



## Emotion and ocular responses in Parkinson's disease

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### ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disease that affects motor, cognitive, and emotional functioning. Previous studies reported reduced skin conductance responses in PD patients, compared to healthy older adults when viewing emotionally arousing pictures. Attenuated skin conductance changes in PD may reflect peripheral autonomic dysfunction (e.g., reduced nerve endings at the sweat gland) or, alternatively, a more central emotional deficit. The aim of the current study was to investigate a second measure of sympathetic arousal—change in pupil dilation. Eye movements, a motor-based correlate of emotional processing, were also assessed. Results indicated that pupil dilation was significantly greater when viewing emotional, compared to neutral pictures for both PD patients and controls. On the other hand, PD patients made fewer fixations with shorter scan paths, particularly when viewing pleasant pictures. These results suggest that PD patients show normal sympathetic arousal to affective stimuli (indexed by pupil diameter), but differences in motor correlates of emotion (eye movements).

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### 1. Introduction

Parkinson's disease is the second most common degenerative disease of the central nervous system, next to Alzheimer's disease, and affects motor, cognitive and emotional functioning. Parkinson's is most often recognized by its cardinal motor symptoms of tremor, rigidity, postural instability, and bradykinesia. Parkinson's patients tend to show motor slowing and reduced movement initiation (Bartels & Leenders, 2009; Bowers, Miller, Bosch, et al., 2006a) and the cognitive performance of Parkinson's patients somewhat mirrors the pattern of motor functioning, with a neuropsychological profile characterized by slowed processing speed on frontal-based cognitive tasks (e.g. Schneider, 2007; Taylor & Saint-Cyr, 1995). These cognitive symptoms are thought to be related to dysfunction of frontal–subcortical basal ganglia circuitry.

The nature of emotional dysfunction in PD is less well characterized. Parkinson's patients experience high rates of apathy and depression and recent research suggests that apathy may be a core feature of Parkinson's disease, with estimates of apathy in PD ranging from 38% to 51% across studies (Isella, Melzi, Grimaldi, Iurlaro, & Piolti, 2002; Pluck & Brown, 2002; Sockeel et al., 2006; Starkstein, Mayberg, & Preziosi, 1992). A recent study that compared rates of depression, apathy, and combined apathy and depression in Parkin-

son's disease and a comparative movement disorder population, dystonia, found that 29% of PD patients endorsed clinically significant apathy *without* depression, whereas no dystonic patients endorsed significant apathy in the absence of depression (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006).

Nonetheless, the specific mechanism underlying emotional dysfunction in PD remains unclear. A number of studies have reported that PD patients have abnormal recognition of facial emotion (Ariatti, Benuzzi, & Nichelli, 2008; Delaveau et al., 2009; Sprengelmeyer et al., 2003; Tessitore et al., 2002). However, few studies have employed experimental methods using a wide range of emotional stimuli in order to investigate the nature of emotional processes in PD. Of those that have, results have been mixed. Bowers, Miller, Mikos et al. (2006b) found that Parkinson's patients demonstrated a blunted startle eye-blink response compared to controls while viewing unpleasant pictures and Miller, Okun, Marsiske, Fennell, and Bowers (2009) reported a trend such that healthy controls showed increased startle potentiation to high vs. low arousing stimuli, whereas Parkinson's patients did not. Based on these findings, Miller et al. speculated that Parkinson's patients might be hypoaroused to emotional stimuli.

This hypothesis is consistent with preliminary findings from our laboratory that Parkinson's patients showed a blunted skin conductance response when viewing emotional (pleasant and unpleasant) pictures compared to healthy older adults (Bowers et al., 2008). While one interpretation of these findings is that Parkinson's patients are hypoaroused to emotional stimuli, these findings are complicated by the fact that Parkinson's patients also have damage to the peripheral autonomic nervous system, including reduced

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nerve endings at the sweat glands of the palm (Dabby et al., 2006). Thus, peripheral autonomic dysfunction could be an important factor mediating reduced skin conductance responses. The aim of the current study was to investigate the utility of measuring changes in pupil diameter as an alternative measure of emotional arousal in PD.

Investigations of pupillary changes have concluded that pupil constriction, including the initial light reflex following onset of visual stimulation, is predominantly controlled via parasympathetic input to the sphincter muscle from the Edinger Westphal nucleus. On the other hand, pupil dilation is predominantly controlled via sympathetic input to the dilator muscle from the thoracic cell columns in the spinal cord. 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 the inhibition of parasympathetic input to the sphincter muscle, primarily mediated by the reticular formation, locus coeruleus and other direct and indirect cortical pathways (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Lowenstein, 1955; Steinhauer, Siegle, Condray, & Pless, 2004).

