

THE PUPIL AS A MEASURE OF EMOTION-MODULATED AROUSAL IN
PARKINSON'S DISEASE

By

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Abstract of Thesis Presented to the Graduate School
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Parkinson's disease (PD) is a neurodegenerative disease that primarily affects motor function, but also has cognitive and emotional consequences. Previous studies have demonstrated muted physiologic reactivity to emotional stimuli in Parkinson's patients. In particular, a recent study showed that Parkinson's patients demonstrated a reduced skin conductance response (SCR), a measure of autonomic arousal, in response to pleasant and unpleasant pictures, as compared to a healthy older adult group. The basis for the reduced SCR in PD is unclear, but may relate to peripheral autonomic dysfunction (e.g., reduced nerve endings at the sweat gland) or to a more central arousal deficit. In the present study, we used another index of autonomic arousal, the pupillary response, to test the hypothesis that PD patients would show muted reactivity to emotional pictures due to a hypoarousal deficit. Participants included 14 nondemented PD patients and 12 healthy controls. Pupil diameter was recorded while participants viewed unpleasant, neutral, and pleasant images (total N=42) from the International Affective Picture System (IAPS). Analyses revealed a significant effect of picture valence ($F(1.6,38.5) = 21.3, p < .01, \eta_p^2 = .47$) such that, for

both groups, emotional images (pleasant and unpleasant) elicited significantly greater pupil dilation than neutral pictures. There was no significant Group difference nor was there a Group x Emotion interaction. Results also showed that Parkinson's patients demonstrated a smaller light reflex compared to controls, as is consistent with previous literature. Moreover, both groups evidenced smaller light reflexes while viewing emotional pictures than when viewing neutral pictures ($F(2,48)=9.14, p<.001, \eta_p^2=.28$), suggesting that sympathetic input to the pupil in the context of emotional picture viewing occurs early and is concurrent with the light reflex. Overall, the results of the current study demonstrate that Parkinson's patients show a differential arousal response to emotional stimuli (similar to that in a healthy control group) and suggest that our previous finding of a muted skin conductance response in PD is likely related to peripheral autonomic dysfunction.

CHAPTER 1 INTRODUCTION

Emotional Symptoms in Parkinson's Disease

Parkinson's disease (PD) is a degenerative disease of the central nervous system. It is the second most common neurodegenerative disease, next to Alzheimer's disease, and is typically recognized by its cardinal motor symptoms of tremor, rigidity, postural instability, and bradykinesia. Less recognized are the emotional symptoms experienced by PD patients, which can impact their mental health, quality of life, and social relationships. For example, many patients have difficulties with the behavioral expression of emotion, such as the "masked face", or the inability to register emotional facial expression, and a lack of expressive prosody, which can cause particular difficulties in the context of social relationships due to misleading or ambiguous social cues. Moreover, Parkinson's patients experience high rates of apathy, depression and anxiety. Prevalence of depression in PD is estimated to be approximately 30-40% (Slaughter, Slaughter, & Nichols, 2001).

On the one hand, mood dysfunction such as depression is common in many serious, chronic illnesses, due to the psychological burden of living with a debilitating condition. However, it has been debated to what extent mood difficulties in PD are psychological "reactions" to having a chronic and debilitating disease, and thus will depend on some extent on the nature of a given individual's predisposition and coping skills, versus to what extent emotional symptoms are byproducts of the disease itself (c.f. Frisina, Borod, Foldi, & Tenenbaum, 2008). In all likelihood, depression in PD is likely linked to multiple underlying etiologies; however, at least some evidence points to mood dysfunction as being intrinsic to the neuropathology of PD itself.

For instance, studies have shown that PD patients endorsed significantly higher levels of depression than paraplegics, amputees, and people with other medical conditions that are also chronic and physically debilitating (Wartburton, 1967; Horn, 1974; Robins, 1976). However, these studies have been criticized for not adequately controlling for disease severity or duration, variables that are important contributors in the development of depression. A more recent study that controlled for symptom duration still found no difference in severity of mood symptoms between a Parkinson's group and other movement disorders such as Dystonia and an Essential Tremor group (Miller et al., 2006).

However, recent evidence has suggested that apathy, rather than depression, may be a core feature of Parkinson's disease. Apathy is a syndrome marked primarily by a loss of motivation and has cognitive, affective and behavioral components (Marin, 1991). The cognitive component includes loss of interest and lack of concern. The behavioral component includes a lack of effort and reduced behavioral activation or productivity. The affective component is one of emotional indifference—or “a” “pathos,” which is Greek for “lack of passions.” Thus, apathy is characterized as blunted affect or a lack of responsivity to both pleasant and unpleasant stimuli.

While apathy can certainly be a feature of depression, apathy as a unique syndrome is dissociable from depression in that it lacks the key symptom of sad or dysphoric mood that is inherent to depression. A recent study compared rates of depression, apathy, and both apathy and depression in PD and a comparative movement disorder population, dystonia (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006). The groups were matched in terms of disease severity and duration.

Apathy, specifically, was found to be more severe and more frequent in the PD group than in the dystonia group, with 29% of Parkinson's patients endorsing clinically significant apathy in the absence of depression, whereas no dystonic patients endorsed significant apathy in the absence of depression. This finding lends support that apathy may actually be a core feature of PD pathology (Kirsch-Darrow et al. 2006).

Neuropathology of Emotion Dysfunction in Parkinson's Disease

The exact neuropathological mechanism underlying emotional dysfunction in PD is unclear. The most well studied Parkinson's-related pathology is the depletion of dopaminergic neurons in the substantia nigra. This pathology is also the most overtly recognized in terms of the symptoms it produces, since it disrupts a major source of input to the striatum of the basal ganglia, which has severe motor consequences. Moreover, this dopaminergic input ordinarily serves to fine-tune a vast array of motor, cognitive, and affective functions mediated by the basal ganglia. These functions are thought to be linked to six distinct and parallel cortico-subcortical loops that were outlined by Alexander, DeLong, and Strick (1986). Two of these loops, one of which projects to the anterior cingulate cortex and another that projects to the lateral orbitofrontal cortex, are considered to be limbic-based loops that subserve a variety of functions related to emotional processing, including reward-based learning and motivated behavior. Of note, one of the primary consequences of dysfunction of the anterior cingulate cortex is an amotivational apathetic state (Cummings & Miller, 2007). Disruption of these limbic loops due to dopamine depletion in the substantia nigra represents one potential mechanism underlying emotional dysfunction in PD.

Another possibility is that emotional symptoms result from dysfunction of another primary dopaminergic circuit in the brain, the mesolimbic pathway, which projects from

the ventral tegmental area to the ventral striatum. This pathway is implicated in emotion, motivation, and reward-based behavior.

A third possibility is that emotional symptoms are linked to Lewy body pathology in Parkinson's disease. Although motor symptoms in PD only manifest after the loss of approximately eighty percent of dopaminergic neurons in the substantia nigra (see Roth, 1986), evidence based on post-mortum studies now shows that extensive Lewy body pathology is acquired prior to the onset of clinical motor symptoms. A Lewy body is an aggregation of alpha-synuclein fibrils that develop inside neurons and can lead to cell death (see Engelender, 2008). Braak et al. (2003) have outlined six stages of the development of Lewy body pathology in PD, the earliest of which originate in cranial nerves V and IX (vagus and glossopharyngeal), brain stem autonomic centers, and the amygdala—prior to any clinical manifestation of PD (see Braak et al., 2003; Hawkes, Tridici, & Braak, in press). In fact, clear and consistent Lewy body pathology of the amygdala, particularly in the central nucleus, has been documented (Harding, Stimson, Henderson, & Halliday, 2002). Thus, damage to the amygdala is particularly relevant in considering potential mechanisms of emotional dysfunction in PD, due to its ubiquitous role in emotional information processing.

Beyond that, the central nucleus of the amygdala is directly connected to brainstem autonomic centers and the hypothalamus, thus contributing to increased autonomic activation in the context of emotional arousal. Because of the fact that the central nucleus and other brain stem autonomic centers (e.g., intermediate reticular zone, locus coeruleus, and caudal raphe nuclei) have been found to have consistent and early Lewy body pathology in PD, it is possible that disruption of autonomic

activation or a hypoarousal phenomenon is linked to emotion dysfunction in PD. This idea is particularly relevant in considering apathy, which is characterized by blunted affect, or a lack of responsivity to both pleasant and unpleasant stimuli that may be driven by hypoarousal to emotional stimuli.

The Bio-informational Theory of Emotion

To understand the nature and origin of emotional blunting in apathy, it is instructive to investigate its function within an underlying framework of a bioinformational theory of emotion (Lang, 1995). According to Lang (1995), emotions are “action dispositions” that are characterized primarily by the activation of primitive and evolutionarily evolved appetitive and aversive motivational systems in the brain. These systems mediate basic approach and avoidance behavior that, from an evolutionary perspective, serve to sustain life and defend against threat. The activation of these motivational systems is defined by a two dimensional “affective space,” constituted by the parameters of valence and arousal. While valence determines which of the opponent motivational systems is selected, arousal is thought to reflect the intensity of motivational activation, irrespective of valence (Lang, 1995). Extensive research has shown that emotionally evocative pictures can evoke an array of reliable psychophysiological responses that are uniquely affected by the hedonic nature (valence) and intensity (arousal) of the picture (see Lang, Greenwald, Bradley, & Hamm, 1993). These responses can be thought to reflect the extent of central activation and preparation for action. During a passive picture-viewing context, activation of the motivational system is rarely strong enough to actually elicit motivated behavior; thus, we conceptualize changes in central and peripheral physiology during picture viewing to primarily represent a state of affective vigilance and active orienting to a motivationally salient stimulus.

