the corresponding structure was identified using software designed to identify the structure based on a given set of Talairach coordinates.

Results

Behavioral and Cognitive Testing Data

Participants completed two psychological questionnaires and a battery of tests that measure multiple domains of cognitive functioning. The data resulting from these items are presented in table 3. In reference to measures of mood and apathy level, the Parkinson's disease group endorsed a significantly higher level of depressive symptoms ($t(30) = 2.32$, $p < .05$), however, there were no significant differences in reported activity level or apathy among the groups ($t(30) = -.44$, $p = .537$). In regard to measures of cognitive functioning, there were no significant differences between the groups on the measure of global cognitive functioning (MMSE) or vocabulary (Shipley) although there was a near significant trend for the control group to score higher on the MMSE ($t(30) = 2.02$, $p = .056$) and a trend for the control group to score higher on the vocabulary test ($t(30) = -1.94$, $p = .063$). There were no significant differences between the groups on a test of immediate memory (HVLT-R total), long term recall (HVLT-R recall) or long term recognition (HVLT-R recognition). In contrast, a comparison of the Parkinson's disease group and control group revealed significantly lower scores on a timed test of reading words on a page (Stroop Word) ($t(30) = -3.24$, $p < .005$), and identifying the color of multiple groups of x's on a page (Stroop Color) ($t(30) = -3.10$, $p < .005$) for the Parkinson's disease group. Patients in the Parkinson's disease group also scored significantly lower on a test of executive functioning (Stroop CW) ($t(30) = -2.73$, $p <$

.05) although there was no significant difference between the groups on the Stroop Interference score, a measure of the slowing of performance due to suppression of an automatic response adjusted for overall speed ($t(30) = 1.16$, $p = .256$). As described above, during the card choosing task, participants were given five seconds to enter a response in each trial. Analysis of the number of trials where participants failed to make a choice within the maximum time limit of five seconds revealed the participants in the Parkinson's disease group ($M = 8.93$, $S.D. = 13.53$) failed to make this choice within this time limit significantly more often than the participants in the control group ($M = 1.50$, $S.D. = 3.14$) ($t(30) = 2.14$, $p < .05$).

Table 3

Scores on cognitive and psychological measures for control and Parkinson's disease groups

	Controls		Parkinson's disease	
	Mean	SD	Mean	SD
MMSE	29.5	(0.63)	28.75	(1.34)
HVLT Total	24.68	(3.94)	22.38	(4.73)
HVLT-R Recall	8.75	(2.11)	7.33	(2.71)
HVLT-R Recognition	10.75	(1.24)	9.85	(1.77)
Stoop Word	98.36*	(9.86)	81.70	(15.95)
Stoop Color	70.58*	(9.08)	56.77	(13.48)
Stroop CW	36.71*	(10.32)	25.84	(10.36)
Stroop Interference	4.24	(7.33)	6.02	(6.79)
Shipley	36.00	(4.35)	32.73	(4.99)
BDI-2	4.81*	(4.35)	10.0	(7.57)
AES	63.6	(5.59)	62.4	(8.86)
No answer trials	1.5*	(3.14)	8.93	(13.53)

* $P < .05$

Compared to participants of past studies exploring ERN characteristics in those with Parkinson's disease, the sample in the present study were of similar stage of severity and cognitive ability. See table 4 for staging data and scores on cognitive measures.

ERP Data Analysis

The grand average waveforms for both groups are shown for the electrodes Fz, FCz, CZ, PCz, and Pz in figure 4. Visual inspection of the ERP data revealed a negative

Table 4

Disease severity and cognitive functioning of participants in studies exploring ERN in Parkinson's disease

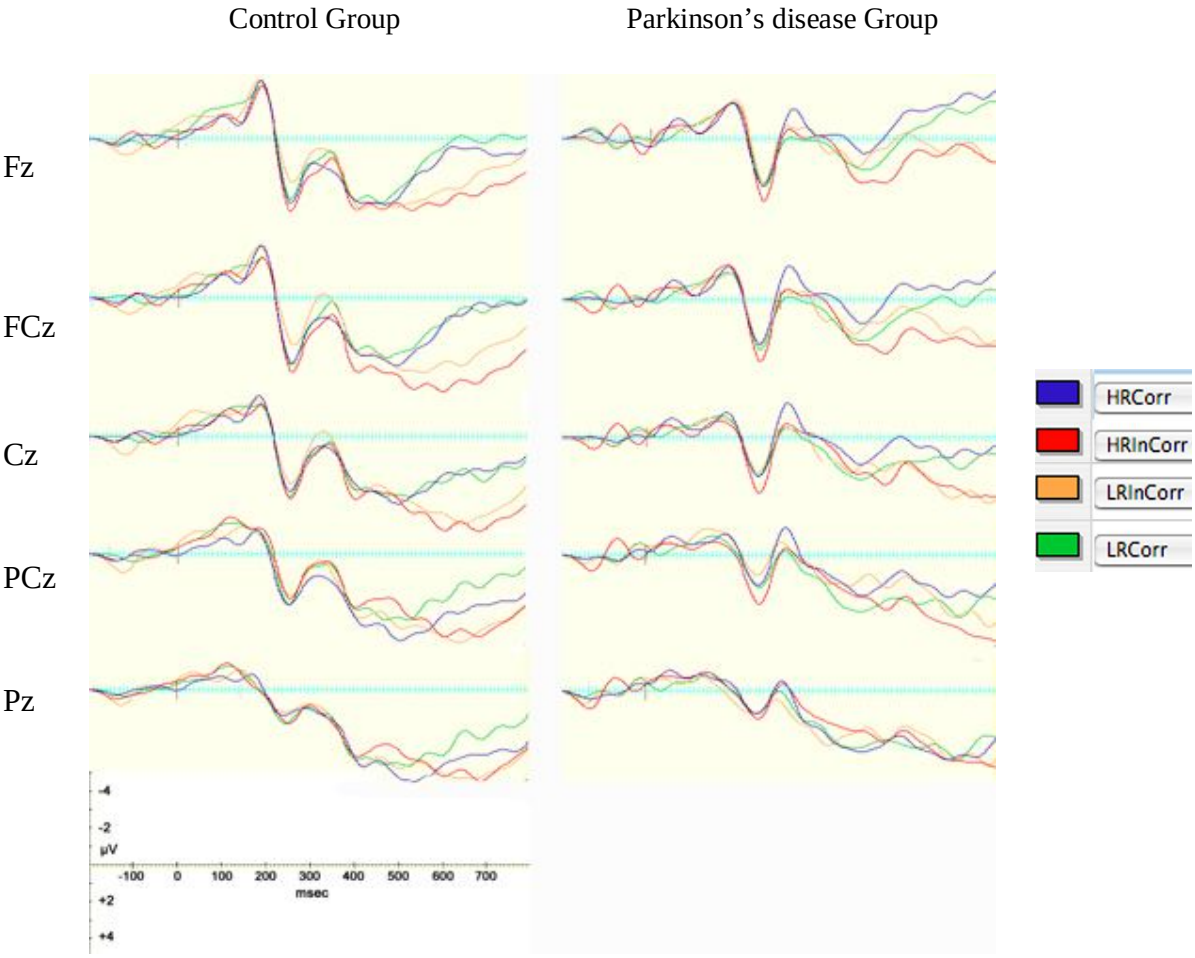
Study	Number participants	HY Score of PD participants	MMSE score of PD participants
Present study	Control: N = 16 PD: N = 16	2.50 (0.9)	28.75 (1.34)
Stemmer et al. (2007)	Control: N = 14 Medicated PD: N = 9 Nonmed PD: N = 9	 Medicated: 2.6* Nonmed: 2.1*	 Medicated: 28.2* Nonmed: 27.1*
Ito & Kitagawa (2007)	Control : N = 15 PD : N = 17	2.12 (0.70)	28.6 (0.8)
Holroyd et al. (2002)	Control : N = 9 PD : N = 9	2.50 (0.43)	28.6 (1.6)
Falkenstein et al. (2001)	Control : N = 13 PD : N = 13	No data	No data

* Standard deviations not reported in this study

deflection wave occurring approximately 320 milliseconds after feedback for the group of participants with Parkinson's disease and approximately 328 milliseconds for the control group free from neurological disorder. The negative deflection was largest for both groups at FCz and was smaller at electrodes that are more posterior. Thus, the negative deflection appears to be consistent with the timing, scalp distribution, and polarity of an error related negativity wave associated with feedback. However, it differs in the usual characteristics of a fERN in that there appears to be no difference between

the amplitude of the wave when the answer was deemed correct compared with when it was deemed incorrect.

