DIMINISHED AFFECTIVE MODULATION OF STARTLE TO THREATENING STIMULI IN PARKINSON'S DISEASE

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE

UNIVERSITY OF FLORIDA

2004

ACKNOWLEDGMENTS

I would like to acknowledge my research mentor, Dawn Bowers, for her constant availability and support. I would like to thank the graduate students and research assistants in the Cognitive Neuroscience Laboratory who helped in the collection of this data. I would like to thank Michael Okun and his colleagues at the Movement Disorders Center for providing access to patients, and the patients themselves who endured many long hours of testing.

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May 2004

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Major Department: Clinical and Health Psychology

Rationale. Studies of patients with Parkinson's disease have suggested various deficits in emotional processing. These impairments may be linked to a decrease in dopamine levels regulating key limbic circuitry, and pathology of the amygdala in Parkinson's patients. In the present study, the issue as to whether patients with Parkinson's disease display normal emotional modulation of startle to unpleasant and pleasant pictures was examined. Furthermore, within the category of unpleasant pictures, reactivity to threat-eliciting versus other types of aversive pictures was investigated. It was hypothesized that Parkinson's patients would show diminished emotional reactivity in general to the emotional pictures, based on suggestions of amygdala and limbic circuitry dysfunction. Additionally, it was hypothesized that Parkinson's patients would exhibit reduced emotional reactivity, relative to controls, to threat-eliciting pictures specifically, due to the role of the amygdala in processing of threatening stimuli.

Methods. To test this hypothesis, twenty Parkinson's patients and fifteen age-matched healthy Controls viewed standard sets of pleasant, unpleasant, and neutral pictures for six seconds each. During this time white noise bursts were binaurally presented to elicit startle eyeblinks. Subjective ratings of valence and arousal were also obtained. The Parkinson's patients were tested while "on" dopaminergic medication.

Results. Data were analyzed using 2 X 2 repeated measures Analyses of Variance. Both the Parkinson's patients and Controls showed significantly larger startle amplitude during unpleasant versus pleasant pictures, which is the normal pattern of emotion modulation. This effect was significantly weaker and less robust in the Parkinson's patients than the Controls, as revealed by a Group X Affect interaction. Specifically, startles to negative pictures were significantly smaller in Parkinson's than Controls, with no group differences for pleasant pictures. Within the unpleasant pictures, Controls showed a significantly larger startle amplitude during threatening versus other types of unpleasant pictures, whereas the Parkinson's patients did not. The Parkinson's and controls rated the emotional pictures similarly.

Conclusions. The current study found that Parkinson's patients were less emotionally reactive than controls to aversive pictures, specifically with regards to threat-eliciting pictures. The basis for this diminished reactivity is unknown, but may reflect pathological changes in the amygdala of PD patients, a structure consistently implicated in processing of fearful stimuli, as well as a reduction in dopamine levels within limbic neural circuitry.

CHAPTER 1
INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder next to Alzheimer's disease, affecting approximately half a million to a million people in the United States (McDonald, Richard, & DeLong, 2003). About 50,000 new cases are reported annually, and this figure is rising as the average age of the population increases (National Institute of Neurological Disorders and Stroke, 2001). Slightly more males than females suffer from Parkinson's disease. The average age of onset is approximately 60-65 years old, although a small proportion of PD patients (5-10%) display symptoms before age 40 (Fahn, 2003; Lang & Lozano, 1998). The likelihood of developing PD increases with age, with a lifetime risk of about 2% (Fahn, 2003).

Although the motor and cognitive symptoms of Parkinson's disease have been well studied over the years, relatively few studies have specifically examined changes in emotional reactivity. This is surprising in light of the fact that aspects of the neural circuitry affected by dopaminergic depletion in PD involve "limbic" regions that are known to be important in emotional behavior (i.e., amygdala, nucleus accumbens, orbitofrontal region). Thus, the goal of the present study was to investigate emotional reactivity in Parkinson's disease by using experimental measures that assessed physiologic reactivity to emotional pictures. To do this, patients' physiological responses to pictures of varying valence and arousal levels were measured and compared to the responses of control subjects. Before turning to a review of the literature on emotional processing in PD, the core symptoms of Parkinson's disease will be briefly discussed.

Motor and Cognitive Symptoms in Parkinson's Disease

Behaviorally, Parkinson's disease is characterized by motor symptoms including resting tremor, bradykinesia (slowed movement), rigidity (increased muscle tone), and akinesia (difficulty initiating or maintaining a body movement (Hughes, Ben-Shlomo, Daniel, & Lees, 1992; Hughes, Daniel, Kilford, & Lees, 1992)). Additionally, Parkinson's patients may experience diminished facial expressivity ("masked facies"), loss of postural reflexes, and/or motoric "freezing" when attempting to walk (Fahn, 2003). These motoric symptoms are thought to be caused primarily by a depletion of dopaminergic neurons in the substantia nigra. This dopaminergic depletion then affects a whole cascade of structures involved in the production of voluntary movement, particularly the basal ganglia. A diagram of the neural circuitry involved in Parkinson's disease is depicted in Figure 1-1. It has been estimated that patients with PD have an approximately 60-85% loss of dopaminergic neurons in the substantia nigra (Pogarell & Oertel, 1999). As such, dopamine replacement therapy (using levodopa, a dopamine precursor that is able to cross the blood-brain barrier) is the major medical approach to treating the motor symptoms of Parkinson's (Fahn, 2003). Initially, the motor symptoms of Parkinson's disease are dramatically improved by dopaminergic therapy. Over time, however, medications become less effective and are associated with dramatic "on" and "off" fluctuations in symptoms. This has led to recent surgical treatments for Parkinson's disease, including the implantation of small stimulating micro-electrodes into specific brain regions within the basal ganglia (i.e., globus pallidus internus, subthalamic nucleus). The basic idea behind deep brain stimulation and other surgical treatments for Parkinson's disease is to change the imbalance of activation and inhibition that results from dopaminergic depletion (Benabid, 2003).

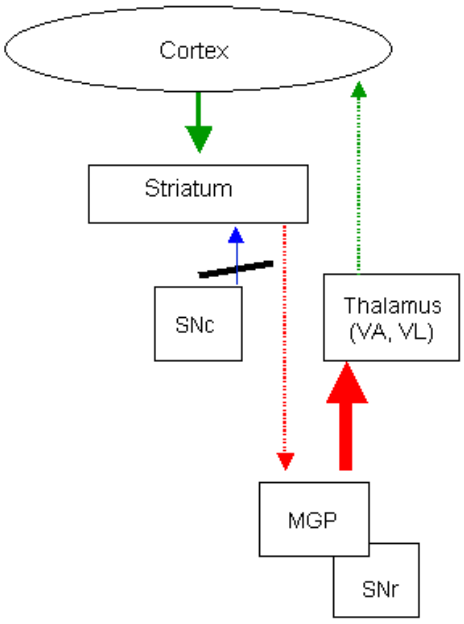

Figure 1-1. Simplified Direct Loop in the PD patient's Dysfunctional Motor System. The striatum receives excitatory projections from the cortex, but input from the SNc is impaired due to a reduction of dopamine. This results in the striatum not receiving enough excitatory input to exert its inhibitory influence over the MGP and SNr. The MGP and SNr, free of inhibition from the striatum, provide inhibitory influence over the thalamus, thus preventing the thalamus from providing excitatory output to the cortex. The inhibition of the thalamus and lack of cortical activation results in poverty of movement. (SNc = substantia nigra pars compacta, MGP = medial globus pallidus, SNr = substantia nigra pars reticularis).

Although the motor symptoms of Parkinson's disease are the primary focus of pharmacotherapy and surgical treatments, various nonmotor symptoms also occur and can be particularly disturbing and disabling. These include insomnia, autonomic dysfunction, mood disturbance, psychosis, and cognitive changes. Common cognitive sequalae are slowed thinking (bradyphrenia), impaired "set-shifting," reduced working memory, and forgetfulness (Cools, Barker, Sahakian, & Robbins, 2001; Dimitrov, Grafman, Soares, & Clark, 1999; Fahn, 2003; Gauntlett-Gilbert, Roberts, & Brown, 1999; van Spaendonck, Berger, Horstink, Borm, & Cools, 1995). Moreover, about 20% of Parkinson's patients develop a frank dementia (Brown & Marsden, 1984), which is

most common in PD patients with a later age of onset. When a patient suffers from both dementia and PD, they are referred to as having "Parkinson's plus syndrome" (Fahn, 2003).

Myriad studies have investigated the pattern of motoric and cognitive deficits found in Parkinson's disease. Fewer have delved into the domain of emotional changes that accompany Parkinson's disease, the focus of the current study. In the following sections, a brief overview of some of the emotional changes that accompany Parkinson's disease will be presented.

Emotional Processing in Parkinson's Disease

Emotional processing can be broadly conceptualized as encompassing four domains: mood (subjective emotional experience), perception, expression, and physiology. Research to date suggests that Parkinson's patients may exhibit difficulties in at least three of these domains. Each of these will be briefly reviewed below.

Mood Disturbance in Parkinson's Disease

A variety of studies have consistently found mood disturbances among patients with Parkinson's disease, with an average of 40-50% of PD patients experiencing depressive symptoms (Cummings, 1992; McDonald et al., 2003; Zgaljardic et al., 2003). Accumulating evidence over the years suggests that depression in PD may be secondary to the underlying neuroanatomical degeneration, rather than simply a reaction to psychosocial stress and disability, although the latter may clearly play a role as well. The incidence of depression is correlated with changes in central serotonergic function and neurodegeneration of specific cortical and subcortical pathways (Burn, 2002; Mayberg et al., 1990). In addition to decreasing quality of life, depression and other psychiatric

disturbance in Parkinson's patients appear to exacerbate motoric symptoms (Cummings, 1992).