Application of the Bio-Informational Approach to Emotional Dysfunction in Parkinson's Disease

Exploration of the pattern of psychophysiological responses to affective stimuli in PD patients can help to inform our conceptualization of a disease-related breakdown in the typical bio-informational model of emotion processing that occurs in patients with PD. Comparison of psychophysiological responsivity in Parkinson's patients to well-established psychophysiological correlates of emotion also aims to determine at what node, within an information processing model, emotion processing becomes aberrant in PD. Additionally, our expanding knowledge of the neuropathology of PD can, in turn, help to inform us of the relevant underlying neurophysiological and neuroanatomical correlates of the bio-informational model. Due to these many relevant and informative applications, psychophysiological correlates of emotion in PD have served as the focus for a number of recent studies.

Two of these studies have been investigations of the startle response to affective stimuli in Parkinson's patients. The startle eyeblink is a reflexive blink that occurs in response to a brief burst of white noise. The magnitude of the blink is modulated by emotional valence, such that it is potentiated (larger) when participants are viewing unpleasant, aversive pictures. This phenomenon can be conceptualized as the augmentation of a defensive reflex (the startle eyeblink) in the context of an ongoing aversive state, during which the defensive system is already primed. In contrast, the startle eyeblink is actually attenuated (smaller) when participants are viewing pleasant, appetitive pictures, conceivably because the ongoing affective motivational state is incongruent with the defensive reflex elicited by a noxious stimulus (for a review, see Lang, Bradley, & Cuthbert 1990).

Bowers et al. (2006) found that Parkinson's patients demonstrated blunted startle potentiation to aversive pictures compared to healthy older adults. Parkinson's patients also rated the unpleasant pictures as less arousing than the control group. Bowers et al. (2006) interpreted this result as a deficit in translating an aversive motivational state into an appropriate physiological response. Because the amygdala plays an important role in potentiation of the startle reflex and given what is known about amygdala dysfunction in PD, the results were interpreted as "an amygdalar-based translational defect." Typically, the amygdala is under tonic inhibitory control from the prefrontal cortex and is disinhibited via dopaminergic input, particularly during emotional states (Marowsky, Yanagawa, Obata, & Vogt, 2005; Inglis and Moghaddam, 1999). Bowers et al. (2006) hypothesized that disinhibition of the amygdala is disrupted due to dopamine dysfunction in PD, leading muted startle potentiation in response to aversive pictures.

Following this interpretation, it was predicted that startle attenuation would be most pronounced in response to fear-eliciting pictures, given that the amygdala has a pronounced role in fear-conditioning (Davis, 1992.) Therefore, a second study was conducted that investigated the startle response to fear versus disgust (contaminations, mutilations) picture categories (Miller, Okun, Marsiske, Fennell, & Bowers, 2009). Contrary to Miller's prediction, there was no difference in startle magnitude to fear-eliciting stimuli between the PD and control group. A subsequent analysis comparing high arousing aversive pictures to low arousing aversive pictures revealed a trend such that startle potentiation was greater when participants in the control group viewed high arousing unpleasant pictures compared to low arousing unpleasant pictures, consistent with previous research showing that startle potentiation is modulated by arousal

(Cuthbert, Bradley, & Lang, 1996). There was no difference, however, in the magnitude of startle reflex between low and high arousing unpleasant stimuli in the Parkinson's group. Thus, it was hypothesized that aberrant startle reactivity in PD is linked to a hypoarousal deficit. To elaborate, Miller suggested that Parkinson's patients demonstrate a normal level of arousal in response to low to moderately arousing stimuli, but they reach a theoretical ceiling whereby they demonstrate inadequate or a lesser level of arousal to highly arousing affective stimuli than the healthy control group. Thus, Miller contended a "threshold model" that suggested that highly arousing aversive stimuli (such as mutilation pictures) are needed to detect differences in physiological reactivity between controls and PD patients.

With an arousal-specific hypothesis in mind, it was befitting to investigate a measure of physiological reactivity that is more directly linked to arousal than the startle reflex. The skin conductance response (SCR) is an index of sympathetic-mediated autonomic arousal, measured via electrodermal activity at the surface of the palm. Previous studies have consistently shown that SCR changes are greater while participants view pleasant and unpleasant pictures, compared to neutral pictures and that this response is strongly correlated with emotional arousal (Lang, Greenwald, Bradley, & Hamm, 1993). Bowers et al. (2008) demonstrated that PD patients showed a reduced SCR to emotional (both unpleasant and pleasant) pictures compared to healthy older adults, and SCRs were negatively correlated with apathy but not depression symptoms. These findings indicated that as apathy severity increased, the skin conductance response decreased. These results seemed to suggest an arousal-

specific hypothesis with respect to aberrant physiological reactivity to affective stimuli and apathy in PD.

However, using the skin conductance as a measure of arousal in PD may be confounded by autonomic nervous system dysfunction that broadly affects cardiovascular, gastrointestinal and sudomotor systems in the early stages of PD (Akaogi, Asahina, Yamanaka, Koyama, & Hattori, 2009; Micieli, Tosi, Marcgesekum, & Cavallini 2003). Dabby et al. (2006) demonstrated significantly reduced innervation of the sweat glands at the palm that is present in early-disease stages of Parkinson's. Therefore, another measure is needed to more fully investigate emotion-modulated arousal in PD. A recent study conducted by Bradley et al. showed that pupil dilation was significantly greater while participant's viewed pleasant and unpleasant pictures, compared to neutral pictures (Bradley, Miccoli, Escrig, & Lang, 2008). The study also demonstrated that the pupillary response covaried with the skin conductance response, indicating that pupillary dilation to high arousing stimuli is an index of sympathetic activation within a picture-viewing context and is also tightly coupled with arousal. Thus, the pupil is a fitting alternative to the skin conductance measure, in order to investigate physiologic arousal in PD.

Therefore, it is relevant to discuss neural mechanisms that influence pupil motility and previous findings on pupil motility in PD. Pupil constriction is predominantly controlled via parasympathetic input to the sphincter muscle from the Edinger Westphal nucleus, whereas pupil dilation is predominantly controlled via sympathetic input to the dilator muscle from the thoracic cell columns in the spinal cord. However, pupil dilation can result from either direct sympathetic input, which is modulated by noradrenergic

brain stem nuclei, the hypothalamus, and the central nucleus of the amygdala, or from inhibition of parasympathetic input to the sphincter muscle, primarily mediated by reticular and direct and indirect cortical pathways (Lowenstein, 1955).

Previous investigations of pupil motility in PD have consistently found that Parkinson's patients show a reduced amplitude of the initial light reflex (Beaumont, Harris, Leendertz, & Phillipson, 1987; Harris, 1991; Micieli et al., 1991; Granholm et al., 2003), but no differences in the maximum dilation during dark adaptation (Micieli et al., 1991) or in response to tropicamide, an acetylcholine antagonist which blocks the parasympathetic input to the sphincter muscle (Granholm et al., 2003). Thus, the results of these previous studies do not preclude utilizing the pupil as an index of arousal-mediated pupil dilation in PD.

The primary aim of the current study was to utilize the pupil as a measure of autonomic arousal to investigate whether Parkinson patients would display emotion-modulated arousal similar to that described in normal individuals by Bradley et al. (2008). Findings from this study could potentially help us determine whether previous skin conductance findings in our lab may be related to peripheral autonomic dysfunction or indicative of a centrally-instantiated hypoarousal phenomenon in PD.

CHAPTER 2 STATEMENT OF THE PROBLEM

Many Parkinson's patients experience emotional symptoms in addition to motor dysfunction. Although there is some debate over the extent to which symptoms are secondary psychological reactions to a chronic and debilitating illness or whether they are the inherent result of PD pathology, increasing evidence shows that at least some emotional symptoms and or mood dysfunction is inherent to the underlying progression of neuropathology in Parkinson's disease. However, the exact neural mechanisms underlying emotional dysfunction in Parkinson's disease remain unclear. For instance, it is not yet understood whether dysfunction is predominantly related to disruption of basal ganglia loops or more diffuse Lewy body pathology in mesolimbic and mesocortical systems. Along the same vein, it is unclear as to whether emotional dysfunction is a dopamine-specific phenomenon, as is the case for motor symptoms, or if the emotional systems have to a unique, dopamine-independent neurophysiological basis. Understanding the specifics with respect to neurophysiology of non-motor symptoms will have important implications for pharmacological treatment.

Moreover, from a cognitive perspective, it remains unclear as to what node within an information processing model of emotional processing is affected by PD pathology. Affective stimuli activate motivational systems that initiate a cascade of perceptual and motor processes. Disruption of these processes in PD might occur very early, affecting the initial orienting response to motivationally significant stimuli, or may be related to a lack of enhanced perceptual processing or preparation for action, slightly later components of the orienting cascade (Bradley, 2009). Additionally, it is possible that emotional symptoms in Parkinson's are less related to a deficit in the orienting response

to affective stimuli (as is most relevant in a picture-viewing context; see Bradley, 2009) and more a result of failure to engage appropriate downstream limbic-motor interfaces. The development of a bio informational model of emotion dysfunction in PD is needed to understand the cognitive mechanisms at play and to be able to target cognitive-behavioral interventions that are specific to emotional and behavioral difficulties experienced by Parkinson's patients.