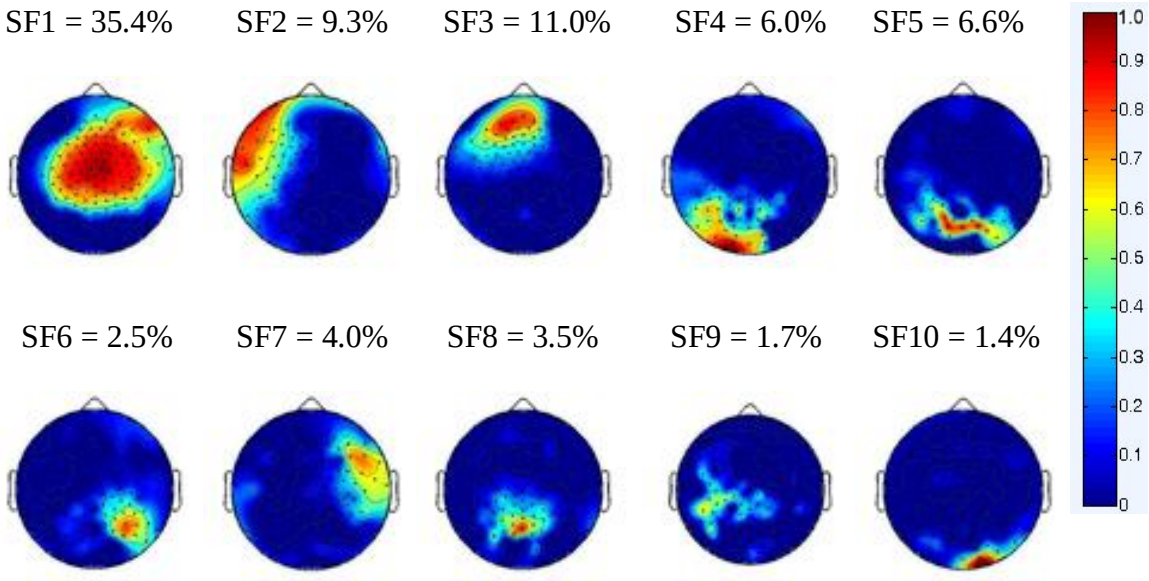
Figure 4: Grand average waveforms for both groups at electrodes: Fz, FCz, Cz, PCz, Pz



Principal components analysis results. In order to more accurately ascertain the scalp distribution and timing, and to test hypotheses regarding the amplitude of the midfrontal negativity identified in the data, a spatial PCA and temporal PCA were performed in accordance with the procedures described above. Data consisted of voltage readings obtained from all 32 participants, across 4 conditions, and 200 time points (time

points associated with data collected after the onset of feedback) for 129 electrodes, forming a 25600 X 129 matrix of raw voltage readings. The spatial PCA was conducted on the covariance matrix of the original data. The scree plot suggested retention of ten spatial factors that accounted for 81.4% of the total variance. These factors were rotated with varimax rotation. The rotated factor loadings of each spatial factor were plotted and are shown in figure 5. Both spatial factors one and three appear to have topographical distributions that are similar in nature to a typical fERN waveform. Spatial factor one bares the strongest resemblance to the theoretical scalp distribution of a typical fERN in

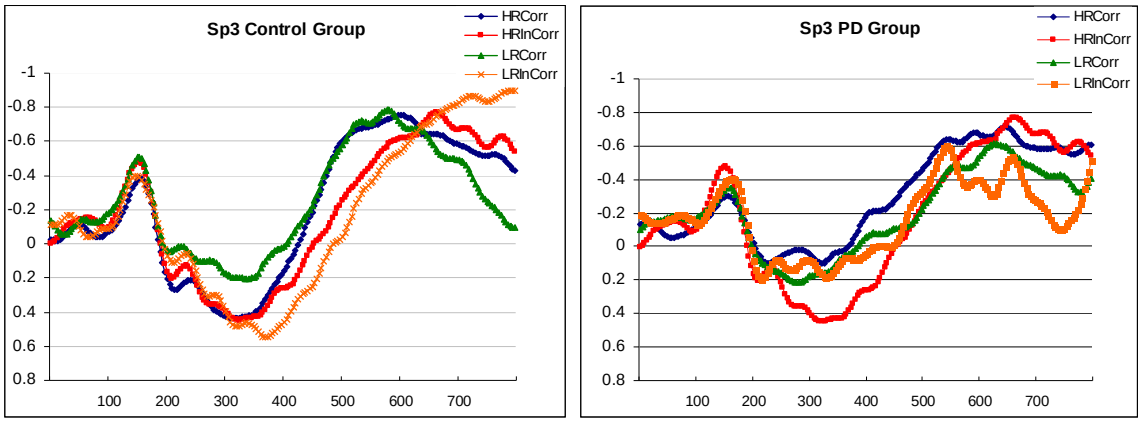
Figure 5. Topographical map of factor loadings of each spatial factor.



that it has a more central frontal distribution while spatial factor three is somewhat more frontal and shifted to the left. Spatial factor one is slightly shifted to the right but this is consistent with the spatial distribution of the feedback ERN present in past studies (Donkers et al.; Gehring & Willoughby, 2004; Nieuwenhuis et al., 2001).

According to Spencer and colleagues (2001) spatial factors can be explored by plotting the spatial factor scores for a given spatial factor at each time point. This procedure will result in a "virtual ERP" which represents the activity associated with each virtual electrode. Because the distribution of the electrodes where spatial factor one and three are most active match the typical distribution of an fERN, the virtual ERP's of these factors were plotted to explore them more completely. The virtual ERP's for spatial factor three are displayed in figure 6.

Figure 6. Spatial factor 3 plotted by time points for each group

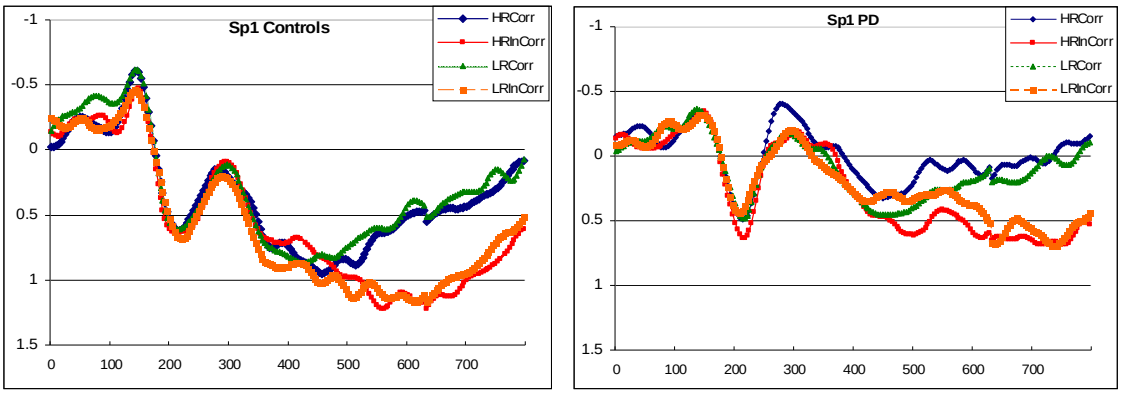


A visual assessment of the virtual ERP's formed by plotting spatial factor scores of spatial factor three across all time points shows a negative deflection similar to the first negative deflection in the grand average waveforms. However, this waveform occurs much earlier than a typical feedback ERN that peaks around 200-350 milliseconds after feedback presentation. Unlike the grand average waveforms, this virtual ERP does not have a negative deflection that was identified as a midfrontal negativity with traits similar to a typical fERN. Interestingly, there is some negative slow wave activity beginning around 400 milliseconds after feedback, peaking at approximately 600 milliseconds and

continuing onward. Because the midfrontal negativity of interest is not present in this virtual ERP we can conclude this spatial factor does not represent the variance associated with the waveform which might represent the fERN. Instead, this factor seems to be associated with the first negative deflection (possibly an N200) and slow wave activity described above.

The factor scores of spatial factor one at each time point is plotted in figure 7. Both of these virtual ERP's bare a stronger resemblance to the grand average waveforms in the FCz and Cz locations, where the midfrontal negativity appears to be largest. Even more importantly, both of these figures contain a negative deflection with a peak that occurs about the same time (approximately 295 milliseconds) and is of approximately the same shape as the midfrontal negativity of interest. Thus, it is highly likely then that spatial factor one represents the cluster of electrodes where this midfrontal negativity is the largest.

