THE EFFECT OF MOTOR SYMPTOM ONSET LATERALITY ON FACIAL EXPRESSIVITY IN PARKINSON'S DISEASE

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
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To my family.

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The purpose of the present study was to examine the effect of motor symptom laterality commonly found in Parkinson's disease (PD) as well as mood and motor symptoms on different aspects of facial expressivity.

Most patients with PD initially present with lateralized motor symptoms on one side of the body, left or right. This asymmetry usually persists throughout the course of the disease and reflects differential disruption of contralateral basal ganglia-frontal lobe dopaminergic systems. While a growing number of studies have reported that laterality of symptom onset may also influence non-motor symptoms of the disease (i.e., cognition), it remains unknown whether emotional processing is affected by symptom onset laterality. A cardinal symptom of PD is a "masked face," or significantly diminished facial expressivity. Based on views regarding a right hemispheric specialization for emotional behavior, we hypothesized that patients with left-sided motor symptom onset (implicating greater right hemisphere involvement) would display greater impairments in facial expressivity than those with right sided symptom onset. We also predicted that mood and PD-specific motor symptoms would contribute to diminished facial expressivity.

Twenty six patients with idiopathic PD (13 left symptom onset, 13 right onset) and 13 healthy controls were videotaped while posing facial expressions of fear, anger, and happiness.

Facial expressions were digitized and analyzed using custom software that extracted 5 variables: 2 measures of dynamic movement change (total and peak entropy), and 3 temporal variables (initiation time, rise time, duration). Self-report measures of depression (Beck Depression Inventory-II) and apathy (Apathy Evaluation Scale) were also given. Repeated measures ANOVAs and linear regressions were used to analyze the data.

Bonferroni-corrected post-hoc analyses revealed that the left-onset PD patients were significantly slower in initiating facial expressions than were right-onset PD patients or controls, regardless of expression posed [$F(2,36) = 8.21$, $p < .05$]. The groups did not significantly differ in terms of the entropy variables or other temporal variables. Furthermore, mood (i.e., depression or apathy) and disease-specific factors (i.e., symptom type) were unrelated to facial expressivity.

These results suggest an effect of motor symptom asymmetry on initiation of facial expressions among patients with PD. The findings are more in line with views that emphasize the role of the right hemisphere on attentional and intentional behavior, rather than "emotion," per se. In other words, slower initiation times for posed facial expressions among PD patients with greater right cortical-subcortical dysfunction may reflect reduced ability to initiate and respond rather than defective emotional processing as initially proposed. Overall, these findings highlight the potential importance of symptom laterality in non-motor aspects of Parkinson's disease.

CHAPTER 1
INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative movement disorder that arises from dopamine loss in deep brain structures and leads to widespread functional impairment. Prevalence reports estimate approximately one million people in the United States with the disease, with incidence reports of up to 60,000 new cases diagnosed each year (McDonald, Richard, and Delong, 2003). Idiopathic PD is commonly diagnosed after the age of 60, and has a gradual, insidious, and often lateralized onset of motor symptoms which worsen with disease progression. While pharmacological and surgical interventions are available to alleviate symptoms temporarily, there is no known cure to reverse or prevent further degeneration.

An often overlooked yet important symptom of Parkinson's disease is a "masked face." This term refers to the mannequin-like expressionless face that is characteristic of most individuals with PD. Due to their reduced propensity to facially convey either positive or negative emotions, PD patients are often misdiagnosed as being depressed or apathetic. While both these mood states commonly occur in PD, their rates may be inflated due to misperception by healthcare providers. As such, it is important to parcel out the effects of diminished facial expressivity from that of true mood disturbance.

Relative to other neurodegenerative disorders, asymmetric symptom onset is a notably unique feature of PD and reflects greater pathology in contralateral subcortical regions. Hemispheric laterality is also well-documented in emotional research, and different theories speculate on how the right and left cortical hemispheres process a wide array of emotionally-charged information. These views on hemispheric differences in emotional behavior are relevant to Parkinson's disease because subcortical regions affected in the disorder directly project to cortical regions on the same side of the brain. Thus, laterality of motor symptom onset may

potentially play an important role in the occurrence of the masked face and emotional symptoms in Parkinson's disease.

The primary goal of the current study was to compare emotional facial expressivity in right-sided onset and left-sided onset (indicating greater left or right neuropathology, respectively) PD patients. To do so, we used novel computer imaging techniques for calculating dynamic movement changes over the face (i.e., entropy) as opposed to the more traditional subjective judgments used in previous research. Additionally, the effects of mood and PD motor symptoms on facial expressivity were examined. Before discussing the specific hypotheses, a brief review of literature will now be presented pertaining to: 1) Parkinson's disease symptomatology and its neuropathological correlates, 2) theories of hemispheric dominance in emotional behavior, 3) emotion and facial expressivity in PD.

Parkinson's Disease: Symptomatology and Neuropathology

Parkinson's disease is diagnosed based upon the presence of four cardinal motor symptoms: bradykinesia, rigidity, tremor, and postural instability. *Bradykinesia* refers to an overall slowing of movement, and can be witnessed by asking patients to rapidly tap their fingers at a given amplitude. Bradykinesia is a distinctive feature of PD and must be observable for affirmative diagnosis. *Rigidity* refers to muscle stiffness and is characterized by resistance to passive movement of a limb. *Tremor* in PD involves involuntary shaking of the limb and typically occurs as a "resting tremor," which subsides when the person engages in a purposeful movement. Other features of Parkinson's disease include *postural instability*, or poor balance, and gait disturbances, in which patients walk with a stooped posture and take small, quickened steps. Patients may be classified as tremor predominant or rigid/akinetic type depending on which symptoms are most evident during a motor examination. Additional hallmark features of PD are slurred speech, small cramped writing, and diminished facial expressivity.

In terms of pathophysiology, Parkinson's disease essentially originates from the disrupted functioning of the basal ganglia, a midbrain structure composed of the striatum, globus pallidus (GP), subthalamic nucleus (STN), and the substantia nigra. These nuclei operate together to modulate functioning of higher cortical areas via the thalamus. In Parkinson's disease, neurons in the substantia nigra pars compacta (SNc) stop producing dopamine, thereby disrupting connectivity in various parallel closed-loop basal ganglia-thalamo-cortical circuits that are topographically organized and functionally specialized. Alexander, DeLong, & Strick (1986) identified 5 such circuits, each influencing motor, cognitive, or emotional functioning (see Figure 1-1 for motor and limbic circuitry). By the time initial motor symptoms are experienced in PD, the SNc is approximately 70% inactive (Obeso et al., 2002).

In early stages of Parkinson disease, behavioral symptoms are most often lateralized to one side of the body. With further progression, however, these symptoms appear bilaterally, but usually remain worse on the presenting side (Lee et al., 1995). Imaging studies and post-mortem cell counts suggest greater neuronal loss in the substantia nigra contralateral, or opposite, the initially more affected body side (Kempster et al., 1989). It is currently unknown whether asymmetrical neurodegeneration is due to inborn variations in dopaminergic neurons, differential vulnerability to the disease, or by random occurrence (Djaldetti, Ziv, & Melamed, 2006).

The neuropathology associated with specific motor symptoms in PD has been elucidated through neuroimaging studies. Positron emission tomography (PET) studies show that bradykinesia and rigidity both arise from excessive inhibition of the thalamus and subsequent motor cortices due to excitatory glutaminergic projections on the internal globus pallidus (Lozza et al., 2002). The disease mechanism of tremor is not as clear, though some researchers postulate

that it involves hypoactivation of the basal ganglia along with hyperactivation of brain structures outside the basal ganglia-thalamo-cortical loops, specifically in the cerebellum (Antonini et al., 1998; Yu et al., 2007). Thus, loss of nigral dopaminergic cells leads to a gross imbalance of chemical signals which results in motor impairment and, ultimately, cognitive and emotional deficits. Medications (levodopa and dopamine agonists) and surgical interventions, including deep brain stimulation (DBS) and damaging hyperactive areas of the basal ganglia or thalamus, have been successfully employed to quell motor symptoms by temporarily reestablishing neurochemical balance. However, neither medication nor surgical approaches are able to stop or reverse neurodegeneration associated with Parkinson's disease.