Other common psychiatric disturbances in Parkinson's disease are anxiety and apathy (Fahn, 2003). Apathy refers to diminished emotional reactivity to both positive and negative events, lack of motivation to engage in goal-directed behavior or cognition, and a subjective sense of indifference (Marin, 1991). Between 40 and 50% of Parkinson's patients have been described as meeting criteria for apathy, based on various "apathy" scales (Isella et al., 2002; Starkstein, Mayberg, Preziosi, Andrezejewski, Leiguarda, & Robinson, 1992), with higher levels of apathy in Parkinson's patients relative to equally disabled patients with severe osteoarthritis (Pluck & Brown, 2002). Those patients with high levels of apathy are **not** more likely to be depressed or anxious than those with the lowest levels of apathy (Pluck & Brown, 2002). Instead, apathy has been correlated with increasing cognitive impairments. Like depression, it has been argued that apathy is more likely a direct consequence of disease related physiological changes than a psychological reaction or adaptation to disability (Brown & Pluck, 2000; Pluck & Brown, 2002).

Expression and Perception of Emotion in Parkinson's Disease

In addition to mood disturbances, patients with Parkinson's disease also have difficulty communicating emotion using various nonverbal signals such as facial expression and emotional tone of voice (Blonder, Gur, & Gur, 1989; Borod et al., 1990; Buck & Duffy, 1980; Jacobs, Shuren, Bowers, & Heilman, 1995 Smith, Smith, & Ellgring, 1996). In fact, one of the common clinical features of Parkinson's disease is "masked facies," a term that refers to the expressionless facial demeanor of PD patients. Diminished facial expressivity occurs relatively early in the disease course and is

unrelated to depression (Katiskitis & Pilowsky, 1991; Smith, Smith, & Ellgring, 1996). Recent studies using sophisticated computer imaging techniques have found that the facial movements in Parkinson's disease are actually smaller in amplitude, slower to initiate, occur less frequently, and correlate with other motor symptoms of Parkinson's disease such as bradykinesia (Bowers et al., in press). Unfortunately, diminished use of nonverbal communication signals by Parkinson patients poses significant problems, ranging from misdiagnosis of depression to the misattribution of negative emotion states by family members and health care providers.

The research literature regarding the perception of emotional information (faces, scenes, prosody) is inconsistent at best. Some investigators have found that Parkinson's disease patients are impaired when asked to identify emotional faces, emotional prosody, or emotional scenes (Blonder et al., 1989; Jacobs et al., 1995; Scott, Caird & Williams, 1984; Sprengelmeyer et al., 2003). Others, however, have not documented differences between Parkinson's disease patients and healthy controls (Adolphs, Schul and Tranel, 1998; Madeley, Ellis, & Mindham, 1995). Some possibilities that may account for these discrepancies are methodologic inconsistencies regarding the stage of severity of Parkinson's disease, whether patients are tested on versus off medications, and the extent of co-existing cognitive impairment or mood disturbance.

Recently, a particular interest has emerged with respect to the possibility that Parkinson's patients may have difficulties with processing of specific emotions such as "fear" or "disgust" relative to other emotions. Some researchers have found that PD patients appear to be more impaired at recognizing aversive facial expressions (i.e., anger, disgust, fear) than other expressions. For example, Kan and colleagues (Kan,

Kawamura, Hasegawa, Mochizuki, & Nakamura, 2002) found that PD patients were selectively impaired at recognizing fear and disgust facial expressions. However, not all researchers have found impairments in recognition of emotional facial expressions (Adolphs et al., 1998; Madeley et al., 1995).

Physiologic Reactivity

Another approach for examining emotional behavior involves monitoring patients' physiological reactivity to emotional materials. To date, there are no published studies of psychophysiologic reactivity to emotional materials in patients with Parkinson's disease. This is surprising, since using physiology as an index of emotional reactivity in a Parkinson's sample has several advantages. First, it does not require a voluntary motor response (as measurements of facial expressivity or vocal prosody do), thereby eliminating the confounding problem that the movements being used as an index of expressivity may be affected by the motor symptoms of PD. Secondly, measurement of physiological reaction does not depend on self-report (as many paper-and-pencil measures of mood do), and thus the demand characteristics associated with it are minimal. Finally, because the response that is being measured is near impossible to voluntarily control, it does not rely on the subject's attention, motivation, or cooperation (Bradley, 2000).

Skin conductance. One type of physiological reaction frequently measured in psychological research is skin conductance response (SCR) to emotional stimuli. This is accomplished by applying electrodes that essentially measure "palm sweat" to the inside of the hands. The larger the SCR, the larger the physiological arousal the subject has experienced in response to the emotional stimuli. Although measurement of SCR can be useful, it does have serious limitations. First, individuals vary considerably in how their

SCR to emotional stimuli habituates over time. Some individuals habituate after a few trials, whereas others do not appear to habituate much at all. Secondly, 15-20% of healthy people are "nonresponders;" that is, they to do not exhibit a discernable difference in SCR to varying types of stimuli (Bradley, 2000; O'Gorman, 1990). Finally, excess motor activity (such as tremor in the hands) can dramatically interfere with skin conductance recordings (Bradley, 2000). For these reasons, SCR data do not always produce consistent results, may not detect subtle between-groups differences in physiological responding, and may not be the most appropriate physiologic measure for patients with a movement disorder.

Startle eyeblink response. Another widely used index of emotional reactivity is the affective modulation of the startle eyeblink response (Lang, Bradley, & Cuthbert, 1990; Vrana, Spence, & Lang, 1988). It is this measure that was chosen to serve as the index of emotional reactivity in the present study. In order to understand the mechanism of this phenomenon, it is first necessary to describe the basic startle response and how it is neurally mediated. In mammals, an automatic startle response occurs at the abrupt onset of a stimulus, such as a jarring noise or flash of light. It is characterized by limb and trunk movements of the body, as well as a reflexive eyeblink (Bradley & Vrana, 1993). A variety of studies over the past decade have documented that size of the startle eyeblink is directly modulated by an individual's affective state (i.e., negative, positive). In humans, startle response magnitude (as indexed by reflexive eyeblink) is augmented during emotionally aversive tasks and attenuated during more pleasant tasks. This valence modulation of startle is observed across a variety of tasks involving slide viewing, imagining emotional situations, and anticipation of shock (Bradley, Cuthbert, &

Lang, 1990, 1991; Grillon, Ameli, Woods, & Merikangas, 1991; Lang, Bradley, & Cuthbert, 1990). Lang et al. (1990) proposed that startle response magnitude reflects the valence of the individual's central motivational state (appetitive versus aversive), rather than being a tactical response in a specific affective context.

The neural circuitry underlying the startle response has been exquisitely mapped out by Mike Davis and colleagues (Davis, 1992; Davis, Gendelman, Tischler, & Gendelman, 1982). Davis' group has shown that the basic startle circuitry is mediated entirely subcortically (at the level of the brainstem-spinal cord), and can be directly modulated by the *amygdala* (at least in rodents) via its projection to the brainstem. Electrical stimulation of the amygdala in rats facilitates startle (Rosen & Davis, 1988), while lesions of the amygdala diminish fear potentiated and shock sensitized startle responses while leaving the basic startle intact (Hitchcock & Davis, 1991; Hitchcock, Sananes, & Davis, 1989). Further, lesions at some cortical sites that relay information to the amygdala appear to attenuate fear potentiated startle in rodents (Rosen, Hitchcock, Miserendino, Falls, Campeau, & Davis, 1992). In humans, temporal lobe ablations involving the amygdala are associated with reduced startle potentiation during the viewing unpleasant pictures.

Taken together, these findings suggest that increases in the startle response during negative emotional states may reflect the amygdala's role in both threat detection and in modulating subcortical startle circuitry.

Pathophysiology of Emotional Changes in Parkinson's Disease

Before turning to the rationale for the current study, the question arises as to the basis for changes in emotional behavior in Parkinson's disease. There appears to be at least two possible mechanisms that might potentially affect emotional processing in

Parkinson's disease. First, the reduction in nigrostriatal dopamine found in PD influence neural circuits that have been implicated in emotion. Secondly, evidence has been found that the amygdala, a key limbic structure, exhibits significant pathological changes in Parkinson's disease. Each of these possible mechanisms will be discussed below.

Neural Circuitry Involved in Emotional Behavior

The deficits in emotional processing described previously may be linked to limbic circuitry subserved by the neurotransmitter dopamine. There are three main systems through which dopamine may affect emotional processing in PD: the striato-thalamo-cortico loops, the mesolimbic circuit, and the mesocortical circuit. Beginning with the first of these, Alexander, DeLong, & Strick (1986) proposed a network of five parallel striato-thalamo-cortical circuits that allow frontal cortical activity to be modulated by ascending input from the basal ganglia/thalamus through direct and indirect pathways. Two of these circuits involve key limbic areas such as the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the nucleus accumbens. General schematas of these two circuits are depicted in Figure 1-2.