While a number of studies have explored the neural mechanisms underlying cognitive effects on the pupil (e.g. Steinhauer, Condray, & Kasperek, 2000; Steinhauer et al., 2004), less attention in the last decade has been directed towards elucidating the exact mechanisms underlying the effect of emotional arousal on the pupil. Early studies by Hess and Polt in the 1960s reported bidirectional effects on pupil dilation depending on the pleasantness of the emotional stimulus. These findings were difficult to replicate, perhaps due to imprecise measurement, lack of statistical analyses, and small numbers of stimuli and participants (see Bradley, Miccoli, Escrig, & Lang, 2008).

More recently, Bradley and colleagues (Bradley et al., 2008) utilized a wide range of standardized emotional picture stimuli and found that, rather than bidirectional effects, pupil dilation was significantly greater when participants viewed both pleasant and unpleasant pictures, compared to neutral pictures. Following the initial parasympathetically-mediated light reflex, pupil changes covaried with skin conductance responses in these healthy college students, prompting the conclusion that pupil dilation is an index of sympathetic activation during emotional picture processing. This response may be driven by enhanced sympathetic input to the pupil via modulatory input from the central nucleus of the amygdala and the hypothalamus (see Ranson & Clark, 1959 as cited in White & Depue, 1999). Bradley, Houbova, Miccoli, Costa, and Lang (2010) also found that healthy adults make a greater number of voluntary visual fixations, and with longer scan paths, when viewing pictures with emotional, compared to neutral content. These differences were interpreted as reflecting increased information seeking in a motivationally relevant context, as a prelude to selecting/initiating an appropriate defensive or appetitive action.

The current study measured both pupil diameter and ocular movements as indices of emotional processing in PD patients and healthy older adults during affective picture processing. Prior studies have reported a variety of saccadic deficits in Parkinson's disease. For instance, one study concluded that PD patients show normal voluntary saccade movements but impaired reflexive movements (Yoshida, Yamada, & Matsuzaki, 2002) whereas another found the opposite results (Briand, Strallow, Hening, Poizner, & Sereno, 1999). Studies have also found that PD patients show hyper-reflexive saccades (Fielding, Georgiou-Karistianis, & White, 2006; van Koningsbruggen, Pender, Machado, & Rafal, 2009). Finally, a recent study (Clark, Nearing, & Cronin-Golomb, 2010) found no difference in number or duration of visual fixations for PD patients when viewing emotional faces.

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; Granholm et al., 2003; Harris, 1991; Micieli et al., 1991), 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). Therefore, while the parasympathetically mediated initial light reflex may be compromised in PD, there is no significant evidence that sympathetic input to the pupil is jeopardized by PD. In the current study, visual parameters were selected to elicit a measurable light reflex following picture onset. We expected that PD patients would show attenuation of this parasympathetically mediated reflex, in line with previous studies. Because effects of emotional arousal on pupil dilation are likely to be mediated by sympathetic nervous system activity (Bradley et al., 2008), measuring pupil diameter following the light reflex during emotional picture viewing provides an index of the integrity of sympathetic activation in emotional processing in PD.

Because previous studies have hypothesized that disrupted emotional processing in PD may be related to amygdalar dysfunction (Bowers, Miller, Bosch, et al., 2006a; Bowers, Miller, Mikos et al., 2006b; Tessitore et al., 2002) one hypothesis is that PD patients will show reduced emotional reactivity when viewing emotional stimuli for both pupil dilation and eye movements. An alternative hypothesis is that, if emotional dysfunction in PD is driven by disruption of higher cortical circuitry with the basal ganglia, then PD patients and controls might exhibit similar sympathetic arousal, measured by pupil dilation, whereas group differences would be most pronounced in the motor system, as indexed by eye movements.

## 2. Materials and methods

### 2.1. Participants

Fifteen nondemented Parkinson's patients and fifteen healthy older adults participated in the current study. After data collection, one patient and three controls were excluded due to loss of pupil discrimination for over 25% of trials, resulting in a final *N* of 14 PD patients and 12 healthy controls. Parkinson's patients were recruited from the University of Florida Movement Disorders Clinic and had all been previously examined by a movement disorders specialist and met brain bank criteria for idiopathic Parkinson's disease (Hughes, Daniel, Kilford, & Lees, 1992). Patients were tested while continuing to take Parkinson's 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 brain surgery (e.g., pallidotomy, deep-brain stimulation for treatment of PD symptoms.)

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), ranging 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,  $p = .06$ ). Yate's continuity corrected  $\chi^2$  for differences in gender ratio between the groups was nonsignificant ( $p = .78$ ).

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.<sup>1</sup> Yate's continuity corrected  $\chi^2$  for antidepressant usage ratio between the PD and control groups was not statistically significant ( $p = .17$ ). 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 affect 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, only one patient was currently taking an SNRI and there were no differences between the groups in terms of their baseline pupil diameter (see Section 3) It is also unlikely that light reflex differences between PD patients and controls are related to antidepressant usage, as previous studies have shown a blunted light reflex in PD

<sup>1</sup> Of the PD patients, 4 were taking SSRI's, 1 was on an MAO-I, 1 was on an SNRI, and 1 was on Welbutrin. Of the controls, one was taking Welbutrin and one was taking a tricyclic antidepressant.

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