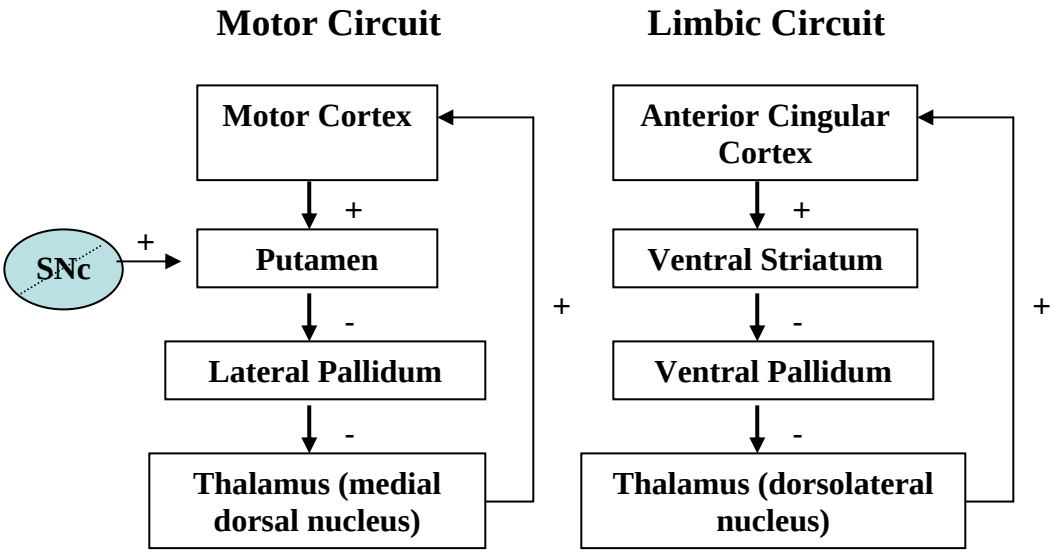

Figure 1-1: Simplified pathophysiological model of motor and emotional dysfunction in Parkinson's disease. Dopaminergic cells in the substantia nigra pars compacta die, leading to an imbalance of excitatory and inhibitory signals passed from higher cortical structures to the striatum via the thalamus. There are 5 segregated parallel basal ganglia loops, each of which involve different cortical and subcortical structures and modulate different areas of functioning. Illustrated here are the motor and limbic circuits, influencing physical and emotional functioning, respectively.

Lateralization of Emotional Processing

The limbic system has long been viewed as the primary neuroanatomic substrate for emotion (Papez, 1995). It includes several key structures (amygdala, hypothalamus, septum, cingulate, nucleus accumbens) that have been linked to appetitive/reward and avoidance/attack behaviors. Basal ganglia systems that overlap with limbic circuitry (i.e., nucleus accumbens, amygdale, cingulate) have also been implicated in emotion. Specifically, neuroimaging studies have revealed activation in the medial prefrontal cortex and anterior cingulate during general emotional processing, regardless of emotion elicited or induction method (Phan et al., 2002). These particular regions are part of a basal ganglia circuit known as the "limbic loop," and are impacted by the subcortical dysfunction as seen in PD.

While involvement of the limbic system and basal ganglia modulation is apparent in emotional behavior, the role of the cortical hemispheres has long been debated. One overarching view is that cortical regions serve to provide higher order modulation of underlying limbic regions. What is less clear is how the two hemispheres play differential roles in this cortical modulation. There are two competing theories as to how emotion is processed in higher cortical areas— the right hemisphere model and the bivalent model. According to the right hemisphere model, the right cortical hemisphere is dominant for mediating all emotional behavior, regardless of affect. This view is supported by lesion studies that demonstrate damage to the right versus left hemisphere leads to significant deficits in the perception and expression of emotional stimuli including facial expressions, emotional prosody, and lexical affective expression and experience (Borod, 1992; Borod et al., 1998; Bowers, Bauer, & Heilman, 1993; Heilman & Bowers, 1990; Liotti and Tucker, 1995). Similarly, patients with right hemisphere lesions show greater impairment in recognizing facial expressions of emotion or emotional prosody (Bowers et al., 1985; Bowers et al., 1987). Regarding emotional experience, a neuroimaging study of apathetic

stroke patients revealed greater hyperintensities in the right fronto-subcortical pathway than in the left, despite stroke severity (Brodaty et al., 2005). Furthermore, studies conducted on facial expressivity have shown that normal adults express their emotions more intensely on the left side of the face, which is contralaterally controlled by the right hemisphere, and that patients with right hemisphere damage are less facially expressive in general (Borod and Caron, 1980; Borod, 1992).

In terms of potential mechanisms underlying the right hemisphere hypothesis of emotion, some have speculated that the functional organization of the right hemisphere has made it more suitable for emotional processing. The right hemisphere has been shown to be specialized in integration and representation of information, which is necessary in nonverbal emotional communication. This explanation of right hemisphere dominance in emotion stems from findings that focal left hemisphere lesions result in discrete cognitive deficits whereas focal damage in the right hemisphere produce diffuse deficits in several domains (Semmes, 1968). Thus, the right hemisphere may be crucial in the cognitive mediation of emotional experience (Liotti & Tucker, 1995). Another line of evidence suggests greater connection density between regions in the right hemisphere, which may result in more varied communication pathways with the limbic system (Tucker, 1991). Moreover, a recent study featuring diffusion tensor tractography confirmed asymmetrical white matter organization in the brain (Barrick et al., 2006).

Another view as to hemispheric laterality of emotional processing is the bivalent hypothesis. According to this hypothesis, the right hemisphere is more specialized in processing negatively-valenced emotions while the left hemisphere is more active in positive emotions. Historically, this view derived from observations of differing emotional changes experienced by

patients who suffered strokes of the left or right hemisphere. Goldstein (1939) noted that individuals with left hemisphere strokes had "catastrophic" reactions, whereas those with right hemisphere strokes were emotionally flattened and apathetic. Furthermore, post-stroke depression following left hemisphere strokes has been shown to be particularly severe when subcortical regions were involved (Starkstein, Robinson, & Price, 1987). These clinical findings, in conjunction with subsequent research on mood-related EEG asymmetries in normals (Davidson, 1995) led to the hypothesis that both hemispheres were involved in emotional processing, though each differed in the specific type of emotions, i.e., positive versus negative. Although intriguing, the bivalent model has not been consistently supported in empirical studies of emotional perception or production (Borod, 2000; Heilman et al., 2003). Moreover, there has been minimal support for the view that the left hemisphere mediates positive emotions (see Harciarek et al., 2006).

In summary, two major models have been proposed regarding the role of the two hemispheres in mediating emotional behavior. In one model, the right hemisphere takes on primary responsibility for mediating all aspects of emotional behavior including perception, expression, and experience. In the second (bivalent) model, the left hemisphere mediates pleasant/approach related emotions whereas the right hemisphere is more involved in negative/avoidance related emotions.

Emotion in Parkinson's Disease

Emotional behavior is often researched in Parkinson's disease as mood disorders are highly comorbid with the disease. Depression is commonly observed with prevalence rates ranging from 4% to 70% among patients (Cubo et al., 2002). The basis for depression in Parkinson's disease is unknown, although it involves both biological and psychological factors. Psychological factors include reactions to receiving a diagnosis of a neurodegenerative illness,

difficulties in adjusting to lifestyle changes, and alterations in family dynamics and spousal roles. Biologically, dopamine loss in the limbic circuit of the basal ganglia as well as disruption of serotonin and other neurotransmitter systems are considered key components in PD-related depression (Lieberman, 2006). While antidepressants such as SSRI's are often prescribed in this population to treat depression, there is a lack of evidence for antidepressant efficacy among PD patients (Weintraub et al., 2003).

Another common mood disorder in Parkinson disease is apathy, which is a relatively new area of research in this population. Apathy refers to a loss of motivation in affective, cognitive, and behavioral domains (Marin, 1991). Symptoms of apathy have traditionally been misdiagnosed as being symptoms of depression, thereby possibly inflating its rates. The depressive symptom of anhedonia, or loss of interest, is especially similar to the characteristic features of apathy. However, the two are dissociable in PD patients according to the Kirsch-Darrow et al. (2006) finding that apathy can occur in the absence of depression and vice versa. The neurobiological substrates of apathy are unknown , although apathy has been associated with dysfunction in mesial frontal and anterior cingulate regions (for review, see Levy & Dubois, 2006).

Facial Expressivity and Parkinson's Disease

Emotional facial expressivity is a fundamental form of communication, and, when impaired as it often is in Parkinson's disease, can have far-reaching consequences in the patient's quality of life and interpersonal relationships. For example, the seemingly ubiquitous symptom of depression among PD patients may be overdiagnosed due to misattribution of negative emotional states by healthcare workers (Pentland et al., 1988). Additionally, diminished facial expressivity can impair communication between patients and loved ones, leading to confusion

and frustration on both ends. Paying greater attention to this debilitating yet underrepresented symptom of PD may ultimately open the doors for more comprehensive treatment options. Thus, it is important to understand the mechanical aspects of facial expressivity and how it is disrupted in Parkinson's disease. Greater elucidation of the process of diminished facial expressivity may lead to better research techniques, and, ultimately, more comprehensive treatment options.

Facial expressions are created through projections from the motor cortex to the brain stem via the corticobulbar system, a white matter pathway which controls the muscles of the face, head, and neck. Corticobulbar projections to cell body groups controlling movements in the lower face come exclusively from the contralateral hemisphere while bilateral projections stimulate the upper face (Rinn, 1984). This system describes production of posed or voluntary expressions that do not involve emotionality. Spontaneous emotional expressivity is more subcortically modulated and was originally thought to involve only an extrapyramidal motor system separate from the corticobulbar pathway. The extrapyramidal system, which includes the basal ganglia and the nigrostriatal pathway, modulates motor activity without directly innervating motor neurons (Rinn, 1984). More recent research states that both the corticobulbar and extrapyramidal systems are implemented to create fluid, effective posed and spontaneous facial expressions (Simons et al., 2004).