Figure7. Spatial factor 1 plotted by time points for each group

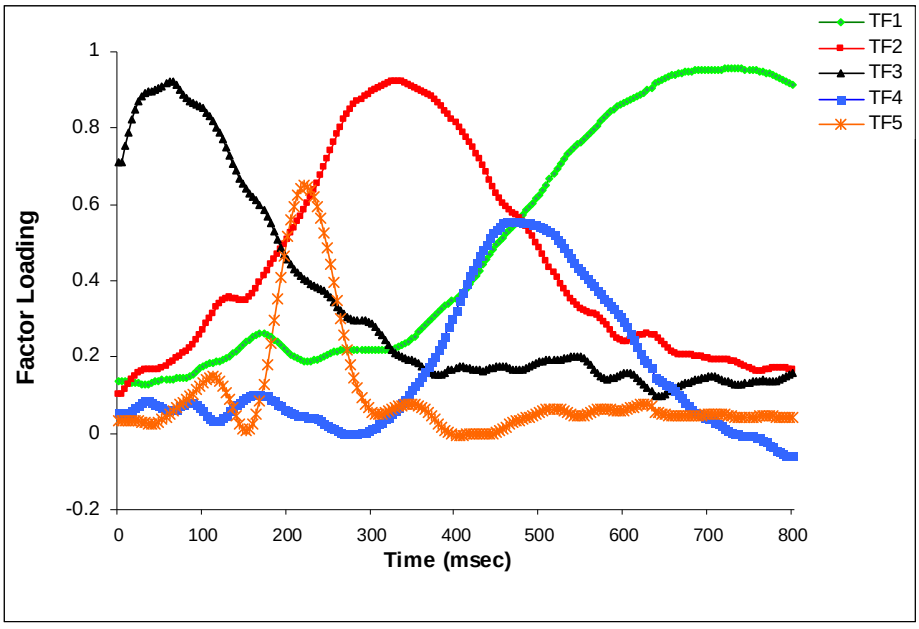


After the "spatial" PCA was complete, the spatial factor scores of each participant, of each condition, at each time point were subjected to a second PCA used to

reduce the time points to a set of "temporal factors." These temporal factors represent clusters of time points which denote the temporal location of various points of activity. Varimax rotation was employed again so that rotated factors remained orthogonal. A scree plot suggested retention of five temporal factors. The five temporal factors accounted for 92.37 percent of the variance. The factor loadings for each factor at each time point are plotted in figure 8. Factors loadings indicate the extent of the influence each factor has on each time point so that higher scores at a specific time point indicate where factors are most "active."

The first factor, accounting for 51.83% of the variance is most active during the later portion of the epoch. This appears to be consistent with the slow wave activity,

Figure 8. Factor loadings of the temporal factors retained



which often emerges as the first temporal factor in this type of analysis (Spencer et al., 2001). The second temporal factor, accounting for 23.98% of the variance peaks at

approximately 328 milliseconds after the feedback and is by far the most active temporal factor during this portion of the epoch. This is consistent with the peak of the negative deflections within the data that exhibit traits similar to a typical fERN. It is apparent that no other temporal factor peaks at this time and thus spatial factor 2 is highly likely to account for most of the temporal variance within the waveform of interest. The third factor, accounting for 7.82% of the variance, appears to denote early activity which could be the sensory processing of the onset of the feedback stimulus. None of the other temporal factors are highly active within the area of interest and are fairly negligible.

Hypothesis testing. Having identified the most likely spatial and temporal factor of interest, individual hypotheses may be tested. Specifically, the dependent variables used for statistical analyses from which we will test the proposed hypotheses are the temporal factor scores associated with temporal factor two and spatial factor one. These scores were subjected to a three-way ANOVA with group membership (Parkinson's group and control group) as the between subjects variable and reward magnitude (large and small) and validity of response (correct and incorrect) as the within subject variables. This analysis revealed no significant main effects or interactions. However, there was a trend in the data ($F(1,30) = 3.15$, $p = 0.86$) such that the high reward trials ($M = .063$, $SD = 1.28$) displayed a tendency to be associated with more negative temporal factor scores than the low reward trials ($M = .230$, $SD = 1.45$) in both groups and across all conditions.

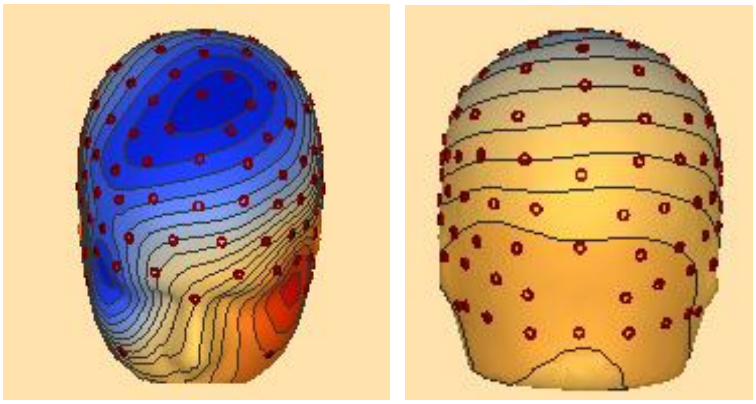
Brain electrical source analysis. As stated above, four separate dipole source analyses were performed where the grand average was reconstructed in order to reflect the portion accounted for by the spatial and temporal factor deemed to represent the mid frontal negativity of interest. Therefore, spatial factor one and temporal factor two were

used and the grand average waveform was reconstructed as described above. The four analyses were performed on the following: trials with control participants where feedback indicated the response was correct, trials with control participants with incorrect feedback, trials with Parkinson's disease participants where feedback indicated the response was correct and trials with Parkinson's disease participants where feedback indicated the response was incorrect. Consequence magnitude was not used as a criterion to separate conditions for source analyses because the PCA revealed no significant effect of this variable. Even though there was also no effect of group, the groups were still separated because neurological impairment may have some effect on the dipole sources.

For the analysis on trials with controls where the feedback indicated the response was correct, dipoles were placed using the data corresponding to a 200-400 millisecond window following feedback. This window was determined through visual inspection of the virtual waveform constructed from spatial factor one of the PCA. Visual inspection of the scalp voltage map constructed from the portion of the grand average that represents spatial factor one and temporal factor two revealed a mid-frontal negativity and a positivity and negativity over the left and right eye respectively (see figure 9). This denotes that the spatial factor which the BESA was performed on may have accounted for the mid frontal negativity of interest but also represented some variance due to horizontal eye movement not factored out by the eye movement removal procedures employed.

One dipole was fit to the data such that it was placed at the location that would lead to the minimal residual variance possible. This dipole was on the central midline and accounted for 85.9 percent of the variance. Although this is a large portion of the

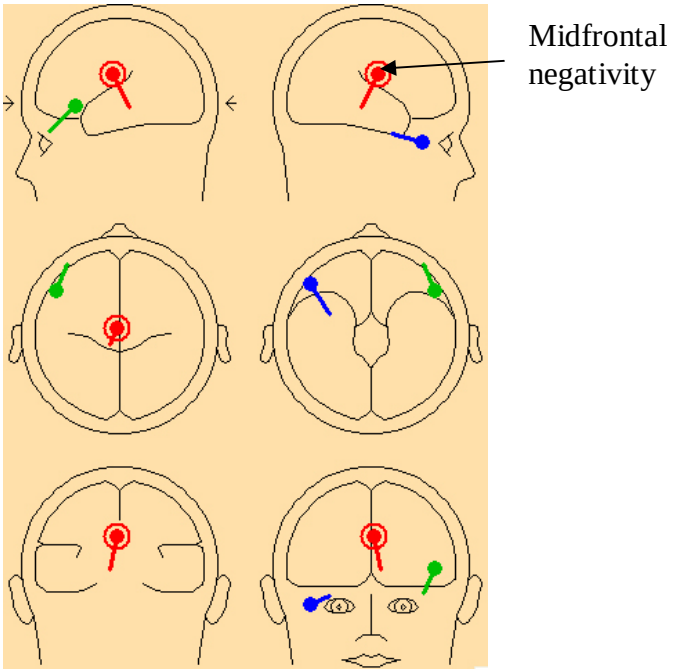
Figure 9. Voltage map of the front and back of the head for control participants when feedback indicates the response was correct.



variance, the residual variance (14.1 percent) is still quite high. Two more dipoles were placed in order to account for the voltage changes due to eye movement. All three were simultaneously fit to the data in a way that would minimize residual variance. The first dipole was refitted to obtain a solution with minimal residual variance but it moved very little. The algorithm placed next two dipoles near the eyes, corresponding voltage map. The final solution had a residual variance of 2.6 percent which is a substantial improvement for the fit of the model (see figure 10). Placement of a fourth dipole did not substantially improve the model so a three source model was accepted. The Talairach coordinates of the first dipole were (2, -13, 27) which falls in the cingulate gyrus or Brodmann's area 23. This indicates that the source of the mid-frontal negativity is likely within this region. Although the mathematical algorithm placed the dipole in the cingulate gyrus, several studies have reported a dipole source of the anterior cingulate cortex for the fERN. In order to test the feasibility of an anterior cingulate source for the mid-frontal negativity in the present study, the dipole was moved to the anterior cingulate

and the residual variance was calculated. This model was only slightly worse than the solution placing the mid-frontal negativity in the cingulate gyrus in that the residual variance was 4.7 percent. This model would therefore account for 95.3 percent of the variance and is still a very good fit.