Various studies in our lab have sought to tease out the pattern of aberrant physiologic responsivity to emotional pictures in Parkinson's patients, with somewhat varied results. The Bowers et al. (2006) study found that Parkinson's patients showed muted startle potentiation to aversive pictures compared to healthy older adults. It was hypothesized that the lack of startle potentiation was due to diminished amygdala activation in PD, and that this effect would likely be strongest for threat-related stimuli, due to the amygdala's pronounced role in threat-related startle potentiation (Lang, Davis, & Ohman, 2000). However, the Miller et al. (2009) study showed that there was no difference between controls and Parkinson's patients in startle potentiation to threat-related stimuli; however, Parkinson's patients did not show increased startle potentiation in response to high arousing stimuli. Miller speculated that the deficit in emotional processing in Parkinson's patients was related to a hypoarousal phenomenon. She proposed a threshold theory, such that differences in physiologic reactivity between controls and Parkinson's patients are driven by high arousing stimuli because Parkinson's patients reach a threshold at which a higher state of arousal cannot be elicited.

To test the hypothesis that PD patients experience an arousal-specific deficit, skin conductance responses to emotional and neutral pictures were examined in the same PD patients who participated in the Bowers et al. (2006) study. This study showed that Parkinson's patients do indeed show a diminished skin conductance response to pleasant and unpleasant stimuli compared to healthy older adults. However, responses to neutral pictures were also diminished, raising the possibility of a global attenuation of this response system.

While these results seemed to lend support towards an arousal-specific deficit in Parkinson's disease, an alternative interpretation relates to peripheral autonomic system dysfunction that is commonly observed in Parkinson's disease, even during the early stages. In particular, a recent study showed that Parkinson's patients have substantial denervation at the sweat glands in the palm (Dabby et al., 2006), which are the source for measuring electrodermal activity related to central autonomic activation during emotional picture viewing. Therefore, it is possible that abnormalities of the skin conductance response in PD are a reflection of peripheral nervous system dysfunction, as opposed to a centrally instantiated hypoarousal phenomenon.

Thus, the current study sought to use an alternative measure of centrally-modulated arousal. A recent study showed that the pupil dilates more to both pleasant and unpleasant pictures compared to neutral pictures, and that this response covaries with the skin conductance response (Bradley et al., 2008). To date, there is no significant evidence of Parkinson's-related damage to the peripheral nerve fibers that ascend from the thoracic cell column of the spinal cord to control dilation of the pupil. Studies have shown no differences in magnitude of pupil dilation in Parkinson's disease

compared to controls (Micieli et al., 1991; Granholm et al. 2003). Thus, the pupil seems to be a viable alternative to skin conductance as a measure of arousal in PD.

Specific Aims and Hypotheses

Primary Aim and Hypothesis

The primary aim of the current study is to test the hypothesis that PD patients have muted autonomic arousal to emotional pictures. To test this hypothesis, we used the pupil response as an index of autonomic arousal. We recorded pupil diameter while participants (Parkinson's patients and healthy older adults) viewed a series of pleasant, unpleasant, and neutral pictures. The predictions were as follows: If Parkinson's patients are autonomically hypoaroused to emotional stimuli, then the PD group will show a smaller increase in pupil dilation to emotional pictures compared to a group of healthy older adults. This finding would correspond to the previous SCR results. Alternatively, if the PD group and controls show similar changes in pupil dilation to emotional vs neutral pictures, this would indicate that Parkinson patients do not have pervasive autonomic hypoarousal.

Secondary Aims

A secondary aim of the current study is to compare subjective ratings of valence and arousal between the PD and healthy older adult groups. Most previous studies have shown minimal differences in subjective ratings of valence and arousal and subjective emotional experience (Miller et al., 2009; Mikos et al., 2009; cf Bowers et al., 2006; Weiser, Muhlberg, Alpers, Macht, Ellgring, & Pauli, 2006). Thus, it is predicted that there will be no difference in subjective ratings of valence and arousal between the Parkinson's and Control groups.

Another secondary aim of the current study is to explore the relationship between disease severity and mood variables and the emotion-modulated pupillary response. To do so, the emotion-modulated pupillary response for each individual will be calculated as the average difference in dilation to neutral vs. emotional pictures. This variable will be correlated with disease variables such as disease duration, Hoehn Yahr scores (a measure that indicates the stage of disease progression), and the UPDRS motor scores (an index of severity of motor symptoms), and mood variables including scores on the Beck Depression Inventory and the Apathy Scale. Bowers et al. (2008) found a moderate association between skin conductance responses and scores on the Apathy Scale. Thus, it is predicted that, if the pupil response parallels our previous findings of a muted skin conductance response in Parkinson's patients, there may be a positive association between the emotion-modulated pupillary response and apathy.

CHAPTER 3 METHODS

Participants

Fourteen nondemented Parkinson's patients and twelve healthy older adults participated in the current study. Parkinson's patients were recruited from the University of Florida Movement Disorders Clinic and were tested "on" their dopamine-replacing medications. The control group was recruited from the community and from spouses of PD patients. Participants were characterized as nondemented (Mini Mental State Exam >25), free of any self-reported major psychiatric disturbance (e.g., major depression or anxiety, psychotic symptoms, etc.), and had no history of surgery in the brain (e.g., deep-brain stimulation for treatment of PD symptoms.) Two participants were candidates for deep brain stimulation surgery.

Table 1 displays the demographic and clinical characteristics of the PD and control group. Overall, participants were well educated and predominantly male (17 men and 9 women.) They ranged in age from 57 to 81 years; the PD group was slightly younger than the control group (PD mean=69.4 years; control mean=74.4 years, $p=.06$.) With respect to antidepressant usage, 7 out of the 14 PD patients compared to 2 out of the 12 controls were currently taking antidepressant medications. Yate's continuity corrected X^2 were calculated (due to cell counts <5) to compare the gender and antidepressant usage ratio between the PD and control groups. Neither was statistically significant ($p=.78$ for gender, $p=.17$ for antidepressants). The only significant difference between the groups was in Mini Mental State Examination (MMSE; Folstein et al., 1975) scores, such that the PD group scored an average of 1.2 points lower than the control group ($t(24) = 2.23, p < .05$). On the Beck Depression Inventory-II (BDI-II, Beck et al.,

1996), there was a marginal effect such that the PD group scored higher than the Control group ($t(24)=2.11, p = .05$). Even so, the BDI score of the PD group (mean of 8.1) fell well below the cutoff for depression (14).

The PD patients ranged from moderate to severe disease severity, according to standard staging and severity criteria including the Hoehn–Yahr classification (Hoehn and Yahr, 1967) and the motor score of the Unified Parkinson Disease Rating Scale (UPDRS; Fahn et al., 1987). The UPDRS and Hoehn–Yahr staging took place within 6 months of the experimental protocol.

Table 3-1. Demographic and clinical characteristics of Parkinson’s and healthy older adults samples.

	Parkinson's Group (N=14)	Control Group (N=12)	P-Value
Gender (M / F)	10 / 4	7 / 5	0.78
Antidepressant (Y / N)	7 / 7	2 / 10	0.17
Age	69.4 (8.4)	74.4 (3.9)	0.06
Education	18.4 (3.6)	16.5 (3.8)	0.19
Mini Mental State Exam (MMSE)	28.2 (1.7)	29.4 (0.9)	0.04*
Beck Depression Inventory (BDI)	8.1 (6.2)	3.8 (4.0)	0.05*
Apathy Scale (AS)	8.2 (4.9)	7.2 (3.4)	0.54
State Anxiety (STAI-Y1)	29.1 (11.9)	29.0 (11.5)	0.98
Trait Anxiety (STAI-Y2)	30.8 (11.3)	32.9 (12.1)	0.65
Disease duration	7.4 (3.5)	-	-
Levodopa Equivalent Dosage (LED)	737.1 (537.9)	-	-
UPDRS "On" Meds	25.1 (6.9)	-	-
Hoehn-Yahr "On" Meds	2.3 (0.4)	-	-

Note: Categorical variables are presented as ratios; quantitative variables are presented as Mean (Standard Deviation). Variables marked with an asterisk (*) denote significant group differences at $\alpha=.05$.

Materials and Design

Forty-two pictures¹ were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) consisting of 14 unpleasant (mean

¹ The library numbers for IAPS pictures used in this study are: pleasant: 2080, 4220, 4607, 4641, 4660, 4680, 5470, 7330, 8030, 8080, 8200, 8370, 2160, 8280; neutral: 2190, 2200, 5500, 7000, 7010, 7030,

pleasure/arousal = 2.4, 6.4), 14 neutral (mean pleasure/arousal = 5.0, 3.0), and 14 pleasant (mean pleasure/arousal = 7.4, 5.9) pictures. Unpleasant and pleasant stimuli were significantly more arousing than the neutral stimuli, based on the IAPS normative arousal ratings ($t=14.7$, $p<.001$ for unpleasant and $t=3.4$, $p<.001$ for pleasant).