The mechanism underlying diminished facial expressivity in Parkinson's disease is not fully understood. One view indicates that dopamine depletion in the basal ganglia disrupts healthy functioning of the extrapyramidal pathway, thereby greatly affecting spontaneous expressivity (Turner et al., 2003; Rinn, 1984). However, Bowers et al. (2006) demonstrated that voluntary expressions are also diminished in PD patients, as impairment in frontostriatal circuitry may have a dampening effect on expression intensity, regardless of intention. Another view

speculates that depressive symptoms may lead to reduced emotional expressivity, although non-depressed patients also present with masked faces. Thus, diminished facial expressivity is not simply a result of affective dysfunction (McDonald et al., 2003; Bowers et al., 2006). Furthermore, Bowers et al. (2006) found that PD patients were less expressive than healthy controls regardless of emotional valence (i.e., happy vs. sad). The loss of muscle tone in the face resulting from overall motoric disability in PD may also cause problems in facial expressivity (De Letter et al., 2003). In sum, speculations as to the physical and emotional substrates of the masked face in PD have been inconclusive, reflecting the elusive nature of this symptom and the relative dearth of research conducted in this area.

CHAPTER 2
STATEMENT OF THE PROBLEM

Although Parkinson's disease (PD) is classically considered a "motor" disorder, it is now viewed as a multi-modal disorder affecting motor, cognitive, and emotional processing. However, there are still many unanswered questions regarding patients' behavioral functioning. One such question relates to the importance or relevance of motor symptom onset asymmetry. While motor asymmetry clearly reflects disruption of subcortical-frontal dopaminergic systems on one side of the brain, the issue becomes whether this neuropathological asymmetry has any consequences for non-motor behaviors (i.e., cognitive or emotional).

Neuropsychological research of motor symptom onset asymmetry in Parkinson's disease has primarily focused on the impact of laterality on cognitive impairment. This comes as no surprise given that lateralized brain damage is often associated with material specific deficits, depending on whether the left (verbal) or right (visuospatial) hemisphere is affected. Historically, inferences about laterality of function were based on studies of patients with focal "cortical" lesions (Geschwind, 1979). Over time, observations of material-specific cognitive deficits were also described in patients with lateralized subcortical damage (i.e., thalamus) (Stuss et al., 1988). The basis for these subcortical laterality effects was unclear, as they could reflect intrinsic right-left processing differences by subcortical regions and/or disrupted projections to cortical regions via dysfunctional subcortical pathways. Regardless of the underlying mechanism, several studies with Parkinson's disease patients have shown that right sided symptoms (indicating greater left hemisphere dysfunction) were associated with verbal deficits whereas left sided symptoms were associated with spatial deficits. Such findings indicate a clear double dissociation of impairment based on lateralized cognitive abilities (Amick et al., 2006; Blonder et al., 1989a). Double dissociation is the strongest level of inference in

neuropsychology and behavioral neurology (Teuber, 1955), thus providing substantial weight to these findings. However, it should be noted that not all studies have found a significant association between laterality and various cognitive deficits in patients with PD, and, thereby, continues to call into question the importance of laterality (Cubo et al, 2000; St. Clair et al., 1998).

In contrast to cognitive studies, the relationship between motor asymmetry and emotional symptoms in PD has largely gone untouched. This hole in the literature is quite remarkable given that there are dozens of replicated studies showing hemispheric specialization in processing emotion as well as separate studies conducted on emotional behavior in PD. Although several studies have focused on the effect of asymmetrical symptomatology on depression in PD and yielded inconclusive and conflicting results (Fleminger, 1991; Spicer et al., 1988; Starkstein et al., 1992), minimal attention has been paid to facial expressivity in relation to laterality of symptom onset.

Thus, the **overall goal of the present study** was to examine the influence of motor symptom laterality in Parkinson's disease on different aspects of emotional behavior, particularly facial expressivity and mood. The underlying basis for such an endeavor derives from two lines of evidence: a) the tightly coupled functional relationship between subcortical regions within each hemisphere, namely the basal ganglia and thalamus, and the cortical regions to which they project and influence (Alexander et al., 1986), and b) hemispheric lateralization and specialization of function for emotional behavior (Liotti and Tucker, 1995).

The current study addressed several issues pertinent to behavioral sequelae of Parkinson's disease. First, this study examined lateralized subcortical contributions to expressivity. As subcortical structures have been shown to be influential in cognitive processing in asymmetrical

PD presentation, it may affect emotional processing as well. Thus, we investigated whether the right cerebral hemisphere hypothesis of emotional behavior is still supported when examining facial expressivity in PD. Second, the current study examined mood symptomatology via self-report measures of depression and apathy in PD patients as a separate additional measure of emotional processing, which presents a more global perspective of patients' emotional profile and may help discriminate emotional experience from expressivity. Finally, one of the unique aspects of the current study was the manner in which facial expressivity was measured and quantified. In contrast to most studies which involve subjective ratings of facial emotion by blinded judges (St. Clair et al., 1998; Blonder et al., 1989b), the present study used a computer-based imaging approach for quantifying facial expressions. This approach involved videotaping participants while they posed different facial expressions in response to tone cues. Semi-automated computer software developed in Dr. Bowers' laboratory was then used to digitize each video frame of the dynamic expression. This method allowed us to capture both total movement of the face as well as the time it took to initiate the expression and the temporal trajectory of the entire expression. The time variables in this experiment were thought to be particularly important since "slowness" or bradykinesia is one of the prominent features of Parkinson's disease.

The current study had two specific aims. The **primary aim** was to learn whether onset side of Parkinson's disease motor symptoms was related to changes in posed facial expressivity. To address this aim, PD patients with lateralized symptom onset were evaluated in terms of quantitative aspects of their facial expressions. Based on the right hemisphere model of emotional behavior, it was hypothesized that PD patients with left-sided motor symptom onset, indicating greater right hemisphere neuropathology, would display greater facial expressivity

impairment than patients with right-sided motor symptom onset. Therefore, it was predicted that facial expressions posed by left-onset PD patients would entail overall less movement and would be slower to form than those posed by right-onset PD patients, regardless of the particular emotion posed.

The **secondary aim** of the present study was to examine the relationship between mood and disease-specific motor variables and PD patients' facial expressivity. Given previous research indicating the effect of nigrostriatal dopamine loss on emotional and motor functioning, it was hypothesized that depression and apathy as well as greater motor disturbance would be associated with greater impairment in facial expressivity. Thus, it was predicted that higher scores on the self-report mood measures such as the Beck Depression Inventory (BDI) and the Apathy Evaluation Scale (AES) would correspond to slower and slighter facial movement. Similarly, it was predicted that increased severity of motor symptoms, particularly bradykinesia and rigidity, on the standard Unified Parkinson Disease Rating Scale (UPDRS) would also be associated with reduced facial expressivity.

CHAPTER 3
METHODS

Participants

Participants included 26 patients with idiopathic Parkinson's disease and a healthy control group of 13 participants. Parkinson's disease patients were assigned to right or left symptom onset groups based on their self-report. Patients who described bilateral onset of motor symptoms or could not recall their initial side of onset were not included. Patients were divided into groups based on onset side rather than current motor symptom presentation because studies indicate that the classification of current side predominance according to the UPDRS score oversimplifies the clinical picture and may be subjectively evaluated (Katzen et al., 2006; Tomer et al., 1993). The final PD sample included 13 patients with right-sided motor symptom onset (RSO-PD) and 13 patients with left-sided motor symptom onset (LSO-PD). Both PD patients and healthy control participants were recruited through a larger NINDS-funded study entitled Masked Faces in Parkinson's Disease: Mechanisms and Treatment being conducted in the Cognitive Neuroscience Laboratory at the University of Florida (Director: Dr. Dawn Bowers), and participated in the complete or partial protocol designed for the parent study. Additionally, several patients were recruited from the University of Florida Movement Disorders Center, which maintains an extensive IRB and HIPAA-compliant database of current PD patients (Directors: Dr. Michael Okun, Dr. Hubert Fernandez, Dr. Kelley Foote).

Patients included in the present study had to be between 45 and 80 years old and, according to the UK Brain Bank criteria for diagnosis of idiopathic Parkinson's disease, had to display the presence of bradykinesia and at least one other motor sign (rigidity, resting tremor, or gait disturbance) during their UPDRS Motor Examination (Hughes et al., 1992). Additionally, a positive response to dopaminergic therapy was required to affirmatively diagnose idiopathic PD.

Diagnosis of idiopathic PD was ruled out if patients had a history of traumatic brain injury, definite encephalitis, supranuclear gaze palsy, cerebellar signs, or displayed signs of Parkinson's plus syndromes, such as Lewy body disease.

Exclusion criteria for PD patients were as follows: (1) bilateral *onset* of Parkinson's disease (motor symptoms may be present on both sides of the body after initial unilateral onset); (2) evidence of dementia or significant cognitive impairment; (3) evidence of a current or chronic major psychiatric or psychological disturbance; (4) excessive oro-facial dyskinesias that interfere with their facial expressivity; (5) unwillingness to shave facial hair or remove facial jewelry that would compromise the quality of the image capture, (6) history of deep brain stimulation or other surgical procedures designed to treat PD motor symptoms; (7) evidence of Parkinson's plus syndromes (i.e., Lewy body disease, corticobasal degeneration, multiple systems atrophy). Exclusionary criteria for healthy control participants were the same as those for PD patients with the additional exclusion criterion of diagnosed unilateral or bilateral Parkinson's disease or parkinsonian symptoms. Healthy control participants were between the ages of 45-80 years old.