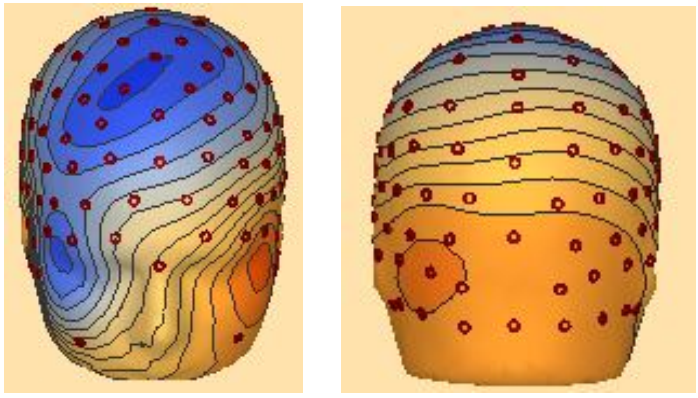
Figure 10. Elliptical head model of dipole sources for trials control participants where feedback indicates the response was correct.



For the analysis on trials with controls where the feedback indicated the response was incorrect, a window of 200-400 milliseconds after the feedback was used once again. Visual inspection of the voltage map revealed a similar scalp distribution to the scalp distribution for trials with control participants where the feedback indicated response was correct except that the mid-frontal negativity was a little more right lateralized. Specifically, there was a slightly right lateralized mid-frontal negativity along with a

positivity and negativity concentrated over the left and right eyes respectively (see figure 11).

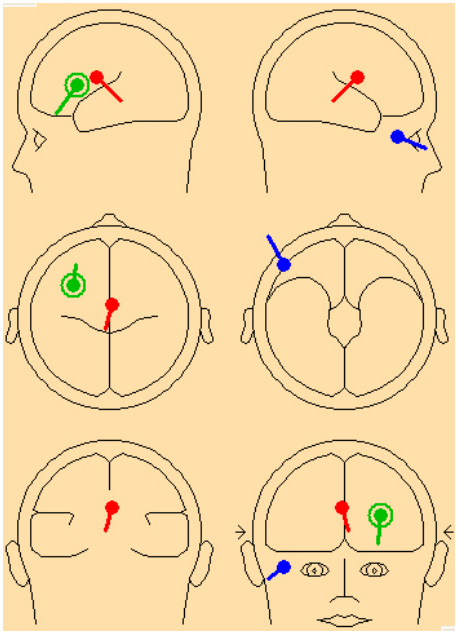
Figure 11. Voltage mappings for the front and back of the scalp for trials with control participants where feedback indicated the response was incorrect.



Once again, a single dipole was fit to the data. The single dipole model accounted for 86.8 percent of the variance. Two more dipoles were added to improve the model. The two dipoles reduced the residual variance substantially in that the three dipole model accounted for 97.2 percent of the variance (see figure 12). The addition of another dipole did not substantially improve the fit and therefore a three dipole solution was accepted. The first dipole was located at the Talairach coordinates (2.5, -4, 25) which is in the corpus callosum but very close to the cingulate gyrus. A corpus callosum location is not valid however in that it is physiologically not possible for the corpus callosum to generate ERP's that can be measured from the scalp. It is more likely that the modeling procedure is estimating the dipole to be deeper than it is because the activation on the scalp is wide spread. A more valid assumption is to conclude that the generator is likely in the cortical region near the area where the dipole was placed by the mathematical procedures used by

BESA. Assuming the real source is more shallow but in the direction of the dipole, the source would be located in either the cingulate gyrus in Brodmann's area 24 or the anterior cingulate cortex. In order to test the feasibility of this assumption the first dipole was moved to the anterior cingulate cortex. This model accounted for 96.6 percent of the variance which represents only a .6 percent reduction from the above model and still is a good fit for the data.

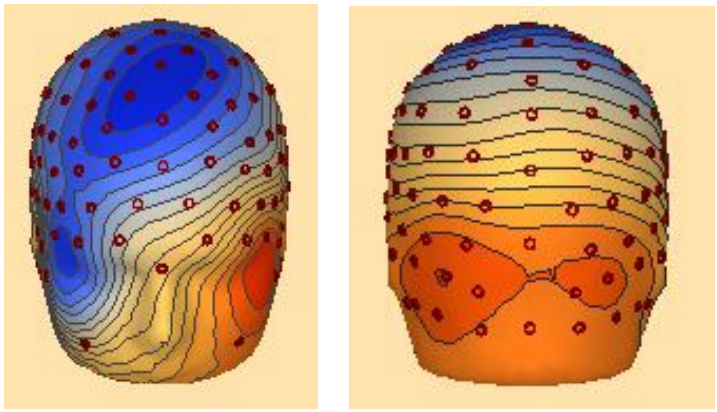
Figure 12. Elliptical head model of dipole sources for trials control participants where feedback indicates the response was incorrect.



For the analysis of the trials for participants with Parkinson's disease where feedback indicated the response was correct, dipole sources were modeled to the window of data corresponding to 200-400 milliseconds after the feedback. A visual scan of the voltage map revealed three areas where the voltage changes are centralized on the scalp (see figure 13). One appeared to be a negativity concentrated on the mid-frontal surface

of the scalp. Two of the areas were a positivity and negativity over the left and right eye respectively, probably representing some horizontal eye movement not fully filtered out by the eye movement correction procedures. This scalp distribution strongly resembled the scalp distribution of the previous two conditions.

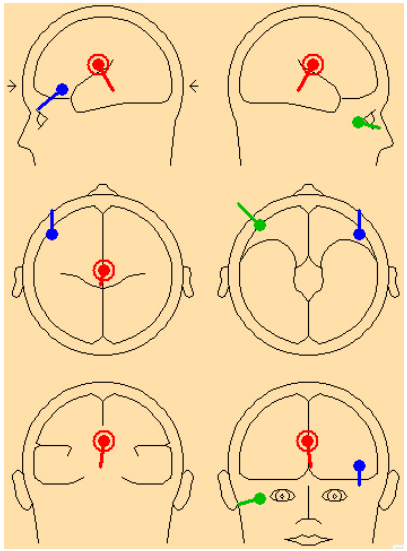
Figure 13. Voltage maps for trials with Parkinson's disease participants where feedback indicated the response was correct.



The first dipole fit to the data accounted for 87.4 percent of the variance. Adding two more dipoles to account for the variance due to the horizontal eye movement substantially improved the fit so that it accounted for 96.8 percent of the variance. Adding a fourth source did not substantially improve variance accounted for by the model so the three dipole model was accepted. The first dipole, representing the widespread negativity over the mid-frontal area of the scalp had Talairach coordinates of (-2, -6, 22) placing it in the corpus collosem (see figure 14). Considering that the corpus collosem is not an area where the activity can be readily measured from the scalp, and the imprecision of the measure of depth for BESA techniques, it is more likely the activity represented a wider spread sheath of activity in a more shallow area of nearby cortex.

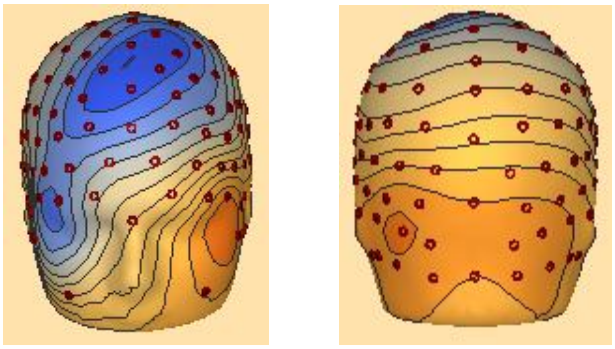
The most likely locations would be either the cingulate cortex or perhaps the anterior cingulate cortex. In order to test whether a dipole solution in the anterior cingulate cortex is reasonable, the variance accounted for by the model was calculated after moving the dipole in the anterior cingulate. This model was slightly worse than the above model and accounted for 95.2 percent of the variance. This model would still be a good fit to the data.

Figure 14. Elliptical head model of dipole sources for trials Parkinson's disease participants where feedback indicates the response was correct.