Normative arousal ratings did not significantly differ between pleasant and unpleasant picture categories ($t=2.04$, $p=.143$). The stimulus set was adapted from the set used in the Bowers et al. (2006) startle study. Six additional pictures were included in analysis (2 per condition) that had served as “no-startle” trials in the Bowers et al. study, and 3 pictures were replaced to ensure that pleasant and unpleasant picture categories did not differ from one another in average arousal. Unpleasant pictures included mutilations, vicious animals, physical violence, etc., whereas pleasant pictures consisted of babies, couples, food and sports activities. The neutral picture category included pictures of buildings, office scenes, plants, furniture, etc. Pictures were landscape (1024 x 768) in orientation and were displayed in 16-bit grayscale. Using Adobe Photoshop (version 5.0.2; Adobe Systems Inc., San Jose, CA), the mean luminosity of the selected pictures was modified such that the mean and distribution of luminosity values for each of the pictures sets (pleasant, neutral, unpleasant) did not differ, following the methods used in the Bradley et al. (2008) pupillometry study.

Additionally, a blank white slide (luminosity=255, according to luminosity parameters indicated by Adobe Photoshop version 5.0.2 for a slide filled with default “White” background) and a blank black slide (luminosity=0, see Adobe Photoshop version 5.0.2 luminosity parameters for a slide filled with default “Black” background)

7090, 7130, 7170, 7500, 7550, 7700, 6150, 7190; unpleasant: 1090, 1301, 2120, 3000, 3010, 3100, 3130, 3530, 6230, 6370, 9040, 9050, 7380, 9810

were included in the stimulus set in an attempt to gage a participant's maximum dilation and maximum constriction to a null (non-picture) stimulus.

A grayscale slide and a centered black fixation cross were displayed for 3 seconds before picture presentation on each trial. The first four trials alternated between the white and black slides (white, black, white, black), each presented for 6 seconds and each followed by an intertrial interval of 4.5 seconds. Following the initial four trials, each IAPS picture was presented for 6 seconds, followed by a variable inter-trial interval ranging from 4.5 to 8.5 seconds. Startle probes were also delivered at either 4200, 5000, or 5800 ms post picture onset; however, startle data are not reported. The IAPS pictures were presented in blocks of six, with two pictures from each condition (pleasant, neutral, unpleasant) in each block. The order of pictures within each block was generated randomly and each participant saw the picture set in the same order.

Apparatus

Picture presentation was controlled by an IBM-compatible computer running Presentation software (Neurobehavioral Systems, San Francisco, CA). Pictures were displayed on a 19-in. monitor (Samsung SyncMaster 191T) located in the experimental room.

Pupil diameter was recorded using an ASL EYE-TRAC 6000 eyetracker system (Applied Science Laboratories, Bedford, MA), which allows free movement of the head and consists of a video camera and an infrared light source pointed at the participant's right eye. A magnetic sensor, attached to a headband, tracked and adjusted for head movement. The recording video camera was located in a wood box in front of the subject, and a red translucent screen obscured it from view. Pupil diameter was

sampled at 60 Hz for 3 seconds prior to picture onset, for 6 seconds during picture onset, and 3 seconds following picture offset.

Procedure

Upon arrival at the laboratory, each participant signed a consent form and was subsequently administered the MMSE. He or she was then seated in a chair in a small, sound attenuated, dimly lit room. Ambient light intensity was the same for every experimental session. The magnetic headband for tracking head movements was placed on the participant's head. Sensors to measure heart rate, skin conductance and startle response were also placed on the participant (data not reported.) The participant was then told that he or she would be viewing a series of pictures. The participant was told not to look away or close his or her eyes, but rather to continue viewing the picture the entire time it was on the screen. The session began with the participant viewing the alternating white and black slides (2 of each). This was followed by two neutral pictures that served as filler trials to orient the participant to the picture-viewing task and followed by the series of 42 pictures used in analysis. When the participant was finished viewing the pictures, the headband and sensors were removed, and the participant completed a series of mood questionnaires. Finally, the participant rated each picture he/she saw along the dimensions of valence and arousal using the Self Assessment Manikin (Bradley and Lang, 1994), a cartoon figure for making ratings on using a 1 to 9 ordinal scale. For valence, ratings ranged from unpleasant (1) to neutral (5) to pleasant (9). For arousal, ratings ranged from calm (1) to neither calm nor excited (5) to very excited (9). At the completion of the study, the participant was debriefed, paid, and thanked for participating.

Data Reduction

A series of steps were taken to reduce the raw pupil data collected for use in analysis. It was necessary to account for time points where the technology did not reliably detect a signal in order to sample a valid measurement of pupil diameter and also to account for time points where pupil samples were not collected due to blinks. Trials that had 50% or more of pupil samples missing (due failure of the EyeTracker system to obtain automatic discrimination of the pupil) were considered invalid trials and eliminated from the data. Because the number of dropped trials for each individual was positively skewed, nonparametric Mann-Whitney U tests were conducted to investigate whether the number of invalid trials differed by group. Three separate Mann-Whitney U tests were conducted, one for each condition (unpleasant, neutral, pleasant). There were no significant between group differences in the number of trials dropped for the unpleasant condition (Mann-Whitney U = 60.5, $p = .23$), neutral condition (Mann-Whitney U = 52.5, $p = .11$), or the pleasant condition (Mann-Whitney U = 70.5, $p = .49$). Figure 3-2 lists the total number of invalid trials by condition and group. Total number of invalid trials per participant never exceeded 10 (<25% total trials.) If pupil discrimination failed to be achieved for greater than 25% of trials, the data for that participant was deemed invalid was not included in analysis. Four participants were thus excluded (1 PD and 3 controls). Anecdotally, these were typically individuals with very small pupils and clouded eye whites which made it very difficult to obtain automatic detection of the pupil with the ASL technology. For all valid trials, pupil samples where the pupil was obscured due to blinks were identified and linear interpolation was used to estimate pupil size (using an algorithm provided by the Applied Science Laboratories File Analysis Program, ASL Results, version 1.11.02.) Momentary losses of pupil

discrimination (not due to blinking), where the technology failed to obtain a pupil measurement, were manually filtered out post linear interpolation.

Table 3-2. Total number of invalid trials per group, per picture type.

	Unpleasant	Neutral	Pleasant
Parkinsons	11	23	14
Controls	5	8	8

Figure 3-1 provides an illustration of the average pupil diameter (mm) across the time course of an individual trial and shows how each variable was calculated for analysis. Based on the averaged waveforms, the initial light reflex during picture viewing was scored as the maximum magnitude of pupil constriction in a window from 0 to 2 seconds after picture onset. Pupil diameter in response to each picture type (unpleasant, neutral, and pleasant) was calculated as the average pupil diameter in the time window following the initial light reflex, 2.5 to 6 seconds after picture onset. In order to score the magnitude of the light reflex for each individual, a one-second pre-picture baseline, measured in millimeters, was calculated for each trial and this baseline was subtracted from subsequent pupil samples throughout the trial in order to obtain the change from baseline. The average initial light reflex for each participant was then scored as the maximum pupil constriction in a window from 0 to 2 seconds after picture onset, averaged across all picture-viewing trials.

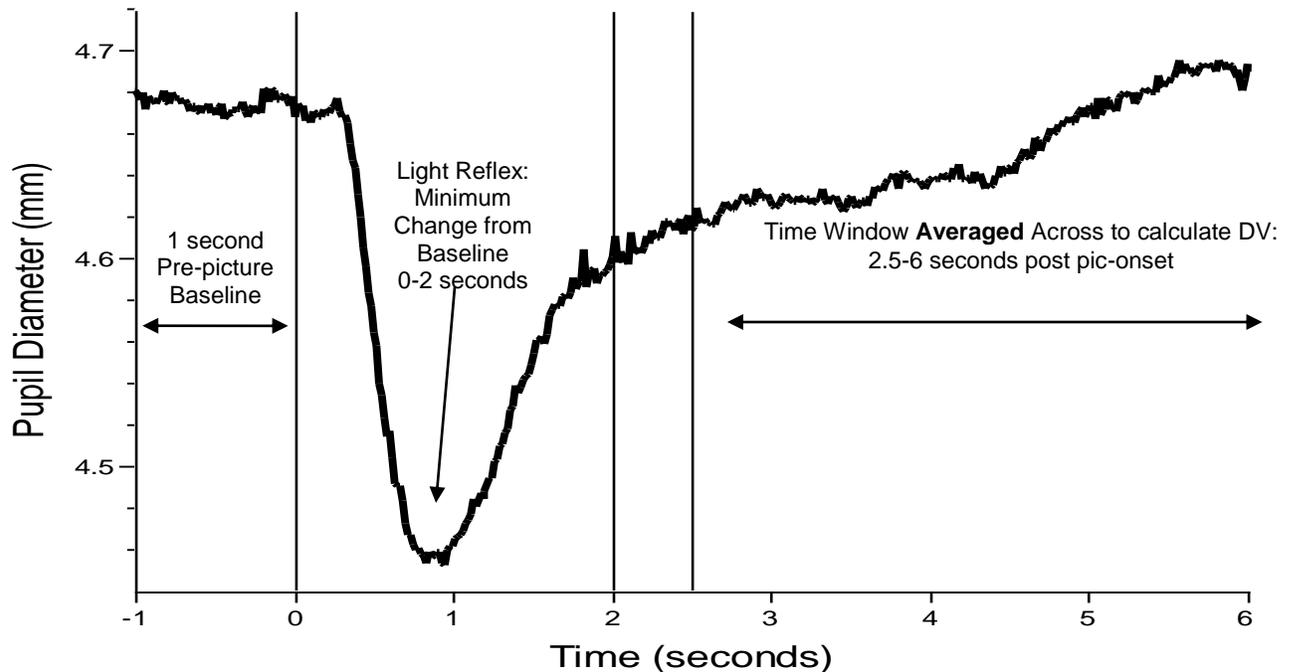


Figure 3-1. Pupil diameter plotted across the timecourse of one trial. The dependent variable used in primary analysis is calculated as the average pupil diameter across a time window of 2.5-6 seconds post-picture onset. The light reflex was scored as the maximum change in pupil diameter from 0-2 seconds.