As shown in Table 3-1, the two PD patient groups (RSO-PD and LSO-PD) and healthy controls were carefully selected from the parent study to be very well matched on demographic variables such as age, education, sex, and handedness. Additionally, a review of patients' medical records was performed in order to confirm unilateral onset side. A one-way ANOVA was conducted to ensure well-matched groups. Results of this ANOVA did not reveal statistical difference between the groups in age [$F(2,38)= 0.41$, $p= 0.70$] or education [$F(2,38)= 0.52$, $p= 0.60$]. The age range of the right-sided onset PD group (RSO-PD) was 52-76 years old ($M= 67.69$, $SD= 7.10$) and the age of left-sided onset PD patients (LSO-PD) ranged from 56-80 years

old (M= 70.08 , SD= 7.84). The age of healthy control participants ranged from 53-80 years old (M= 67.60, SD= 8.74). Each group had 8 males and 5 females, reflecting established sex-based differences in incidence of PD (Wooten et al., 2004). The RSO-PD group and healthy controls each had 11 right-handed and 2 left-handed individuals while the LSO-PD had 10 right-handed and 3 left-handed participants. The groups, on average, were highly educated and did not present evidence of dementia as assessed by the Mattis Dementia Rating Scale-II.

The PD groups were also selected to be comparable on duration of symptoms and total UPDRS motor score, as evidenced by insignificant differences in two-tailed independent samples t-tests conducted on these disease-specific variables [duration of PD symptoms, $t(24)= 0.66$, $p= 0.52$; total UPDRS score, $t(24)= -0.52$, $p= 0.48$]. The average duration of symptoms in the RSO-PD group was 8.23 years (SD= 4.88 years) and the group's average UPDRS Motor score was 21.08 (SD= 8.25); the average duration of symptoms in the LSO-PD group was 7.08 years (SD= 4.01) with an average UPDRS Motor score of 24.15 (SD=10.00).

Table 3-1. Participant Demographics

	RSO-PD	**LSO-PD**	**Controls**	**Significance**
Demographic	**N=13**	**N=13**	**N=13**	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	
Age	67.69 (7.10)	70.08 (7.84)	67.62 (8.74)	NS
Education	16.46 (2.82)	16.23 (2.31)	15.46 (2.67)	NS
Sex Ratio (Male: Female)	8:5	8:5	8:5	NS
Handedness (Right: Left)	11:2	10:3	11:2	NS
DRS Score	140.77 (2.95)	137.62 (5.64)	139.85 (4.58)	NS
Duration of Symptoms (in years)	8.23 (4.88)	7.08 (4.01)	*	NS
UPDRS Total	21.08 (8.25)	24.15 (10.00)	*	NS

Measures

Prior to enrollment, all PD patients underwent a thorough neurological examination to verify their diagnosis and rate the severity of their motor symptoms. All participants were also administered neurocognitive and psychiatric measures by a trained doctoral student to screen for dementia, cognitive impairment, significant psychopathology or other factors that would exclude them from the study. These measures are listed below.

Unified Parkinson's Disease Rating Scale-III Motor Examination (UPDRS-III) (Lang & Fahn, 1987): The UPDRS-III is a tool used by neurologists to assess the severity of various motor symptoms and impairment of daily living activities in PD patients. Symptoms on the right and left side of the body are rated separately in areas of resting and acting tremor, bradykinesia, and rigidity on a 0-4 scale with higher values indicating greater motor impairment. The range of possible scores on the UPDRS-III Motor Examination is 0 to 56.

Mattis Dementia Rating Scale-II (DRS-II) (Mattis, 2001): The DRS-II is a screening measure for dementia in older adults with well-established psychometric properties that covers the domains of memory, attention, initiation, language, and visuoconstruction. There are 144 possible points; a score of 125 or below suggests significant evidence for dementia.

Mental Health Screening Form-III (MHSF-III) (Carroll & McGinley, 2001): The MHSF-III is a brief structured psychiatric interview measure used to screen for mental health problems and refer identified cases for further diagnosis.

Beck Depression Inventory-II (BDI) (Beck et al., 1996): The BDI-II is a self-report measure in which individuals are asked to rate the severity of symptoms associated with depression, such as sleep, appetite, worthlessness, and anhedonia on a 0-3 Likert scale. There are 21 items on the BDI-II, yielding scores that range from 0-63 with higher scores indicating greater

depressive symptoms and a score ≥ 14 suggesting mild to moderate depression. Levin et al. (1988) demonstrated that the BDI-II is a highly reliable and valid measure to assess depression, particularly in PD patients.

Apathy Evaluation Scale-modified (AES) (Starkstein et al., 1992): Modified from the original 18-item AES created by Marin (1991), the modified AES is a 14-item scale assessing cognitive, emotional, and behavioral aspects of apathy on a 0-3 Likert scale. Scores range from 0-42 with higher scores indicating higher apathy and a score ≥ 14 suggesting significant signs of apathy. The modified AES is shown to have excellent psychometric properties in Parkinson's disease (Kirsch-Darrow et al., 2006).

Procedures

All participants were asked to read and sign an informed consent agreement consistent with the University of Florida Institutional Review Board and Federal HIPAA regulations at the commencement of the study. Following informed consent, all participants underwent the cognitive and psychiatric screening procedures and UPDRS-III motor scores were obtained for the PD patients. All PD patients were "on medication" during testing, meaning they were instructed to take their anti-parkinsonian medication (i.e., Levodopa, dopamine agonists) according to their normal regimen on the day of testing.

Videotaping of facial expressions. Subjects were videotaped with a black and white Pulnix camera (TM-TCN) and a Sony video recorder (SLV R 1000). The camera was positioned approximately five feet in front of the patient. Indirect lighting was produced by reflecting two 150-watt tungsten light bulbs onto white photography umbrellas positioned approximately 3 ½ feet from the face. Lighting on each side of the face was balanced within one lux of brightness using a Polaris light meter. To reduce extraneous facial movement, subjects were reminded to

not blink during the expression. To minimize head movement, an adjustable head restraining device, the Vac-Loc Head Stabilization system, was employed. The Vac-Loc system consists of a pliable plastic pillow filled with polystyrene beads. The pillow was molded around the subject's head, and then air was vacuumed from the bag to form a rigid mold to the individual's head, thereby effectively minimizing the impact of tremor or shifting.

During testing, participants were asked to pose three emotional expressions, "angry," "fearful, and "happy" at the onset of a tonal cue. These three particular facial expressions were chosen for two reasons: a) they all have a strong, distinguishable affective quality, and b) they incorporate both positively and negatively-valenced emotions. Each expression trial consisted of the experimenter informing the participant of the target facial emotion. Participants were told to make the target emotion as soon as the tone cue was presented, and to make the expressions as distinctly and clearly as possible so that others would recognize the emotions they were trying to convey. Tone onset was controlled by the experimenter and was created by a hand-held buzzer synchronized to a light emitting diode (LED) placed within the video frame. The LED was subsequently used during the face digitizing process to precisely measure the initiation of the expression from the onset of the tonal cue. Participants were asked to produce each expression twice to increase the chances of obtaining a trial free of extraneous motion or artifact.

Data processing of videotaped facial expressions. First, videotaped facial expressions were viewed by two trained raters who independently viewed each expression and selected those with the least motion artifact. Next, individual expressions were digitized using a Sony video player, personal computer with Iscan-PCI video card, and EYEVIEW software (Imaging Technology). Beginning with the onset of the trial (e.g., after the tone cue sounds), 90 video frames (3 seconds or 30 frames/second) were captured for each expression and saved on the

computer to be analyzed. Finally, the digitized video facial expression images were quantified in terms of movement changes using custom computer software, previously developed by Didem Gokcay in the Cognitive Neuroscience Laboratory at the University of Florida. This software, known as Computer Human Expression Evaluation System (CHEES), enables semi-automatic processing and quantification of facial expression data (Bowers et al., 2006). In order to process the expression, sixteen anatomic landmarks were first identified on the target face and denoted on the first frame of an expression sequence. CHEES then uses these landmarks to automatically compute nine geographic boundaries or regions of interest (ROIs) that are applied to all subsequent frames of a particular expression (See Figure 3-1). These ROIs are compared over consecutive frames to establish movement changes via an entropy calculation. Entropy is defined as a measure of pixel intensity changes that occur during a dynamic expression. It is calculated by subtracting the values of corresponding pixel intensities between adjacent frames, summing their differences, and dividing that amount by the number of pixels used. This computation is repeated over each pair of successive frames, yielding 89 difference images over 90 frames. Entropy is a valid and reliable facial expression qualifier that indicates a normalized value with respect to individual differences in faces (Bowers et al., 2006).

In the present study, only the lower 2/3 of the face (from beneath the eye to the bottom of the chin) was analyzed. The decision to restrict analyses to the lower 2/3 of the face was based on theoretical reasons and practical concerns. Theoretically, movement in the lower 2/3 of the face is controlled primarily by contralateral hemispheric projections while the upper face is controlled bilaterally. Thus, expressivity in the lower 2/3 of the face is more influenced by asymmetrical neuropathophysiology, which is of primary interest in the current study.

Practically speaking, focusing on the lower 2/3 of the face also eliminated extraneous movement caused by occasional eyeblinks in some participants.