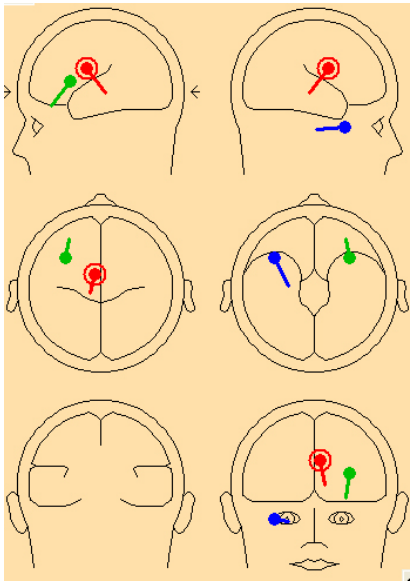
Finally, the same 200-400 millisecond temporal window was used in the dipole analysis for trials with Parkinson's disease participants where feedback indicated the response was incorrect. A visual inspection of the voltage map showed a similar scalp distribution to the other conditions. Specifically, the analyses revealed a widespread mid-frontal negativity and a positivity and negativity in the right and left eyes respectively. (see figure 15).

Figure 15. Voltage maps for trials with Parkinson's disease participants where feedback indicated the response was incorrect.



The resulting solution was a three dipole solution similar to the solution in the other conditions (see figure 16). The first dipole was placed such that it was set in the

Figure 16. Elliptical head model of dipole sources for trials Parkinson's disease participants where feedback indicates the response was incorrect.



location where there would be the least amount of residiual variance possible. This single dipole model accounted for 86.6 percent of the variance. When two more dipoles

were placed to account for the variance associated with eye movement, the model improved by accounting for 95.4 percent of the variance. The Talairach coordinates of the first dipole were (-5, -3, 26) placing it within the cingulate gyrus. Because a feedback ERN is usually located in the anterior cingulate, the first dipole was moved to see if such a model was feasible. Moving the dipole more anterior and shallow so that it was located in the anterior cingulate produced a model that would account for 95.1 percent of the data instead of 95.4 percent.

Exploratory Analyses Unrelated to the Original Hypotheses

Visual inspection of both the grand average waveforms and the "virtual waveform" depicted by spatial factor one revealed what appeared to be a difference in regard to voltage readings between trials with correct or error feedback such that there was more positivity late in the epoch when feedback indicated an error was made . This difference appears to begin approximately 450 milliseconds after presentation of feedback and continues through the end of the segment which extends to 800 milliseconds after feedback. In order to explore this difference more fully, further analyses were completed.

The timing of the waveform appeared to be depicted by temporal factor one. Therefore, the temporal factor scores associated with spatial factor one and temporal factor one were subjected to a three way ANOVA with the same variables as described above. As expected, there were no significant effects of group or consequence magnitude and no significant interactions. However, there was a significant main effect of response validity ($F(1,30) = 36.79$, $p < .05$) such that feedback indicating the response was

incorrect (M = .598, SD = .132) was associated with more positive variance than feedback indicated the response on the trial was correct (M = .111, SD = .132).

Errors appeared to be associated with a positive deflection late in the epoch. Because the spatial distribution of this deflection was not known, the other spatial factors were visually inspected and the temporal factor scores associated with temporal factor one and each spatial factor were subjected to three-way ANOVA's with group as the between subjects factor and validity of response and consequence magnitude as within subject factors. The analyses did not reveal any main effects or interactions except within spatial factor eight. Within spatial factor eight, there was a main effect of response validity ($F(1,30) = 6.31$), $p < .05$ such that trials with feedback indicating the response was incorrect (M = .421, SD = .145) were associated with more positive variance than trials with feedback indication the response was correct (M = .250, SD = .140).

Discussion

The present study was performed in order to accomplish two purposes. The first was to test some of the assumptions of a model presented by Holroyd and Coles (2002) stating that the ERN is due to decreased dopamine innervation of the anterior cingulate cortex from the basal ganglia. The second purpose as to assess the effect of the magnitude of monetary penalties and rewards on ERN amplitude and then ascertain whether the difference in amplitude would be attenuated in individuals with Parkinson's disease. As described elsewhere, the present study attempted to employ methodology where fERN amplitude would be used as the dependent variable. This differs from previous studies that have studied ERN in Parkinson's disease in that they all used tasks that would elicit a response ERN. The methodology of the present study was set up to elicit an fERN in order to overcome several confounds stated by Holroyd and colleagues (2002).

An unexpected finding of the current study was the lack of an effect for response validity in the statistical analyses. Specifically, there was a mid-frontal negativity elicited by the task used in the present study. However, the amplitude of the negativity associated with trials where participants received feedback stating they chose the correct card was approximately the same as the amplitude of the negativity associated with trials where participants received feedback stating they had made an error. Although many studies have reported a negative deflection associated with feedback indicating a correct

response, this is usually smaller than the negative deflection associated with feedback indicating an error. Larger negativity on error trials is a defining characteristic of the fERN (Gehring et al., 1993) and quite robust. In contrast, a CRN that is not significantly different in amplitude from an ERN is unusual and therefore casts some doubt as to whether the mid-frontal negativity recorded in the present study is a fERN.

Despite the lack of an effect for response validity, the mid-frontal negativity in the present study has many traits that resemble a feedback induced ERN. A waveform is defined by polarity, scalp distribution, timing, and response to eliciting conditions. The mid-frontal negativity in the present study is consistent with a typical fERN in terms of three of these criteria. Specifically, the scalp distribution of the mid-frontal negativity is consistent with the scalp topography expected of a typical fERN. The timing of the mid-frontal negativity in the present study is also identical to that of an fERN and the polarity is the same.

A dipole source analysis was conducted on the portion of the grand average waveform accounted for by the spatial and temporal factor of interest. This analysis was completed in order to assess whether the dipole source of the mid-frontal negativity of the present study was the same as the dipole source of fERN waves elicited in other studies. Thus, it was expected that the source would either be in the anterior cingulate cortex as reported by several studies (Hewig et al., 2007; Miltner et al.; Ruchsow et al., 2002) or in more posterior cingulate areas such as the cingulate gyrus as reported by two past studies (Badgaiyan & Posner, 1998; Muller et al., 2005). The voltage maps and the dipole sources of each of the four conditions were very similar to each other. The sources were determined to be in the corpus callosum in two of the conditions and the cingulate gyrus

in two of the conditions. Although the identified source structures differed, the Talairach conditions among the four conditions were very similar. It is important to note that the mathematical algorithms used by the dipole source software will place dipoles in the area that will yield the model with the most minimal residual variance, regardless of whether the solution is physiologically feasible. In two of the conditions, the mathematical solution did place the dipole source in the corpus callosum, a structure that can not generate activity that would yield ERP's which could be measured at the scalp. The nearest cortical region to the coordinates generated by the source analysis in these two conditions is the anterior cingulate cortex or perhaps more posterior cingulate regions. Placing the dipole within the anterior cingulate cortex during the two analyses discussed above yielded models that accounted for a very large portion of the variance. In both conditions the anterior cingulated cortex models accounted for at least 95 percent of the variance which is typically considered a good model. In addition, the quality of the fit to the data for the anterior cingulate cortex placed models were very close to as good as the models that were completely mathematically determined. Therefore, it is reasonable to conclude that the source of the four conditions is somewhere in the cingulate region, specifically in the cingulate gyrus or possibly in the anterior cingulate cortex. This is consistent with other fERN dipole source analyses which concluded the fERN was in the posterior regions of the cingulate but less consistent with the larger bulk of the literature that places the source of the fERN in the anterior cingulate. With respect to the contention that the mid-frontal negativity of the present study is a fERN, the dipole source analysis does not refute this conclusion. However, if the analysis yielded a dipole source that was more anterior and thus clearly with the anterior cingulate cortex, it would

have provided stronger support for the contention that the mid-frontal negativity of the present study is an fERN.

Returning to the issue of the lack of validity of response in the analysis, while this is a concern, there are several possibilities that could explain how the present study might elicit a CRN and fERN with similar amplitudes. There is some debate regarding whether the fERN and ERN represent the same phenomena or whether they differ in some ways. Both waveforms are negative and have a similar scalp distribution although several studies have reported the fERN may be more shifted to the right (Donkers et al. 2005; Gehring & Willoughby, 2004; Nieuwenhuis et al., 2001) and two source analyses report the fERN is more posterior than ERN (Badgaiyan & Posner, 1998; Muller et al., 2005). It is difficult to determine whether ERN and fERN differ in terms of voltage amplitude as there is great variance between labs and tasks in regard to amplitude of the ERN being observed. Only one study has directly measured fERN and ERN in the same participants (Donkers et al.). This study compared the negativity associated with a time estimation task (fERN) and a flankers task (ERN) and reported larger amplitudes with errors associated with the flankers task. In contrast, correct response negativity was larger for the task associated with the fERN than the ERN. In the present study, the waveform of interest is elicited by feedback on performance (possibly an fERN). If the fERN is typically smaller than ERN and if the CRN associated with feedback is larger than CRN associated with a task where the validity of response is immediately known then the choice to use a task involving fERN may have contributed to the lack of difference in the amplitude between the amplitude of the mid-frontal negativity elicited by feedback

indicating the response was incorrect and the amplitude when feedback indicating the response was correct which occurred in the present study.