Data Analytic Plan

Preliminary Analyses

Baseline pupil diameter and average light reflex. Before proceeding to the primary analysis, a number of preliminary analyses were conducted to examine baseline features of pupil motility between the groups. An independent t-test was conducted to investigate differences in baseline pupil diameter, measured as the average pupil diameter one-second prior to picture onset, between the groups. An independent t-test was also conducted to examine whether the average light reflex differed between the Parkinson's group and the Control group.

Pupil reactivity to black and white slides. Separate independent t-tests were conducted to explore potential differences in each group's maximum dilation to a black slide and maximum constriction to a white slide. For the maximum dilation analysis, maximum dilation was calculated as the average change in pupil diameter from 2.5-6 seconds post slide onset. For the maximum constriction analysis, the light reflex was obtained by averaging across both (2) trials and scoring the minimum pupil diameter between 0-2 seconds.

Primary Analysis

In order to test the prediction that Parkinson's patients would show a muted pupillary response to emotional pictures compared to a healthy control group, a mixed analysis of variance was conducted, with magnitude of pupil diameter as the dependent variable. Group (Parkinson vs. Control) was the between-subjects factor and Emotionality (Unpleasant, Neutral, Pleasant) was the within-subject factor.

Potential differences in subjective ratings of valence and arousal were explored by conducting two separate mixed analyses of variance with Group (Parkinson's vs. Controls) as the between-group factor and Emotionality (Unpleasant, Neutral, Pleasant) as the within-subject factor.

Lastly, all continuous variables, including the emotion-modulated pupillary response variable, disease severity, and mood variables were screened for violations of normality by investigating skewness and kurtosis values for each distribution and conducting Shapiro-Wilks tests of normality. The distribution for the emotion-modulated pupillary response variable (average pupil diameter during emotional pictures minus average pupil diameter to neutral pictures) was rather leptokurtic; thus, nonparametric

Spearman's correlations were conducted to explore associations between disease severity indices, mood variables, and the emotion-modulated pupillary response.

CHAPTER 4 RESULTS

Preliminary Analyses

Baseline Measurements of Pupil Motility

Sets of initial analyses were conducted in order to examine indices of pupil motility including baseline pupil diameter, pupil reactivity to simple black and white screens, and the basic light reflex.

Pupil diameter. To determine whether there were baseline differences in pupil diameter between the PD and Control groups, pupil magnitude was examined during the one second period prior to picture onset. During this time, subjects were viewing a black cross on a grey screen. Mean pupil diameters (mm) and standard deviations were 4.8 (.83) for the PD group and 4.6 (.67) for the Control group. These values were not significantly different based on an independent t-test ($t(24) = .74, p = .47$). Since there was no significant difference in baseline pupil diameter between the groups, it was deemed appropriate to use the raw magnitude of pupil diameter for the primary analysis.

Pupil reactivity to simple black and white slides. Pupil responses to two, alternating plain black and plain white slides were examined in an attempt to gauge maximum dilation and maximum constriction to a null (non-picture) stimulus. It was of particular interest to ensure that there were no significant differences in the maximum feasible dilation between the groups in order to rule out the possibility that a baseline difference in maximum pupil motility might confound between-group comparisons of magnitude of pupil dilation to emotional pictures. Figure 4-1 illustrates each group's average pupil dilation in mm to a black screen presented for six seconds, averaged

across two trials (luminosity value=0). The maximum dilation in mm was calculated as the average change from baseline (one second pre-picture) across 2.5-6 seconds post slide onset. There was no significant difference in average magnitude of pupil dilation to a black screen between the groups ($t(24)=-.24$, $p=.82$), indicating that maximum extent of dilation was comparable between the groups (Parkinson's group: Mean (SD) = .50 mm (.32), Control group: Mean (SD) = .47mm (.17)). Figure 4-1 also illustrates each group's magnitude of pupil constriction to a white screen (luminosity value=255). Parkinson's patients average magnitude of constriction (Mean (SD) = -.61mm (.31) was smaller than controls (Mean (SD) = -.76mm (.28); however, this difference was not statistically significant ($t(20)=1.17$, $p=.26$).

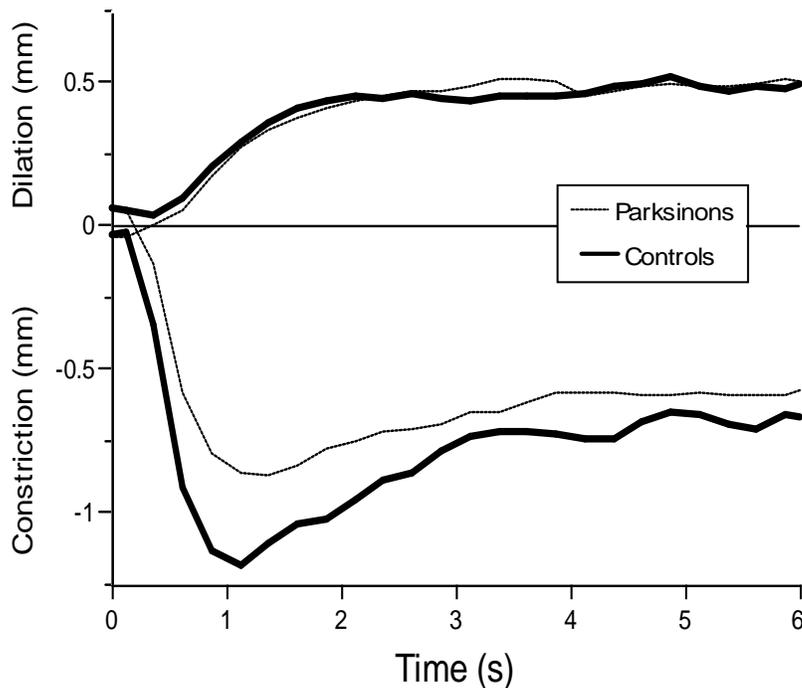


Figure 4-1. Pupil dilation to a black screen (top) and pupil constriction to a white screen (bottom) in Parkinson's patients and healthy older adults.

Light Reflex. Figure 4-2 shows the average change in pupil diameter for the PD and Control groups throughout the duration of picture display, averaged across all emotional and neutral pictures (total N = 42.) As shown, both groups appeared to demonstrate an initial light reflex to the picture onset from 0-2 seconds. This was followed by pupil dilation during the remainder of the picture display (2.5-6 seconds post picture-onset.) The light reflex for each individual was scored as the minimum change in pupil diameter from 0-2 seconds after picture onset. To determine whether there were group differences in the magnitude of the light reflex, an independent samples t-test found that the light reflex was significantly smaller in the PD group compared to the control group ($t(24) = 4.08, p < .001$).

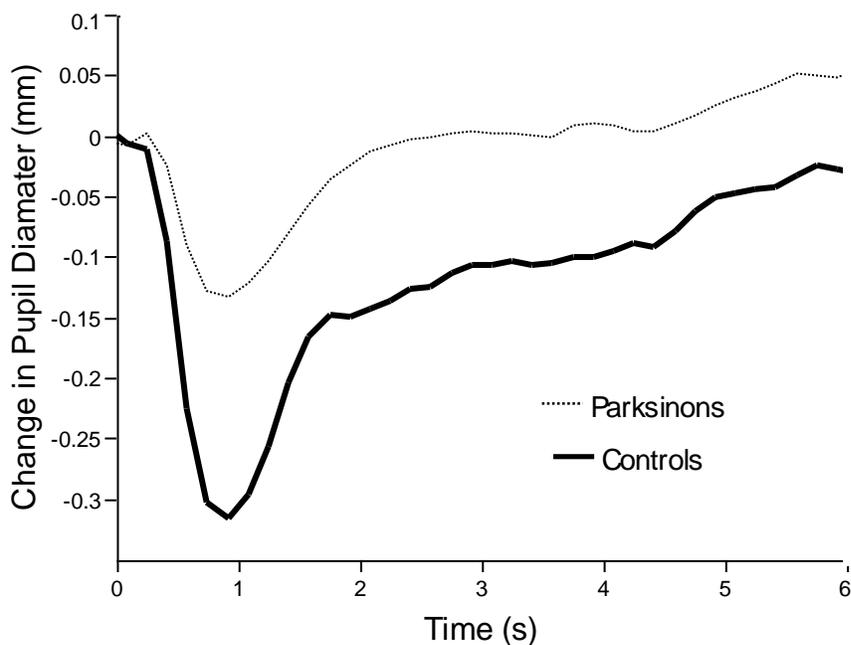


Figure 4-2. Pupil response following picture onset, averaged across all picture-viewing trials, in the Parkinson's patients and in healthy older adults. The initial light reflex occurs in response to the picture onset and lasts from approximately 0-2 seconds, followed by increasing dilation of the pupil.