Outside of these striato-thalamo-cortical circuits, the dopamine-mediated mesolimbic pathway is implicated in emotional processing as well. The ventral tegmental area has dopaminergic connections to the ventral striatum (which consists of the nucleus accumbens and olfactory tubercle) of the basal ganglia. Changes in dopaminergic input to the ventral striatum can then affect the associated striato-thalamo-cortical circuits, and thus depletion of dopamine may affect the ability of limbic structures to influence frontal cortical activity. Finally, the mesocortical circuit connects the ventral tegmental area to the cortex, and provides yet another way in which dopamine

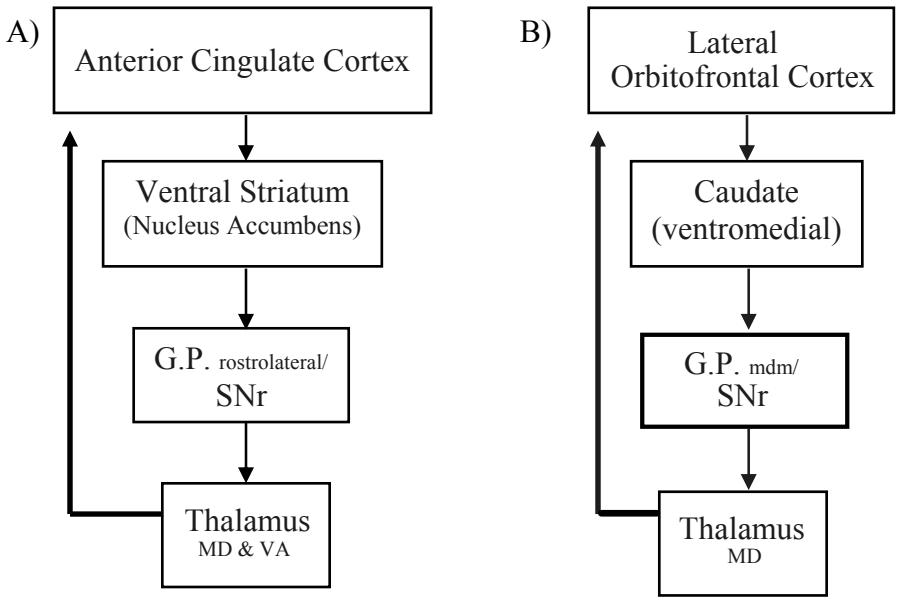

Figure 1-2. Two Hypothesized Striato-Thalamo-Cortical Loops Involved in Emotion. A) ACC loop, B) OFC loop. G.P.= globus pallidus, SNr = substantia nigra pars reticulata, mdm = medial dorsomedial.

depletion may affect emotional functioning. Cortical dopamine release modulates the descending cortico-striatal fibers, potentially influencing the activity of the striato-thalamo-cortico circuits (Brown & Pluck, 2000).

In summary, there are myriad hypothesized dopamine-mediated circuits that connect the limbic system to the frontal cortex and thus allow for emotional modulation of cognitive processes. The depletion of dopamine that characterizes Parkinson's disease may affect regulation of these circuits, potentially leading to dysfunction in emotional processing.

Amygdala Pathology

One of the key limbic structures involved in emotion is the amygdala, a small almond-shaped structure located within the anterior temporal lobe. The amygdala has consistently been implicated in the recognition of fearful stimuli and responding to

threatening situations. Monkeys with lesions of the amygdala do not display normal fear reactions to threatening stimuli, such as snakes (Amaral, 2003; Klüver & Bucy, 1939). In humans, lesions of the amygdala have been associated with behavioral placidity, diminished physiologic reactivity, and impairments in recognizing fearful faces (Aggleton, 1992; Calder, Young, Rowland, Perrett, Hodges, & Etcoff, 1996; Young, Aggleton, Hellawell, Johnson, Broks, & Hanley, 1995). Electrical stimulation of the amygdala elicits many of the behaviors used to define the state of "fear," such as tachycardia, increased galvanic skin response, corticosteroid release, and increased startle (Davis, 1992).

Recently, several investigators have found evidence of pathological changes in the amygdala of Parkinson's patients. In a post-mortem study, Harding and colleagues (Harding, Stimson, Henderson, & Halliday, 2002) found a 20% reduction in the amygdala volumes of PD patients compared to normal controls. Ouchi and colleagues (1999) found a 30-45% reduction of dopamine agonist binding in the amygdala of PD patients, which they speculated might be due to a loss of pre-synaptic dopamine terminals in this region. Additionally, post-mortem studies have found the presence of Lewy bodies in the amygdala of PD patients (Braak & Braak, 2000).

The fact that the amygdala has been shown to exhibit neuropathology in PD brings up the issue as to whether Parkinson's patients might have a diminished emotional reactivity to threatening stimuli, or difficulty interpreting expressions of fear in others. The findings thus far with respect to these questions are reviewed below.

Rationale for the Present Study

To date, there are no published studies that have used psychophysiology as a marker of emotional responsiveness in Parkinson's disease. Because of the symptoms of

PD include motor rigidity and slowing, using facial expressivity or vocal prosody as an index of emotional reactivity (as has been done in past studies) may potentially confound motoric deficits with emotional deficits. Thus, measurement of affective startle eyeblink magnitude may provide a clearer methodological approach to investigating emotional reactivity in this patient group. Seignorel and colleagues (Seignorel, Miller, Bowers, & Okun, 2003) found no significant differences in either latency or magnitude of startle eyeblink responses in a group of PD patients compared to controls, suggesting that despite motor impairments, basic eyeblink startle startle remain intact in Parkinson's patients. Similar findings with respect to the magnitude of basic startle responses have also been described by other researchers (Kofler et al., 2001; Vidailhet, Rothwell, Thompson, Lees, & Marsden, 1992).

The primary purpose of the present study was twofold: 1) To determine if PD patients and controls differ in degree of startle modulation produced by positive and negative stimuli; and 2) To determine if PD patients exhibit less startle potentiation to threatening stimuli, relative to controls. To date, no studies have investigated PD patients' *reaction* (as opposed to ability to recognize) to non-facial threat-evoking stimuli. For this reason, the issue of whether PD patients exhibit a normal response to threatening stimuli is unknown, although observations of amygdala pathology raise the possibility that threat responding may potentially be disrupted. The only existing studies that address threat processing in PD patients have focused on the ability to recognize fearful facial expressions. Findings from these studies have been mixed. In a task involving recognition of prototypical emotional facial expressions, Sprengelmeyer et al. (2003) found that medicated PD patients were specifically impaired at recognizing anger

and fear, compared to controls. However, when these same patients were tested on a different emotion recognition task (involving morphed images of emotional expressions), they demonstrated no deficit. Kan et al. (2003) found that PD patients were impaired in the recognition of fear and disgust when moving facial stimuli were used. Thus, these studies raise the possibility that recognition of fearful faces may be impaired in PD patients, but do not address the issue of whether an abnormal reaction to a threat-eliciting stimulus exists at the physiologic or subjective level in Parkinson's.

Hypotheses and Predictions

In healthy subjects, unpleasant stimuli are consistently associated with larger blinks compared to pleasant stimuli. Keeping this in mind, the following hypotheses were made:

Hypothesis 1

Parkinson's disease patients will display diminished emotional reactivity relative to normal controls, as indexed by startle modulation during affective pictures. Thus, it was predicted that PD patients would exhibit a significantly smaller eyeblink magnitude than controls while viewing unpleasant slides, and a significantly larger eyeblink magnitude than controls while viewing pleasant slides. This prediction is based on the observations that PD patients show 1) reduced striatal dopamine, which may affect dopamine-mediated limbic circuits; and 2) amygdala neuropathology, which may affect the ability of the amygdala to modulate the basic startle response.

Hypothesis 2

Parkinson's patients will show a more diminished emotional response to threatening pictures as compared to other categories of unpleasant pictures. Specifically, it was predicted that PD patients would display a significantly smaller eyeblink

magnitude than controls in response to threatening slides, whereas their eyeblink magnitude during other unpleasant pictures would not significantly differ from that of controls. This prediction is based on the fact that the amygdala is known to play a key role in responding to threatening stimuli, is implicated in the fear-potentiated startle, and exhibits pathology in PD patients.

Exploratory Questions

In addition to the major hypotheses described above, several exploratory questions were addressed. For example, would Parkinson patients rate the affective pictures as intensely emotional as the controls in terms of valence? This is an important question for several reasons. First, if PD patients rated the emotional pictures as less intense, then this might be due to perceptual problems in appraising the stimuli, which could potentially influence emotional reactivity. Alternatively, reduced ratings might be due to some alteration in emotional appraisal. As mentioned previously, approximately 40% of PD patients experience apathy (Marin, 1996). One component of apathy is diminished emotional response to both positive and negative events. Whether this holds true for positive and negative pictures in an experimental setting, which is obviously much different from the natural environment, is unknown. If it does indeed hold true, then patients with PD should find unpleasant pictures less unpleasant than controls, and pleasant pictures should be rated as less pleasant than control' ratings. On the other hand, Smith et al. (1996) found that PD patients rated emotional scenes from movies no differently from healthy controls. This raises the possibility that patients in the current study might rate pictures similarly to controls, yet nevertheless show differences in emotional reactivity as indexed by startle. This situation would suggest a "decoupling" between appraisal and the translation of the results of this appraisal into a motivational

state. The amygdala is thought to play a pivotal role in this translational process based on lesion studies of patients who have undergone resection of the mesial temporal region including the amygdala (Bowers et al., 1998). Should a decoupling be found in Parkinson's patients, this finding would be consistent with some abnormality in the "translational" process, possibly related to alterations in amygdala functioning. An additional question was whether controls and PD patients would find the pictures similarly arousing. If PD patients are experiencing emotional "blunting", one might expect them to find the emotional stimuli less arousing than controls. Finally, it was important to determine if any differences between patients' and controls' emotional startle modulation could be attributed to differences in level of depression. Therefore, an additional exploratory goal was to investigate any possible association between depressive symptoms and startle eyeblink magnitude.