A second contributing factor is that the current study measured fERN in elderly participants. The onset of Parkinson's disease typically occurs later in life than the age of a typical college aged sample. The control participants were matched to the participants with Parkinson's disease so that the nature of the design necessitated a sample of higher age than most other studies that have explored fERN. Studies that have investigated age-related changes in the ERN have consistently reported an attenuation of this waveform (Mathalon et al., 2003; Themanson et al., 2006; West, 2004) when compared to a sample of college students such that the difference between ERN and CRN in elderly participants is very attenuated or disappears entirely. At the present time, no study has compared fERN of younger adults with the fERN of elderly participants. Nonetheless, it is reasonable to assume that the fERN might show a similar age-related decline in amplitude given that the effect is quite robust for the response ERN.

The combination of the decision to use the amplitude of the negativity elicited by feedback and the need to use older participants in the present study might explain the lack of effect for response validity. Eliciting the negativity with feedback might result in a larger negativity for trials where feedback indicates the response was correct and smaller negativity for trials where feedback indicates the response was incorrect as compared to the negativity that might have been elicited by a task associated with a response ERN. In addition, an age-related attenuation of the negativity associated with error trials might have contributed to a lack of response validity as well. In summary, the lack of an effect of response validity is not entirely inconsistent with the literature regarding the fERN

when taking into account this effect is not robust in studies where participants are older and that the CRN and fERN difference is smaller for studies when the negativity is elicited by feedback. Nonetheless, the negativity generated in the present study will be referred to as a mid-frontal negativity in order to take a conservative stance. However, if the mid-frontal negativity of the present study is a fERN then the other analyses have ramifications on Holroyd and Cole's model. Therefore, the further analyses will be discussed in terms of what conclusions would be drawn based on the assumption that the mid-frontal negativity of the present study is an fERN.

The first purpose of the present study was to test a model proposed by Holroyd and Coles (2002) stating that the ERN occurs when an outcome that is "worse than expected" leads to a decrease in anterior cingulate cortex innervation from the mesencephalic dopamine system. The present study tested this hypothesis by comparing the negativity elicited by feedback that is generated by individuals with Parkinson's disease to the feedback elicited negativity of individuals free from neurological disorder. The hypothesis of the present study was that if the model presented by Holroyd and Coles is correct, the present study would reveal decreased amplitude associated with error trials for individuals with Parkinson's disease compared to age matched controls. This hypothesis was not supported in that there was neither a main effect nor any interaction for group membership in the analyses. Specifically, the amplitude of the mid-frontal negativity observed did not differ among the groups for any condition. Thus, participants with Parkinson's disease displayed normal mid-frontal negativity to error feedback (i.e. amplitudes comparable to the control group free of neurologic disease). Our findings are in conjunction with the results reported by one study (Holroyd et al., 2002) but contradict

the findings of several studies that reported decreased amplitude in the ERN for their participants with Parkinson's disease (Falkenstein et al., 1991; Ito, & Kitagawa, 2006; Stemmer et al., 2007).

There are two potential confounds noted by Holroyd and Coles that plague the articles reporting a decreased ERN among their participants with Parkinson's disease. First, an increased error rate in the Parkinson's disease participants could cause a reduction in ERN amplitude. Second, higher variation in between the intention to make a movement and the time a movement is registered may cause greater "response jitter" in the Parkinson's disease participants which would decrease the amplitude of the ERN. The methodology of the present study was such that error rate was fixed. Thus, there was no difference in the error rate among the groups and there was no "response jitter" as the timing of the ERN depended only on reaction to feedback, not an action requiring movement. The lack of a significant main effect or interaction with group membership supports the argument presented by Holroyd and colleagues that individuals with Parkinson's disease display normal ERN and that the reduction in ERN reported in previous studies would not be present if the potential confounds were addressed.

With respect to the first confound, an increased error rate in general could make errors more common and therefore more expected. Several studies that demonstrate a decreased ERN amplitude when the error rate is higher on a task (Hewig et al., 2006; Holroyd et al., 2003; Yasuda et al., 2004) and past studies reporting decreased response ERN amplitudes among their Parkinson's disease participants are subject to this confound (Falkenstein et al., 1991; Ito & Kitagawa, 2006; Stemmer et al., 2007). Because Parkinson's disease participants in previous studies have also had a larger error

rate than controls in past experiments studying the ERN, this increased error rate could account for the reduction in ERN amplitude. The present study used a fixed error rate. Thus, there was no difference in the error rate among the groups. Because there was no difference in the error rate among the groups, there was no reduction in fERN amplitude for either group caused by differences in error rate. The present study was not plagued by this potential confound and the analyses did not reveal an effect of group membership. This provides support for the argument made by Holroyd and colleagues (2002) that individuals with Parkinson's disease have normal ERN amplitude and would demonstrate this normal ERN amplitude if the confound of differential group error rates was addressed.

With respect to the second confound, response jitter, the current study measured response to feedback rather than measuring brain electrical activity occurring immediately after an erroneous response. Holroyd and colleagues state that individuals with Parkinson's disease have difficulty initiating movement. Therefore, for individuals with Parkinson's disease, there is increased variability in the time between the intention to make a movement and the time the movement is actually registered during an experiment. This increase in variability termed "response jitter" can artificially decrease ERN amplitude. The present study measured electrical brain response to feedback. Thus, the fERN amplitude is independent of "response jitter" because the electrical brain response to the movement is not used as the dependent variable. In addition, a mental reaction to feedback does not depend on a physical response on the part of the participant. Therefore, the present study also supports the argument made by Holroyd and colleagues

(2002) that individuals with Parkinson's disease will display normal ERN amplitude if this potential confound were adequately addressed.

An alternate explanation for the lack of an attenuation of the mid-frontal negativity for the individuals with Parkinson's disease in the present study is that a Type II error was made because the sample size did not permit sufficient power to detect a difference between the groups. While this may be a plausible argument, it is unlikely for two reasons. The first reason is that the sample size of 16 participants in each group in the current study is larger than all previous studies which explored the ERN within individuals with Parkinson's except for one study (see table 3). Secondly, although the analyses of the present study revealed no significant differences between the groups in regard to mid-frontal negativity amplitude, the amplitude of the mid-frontal negativity is numerically larger for the Parkinson's disease group. The temporal factor scores associated with the spatial factor and temporal factor thought to represent the mid-frontal negativity most consistent in nature with a typical fERN were also more negative for participants in the Parkinson's disease group than for the group free of neurological disorder. Thus, there is no indication within the data that there is even a tendency for smaller mid-frontal negativity amplitudes among those with Parkinson's disease. It is unlikely the addition of just a few more participants would cause the mean amplitude of the mid-frontal negativity of the participants free of neurological disorder to become greater than that Parkinson's disease group such that a statistically significant difference would be found.

It is possible that the disease severity of the Parkinson's disease group within the present study was not sufficient to cause a substantial enough decrease in dopamine

activity that would result in a disruption of the mesencephalic dopamine system described by Holroyd and Coles (2002). The mean Hoehn and Yahr score of the Parkinson's disease group in the present study was 2.5. Thus, the majority of the participants in this group were in the mild to moderate stages of the disease. Likewise, they demonstrated some mental slowing and executive functioning difficulty but only small decreases in memory or overall cognitive functioning. This is typical of the pattern of deficits expected within the first stages of the disease. Although there was a trend within the Parkinson's disease group's MMSE scores to be lower than the control group's score, the mean score of the Parkinson's disease group was 28.75 which is well within the range considered to denote normal cognitive functioning (Folstein, Folstein & McHugh, 1975).