Analysis of Primary Aim

Effect of Picture Emotionality on Pupil Dilation

The primary aim was to assess whether or not Parkinson's patients demonstrate an emotion-modulated pupillary response and examine how this response compares to controls. Figure 4-3 shows the Parkinson and Control group's average pupil diameter from 2.5 to six seconds while viewing each picture type (pleasant, unpleasant, neutral). Table 4.1 shows the mean pupil diameter associated with pleasant, unpleasant, and neutral pictures for each group.

To test the prediction that Parkinson's patients would show a muted arousal response to affective pictures, a Group (2) x Emotion (3) mixed analysis of variance (ANOVA) was conducted using pupil diameter as the dependent variable. Mauchly's sphericity assumption was violated ($p < .05$); therefore Greenhouse-Geisser F approximations are reported. Results of the ANOVA yielded a significant main effect of picture emotionality ($F(1.6, 38.5) = 21.3, p < .001, \eta_p^2 = .47$). Post-hoc comparisons revealed that both unpleasant and pleasant pictures elicited significantly greater pupil dilation compared to neutral pictures ($t(24) = 5.22$ and 4.85 , respectively, p 's $< .001$.) There was no significant difference in the pupillary response to pleasant and unpleasant images ($t(24) = .59, p = .56$). No other main effects or interactions were significant (i.e., neither Group, nor Group X Emotion). Results of the ANOVA are presented in Table 4-2.

Table 4-1. Average change in pupil diameter (Δ mm) from baseline (mm) and standard deviation while viewing unpleasant, neutral, and pleasant pictures.

	Parkinson	Controls
Unpleasant	4.9 (0.86)	4.5 (0.68)
Neutral	4.7 (0.79)	4.4 (0.69)
Pleasant	4.8 (0.87)	4.5 (0.70)

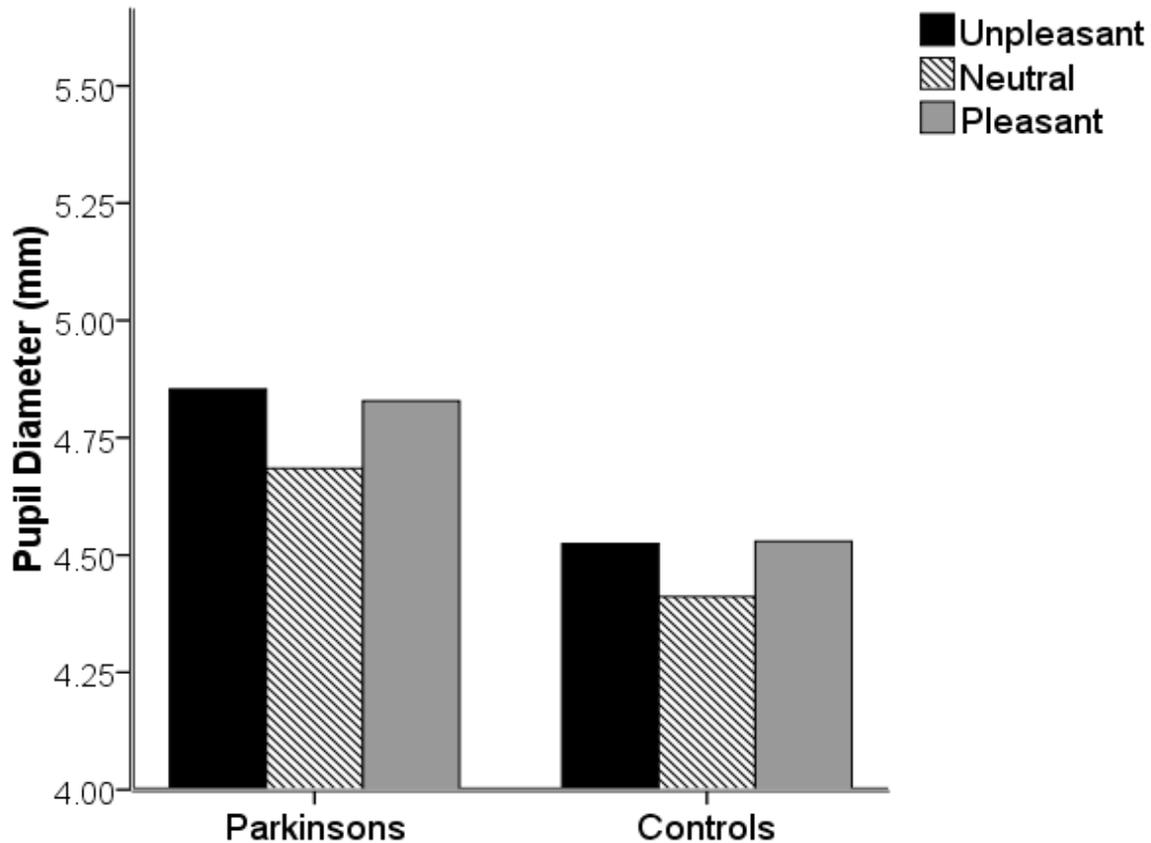


Figure 4-3. Average pupil diameter while viewing affective pictures compared to neutral pictures in Parkinson's patients and healthy older adults.

Table 4-2. Results of mixed ANOVA for the effect of picture emotionality on pupil dilation.

	<i>df</i>	F	Sig.	Partial Eta Squared
Emotion	1.606	21.316	.000	.470
Emotion x Group	1.606	.678	.483	.027
Error (Emotion)	38.536	-	-	-
Group	1	.978	.332	.039
Error (Group)	24	-	-	-

Exploratory Analysis

Light Reflex and Emotion

As an exploratory analysis, the magnitude of the light reflex was calculated for each condition: pleasant, unpleasant, and neutral. Figure 4-4 displays the magnitude of

the pupillary light reflex by picture category in the Parkinson's and the Control group. As illustrated by Figure 4-4, the light reflex is smaller when participants viewed emotional compared to when they viewed neutral pictures. Results of a Group (PD, Control) X Emotion (Pleasant, Neutral, Unpleasant) ANOVA revealed a significant main effect for Emotion ($F(2,48)=9.14, p<.001, \eta_p^2=.28$). Post-hoc comparisons indicated that the light reflex was significantly smaller when subjects viewed emotional pictures (both pleasant and unpleasant, $p's<.01$) compared to neutral pictures. Means and standard deviations for each picture category are presented in Table 4-3. There was also a significant main effect of group, such that the Parkinson's group evidenced a significantly smaller light reflex across all picture categories compared to the healthy older adults ($F(1,24)=20.83, p<.001, \eta_p^2=.45$).

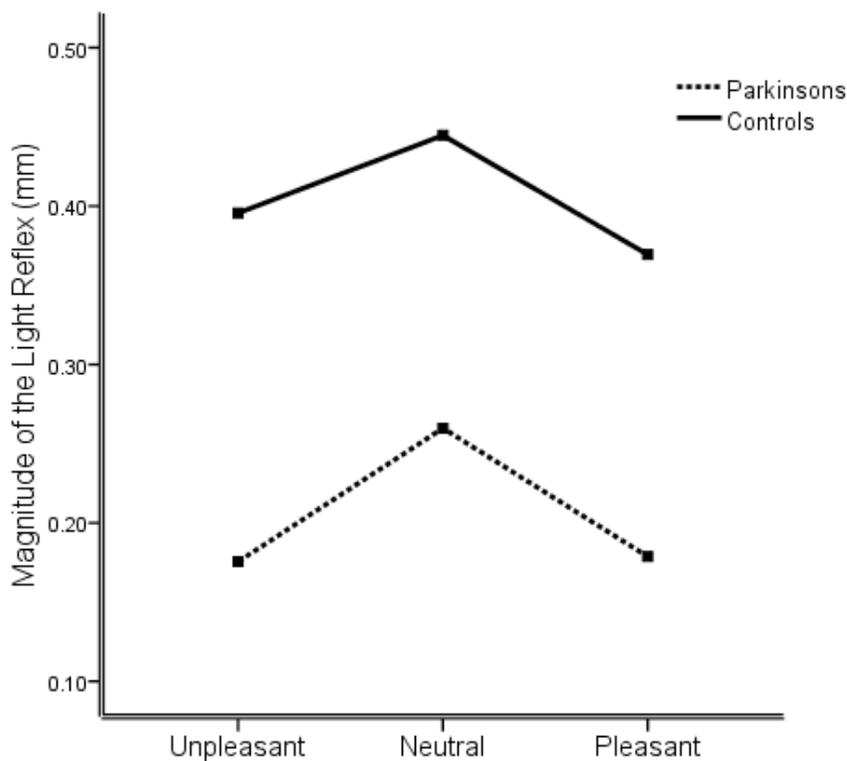


Figure 4-4. Magnitude of the light reflex while Parkinson's and healthy older adults view unpleasant, neutral, or pleasant pictures.