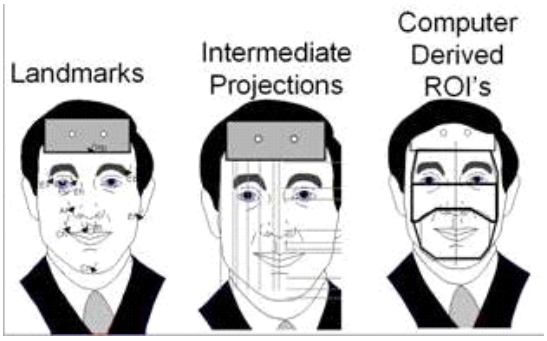

Figure 3-1. Digitizing the Moving Face. The face is first landmarked using 20 anatomical points. Then, these marks are used to partition the face into 9 regions of interest based on muscular boundaries, which will be used to derive entropy and temporal variables of dynamic movement.

Dependent variables. Five major outcome variables were derived from the CHEES process: 2 entropy variables and 3 temporal variables. The two entropy variables included total entropy (total amount of movement change during a dynamic expression), and peak entropy (the most rapid movement change that occurs when the expression can first be identified for its emotion). The three temporal variables, measured in seconds, included latency, or initiation time between the tonal cue and facial movement, rise time to peak entropy, and duration of movement. The entropy curve and temporal points along the curve are depicted in Figure 3-2.

Statistical Analyses

To evaluate the Aim 1 prediction that LSO-PD patients would display greater overall facial expressivity impairment than RSO-PD patients and controls, 5 separate Repeated Measures ANOVAs were conducted, one for each of the 5 dependent variables described previously. For each ANOVA, the within-subjects factor was Emotion expressed (angry, fearful, and happy) and the between-subjects factor was Group (RSO-PD, LSO-PD, and controls).

To test the Aim 2 prediction that greater mood and motor disturbance would be associated with decreased facial expressivity, a series of linear regression analyses were conducted on each of the 5 facial expression dependent variables. First, in order to evaluate the association between mood (i.e., depression and apathy) and expressivity, scores on the Beck Depression Inventory (BDI-II) and Apathy Evaluation Scale- modified (AES) were examined in relation to the facial expressivity variables. A second set of linear regressions looked at the relationship between motor disturbance in PD patients and facial expressivity. The motor disturbance variables included composite scores derived from the Unified Parkinson Disease Rating Scale (UPDRS), specifically the bradykinesia/rigidity score and a tremor score.

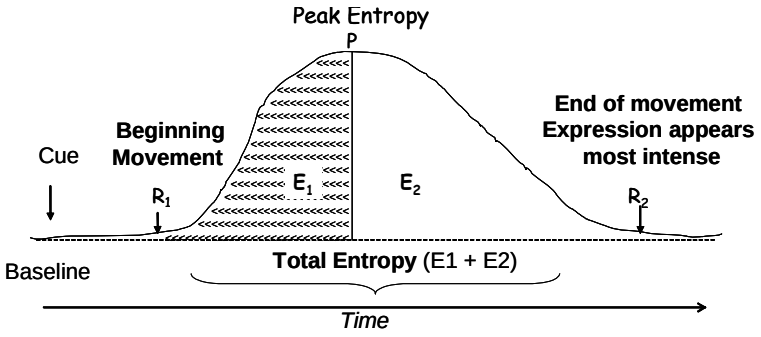

Figure 3-2. Entropy Curve. The outcome variables in the current study are as follows: (1) *Total Entropy* ($E_1 + E_2$) = total amount of movement change during a dynamic expression; (2) *Peak Entropy* (E_1) = most rapid movement change (corresponding to the point of initial emotion categorization by observers; (3) *Latency* (time between R_1 and cue) = initiation time to expression; (4) *Rise Time* ($P - R_1$) = time to peak movement change; (5) *Duration* (R_2-R_1) = total time of dynamic movement change.

CHAPTER 4
RESULTS

The Effect of Laterality on Facial Expressivity

The primary focus of this study was to examine differences in facial expressivity between Parkinson's disease patients with right-sided motor symptom onset (RSO-PD) and those with left-sided onset (LSO-PD) as well as healthy controls with the prediction that LSO-PD would be more impaired in performing facial expressions than the other groups. To accomplish this, the groups were compared on 5 aspects of facial expressivity: (1) total entropy, (2) peak entropy, (3) latency to expression, (4) rise time to peak entropy, and (5) duration of movement. Five independent Repeated Measures ANOVAs were conducted with Group (RSO-PD, LSO-PD, and controls) as the between-subjects variable and Expression (Happy, Angry, Fearful) as the within-subjects variable. SPSS computer software was used to complete all analyses. The assumption of sphericity was successfully met in all 5 analyses; therefore, no corrections were necessary in omnibus reports.

Regarding entropy variables, ANOVA results indicate no significant main effects of Group in either total entropy, $F(2,36)= 0.28$, $p= 0.75$, $\eta_p^2 = 0.02$, or peak entropy, $F(2,36)= 0.36$, $p= 0.70$, $\eta_p^2 = 0.02$. In other words, the three groups did not significantly differ in the total amount of dynamic movement during the facial expression or in the peak movement change. Entropy means and standard deviations for the three groups are shown in the Appendix, Table A-1. However, there was a significant main effect of Emotion for total entropy [$F(2,72)= 11.24$, $p< 0.05$, $\eta_p^2 = 0.24$]. Bonferroni-corrected post hoc comparisons indicated that posing Happy expressions ($M= 1.58$, $SD= 1.21$) involved significantly greater total entropy (i.e., movement) than posing Angry ($M= 0.82$, $SD= 0.83$) or Fearful expressions ($M= 0.85$, $SD= 0.92$) at alpha = 0.05. Similarly, there was also a main effect of Expression when examining peak entropy,

$F(2,72)= 7.38$, $p< 0.05$, $\eta_p^2 = 0.17$. Bonferroni-corrected post hoc comparisons revealed that, again, the Happy expression (M= 11.86, SD= 7.35) had a higher peak entropy, or rate of change, than the other two expressions at alpha = 0.05 (Angry: M= 6.42, SD= 6.93; Fearful: M= 7.99, SD= 8.63). The Group x Expression interaction was not significant for either total entropy or peak entropy; thus, the groups did not differ in total amount of movement [$F(4,72)= 1.13$, $p= 0.35$, $\eta_p^2 = 0.06$] or peak rate of change [$F(4,72)= 1.34$, $p= 0.26$, $\eta_p^2 = 0.07$], regardless of emotion posed. A summary of the results from these ANOVAs is shown in the Appendix, Table A-2.

In analyzing the three temporal variables, the only significant main effect of Group was latency to expression, $F(2,36)= 8.21$, $p= 0.001$, $\eta_p^2 = 0.31$. Bonferroni-corrected post hoc analyses revealed that the LSO-PD group (M= 3.62 s, SD= 2.86 s) was significantly slower in initiating movement following the tonal cue than the RSO-PD (M= 1.85 s, SD= 1.45 s) or Control groups (M= 1.59 s, SD= 1.63 s) at alpha = 0.05. Thus, the LSO-PD group initiated their expressions approximately 2 seconds later on average than the other two groups. There was also a significant main effect of Expression [$F(2,72)= 3.56$, $p= 0.03$, $\eta_p^2 = 0.09$]; post-hoc analyses (Bonferroni-corrected) revealed that the Angry expression (M= 3.04 s, SD= 2.72 s) was significantly slower to initiate than the Fearful expression (M= 2.04 s, SD= 2.26 s, $p< 0.05$) or the Happy expression (M= 1.98 s, SD= 1.79 s, $p< 0.05$). The Group x Expression interaction was nonsignificant [$F(4,72) = 0.82$, $p= 0.52$, $\eta_p^2 = 0.04$.] In examining the rise time to peak expression, none of the main effects nor the interaction reached significance [Group: $F(2,36)= 1.32$, $p= 0.28$, $\eta_p^2 = 0.07$; Expression: $F(2,72)= 0.18$, $p= 0.84$, $\eta_p^2 = 0.01$; Group x Expression: $F(4,72)= 0.61$, $p= 0.66$, $\eta_p^2 = 0.03$]. Similarly, an analysis of expression duration revealed no significant main effects or interactions [Group: $F(2,36)= 0.35$, $p= 0.71$, $\eta_p^2 = 0.02$; Expression:

$F(2,72)= 2.31$, $p= 0.11$, $\eta_p^2 = 0.06$; Group x Expression: $F(4,72)= 1.11$, $p= 0.36$, $\eta_p^2 = 0.06$]. In other words, the three groups were comparable in terms of rise time and duration of expression, regardless of affect posed. Descriptive statistics as well as ANOVA results for temporal variables measured are presented in the Appendix, Tables A-3 and A-4, respectively.

To sum the results from the primary aim, only one dependent variable, time to initiate a facial expression, proved to be a significant difference among the groups in the direction predicted. Namely, PD patients with left symptom onset were slower to initiate facial expressions than the other two groups (See Figure 4-1). The groups did not differ in entropy or other temporal variables. Family-wise, 1 of the 5 outcome variables, or 20% of the analyses conducted, reached significance, demonstrating a small to moderate effect as opposed to a chance finding. These results are somewhat surprising given past research showing a significant difference in total amount of facial entropy between PD patients and healthy controls (Bowers et al., 2006); possible reasons for this discrepancy will be discussed in the following section.