The original goal of the present study was to recruit participants in more severe stages than previous studies. However, several practical issues made this goal difficult. Participants were much harder to recruit than originally anticipated so potential participants in the mild stages were not turned away. Furthermore, participants in more advanced stages of the disease had trouble completing the task. Some participants quit and stated the task was too complex while others stated the task was too fast. This occurred even after the various presentation times and response time allowed was increased several times from the speed it was conducted while collecting pilot data on college students. A larger portion of participants with Parkinson's disease also were also prone to movement artifacts which makes data unusable if too many trials need to be removed from analyses. Unfortunately, the complexity of the task meant that data from several participants in more advanced stages of the disease could not be used. Comparison of disease severity levels and MMSE scores for participants of the present

study and participants of former studies (see table 3) reveal that the disease severity and level of cognitive functioning were nearly equal (Falkenstein et al., 1991; Holroyd et al., 2002; Ito, & Kitagawa, 2006; Stemmer et al., 2007). Therefore, the Parkinson's disease participants demonstrated normal feedback ERN amplitude even though they were as impaired as the Parkinson's disease participants from past studies reporting attenuated response ERN's for this group. However, conclusions that may be drawn from the present study are limited in that the results do not eliminate the possibility that Parkinson's disease at moderate or severe stages would lead to a disruption of the mesencephalic dopamine system that would be sufficient enough to cause attenuation of the ERN. In addition, the results do not support that ERN is mediated by dopaminergic mechanisms proposed by Holroyd and Coles (2002) but they do not completely eliminate this possibility for the above reason. Nonetheless, there is a 60 to 80 percent reduction in dopamine cells within the substantia nigra when the first symptoms of Parkinson's disease are evident (Bernheimer et al., 1973). The participants in this study were off medication and obviously symptoms were visible so it is likely that there was a very severe decrease in dopaminergic activity of the Parkinson's disease participants in the present study even though some were in the mild stage of the disease.

Another possible contributing factor to the discrepancy between the results of the present study and past studies reporting decreased ERN amplitude among individuals with Parkinson's disease is that the dependent variable in the present study was the amplitude of a mid-frontal negativity generated by feedback and not a response ERN amplitude. Although previous authors have suggested that the fERN represents the same mechanism as the response ERN, and that the fERN and response ERN are both negative

and share similar scalp distributions (Miltner et al., 1997), slight discrepancies in scalp distribution between fERN and response ERN have been reported in a few studies (Donkers et al., 2005; Gehring & Willoughby, 2004; Nieuwenhuis et al., 2001). It has been suggested that fERN and response ERN are not representative of the same mechanism but there is little literature that poses specific theories in regard to how these two waveforms differ (Donkers et al., 2005; Gehring & Willoughby, 2004). Nonetheless if the two waveforms do represent distinct processes, then it is possible that Parkinson's disease may disrupt one while sparing the other. Specifically, it is possible that the individuals with Parkinson's disease from the current study would demonstrate an attenuated response ERN amplitude but have normal fERN.

The second purpose of the present study was to implement changes in magnitude of the consequence following a response and observe how these changes alter fERN in participants who are either free from neurological disorder or have Parkinson's disease. The first hypothesis in reference to magnitude of consequence was that trials with larger consequences would be associated with greater fERN amplitude than trials with smaller consequences. The second hypothesis was that the participants with Parkinson's Disease would demonstrate a more significant discrepancy in regard to the difference in fERN amplitude between trials with larger magnitude consequences versus trials with smaller magnitude consequences. The analysis of the present study yielded no significant main effect of magnitude of consequence and no significant interaction for magnitude of consequence and either response validity or group membership although there was a trend for higher magnitude trials to be associated with more negativity than lower magnitude trials. Thus, the present study does not support the hypothesis that there will

be a difference between trials associated with larger and small consequences for errors. Furthermore, it also does not support the hypothesis that this difference would be attenuated in those with Parkinson's disease.

Several studies yielded inconsistent findings in regard to the relationship between reward magnitude and the amplitude of the fERN. Although there are studies that report larger fERN amplitudes on error trials under conditions where correct answers yield larger rewards (Dikman and Allan, 2000; Hajcak et al., 2005; Pailing & Segalowitz, 2004) other studies have reported no relationship between fERN amplitude and magnitude of consequence (Hajcak et al., 2006; Holroyd et al., 2006). The lack of a relationship between the magnitude of consequence and fERN amplitude provides some difficulty for the model proposed by Holroyd and Coles (2002) because a failure to obtain a larger reward on an error trial would represent a larger discrepancy between the expected outcome and the outcome of that error trial. However, another possibility is that the model proposed by Holroyd and Coles is correct but that the system only evaluates outcomes on a categorical basis as suggested by Holroyd and colleagues (2006) rather than a graded response basis that depends on a certain magnitude of the difference between expected outcomes and actual outcomes that are worse than expected. That is, it may be the case that the system makes a binary decision to either generate an ERN or not based on whether an outcome is worse than expected or not worse than expected. In addition, the difference between an expected outcome and the actual outcome may need to be sufficiently large in order for an ERN to be generated. Therefore, the lack of main effect for reward magnitude suggests that the model proposed by Holroyd and Coles is incorrect or perhaps the model is correct but that the mechanism which governs the ERN

merely sorts outcomes of responses categorically into being either worse than expected or not worse than expected and generates an ERN when the outcome is worse than expected.

Similar conclusions may be drawn from the lack of an interaction between reward magnitude and group in the present study. If it is true that the deviation between the expected outcome and the outcome of a response is registered as a continuous variable by producing a graded signal, then damage to this system might disrupt the ability of the system to differentiate between larger and smaller violations of expectancy. The analysis might yield an interaction between group membership and magnitude of response such that the difference between the fERN amplitude associated with larger consequences and smaller consequences could be smaller in those with Parkinson's disease. The results of the present study did not support this hypothesis. One possible explanation of this is that the model proposed by Holroyd and Coles is incorrect and that the ERN is caused by a mechanism that remains intact in individuals with Parkinson's disease. Because there was no main effect of magnitude of consequence in the present study, it is possible that the model proposed by Holroyd and Coles is correct but as stated above it might only classify outcomes categorically with no graded response to stimuli that are worse than expected. If stimuli are classified in this matter, then disruption of the system that produces fERN would not cause a decrease in the difference of fERN amplitude associated with large and small consequences because no such difference would exist.

Late Positive Potential

Additional exploratory analyses performed on the data revealed that during the late portion of the wave form (after 450 milliseconds) trials where feedback indicated an

error was made elicited for more positive variance than trials with feedback indicating the response was correct. This occurred in both spatial factors one and eight. This late positive potential was unaffected by the magnitude of the consequence and group membership. Thus, it is unaffected by a manipulation of the size of the penalty administered for errors. It also appears to be unaffected by changes within the brain associated with mild to mid-stage Parkinson's disease. This late positive potential appears to have a large wide spread non-lateralized scalp distribution concentrated in the mid-frontal region. It seems to also extend more posterior than Cz due to it being represented in both spatial factors one and eight which have mid-frontal and middle posterior distributions respectively.

Although the discrepancy at this time in the waveform was unexpected, there are several possible explanations that may be derived from previous studies. However, a definitive explanation of the precise eliciting properties of this waveform is difficult to ascertain from data of the present study because there are multiple attributes of the error trials which may specifically be responsible for the wave deflection. One parsimonious explanation is that this might be merely a delayed p300 or p3b. The positivity might also represent a delayed Pe. Finally, there are several citations which describe a late positive potential of similar timing and scalp distributions that are elicited by tasks where the result of an action is "unexpected."

The first possibility, addressed is that this late positive potential is a delayed P300. Although the scalp distribution of the late positivity presented in the present study is more anterior than a typical P300, it is not inconsistent with the idea that the two spatial factors that comprise the effect might represent a novelty P3 and a P300

waveform. The latency is also not a large issue because there is variability in the latency of the P300 such that it is not implausible that a deflection with the latency of the late positive potential in the present study might be a P300. The P300 has been repeatedly elicited with an "oddball paradigm" during which participants are presented with multiple stimuli which can be classified into separate categories. If one of the two categories appear rarely, the amplitude of the P300 will have a negative correlation with the probability of the appearance of the rarer event. In other words, the rarer the less frequent event is, the larger the elicited P300 will be. Because errors occurred in only one third of the trials in the present study, it is the rarer of the two possible categories of feedback and may elicit a P300. Donchin (1981) proposed that the P300 is elicited by a neural system that becomes active when the current model of the subjects environment requires revision and that the presentation of an unexpected stimulus is an example of such a situation. Because participants in the present study are told that there are patterns that will lead to correct results, an error indicates that the participant must revise their representation of what the rule for obtaining correct answers is. Because of this, an error within this task parameter does represent a situation where the model of the environment needs revision. It is important to note that it is doubtful that the rarity of the presentation of error feedback alone it sufficient to elicit the late positive potential within the present study because neither report or visual inspection of the grand average waves of similar feedback studies where feedback indicating an error is rare revealed this same late positivity potential (Holroyd et al., 2003; Yasuda et al., 2004).