CHAPTER 2
METHODS

Participants

Participants included twenty patients with idiopathic Parkinson's disease and fifteen healthy age-matched controls. The Parkinson's patients were recruited through the Movement Disorders Center of the University of Florida and had been evaluated within the preceding three months by a movement disorders neurologist (Dr. Okun or Dr. Fernandez). As part of their routine workup in the Movement Disorders Clinic, the Parkinson's patients received standard measures for staging the severity of their motor symptoms and disease course. These included: the *United Parkinson Disease Rating Scale-Third Edition*[1] *(*motor subscale [Fahn & Elton, 1987]), a modified *Hoehn-Yahr scale*[2] (Hoehn & Yahr, 1967), and the *Schwab and England Activities of Daily Living*[3] *(*Schwab & England, 1969*).* Patients were evaluated on these scales "off" medication (12 hours after last levodopa dose) and again one hour after taking their medication ("on" state). During this clinical evaluation, PD patients were also screened for dementia (*Mini-Mental State Exam* [Folstein, Folstein, & McHugh, 2001]), depressed mood (*Beck*

[1] This is a rating tool designed to assess the severity of various motor symptoms over the course of the disease. Higher scores indicate greater severity. Patients were assessed while on and off dopaminergic medication.

[2] This scale is used to rate the "stage" of severity/disability in the PD patient. Stages range from 1-5, with five being the most severe (cannot walk without assistance, or is confined to wheelchair). Patients were assessed while on and off dopaminergic medication.

[3] This rating scale is an index of the PD patient's level of functioning in activities of daily life. Scores range from 0-100%, with 100% indicating complete independence, and 0% indicating that the patient is bedridden.

Depression Inventory [Beck, 1978]), and decreased quality of life (*Parkinson Disease Quality of Life Scale-39* [Peto, Jenkinson, & Fitzpatrick, 1998]).

To be included in the PD group, patients had to meet stringent diagnostic criteria for Parkinson's disease, be free of other neurologic or medical illness that would compromise their participation (or interpretation of findings), and be free of dementia and significant psychological distress (i.e., a psychiatric disorder). The clinical diagnosis of idiopathic PD was based on: (a) the presence of at least two of four cardinal motor signals (i.e., akinesia, bradykinesia, resting tremor, rigidity [Hughes, Ben-Shlomo, et al., 1992; Hughes, Daniel, et al., 1992]); and (b) a demonstrated therapeutic response to dopamine replacement therapy, as defined by a marked improvement in Parkinsonian motor signs, based on the motor subscore of the United Parkinson Disease Rating Scale (UPDRS) following administration of levodopa during their screening neurologic examination. A demonstrated good response to levodopa therapy was required in order to exclude patients with Parkinson's plus syndromes (e.g., Shy-Drager, multiple system atrophy, Lewy body disease, corticobasal degeneration). Only Parkinson patients who scored in the nondemented range on the Mini-Mental State Exam (>26) were invited to participate in the present study.

The PD patients included sixteen men and four women, who ranged in age from 43 to 85 ($X = 61.9$, $SD = 10.0$). As a group, they had been treated for Parkinson's disease for eleven years and were in the mid-stages of their disease, based on staging criteria from the Hoehn and Yahr scale. This information is depicted in Table 1-1. In order to assess depressive symptomatology, all patients received the Beck Depression Inventory (BDI) on the same day they received the experimental emotional tasks. The BDI scores

for the PD patients included in the present study ranged from two to nineteen (means and standard deviations are shown in Table 1-1). Two patients met criteria for Mild Depression (BDIs = 14 and 19), as defined by Beck, Steer, & Brown (1996).

Control participants included fifteen healthy individuals (ten men, five women) who had been recruited from the community. Any control participant with reported psychiatric disorder, head previous head injury, learning disability, or neurological disorder was excluded. Controls were also given the BDI. There were no instances in which Control participants produced BDI scores that exceeded thirteen (the recommended cutoff score for Mild Depression; Beck et al., 1996).

A comparison of patient and control demographic variables is presented in Table 1-1. As shown, the PD and Control groups did not **significantly** differ with respect to age ($t(33)= 1.90$, $p = .40$), although the mean age of the PD patients was about ten years greater than that of the controls. The reason for this discrepancy related to the young age of two of the control subjects (these subjects were twenty-five and twenty-nine years old, respectively). Additionally, the PD patients were slightly more educated than the controls ($t (28.7)= 2.04$, $p = .05$). The PD patients had a mean of fifteen years of education, whereas controls had a mean of 13.5 years of education. Finally, PD patients and controls significantly differed with respect to their mean BDI scores ($t(31) = 3.06$, $p<.005$), with BDI scores of the PD group ($X = 8.5$) being significantly higher than those of the Controls ($X = 4.1$).

Materials

International Affective Picture System Slides

Participants viewed a subset of forty-four pictures (twelve pleasant, twelve unpleasant, twelve neutral, and eight "filler") taken from the International Affective

Table 1-1. Patient and Control Characteristics

	PD patients	**Controls**	
	(N= 20)	*(N= 15)*	
Men: Women	16:4	10: 5	
Age	62.9 (10)	53.8 (15.2)	*ns*
Yrs. Ed	15. (2.9)	13.5 (1.3)	$p = .05$
Hoehn-Yahr*	2.7 (.52)	--	
UPDRS motor*	27.2 (10.2)	--	
Yrs. with PD	10.8 (6.0)	--	
BDI	8.5 (4.0)	4.1 (4.0)	$p < .005$

* Assessed while on dopaminergic medication.

Picture System (Lang, Bradley, & Cuthbert, 2001a). Efforts were made to equate the pleasant and unpleasant pictures on the basis of normative ratings of arousal (Lang, Bradley, & Cuthbert, 2001b); however, a t-test revealed that the normative sample of men and women found the unpleasant pictures to be more arousing on average than the pleasant pictures, $t(11) = 2.73$, $p < .05$ (mean of Unpleasant pictures = 6.6, SD = .664; mean of Pleasant pictures = 5.8, SD = 1.03 [ratings range from one to nine, with nine being the most arousing]).[4] The experiment began with two filler slides for practice, followed by six blocks of seven trials. Each block contained two unpleasant slides, two pleasant slides, two neutral slides, and one filler slide, presented in randomized order.

In order to investigate the impact of threatening pictures on emotional reactivity, the negative pictures were further divided into two additional categories: "Threat" versus "other unpleasant" pictures. "Threat" slides were defined as any slide suggesting imminent attack, such as a snake preparing to bite, a gun pointed at the viewer, or a dog with saliva-dripping fangs spread open. All remaining unpleasant pictures were then

[4] These normative ratings were obtained from a large sample of college students, and thus may not be applicable to older participants. Additionally, the male to female ratio of the normative sample differs from that of the current study.

categorized as “other unpleasant” pictures. This post-hoc division resulted in seven “threat” pictures and five “other unpleasant” pictures. The IAPS numbers for the threat pictures are: 1090, 2120, 1300, 3000, 3530, 6230, 6370). The IAPS numbers for the “other unpleasant” pictures are: 3010, 3100, 3130, 9040, 9050). “Threat” pictures had a mean normative arousal rating of 6.40 (SD = 0.862) and “other unpleasant” pictures had a mean normative arousal rating of 6.56 (SD = 0.52 [Lang, Bradley, & Cuthbert, 2001b]).

Self Assessment Manikin (SAM)

Each participant rated the pictures for valence (pleasant, unpleasant) and arousal using the Self Assessment Manikin (SAM). SAM is a graphic display depicting a cartoon figure that varies along the dimensions of valence and arousal (Greenwald, Cook, & Lang, 1989; Lang, 1980). For valence, nine versions of the cartoon figure were shown, ranging from positive to neutral to negative. For arousal, nine versions of the cartoon figure were shown ranging, from sleepy to neutral to highly excited. During the experiment, participants were asked to rate their reactions to each IAPS picture immediately after viewing it by referring to the SAM figures. The SAM figures were vertically displayed on a computer screen in front of the participants. The participants verbally gave their valence and arousal ratings which were heard, via an intercom, by an investigator in an adjacent room.

Procedures

Data Collection

Prior to beginning the study, informed consent was obtained from each participant according to University and Federal guidelines. All testing took place in the Cognitive Neuroscience Laboratory of the UF Brain Institute. The session began with completion of various questionnaires, including the BDI. This was followed by a detailed

description of the study and attachment of electrodes over the face and hands. (For the purpose of the present study, only the startle component will be described). After cleaning the area under the eye, two 3 mm Ag/AgCl electrodes were filled with a conducting gel (Medical Associates, Inc., Stock # TD-40, Lot # 70204) and were positioned under the left and right eyes to record EMG activity from the orbicularis oculi muscle. Electrodes were affixed to the skin surface with adhesive collars. During the experiment, participants sat in a reclining chair that was located in a sound-attenuated and electrically shielded 12'x12' room. Visual stimuli were displayed on a 21" computer monitor located directly in front of the participant. After the participant was taught how to use SAM and practiced with two sample slides, the experiment commenced. Each trial began by presentation of the picture for six seconds. During this time, startle eyeblinks were elicited by a 50 ms burst of white noise (95dB, instantaneous rise time) that was delivered binaurally via Telephonics (TD-591c) headphones. A Colbourn S81-02 module generated the white noise bursts that were gated through a Colbourn S82-24 amplifier. These white noise bursts (startle probes) were randomly presented at various points following picture onset (i.e., 4200, 5000, or 5800 ms) and counterbalanced across valence category. Following each picture, the SAM figure appeared on the computer screen and the participant verbally rated his/her subjective level of valence and arousal.

Data Reduction of the Eyeblink Component of the Startle Response

The eyeblink component of the startle response was measured by recording EMG activity from the orbicularis oculi muscle beneath each eye. The raw EMG signal was amplified and frequencies below 90 Hz and above 1000 Hz were filtered using a Colbourn bioamplifier. Amplification of acoustic startle was set at 30,000. The raw signal was then rectified and integrated using a Colbourn Contour Following Integrator

with a time constant of 200 ms. This information was sent to a Scientific Solutions A/D board interconnected with a custom personal computer. Digital sampling at 1000 Hz began 50ms prior to startle probe onset and continued at this rate for 250 ms after the probe onset. The startle data were reduced off-line using custom software programs. These programs automatically eliminate trials with an unstable baseline and derive baseline, peak, and blink amplitude values in arbitrary A-D units for each trial. Each trial was scored for amplitude (i.e., peak – baseline in microvolts) during the 25-130 ms interval following startle onset. Trials that failed to reach peak during this interval were rejected. Latency to peak blink magnitude (in ms) was also derived on a trial-by-trial basis.