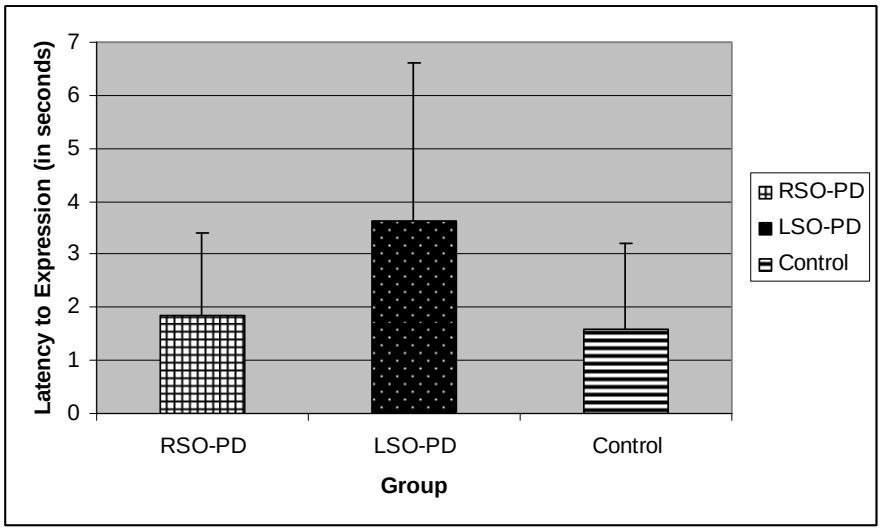

Figure 4-1. Latency to Initiate Facial Expression in right-sided motor symptom onset PD patients, left-sided motor symptom onset PD patients, and healthy controls. Latency refers to time, in seconds, between tone cue and expression onset.

Mood and Motor Correlates of Expressivity

A secondary aim of this study was to examine the relationship among mood variables (depression, apathy), PD-specific disease variables (motor symptoms) and facial expressivity. Initial one-way ANOVAs and independent samples t-tests were conducted to learn whether the participant groups differed in terms of depression (BDI), apathy (AES), or severity of motor symptoms. Motor symptoms included composite scores for bradykinesia/rigidity and tremor from the Unified Parkinson Disease Rating Scale (UPDRS). Table 4-1 depicts the means and standard deviations of mood and motor symptom scores for the 3 subject groups. Results of the ANOVAs revealed no significant group differences for the BDI [$F(2,36)= 0.50$, $p= 0.61$] or the AES [$F(2,36)= 0.91$, $p= 0.41$]. Similarly, the t-tests indicated that there were no significant differences between the two PD groups in severity of bradykinesia/rigidity [$t(24)= -0.72$, $p= 0.48$] or tremor scores [$t(24) =0.91$, $p= 0.24$].

Table 4-1. Descriptive Statistics for Mood and Motor Variables

	RSO-PD	LSO-PD	Controls	Significance
Variable	N=13	N=13	N=13	
	Mean (SD)	Mean (SD)	Mean (SD)	
Mood				
BDI	5.46 (3.60)	4.85 (4.16)	3.85 (4.69)	NS
AES	9.00 (5.03)	10.54 (6.06)	7.92 (3.50)	NS
Motor				
Tremor	1.69 (1.49)	2.38 (1.45)	*	NS
Bradykinesia/ Rigidity	12.23 (5.00)	13.92 (6.85)	*	NS

Relationship between Mood and Facial Expressivity

Linear regression analyses were conducted to examine the effect of mood (BDI-II, AES) on the five facial expression variables (total entropy, peak entropy, latency, rise time, total duration). All participants were grouped together and the outcome variables were averaged across the expression type posed. It was predicted that higher scores on the Beck Depression

Inventory (BDI-II) and Apathy Evaluation Scale- modified (AES) would be associated with reduced facial movement (total entropy, peak entropy) and longer/slower movement times (i.e., initiation time, rise time, duration). The results of the linear regression analyses are depicted in Table 4-2. As shown, the mood variables of depression and apathy did not significantly explain variance in any of the 5 facial expressivity variables. There was a trend towards significance in the effect of the BDI-II on duration of expression [β= -0.59, t(2,38)= -1.92, p= 0.06]; however, the overall model did not reach significance, R^2 = 0.10, F(2,38)= 2.03, p= 0.15.

Because motor symptom onset side significantly affected the latency variable in facial expressivity, a hierarchical regression was conducted with onset side in Block 1 and the mood variables in Block 2 to see whether depression and apathy contributed to this facial expressivity variable. Results indicate that the overall model was significant [R^2 = 0.32, F(4,34)= 4.01, p= 0.01], but that only left-sided onset uniquely contributed to the relationship (β= 0.53, t(4,34)= 0.53, p< 0.01). Neither mood score effectively explained variance in the model [BDI-II: β= 0.09, t(4,34)= 0.61, p= 0.55; AES: β= -0.03, t(4,34)= -0.17, p= 0.86]. Thus, change statistics did not reveal an additional effect of mood on the relationship between onset side and latency as evidenced by the negligible change in R^2 from 0.31 to 0.32 in the hierarchical regression [F change test: R^2 = 0.01, F(2,34)= 0.18, p= 0.83]. However, this analysis confirmed the impact of left-sided motor symptom onset on latency, as this independent variable accounted for 31% of the variance. These results should be interpreted with caution, however, as the relatively low number of participants per regressor in this analysis may severely limit power.

Table 4-2: Linear Regression Analysis of Mood Variables on Facial Expressivity

	M (SD)	R^2	β	p-value
Total Entropy (N=39)	1.09 (0.75)	0.003		
BDI-II			-0.05	0.78
AES			0.05	0.79
Peak Entropy (N=39)	8.76 (5.57)	0.03		
BDI-II			-0.16	0.36
AES			0.16	0.37
Latency (N=39)	2.36 (1.63)	0.02		
BDI-II			0.07	0.70
AES			0.10	0.58
Rise Time (N=39)	2.43 (1.54)	0.02		
BDI-II			-0.02	0.91
AES			0.13	0.48
Duration (N=39)	2.54 (2.48)	0.10		
BDI-II			-0.59	0.06^T
AES			0.03	0.91

^{T}= Trend towards significance.

The Relationship between Motor Symptoms and Expressivity

To assess whether PD motor symptoms had an effect on facial expressivity, motor symptoms of bradykinesia/rigidity and tremor were regressed on the 5 facial expressivity variables. All PD patients were combined into a common group of 26 participants; healthy controls were not included in this analysis. Collinearity diagnostics did not reveal significant multicollinearity issues with these two regressors. The results of the linear regression analyses are depicted in Table 4-3. As shown, neither bradykinesia/rigidity nor tremor scores were positively associated with any of the facial expressivity variables at alpha = .05.

An additional hierarchical regression analysis was conducted specifically on the latency variable as it was significantly affected by left-onset group status in the primary aim. The PD patient groups (RSO-PD and LSO-PD) were included in Block 1 and UPDRS motor symptoms (bradykinesia/rigidity and tremor) were placed in Block 2 to see whether patients' motor symptomatology explained additional variance in facial expressivity. Results demonstrated that while the overall model was significant [$R^2 = 0.35$, $F(3,22)= 3.95$, $p= 0.02$], the motor symptoms

did not uniquely contribute to the relationship [bradykinesia/rigidity: $\beta = 0.08$, $t(3,22)= 0.42$, $p= 0.68$; tremor: $\beta= 0.19$, $t(3,22)= 0.97$, $p= 0.34$]. Left-sided onset remained the only significant regressor [$\beta= 0.49$, $t(3,22)= 2.77$, $p= 0.01$]. The F-change test confirmed the negligible contribution of motor symptomatology to the relationship between left-onset side and latency to expression, revealing an R^2 change from 0.30 to 0.35 with the added regressors in Block 2 [F-change test: $R^2 = 0.05$, $F(2,22) = 0.84$, $p= 0.44$]. As was the case with regressing both mood and onset side in the previously mentioned analysis, these results must be interpreted with caution, for the low number of subjects per regressor may affect power.

Table 4-3: Linear Regression Analysis of Motor Variables on Facial Expressivity

	M (SD)	R^2	β	p-value
Total Entropy (N=26)	1.04 (0.79)	0.002		
Bradykinesia & Rigidity			-0.03	0.91
Tremor			0.04	0.85
Peak Entropy (N=26)	9.06 (6.10)	0.01		
Bradykinesia & Rigidity			-0.09	0.70
Tremor			0.10	0.67
Latency (N=26)	2.74 (1.65)	0.12		
Bradykinesia & Rigidity			0.11	0.62
Tremor			0.29	0.19
Rise Time (N=26)	2.36 (2.20)	0.10		
Bradykinesia & Rigidity			-0.23	0.30
Tremor			0.13	0.55
Duration (N=26)	6.85 (4.37)	0.02		
Bradykinesia & Rigidity			0.12	0.61
Tremor			-0.13	0.56

CHAPTER 5
DISCUSSION

The primary aim of the present study was to investigate the effect of asymmetric motor symptom onset in Parkinson's disease (PD) on emotional behavior as defined by facial expressivity. The "masked face" of PD can sharply impact effective communication with family and caregivers, yet is relatively understudied among the cardinal motor symptoms in PD. Even more rarely examined is the effect of motor symptom onset laterality on emotional expression. Thus, this project was undertaken to examine the relationship between hemispheric laterality and different aspects of facial expressivity. It was predicted that PD patients with left-sided motor symptom onset would have reduced facial expressivity, both in degree and timing, than patients with right-sided motor symptom onset. This prediction was based upon the well-supported right hemisphere hypothesis of emotion, which states that the right cerebral hemisphere is dominant in the perception and expression of emotional behavior. Drawing from this model, it was posited that right subcortical dysfunction, as is seen in PD patients with left body side motor symptoms, would result in similar emotional deficits. A secondary aim was to discover the impact of mood and motor symptoms on facial expressivity with the prediction that worse symptoms would be positively correlated with expressivity impairment. This idea was based upon research suggesting that diminished facial expressivity in PD may be related to both emotional and motor disturbances (Simons et al., 2004). The overall purpose of this study was to examine the effect of asymmetric neuropathology upon the masked face in Parkinson's disease.