A second possibility is that the late positive potential revealed in the present study might represent a late positive potential (Pe) often reported in studies where a response

ERN is elicited. The Pe is a positive deflection having a slightly more posterior distribution than the ERN. It peaks approximately 200-400 milliseconds after an error and often follows an ERN (Falkenstein et al., 2000). Like the ERN, the Pe is larger during error trials. Source localization data suggest a generator in the ACC (Hermann, Rommler, Ehlis, Heidrich, Fallgatter, 2004; Van Veen & Carter, 2002). Several hypotheses have been proposed regarding the function of the Pe including: conscience recognition of an error, error-motivated refinement of response strategy, or simply the emotional response to the error (Falkenstein et al., 2000). Unlike the ERN, the Pe is only elicited when participants are aware of errors (Nieuwenhuis et al., 2001). In support of it's role in error compensation, multiple studies report a correlation between Pe amplitude and post-error slowing (Debener et al., 2005; Hajcak, McDonald & Simons, 2003). In support of Pe as an emotional response to an error, Pe amplitude is correlated with scores on the behavior activation system subscale (BAS) of the BAS/BIS scales (Boksem, Tops, Wester, Meijman & Lorist, 2006).

The late positivity found in the data of the present study is consistent with the proposed functionality of the Pe. In particular, because the instructions implied that learning patterns could reveal the correct answer on future trials, error feedback would indicate that the pattern the participant currently is using to guide responses needs refinement. Likewise, it is plausible that error feedback elicited an emotional reaction as well. However, the late positive potential in the current study does differ from a typical Pe deflection in that the scalp distribution is more anterior. Thus, it is appropriate to consider a third possibility that the deflection in the current study is similar to a late

positive potential with a more similar scalp distribution that has been reported in several studies.

In comparison to the late positive potential found in the current study, several studies have reported a late positive potential of similar scalp distribution, polarity, and a slightly faster latency. Authors proposed that these late positive potentials are elicited by an action leading to an expected consequence (Adachi, Morikawa & Nittono, 2007; Ehlis, Herrmann, Bernhard & Fallgatter, 2005). The small discrepancy in latency between the above studies and the present study could be attributed to the present study involving participants that were significantly older than the above mentioned studies. Nonetheless Ehlis and colleagues report a LPP elicited during an Eriksen's Flanker task where feedback indicating the response was incorrect was given on 4 percent of the trials where the response was actually correct. This positive wave deflection was centrally distributed and more anterior than the Pe elicited during the traditional error trials. In addition, this feedback did not elicit an ERN, indicating that mistakes generated by the computer and not their own behavior did not result in a fERN. Authors surmised that this wave was distinct from the Pe in terms of both timing and scalp distribution and perhaps represented detection of "surprising" events. Similarly Adachi and colleagues implemented an Eriksen's Flanker task where a stimulus indicated their inputted response. During 20 percent of these trials, the computer indicated the response registered differed from their actual response. This elicited an LPP with a slightly posterior central distribution beginning at 500 milliseconds after the presentation of the erroneous registration of their response. Authors conceptualized this represents registration of a mismatch between the expected and actual effects of a behavior. This is

consistent with the present study in that participants are told that the correct response can be determined by a pattern. Feedback indicating an error was made would be unexpected for participants that believe they have deduced the pattern of correct responses.

With respect to the present study, it is difficult to determine whether the late positive potential observed is elicited by the emotional reaction or individual salience of the error feedback as compared to feedback indicating a correct response. However, the attributes of the reported late positive potential in the above studies do bare strong resemblances to the waveform in this study.

It is important to note that the above discussed possibilities for the functionality of the observed late positive potential observed in the present study are not mutually exclusive. Whether the Pe or the late positive potential described in the above studies is a P300-related phenomena has yet to be determined. Nonetheless, the conclusions that can be drawn are that error feedback in the current study elicited a late positive potential with a mid-central scalp distribution and an onset of approximately 450 milliseconds. This waveform is not common in other feedback studies. However, the present study did differ from past fERN studies in that the instructions directly stated that there were patterns of correct responses and one could derive the correct answer on future trials when these patterns were discovered. This contrasts with other fERN that merely implied there might be patterns of correct responses by instructing participants to try to implement strategies that will lead to as many correct answers as possible.

Final Conclusions and Future Directions for Subsequent Research

In order to test hypotheses derived from the theory that the ERN is caused by a decrease in mesencephalic dopamine system enervation of the anterior cingulate cortex,

we measured fERN amplitude on a card selecting task completed by a sample of participants with Parkinson's disease and a sample of neurological intact "control" participants. The present study also used large and small rewards and punishments on correct and error trials respectively to explore the effect of magnitude of consequence on a fERN in these two samples of participants. The proposed hypotheses were not supported in that there were no significant main effects or interactions in regard to the amplitude of the elicited mid-frontal negativity. The results of the present study therefore suggest for individuals suffering from Parkinson's disease, the amplitude of the mid-frontal negativity elicited is normal and not attenuated. Although previous studies have reported decreased response ERN amplitudes among their Parkinson's disease participants, the present study overcome several potential confounds that render the other studies difficult to interpret.

In addition, magnitude of the consequence associated with a trial had no significant effect on the amplitude of the mid-frontal negativity elicited in the present study although the analysis did reveal a trend for the variance associated with higher magnitude trials to be more negative in the spatial and temporal areas identified to be variance associated with the mid-frontal negativity of interest. The design of the present study overcame the methodological flaws that plagued studies reporting decreased ERN amplitudes among participants with Parkinson's disease so it is not surprising the analyses demonstrated normal mid-frontal negativity amplitudes among those with Parkinson's disease. There are multiple conclusions that can be drawn from this study. One conclusion is that predictions from the model proposed by Holroyd and Coles (2002) may be incorrect and that disruptions in the mesencephalic dopamine system will not

disrupt the ERN. Another possibility is that the proposed theory is correct but that only very severe disruptions in the mesencephalic dopamine system, such as what would be displayed by those with Parkinson's disease in the severe stages effect the ERN.

Clearly there is a need then for further research where participants in the later stages are recruited. However, this could prove difficult as those in later stages may have difficulty initiating the movement needed to complete a response ERN task and they appeared to have trouble understanding a task that is as complex as the one in the present study. Future research could employ a less complex task where the validity of response is indicated by feedback. One possible design is to eliminate the idea that there are strategies or patterns that will help participants get more answers correct and to present the task as merely a guessing task. Another possibility is to use a passive reward design similar to the design used by Potts and colleagues (2006). In this study, participants watched stimuli being presented on a computer screen that informed them whether money would be added (signified by presentation of a bar) or subtracted (signified by presentation of a lemon) from their total earned for participation. They only had to attend to the presentation of stimuli and no response was required. Even though no active response was required, participants still demonstrated a robust fERN to the stimuli indicating money would be subtracted from their total. Such a design may be ideal for those in the later stages of Parkinson's disease as no response and no behavior strategies would be required. However should participants with Parkinson's disease display an attenuated fERN amplitude, it would be difficult to assess whether the decrease was from a Parkinson's related disruption in the mesencephalic dopamine system or the result of diminished attendance to the stimuli.

A potential shortcoming of the present study is that the participants were not required to give confidence ratings during the experiment. Past studies have demonstrated that fERN amplitude on a guessing task is larger when the probability of getting a correct answer is greater. The presumed mechanism behind this is that the participant is more confident when they are correct more often and thus, an error in this situation represents a larger deviation from the expected outcome than when errors are more frequent. In the present study, confidence should fluctuate because there will be trials the participants think they know the pattern from which a correct answer can be obtained and trials where they think they do not know the proper pattern. A confidence rating at the end of each trial would provide a method to estimate participants' confidence and therefore an ability to identify outcomes that deviate more or less from the participants' expected outcomes. Past studies have accomplished this by requesting that the participant rate their confidence on a four point scale. However, because there is variance in the way participants will define the points on a scale, a better method would be to have the participants state the probability of getting a correct answer on the next trial. This would provide a more universal quantification of their confidence level. One potential difficulty with confidence ratings is that the time it takes for the participant to make a rating and the subsequent interstimulus interval adds to the time necessary to complete a trial. When dealing with a sample that may be prone to fatigue, this would be an issue. A methodology that would alleviate this difficulty the use of experiment defined probabilities of getting a correct answer on the next trial such as presenting a number indicating the number of choices out of four that would be deemed correct. This would eliminate the added time necessary to make a confidence rating. Unfortunately,

there would be no guarantee the participant will be able to ascertain the probability of getting a response correct on the next trial by calculating it and no way to ensure participant believes the number is valid.

Implications for the present study are far reaching in that it did not provide support for Holroyd and Coles' model of proposed dopaminergic mechanisms underlying the ERN and fERN. Refinement of models regarding the neural mechanisms of these waveforms may be needed as the present study provides evidence that the system generating the fERN functions properly even in the face of substantial dopaminergic deprivation. It may be that protective factors allow the system to function adequately within individuals with Parkinson's disease under certain circumstances. Investigation of possible compensatory mechanisms or possible contributions of alternate neurotransmitter systems may provide interesting and fruitful avenues for future investigation and may provide greater understanding of the complexities of this model.

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