Statistical Analyses

To test the first prediction (PD patients will exhibit a significantly smaller eyeblink magnitude than controls while viewing unpleasant slides, and a significantly larger eyeblink magnitude than controls while viewing pleasant slides), valence-modulation of startle was evaluated by conducting a 2 (PDs, controls) X 2 (pleasant, unpleasant) Repeated Measures Analysis of Variance with eyeblink magnitude T-scores as the dependent variable. The eyeblink magnitudes in response to neutral pictures were not included in the analysis for several reasons. First, although the neutral pictures have normative subjective valence ratings that fall midway between ratings of pleasant and unpleasant pictures, individuals' physiologic responses to these pictures vary widely. One subject may respond to an ostensibly neutral picture as if it is somewhat negative in valence, while another may respond to the same picture as if it is positive in valence. Furthermore, research suggests that individual differences in current state anxiety levels can affect startle modulation while viewing emotionally valenced pictures (Grillon,

Ameli, & Davis, 1993). Potentially, the same subject could respond differently to the same "neutral" picture on two separate occasions, depending on factors such as the individual's mood and the situation. Finally, the inclusion of only strongly valenced pictures in the analysis, as opposed to more ambivalent pictures, increased the chances of detecting any potential differences between the PD and Control groups.

To test the second prediction (PD patients will display a significantly smaller eyeblink magnitude than controls in response to threatening slides), a 2 (PDs, controls) X 2 (threat, other unpleasant) Repeated Measures Analysis of Variance was conducted, with eyeblink magnitude as the dependent variable once again.

Next, to investigate whether PD patients and controls rated pleasant and unpleasant slides similarly with respect to valence, a 2 (PDs, controls) X 2 (pleasant, unpleasant) Repeated Measures ANOVA was conducted, with subjective valence ratings as the dependent variable. This analysis was then repeated with "threat" and "other unpleasant" pictures as the independent variables.

To investigate whether PD patients and controls differed in their arousal ratings of pleasant and unpleasant pictures, a 2 (PDs, controls) X 2 (pleasant pictures, unpleasant pictures) Repeated Measures ANOVA was conducted with subjective arousal ratings as the dependent variable. This analysis was then repeated with "threat" and "other unpleasant" pictures as the independent variables.

A final set of analyses examined the relationship between emotional reactivity, as indexed by startle magnitude, and scores on the Beck Depression Inventory. Although only two of the PD patients scored below the clinical cutoff for depression on the Beck Depression Inventory, the PD patients did obtain significantly higher scores on the BDI

(X = 8.5) than the Controls (X = 4.1). Thus, correlational analyses were performed in order to learn whether BDI scores varied in any systematic way with emotional reactivity, as indexed by startle. A startle reactivity index score was derived using the following formula: [Unpleasant T-score] – [Pleasant T-score]. This index score is a measure of overall emotional reactivity; the larger the difference between the eyeblink peak magnitudes for pleasant and unpleasant pictures, the greater reactivity to the stimuli the participant is displaying. A second correlational analysis was performed using an index score derived from the Threat and Other Unpleasant pictures (i.e., [Threat T-score] – [Other Unpleasant T-score]).

CHAPTER 3
RESULTS

Startle Eyeblink

Startle eyeblink responses were converted to T-scores (X=50, SD=10) following the procedures of Bradley & Vrana (1993). This was done order to minimize between-subject variability in the absolute size of startle responses that might otherwise obfuscate the pattern of the relationship among pleasant, neutral, and unpleasant conditions. For each participant an overall *mean* startle magnitude (and standard deviation) was derived from the values of that subject's individual trials. T-scores for each subject were computed on a trial-by-trial basis, based on the unique array of values for a particular subject. From these data, average startle responses (T-scores) were derived for the unpleasant, neutral and pleasant pictures. Because startle values were similar for the left and right eyes, a composite score was created (by averaging the left and right eye T-scores) and used as the dependent value in the analyses described below. Since left and right eye startle values did not significantly differ, for instances in which one eye contained greater than 50% invalid trials, values from the other eye were used instead of a composite score. Valid trials were defined as blinks that reached peak amplitude during the 25-130 ms interval following startle onset.

Pleasant versus Unpleasant Pictures

The initial analysis examined whether Parkinson patients differed from Controls in their emotional reactivity during pleasant versus unpleasant pictures. A repeated measures Analysis of Variance (ANOVA) was conducted, with Group (PDs, Controls) as

the between-subjects factor and Type Affect (pleasant, unpleasant) as the within-subjects factor. Results revealed a significant main effect for Type Affect ($F(1, 33) = 31.39$, $p<.001$). Consistent with previous findings (Bradley & Vrana, 1993), startle eyeblinks during unpleasant pictures ($X = 51.4$, $SD = 2.41$) were significantly larger than those during pleasant pictures ($X = 48.1$, $SD = 2.10$). Additionally, there was significant Type Affect X Group interaction ($F(1,33)= 4.60$, $p<.05$). This is depicted in Figure 3-1. Post hoc t-tests indicated that: (a) for the PD group, startle eyeblinks were significantly larger during unpleasant ($X = 50.62$, $SD = 2.67$) than pleasant pictures ($X = 48.60$, $SD = 2.23$; $t(19) = 2.35$, $p < .05$); (b) for the Control group, startle eyeblinks were significantly larger during unpleasant ($X = 52.17$, $SD = 1.71$) than pleasant pictures ($X = 47.67$, $SD = 1.80$; $t(14) = 6.43$, $p < .001$); (c) for unpleasant pictures, the Controls ($X = 52.17$, $SD = 1.71$) exhibited significantly larger eyeblinks than the Parkinson's patients ($X = 50.62$, $SD = 2.67$; $t(33) = -2.11$, $p < .05$; (d) for pleasant pictures, Controls ($X = 47.67$, $SD = 1.80$) and Parkinson's patients ($X = 48.60$, $SD = 2.23$) did not significantly differ with respect to peak eyeblink amplitude ($t(33) = 1.33$, $p > .19$).

In summary, these findings indicate that both groups displayed greater emotional reactivity, as indexed by startle modulation, during unpleasant versus pleasant picture viewing. However, the Controls' reactivity was significantly greater than the Parkinson's patients' during presentation of unpleasant pictures.

Threatening versus Other Unpleasant Pictures

A second ANOVA was conducted in order to determine whether Parkinson's patients were less reactive to "threat" versus other types of unpleasant emotional pictures. One control and four PD patients were excluded from this analysis due to the fact that

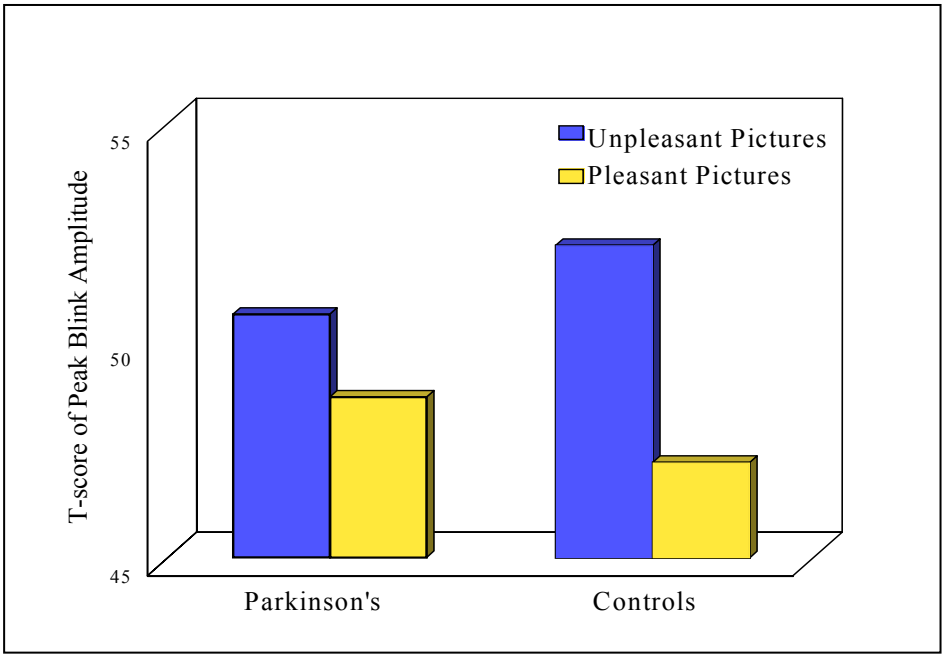

Figure 3-1. Peak Eyeblink Amplitudes for Unpleasant versus Pleasant Pictures

these participants had less than 50% valid trials for either the "threat"or"other unpleasant" category.A repeated measures ANOVA was conducted with Group (PD, Controls) as the between-subject factor and Type Affect (Threat, Other unpleasant) as the within-subject factor. Results of this ANOVA revealed a significant main effect for Type Affect ($F(1, 28)= 15.4$, $p<.001$), indicating that startle eyeblink responses were larger during threatening pictures ($X = 53.36$, $SD = .612$) as compared to other types of unpleasant pictures ($X = 49.21$, $SD = .696$). Again, the Condition X Group interaction was significant ($F(1, 28)= 5.31$, $p<.05$). Post hoc t-tests indicated that: (a) for the PD group, startle eyeblinks did not significantly differ with respect to peak eyeblink amplitude for "threat" ($X = 51.91$, $SD = 4.10$; $t(15) = -1.05$, $p >.30$) versus "other unpleasant" pictures ($X = 50.20$, $SD = 3.84$); (b) for the Control group, startle eyeblinks were significantly larger while viewing "threat" ($X = 54.80$, $SD = 2.17$) versus "other unpleasant" pictures ($X = 48.22$, $SD = 3.76$; $t(13) = -5.13$, $p <.001$); (c) for "threat"

pictures, the Controls exhibited significantly larger eyeblinks (X = 54.80, SD = 2.17) than the Parkinson's patients (X = 51.91, SD = 4.10; t(30) = -2.74, p < .05); (d) for "other unpleasant" pictures, Controls (X = 48.22, SD = 3.76) and Parkinson's patients (X = 50.20, SD = 3.84) did not significantly differ with respect to peak eyeblink amplitude (t(30) = 1.20, p > .20).