Table 4-3. Means and standard deviations for the magnitude of the light reflex for each picture category in the Parkinson's and Control groups.

	Unpleasant	Neutral	Pleasant
Parkinsons	.18 (.12)	.26 (.14)	.18 (.12)
Controls	.40 (.14)	.44 (.12)	.37 (.10)

Table 4-4. Results of mixed ANOVA for the effect of picture emotionality magnitude of the light reflex.

	<i>df</i>	F	Sig.	Partial Eta Squared
Emotion	2	9.144	.000	.276
Emotion x Group	2	.442	.646	.018
Error (Emotion)	48			
Group	1	20.825	.000	.465
Error (Group)	24			

Analysis of Secondary Aims

Influence of Mood and Disease-Severity Indices on the Pupillary Response

In order to investigate the effect of mood symptoms on the emotion-modulated pupillary response, the difference between average pupil diameter during emotional pictures (positive and negative) and pupil diameter during neutral pictures was calculated for each individual. There was no significant correlation between emotion-specific changes in pupil dilation and BDI-II or Apathy Scale scores. Nor was there a significant correlation between this variable and indices of Parkinson disease severity (disease duration, Hoehn-Yahr stage, LED, UPDRS). Additionally, Parkinson disease severity variables did not significantly correlate with the magnitude of the light-reflex across all picture-viewing trials or average dilation during picture-viewing trials.

Subjective Picture Ratings of Valence and Arousal

The mean valence and arousal ratings made by the PD and Controls are shown in Table 4-5. A Group (2) x Valence (3) mixed ANOVA was conducted to determine if the Parkinson's and Control groups differed in their subjective ratings of arousal. Mauchly's

sphericity assumption was violated ($p < .01$); therefore Greenhouse-Geisser F approximations are reported. The analysis revealed a main effect of emotionality on arousal ratings, $F(1.4, 32.1) = 35.63$, $p < .001$, $\eta_p^2 = .61$. Planned contrasts demonstrated that emotional pictures (both pleasant and unpleasant) were rated as more arousing than neutral pictures, F 's(1,23) = 38.28 and 48.24 for unpleasant and pleasant, respectively, p 's $< .001$. There were no significant differences in average subjective ratings of arousal between groups ($p = .40$) nor was there a significant Group x Valence interaction ($p = .49$.)

The same mixed ANOVA model was conducted to examine subjective valence ratings between groups, using Greenhouse-Geisser F approximations. The analysis yielded a main effect of valence, $F(1.3, 30.0) = 155.35$, $p < .001$, $\eta_p^2 = .87$. Planned contrasts demonstrated unpleasant images were rated as less pleasant than neutral images, $F(1, 23) = 119.31$, $p < .001$, and pleasant images were rated as more pleasant than neutral images, $F(1, 23) = 119.78$, $p < .001$. There was no significant difference in average subjective ratings of valence between groups ($p = .73$). Nor was there a significant Group x Valence interaction ($p = .83$).

Table 4-5. Means and standard deviations for subjective valence and arousal ratings by group.

	Valence		Arousal	
	Parkinson	Control	Parkinson	Control
Unpleasant	2.57 (1.1)	2.63 (1.1)	6.17 (1.5)	5.48 (2.3)
Neutral	5.22 (.57)	5.39 (.67)	3.19 (1.3)	3.11 (2.1)
Pleasant	7.11 (.52)	7.06 (1.0)	5.78 (1.2)	5.01 (2.4)

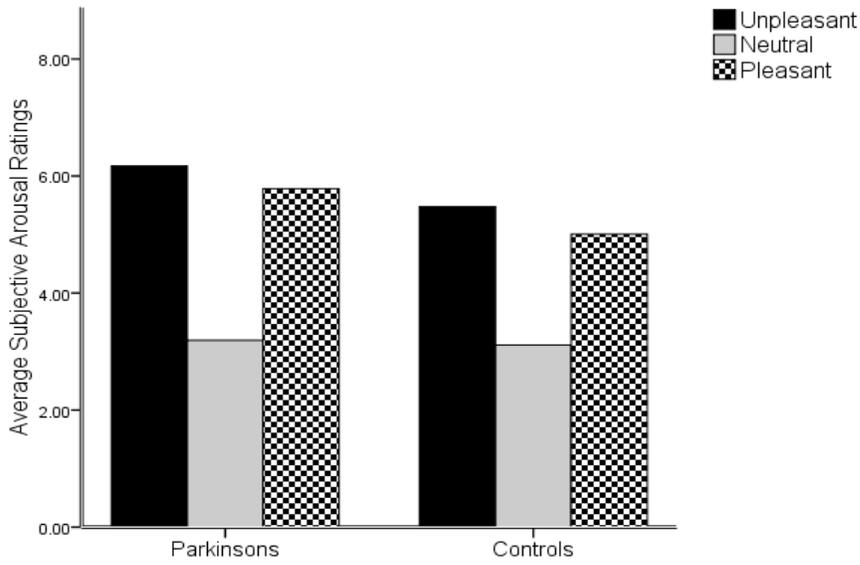


Figure 4-5. Subjective arousal ratings for unpleasant, neutral, and pleasant pictures in the Parkinson's group and healthy older adult group

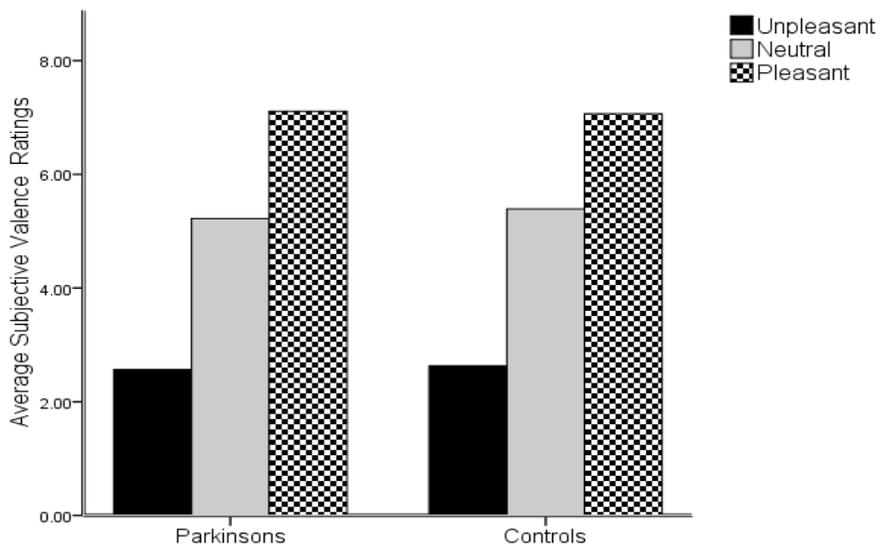


Figure 4-6. Subjective valence ratings for unpleasant, neutral, and pleasant pictures in the Parkinson's group and healthy older adult group.

CHAPTER 5 DISCUSSION

Emotion-Modulated Pupil Response in PD

The primary finding of this study was that both Parkinson's patients and healthy older adults show an emotion-modulated pupillary response, such that the pupil dilated significantly more to emotional (both pleasant and unpleasant) than neutral pictures. These results somewhat conflict with those of Bowers et al. (2008) who failed to find an emotion-modulated skin conductance response in PD patients. It is possible that the attenuated skin conductance findings may have been secondary to peripheral autonomic dysfunction that commonly occurs in PD. Thus, the reduced skin conductance response in PD may represent an index of severity of disease progression and impairment of the peripheral autonomic nervous system, rather than an index of "emotional" hypoarousal.

Furthermore, the results of the current study help to disentangle the potential mechanisms underlying emotional abnormalities in Parkinson's disease. Bowers et al. (2006) speculated that Parkinson's patients may have a deficit in translating an aversive motivational state into a physiological response due to decreased disinhibition of the amygdala in Parkinson's disease. To elaborate, the amygdala is typically under tonic inhibitory control from the prefrontal cortex and is disinhibited via dopaminergic input, particularly during emotional states (Marowsky et al., 2005; Inglis and Moghaddam, 1999). Bowers et al. (2006) hypothesized that disinhibition of the amygdala is disrupted due to dopamine depletion in PD. Miller et al. (2009) elaborated on this hypothesis, speculating that emotional deficits in PD are arousal-dependent, and that differences in physiologic reactivity in Parkinson's patients are specifically driven by muted reactivity

to high arousing stimuli, and that these stimuli may have driven the lack of startle modulation to aversive stimuli in the Bowers et al. (2006) study. Miller et al. (2009) specifically proposed that differences in the magnitude of the startle reflex to aversive stimuli in the Bowers (2006) study were likely driven by the large proportion of mutilation pictures in the unpleasant picture category, suggesting a “threshold model” in which differences in physiologic reactivity in Parkinson’s patients are only detected by the use of high arousing stimuli. However, given that the current study utilized the same stimulus set of the Bowers et al. (2006) study and there was no difference between controls and Parkinson’s patients in the pupil response to unpleasant and pleasant stimuli, it is unlikely that the previously reported muted startle potentiation in PD is due to hypoarousal to high arousing stimuli.