Summary and Interpretation of the Findings

The hypothesis that left-sided motor symptom onset PD patients (LSO-PD) would be less facially expressive than those with right-sided onset (RSO-PD) was not entirely supported. The groups differed only in latency to initiate target facial expressions. Namely, PD patients whose

motor symptoms initially presented on the left body side (i.e., right brain involvement) were significantly slower to initiate their expressions, regardless of valence, than PD patients with right body symptoms and healthy control participants. The other aspects of facial expressivity, including entropy, rise time to peak movement, and movement duration, were not influenced by laterality of symptom onset. Neither mood symptoms, such as depression and apathy, nor motor symptom variables of bradykinesia, rigidity, and tremor contributed to changes in facial movement.

These findings do not robustly support the right hemisphere hypothesis of emotion, upon which the predictions from this study were based. Only one measure, initiation time, was influenced by laterality of PD symptoms. Thus, greater damage to the basal ganglia-thalamo-cortical loops in the right hemisphere, as is the norm in PD patients who present with left-sided symptoms, did not negatively impact facial emotional behavior as defined by overall movement and duration during posed facial expressions. The data also do not support the bivalent hemisphere emotion mode (i.e., nonsignificant Group X Emotion interaction). According to this model, negative emotions such as fear and anger are mediated more so by the right hemisphere, and positive emotions, such as happiness, by the left hemisphere. Therefore, it seems that neither model of hemispheric lateralization of emotion appropriately accounted for the results of the present study.

There are several possible factors that may contribute to the failure to support either model. One possibility relates to the nature of the facial expressions that were posed by the participants. For instance, it may be argued that, because participants were asked to "look" happy, frightened, or angry, they were not expressing true emotion. Thus, the expressions occurred in response to a command rather than arising from particular affective states. Although a variety of studies have

found that posing an emotion on the face can actually induce psychophysiological changes associated with true emotions (Lee et al., 2006; Ekman, 1992; Adelmann & Zajonc, 1989), we have no independent verification that participants in the present study experienced emotions associated with the expressions they were asked to produce. Moreover, a large neuroanatomic literature has drawn a distinction between voluntary (posed) and spontaneous facial expressions, with each being mediated by somewhat distinct neural circuitries (Rinn, 1984). The former (posed) is primarily mediated by frontal pyramidal systems of the brain, whereas the latter (spontaneous) involves more limbic and extrapyramidal regions. Following from this argument, emotional processing centers in the brain may not have been involved in the present study. One way to better address this would be to examine whether side of PD symptom onset influences spontaneous facial expressivity.

Another possible reason why the results did not support either model of hemispheric lateralization of emotion is that motor symptom onset is not necessarily indicative of the current state of neurodegeneration. While motor symptoms usually remain worse on the body side of initial presentation, this is not always the case. In the current sample, motor scores from the Unified Parkinson Disease Rating Scale (UPDRS) recorded directly prior to study participation revealed a discrepancy between laterality of symptom onset and current symptom laterality in 6 of the 26 PD patients. Two PD patients had slightly higher values (e.g., greater pathology) on the body side opposite of their onset presentation, whereas 4 patients had equally bilateral motor symptoms at the time of testing. Although these scores do not indicate that those specific patients have "switched" motor symptom side as the difference between right and left motor symptoms in these cases were very slight, it does show that motor asymmetry in PD is not always a stable characteristic. Additionally, bilateral dysfunction may be present when motor

symptoms are first apparent despite unilateral presentation. Neurophysiological studies have confirmed that even in hemi-parkinsonism, there is almost always some degree of bilateral subcortical damage, which must be taken into account when assessing functional lateralization in PD (St. Clair et al., 1998). Thus, perhaps the current study could not accurately portray activation of parallel emotional pathways in the two hemispheres as the damage to the basal ganglia circuits may have already been bilateral. Despite this caveat, most studies suggest that even with bilateral dysfunction, there is some asymmetry, as evidenced by the plethora of studies examining structural and functional correlates of lateralized motor symptoms in PD.

Latency to Expression as an Action-Intentional Deficit

The primary finding of the present study was that the left-onset PD patients were slower in initiating facial expressions than the other two comparison groups. This slower response by the left-onset group was present across all expressions and appeared to represent a more global defect in rapidly initiating movement in the face. Bowers et al. (2006) also reported facial bradykinesia in a small group of more severely affected PD patients who posed facial expressions. However, these authors did not disentangle initiation time from overall movement time and were therefore unable to determine which of these two processes, initiation or execution, accounted for the slowing. The findings of the present study, however, seem to imply that it is the time to initiate facial movement that is slowed in left-onset PD patients, and that, once commenced, the expression occurs within a normal temporal window.

Turning to the literature, there are few studies that have associated slowed motor processing with laterality of symptom onset. Some investigators (Zetusken & Jankovic, 1985) have posited that PD patients with greater left-sided disease are more likely to exhibit overall slowness and rigidity than patients who initially present with right-sided symptoms. These observations have not been described in other reports, and currently there is very little

information as to whether greater left-sided symptoms are associated with a slowed response time to external stimuli.

One key question concerns the basis for the slowed initiation of facial movements by the left symptom onset PD patients in the present study. What might account for this laterality effect in initiation time? In reviewing the neuropsychology and behavioral neurology literature, a variety of studies over the past 30 years have reported that focal lesions of the right hemisphere induce slowed reaction times on various cognitive and motor tasks, whereas this effect is not seen in patients with left hemisphere lesions (Coslett and Heilman, 1989; De Renzi & Faglioni, 1965; Heilman and Boller, 1975). These findings, coupled with a vast literature on hemispatial neglect following right hemisphere lesions (Meador et al., 1989; Gainotti et al., 1972) and various attentional studies in those without brain damage (Petit et al., 2007; Stevens et al., 2005) have led some to posit that the right hemisphere plays a special role in mediating intention, or the physiological readiness to respond (Heilman, Watson, & Valenstein, 2003). This has been identified as the right hemisphere attention/intention hypothesis.

Extending this line of reasoning to the present study, perhaps the slowed facial expression initiation time by the left-symptom onset PD patients reflects a dominant role of the right hemisphere in mediating readiness to respond. In other words, the significant finding may actually stem from an action-intention deficit, associated with right hemisphere dysfunction, rather than defective emotional processing, as originally predicted. In order to fully test the hypothesis that left-sided onset PD patients are slower to initiate their expressions due to a greater deficit in intentional behavior, it would be necessary to more broadly examine the performance of PD patients across a series of timed tasks with signal/warning cues. Thus, more

studies must be conducted prior to further speculation on this post-hoc explanation of the finding in the present study.

The second aim of the present study examined mood and motor correlates of facial expressivity, with the prediction that greater severity of depression and apathy as well as more severe symptoms such as bradykinesia and rigidity would negatively impact facial movement during emotional expressions. However, regression analyses did not reveal a significant contribution of mood or specific motor symptoms to changes in facial expressivity; moreover, they did not affect the relationship between left-sided onset and latency to expression in additional analyses. Several factors could account for the insignificant findings. As mentioned earlier, the posed facial expressions may not have elicited the experience of emotion, and, therefore, emotional centers in the brain may not have been activated. If this is the case, the participants' mood would have very little to do with their ability to pose the particular facial expressions. Thus, an examination of the effect of mood on spontaneous facial expression derived through known emotional experience may be more revealing. Another factor is that the range of mood and motor symptom scores may not have been sufficiently large enough to allow for adequate correlation with facial expression variables. As a group, the participants were not depressed or apathetic and the severity of PD symptoms was moderate. Finally, the facial variables themselves represented quantitative indices of facial movement, rather than subjective ratings of emotion by independent judges. It is possible that subjective ratings, which involve more of a gestalt impression, might relate more so to mood and ratings of motor severity.

Limitation of the Present Study

The current study had several limitations. First, the number of participants in each group was less than originally desired, and may have considerably limited the power of the relationships tested, thereby potentially precluding significant findings in several analyses.

However, given the weak effects of group on facial expressivity observed in 4 out of the 5 outcome variables in the primary aim and the minimal unique contributions of mood and motor variables reported in the secondary aim, it is doubtful that a true relationship exists in these analyses using the current sample. Additionally, the lack of ethnic and racial diversity in the current sample may have significantly reduced the external validity of the results. Amongst 39 participants, there were only 2 African-Americans tested (1 RSO-PD and 1 healthy control) and the rest were identified as Non-Hispanic Caucasian. Although there is currently no firm data to suggest racial or ethnic differences in the prevalence, presentation, or course of Parkinson's disease, the results of this study are nonetheless limited in terms of generalizability to a broader population.