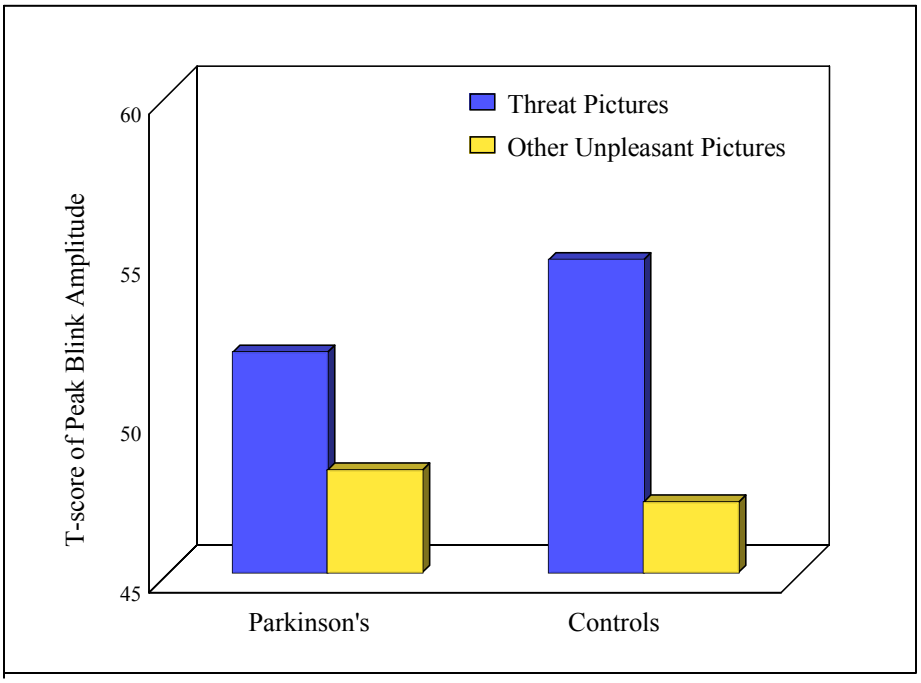

Figure 3-2. Peak Eyeblink Amplitude for Threat versus Other Unpleasant Pictures

In summary, Controls demonstrated greater emotional reactivity to "threat" pictures in comparison to the "other unpleasant" pictures, where as the Parkinson's patients did not. However, both groups responded similarly to the "other unpleasant" pictures.

Subjective Ratings: Valence and Arousal

Pleasant versus Unpleasant Pictures

A third set of analyses was conducted to examine subjective ratings of the emotional pictures by the Parkinson's patients and Controls. The mean valence and

arousal ratings for the pleasant and unpleasant pictures are depicted in Table 3-1. Two PD patients and two controls were excluded due to missing data. The valence ratings and the arousal ratings were independently analyzed in separate Group X Type Affect (Pleasant, Unpleasant) repeated measures ANOVAs. Results of the valence ANOVA indicated a main effect for Type Affect ($F(1,29) = 54.2$, $p<.001$). Namely, unpleasant pictures ($X = 2.85$, $SD = 1.68$) were rated as significantly more negative than the pleasant pictures ($X = 6.80$, $SD = 1.48$). The Group X Type Affect interaction was not significant, $F(1,29) = 2.08$, $p = .16$. Results of the ANOVA for the arousal ratings revealed no significant main effects or interactions. Taken together, these findings indicate that the pleasant and unpleasant pictures elicited ratings that differed in terms of valence. However, both the Controls and PD groups found the negative and positive pictures to be similar in terms of how "arousing" they found them.

Table 3-1. Means and SDs of Pleasantness and Arousal Ratings for Unpleasant and Pleasant Pictures.

	Unpleasant Valence*	**Pleasant Valence***	**Unpleasant Arousal†**	**Pleasant Arousal†**
PD Patients	2.57 *(1.70)*	7.14 (1.16)	5.22 *(2.01)*	6.10 *(1.36)*
Controls	3.24 *(1.65)*	6.32 *(1.77)*	5.78 *(1.66)*	5.47 *(1.67)*

* Valence ratings ranged from 1 (highly negative) to 9 (highly pleasant).
† Arousal ratings ranged from 1 (low arousal) to 9 (high arousal)

Threatening versus Other Unpleasant Pictures

A fourth set of analyses was conducted to examine subjective ratings of the "threat" and "other unpleasant" pictures by the Parkinson's patients and Controls. The mean valence and arousal ratings for these categories are shown in Table 3-1. As with the analyses of subjective ratings for pleasant and unpleasant pictures, two PD patients and two controls were excluded from the analyses due to missing data. The valence ratings

and the arousal ratings were independently analyzed in separate Group X Type Affect (Pleasant, Unpleasant) repeated measures ANOVAs. Results of the valence ANOVA indicated a main effect for Type Affect, $F(1,29) = 10.3$, $p<.005$. Suprisingly, participants subjectively found the "other unpleasant" pictures ($X = 2.49$, $SD = 1.93$) to be more unpleasant than the "threatening" pictures ($X = 3.11$, $SD = 1.62$), even though both groups showed greater startle eyeblink potentiation for the threatening pictures. The Group X Type Affect interaction was not significant, $F(1,29) = 0.308$, $p= .58$. Results of the ANOVA for the arousal ratings revealed no significant main effects or interactions. Taken together, these findings indicate that both groups found the "other unpleasant" pictures more unpleasant the "threat" pictures, although greater startle potentiation was demonstrated for "threat" pictures. However, participants did not find the two categories of pictures to differ in terms of level of arousal they evoked.

Table 3-2. Means and SDs of Pleasantness and Arousal Ratings for Threatening and Other Unpleasant Pictures.

	Threatening Valence*	**Other Unpleasant Valence***	**Threatening Arousal†**	**Other Unpleasant Arousal†**
PD Patients	2.86 *(1.71)*	2.16 *(1.80)*	5.42 *(2.15)*	4.94 *(2.33)*
Controls	3.45 *(1.47)*	2.95 *(2.01)*	5.76 *(1.74)*	5.80 *(1.89)*

* Valence ratings ranged from 1 (highly negative) to 9 (highly pleasant).
† Arousal ratings ranged from 1 (low arousal) to 9 (high arousal)

Eyeblink Magnitude and BDI Correlations

A final set of analyses examined the relationship between emotional reactivity, as indexed by startle magnitude, and scores on the Beck Depression Inventory. Although all but two Parkinson's patients and none of the Controls scored below the cutoff for Mild Depression on the BDI, the PD patients did obtain significantly higher scores ($X = 8.5$) than the Controls ($X = 4.1$). Thus, correlational analyses were performed in order to

learn whether BDI scores varied in any systematic way with emotional reactivity, as indexed by startle. A "startle reactivity index score" was computed ([Unpleasant T-score] – [Pleasant T-score], see Chapter 2 for an explanation of this formula) to serve as a measure of overall emotional reactivity. The Pearson's product-moment correlation between this index score and the BDI score was nonsignificant ($r = -0.167$, $p = .352$). Two control subjects were excluded from the analysis due to missing BDI scores. A second correlational analysis was performed using an index score derived from the "threat" and "other unpleasant" pictures (i.e., [Threat T-score] – [Other Unpleasant] T-score). The results of this analysis indicated that the Pearson's correlation between this difference score and BDI scores was again nonsignificant ($r = -0.304$, $p = .102$). In summary, these findings suggest that level of depressive symptomatology, as indexed by the BDI, does not vary in any systematic fashion with emotional modulation of startle.

Next, correlational analyses were performed in the Parkinson's disease group to examine the relationships among the Hoehn and Yahr stage (assessed while on medication), UPDRS motor subscale score (assessed while on medication), duration of illness, and BDI score. These analyses were performed in order to determine if severity or duration of Parkinson's disease is associated with depression symptomatology. The correlations between these variables are displayed in Table 3-3. The correlation between Hoehn and Yahr stage and BDI score was nonsignificant ($r = -.008$, $p > .97$), as was the correlation between number of years with Parkinson's disease and BDI score ($r = .089$, $p > .62$). However, UPDRS score and BDI score were significantly positively correlated, $r= .518$, $p < .05$. Although the UPDRS and Hoehn and Yahr both measure level of motor impairment, the UPDRS assesses impairment at the level of highly specific motor

symptoms and has a greater range of possible scores. This may be why a significant correlation was found between the UPDRS and the BDI, but not Hoehn and Yahr Stage and BDI. Finally, UPDRS score and Hoehn and Yahr stage were highly significantly correlated in the positive direction (as would be expected since they both assess level of motor impairment in the PD patient), $r = 67$, $p < .005$, and Hoehn and Yahr stage and years with PD were significantly positively correlated, $r = .44$, $p = .05$. In sum, these analyses demonstrate that a) degree of motor impairment (as assessed by Hoehn and Yahr stage) increases with duration of illness; and b) greater motor limitation is associated with greater depression severity.