Thus, it seems that aberrant startle reactivity in Parkinson’s disease patients is not an arousal-specific deficit, but may be indicative of abnormal activation of the defensive motivational system. Potentiation of the startle reflex is thought to reflect the priming of the motivational system that mediates defensive behavior, (Lang, Bradley, & Cuthbert, 1997) thus in some way reflecting preparation for action. It is arguable that “preparation for action” and affective modulation of somato-motor responses are functionally independent and temporally downstream components of the emotional response cascade that are preceded by initial orienting and attention processes that are also modulated by affective arousal. As Bradley (2009) explains, there are multiple components of the passive orienting response, including heightened arousal, increased attention and enhanced perceptual processing, and preparation for action. The defense cascade model (Lang, Bradley, & Cuthbert, 1997) suggests that as defensive distance

diminishes (and threat becomes more imminent), emotional intensity (arousal) increases and the motivational system (and its physiological correlates) shift from increased orienting and enhanced perceptual processing to mobilization for action. Therefore, it is possible that the emotion-modulated pupillary response in PD is reflective of early arousal-mediated increase in orienting and enhancement of perceptual processes (see Bradley, 2009) whereas aberrant startle reactivity in PD reflects inadequate or abnormal activation of the defensive response system, at the somato-motor level.

This interpretation suggests that different functional components of the defensive/appetitive response cascade might be differentially affected in Parkinson's disease. Although the arousal-mediated increase in the orienting response to affective pictures (as measured by the pupil) appears normal, there may be dysfunction in the concurrent activation of motivational systems that modulate preparation for action. Support for this hypothesis is reflected by aberrant startle reactivity in Parkinson's disease and also ecological support, evidenced by the fact that Parkinson's patients often demonstrate diminished behavioral activation that is frequently recognized as apathy.

Neural Mechanisms of the Emotion-Modulated Pupillary Response and Implications for Pathology of Emotion Dysfunction in PD

It is of note to discuss what the results of the current study imply about neural mechanisms underlying emotional processes in PD by utilizing what is known about underlying modulatory pathways to the pupil. While significant attention has been granted to neural mechanisms underlying cognitive effects on the pupil (e.g.: Steinhauer, Siegle, Condray, & Pless, 2004; Steinhauer, Condray, & Kasparak, 2000),

less has been directed towards elucidating the exact mechanisms underlying the effect of emotional processes on the pupil. However, the emotion-modulated pupillary response closely covaries with sympathetic activation (Bradley et al., 2008) and is likely driven by enhanced sympathetic input to the pupil via modulatory input from the central nucleus of the amygdala and the hypothalamus (see Ranson and Clark, 1959 as cited in White and Depue, 1999). Since the pupil response to affective stimuli did not differ between the Parkinson's and control groups, it seems that these limbic/cortico-limbic modulatory pathways to the pupil's dilator muscle are relatively intact.

It has also been suggested that emotion effects on the pupil are partially driven by central inhibition of the Edinger-Westphal nucleus that is primarily influenced by cortical and reticular inputs linked to arousal (Lowenstein 1955; Bonvallet and Zbrozyna, 1963; Steinhauer et al. 2000; Steinhauer et al., 2004). Thus, this mechanism may also contribute to the emotion-modulated pupillary response observed in the current study. However, given the aberrant light reflex that was observed in the Parkinson's group, the integrity of parasympathetic pathway to the pupil in the PD group is in question. The fact that this pathway may be jeopardized in PD and yet we see a robust effect of emotion on the pupil in the PD group lends support to the conjecture that this effect is primarily sympathetically driven.

Nonetheless, although the smaller light reflex in Parkinson's patients was expected and is consistent with previous research (Beaumont et al., 1987; Harris, 1991; Micieli et al., 1991; Granholm et al., 2003), its neural basis is not clear. Dysfunction of the light reflex may be linked to hyporeactivity of dopamine retinal cells, pathology in the Edinger Westphal nucleus itself, or pathology along the peripheral pathway to the pupil, possibly

in the ciliary ganglion (Granholm et al., 2003). Thus, it remains unknown whether the underlying pathology occurs along the afferent pathway to the Edinger Westphal nucleus or the efferent pathway to the pupil. If the pathology resides in the afferent pathway, central inhibition effects on the EW nucleus would be relatively spared and could still contribute to the emotionality effect on the pupil observed in the current study.

Modulation of the Light Reflex

Central inhibition of the EW nucleus has also been linked to modulation of the light reflex. Interestingly, an unforeseen finding of the current study was that the light reflex was smaller when participants viewed emotional pictures. This finding was not reported in the previous study conducted by Bradley et al. (2008). However, prior studies have shown that both increasing task demand and threat of shock can result in a smaller light reflex (Steinhauer et al., 2000; Bitsios, Szabadi, & Bradshaw, 1996), suggesting that arousal can have an effect on the magnitude of the light reflex. Previous authors have explained an arousal-related modulation of the reflex as direct inhibition of the EW nucleus; however, this “effect” on the measured magnitude of the light reflex could reflect the summative effect of light-reflex related parasympathetic input to the pupil concurrent with increased sympathetic activity in the context of emotional picture viewing. This would suggest that the effect of emotionality on pupil dilation begins early (<1 second post picture onset) and is sustained throughout the following 1-6 second window. However, it cannot be ignored that these results dissent from those reported by Bradley et al. (2008). Therefore stimulus properties may somehow be involved, although there was a concerted effort to control for luminosity across picture types. Future studies should seek to provide additional knowledge about the precise nature and time course of emotion effects on the pupil, which will help to inform the design and

methods of data analysis in future studies. Furthermore, future studies should make a more concerted effort to elucidate the precise relative influences of sympathetic and parasympathetic inputs to the pupil during emotion processing contexts, independent of cognitive load manipulations.

Limitations

There were some limitations in the current study. The sample size was small, particularly for study with clinical patients. Although smaller sample sizes are typical in experimental psychophysiology studies, the Parkinson's group in the current study may not be representative of a typical or comprehensive disease sample. For instance, Hoehn Yahr scores in the Parkinson's group only ranged from 2-3 on a scale of 1-5, which is relatively limited. However, this included only patients whose symptoms were already bilateral, thus eliminating a source of variability that could be particularly relevant since pupil diameter was measured unilaterally. Furthermore, half of the Parkinson's patients (7/14) as compared to 2 controls (2/12) were taking antidepressants. Although the chi-square test indicated that the difference in ratio of antidepressant usage was not statistically significant, it is unclear whether or not antidepressants may have affected the pupil motility or the emotion-modulated pupillary response. Prior studies have shown that norepinephrine reuptake inhibitors, in particular, can increase resting pupil diameter and reduce the amplitude of the pupillary light reflex (Phillips, Bitsios, Szabadi, & Bradshaw, 2000; Siepmann, Ziemssen, Mueck-Weymann, & Siepmann, 2007). However, it is unlikely the light reflex differences in our study are related to antidepressant usage, as previous studies have shown this effect, including one that examined newly diagnosed PD patients who were not yet taking any medications (Micieli et al., 1991).

Additionally, the Parkinson's group was tested on their dopamine replacing medications, thus it is unclear whether or not the results of the current study would be the same had the patients been tested in a hypodopaminergic state. It was elected to test patients in the "on" medication state for a few reasons. For one, testing patients on their dopaminergic medications is better representative of their daily state of functioning. It is important to understand emotional processes in patients on dopaminergic medications because, although they gain improvements in motor function while on these medications, they continue to experience emotional symptoms. This is likely because dopamine differentially affects motor, limbic, and cognitive functions and, in theory, each function requires a unique dopaminergic dosage in order to achieve optimal functioning (Cools, 2006; Rowe et al., 2008). It is also relevant to note that the time of most recent dose of medication varied between subjects in the current study; thus, the level of in vivo dopamine for any given subject at the time of testing was variable.

Lastly, this sample of Parkinson's patients was a relatively emotionally "healthy" group of Parkinson's patients. Their BDI-II and apathy scores were not indicative of significant depression or apathy, nor were they significantly different from the control group. Therefore, although we did not observe a difference in the emotion-modulated pupil response between the Parkinson's and the control group, this is not to say that a specifically apathetic or depressed group of Parkinson's patients would not show differences in their physiological responses to affective stimuli. A subgroup of apathetic Parkinson's patients might show aberrant physiological reactivity that is indicative of a particular pattern of disease progression that differentially affects underlying limbic

and/or autonomic systems. On the other hand, potential differences evidenced by a subgroup of Parkinson's patients could also reflect a byproduct of the fact that these patients are, in fact, depressed or apathetic, which returns us to the age-old "chicken-or-the-egg" question.

Conclusion

Thus, the current study at least serves as a baseline, showing that a sample of relatively emotionally healthy Parkinson's patients, on dopamine-replacing medication, show normal emotion-modulated arousal responses to both unpleasant and pleasant stimuli as measured by pupillary response. This finding can serve as the baseline for comparison in future studies that investigate particular subgroups of Parkinson's patients (i.e.: apathetic vs. non-apathetic). It also serves to fill in a piece of the puzzle in developing a bio informational model of emotion dysfunction in PD. Specifically, the results of the current study demonstrate that Parkinson's patients show an initial, emotion-modulated orienting response similar to that which we would expect in a healthy control group. This raises the possibility that emotion dysfunction in PD may occur at a later component in the emotional response cascade and relate more to inadequate activation of motivational systems that support motivated behavior.

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BIOGRAPHICAL SKETCH

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