Another limitation of the current study is that there may have been a selection bias in our sample as participants were recruited from a larger study also examining facial expressivity in PD, but not specifically the influence of laterality. Because of this crucial feature in the current study, several participants were excluded from analyses for various reasons (i.e., bilateral or unknown onset) while others were selected to create equal, matched groups. Furthermore, because evidence of a major psychiatric disturbance was an exclusion criterion in the larger study, participants with depression as measured by the BDI were also excluded in the present study. Depression in the PD groups may have been especially interesting to examine given the emotional focus of the study and the hypotheses concerning hemispheric roles in emotion. Thus, there may be a chance that the current sample and subsequent results may not have accurately represented the greater population given the goals of the present study.

There were also concerns regarding the methodology of our study. The decision to use posed expressions rather than those induced by actual emotion may have limited the activation in

the extrapyramidal pathways described earlier. In other words, by potentially reducing the involvement of emotional centers in the brain, the differences in true emotional expression between groups may not have been captured. Of note, Bowers et al. (2006) had found that PD patients exhibited less entropy than healthy controls in posed expressions, thereby providing support for the idea that both cortical and subcortical enervations of the face are affected by PD. However, because the goal of the present study was to examine the effect of laterality on emotional behavior rather than to understand the nature of diminished facial expressivity, an analysis of spontaneous expressivity may still have been more indicative of asymmetrical emotional dysfunction. Another methodological concern in the present study was the decision to only examine PD patients when fully on their levodopa therapy. This decision was made because we wished to reveal any noticeable differences in expressivity between the PD patients and controls in their normal, daily state of functioning. While this look at facial expressivity in PD is highly ecologically valid, it may have negated some differences between groups by placing the patients' levels of motor functioning closer to that of healthy controls.

Another notable limitation in the current study was its failure to replicate the results in the Bowers et al. 2006 study, which used the same face digitizing procedure in a group of 12 PD patients and 12 controls and found that patients exhibited significantly less entropy during their expressions than the control group. Following this finding, it was expected that the two patient groups in the current study, regardless of how they compared with each other, would at least display reduced facial expressivity compared to the control group. There are several methodological differences that may account for this disparity. First, the sample of patients in this study presented with mild to moderate PD, and some only had unilateral symptoms, qualifying them as Stage 1 in the disease according to the Hoehn and Yahr Rating Scale.

Because diminished facial expressivity is more noticeable in later stages of PD, the current study may not have captured the differences in facial expressivity as the Bowers et al. (2006) study was able to do through inclusion of more severely affected patients. Secondly, the present study only examined the lower 2/3 of the face while Bowers et al.'s results were based on the whole face. Excluding emotional expressivity around the eyes most likely significantly reduced entropy values. Thus, by controlling for extraneous movement, the results of the current may not be telling the whole story regarding differences between groups in facial movement during an emotional expression.

Directions for Future Research

To address some of the limitations of the present study, several changes in methodology may be made in future paradigms. First, spontaneous expressions, which are also collected from participants in the Cognitive Neuroscience Laboratory, may be used instead of posed expressions to assess this aspect of emotional behavior. To induce involuntary emotional expression, participants are shown clips from humorous or disgusting television shows (i.e., America's Funniest Home Videos, Fear Factor, etc.) and isolated expressions are selected to be digitized. While spontaneous expressions are more difficult to capture as there is often uncontrollable extraneous movement such as blinking or head shaking during laughs, they would afford a better look at emotional experience and subsequent expression in the three groups. Another change that could be made for future studies would be to compare the emotional expressions of right and left motor symptom onset PD patients when not on their levodopa medication. This analysis is perfectly feasible in the near future as PD patients are tested both on and off their medication in our laboratory using the same protocol. Given the results of the current study, it is predicted that there would be an even greater difference between right-sided and left-sided onset PD patients in

their expression initiation time and perhaps in other temporal variables that require intentional movement, such as rise time to peak expressivity.

Conclusion

While the results of the present study did not support the right hemisphere hypothesis of emotional behavior as originally predicted, they may be interpreted in terms of hemispheric differences in controlling intentional behavior. The highly significant finding that patients with left-sided motor symptom onset displayed greater latency to expression is thought to reflect greater dysfunction in the right hemisphere via nigrostriatal dopamine depletion characteristic of Parkinson's disease. As the experimental design requires participants to respond to a sounded cue with a posed facial expression, it can be viewed as a reaction time task in which one must perform an intentional act. Because intentional deficits are more commonly associated with right hemisphere damage, it is believed that the patients who presented with left-sided motor symptoms in our study demonstrated defective activational behavior as opposed to dysfunctional emotional processing.

The findings from this study are both clinically and scientifically relevant. The ability to communicate through facial expressions is often taken for granted as it is an automatic process for most individuals. Timing is an essential part of facial expressivity for it lets others know that you are present and engaged. If the timing of a facial expression is delayed, even by a few seconds as seen in the left-onset patients in this study, it can be very disconcerting to those on the receiving end. It has been mentioned previously that depression may be overdiagnosed in PD patients as clinicians may misattribute diminished facial expressivity and prosody for disturbed mood. A dissonant reaction during a conversation may lead health care workers to assume emotional problems in patients as well. To conclude, the current study may generate more research on action-intention disorders in PD and how they differ from the cardinal motor

symptoms of the disease. Also, our study may stimulate interest in the effect of asymmetrical symptomatology in Parkinson's disease in domains other than cognition.

APPENDIX
DESCRIPTIVE STATISTICS AND ANOVA TABLES FOR PRIMARY AIM

Table A-1. Descriptive Statistics for Entropy Variables

Outcome Variable (Entropy)	RSO-PD	LSO-PD	Control
	M (SD)	M (SD)	M (SD)
Total Entropy			
Group	0.96 (1.07)	1.13 (0.92)	1.17 (0.90)
Expression			
Angry	0.95 (0.95)	0.86 (0.94)	0.66 (0.58)
Fearful	0.54 (0.64)	0.80 (0.86)	1.22 (1.12)
Happy	1.39 (1.61)	1.73 (0.96)	1.63 (1.01)
Peak Entropy			
Group	6.13 (7.45)	9.84 (8.32)	8.14 (6.89)
Expression			
Angry	8.21 (8.49)	7.28 (6.93)	3.78 (4.47)
Fearful	6.46 (6.37)	8.82 (10.73)	8.69 (8.73)
Happy	10.17 (7.49)	13.43 (7.31)	11.97 (7.48)

Table A-2. ANOVA Summary: Entropy Variables

Outcome Variable (Entropy)	SS	MS	F	p	η_p^2	Observed Power
Total Entropy						
Group	0.99	0.49	0.28	0.75	0.02	0.09
Error (Group)	62.63	1.74				
Expression	14.45	7.22	11.24	<0.001*	0.24	0.99
Error (Expression)	46.29	0.64				
Group x Expression	3.44	0.86	1.34	0.26	0.07	0.40
Peak Entropy						
Group	69.55	34.77	0.36	0.70	0.02	0.10
Error (Group)	3472.54	96.46				
Expression	610.19	305.10	7.38	.001*	0.17	0.93
Error (Expression)	2978.50	41.37				
Group x Expression	187.65	46.91	1.34	0.26	0.07	0.34

*= significant finding at alpha level 0.05.

Table A-3. Descriptive Statistics for Temporal Variables

Outcome Variable (Temporal)	RSO-PD	LSO-PD	Control
	M (SD)	M (SD)	M (SD)
Latency			
Group	1.85 (1.45)	3.62 (2.86)	1.59 (1.63)
Expression			
Angry	2.51 (1.72)	4.79 (3.42)	1.82 (1.89)
Fearful	1.85 (1.70)	2.79 (3.26)	1.49 (1.29)
Happy	1.21 (0.93)	3.28 (1.89)	1.46 (1.70)
Rise Time			
Group	1.74 (1.42)	3.25 (4.01)	2.91 (4.52)
Expression			
Angry	2.31 (1.82)	2.49 (2.41)	3.59 (5.99)
Fearful	1.33 (1.15)	3.85 (5.78)	3.03 (5.33)
Happy	1.56 (1.28)	3.41 (3.83)	2.10 (2.25)
Duration			
Group	6.83 (6.62)	6.88 (4.93)	8.19 (6.92)
Expression			
Angry	7.23 (5.65)	7.21 (5.34)	11.31 (8.87)
Fearful	6.46 (8.24)	7.69 (5.82)	7.95 (8.58)
Happy	6.79 (5.99)	5.74 (3.65)	5.31 (3.29)

Table A-4. ANOVA Summary: Temporal Variables

Outcome Variable (Temporal)	SS	MS	F	p	η_p^2	Observed Power
Latency						
Group	858.58	429.29	8.21	0.001*	0.31	0.95
Error (Group)	1882.87	52.30				
Expression	248.84	124.42	3.56	0.03*	0.09	0.64
Error (Expression)	2520.05	35.00				
Group x Expression	115.11	28.78	0.82	0.52	0.04	0.25
Rise Time						
Group	441.86	220.93	1.32	0.28	0.07	0.27
Error (Group)	6027.03	167.42				
Expression	39.20	19.60	0.18	0.84	0.01	0.08
Error (Expression)	7965.44	110.63				
Group x Expression	266.03	66.51				
Duration						
Group	416.46	208.23	0.35	0.71	0.02	0.10
Error (Group)	21469.64	596.38				
Expression	1218.67	609.33	2.31	0.11	0.06	0.46
Error (Expression)	18977.13	263.57				
Group x Expression	1172.87	293.22	1.11	0.36	0.06	0.33

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BIOGRAPHICAL SKETCH

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