Correlational analyses were also performed between the general index of startle reactivity ([Unpleasant T-score] – [Pleasant T-score]) and UPDRS motor subscale score, Hoehn and Yahr stage, and years with PD in order to determine if severity or duration of Parkinson's disease is associated with reduced startle reactivity. Hoehn and Yahr stage and startle reactivity index were significantly negatively correlated, $r = -0.70$, $p < .005$, as

Table 3-3. Correlations Between Number of Years with Parkinson's Disease, BDI Score, Hoehn and Yahr Stage, and UPDRS Motor Subscale Score.

	Yrs. PD	**BDI**	**Hoehn &Yahr**	**UPDRS motor subcale**
Yrs. PD	1.00	0.089	0.444*	0.107
BDI	--	1.00	-.008	.518*
Hoehn & Yahr	--	--	1.00	.665**
UPDRS motor subcale	--	--	--	1.00

*. Correlation is significant at the .05 level (two-tailed).
**. Correlation is significant at the .01 level (two-tailed).

were number of years with illness and startle reactivity index, $r = -0.36$, $p < .05$. Additionally, the correlation between UPDRS score and startle reactivity approached

significance, $r = -0.48$, $p = .053$. Taken together, these findings suggest that greater motor impairment and longer disease duration in Parkinson's patients are associated with reduced emotional reactivity, as indexed by startle modulation.

CHAPTER 4
DISCUSSION

The present study sought to examine two hypotheses. The first hypothesis was that Parkinson's patients would show diminished emotional reactivity to affectively valenced pictures. This led to the specific prediction that PD patients would exhibit a significantly smaller eyeblink magnitude than controls while viewing unpleasant slides, and a significantly larger eyeblink magnitude than controls while viewing pleasant slides. This prediction was based on previous findings that PD patients show reduced striatal dopamine, which may affect dopamine-mediated limbic circuits; as well as amygdala neuropathology, which may affect the amygdala's modulation of the basic startle response. The second hypothesis was that Parkinson's patients would exhibit greater emotional blunting for threatening pictures, as opposed to other categories of negative pictures. Specifically, it was predicted that PD patients would display a significantly smaller eyeblink response than controls in response to threatening slides, whereas their eyeblink responses during other unpleasant pictures would not differ from that of controls. This prediction was based on the fact that the amygdala is known to play a key role in responding to threatening stimuli, is implicated in fear-potentiated startle, and exhibits pathology in PD patients.

Hypothesis 1 was partially supported by the data. Parkinson's patients exhibited significantly smaller eyeblink responses than controls while viewing the unpleasant pictures; however, their eyeblink responses during pleasant pictures did not differ from

those of controls. Thus, the PD patients demonstrated diminished emotional reactivity to negatively valenced pictures but not positively valenced pictures.

Hypothesis 2 was also supported by the data. That is, PD patients exhibited significantly smaller eyeblink responses while viewing threatening pictures relative to controls. The patients and controls did not differ significantly with respect to eyeblink responses during other types of unpleasant pictures.

In summary, PD patients demonstrated diminished emotional reactivity to unpleasant pictures compared to healthy controls (as indexed by startle eyeblink modulation), but did not differ from controls in terms of emotional reactivity to pleasant pictures. Furthermore, this effect seems to be driven by the PD patients' diminished emotional reactivity towards threatening stimuli specifically.

Basic Acoustic Startle in PD Patients

Before discussing some possible explanations for the present findings, an obvious question concerns whether the Parkinson's patients might have a basic defect in startle eyeblink reactivity per se. Conceivably, Parkinson's patients could have motor abnormalities that might reduce or minimize the size of the eyeblink response itself. This, in turn, would result in reduced size of startle eyeblink responses during negative emotional pictures, giving rise to the impression of diminished emotional reactivity to unpleasant and threatening stimuli. To explore this, it is necessary to look at past research on the basic startle response in patients with Parkinson's disease. Vidailhet and colleagues (1992) examined startle eyeblink responses elicited by an abrupt noise in eleven patients with idiopathic PD and a group of controls. Both the magnitude of the startle eyeblink response and the pattern of muscles recruited were similar in the PD patients and controls. However, the latency of the eyeblink response was significantly

delayed in the Parkinson's patients. Similar findings were described by Kofler and coworkers (2001). In contrast, Seignorel and colleagues (2003) found no significant differences in either latency or magnitude of startle eyeblink responses in PD patients and controls.

In the present study, basic startle data were available from ten controls and ten Parkinson's patients. Basic startle eyeblink responses were obtained immediately prior to presentation of the emotional pictures. These data consisted of twelve startle eyeblink responses that had been elicited in response to a burst of white noise delivered through headphones. The results of a one-way ANOVA revealed no significant differences between the PD and Control groups in terms of latency to peak startle eyeblink, ($F(1,18) = 1.62$, $p > .20$ [Control mean = 73.3 ms, SD = 8.27; PD mean = 66.9 ms, SD = 13.5]). Similarly, there was no significant difference between the PD patients and Controls with regard to the magnitude of the startle eyeblink response ($F(1,18) = 2.50$, $p > .10$ [Control mean = .0170 mV, SD = .009; PD mean = .0113 mV, SD = .008])

Taken together, some inconsistency exists with respect to latency of basic startle eyeblink responses described in the literature. Some studies report slowed startle eyeblink responses in Parkinson's patients (Kofler et al., 2001; Vidailhet et al., 1992), whereas others have found no difference between PD patients and Controls (Bowers, Miller, Springer, Foote, & Okun, submitted; Seignorel et al., 2003). Importantly, however, all studies are consistent with respect to magnitude of startle responses in Parkinson patients and controls. Specifically, the PD patients appear normal with regards to the absolute size of the startle eyeblink peak. This, of course, is the variable of interest in the current study.

Possible Effects of Depression on the Present Findings

One possible explanation for the present findings is that the PD patients had diminished potentiation of startle eyeblink in response to unpleasant pictures due to depression and/or apathy. Every attempt was made to exclude PD patients that may be depressed from the study by only including patients that did not meet criteria for Major Depression. However, two of the twenty PD patients did meet criteria for "mild depression" as determined by BDI score, and PD patients and controls did significantly differ with respect to mean BDI scores. Another possibility is that some of the patients may have experienced depression in the past and abnormal emotional reactivity may have persisted (even though they were asymptomatic at the time of testing). Findings from a recent study with depressed patients suggest that this is an unlikely explanation. Using pictures from the International Affective Picture System, Allen and coworkers (Allen, Trinder, & Brennan, 1999) found that moderate to severely depressed subjects (BDI scores ranging from 19 to 29) showed normal emotional startle modulation. Patients who were extremely depressed (i.e., BDI scores greater than 30) showed a larger startle potentiation for pleasant versus unpleasant pictures (i.e., they responded to the pleasant pictures as if they were aversive). Although this study involved a small sample size, it suggests that abnormal startle modulation is not exhibited by depressed subjects unless they are severely depressed; furthermore, the pattern of startle potentiation found was opposite to that of the current study. Namely, the PD patients in the present study demonstrated normal startle modulation for pleasant pictures, but diminished startle modulation for unpleasant pictures.

Similarly, the pattern of responding in the current study does not appear to be due to a generalized apathy. Since apathy is the diminished reaction to all stimuli, both

positive and negative (Marin, 1996), one would expect a diminished reaction to emotional pictures of all valence categories if apathy were indeed the driving force behind the observed responses in PD patients. However, the present study did not formally test level of apathy by use of standard scales, and thus this possibility cannot be addressed by the current data.

The Role of the Amygdala in Response to Threatening/Fearful Stimuli

The finding of reduced emotional responsivity to unpleasant pictures, and more specifically, threatening pictures, is consistent with previous reports of pathological changes in the amygdala of patients with Parkinson's disease (Braak & Braak, 2000; Harding et al., 2002; Ouchi et al., 1999). Several studies of patients with lesions that include the amygdala have reported impaired identification of fear facial expressions (Adophs et al. 1994, 1995; Calder et al. 1996; Young et al. 1995;). Additionally, fMRI studies have found that the viewing of facial expressions of fear is associated with robust amygdala activation (Breiter et al., 1996; Davidson & Irwin, 1999; Davis & Whalen, 2001; Morris et al., 1996; Whalen et al., 1998). Importantly, however, amygdala activation is sometimes found for other negative facial expressions of emotion as well, including disgust (Schienle et al., 2002) and anger (Tessitore et al., 2002). In an experiment utilizing threatening pictures from the IAPS series (similar to the current study), Hariri et al. (2003) found a significant bilateral amygdala BOLD response when healthy subjects were asked to simply match a picture to a picture identical to it. In light of this evidence implicating the amygdala in the processing of threatening stimuli, it is possible that the PD patients in the present study suffer from significant amygdala pathology that is causing a diminished emotional reactivity to threat-evoking stimuli. The Parkinson's patients in the current study each received head MRI scans; however, at this

time volumetric measurements of the amygdala have not been performed, and thus this prediction remains speculative. Additionally, Tessitore et al. (2001) have found evidence that dopamine may modulate the functioning of the amygdala. The implication of this finding with regards to the current study is that dopamine modulation of the amygdala may be disrupted in PD patients due to loss of striatal dopamine.

An alternative or additional explanation for the current findings is that reduced dopaminerigic innervation (i.e., nigrostriatal, mesolimbic, and/or mesocortical) in PD patients may be disrupting the neural circuitry involved in emotion processing. Although the patients in the present study were tested while on dopaminergic medication, it is unlikely that this makes them similar to healthy people with respect to dopamine levels. For example, Ouchi and coworkers (1999) found a reduction of dopamine (DA) agonist binding in the amygdala, striatum, and orbitofrontal cortex of unmedicated PD patients. The authors suggested that this might be due to a loss of presynaptic DA terminals in these regions. To relate this back to the present study, a loss of dopaminergic terminals would decrease levadopa binding in the medicated patients, leaving them with abnormally low DA levels even when on medication. Additionally, the results from Ouchi and colleagues' laboratory suggest an alteration in the mesocortical, mesolimbic, and striato-thalamo-cortico orbitofrontal dopaminergic systems' functioning in PD patients. As mentioned previously, these are circuits thought to be involved in emotional processing.

Dissociation of Subjective Ratings and Physiological Response

Interestingly, although the PD patients showed diminished modulation of startle in response to negative stimuli (particularly threatening stimuli) compared to controls, the two groups did not differ with respect to their subjective ratings of valence and arousal

levels in response to the pictures. Although the literature is sparse, there is evidence that "decoupling" of subjective emotional experience and physiological response can occur in patients following brain damage. For example, a dissociation between skin conductance responses (SCRs) and verbal report during anticipatory anxiety of electric shock was reported by Slomine et al. (1999). Patients with both right and left hemisphere brain damage exhibited smaller SCRs than healthy controls while anticipating the shock, yet all groups reported feeling less pleasant, less in control, and more aroused while awaiting shock as opposed to during a no-shock condition. In contrast, Meadows & Kaplan (1994) reported that patients with right hemisphere damage showed diminished SCRs to emotional and neutral slides relative to controls, while patients with left hemisphere brain damage exhibited increased SCRs to both emotional and neutral slides. The groups did not differ with respect to subjective ratings of the slides, or in orienting and habituation to loud tones.

Decoupling of physiological and subjective emotional responses in Parkinson's disease patients has not been discussed in the literature, and is certainly an area towards which future research should be directed. Although the mechanism underlying this "decoupling" is unknown, one possibility is that subjective emotional experience typically incorporates feedback from the body's physiological pattern of response. In Parkinson's disease as well as other neurological disorders, brain abnormalities can cause a functional disconnect between the two (Slomine et al., 1999). Alternatively, it may be that patients know the typical valence rating that is expected from them for each slide (i.e., mutilation pictures should be rated as very unpleasant, puppies as pleasant) and are conforming to experimenter demand characteristics.

Limitations of the Present Study

Several limitations of the current study must be acknowledged. First, the study suffers from a small sample size, and thus it is uncertain whether these findings would be replicated in a larger sample. Secondly, women and men were included together, although men and women are generally regarded as responding to emotional stimuli differently, and expressing emotional reactivity to different degrees.[5] The study also utilized a rather homogeneous sample of Parkinson patients who were highly educated and who had moderate motor impairments (mean Hoehn-Yahr stage of 2.7). Further research is needed to determine whether the same pattern of affective startle modulation exits in patients with milder or more severe PD.

Turning to a methodological critique of the study, one limitation is the fact that the analysis of eyeblink magnitude to threatening versus other types of fearful stimuli was conducted post-hoc. Thus, the original set of forty-four pictures was designed to measure emotional reactivity to neutral, pleasant, and unpleasant stimuli; later, pictures depicting imminent attack were grouped together and labeled as "threatening," and all other remaining unpleasant pictures were grouped together and labeled "other unpleasant pictures." Ideally, a larger sample of pictures should be used, expressing a variety of threatening situations, and designed explicitly to assess startle modulation during viewing of threatening stimuli versus other specific types of aversive stimuli (for example, disgust-eliciting pictures).

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[1] However, separate t-tests conducted on PD and control data yielded no significant differences between men and women for unpleasant or pleasant blink magnitudes (controls unpleasant: $t(13) = -0.038$, $p > .9$; controls pleasant: $t(13) = 0.31$, $p > .7$; PD unpleasant: $t(18) = -0.089$, $p > .9$; PD pleasant: $t(18) = 0.56$, $p > .5$).

Another limitation of the current study is that startle eyeblink modulation to unpleasant and pleasant stimuli was assumed to reflect emotional reactivity to the valence of the pictures. However, the arousal level of a picture also affects startle modulation by intensifying the magnitude of the eyeblink in the direction of the individual's motivational activation (i.e., appetitive/pleasant or defensive/unpleasant). Namely, the more arousing an unpleasant picture is to a participant, the greater the startle potentiation. Similarly, the more arousing a pleasant picture is to a participant, the more attenuated the startle eyeblink (Bradley, Codispoti, Cuthbert, & Lang, 2001). It may be that Parkinson's patients display an overall pattern of "hypoarousal" in response to emotional materials. If this is true, than Parkinson's patients might have shown a smaller difference between unpleasant and pleasant picture eyeblink magnitudes relative to controls because they did not exhibit a level of arousal that would serve to intensify the magnitude of their eyeblink in line with the direction of the picture valence. Although PD patients reported experiencing levels of arousal equivalent to those of Controls, they also rated picture valences similar to Controls, suggesting that their subjective experience and physiologic reactions are not necessarily congruent. Thus, the possibility that the findings of the current study were due to a general diminished psychophysiologic reactivity to emotional material in Parkinson's patients cannot be ruled out.

A further limitation is that analyses in the present study used T-scores, as opposed to raw eyeblink magnitudes, as a way to measure emotional startle modulation. This was done to minimize individual differences in eyeblink magnitude modulation, such that all subjects could be compared on a common metric. However, it is possible that converting raw scores to T-scores could obscure differences between the PD group and Controls. In

the future, raw startle data should be analyzed as well, to check that it exhibits the same pattern as the transformed data.

Finally, the current study did not use a manipulation check to determine whether participants subjectively felt threatened during presentation of slides categorized as "threatening." Although PD patients did exhibit diminished startle eyeblink potentiation for threatening pictures compared to controls, this assumes that threat was indeed the emotion subjectively experienced by participants, which may or may not have been the case. This issue is further confounded by the fact that both groups rated the "other unpleasant stimuli" as being more unpleasant than the "threatening" stimuli, yet they displayed larger eyeblink potentiation during viewing of the threatening pictures.

Directions for Future Research

Future directions for research include an exploration as to whether different subtypes of PD are associated with differential patterns of affective startle eyeblink modulation. For example, some researchers classify PD patients as either akinetic/rigid or tremor predominant, depending on the key symptoms of the individual patient (Ransmayr, Poewe, Ploerer, Birbamer, & Gerstenbrand, 1987; Ransmayr, Poewe, Plorer, Gerstenbrand, Leidlmair, & Mayr, 1986). It is thought that the akinetic/rigid type involves greater involvement of the mesolimbic and mesocortical pathways, and thus these patients may display more aberrant patterns of startle modulation. The emotional modulation of startle paradigm could also be used in different groups of patients with basal ganglia disorders, such as those with essential tremor, Progressive Supranuclear Palsy, and Huntington's Disease, as a way to measure emotional reactivity in these patient groups without the confounding variable of motor output abnormalities. It may be that disorders that often appear clinically similar on the behavioral level (such as essential

tremor and PD) may be distinguished from one another by their pattern of emotional startle modulation.

Another important future line of research will be to determine if diminished reactivity to threatening pictures correlates with measures of amygdala pathology, such as decreased amygdala volume or decreased BOLD signal (relative to controls) during fMRI with concurrent presentation of threatening pictures. The results of the current study, supported by past literature, suggest that reduced emotional reactivity to threatening stimuli may be linked to amygdala abnormalities, but this hypothesis is purely speculative as of now. Additionally, PD patients should be tested off their dopaminergic medications using the emotional startle modulation paradigm, in order to determine how dopamine levels affect emotional reactions as assessed by the startle paradigm.

An idea for a future study might include threatening pictures from the IAPS series intermixed with disgusting pictures. Previous investigators have used pictures such as body excrement, food contamination, and unsanitary conditions in an attempt to evoke disgust in participants (e.g., Schienle et al., 2002; Shapira et al., 2003;). Studies have implicated several structures that are part of the nigrostriatal loop affected in PD as being involved in the recognition of disgust. For example, in an fMRI study, Sprengelmeyer and coworkers (1998) found that viewing pictures of facial expressions of disgust caused activation of the left anterior insula, right anterior globus pallidus, and putamen in healthy subjects. Activation of the left anterior insula, bilateral putamen, and right globus pallidus and caudate nucleus was reported by Phillips et al. (1997), who presented images of faces depicting different degrees of disgust intensity to normal controls. As such, one might predict that PD patients presented with disgust-evoking pictures would exhibit

diminished startle potentiation, much as they displayed a diminished startle potentiation in response to threat-evoking stimuli in the present study.

To conclude, the finding of reduced emotional reactivity to negative stimuli in PD patients, and threatening stimuli specifically, does not appear to be an artifact of a motor output problem or depressive symptomatology. For these reasons, it offers a unique advantage compared to other measures of emotionality in PD (such as facial expressivity or vocal prosody), which are wrought with the confounding problem that these movements may be affected by the motor symptoms of PD. Furthermore, the acoustic startle is an involuntary physiological reaction that is very difficult, if not impossible, to inhibit or voluntarily control, and thus does not rely on the participant's attention or motivation (Bradley, 2000). These characteristics make measurement of affective modulation of eyeblink amplitude a paradigm that may afford a purer, more objective method of exploring emotional reactivity in patients with basal ganglia disorders.

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BIOGRAPHICAL SKETCH

Kimberly Miller was born in San Jose, CA, and received her B.A. in psychology from the University of California, Berkeley. After gaining research experience in cognitive neuroscience at the Martinez V.A., she moved to Gainesville to pursue her doctorate in clinical psychology at the University of Florida, specializing in neuropsychology. Current clinical interests include learning disorders and speech and language disorders. Current research interests include the affective modulation of startle in chronically depressed patients, as well as the effect of psychiatric disorders on cognitive processes.